
Intensive Care Medicine

Study Notes

Compiled by David Tripp
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Scoring Systems

- Desirable features of a scoring system:
 - Calculated on the basis of easily/routinely recordable values
 - Well calibrated
 - A high level of discrimination
 - Applicable to all patient populations in ICU
 - Can be used in different countries
 - Predicts mortality, functional status or quality of life after ICU discharge
- Limited value for individual patients decisions – decisions will remain based on clinical judgement for the foreseeable future
- Prognosis is also affected by local organisation, case-mix, patient's original location, etc.
- Factors affecting severity (and hence outcome):
 - Physiological disturbance – severity measured by physiological response rather than initial insult: normal → compensated → overwhelmed → decompensated. Confounded by supportive therapy
 - Primary pathology: degree of reversibility affects outcome
 - Physiological reserve: broadly combines effect of age and prior health status
 - Source and mode of presentation
 - Organ support prior to admission
 - Unit characteristics
- Most models based on hospital mortality
- Development: part of a database used to develop a logistic regression equation, the remainder is used to validate it
- To describe discriminating ability: plot sensitivity (true positive predictions) on y axis, 1 – specificity (false positive predictions) on x axis, for several different mortality cut-off points. The area under the receiver operating characteristic curve (ROC) gives overall discriminating ability – perfect = 1, non-discriminating = 0.5
- Standardised mortality ratio (SMR):
 - Comparison of predicted with observed mortality rate, using the mortality rate generated by a scoring system
 - > 1 worse than normal, < 1 better than normal
 - Potential limitations:
 - Inconsistencies or inaccuracies associated with data collection and scoring (eg GCS)
 - Missing data on some patients
 - Patient case mix not adequately accounted for by the original population used to construct the formulae
 - Small number of patients (increases SMR error)
 - Accuracy of the prediction model
 - Relying on mortality as a surrogate marker of quality of care
 - Cost of use of proprietary system

Common Scoring Systems

- Glasgow Coma Score (1974): See Resuscitation in Traumatic Brain Injury, page 236
- Therapeutic Intervention Scoring System (TISS): good indicator of nursing and medical work, poor measure of illness severity
- Acute Physiology and Chronic Health Evaluation Systems 1 – 4 (APACHE):
 - APACHE 2 the most common. APACHE 1 & 4 are proprietary
 - APACHE 2 validated on non-CABG, non-burns patients
 - Based on a physiological score, chronic health score based on premorbid states and age (a surrogate for physiological reserve)
 - Calculated from the most abnormal measurements in the first 24 hours of ICU stay
 - As management and organisation have improved, overestimates mortality
 - APACHE 2 ROC 0.85, APACHE 3 ROC 0.9
 - Standardised mortality ratios can be used for large patient populations
- Simplified Acute Physiology Score (SAPS 1 – 3):

- No diagnostic or chronic health status
- ROC 0.96.
- Most commonly used system in Europe
- SAPS 3: 2005, includes pre-admission, admission and acute physiological variables. Calibration depends on geographic area
- Mortality Prediction Models: derived from a single US institution – models mortality at 24, 48 and 72 hours
- Organ Failure Scores:
 - Multiple Organ Dysfunction Score: based on respiratory, renal, neurological, haematological, CVS and hepatic
 - Sequential Organ Failure Assessment (SOFA):
 - Originally designed for sepsis, now validated for organ dysfunction not related to sepsis
 - Defined score (1 – 4) for each of six organ systems: respiratory, CVS, CNS, renal, coagulation, liver
 - Classifies daily status for use in clinical trials – response of organ dysfunction to therapy can be followed over time
 - Not designed for outcome probability. In general, higher SOFA scores are associated with worse outcome
- Trauma: see Trauma Scoring Systems, page 229

MET/Rapid Response Teams

- Principle:
 - In hospital arrests usually preceded by some deterioration in physiological criteria. Want to detect and respond to these early with skilled assessment
 - Minor derangements in vital signs predict adverse outcomes – many of these are below the usual threshold for a MET call
- Components of a MET System:
 - Call criteria for alerting the team to a sick patient:
 - Single trigger systems: simple, in order to be sufficiently specific must set a high (or even extreme) threshold → ↓ sensitivity. Respiratory rate is the most predictive of physiological variables so far prospectively assessed
 - Scoring systems (MEWS – medical emergency warning score): based on a number of physiological variables. More sensitive and specific. More complex to calculate (↑ errors). Lend themselves to computer based recording systems (which could then also be combined with electronic laboratory data....)
 - Specific scoring systems exist for paediatric populations. The next “frontier” would be scoring systems for different disease states
 - Education of ward staff to recognise deteriorating patient condition
 - Effective training and composition of MET team with diagnostic and procedural skills
 - Review of calls, aggregation of data and follow up
- Evidence:
 - Previous single centre studies using before and after models had shown a more impressive difference - ?a result of confounding from an enthusiast driving quality initiatives – one of which could be MET. Goldhill 1999, Buist 2002, Bellomo 2003, Bristow 2000, Kenward 2004
 - MERIT: Cluster randomised trial of MET teams vs none. Hillman et al, Lancet 2005
 - Difficult trial:
 - Want to identify patients with reversible pathology that would otherwise be missed. Baseline mortality of this group so small that detecting the impact of a change in management very difficult – especially with a complex, unblinded intervention ⇒ ?underpowered
 - Cluster trial between hospitals – risk of contamination of new practice into the placebo arm with circulating staff, etc.
 - Still a fairly low call-out rate in the treatment hospitals
 - 23 Australian hospitals, 12 implemented, 11 did not. Training (2 months), implementation (4 months), study (6 months), n = 741,744
 - Greatly increased call-outs, doesn’t affect incidence of cardiac arrest, unplanned ICU admissions or unexpected deaths
 - Other unmeasured benefits? Eg end-of-life care and patient and staff satisfaction
 - Mortality decreased in all hospitals by 30% (?contamination)

- Underpowered, base line event rate assumed to be 30 per 1000 when it was actually 7 per 1000
- Cochrane Review, 2007, Outreach and early warning systems for the prevention of intensive care admission and death of critically ill adult patients on general hospital wards. The role and effectiveness of outreach has been questioned as expensive and introduced without strong supporting evidence. Eg The Practical Study of nurse led, intensive care follow-up, RCT in BMJ 2009
- Post-hoc Analysis of the MERIT Study, CCM 2009, as the proportion of early emergency team calls increase, the rate of cardiac arrest and unexpected death decreases
- Howell et al, CCM 2012, single centre study over 6 years, a rapid-response from the usual primary-care team vs ICU-based care team was associated with ↓unexpected mortality, and no difference in total mortality (ie more deaths became expected). High rapid response dose: > 50 per 1,000, and high number of ICU transfers (20%) – may reflect high number of ICU beds in that institution
- See systematic review: Winters et al, Annals of Medicine 2013. MET has bigger impact on non-ICU arrests than hospital mortality.
- Potential problems:
 - Cost: staff and equipment
 - Diversification/distraction of staff from other roles
 - Requires larger context: policies and education
 - Risk of primary team stepping back from carefully monitoring (the MET Team will do it)
 - Risk of people new to the patient having to manage end of life decision making
 - No study has attempted to quantify these risks
- Other issues:
 - Some evidence of a dose-response relationship: don't get reduced mortality till about 25 calls per 1,000 inpatients
 - Not a marker of poor ward care, but of mismatch between patient acuity and the clinical setting

Pandemic Planning

- Overall co-ordination:
 - Activate hospital pandemic plan
 - Liaison with other hospital departments, ambulance services, other ICUs, health authorities
 - Community influenza surveillance
- Increasing ICU bed capacity:
 - Open non-commissioned bed spaces
 - Defer elective surgery
 - Identify other spaces for ventilated patients: eg recovery, respiratory services
 - Decant stable patients to HDU settings
 - Maximise use of non-ventilatory strategies
 - Facilitate end-of-life discussions in appropriate patients
 - Consider private hospital ICU capacity
- Increased ICU staffing:
 - Increase shift length (eg 8 to 12 hours)
 - Use of casual and agency staff
 - Cancel leave
 - Vaccinate staff to reduce absenteeism
 - Second non-ICU staff
 - Reduce nurse: patient ratio
- Anticipate and source extra equipment
- Infection control to reduce spread

Clinical Information Systems

- = computerised systems for managing the clinical record, may be integrated into broader electronic medical records
- Additional features: PACS (picture archiving and communication system), electronic prescribing and computerised physician order entry (COPE – reduced duplicate ordering)
- Benefits:
 - Automation of repetitive tasks
 - Improved accuracy (transcription, legibility, built in error checking)
 - Bedside access to other clinical information: pathology, radiology, etc.

- Integration with other bedside equipment → automated recording of bedside observations (labour saving, ↓transcription errors)
- Electronic record of orders, prescriptions
- Records simultaneously available
- Access to passive knowledge bases and active decision support systems (tricky to migrate across systems and international practice)
- Medicolegal: archiving and audit trail
- Clinical database for review and research
- System components:
 - Clinical workstations
 - Bedside devices
 - LAN
 - Server farms
 - Other clinical applications (labs, PACs) integrated through software interfaces (often legacy systems necessitating expensive, customised solutions)
 - Healthcare WAN
 - Back-up and recovery facilities
- Costs:
 - Annual recurrent costs are significant
 - Technology rapidly changing → short shelf life
 - Integration with other systems often problematic
- Implementation issues:
 - Implementation costs (managerial, human resource, opportunity costs) frequently underestimated
 - Lack of computer literacy amongst users → high training costs
 - Need to maximise perceived benefits early to encourage system acceptance
 - Post-implementation review essential
- No evidence that CIS → ↓workloads or ↑outcomes
- Electronic Health Records currently fail to meet anticipated goals. Efforts intended to improve quality and reduce health care costs instead seem to have stimulated sales and implementations of systems that do not work well. Editorial, Ann of Int Med, 158:11, 2013

Quality Assurance

- See College Policy IC-8: Quality Improvement
- Quality Improvement = “an interdisciplinary process designed to raise the standards of the delivery of preventive, diagnostic, therapeutic and rehabilitated measures, in order to maintain, restore and improve health outcomes of individuals and populations”
- Measuring quality:
 - Structural measures: eg size, staffing, IT, case mix
 - Process measures: eg rate of DVT or stress ulcer prophylaxis, early enteral feeding, hand washing, time to antibiotics
 - Outcome measures: severity adjustment mortality rate, unplanned readmissions, VAP rate, CVL bloodstream rate, family satisfaction
- Quality Improvement process:
 - Planning: design or project, key indicator to be improved, method to improve it, data to be collected
 - Implementation: introduction of strategies to create the change
 - Evaluation: Determination of whether the indicator is changing
 - Ensuring sustainability: modification of behaviour to sustain the improvement and incorporation into new standards or guidelines. Sustaining leadership
- Risk management is related: risks identified from incident reports, M&M, complaints. Then risks identified, assessed and analysed, managed and re-evaluated (“closing the loop”)
- US national Quality Strategy specifies 6 domains for quality improvement:
 - Safety
 - Care co-ordination
 - Clinical care
 - Population and community health
 - Patient experience and engagement
 - Cost and efficiency

Audit

- Audit Cycle:
 - Identification of the problem
 - Research into best practice
 - Information gathering on current practice and comparison to benchmarks
 - Targeted intervention
 - Re-assessment
- Cost-effectiveness

Open Disclosure

- Human's make mistakes
- Most patients from errors is common
- Principles of open disclosure:
 - Open and timely disclosure
 - Say there's been an error
 - Express regret
 - Recognise expectations of patients and family
 - Ensure confidentiality
 - Have and follow a process for investigating errors and improving future processes

Key Literature in Outcomes/Quality

- See Shekelle et al, Annals of Med 2013, for a framework for evaluating the effectiveness of patient safety strategies (across all areas of health care). On the basis of this framework, they conclude:
 - There is evidence to "strongly encourage":
 - Pre-op checklists
 - CLABSI bundles
 - VAP bundles
 - Hand hygiene
 - The "do not use" list for hazardous abbreviations
 - Bundles to prevent pressure sores
 - Barrier precautions to prevent health care associated infections
 - Use of real time ultrasound for central line placement
 - Interventions to improved prophylaxis for VTE
 - There is evidence to "encourage":
 - Multicomponent interventions to prevent falls
 - Use of pharmacists to ↓adverse drug events
 - Documentation of patient preferences for life sustaining treatments
 - Obtaining informed consent for procedures
 - Team training
 - Medication reconciliation
 - Practices to reduce radiation exposure from fluoroscopy and CT
 - Rapid response systems
 - Use of systems to detect adverse events
 - Computerised provider order entry
 - Use of simulation exercises on patient safety efforts
- JAMA 2011, Scales et al, A multifaceted intervention for quality improvement in a network of intensive care units: a cluster randomized trial. Showed a multifaceted intervention can improve uptake of practices that improve clinical outcomes
- A surgical safety checklist to reduce morbidity and mortality in a global population, NEJM 2009, Haynes et al. 7688 patients in 8 hospitals. Reduced death rates and complications
- FASTHUG - Crit Care Medicine 2005, Vincent JL, offers a number of benefits including ↓VAP
- Bundles: invented by the Institute for Healthcare Improvement. A set of evidence based interventions that together produce a synergistic effect on a targeted outcome. Some concern that some components of bundles are based on poor quality evidence. See Zilberberg, Crit Care Medicine 2009, "Implementing quality improvements in the ICU: ventilator bundle as an example"
- "Quality measurement at intensive care units: which indicators should we use?", J Crit Care 2007, de Vos et al. Of 62 indicators, selected 12 of which one was dropped after the feasibility study. Indicators were:

- Structure: availability of an intensivist, patient to nurse ratio, medication error prevention strategy, patient/family satisfaction measurement
- Process: ICU LOS, duration of mechanical ventilation, proportion of days with all ICU beds occupied, proportion of measures of uncontrolled glucose
- Outcomes: standardised mortality by APACHE II scores, incidence of decubitus ulcers, number of unplanned extubations
- A number of trials on Medication Errors
- Consultant intensivists:
 - Impact of 24 hour in-house intensivists on a dedicated cardiac surgery intensive care unit, Kumar et al, Annals of Thoracic Surgery 2009. 24 hour in house intensivist. No differences in mortality or readmission, but ↓packed cell transfusion rates, ventilation duration and LOS
 - 24 hour intensivists improved mortality in open units (where consultation with an intensivist was optional – ie ‘low intensity unit’), but not in high closed units. Multicentre retrospective audit. Wallace et al, NEJM 2012
- “Structure, Process & Annual ICU Mortality across 69 [USA] centres”, Checkley, CCM 2014, found the following factors associated with ICU mortality:
 - Surgical vs medical patient
 - Lower bed/nurse ratio
 - Daily plan of care review
 - Not associated with mortality were:
 - 24 hour intensivist
 - closed unit

CICM Policies

- IC-01 Minimum Standards for Intensive Care Units:
 - Generic requirements:
 - Medical staffing, including a director, with sufficient experience to provide for patient care, administration, teaching, research, audit, outreach....
 - Nursing staff: Australian College of Critical Care Nurses requires 1:1 for ventilated patients and 1:2 for lower acuity patients. Nurse in charge with post registration ICU qualification
 - Documented educational programme
 - Operational: agreed policies, team approach, surge capacity for emergencies, documented procedures for audit, peer review, quality assurance
 - Structure:
 - Siting: separate unit with appropriate access to ED, theatre, radiology...
 - Design:
 - Patient cubicles (> 20 m²), wash basin, service outlets, appropriate electrical standards, privacy
 - Work areas, equipment and storage areas, staff facilities, seminar room, offices, relatives’ area....
 - Equipment: appropriate equipment (list given) and regular system for checking it’s safety
 - Monitoring equipment: for each patient, for unit (eg gas supply alarms), and for patient transport
 - Criteria for a level I, II and III ICU and a PICU
- IC-02 Intensive Care Specialist Practice in Hospitals Accredited for Training in Intensive Care Medicine
- IC-03 Guidelines for Intensive Care Units Seeking Accreditation for Training in Intensive Care Medicine
- IC-04 The Supervision of Vocational Trainees in Intensive Care Medicine
- IC-05 Guidelines on the Health of Specialists and Trainees:
 - Personal health: should have a GP, not self-prescribe, and not solicit corridor consultations
 - Professional: Strategies for departments to assist with health maintenance: facilitating access to GPs, orientation programmes that engender a culture of support, systems for professional support (eg buddying), reviewing of rostering practices, systems for debriefing
- IC-06 Guidelines for the Relationship Between Fellows, Trainees and the Healthcare Industry:
 - Covers:
 - Transparent relationships (eg disclosure of fees or gifts)
 - Patient benefit is the basis of any association
 - CME meetings, research projects, industry sponsored employment and travel
- IC-07 Administrative Services to Intensive Care Units
- IC-08 Quality Improvement
- IC-09 Statement on the Ethical Practice of Intensive Care Medicine

- IC-10 Minimum Standards for Transport of Critically Ill Patients
- IC-11 Assessment of Overseas Trained Intensive Care Specialists
- IC-12 Intensive Care Services for Areas of Need
- IC-13 Recommendations on Standards for High Dependency Units for Training in Intensive Care Medicine
- IC-14 Statement on Withholding and Withdrawing Treatment
- IC-15 Recommendations on Practice Re-Entry for An Intensive Care Specialist

Ward Rounds

- Meta-analysis of studies on ICU ward rounds (Lane et al, CCM 2013) identified:
 - Facilitators of effective ICU rounds:
 - Multidisciplinary group (a number of studies with pharmacists)
 - Explicitly defined roles
 - Standardised structure
 - Goal orientated approach
 - Best practices check list
 - Barriers to effective rounds:
 - Poor information retrieval and documentation
 - Interruptions
 - Long rounding times
 - Allied health provider perceptions of not being valued
- “Ward rounds in practice”, report of the RCP and RCN, Oct 2012, identified “best practice” as:
 - Multidisciplinary working: valuing the team, nurse at the bedside, explicit communication (task allocation, prioritisation of patients, task ownership) with a structured approach (eg SBAR)
 - Board rounds are useful for prioritisation, facilitating MDT input, recapping rounds or afternoon discharge planning, but shouldn’t replace face to face patient reviews
 - Structure: Pre-round briefing to specify aims, debrief, introduce staff, review patient location and numbers, identify training and education needs
 - Communication: encourage patients in advance to prepare for the round, provide written summary information, introduce all members of the team, particular care with vulnerable patients, protect confidentiality and dignity
 - Managing decisions and tasks: good documentation, safety checklists, discharge planning using a structured approach

Safety

Human Factors

- From APLS course material
- Error is inevitable – safety is not
- Behind an identifiable error, leading to an untoward event, there will be a sequence of factors arising from latent conditions or active failures without which the untoward event would not have happened (Swiss cheese model)
- Simplistically, the more checks that are put in place, the less an error is likely to occur. However, increasing complexity can itself become counterproductive as people will avoid or modify them to make life simpler
- Communication:
 - Verbal and non-verbal communication is easily misinterpreted
 - Feedback loop: the receiver repeating the message to the sender shows an immediate benefit
 - Teamwork: requires good relationships
 - Hierarchy: steep hierarchy can inhibit junior staff speaking up. If someone has information that they think others may need, there is a hierarchy of increasing concern. Both speaker and listener should recognise the level of communication.
 - Probe: I think you need to know what is happening – eg “Are you aware...”
 - Alert: I think something bad might happen – eg “I am concerned.... Should we....”
 - Challenge: I know something bad will happen – Need to engage the key protagonist directly – eg “You must listen to me....”
 - Emergency: I will not let it happen. Take over
 - Anything reaching “challenge” should prompt an in-depth, post-incidence review whether or not there is an adverse outcome

- Situational awareness:
 - Is achieved when we have sufficient and correct information, have interpreted it correctly, accurately project the outcome, and this perception is shared by the whole team
 - Situational awareness often decreases when focused on a clinical task (esp if it's the team leader)
 - Confirmation bias: people favour information that confirms their preconceptions or hypothesis. It may take a new comer to point out the obvious
 - Need to continually question your own thought processes, and the team needs to share impressions of the current situation
- Fatigue:
 - Recognise effect of circadian rhythm disturbance
 - Need to be willing and able to say "I'm not fit to do this"
- Decision making:
 - Under time pressure, cannot gather all information, assess all ambiguities, assess all options, and test all solutions with everyone
 - Main safety net is the ability of team members to raise concerns, and for the decision maker values and considers this input appropriately
- Leadership: optimising team performance. Facilitating team learning

Medication Errors

- Risks:
 - Patient factors:
 - Severity of illness
 - Extremes of age
 - Prolonged hospitalisation → greater exposure to the risk
 - Sedated patients aren't able to say it's wrong
 - Complexity of medications:
 - Infusions or weight based requiring calculation
 - Number of medications
 - ICU environment:
 - Acute patients → more stressful
 - Emergency admissions
 - Multiple team members
 - Worse with high staff turnover
- Interventions to minimise medication errors:
 - Optimise medication process
 - Medication standardisation
 - Technology:
 - Computerised physician order entry
 - Barcode technology
 - Computerised infusion devices
 - Eliminate situational factors:
 - Avoid long consecutive or cumulative working hours
 - Minimise interruptions/distractions
 - Oversight and error interception:
 - Primary doctor in charge of patient's drugs (intensivist)
 - Adequate staffing
 - Pharmacist participation
 - Quality assurance processes
 - Medication reconciliation
 - Staffing factors:
 - Appropriate patient/nurse ratio
 - Trainee supervision and graduated responsibility

Fire Drill

- Evacuation: Rapidly remove all patients and staff from the immediate danger area towards and exit. Safely disconnect lines, monitors, ventilators and bag ventilated patients
- Notify switchboard. Activate fire alarm, state location and nature of fire
- Take instructions from the designated fire warden
- Shut all windows and doors

- Turn off O2 outlets or master O2 switch
- Attempt to control and extinguish the fire with appropriate extinguishers (CO2 or dry powder) and fire blankets provided this is safe
- If fire is uncontrolled commence evacuation of patients via the fire exits, most stable first, least stable last:
 - Horizontal evacuation through at least one set of fire doors to another part of the ICU or an acute care area on the same floor
 - Vertical evacuation via stairs to the floor below
 - Out of building evacuation, with liaison with other buildings/hospitals re on going care
- Review of incident and response to identify cause of the fire, issues with its management, and implementation of staff education and simulation exercises

Electrical Safety

- Electricity can cause damage by electrocution, burns or ignition of a flammable material
- The effects of electrocution are dependent on:
 - The current
 - The pathway (ie what it flows through)
 - The current density: current flowing through a unit area. Eg a very small “micro-shock” can still cause VF if delivery close to the heart (eg via central venous catheters, external pacemaker leads, etc.
 - The type of current: alternating is worst
 - Duration
- Skin burns are worst as this tissue is dry compared to other tissues → higher resistance → ↑heat
- Preventing electrocution:
 - General measures:
 - Adequate maintenance and regular testing of electrical equipment
 - Ensure patient is not in touch with earthed objects
 - Equipment design:
 - Equipment should meet standards e.g. British Standard for the Safety of Medical Equipment
 - Class 1: any part of the equipment accessible to the user is connected to earth by an earth wire. Should have fuses at the equipment end of the mains supply lead, in both the live and neutral conductors, so that this protection works even if the socket is incorrectly wired
 - Class II: Protected from live supply by double or re-enforced insulation
 - Class III: uses voltages no higher than safety extra low voltage (either battery or transformer supply)
 - Equipotentiality: Each piece of equipment in a stack is connected together, to prevent a current flowing through the patient from equipment with a higher potential to a lower potential
 - Isolated circuits: isolating transformer: mains circuit is earthed but patient circuit is not earthed
 - Circuit breakers
- Diathermy:
 - Uses heating effects of high frequency current to coagulate and cut
 - Monopolar: neutral electrode has a large conductive surface area ⇒ low current density ⇒ no heating effect. Active electrode has a small contact area ⇒ gets hot
 - Bipolar: Current between points of a pair of forceps at a much lower power output. No current through the rest of the body. Use for patients with pacemakers

Patient Transport

- See CICM Policy IC-10: Minimum standards for transport of critically ill patients. Covers initiation, coordination, responsibility, staffing, safety, equipment, patients monitoring, documentation, training and audit of transport systems
- Systematic approach to transport:
 - Decision to transport:
 - Evaluation: is transfer appropriate (risks vs benefits) and what is the urgency
 - Consideration of mode of transport: distance vs efficiency vs cost vs urgency vs cost – road, helicopter, fixed wing
 - Communication: local, transferring and receiving teams, establish key contacts
 - Availability of equipment, adequately skilled staff, sufficient remaining staff to cover base hospital
 - Actual transport:
 - Identify team leader, identify tasks to carry out, allocate tasks

- Consideration of ventilation. Plan sedation, vascular access. Catheterise
- Checks of equipment and patient stabilisation and preparation (eg chest tubes)
- Transfer of documentation/images/results
- Informing/transporting next of kin
- Planning of timing and route
- Assessment of patient status before transport
- Monitoring during transport: minimum for ventilated patient is pulse oximetry, capnography, ECG and BP
- After transport:
 - Appropriate handover and documentation
 - Process to facilitate quality assurance
- Referral networks are often driven by historic referral patterns, no patient-centred outcomes (eg quality)
- Risks:
 - All patient movement is associated with ↑ mortality and morbidity, and risk to staff. Prospective multi-centre cohort study matching intra-hospital transported patients to non-transported patients round ↑ complications (OR 1.9), ↑ ICU LOS (12 vs 5 days) but no effect on mortality. Schwebel, Crit Care Med 2013. These risks should be considered when transporting eg to medical imaging.
 - In up to 70% of ICU transports, adverse events occur: 1/3 are equipment related
 - Lack of familiarity with transport O2, suction and communications and other equipment
 - Head injury: changes in body position or PaCO2 → marked changes in ICP. Check EtCO2 on transport monitor before taking off ICU ventilator. Maintain a stable MV to maintain stable EtCO2
 - Respiratory problems:
 - Acute deterioration in PaO2/FiO2
 - Ventilator associated pneumonia is significantly increased
 - Ventilators: CPAP is problematic – as usually requires high gas flows. MHE filters usually sufficient to maintain humidification
 - Need Heimlich or similar one-way valve flap devices for pleural drainage – underwater seal drains tip or siphon...
 - Cardiac: IABP difficult to transport
- All transport involves noise (→ auscultation difficult), vibration, turbulence (→ motion sickness) and acceleration (Trendelenburg and reverse trendelenburg positions during take-off and landing may impact perfusion, oxygenation and ICP)
- Risks and Changes with Altitude:
 - Behaviour of gases:
 - 0 – 4,000 m atmospheric pressure drops from 760 → 480 mmHg – the “safe physiological zone” where aircraft don’t need to be pressurised. Above that need supplemental pressure or oxygen. Gas percentages stay the same – O2 is still 21% - it’s just the absolute amount that drops
 - Dalton’s Law: sum of the partial pressure of each gas is equal to the total pressure ⇒ as altitude increases, gases exert less pressure. PO2 at sea level = 160 mmHg, at 18,000 ft. = 80. ↓ O2 partial pressure → further compromised if already FiO2 dependent.
 - Henry’s law: at a constant temperature, the amount of a given gas that dissolves in a given type and volume of liquid is directly proportion to the partial pressure of gas in equilibrium to the fluid
 - ↑ Gas volumes and ↓ pressure as ↑ altitude (Boyles Law : $P_1.V_1 = P_2.V_2$): physiological air spaces (eg sinuses), pathological air spaces (pneumothoraces, emphysematous bullae, intra-cranial air from open injuries, bowel obstruction, gas emboli), air-containing equipment (eg ET cuffs – fill them with water, PA catheter balloons, wound drainage bags). Amount of expansion is limited by the pliability of the structure surrounding the gas
 - Reduced effect of gas expansion by de-nitrogenation with 100% O2 before and during flight
 - ↑ FiO2 to maintain PaO2
 - ↓ Partial pressure of H2O → dehydration. Water partial pressure falls and is not corrected by cabin pressurisation. Secretions thicken → ET tube clogs
 - Cabin pressure: most turboprops planes can maintain 250 mmHg (46.7 kPa) differential = cabin altitude of 1000m while flying at 6500 m
 - Temperature drops 2°C for every 300 m.
 - Staff should refrain from compressed gas diving for 24 hours prior to transfer
- Special Transport Situations:
 - Perinatal transport. Avoid delivery in transit!
 - Diving injury: decompression sickness or arterial gas embolus. Need transport to decompression facility. Transport at or near sea-level cabin pressure on 100% O2

- MRI more hazardous than CT:
 - Ferrous projectiles accelerating into the scanner
 - Limitations on equipment
 - Problems with PA catheters
 - Movement of metallic foreign bodies, especially in the eye
 - Malfunction/failure of pacemaker
 - Patient getting cold due to longer duration
 - Longer distances to pumps/monitors
 - Patient inaccessibility
 - Can't take resuscitation equipment into the magnet zone
 - Gadolinium → nephrogenic systemic fibrosis
 - Burns from ECG dots

Ethics in Intensive Care

- See:
 - College Policy IC-9: Statement on the Ethical Practice of Intensive Care Medicine, covering ethical principles, patient rights, patient responsibilities, clinical research, clinical teaching and professional conduct
 - Lancet, Oct 16, 2010 article on ethical dilemmas in ICU
- Medical ethics particularly relates to the relationships between health care practitioners and patients
- Principles:
 - Autonomy: individual self-determination
 - Beneficence: Acting in the best interests of patients
 - Non-maleficence: do no harm
 - Fidelity: faithfulness to duties – a principle underlying confidentiality, honesty, continuing professional development
 - Social justice: equitable access for all depending on need
 - Utility: doing the most good for the most people (covers not wasting resources). Consequentialist concept
 - These “pillars” are increasingly seen as very reductionist. Fail to consider the context, including relationships (doctor-patient-family-peers). What is right in one context may not be right in another context
- ICU ethical problems:
 - See Withdrawing or Withholding Treatment, page 356
 - End of life management – complicated by uncertainty. Includes issues around advanced directives, power of attorney, euthanasia and treatment withdrawal
 - Consent
 - Caring for family vs caring for patient
 - Rationing and societal role. What has/should society delegate to professionals
 - Professionalism. Includes:
 - Maintenance of professional standards
 - Appropriate professional relationships with patients
 - Quality of documentation
 - Participation in quality initiatives
 - Industry and conflict of interest
 - Potential to be sorely tested if well-being of the professional is at risk (eg infectious diseases, terrorism)
 - Research – using the patient as an instrument to achieve another's end without express consent
- Resolving ethical conflict:
 - Occurs where there is a clash of values or interests
 - Innate sense of “right” and “wrong” leads to strongly held positions
 - Resolved by discussion, reference to guidelines, professional societies codes' of ethics, ethics committees, recourse to legal system
- Clinical experience: making the same mistakes with increasing confidence over an impressive number of years

Pearls of Wisdom

- Leadership:
 - Doing the right thing not the easy thing
 - Leaders are like tea bags, you can't tell how good they are till they're in hot water
 - No one jumps higher by lowering the bar
- On intervening:
 - I say to my registrars "don't just do something, stand there"
 - Beware the imperative to do what you can, and not what you should
 - Four criteria for something new to be adopted in ICU:
 - Expensive
 - Dangerous
 - Useless
 - Fun
- You do not need RTCs to prove parachutes
- On quality and safety:
 - Everyone in health care has 2 jobs to do: to do their work and to improve it
 - A safety culture is critically dependent on the ability of people to challenge hierarchy
 - There is a tendency to make the measurable important rather than the important measurable
 - The system response to poor performance is often to add another layer in the Swiss cheese model, rather than making the holes smaller
 - If we think we are infallible we will not consider human factors
- On certainty:
 - "Half the money that money I spend on advertising is wasted, I just don't know which half."
 - We have to be certain of what we do. So when knowledge changes we find it hard to change
 - Doubt is uncomfortable, certainty is absurd (Voltaire)
- Responding to a problem or crisis:
 - Run to the problem
 - Apologise and fix what you can
 - Take responsibility
 - Shower people with information
 - Evaluate – get better not bitter
 - Support each other
 - Don't slip into silos – never at the expense of another part of the team
 - Mistakes will always happen – it's how we deal with them that matters

Clinical Trials

- Current ANZICS CTG trials:
 - Proposed trials:
 - SPICE: Phase 3 RCT of dexmedetomidine vs usual light sedation
 - RELIEF: Conservative or liberal fluid strategy in high risk abdominal surgery
 - IPHIVAP: RCT to test effectiveness of inhaled heparin to prevent VAP
 - BLISS: Subgroup of ARISE study to see if bacterial burden in septic patients is a determinant of mortality and MODS
 - Current or recent trials:
 - CHEST
 - ARISE: early-goal directed care vs standard care
 - POLAR: early hypothermia in TBI
 - EPO-TBI: erythropoietin in TBI
 - ADRENAL: hydrocortisone for septic shock
 - TRANSFUSE: fresh vs standard aged red blood cells
 - PHARLAP: Open lung strategy for ARDS
 - BLING: infusion of beta-lactam antibiotics
 - HEAT: paracetamol vs placebo for fever
- Evidence based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients
- Phases of drug testing after animal studies:
 - Phase 1: testing in healthy volunteers
 - Phase 2: Small trials in patients with disease: assess safety and efficacy
 - Phase 3: Large trials to determine treatment effect, compared to standard treatment.
 - Phase 4: Post market open label trials
- Ethical issues in intensive care research:
 - Ethical principles outlined the International Ethical Guidelines for Biomedical Research Involving Human Subjects
 - Participants in critical care research are particularly vulnerable
 - Informed consent:
 - Rarely possible in ICU. Patient (if awake) or surrogate (if not) usually stressed and facing life-threatening condition. Need to balance that against the fact that treatment can only be improved through research
 - Can be accommodated through waiver of consent if time dependent research (eg during cardiac arrest) or delayed consent (both have problems)
- Critical appraisal/applying evidence:
 - Are the results valid: randomised, sufficient follow-up, intention-to-treat, blinding, single or multi centre RCT
 - What were the results: how large and precise was the treatment effect
 - Are the results generalisable to my patients (external validity)
 - What are the benefits (is it a clinically relevant endpoint), harms
 - What are the financial and logistical implications

Study Endpoints

	Pros	Cons
ICU Mortality	<ul style="list-style-type: none"> • Single metric • Easily measured • In most databases • Variation over time may reflect +ive or -ive ICU changes • Useful/tangible in quality programme 	<ul style="list-style-type: none"> • Definition of ICU varies a lot • Can be gamed (eg transfer to die on wards) • Masks problems in low volume diagnoses • Poor correlation between mortality and quality of care • Need complicated statistics to adjust

Hospital Mortality	<ul style="list-style-type: none"> Reasonable surrogate for 90 day mortality Easy to obtain Avoids ICU definition problems 	<ul style="list-style-type: none"> Confounds ICU quality with ward issues No functional outcome
90 day mortality	<ul style="list-style-type: none"> Picks up post-discharge mortality (only about 10%) Simple via linkage with registries 	<ul style="list-style-type: none"> Follow up difficult 90 days not enough for ICU attributable mortality Ethical problems of contacting patients
1 year functional	<ul style="list-style-type: none"> Patient centred 	<ul style="list-style-type: none"> Expensive, loss to follow-up No ideal scoring tool May reflect disease no ICU care

Randomised Controlled Trials

- RCTs reduced bias and confounding
- Result of a trial may be:
 - True treatment effect
 - Effects of bias or confounding
 - Chance
- Focused clinical question:
 - Patient group...
 - Intervention...
 - Compared with...
 - Outcome...
- Sample Size:
 - Efficacy trials: small focused population with lots of exclusions
 - Effectiveness trials: large populations with few exclusions
 - Size is determined by:
 - Control group outcome rate: expected % with outcome in control group
 - Treatment effect: expected change from the treatment
 - Significance level (α): the level of probability accepted as indicating it did not occur by chance
 - Power: percentage chance of detecting a true treatment effect if one exists (usually > 80%)
- Randomisation gives each participant a (usually) equal chance of being assigned to any treatment groups. It requires:
 - A genuinely random allocation sequence
 - Allocation concealment from the patient and investigators (single and/or double blinding). Often requires blinded adjudication (eg of subjective diagnoses)
 - Reduces:
 - Selection bias
 - Confounding – both known and unknown confounders are randomly allocated to control and treatment groups
- Blinding:
 - Blinding and allocation concealment are methods used to reduce bias in trials
 - Blinding = a process by which trial participants and their relatives, care-givers, data collectors and those adjudicating outcomes are unaware of which treatment is being given to the individual participants.
 - Prevents:
 - Clinicians from consciously or subconsciously treating patients differently based on treatment allocation
 - Data collectors from introducing bias when there is a subjective assessment to be made (eg pain score)
 - Outcome assessors from introducing bias when there is a subjective outcome assessment to be made, eg GCS
 - 2010 CONSORT Statement recommends not using the terms “single” or “double” blinded. Instead, reports should state who was blinded after assignment (eg participants, care providers, outcome assessors, etc.)
 - Allocation concealment: refers to the concealment of the allocation of the randomisation sequence from both the investigators and the patient. Poor concealment may exaggerate treatment effects.

Methods for allocation concealment include sealed envelope technique, telephone or web based randomisation. *Allocation concealment ensures the treatment allocation is not known before the patient is entered into the study. Blinding ensures that the patient and carers are blinded to the treatment allocation after enrolment into the study*

- Outcome measures are ideally clinically meaningful outcomes, otherwise surrogate outcomes that have been validated
- Analysis:
 - Done according to a predetermined statistical analysis plan - ↓temptation to perform multiple analyses and only report those that support the investigators preconceived ideas
 - Subgroups should be pre-defined and kept to the minimum possible (increased chance of type 1 error with multiple subgroups)
 - Intentional to treat analysis:
 - Patients are analysed in the group to which they were randomised
 - Preserves the baseline comparability between treatment groups achieved by randomisation
 - Simplifies the task of dealing with suspicious outcomes – guards against conscious or unconscious attempts to influence the results of the study by excluding odd outcomes
 - Reflects the way treatments will perform in the population by ignoring adherence
 - Excludes loss of patients occurring as a non-random event
- Reporting:
 - According to Consolidated Standards of Reporting Trials (CONSORT) group – a structured framework and checklist, allowing the reader to more readily assess the internal and external validity of the study
 - Should include:
 - Probabilities: P value – probability the results have arisen by chance
 - Confidence intervals: indication of the precision of the result; the limits within which we would expect 95% of study results to lie if the study was repeated and infinite number of times.
 - Number needed to treat or harm
- Assessing the methodological quality of an RCT:
 - Where inclusion and exclusion criteria relevant
 - Was assignment randomised and was the randomisation list concealed (minimise bias)
 - Were the groups similar at the start of the trial
 - Were the patients and clinicians kept blind to treatment
 - Were the groups treated equally apart from the treatment
 - Was follow-up sufficiently long and complete to ensure the end points were adequately addressed
 - Were patients analysed in the groups to which they were randomised

Observational Studies

- Especially when the disease is rare, or the outcome is rare or the treatment associated with harm
- Descriptive Studies:
 - Eg in the initial identification of new diseases
 - Describe who, when, where, what and why to understand epidemiology
- Analytical Observational Studies:
 - Case-control studies: if long latency or condition is rare
 - Cohort studies: group who have been exposed to a risk factor and an otherwise similar group that haven't
 - Prone to bias
 - Known confounders can be corrected for using multivariate analysis, but cannot measure effect of unknown confounders

Systematic Reviews

- Identify and appraise all RCTs that address a particular clinical question
- If possible, statistically combine the results of the primary RCTs
- Reduce the impact of type 2 errors from small or underpowered studies
- Need careful attention to methodological detail

Levels of Evidence

- 1a – Systematic Review with homogeneity of RCTs
- 1b – RCT with narrow confidence interval, good follow-up, etc.
- 2a – Systematic review of Cohort studies with homogeneity

- 2b – Individual cohort studies, retrospective studies, RCT with poor randomisation, etc.
- 3 – Case control studies
- 4 – Case series or poor quality cohort or case-control studies
- 5 – Expert Opinion

Meta-analysis

- A form of systematic review that uses statistical methods to combine the results from different studies
- Advantages:
 - ↑ statistical power by ↑ sample size
 - Resolve uncertainty when studies disagree
 - Improve estimates of effect size
 - Establish questions for future RCTs
- Evaluation of a meta-analysis:
 - Are the research questions defined clearly?
 - Are the search strategy and inclusion criteria described?
 - Have significant studies been missed
 - How did they assess the quality of studies?
 - Have they inspected the data for heterogeneity?
 - Is the methodology reproducible (eg use of two reviewers)
 - Have they plotted the results?
 - How have they calculated a pooled estimate?
 - Have they looked for publication bias?
- Forest Plot:
 - Position of the square indicates the point estimate
 - The length of the line indicates the (usually) 95% confidence intervals of the odds ratio respectively
 - Size of the square indicates the weight of the study
 - To gauge the adequacy of the meta-analysis, also need to know that inclusion criteria for studies, the adequacy of the search protocol, assessment of the methodological quality, measurement of heterogeneity and assessment of publication bias

Statistics

Statistics Glossary

- Study Design for causation studies:
 - Experimental – RCT
 - Non-experimental, ie observational – no randomisation, can be descriptive (eg case series) or analytical (eg case-control studies).
- Basic statistics:
 - A statistic is an estimate of an unknown quantity
 - Standard deviation = Square Root (Variance). Variance = average of the sums of the squares of deviation from the mean
 - P value: indicates the probability that the observed result occurred by chance. The probability the null hypothesis has been rejected when it is true
 - Confidence Interval: indicate the level of certainty that the true value for the parameter of interest lies between the reported limits. The range where, with repeated sampling and analysis, these intervals would include the true value 95% of the time
- Bias: systematic deviation of study results from true results due to the study design.
 - Selection bias: a bias in study design rather than chance when study and control groups differ in ways that may affect the outcome
 - Interviewer bias: systematic error due to interviewer's gathering of selective data.
 - Observation/Measurement bias: unreliable or invalid measurement (eg asking weights rather than measuring them)
 - Recall bias (a type of observation or measurement bias): systematic error due to differences in accuracy or completeness of recall. Referral filter bias – process of referral from primary to secondary ↑ proportion of severe cases → ↑ unfavourable outcomes.
 - Lead time bias: if patients not enrolled at similar point in their illness, differences in outcome may only reflect differences in duration in illness. Eg Survival time is the time from diagnosis to death – which is longer in screened patients

- Length Time Bias: Diseases with long lead time (pre-diagnosis) are more likely to be detected by screening. Longer survival then gives the impression that screening was beneficial
- Publication Bias: results from studies with positive results are more likely to be published
- Study Analysis:
 - Confounding: a third variable is associated with both the exposure and the disease outcome. Unless it is possible to adjust for the confounding variables (eg stratification, multivariate analysis), their effects cannot be distinguished from those of the factors being studied
 - Intention to Treat Analysis: groups subjects according to the treatment they were randomised to, regardless of what actually happened, as opposed to per-protocol analysis (analyses according to what they actually got)
 - Efficacy: benefit of an intervention under ideal conditions (ie greater internal validity, less generalisability)
 - Effectiveness: benefit of intervention, including efficacy and acceptance (e.g. compliance, side effects – does it do more harm than good)
 - Precision: lack of random error. The range in which the best estimates of a true value approximate the true value
 - Strength of inference: likelihood that an observed difference represents a real difference, rather than due to chance. Is weakened by bias and small sample sizes
 - Validity = Accuracy: Lack of systematic error. Results are unbiased and give true estimate of the measured effect. Extent to which a variable or intervention measures or accomplishes what it is supposed to. Does it measure what it claims to measure – described by specificity and sensitivity, etc.
 - Internal validity: degree to which study results are correct for the sample studied
 - External validity/generalisability: degree to which results hold true in other settings
 - Multivariate Regression Analysis: multiple regression is used when the outcome is a continuous variable (eg blood pressure). Logistic regression is used when the outcome is dichotomous (eg alive or dead)

Statistical Tests

X = independent	Y = Outcome	
	Categorical	Continuous
Categorical (nominal, ordinal)	Chi squared (np)	ANOVA (p) T-test (p) Wilcoxon (np)
Continuous	Logistic regression (np)	Linear regression (normality) – can be stepwise Correlation (np). R ² = % of variability explained by X

- Parametric tests:
 - Used to compare different groups of continuous, numerical variables when data is normally or near normally distributed
 - T test:
 - Unpaired t-test used to compare 2 independent groups or samples with continuous variables(eg birth weights of male and female children) but where the sample size is too small for the z test (negligibly different when $n > 100$)
 - Paired t-test used to compare two dependent samples (ie same sample group – eg before and after measurements of blood pressure)
 - ANOVA: Analysis Of Variance, comparing multiple groups with continuous variables (eg P/F ratio in medical/surgical/trauma patients)
- Non parametric tests (np): do not make any assumption about the normality of the data. Type 2 errors are more common. Used for data that is abnormally distributed (eg significantly skewed) or data which represent ordered categories but may not be linear (eg pain scores, NYHA score):
 - Mann-Whitney U test: 2 different groups with continuous variables, eg ICU stay in males and females
 - Kruskal-Wallis test: comparing continuous variables in more than 2 groups
 - Chi-squared: comparing categorical data (often displayed in a contingency table). Assess whether there is likely to be a real difference in the *frequency of a categorical event* between two or more groups. Less appropriate when total numbers are small ($N < 20$) or the smallest expect value is < 5

- Fisher's exact test: comparing categorical data, but generally only applicable in a 2 * 2 contingency table (2 columns, 2 rows). Specifically indicated when total numbers are small ($N < 20$) or the smallest value expected is < 5
- Logistic Regression:
 - Used when comparing a binary outcome (yes/no, lived/died) with other potential variables
 - Most commonly used to do multivariable analysis (controlling for various factors) and these variables can be either categorical (eg gender) or continuous (eg weight) or any combination of these.
 - $y = 0$ or 1 , $p = \text{pr}(y=1)$, model $\log(p/(1-p)) = \alpha + \beta * X$

Type Errors

Trial Result	True Situation	
	Treatment works (ie null hypothesis false)	Doesn't work
Treatment works	Should use the new treatment	Type 1 error: start using new treatment (false positive)
Treatment doesn't work	Type 2 error: keep using old treatment (false negative)	Shouldn't use the new treatment

- Type 1 error (α error): the null hypothesis is incorrectly rejected. The proportion of times we make a type 1 error is (all other things equal) governed by the significance level of the test
- Type 2 error (β error): the null hypothesis is incorrectly accepted. Type 2 error rate is controlled by the true size of the difference, variability in the outcome measurement (ie SD) and the sample size
- Statistical Power =:
 - Statistical chance of a study being able to detect a statistically significant difference if one actually exists (at a given significance level). Is the study big enough to answer the question? Done by predicting the likely differences between the groups being studied, which in terms determines the size of the study
 - Probability of making a correct decision that the new treatment doesn't work = $1 - \text{type 1 error rate}$
 - Power is affected by sample size, the difference between the populations compared, and the level of significance
- Effect size: the clinically significant difference the investigator wants to detect between the study groups. The effect size helps us to know whether the difference observed is a difference that matters. This is arbitrary but needs to be accepted by peers. It is harder to detect a small difference than a large difference
- Confidence interval gives information about both the type 1 and 2 error rates
- Factors influencing sample size:
 - Significant level
 - Power
 - Effect size (smaller values mean larger sample size)
 - Variance in the underlying population (larger variance means larger sample size)

Risks and Odds

- Two commonly used measures of the strength of an association are relative risk and odds ratios
- NB: probability of rain in the next hour is 0.8, the odds in favour of rain in the next hour are 4:1

Exposure/Factor	Outcome/Disease	
	Yes	No
Yes	A	B
No	C	D

- Event Rate: proportion of patients in a group in whom an event is observed. Applied to Controls and Experimental groups \rightarrow CER and EER
- Relative Risk = $(A/(A+B))/(C/(C+D)) = \text{EER}/\text{CER}$
- Relative Risk = probability of getting the disease when the factor is present/probability of getting the disease when the factor is absent. The difference in event rates between 2 groups expressed as a proportion of the event rate in the untreated group

- Absolute Risk: the actual event rate in the treatment or placebo group
- Absolute Risk Reduction (ARR) = $C/(C+D) - A/(A+B) = CER - EER$
- Relative Risk Reduction: percent reduction in events in the treat group event rate compared to the control group = $(CER - EER)/CER * 100 = (C/(C+D) - A/(A+B))/(C/(C+D))$
- Risk Ratio = EER/CER
- Odds ratio (used in case-control studies as the incidence can't be calculated so an RR can't be calculated): odds of an experimental patient suffering an adverse event relative to a control patient = $(A/C)/(B/D)$. Odds in favour of the disease when the factor is present/odds in favour of the disease when the factor is absent
- Time frame: all measures (RR, RRR, ARR, OR) must be qualified by giving them a time frame (e.g. the length of the period of the study)
- When the probability of the disease is small, B and D tend to 1 and the OR is equivalent to the RR
- When RR and OR are around 1, there is no association between the factor and the disease
- Number needed to treat (NNT): number of patients needing treatment to achieve one favourable outcome = $1/ARR$ – always rounded up to the nearest whole number and accompanied by the 95% CI. Caution: NNT depends on the event rate in the control arm, the placebo rate may vary between trials
- Number needed to harm (NNH): number of patients who need to be treated to achieve one adverse outcome = $1/Absolute\ Risk\ Increase\ (ARI = EER - CER)$
- RRR and OR do not say anything about absolute risk. An RR of 30% can mean a risk reduction from 60% to 20%, or from 3% to 1%. The ARR and NNT varies dramatically
- Attributable risk is a measure of absolute risk, calculated by subtracting the incidence of a disease in non-exposed from the incidence in exposed

Evaluation of Diagnostic Tests

Sensitivity and Specificity

- Sensitivity: proportion of people with disease who have a positive test (i.e. true positive). How good is the test at picking up people who have the condition? SnNout = when a test has a high sensitivity, a negative result rules out the diagnosis
- Specificity: the proportion of people free of a disease who have a negative test (i.e. true negative). How good is this test at correctly excluding people without the condition? SpPin = When a test is highly specific, a positive test rules in the diagnosis
- Receiver Operating Characteristic Curve:
 - A graphical representation of sensitivity vs $1 - specificity$ for all the observed data values for a given diagnostic test. Graphing the trade-off between true positives and false positives for different thresholds
 - Eg could take several different Troponin concentrations, and compare against a gold standard (eg abnormal wall motion on echo). The sensitivity and specificity of each chosen troponin level would be determined and plotted. The ideal cut-off point is one which picks up a lot of disease (high sensitivity) but has very few false positives (high specificity)
 - Area under the curve gives the discriminating ability of the test at that threshold
 - Advantages:
 - Simple and graphical
 - Represents accuracy over the entire range of the test
 - Independent of prevalence
 - Allows comparison of accuracy between several tests on the same scale
 - Uses:
 - Gives a visual assessment of test accuracy
 - Can generate decision thresholds (cut-off values)
 - Can be used to generate confidence intervals for sensitivity and specificity and likelihood ratios

Pre-test Probability

- $= P(D+) =$ probability of target disorder before a diagnostic test result is known. Depends on patient (history and risk factors), setting (e.g. GP, A&E, etc.) and signs/symptoms
- Is useful for:
 - Deciding whether to test at all (testing threshold)
 - Selecting diagnostic tests
 - Interpreting tests

- Choosing whether to start treatment without further tests (treatment threshold) or while awaiting further tests

Likelihood Ratio

- Positive Likelihood Ratio = the likelihood that a positive test result would be expected in a patient with the target disorder compared to the likelihood that the same result would be expected in a patient without the target disorder
- Negative Likelihood Ratio = same but for negative result
- Less likely than sensitivity and specificity to change with the prevalence of a disorder
- Can be calculated for several levels of the symptom or test
- Can be used to calculate post-test odds if pre-test odds and LR known
- Impact of LR:
 - < 0.1 or > 10: large changes in disease likelihood (i.e. large change to pre-test probability)
 - 0.2 – 0.5 or 2 – 5: small changes in disease likelihood
 - 1: no change at all

Post-test Probability

- = Proportion of patients with a positive test result who have the target disorder
- Sensitivity and Specificity depend on setting. E.g. if screening for a disease occurring 1 in 10,000 in a population of 100,000 then a test with sensitivity of 99% and specificity of 99% will find 9.9 true positives and 999.9 false positives. But if the disease occurs 1 in 100 then you'll find 9990 true positives and 998 false positives – far better strike rate
- Positive Predictive Value (+PV): proportion of people with a positive test who have disease. If the person tests positive, what is the probability that s/he has the disease? Determined by sensitivity and specificity, AND by the prevalence of the condition
- E.g., for a test with 99% sensitivity:

Prevalence	Positive Predictive Value
1	19
2	33
5	56
10	73
20	86

- So significance of test may vary between, say, hospital and GP

Formulas

		Diseased	Normal
Test	+ive	a	b
	-ive	c	d

$$\text{Sensitivity} = a/(a+c)$$

$$\text{Specificity} = d/(b+d)$$

$$\text{LR} + = \text{sensitivity} / (1 - \text{specificity}) = a/c * b/d$$

$$\text{LR} - = (1 - \text{sensitivity}) / \text{specificity}$$

$$\text{Positive Predictive Value} = a/(a+b)$$

$$\text{Negative Predictive Value} = d/(c+d)$$

$$\text{Prevalence} = (a+c)/(a+b+c+d)$$

$$\text{Pre-test odds} = \text{prevalence} / (1 - \text{prevalence})$$

$$\text{Post-test odds} = \text{pre-test odds} * \text{LR}$$

$$\text{Post-test probability} = \text{post-test odds} / (\text{post-test odds} + 1)$$

$$\text{Accuracy} = (a+d)/(a+b+c+d) = \text{what proportion of results have given the correct result}$$

Study design for researching a test

- Spectrum composition: what population was it tested on. Sensitivity and specificity may vary between populations with significant disease and the general population

- Are pertinent subgroups assessed separately? Condition for test use must be narrowly defined to avoid heterogeneity
- Avoidance of work-up bias: if there is bias in who is referred for the gold standard. All subjects given a test should receive either the gold standard test or be verified by follow-up
- Avoidance of Review Bias: is there objectivity in interpretation of results (e.g. blinding)
- Precision: are confidence intervals quoted?
- Should report all positive, negative and indeterminate results and say whether indeterminate ones were included in accuracy calculations
- Test reproducibility: is this tested in tests requiring interpretation

Screening

- Criteria:
 - Illness being screened for must be bad
 - There must be a pre-symptomatic phase detectable by the screening test
 - Intervention at this time should change the course of the illness to reduce morbidity and mortality
 - Test needs to be inexpensive, easy to administer and acceptable to patients, with high sensitivity
 - Screening programme should be feasible and effective
- If a condition is extremely prevalent, everyone is treated (eg iodised salt, fluoridated water, folate fortification, etc.)

Monitoring Definitions

- Zeroing: confirms that atmospheric pressure results in a zero reading by the measurement system. Intermittent confirmation ensures the absence of baseline drift (common in disposable transducers)
- Levelling: Or establishing a zero reference point. Determining the point on the patient you wish to be considered as a zero point, eg the phlebostatic axis. Significant errors occur if levelling is not maintained
- Calibration: process of adjusting the output of a device to match a known input value, by comparison to a gold standard. Often two values used (0 = 0 and 100 = 100) to confirm linearity. The calibration of disposable transducers is pre-set and cannot be altered

Monitoring Oxygenation

- See Hazards of O₂ Therapy, page 85

Hypoxia

- Definitions:
 - Hypoxemia: low PaO₂ (regardless of FiO₂)
 - Hypoxia: lack of O₂ in the cell
 - $DO_2 = CO * \text{arterial O}_2 \text{ content}$ – so cardiac output can compensate for hypoxaemia to avoid hypoxia
- Normal individuals adapt to hypoxia. Climbers on Mt Everest have had PaO₂ < 20 measure. Most adaption appears to be sub-cellular (eg change in mitochondria) and changes in micro-circulation
- Roles of Oxygen:
 - Bioenergetics: terminal electron acceptor (with two protons → H₂O) in mitochondrial respiration → ATP. Uses 90% of O₂
 - Biosynthetics: Oxygen transferase systems incorporate O₂ into substrates (catecholamines, some neurotransmitters)
 - Biodegradation: mixed function oxidase reactions (eg cytochrome P-450 hydroxylases)
 - General reactive O₂ species: antimicrobial defences in neutrophils and macrophages
- Categories of hypoxia:
 - Hypoxaemic hypoxia: ↓arterial O₂ tension due to ↓environmental O₂ (altitude - rare), ventilatory failure, anatomical or physiological pulmonary shunt
 - Anaemic hypoxia: ↓haemoglobin concentration
 - Stagnant hypoxia: ↓reduced tissue blood flow
 - Cytopathic/histotoxic hypoxia: abnormal cellular oxygen utilisation despite adequate O₂ delivery
 - Oxygen toxicity: abnormal cell function due to high O₂ tensions
- Tissue hypoxia:
 - Oxidative phosphorylation starts to fail at intracellular PO₂ of < 1 mmHg (~extracellular PO₂ of 5 mmHg)
 - Adaptive strategies:
 - Reduce metabolic rate
 - ↑oxygen extraction
 - Anaerobic metabolism
 - Feedbacks on local circulation to improve O₂ delivery, replicated regionally then systemically
 - DO₂ can be controlled regionally (eg ↓splanchnic flow) – we normally only assess it globally
 - Increasing evidence of the impact of genetic and epigenetic variation in response to hypoxic challenge
 - Reoxygenation → release of reactive oxygen species → further oxidative stress

Oxygen Cascade

- Inspired gas: PiO₂ (inspired O₂ tension) = FiO₂ * (Barometric pressure – saturated vapour pressure of water [47 mmHg]) = 160 mmHg at sea level
- Alveolar gas:
 - Room air at sea level is 100 mmHg
 - Distribution of alveolar ventilation: electrical impedance tomography being developed to track lung volume changes in real time which may allow optimisation of alveolar ventilation distribution while limiting over distension

- For efficient gas exchange, majority of lung units must have well-matched alveolar ventilation and perfusion. The normal spread of low to high V/Q scatter is much greater in diseased lungs \Rightarrow bedside measurement difficult
- $PAO_2 = PiO_2 - PaCO_2/0.8$. This is an artificial construct
- $PaCO_2$ is determined by alveolar ventilation: $V_A = V_E$ (minute ventilation) $- V_D$ (dead space ventilation)
- Volume of an ET tube is less than the pharynx, so intubation can \downarrow dead space. Positive pressure \rightarrow \uparrow distension of the airways \rightarrow \uparrow dead space
- Transfer of gas from alveoli to arterial blood:
 - Alveolar capillary membrane is 0.3 μm and surface area of respiratory membrane is 50 – 100 m^2
 - Two biggest causes of reduced pulmonary O_2 transfer in critical illness are V/Q mismatch and intrapulmonary right-to-left shunt
 - Tension based indices:
 - A-a gradient: = $PAO_2 - PaO_2$. $PAO_2 = (760 - 47) * FiO_2 - PaCO_2/0.8$**
 - Rule of thumb: A-a gradient = $FiO_2 * 5$ (except if abnormal CO_2)
 - Normal gradient is due to some venous admixture through the lungs and a small R \rightarrow L shunt through the bronchial veins
 - Classifies hypoxaemia as:
 - Normal A-a: alveolar hypoventilation or low PiO_2
 - Raised A-a: diffusion defect (rare, eg interstitial lung disease), usually a V/Q mismatch, right to left shunt (intrapulmonary or cardiac), or increased O_2 extraction ($CaO_2 - CvO_2$)
 - Ie differentiates between hypoventilation and V/Q mismatch – which Pa/FiO_2 doesn't. Drawbacks include normal values which vary with FiO_2 and age:

	Young adult	Elderly
Room Air	7 - 15	14 - 30
100% O_2	31	56

Rule of thumb: Normal is $Age/4+4$ on FiO_2 of 21% (formula for kids tube size)

PB	PH20	FiO_2	(PB-PH20) * FiO_2	$PACO_2$	R	PAO_2	PaO_2	A-a gradient
760	47	0.21	150	40	0.8	100	80	20
760	47	0.3	214	40	0.8	164	80	84
760	47	0.4	285	40	0.8	235	80	155
760	47	0.5	357	40	0.8	307	80	227
760	47	0.6	428	40	0.8	378	80	298
760	47	0.7	499	40	0.8	449	80	369
760	47	0.8	570	40	0.8	520	80	440
760	47	0.9	642	40	0.8	592	80	512
760	47	1.0	713	40	0.8	663	80	583

- PaO_2/FiO_2** (variable in the SAPS II score). Sea level normal value > 500 mmHg, ARDS < 300 . Values reduce with barometric pressure, *doesn't distinguish between hypoventilation and other causes of hypoxaemia* (\downarrow cardiac output, anaemia), and it is *very dependent on FiO_2 in R-to-L shunt (the main ARDS abnormality) and wide V/Q scatter (COPD)*
- Content-Based Indices:
 - Venous admixture (Q_s/Q_t): the proportion of mixed venous blood flowing through the shunt ($V/Q = 0$) compartment. Calculated from arterial and mixed venous blood and CO oximetry. Is unaffected by barometric pressure, alveolar hypoventilation, and is stable across FiO_2 range as long as the predominant pathology is R-to-L pulmonary shunt (ie doesn't hold in COPD) but requires PAC
 - Gas Transfer: diffusing capacity. Typically assess with carbon monoxide. As it's completely absorbed by Hb (ie $PaCO$ is always zero), volume taken up directly corresponds to transfer. Usually corrected for lung volume as diseases such as emphysema and fibrosis affect both volume and diffusion
- O_2 carriage in arterial blood:
 - O_2 is poorly soluble in blood (PaO_2), binds quickly to haemoglobin (SaO_2)
 - PaO_2 in pulmonary capillaries at room air is 90 mmHg

- Hypoxaemia defined as $\text{PaO}_2 < 60 \text{ mm Hg}$ or $\text{SaO}_2 < 0.9$
- Linked by the HbO₂ dissociation curve, O₂ tension (mmHg) on X axis, Saturation (of haemoglobin) on the y
- Hb-O₂ affinity:
 - P₅₀ is the O₂ tension at $\text{SO}_2 = 0.5$ (50% of Hb saturated). Normal value is 26.7 mmHg
 - Factors which ↓ haemoglobin-oxygen affinity increase the P₅₀ (right shift):
 - *Acidaemia* (Bohr effect),
 - ↑*CO*₂
 - ↑*2,3DPG* (by product of glycolysis and therefore binds haemoglobin in predominantly hypoxic tissues)
 - *Fever* → ↑O₂ availability
 - Leading to greater release of O₂ in tissues. Insufficient data to support manipulation of the O₂-Hb curve to improve O₂ delivery. If alveolar O₂ is low, right shift may impair O₂ binding in the lungs
 - ↑Affinity (↓P₅₀, left shift) due to *alkalaemia*, ↓*CO*₂, ↓*2,3DPG*, *hypothermia*, *COHb*, *MetHb*, *FHb*
 - Changes in affinity in critical illness are small, so not routinely measured
- Errors on blood gas measurement: O₂ diffusing into or out of air bubbles, 7 – 8% inter-analyser variability on the same sample, non-linearity at $\text{PO}_2 > 150 \text{ mmHg}$. PO_2 changes by 7% for every degree C of temperature change, and arterial blood gas tensions fluctuate breath to breath
- Transcutaneous PCO₂ is reliable in adequately perfused patients, transcutaneous PO_2 is only useful for trend analysis
- Diffusion from blood to mitochondrion:
 - PO_2 in some mitochondria can be as low as 1 mmHg
 - Driving pressure for O₂ to enter a cell is the partial pressure gradient – it is not a cascade – O₂ is “sucked in”. The cell is autonomous and uses what it needs. Adequate O₂ delivery is important, excess O₂ is of no benefit

Oxygen Dynamics

- Shock = failure of oxygen delivery to match demand
- Oxygen delivery:
 - Functional saturation: $\text{SO}_2 = [\text{HbO}_2] / ([\text{HbO}_2] + [\text{Hb}])$ – arterial normal is 0.97, venous is 0.75
 - Oxygen content = $\text{CaO}_2 = \text{Hb} * \text{SaO}_2 * \text{constant}$. Concentration of O₂ in the blood. 1 gm Hg binds 1.34 ml O₂
 - Oxygen delivery $\text{DO}_2 = \text{CO (L/min)} * \text{CaO}_2 * 10$. Normal resting DO_2 is 1000 ml/min
 - Oxygen delivery index $\text{DO}_2\text{I} = \text{CI (cardiac index)} * \text{CaO}_2 * 10 \text{ ml/min per m}^2$
 - Oxygen demand is so variable in critical illness that isolated DO_2 measurements are difficult to interpret
- Oxygen consumption:
 - Oxygen consumption index VO_2I
 - $= \text{CI} * (\text{CaO}_2 - \text{CvO}_2)$
 - $= \text{CI} * \text{Hb} * (\text{SaO}_2 - \text{SvO}_2) * \text{constant}$. So ↓ in DO_2 can be compensated for by ↑CI, ↑Hb or ↑extraction
 - VO_2 is measured by:
 - Reverse Fick method: requires a PA and has large errors, larger errors if lung inflammation
 - Indirect calorimetry: Determined from volumes and oxygen concentrations of inspired and expired gas. High FiO_2 increases error
 - Approximately 250 ml/min, in exercise can reach 1500 ml/min
 - VO_2 rises with:
 - ↑metabolism: sepsis, pyrexia, thyrotoxicosis, shivering, seizures, anxiety, pain
 - Adrenergic drugs
 - Certain feeding strategies
- $\text{RQ} = \text{VCO}_2 / \text{VO}_2$. See Nutritional Requirements, page 341
- Oxygen extraction ratio (OER) = $\text{VO}_2 / \text{DO}_2$:
 - At rest 0.2 – 0.3, can increase by up to 0.7 – 0.8 at maximum in young people. This means compensating variables we can monitor (eg pulse, BP, urine output) may change only late in the decline of DO_2
 - Higher values suggest O₂ delivery is inadequate

- Normal values in a shocked person suggest inadequate uptake due to shunting, microvascular occlusion and failure of cellular uptake → ↑lactate
- The level of DO₂ at which VO₂ begins to fall is the 'critical DO₂':
 - Approximately 300 ml/min
 - Impairment can happen at any point of the O₂ cascade, including increased demand unable to be matched by increased DO₂
 - Lactate generally starts to rise at this point

Measurement of Oxygenation

Pulse Oximetry

- Based on Beer-Lambert Law: concentration of an absorbing substance in solution can be determined from the intensity of light passing through the solution....
- Determines SpO₂ from absorbance of light at 600 nm (red) and 940 nm (infrared) – the point at which there is maximum separation of the absorption of reduced Hb and oxyhaemoglobin. The signal is pulsatile due to arterial volume fluctuations. Subtracting the background signal isolates arterial blood from the continuous signal from tissue, capillary and venous blood
- Factory calibration is based on nomograms from young normals
- False reading occur with:
 - Optical interference, eg abnormal haemoglobin, dye
 - Signal artefact, eg florescent light
 - False assumptions/calibration, eg inaccurate saturations below 80%
- Is accurate in the 90 – 97% range with precision < 3%. Significant imprecision at SaO₂ < 80%
- Insensitive to changes in arterial oxygenation at high PaO₂ values (> 70 – 100 mmHg)
- SpO₂ (pulse oximetry) – co-oximetry: a saturation gap arises with abnormal haemoglobins which are only detected with co-oximetry:
 - Carboxyhaemoglobin (normally < 2%), so SpO₂ will be overestimated (eg in inhalational burn)
 - Methaemoglobin (normally < 2%). See Specific Therapy for Poisons page 264
 - Sulfhaemoglobin (normally undetectable)

Measuring Regional O₂

- PtO₂ (tissue O₂) is the balance between supply and demand and varies widely around the body
- Gastric tonometry: splanchnic hypoperfusion occurs early in circulatory shock, can be measured via a modified NG tube – but not widespread due to technical difficulties (variation especially in feeding and bleeding) and no outcome data (No benefit in RCT of tonometry guided therapy (CCM March 2000))
- Sublingual capnometry: Possibly correlates with more severe haemodynamic disturbance and survival – but no data on how it should guide therapy
- Other sites of measurement investigate: oesophagus, bladder, skin....

Measuring Venous Oxygenation

- See also Use of a central venous line, page 32
- Mixed venous O₂ Saturation (SvO₂):
 - Obtained from distal port of an unwedged PA catheter → flow weighted average of the venous O₂ of multiple tissues
 - Normal > 70%. Arrest at ~ 35%
 - Some catheters can continuously monitor central venous oxygen saturation (ScvO₂)
 - A global indicator of VO₂, and indirectly of the adequacy of DO₂ ⇒ an indirect index of tissue hypoxia. Low levels indicate low delivery most commonly, or increased uptake. A normal or high SvO₂ does not exclude regional hypoxia
- Central venous O₂ Saturation (ScvO₂):
 - From a CVL catheter – as opposed to mixed venous saturation. Central venous saturation is more practical and usually adequate.
 - In health SvO₂ > ScvO₂ as upper body generally extracts more O₂. Relationship changes in shock states, but trend will be similar
 - Can be measured continuously by fibre-optic reflectance oximetry
 - 0.5 is critical. Lactic acidosis appears from 0.3 – 0.5.
 - 0.7 represents a balance between average O₂ supply and demand
 - > 0.8 ⇒ high output states (sepsis, hyperthyroidism, severe liver disease)

- Can be used to calculate $CvO_2 \rightarrow Q_s/Q_t$, VO_2I , oxygen extraction ratio and cardiac output (Fick method)
- Evidence for use:
 - For $ScvO_2$: Rivers et al: Included $ScvO_2 > 70\%$ in the monitoring bundle to guide early goal-directed in ED, ↓mortality
 - For SvO_2 : Polen et al (Anest Anal 2000) SvO_2 and lactate in cardiac surgery patients over first 6 hours → ↓complications and LOS
 - Against SvO_2 : Gattoni et al (NEJM 1995) RCT in critically ill over 5 days using SvO_2 to guide therapy. No change in mortality or morbidity
- $ScvO_2$ is higher than SvO_2 in:
 - Anaesthesia: ↑cerebral blood flow and ↓metabolism
 - Brain injury: ↓cerebral metabolism
 - Sepsis/Shock: redistribution of blood from splanchnic circulation + ↑extraction → ↓IVC oxygenation
- Differential of $SvO_2 < 65$:
 - ↑consumption: stress, pain, hypothermia, shivering
 - ↓delivery: anaemia, hypoxia, ↓cardiac output
- Differential of $SvO_2 > 80\%$:
 - ↓consumption: sedation, analgesia, ventilation, hypothermia, cytotoxic dysoxia (cyanide poisoning, mitochondrial disease, severe sepsis), microcirculatory shunting (severe sepsis, liver failure, hyperthyroidism)
 - ↑ O_2 delivery: ↑CO, high PaO_2

ETCO₂ monitoring/Capnography

- Infra-red absorption spectrophotometry measures the fraction of energy absorbed and converts this to a percentage of CO_2 . End tidal CO_2 is normally only slightly less than the $PaCO_2$, but the gradient increases when alveolar dead space increases (eg ↓CO, PE, ↑alveolar pressure). $PetCO_2$ correlates directly with cardiac output and can assess the adequacy of CPR
- Uses:
 - ET tube placement: sensitive and specific in the presence of pulmonary blood flow
 - Pattern recognition of $ETCO_2$ waveform:
 - Gas trapping or expiratory flow obstruction
 - Attempt at spontaneous breathing in apnoea test
 - Circuit leak
 - Changes in $ETCO_2$:
 - Progressive increase ⇒ ineffective ventilation
 - During CPR ⇒ indicates effective CPR
 - PE: ↓value, will rise with successful thrombolysis
 - For targeting PCO_2 in ↑ICP
 - $PETCO_2$ is an indirect index of cardiac output ($PETCO_2 > 30$ mmHg signifies a CO of more than 4L/min under constant ventilation)
 - Hypermetabolic states are associated with ↑ CO_2
- Risks:
 - Normal capnogram may indicate a patent airway, but not a secure one
 - Absent capnogram may indicate airway obstruction or critical bronchospasm, not tube misplacement
 - Secretions in the circuit can affect $ETCO_2$
 - Does not accurately reflect PCO_2 in a large PE or shunt
- Options:
 - Mainstream monitor: condensation affects measurement, ↑weight on end of tube, difficult if prone
 - Side stream monitor: delay in recording, risk of tube obstruction

Haemodynamic Monitoring

- See also Haemodynamic monitoring in shock and implications for management, International Consensus Conference, Paris, France, Intensive Care Medicine 2007 33: 575 - 590
- = Monitoring of blood flow through the CVS
- Increasing difference seen between:
 - Macro-circulation, measured by eg MAP, and managed with fluids, inotropes, etc.
 - Micro-circulation, measured by a variety of imprecise measures of regional/tissue blood flow. Circulation is not homogenous

- Clinical questions are:
 - Will stroke volume increase with fluid loading
 - Is CO too low and compromising global O₂ delivery
 - Is a dilator, constrictor or inotropic therapy needed
- Scant data to show benefits of invasive monitoring → trend to less of it. However, it's unlikely any single modality on its own will improve outcome. All monitoring is a tool – its safety and benefit depends on how and by whom it is used
- Aggressive pursuit of hyperdynamic goals is usually counterproductive (eg supra-normal DO₂)
- Types of variables:
 - Static: eg SBP, MAP
 - Dynamic variables: eg systolic pressure variation, pulse pressure variation
- ICU patients are usually more complex and unstable than theatre patients – which is where much of the evidence comes from

Cardiac Physiology

- Models of circulatory system:
 - Standard model: non-pulsatile pump and hydraulic circuit with discrete sites of resistance. HR and SV → CO. SV depends on pre-load, contractility and afterload. These values difficult to quantify clinically or in the lab. Ventricular performance is then defined by:
 - R and L atrial pressures (RAP and LAP) ⇒ ventricular preload
 - Mean systemic and pulmonary arterial pressures (MAP, PAP) ⇒ afterload
 - Heart rate (HR)
 - Cardiac output (CO or Qt)
 - Standard model doesn't allow for pulsatile interaction of the pump with elastance of the arterial tree. More complex models are still unable to quantify afterload and contractility precisely

Key Points When Assessing Cardiac Function

- Pressure is no guarantee of flow
- Trends are more important than a single observation
- Dynamic tests (fluid challenge, pulse pressure variation with respiration) are more revealing than static tests (RAP, CVP)
- Monitoring devices may be complex with many potential sources of error
- Invasive monitoring has its own complications (infection, trauma, immobility) – remove it if you don't need it

Ventricular Preload

- Determines end-diastolic volume → stroke work of next contraction (given contractility). Resulting stroke volume depends also on afterload
- Systemic venous bed is the major intravascular capacitance or reservoir of the circulation with compliance that can vary from 30 – 300 ml/mmHg. As volume is lost, venous tone increases. Rapid replacement of volume may not allow sufficient time for venous and arteriolar tone to fall which may → ↑LAP → pulmonary oedema
- ↑Preload may be due to:
 - ↑Volume. Treat with diuretics or ↑capacity of the vascular bed (eg GTN, morphine)
 - ↓contractility
 - ↑afterload
- When assessing pre-load, end-diastolic *volume* rather than pressures are relevant, so need to adjust for:
 - Intrathoracic pressure: true distending pressure that determines ventricular end-diastolic volume is the transmural pressure (P_v – P_t). Consider if alveolar gas trapping generating PEEP (eg asthma), positive pressure ventilation with high PEEP, and inverse I:E ratio
 - Dilated ventricle with poor compliance: pressure-volume relationship is not linear, and pressure may not reflect the adequacy of volume preload

Ventricular Afterload

- Vascular resistance = pressure gradient across vascular bed/CO (ie resistance = pressure/flow)
- SVR = (MAP – CVP)/CO
- If ventricular work is constant, ↑resistance → ↑pressure and ↓CO. A dilator → ↓resistance and ↓pressure but ↑CO

Ventricular Contractility and Efficiency

- The work the ventricle performs under given loading conditions defines contractility. Impaired contractility leads to a flattened filling pressure/stroke volume relationship
- Left ventricular efficiency is the ratio of work output to energy input – may be less than 20% in patients acute heart failure, with over 80% lost as heat
- If contractility is poor, and atrial-pressure reflects volume preload, then further volume will → distension → impaired epicardial to endocardial blood flow → ischaemia
- Options for management:
 - Reduce afterload: use an arteriolar dilator (nitrates, α -blocker, phosphodiesterase inhibitor, ACEI) but limited by fall in systemic pressure
 - Increase myocardial contractility: Either
 - Remove negative inotropic influences: acidaemia, $\uparrow K$, β -blockers
 - Positive inotrope: → $\uparrow SV$ for same pre-load and afterload

Heart Rate and Rhythm

- In cardiac failure the stroke volume is usually constant for rates up to 100/min and then falls as \downarrow diastolic filling time limits end-diastolic volume
- \uparrow rate from 70 – 90 → $\uparrow CO$ by 30%:
 - Using a chronotrope → \uparrow myocardial work and O_2 consumption and ventricular irritability
 - Pacing with atrial or atrioventricular sequential pacing → better haemodynamics without \uparrow myocardial metabolism and \uparrow irritability
- For heart rates > 110 :
 - Correct plasma K and Mg
 - SVT with intermittent SR: digoxin (good for AF and a +ive inotrope) or amiodarone (good for all SVTs, and more likely to revert to SR, but negative inotropy can be significant in severe heart failure)
 - If AFI then adenosine

Arterial Blood Pressure

- Pulse wave propagates at 6 – 10 m/s, with progressive \uparrow in SBP and \downarrow DBP (called distal pulse amplification). So BP depends on site of measurement
- MAP is a more reliable measure – less variation by site or invasive/non-invasive. MAP also determines tissue blood flow via autoregulation (apart from LV which is determined by DBP)
- Arterial blood pressure correlates poorly with CO
- Non-invasive measurement:
 - Usually automated intermittent oscillometric devices
 - Overestimates low pressures and underestimates high pressures
 - In normotensive range 95% confidence interval is ± 15 mmHg. Dysrhythmias → \uparrow error
 - Cuff width should be 40% of the mid circumference of the limb. Narrow cuffs over-estimate
- Invasive measurement:
 - Cannula infused with normal or heparinised saline at 3 ml/hr. Heparin doesn't prolong patency but may improve accuracy
 - Snap flush rate of 30 – 60 ml/h
 - Femoral artery more accurately reflects aortic pressure in low-output states
 - Changed every 5 – 7 days, peripheral circulation checked every 8 hours
 - System zeroed at the phlebostatic axis (mid-axillary line at the 4th intercostal space)
 - Pressure transducer transduces pressure via strain to electrical resistance using a Wheatstone bridge
 - Risks: Thrombosis (remove cannula, usually self-limiting), distal embolisation, vascular spasm, bleeding, accidental drug injection (leave cannula in – may need analgesia, sympathetic block of limb and anticoagulation), infection (start ABs if sepsis present), damage to structures (eg pseudo-aneurysms)
 - Damping: any property of an oscillatory system that reduces amplitude of oscillations (clots, air bubbles, loose connections, long soft tubing). Assessed with fast-flush test.
 - Wave form analysis:
 - With normal inspiration, pressure drops on inspiration. With ventilated inspiration, pressure may rise on inspiration and fall on expiration
 - Pulsus paradoxus:
 - > 10 mmHg \downarrow in SBP during inspiration if spontaneously breathing or during expiration in PPV
 - Not paradoxical – just exaggerated normal. Can hear a heart sound but not palpate a pulse

- Due to: reduced preload (eg *hypovolaemia*), *pericardial tamponade*, *severe bronchospasm* (ie either dry or respiratory distress)
- Pulsus alternans: Alternating beats of higher systolic pressure
- Slow upstroke: AS, ↓contractility
- Wide pulse pressure: AR, ↓SVR
- Narrow pulse pressure: ↑SVR
- See Thermodilution for Estimating Cardiac Output, page 36, for the use of arterial pressure waveform in CO estimation

Central Venous Catheterisation

- See:
 - ANZICS Central line Insertion and Maintenance Guideline, April 2012
 - Central Line Infections, page 285
- NICE guidelines recommend US guidance for elective IJV. Based on meta-analysis of 1646 patients, BMJ 2003, Hind et al
- Femoral venous catheterisation with positioning of the tip close to the RA gives good correlation with subclavian CVP measurements.
- Can also use median cubital and basilic veins
- Complications: bleeding (**check coagulation**), loss of guide-wire, air embolism (treat with left lateral Trendelenburg position, 100% O₂, tighten connections and attempt to aspirate air), dysrhythmias, damage to structures (pneumothorax, haemothorax, chylothorax), nerve injury, arterial puncture, bleeding, infection, thrombosis

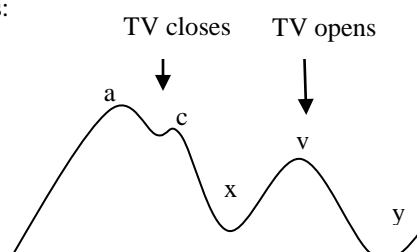
Subclavian Line (infraclavicular approach)

- Anterior scalene muscle attaches to the 1st rib posterior to the subclavian vein and anterior to subclavian artery
- Posteriorly displaced shoulder → clavicle compressing vein ⇒ keep shoulder neutral. Optimal position (maximum cross sectional area) is with Trendelenburg position and no shoulder roll, +/- head turned away
- Insertion point is 1 cm inferior and lateral to the junction of medial and middle clavicle, aiming for the sternal notch
- Ultrasound:
 - Along, not perpendicular to vein
 - US superior to landmark method in RCT (Fragou et al, CCM 2011): ↑success, ↓complications
- Meta-analysis of IJV vs SV (Ruesch et al 2002) showed ↑ arterial punctures but less catheter malposition with IJV in observational studies

Use of a central venous line

- See Measuring Venous Oxygenation, page 28
- Pressures: measured from the mid-axillary line in the 5th intercostal space (not the sternal angle)
 - Normal CVP 0 – 5 mmHg
 - Ventilated up to 8 - 15 mmHg
 - Relationship breaks down in pulmonary hypertension, PE, RF infarction, LV hypertrophy, MI
- Usually monitor from the distal lumen. Maybe should use proximal lumen as you'll notice sooner if the line is coming out
- Accuracy depends on:
 - Technical factors:
 - Zeroing, levelling, calibration (see Monitoring Definitions, page 25)
 - Dampening: not over or under, assessed by square wave or balloon bursting, prefer coefficient approximately 0.7. Frequency response of the system (intrinsic plus additional tubing) may significantly impact on damping – prefer shorter and stiffer tubing
 - Running averages alters ability to interpret variability associated with changes in intrathoracic pressure (better with displayed waveform)
 - Placement: SVC, femoral
- Uses:
 - Central venous pressure (CVP) is a poor measure of preload although may be a reasonable surrogate for preload (~PAOP) in uncomplicated hypovolaemic shock. Except at extremes static CVP doesn't tell you who will respond to fluids – however dynamic changes in response to fluid helpful. High static levels don't exclude hypovolaemia in a ventilated patient

- CVP had no ability to predict fluid responsiveness, nor in subgroups of OR or ICU studies, and recommends the practice should be abandoned (Meta-analysis of 43 studies, Marik, CCM2013)
- However, pathology affects accuracy of CVP as a measure of preload – including anything affecting compliance of central compartment:
 - Cardiac: Tricuspid, pulmonary and mitral valve disease, right heart failure, tamponade, restrictive pericarditis
 - Respiratory: changes in intra-thoracic pressure, any cause of ↑pulmonary vascular resistance
 - Venous capacitance
- Severe hypotension with normal CVP is unlikely to be obstructive (eg PE, tamponade or tension pneumothorax)
- Determinants of CVP:
 - Intravascular volume status
 - Mean systemic filling pressure
 - Right and left ventricular status and compliance
 - Pulmonary vascular resistance
 - Venous capacitance/tone
 - Intra-thoracic pressure
 - Intra-abdominal pressure
- Waveform analysis:



Wave	Mechanism	Pathology
a wave	Right atrial contraction at end of diastole → ↑atrial pressure. Coincides with first heart sound and precedes carotid pulse	Dominant a wave: pulmonary hypertension, tricuspid and pulmonary stenosis Cannon a Wave: AV dissociation (complete heart block, single chamber ventricular pacing, nodal rhythm)
c point	Bulging of AV valves into atria during systole → ↑atrial pressure. Not usually visible	
x descent	atrial relaxation between S1 and S2	Absent: AF with TR Exaggerated: tamponade, constrictive pericarditis
v wave	End of atrial filling during systole – venous inflow into atria with AV valve closed → ↑atrial pressure	Dominant v wave: tricuspid regurgitation
y descent	Passive ventricular filling after opening of tricuspid valve	Tricuspid stenosis, right atrial myxoma

- TR: ↑RA pressure, ↑v wave, no x descent, sharp y descent
- Constrictive pericarditis: prominent x and y descents
- Pericardial tamponade: ↓y descent

Pulmonary Artery Catheter

- Gives information about pressure not volume

Traditional indications for a PAC

- Optimising preload using measurement of stroke volume and cardiac index
- Differentiating types of shock

	Septic	Cardiogenic	Hypovolaemic	Obstructive
Cardiac Index	↑	↓	↓	↓
PAOP	-/↓	↑	↓	-/↑

CVP	-/↓	-/↑-	↓	↑
SVR	↓	↑	↑	↑
O2 delivery (DO2, ml/min)	↑	↓	↓	↓

- Differentiating cardiogenic from non-cardiogenic pulmonary oedema
- Guiding the use of vasoactive drugs, fluids and diuretics, especially when haemodynamic instability *and* ↑lung water, RV or LV dysfunction, or pulmonary hypertension
- In ARDS, pulmonary hypertension and ↑RV after-load are linked to mortality. PA catheter can guide afterload-reducing therapies (inhaled prostacyclin or NO). TTE can also assess RV loading and PA pressures – but snapshot only, and difficult in ventilated patients
- Problems with interpretation:
 - Error of at least 10% in measuring CO, even with fastidious attention to technical detail
 - Variable relationship between pressure and volume
 - Inaccurate measures if valvular disease or intra-cardiac or intra-pulmonary shunts
 - Risks of using derived variables

Insertion of a PAC

- 7.5 – 9 F 15 cm introducer sheath
- Subclavian and IJ veins most common, can do it with a 110cm catheter through median cubital, basilic and femoral veins
- Balloon volume is 1.5 ml. Test before insertion. Inflation should not alter waveform prior to wedging. Always deflate passively
- RA at 15 – 20 cm from IJ, 10 – 15 cm from subclavian, 30 – 40 from femoral, 40 and 50 from R and L basilic veins.
- RV, PA, and PA occlusion then at 10 cm intervals
- Complications:
 - Air embolism
 - Dysrhythmia. For sustained VT remove PAC from RV. For VF remove PAC and defibrillate
 - RBBB: avoid use in LBBB otherwise risk of complete heart block (→ pacing)
 - Catheter knotting/kinking: do not advance against resistance
 - Valve damage: avoid by inflating for forward passage and deflating for retraction
 - Pulmonary artery rupture from balloon inflation. May present with haemoptysis and infiltrate around catheter tip on CXR. Management:
 - Deflate balloon, withdraw it 2 – 3 cm and reinflate to tamponade
 - Insert double lumen ETT, or advance existing one to the opposite side, to isolate affected lung. Position with good lung up
 - Angiogram or bronchoscopy may isolate affected vessel. Otherwise immediate lobectomy if bleeding does not settle
 - Increased PEEP may help
 - Pulmonary infarction

Measured variables from a PAC

- Measures provided by a PAC:
 - RV Pressure: Normal systolic 15 – 25 mmHg, diastolic 0 – 8 mmHg
 - PA Pressure: Normal systolic 15 – 25 mmHg/Diastolic 8 – 25 mmHg/ mean PAP 10 – 20 mmHg
 - PAOP (LA pressure via wedging): Normal 10 – 20 mmHg
 - True mixed venous saturations – either continuous or intermittent
 - Measurement of cardiac output via thermodilution – either continuous or intermittent
 - Also can monitor core temperature
- Pulmonary Artery Occlusion Pressure (PAOP):
 - Over-wedging may lead to ↑occlusion pressures and PA rupture. May need less than 1.5 ml
 - Deflation should → normal PA waveform
 - PAOP should be measured in end-expiration and ideally in end-diastole (use P wave as marker)
 - Wedging creates a static column of blood equilibrating with the pulmonary venous system
 - It's surrogacy as a LV preload measure depends on:
 - Tip positioned in West's zone 3 at a level at or below the left atrium where alveolar pressure < pulmonary venous pressure (otherwise ↑pulmonary vascular resistance). ↑Chance of wedging in zone 1 or 2 if COPD/high PEEP and low cardiac output. Bedside tests for zone 3 include: catheter tip below atrium on lateral supine CXR, clear atrial waveforms, respiratory variation of

PAOP is < 50% static airway pressure (peak – plateau), PAOP alters by < 50% of PEEP alterations, O₂ sats in wedged position > O₂ sats in unwedged. If PAOP varies significantly with respiration you're just measuring intra-thoracic pressure, not LA pressure

- PAOP will be > than LAEDP if:
 - Pulmonary venous obstruction/vascular bed abnormalities (fibrosis, vasculitis, PE, COPD, IPPV)
 - Valve dysfunction: mitral stenosis, mitral regurgitation ⇒ Left arterial pressure doesn't approximate LVEDP
 - Left → Right shunt
- LVEDP ~ LVEDV – doesn't hold if abnormal or changing ventricular compliance (eg diastolic dysfunction) or ↑intrathoracic pressure
- PA diastolic pressure to PAOP gradient is usually < 5 mmHg, so can approximate it. But tachycardia > 120 or ↑vascular resistance (ARDS, COPD, PE) variably increase the gradient
- Pulmonary capillary hydrostatic pressure: PAOP can substitute for this, but ARDS and sepsis upset the relationship due to changes in pre and post capillary resistance. Can use waveform analysis at the bedside to more accurately quantify it.
- Derived values:
 - Mean pulmonary artery pressure (MPAP): $PADP + 0.33 * (PASP - PADP)$, normal range 9 – 16
 - Mean right ventricular pressure (MRVP)
 - LV coronary perfusion pressure (LVCPP): $DBP - PAOP$
 - RV coronary perfusion pressure (MAP – MRVP)
 - Cardiac index (CI): CO/BSA , normal range 2.8 – 4.2 l/min/m²
 - Stroke Volume: 1 ml/kg
 - Stroke Volume Index (SVI): CI/HR , normal range 35 – 70 ml/beat/min
 - Body Surface Area: $Weight (kg) \div 0.425 * height (cm) \div 0.725 * 0.007184$
 - Systemic Vascular Resistance = $[(MAP - RAP)/CO] * 80 \text{ dyn.s.cm}^{-5}$. Normal range 770 – 1500
 - SVRI = $SVR * BSA \text{ dyn.s.cm}^{-9}$. Normal range 1760 – 2600 dyn-s/cm⁵/m²
 - Pulmonary Vascular Resistance = $[(PAP - LAP)/CO] * 80 \text{ dyn.s.cm}^{-5}$
- In summary, not helpful for predicting fluid responsiveness (wedge pressure is not related to LV function). OK for measuring CO and temperature

Evidence of benefit of a PAC

- Some trauma data suggest advantage in the most severely ill
- JAMA 1996, Connors et al: Prospective multicentre cohort study of 5735 ICU patients showed ↑mortality and ↑resource utilisation with PA catheters
- A Randomised, Controlled Trial of the Use of Pulmonary-Artery Catheters in High-Risk Surgical Patients, NEJM 2003, Canadian study. 1994 elderly patients. No difference from PAC + strict goal-directed therapy or CVL without strict haemodynamic goals
- Early use of the pulmonary artery catheter and outcomes in patients with shock and ARDS: an RCT, JAMA Nov 2003. Increased mortality with PACs
- PACMAN, Lancet 2005, Harvey et al, RCT in 64 UK ICUs, n = 1041, showing no difference in mortality between PAC and not. Complications in 10% of PAC insertions. PAC altered treatment within 2 hours in 80%
- 2006 Cochrane review showed no change in mortality in the only 2 studies in ICU
- FACTT (Fluids and Catheter Treatment Trial), NEJM 2006. 2 * 2 trial in ARDS of pulmonary artery catheter vs central venous catheter, with restrictive vs liberal fluid resuscitation strategy. No difference in survival or complications with or without catheter (most PAC complications also occur with CVL)
- Clement, 2011, ARDSNET groups. No benefit in ALI
- ⇒ No data to support that knowing or targeting CO affects shock patient's outcomes. There may be justification for measuring cardiac function to clarify mechanisms when shock does not reverse after initial therapy
- Consensus statements less pessimistic – PACs are safe and useful if used well.... (“No other monitor is expected to save lives by itself....”)

Estimating Cardiac Output

- Why measure cardiac output (an important question – it seems obvious but isn't!):
 - Measuring CO would only be of value if it guided therapy to improve patient outcomes
 - In those not responding to fluid resuscitation (see *Resuscitation Targets*, page 43), knowledge of CO might help if:

- Heart is adequately filled and heart function is poor, then focus on improving heart function (β -agonists in preference to α -agonists, stenting)
- Patient is hypoxic and there are signs of L or R heart failure, where further fluid may worsen oxygenation
- Routine measurement of CO not recommended in shock
- Consider either echocardiography or measure of CO for diagnosis in patients with evidence of ventricular failure and persistent shock
- The question is not is cardiac output normal, but is it adequate. That's quite different

Thermodilution for Estimating Cardiac Output

- Three approaches:
 - Bolus injection of cold 5% dextrose into the RA \rightarrow \downarrow blood temperature in the PA (measured by a thermistor proximal to the balloon)
 - Semi-continuous thermodilution from RV \rightarrow PA:
 - Thermal filament around the RV segment of the catheter which transmits random pulses of heat, detected by the downstream thermistor and summed over time
 - Disadvantages: inaccurate during thermal disequilibrium – rapid infusions or on bypass, MRI contraindicated, delay in detecting sudden changes
 - Transpulmonary bolus injection of cold fluid bolus \rightarrow \downarrow blood temperature in femoral or brachial arteries
- CO inversely proportion to the mean decrease in temperature (via Stewart Hamilton equation)
- Advantages: non-toxic indicator, does not re-circulate, good agreement with Fick and indocyanine green methods
- Room temperature injectate introduces a small decrement in bias and precision
- More reproducible in expiration, as respiration \rightarrow changes in CO and PA temperature
- *Inaccurate in:* catheter malposition, intra-cardiac shunts, TR, dysrhythmias, rapid IV infusions, extremes of cardiac output, slow injection
- PiCCO (Continuous CO by pulse contour analysis)
 - Pulse contour analysis (usually in femoral/brachial cannulation) \rightarrow stroke volume from area under the systolic portion of the pressure waveform
 - Needs calibration from another method of CO estimation – usually thermodilution
 - Needs regular recalibration, and recalibration if changes in position or abdominal pressure. Invalid in aortic aneurysms and material AR
 - Derived values include intrathoracic blood volume index, extravascular lung water, stroke volume variation and cardiac index. *Intrathoracic blood volume is a preferred index of preload in ventilated patients*
 - Compared with PAC CO measurement has good precision

Transpulmonary Indicator Dilution for Estimating Cardiac Output

- Lithium dilution (LiDCO): Small dose of lithium injected, no significant first pass loss. Blood is sampled continuously from an arterial line. Can use peripheral arteries without loss of accuracy. Good agreement with bolus thermodilution and works in adult and paediatric populations. Can't be used in patients on lithium, high peak doses of muscle relaxants or abnormal shunts
- Pulsed-Dye densitometry: based on transpulmonary dye dilution via transcutaneous signal detection. Indocyanine green injected via CVL. CO calculated from Stewart Hamilton formula from dye dilution curve. Technique has significant limitations
- Double indicator technique: combines thermal dilution with dye dilution with indocyanine green (non-toxic, highly albumin bound to remains in the intravascular space, measured with in-vivo fibre-optic sensor)

Interpretation of Cardio Output Measures from Transpulmonary Dilution Techniques

- Thermal and other indicators injected into a central vein and are detected in a systemic artery
- Because they pass through the heart and entire pulmonary circulation they can estimate:
 - Central blood volumes: intrathoracic blood volume (ITBV) – a volumetric rather than pressure based measure of preload, and Intra-thoracic blood volume index (ITBVI)
 - Global end diastolic volume (GEDV)
 - Extra-vascular lung water (EVLW) and extra-vascular lung water index (EVLWI) – a marker of severity of illness, potential as a therapeutic endpoint, and prognostic information in sepsis and acute lung injury

ITBVI	CI	EVLWI	
↓	-	↑	Overloaded ⇒ diuresis
↓	↓ or ↑	↓	Under filled
↓	↓	↑	Vasoactive drugs +/- cautious fluids
↑		↑	Volume restrict/diuresis for improved lung function
↑	-	↓	Sit tight
↑	↓	↑	Diuresis +/- vasoactive drugs
↑	↓	↓	Vasoconstrictor/dilator and inotrope based on SVR

Ultrasound Measurement of Cardiac Output

- Use echo to measure systolic and diastolic LV volumes – labour intensive, operator dependent, not continuous. No data to show echo can improve outcome in shocked patients. However, potential benefits and very low risk
- Doppler measurement of aortic blood flow:
 - Good reproducibility and better agreement with thermodilution. Most accurate results when Doppler beam parallel to flow, but up to 20° approximates OK. Can also give measurement of afterload
 - Oesophageal Doppler :
 - Measures flow in descending aorta
 - RCTs have shown benefit for fluid titration in high risk surgical patients. NICE guidelines encouraging use – but the evidence is mainly on the basis of intra-operative studies showing ↓ complications, no change in mortality
 - Minimally invasive 6 mm probe, and few contraindications (agitation, mouth or oesophagus pathology, aortic balloon pump, dissection or coarctation)
 - Assumes descending aorta is 70% of aortic flow, that flow is laminar not turbulent, maintaining probe position can be difficult and poorly tolerated by unsedated patients
 - Values provided are:
 - Peak Velocity (PV): normally 70 – 100 cm/s, ↑ on inotropes, ↓ in heart failure
 - Mean Acceleration (MA – slope of velocity vs time curve): Can be increased (↑ contractility) or decreased (↓ contractility)
 - Flow time (FT – time of systolic forward flow): Normal 330 – 360 ms. ↑ in vasodilation, ↓ with hypovolaemia, vasoconstrictors
 - Area under the velocity vs time curve is approximately proportional to stroke volume
 - Transcutaneous measurement of transpulmonary (parasternal) and transaortic (suprasternal) flow now available

Other Applied Measures of Cardiac Output

- Gap or Gradient CO₂:
 - = difference between arterial and venous CO₂
 - Variation in CO₂ between arterial and venous circulation is only due to differences in tissue flow ⇒ potential at the macro level as another indicator of CO (whole body tissue flow)
 - Abnormal > ~ 6 mmHg
 - ↑ In the gap is associated with ↓ tissue flow in animal models. ↑ δCO₂ is associated with ↑ δ lactate
 - Advocated by some as an additional resuscitation target
 - Contrasts with SaO₂ – SvO₂ which does not necessarily correspond to DO₂
- Partial rebreathing of CO₂: Indirect Fick method estimates cardiac output from whole body CO₂ elimination, and CO₂ contents of arterial and mixed venous blood. Works by introducing 150 ml extra dead space into the circuit and measuring new equilibrium. Relies on EtCO₂ accurately reflecting change in end-capillary CO₂ (may not hold in chronic lung disease)
- Transthoracic Impedance Monitoring: proposed for providing further information on extra-vascular lung water

Pathophysiology of Shock

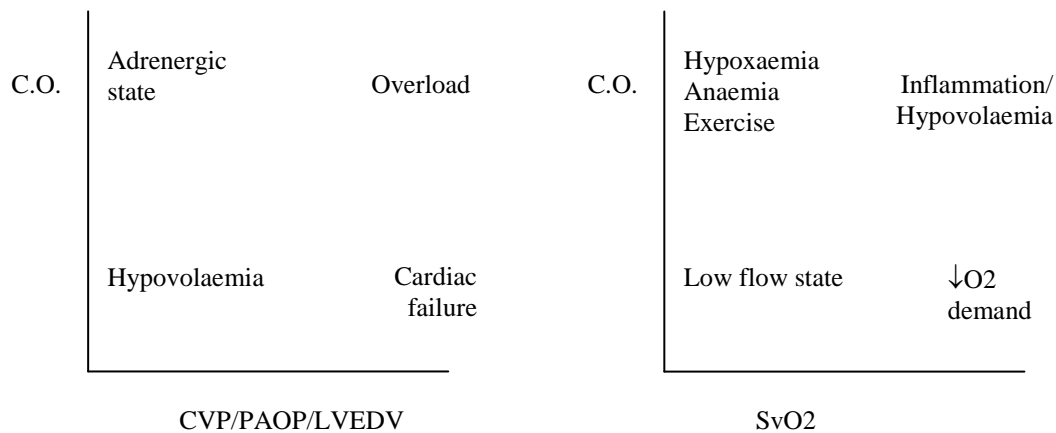
- = “failure to deliver and/or utilise adequate amounts of oxygen”
- Imbalance between oxygen supply and demand
 - See also Hypoxia, page 25
 - DO₂ (O₂ delivery to tissues) is ↓ in all but septic shock
 - → tissue hypoxia
 - Insufficient tissue O₂ delivery may not be the only thing going on – especially in septic shock cellular and mitochondrial dysfunction may be present
 - Initially, tissues maintain VO₂ (oxygen uptake) at a normal level (170 ml/min/m²) by extracting more O₂ from blood. Once DO₂ falls below 330 ml/min/m² VO₂ drops → O₂ debt → Anaerobic metabolism →:
 - ↓ATP → failure of cell membrane Na-K pump → cell swelling
 - lactic acidosis
 - ↓mitochondrial Ca
- Manifest by markers of hypoperfusion such as ↓ScvO₂ or SvO₂, ↑lactate, ↑base deficit, perfusion-related low pH, with or without hypotension
- Hypotension (either SBP < 90, SBP < 40 from baseline, or MAP < 65) is not required to define shock. The issue is the presence of inadequate tissue perfusion
- Catecholamine and neurohormonal release attempts to compensate by:
 - ↑inotropy and peripheral vasoconstriction – at the cost of increasing myocardial O₂ demand
 - ↑sodium and fluid retention, potentially increasing blood pressure but worsening congestion
- Comparing cardiac output to a bicycle....:
 - Heart rate = peddling faster. Works well over a narrow range
 - Contractility = pushing harder
 - Pre-load = a tail wind
 - After load = biking down a smooth straight downhill road – nothing to stop you

Clinical classification of Shock

- See Differential of Shock Hot Case, page 376
- Considerable overlap
- CHODE: Cardiogenic, hypovolaemia, obstructive, distributive (SIRS, neurological, ↓adrenal), error (lab or drug)
- Due to cardiac dysfunction:
 - Cardiogenic: Myocardial disease (infarction, myocarditis), valvular (eg MR from papillary muscle rupture), drug overdose (β-blockers) High mortality.
 - Obstructive: extrinsic compression (tamponade, tension pneumothorax) or vascular occlusion (PE or air embolism)
- Due to loss of control of peripheral circulation → systemic hypotension and requirement for ↑CO to compensate:
 - Hypovolaemic (→ ↓Preload):
 - Haemorrhage, also GI/urinary losses and burns
 - Lower mortality than other types of shock. BP below 95 mmHg is not a sensitive measure for ruling out moderate or significant blood loss
 - Distributive shock (→ ↓Afterload):
 - Sepsis
 - Anaphylaxis (rarer and less fatal than septic or cardiogenic shock):
 - The term anaphylactoid is now obsolete. IgE mediated or not is something to work out later
 - Particular difficulties in surgical anaphylaxis: raid effect due to IV agents (cf stings/food). Mimics other things (eg hypotension on induction). Don't see skin effect under drapes
 - Pickup of specific IgE (RAST) tests varies, depending on agent – chlorhexidine and steroidal NMBA sensitive, whereas latex and antibiotics are low
 - Chlorhexidine anaphylaxis is now on a par with ABs, which are behind NMBA. NMBA cross-reactivity common; cisatracurium (non-steroidal) least likely to cross react with rocuronium

- Test mast cell tryptase at 1 and 4 hours, and at 24 hours (baseline). False positives in bypass surgery and prolonged CPR
- Don't give IV antihistamine (due to associated hypotension)
- Non-specific inflammatory states:
 - Pancreatitis
 - Burns
 - Post-cardiac bypass
- Neurogenic: intracranial haemorrhage, spinal cord injury
- Hypoadrenalism can contribute
- Other:
 - Severe anaemia
 - Poisonings
 - Histotoxic: cyanide

Diagnosing Shock



- Shock of any sort → confusion, pallor, tachycardia, tachypnoea, oliguria
- Hypovolaemic, obstructive and cardiogenic shock → ↓CO but BP may be normal due to sympathetic and neurohormonal compensation. May see other signs earlier
- CVP low in hypovolaemia, high in cardiogenic and obstructive
- Septic: hyperdynamic circulation (warm, bounding pulses)
- Hypovolaemia suggested if:
 - Hypotension is precipitated by sedation, analgesia and postural change
 - Respiratory fluctuation in arterial pressure is a ventilated patient. Confirmed if brief disconnection from the ventilator causes BP to rise and venous pressure to fall as pressure off the ventilator more accurately reflects the ventricular end-diastolic transmural pressure
- Response to valsalva (hard in ventilated non-paralysed patient): assesses intra-thoracic blood volume and provides an estimate of true left ventricular preload. If pulse pressure reduces with a lower SBP then more volume
- Investigations:
 - Bloods: FBC, coags, electrolytes, urea/Cr, ABG, lactate, troponin, cultures). Electrolyte abnormalities and haemoconcentration in hypovolaemic, DIC (↑Clotting time, ↓platelets and ↓fibrinogen, low antithrombin III, protein C and S)
 - Lactate (the only biomarker recommended for diagnosis or staging of shock) and/or base excess predict outcomes in ICU patients
 - ECG + CXR
 - Obstructive or cardiogenic shock: echo
 - Hypovolaemic shock: Imaging to exclude intra-abdominal bleed

Management of Shock

DO2 =	• CaO2 (O2 content) * Cardiac Output					
Made up of:	SaO2	* Hb	Pulse	Contractility	Preload	Afterload

Improve with:	↑FiO ₂ ↑PEEP	Transfusion	Pacing Chronotrophy	Inotropes	Fluid Vasopressor	Nitrate
Risks:	Vasoconstriction	Multiple	Not very effective Ischaemia	↑Metabolic demand	Lung oedema	Hypotension

Fluid Resuscitation

- See also:
 - Review article: Myburgh and Mythen, NEJM 2013
 - Early Goal Directed Therapy in Sepsis, page 52
 - Fluid Resuscitation in Trauma, page 231
 - Damage Control Resuscitation, page 231
 - Resuscitation in Traumatic Brain Injury, 236
 - Massive Bleeding, page 303
- Background:
 - Too little fluid resuscitation is bad → poor perfusion, poor preload...
 - Too much resuscitation is bad → overload, oedema of lungs, gut (→ compartment syndrome), brain...
 - You don't know till afterwards whether you got it right → need empiric targets
 - It's unclear what to measure as end-points of resuscitation, and what values of these measures to aim for
 - Suggested targets have included CVP, MAP, ScvCO₂, haematocrit, lactate....
 - Resuscitation targets are likely to vary depending on cause (eg sepsis, head injury, chest trauma) and age/comorbidities. We don't know how to individualise targets
- Wide-spread variation at present:
 - Fluid resuscitation is the 2nd most common medical intervention after O₂ administration
 - Which fluid to use is determined by which country you live in
 - It is titrated to inconsistent outcomes (eg urine output)
 - Maintenance fluids are a major cause of microvascular oedema
- John Myburgh's rules of thumb:
 - Use it like a drug – what is the indication, what is the desired outcome, give it carefully
 - Consider the early use of catecholamines
 - Oedema is associated with adverse outcomes
 - The use of a fluid bolus in the post-resuscitation period is questionable

Crystalloids

- Crystalloid (mmol/L):

	Na	K	Ca	Cl	Buffer	pH	Osmol	Risks
0.9% NaCl	154			154		5.5	308	Hyperchloraemic acidosis
Hartmann's	131	5	2	112	Lactate 29*	6.5	281	↑K
Ringer's Lactate	130	4	1.5	109	Lactate 28*	6.5	273	↑K
Plasmalyte	140	5		98	Bicarbonate 29 Acetate 27 Gluconate 23	5.0	294	↑K
4% glucose + 0.18% NaCl	31			31		4.5	284	Fluid overload
5% glucose						4.1	278	Fluid overload

* = present as lactate which is metabolized to HCO₃ by the liver

- Cheap
- Require slightly more volume to expand intravascular volume
- Normal saline:
 - Is the only isotonic solution, but risks from hyperchloraemic metabolic acidosis
 - Invented by Hartmög Hamburger in 1992 who suggested 0.9% was the concentration of NaCl in human blood (actually it's 0.6%)
 - > 200 million litres used annually in the USA alone
 - Emerging risks with ↑chloride:

- ?Hyperchloraemia → ↓pH → vessel vasoconstriction + other postulated effects. Possible confounders: changes in resuscitation targets, ↓gelatine fluids, ↑lactate in Hartman's (?renally protective)
- Bellomo et al, JAMA 2012, Pilot study showing cohort of N saline compared with subsequent balanced salts → ↓AKI 14% → 8.4%, ↓RRT 10% to 6.3%, no mortality difference
- Double blind cross over trial on volunteers: ↓UO, ↓renal cortical perfusion
- Hypertonic saline
 - Advocate to reduce water overload
 - Demonstrated to restore microvascular flow, decrease tissue oedema, and attenuated inflammatory response
 - Studied: 7.5% saline alone or with dextran 70 for initial resuscitation. No clear advantage in general trauma population, may be of benefit in head injury (→ less cerebral oedema)
- "Balanced solutions":
 - Invented by Sidney Ringer 1885, modified by Alexis Hartmann (1898 – 1964)
 - Are not physiological, despite aiming for a strong ion difference equivalent to plasma
 - All have problems with the carrier ion:
 - HCO₃: leaks from plastics, expensive, unstable in plastic
 - Acetate (cardiotoxicity), malate, gluconate
 - Lactate: hypotonic

Colloids

	kDa	Na	K	Ca	Cl	Buffer	pH	Osmol
Albumin 4%	69	130-160	<1		120	Alb 40 g/l	7.4	309
Albumin 20%		130-160	<1			Alb 200 g/l	7.4	312
Haemaccel	35	145	5	6.2	145		7.3	250
Gelofusin	35	154	0.4	0.4	125		7.4	308
Starches	140-400	154			154		5.5	310
Voluven	130	154			154		4–5.5	308
Volulyte	130	137	4		Mg 1.5	Acetate 34		260 – 130

Albumin

- Background:
 - Obtained from pooled blood by fractionation since 1941. Cannot be regarded as sterile, but is heated to 60°C for 10 hours and prepared at low pH. Prion transfer is feasible
 - Contains 140 mmol/L Na, 128 mmol/L Cl
 - In septic patients with capillary leak, may not remain intravascular
 - Half-life ~ 20 days
 - Is expensive
 - Contains pre-kalikein activator which, although present in low amounts, may produce hypotension and bradycardia with an ACEI. Can't add K to it
- Why the worry?: BMJ 1998 Cochrane review: albumin as a resuscitation fluid → ↑mortality
- SAFE study (NEJM 2004):
 - Designed to answer the challenge of the preceding Cochrane Review which said albumin was possibly bad (when it was commonly used in Australia)
 - Saline vs Albumin for resuscitation in the ICU with 6997 patients given boluses of 500 ml of 4% albumin or normal saline.
 - Excluded cardiac surgery (mortality too low to detect a signal), burns and liver transplant
 - No difference in 28 day outcome, renal replacement therapy, ventilation, ICU or hospital LOS
 - No difference regardless of what baseline albumin is (BMJ 2006 post hoc study)
 - Trend to *lower* mortality with albumin in sepsis, trend to *worse* mortality in trauma, especially brain trauma
 - Ratio of crystalloid to colloid was 1.4:1 over first 4 days (previously ratio reported as 3:1). No difference in MAP or pulse. Clinically small ↑ in CVP

- SOAP Study: Crit Care 2005: Multicentre observational study of 3,147 patients of albumin vs other fluids in general ICU population. Albumin associated with worse mortality in logistic regression analysis. Authors claimed that while SAFE showed albumin was safe as a resuscitation fluid, this observational study raised persisting concerns.... Study also showed ↑mortality with positive fluid balance in regression analysis
- Saline or Albumin for Fluid Resuscitation in Patients with TBI, NEJM 2007, Post hoc 24 month follow-up of 460 patients. Significant increased mortality in TBI given albumin (33% vs 20%), difference in the GCS 3 – 8 subgroup, not the 9 – 12 subgroup
- Albumin in Sepsis:
 - SAFE Sepsis Cohort study published in 2011: Subgroup analysis of the 2004 trial, n = 1218, trend to mortality benefit for albumin, 31% vs 35% – needs further Trial
 - Meta-analysis: Delaney et al Crit Care Med 2011: RCTs involving 1977 patients, 8 studies only in sepsis, 9 studies with sepsis sub-groups. Albumin associated with odds ratio for mortality of 0.82 (0.67 – 1.0, p = 0.47)
 - PRECISE RCT planned in Canada in sepsis
 - FEAST Trial (Fluid Expansion as a Supportive Therapy), NEJM June 2011:
 - Mortality after fluid bolus in septic Sub-Saharan African children (median age 24 months), ~40% with malaria, diagnosis often unclear
 - Albumin 20 - 40 ml/kg vs saline 20 - 40 ml/kg vs nothing, with no rescue therapy (no ventilation if pulmonary oedema, no ICU)
 - Faster resolution of shock in fluid arms
 - 48 hour mortality 10.6% vs 10.5% vs 7.3%. Same pattern in 4 week mortality. Mortality was principally from cardiovascular collapse, rather than fluid overload, suggesting an interaction between fluid and compensatory neurohormonal responses
 - Very difficult to generalise to adult ICU population
 - ALBIOS Study, Caironi et al, NEJM 2014: n = 1818 with severe sepsis in 100 Italian ICUs, randomised to crystalloid or crystalloid + 20% albumin targeting 30 g/L. Albumin group had initial higher MAP and ↓fluid balance but no difference in 90 day mortality (32 vs 31.8%). Post hoc subgroup of septic shock (ie excluding severe sepsis only) showed a just significant mortality benefit
- Bottom line: is as safe as saline. Not proven its better in sepsis (the subgroup analysis of SAFE was hypothesis generating only). Is hypotonic??? (which may have been the cause of ↑ICP in SAFE-TBI). FEAST Trial suggests its role as a bolus fluid now needs to be reconsidered
- Other specific indications for Albumin:
 - ARDS: small trials of albumin +/- frusemide lead to initial improvements in oxygenation and diuresis (Martin, Crit Care Med 2005)
 - General oedema: Albumin + furosemide for treatment of oedema: Conflicting studies. Risk that albumin will make oedema of inflamed tissues worse. Martin et al, CCM 2005, MRCT of 40 hypoalbuminaemic patients with ALI with frusemide +/- albumin → ↑oxygenation and fluid removal with Albumin 25 gm of 25% TDS for 3/7. Excluded those on vasopressors, and with significant renal or hepatic disease
 - Ascites:
 - Albumin infusions for preventing deterioration in renal function in spontaneous bacterial peritonitis and established hepatorenal syndrome (in conjunction with a vasoconstrictor) are well established (??source) → ↓ renal failure and ↓ mortality
 - Some evidence of benefit of albumin + furosemide
 - Paracentesis with albumin support probably better and quicker
 - Oedema in nephrotic syndrome: albumin + furosemide of benefit
 - Acute stroke: ↑early death in broadly defined group, futility in tightly defined group (ALIAS Trial, Ginsberg, 2013)

Synthetic Colloids

- Associated with 4% ↑ in mortality (BMJ 1998; 316:061-4)
- Are not crystalloid sparing – their half life is short and most of the fluid in colloids is crystalloid
- Not a single trial supports the use of colloids over crystalloid. Most use is driven by marketing
- Poor outcomes tend to become apparent later (eg separation of Kaplan Myer curves compared to Ringers after day 20 in the 6S study). ?due to immuno-modulatory effects of accumulation/retention in the reticular/endothelial system
- **Hydroxyethyl starch:**

- A class of naturally occurring starches (in corn, potatoes), with hydroxyethyl substitution of amylopectin. A high degree of substitution on glucose molecules protects against hydrolysis prolonging intravascular expansion but ↑ the potential for accumulation in reticuloendothelial tissues (skin, kidneys, and liver). HES deposition in tissues is common. Found in skin after 8 years in one follow-up study. Associated with itch.
- Molecular weight affects pharmacokinetics:
 - Medium Molecular Weight: HES 200 kDa, 0.6 – 0.66 substitution associated with ↑ *renal failure*
 - High Molecular Weight, newer starches: HES 450 kDa, 0.5 Substitution associated with ↑ *bleeding and abnormal clotting*
- Currently used HES solutions have reduced concentrations with a molecular weight of 130 KD and a molar substitution ratio of 0.38 – 0.45
- Joachim Boldt – 88 fraudulent papers on hydroxyethyl starch retracted from 2010, including 11 studies of HES 130
- CHEST trial (Crystalloid vs Hydroxyethyl Starch Trial): N saline vs Voluven (approved in Australia in 2006) in 7,000 patients (Myburgh et al, NEJM 2012). Slightly better plasma expansion in first 4 hours with starch. Did ↑ CPV by more for longer. No difference in mortality. More renal replacement therapy with HES (7.0 vs 5.8% - both lower than anticipated). More hepatic impairment, pruritis and rash. HES patients showed less renal impairment on RIFLE criteria – but HES is a diuretic so there was less reduction in urine output – it's also nephrotoxic. However, if analysed on Cr criteria only, renal failure was worse with HES
- 6S Study (Scandinavian Starch for Severe Sepsis/Septic Shock): Multicentre RCT of 798 patients with severe sepsis randomised to Tetraspan (HES 130/0.42) vs Ringer's Acetate for resuscitation: 90 day mortality 51% vs 43%, CRRT in 22% vs 16% (NNH of 13). Higher volumes in sicker patients than CHEST. Generally late deaths (Kaplan-Myer curves separated at day 20) due to results of kidney impairment, impaired coagulation, and HES deposited in tissues. No differences in volumes given. Makers of Voluven stated that tetraspan (potato derived, HES 130/0.42) is different to Voluven (corn derived, HES 130/0.40). Meta-analysis have shown them to be equivalent
- Meta-analysis of 9 trials with 3456 patients in sepsis (Haase et al, BMJ 2013) showed ↑ RRT and ↑ red cell transfusion
- Meta-analysis for general fluid resuscitation (Gattos et al, Int Care Med 2013, for general fluid resuscitation in 10,391 patients showed ↑ RRT and borderline ↑ in mortality. Cochrane Review (2013) the same conclusion
- Meta-analysis of 4,529 patients in 59 heterogeneous trials showed no statistical benefit or harm in anaesthetic use (so why use it!): Van Der Linden, Anesthesiology 2012. NB: Physiologically the anaesthetic population is very different to the ICU population – is evidence from one transferable to the other?
- Gels: 2nd most common synthetic colloid. No trials of any substance look at their use. Observational studies now suggesting similar nephrotoxic side effects to starches

Resuscitation Targets

- See Early Goal Directed Therapy in Sepsis, page 52
- FACTT Trial (see Epidemiology of ARDS, page 110 and Prevention of Kidney Insufficiency, page 190) showed mortality benefit in ARDS of fluid restrictive vs fluid liberal resuscitation
- FEAST Trial (see Albumin, page 41) showed mortality benefit from no fluid resuscitation in children in Africa
- Prospective observational study of 479 patients undergoing major surgery requiring post-op ICU found +ive fluid balance was an independent risk factor for death, Silva, Crit Care 2013

Assessing Fluid Responsiveness

- Indications:
 - Preload measurement alone should not be used to predict fluid responsiveness
 - Low values of commonly used static measures of preload (CVP, RAP, PAOP < 4 mmHg and ventricular volumes) should → fluid resuscitation with careful monitoring
 - Use a fluid challenge to predict fluid responsiveness. Possible regimes:
 - 500 – 1000 ml of crystalloid/ 250 – 500 ml colloid over 30 mins (recommended by Surviving Sepsis) with a goal of obtaining a rise in CVP of < 2 mmHg
 - If there is concern about administering a fluid challenge, a 200 ml reversible challenge can be given by elevating the legs to 60° for 2 minutes/45° for 4 mins. Also alters sympathetic tone so changes in BP are not just due to fluid
 - Specify TROL:

- Type of fluid
 - Rate of administration
 - Objective
 - Limits
 - Eg 500 ml N Saline over 10 mins with the aim of increasing BP while keeping CVP < 12
- Consider conservative approach in acute lung injury and in trauma
- Assess responsiveness by looking at cardiac function and tissue perfusion:
 - Dynamic parameters and trends better than static measurement
 - Markers of increasing overload:
 - Invasive: \uparrow CVP > 2 – 5 mmHg, \uparrow PAWP > 3 – 7 mmHg over 30 mins
 - Clinical: \uparrow JVP, signs of pulmonary oedema
 - Signs of resolving shock: \uparrow SvO₂, MAP > 70, \uparrow CO, \downarrow tachycardia, \uparrow urine output (> 0.5 ml/kg/hr), \downarrow lactate
 - Stroke volume variation (SVV) with respiration:
 - Obtained from either:
 - Pulse Pressure Variation with respiration
 - Systolic Pressure Variation with respiration
 - Similar in principle to measurement of aortic blood velocity variation with respiration
 - Assesses the cyclic changes in preload 2nd to ventilation and predicts whether you're on the steep (fluid responsive) or flat (fluid unresponsive) part of the Starling curve
 - Is the best predictor of fluid responsiveness, obtained from analysis of arterial waveform
 - SVV > 12% \Rightarrow Likely to be fluid responsive. Values of < 10% \Rightarrow further volume unlikely to \uparrow CO
 - Doesn't work well in:
 - AF or frequent ectopics due to wide variation in stroke volume
 - Spontaneous breathing (too much breath to breath variation)
 - HR/RR \leq 3.5 (eg bradycardia or β -blocked)
 - Need tidal volume big enough to give a discernible change in SBP (ie less effective for measurement in low tidal volumes)
 - Other proposed endpoints:
 - Intra-thoracic blood volume (from PiCCO)
 - Respiratory variation in SVC/IVC diameter

Inotropic/Vasopressor Support

- For inotropes in children, see **Error! Reference source not found.**, page **Error! Bookmark not defined.**
- See Oh's chapter on inotropes
- Rules of thumb:
 - Rarely required in hypovolaemic shock, unless replacement delayed
 - Vasoactive are drugs required in septic and cardiogenic shock to \uparrow tissue perfusion and \downarrow hypoxia. Little RCT evidence of mortality benefit of inotropes vs none
 - Don't squeeze someone who is under-filled, especially if they have cardiac outflow tract obstruction
 - Inotropes \uparrow metabolic demand, so pushing too hard can be bad
 - Current trend is a shift from seeing vasoactive drugs as "rescue" therapy, towards augmentation of endogenous systems when they are overwhelmed
 - Key role is to \uparrow venous return (\rightarrow \uparrow CO)
- Myburgh rules:
 - Noradrenaline is the vasoactive support of choice in all patients
 - Adrenaline is probably equivalent and associated with metabolic derangement
 - No evidence of other catecholamines in terms of patient centred outcomes
- Side effects of vasopressors:
 - \uparrow myocardial work
 - \downarrow cardiac output
 - Myocardial and splanchnic ischaemia (variable effect)
 - \uparrow myocardial irritability, arrhythmias and tachycardia
 - \downarrow peripheral perfusion and distal ischaemia/necrosis
 - \uparrow pulmonary vascular resistance

Studies Comparing Inotropes

- Difficulty with trials: what is the endpoint (all are imperfect):
 - Resolution of shock
 - Some measure of tissue perfusion
 - “Macro circulation” (eg MAP) is not a good measure of micro-circulation
- Annane et al, Lancet 2007, French multicentre study in 330 patients found no difference between noradrenaline +/- dobutamine and adrenaline, despite the acidosis (day 1 – 4) and ↑lactate (day 1) – are these changes adaptive or even beneficial? – and tachy arrhythmias of the latter
- CAT Trial (Myburgh et al, 2008), 280 patients in 4 Australian units in ICU patients with sepsis or circulatory failure. No difference in time to unsupported MAP or difference in 28 or 90 day mortality between noradrenaline or adrenaline
- SOAP II Study, NEJM 2010: Noradrenaline vs dopamine in shock, multicentre RCT in 1679 patients. No difference in mortality, more arrhythmia with dopamine. Dopamine was worse for mortality in a subgroup analysis of cardiogenic shock, but not difference in hypovolaemic or septic shock. Another nail in the coffin of dopamine...
- Vasopressin:
 - VASST, Vasopressin and Septic Shock Trial, Russell et al NEJM 2008
 - Blinded vasopressin or further noradrenaline in patients already receiving noradrenaline. 0.01 – 0.03 U/min (Surviving sepsis guidelines use it to 1.8 mg/hr.
 - Multicentre trial of 778 patients with septic shock excluding coronary syndromes or heart failure (ie lower risk). Required only non-response to 500 ml bolus to qualify as shocked.
 - No mortality difference. No 28 day difference in cardiac complications or gut ischaemia. Unclear upper limit of safe dose (↓ stroke volume). No evidence that it saves lives as an add on.
 - Post-hoc analysis found mortality decreased in those receiving vasopressin and hydrocortisone, and ↓RRT with early vasopressin
 - Mortality ↓ with vasopressin in less severe septic shock (?because they haven’t exhausted endogenous catecholamines yet)
- The future? Gene mapping and genetic role in risks and appropriate response

Choosing the right agent

- Cardiogenic shock:
 - ↓CO, ↓BP, ↑SVR
 - Need an inodilator, eg dobutamine/milrinone. If → ↑CO but ↓MAP → more powerful inotrope required ⇒ adrenaline and GTN (although risks with adrenaline)
 - If hypotension prominent then inoconstrictor (eg adrenaline) preferred
- Septic shock:
 - ↓MAP, ↓SVR, ↑CO
 - Once preload optimised (by ↑volume), pure vasoconstrictor (eg noradrenaline)
 - If also ↓CO then add dobutamine or milrinone. In theory inoconstrictor dopamine could work but problematic side effects (↓prolactin, GH and TSH, T-cell function, gut perfusion and renal medullary O₂ concentration)
 - No human clinical trials have demonstrated any benefit to any particular vasoactive drug or combination in sepsis
- High afterload: ↑MAP, ↑SVR, ↓CO: a dilating agent (eg GTN) or inodilator
- Pulmonary hypertension: ↑PVR, ↑RAP acutely: pulmonary vasodilator to offload the RV and maintain CO: nitrate or β-agonist (but risk of hypotension from arteriolar dilatation and hypoxaemia due to V/Q mismatch)

Drug	Dose	Usual Mix	Receptor	Contractility	HR	BP	CO	Splanchnic flow	SVR	PVR
Adrenaline	0.01 – 0.1 µg/kg/min	10 mg in 100 ml	β ₁ , α, β ₂	++	+	++	+++	-	+	+
Noradrenaline	0.1 – 2 µg/kg/min	10 mg in 100 ml	Mainly α, also β ₁	0/+	0	++	-	--	++	++
Dopamine < 5 µg/kg/min > 5 µg/kg/min	2.5 – 20 µg/kg/min	200 mg in 100 ml	DA ₁ , β ₁ , α β ₁ , α, DA ₁ , β ₂	+ ++	0/+ +	0/+ +	+ ++	0/+ 0	0/+ +	0/+ +
Phenylephrine	1 – 10 µg/kg/min		Pure α	0	0	++	-	--	++	++
Isoprenaline	0.5 – 5 µg/min,	1 mg in 50	β ₁ , β ₂	+	++	+ / 0	+	0 / +	-	-

	chronotrophy takes ~ 20 mins	ml								
Dobutamine	2.5 – 20 µg/kg/min	250 mg in 100 ml	Mainly β ₁ , also β ₂ , α	+	+	+/-	++	0	-	-
Glyceryl Trinitrate	10 – 200 µg/min		Via NO	0	+	-	+	+	-	-
Nitroprusside	0.5 – 6 µg/kg/min	50 mg in 50 ml.	Via NO	0	+	--	+	+	--	-
Milrinone	Load 50 µg/kg over 10 mins. Then 0.375 – 0.75 µg/kg/min		PDE	+	+	-	++	0/-	--	-
NO (inhaled)			Via NO	0	0	0	0/+	0	0	--
Prostacyclin (inhaled)	20 µg nebulised max 2 hourly			0	+	--	+	+	-	--

DA₁, DA₂ = dopamine receptors

Catecholamines

- See Studies Comparing Inotropes, page 45
- **Adrenaline** (epinephrine):
 - Endogenous adrenergic agonist
 - Actions:
 - ↑Coronary blood flow. Potent bronchodilator
 - ↑contractility and ↑HR → ↑cardiac oxygen consumption
 - Blood pressure may not ↑ initially due to β₂ effects on smooth muscle (vasodilation). At higher doses vasoconstriction predominates. May cause pulmonary arterial vasoconstriction
 - SE: Arrhythmogenic, ↑glucose, ↓K, ↑lactate (consider when tracking lactate – normalises quickly when adrenaline stops. Lactate is OK – its fuel for the brain...). These give adrenaline a bad name, but are physiological responses. Requires central access
 - Pharmacokinetics:
 - Rapidly inactivated by the liver
 - Potentiated by TCAs and MOA inhibitors
 - Pheochromocytoma, stress and prior TCAs → ↑urine catecholamines.
- **Noradrenaline:**
 - Endogenous catecholamine released by post-ganglionic adrenergic nerves
 - Primary α agonist, with ↑β actions as dose increases
 - Peripheral vasoconstrictor, coronary vasodilator, small inotrope and proarrhythmic effect via β₁ activity
 - ↑BP mainly by ↑DBP and thus MAP (→ ↑coronary perfusion pressure)
 - Pharmacokinetics: Rapidly metabolised by COMT and MAO
 - Early small trial suggesting benefit from concurrent esmolol in tachycardic septic patients (Morelli, CCM, 2013)
 - Very expensive cf adrenaline
 - Widely available, familiar agent
 - Use with caution as single agent where inadequate preload or contractility (eg hypovolaemia, tamponade, ↓myocardial function)
- **Dopamine:**
 - Endogenous adrenergic agonist. Immediate precursor of adrenaline. Also a neurotransmitter. Used to ↑cardiac output as a mild vasopressor, and as a diuretic (no evidence to support renal protective role)
 - Only inotrope to work in marked hypothermia
 - Effects:
 - Low dose (0.5 – 2 µg/kg/min) causes:
 - vasodilation in renal vasculature and ↑Na excretion (inhibiting Na reabsorption in proximal tubules → diuresis)
 - Selective vasodilation of mesenteric, coronary and intracerebral vascular beds. Clinical effects are controversial (?harm to GIT via shunting from mucosa)
 - Presumed due to agonist effect on DA-1 and DA-2 dopamine receptors
 - At 2 – 10 µg/kg/min β₁ receptors cause ↑contractility and small ↑HR

- α action increases over 10, and at maximal doses (20 $\mu\text{g/kg/min}$) may become marked with vasoconstriction predominating and potentially compromising limb circulation. Can cause pulmonary vasoconstriction
- Indirect action via release of noradrenaline. Direct stimulation of α , β and noradrenergic receptors. Can lose effect with time (due to depletion of noradrenaline stores in periphery and heart)
- Stimulates receptors in the zone glomerulus of the adrenal cortex \rightarrow \downarrow aldosterone
- Inhibits TSH, GH and PRL release as well as other potentially negative effects on anterior pituitary function
- SE; nausea, tachyarrhythmias (especially AF), anginal pain, impairment of hypoxic ventilatory drive. Local extravasation \rightarrow profound vasoconstriction \rightarrow treat with phentolamine
- Pharmacokinetics:
 - Rapidly inactivated by liver (COMT and MAO)
 - If MAO inhibitors then significant dose reduction. Avoid phenytoin
- Requires central access
- **Dobutamine:**
 - Exogenous adrenergic agonist resembling dopamine. Used as inotrope and in stress test
 - Racemic mixture of two enantiomers (Levo and dextro) with different receptor profile (one potent β_1 and β_2 , other potent α_1 agonist). Metabolite 3-O- methyl Dobutamine is a potent α inhibitor. Net effect is complex, but typically \uparrow contractility, little effect on HR (at least at doses $< 10 \mu\text{g/kg/min}$) with some vasodilation and pulmonary artery vasodilation (CVP and PAWP usually decrease)
 - Given overall vasodilation can safely be administered via a peripheral vein
 - Small study in Int Care Med Aug 2013 suggests dobutamine does not improve microcirculation parameters despite improving macrovascular parameters
 - Effects:
 - \uparrow Contractility and mild \downarrow SVR \rightarrow \uparrow Cardiac index in patients with severe cardiac failure
 - \uparrow urine output due to \uparrow CO, no specific renal vasodilatory or other significant metabolic or endocrine effects
 - Dose: 2 – 15 $\mu\text{g/kg/min}$
 - Pharmacokinetics:
 - $T_{1/2} < 3$ mins, inactive metabolites, excreted in urine and bile
 - Rapidly inactivated by methylation and conjugation
 - Some tolerance with time, but less than dopamine
 - SE:
 - Avoid in cardiac outflow obstruction (tamponade, AS)
 - Causes drug induced myocardial ischaemia, rate/rhythm disturbances (less than dopamine), hypotension, hypertension in excess dose, tachyphylaxis
- **Phenylephrine:**
 - Synthetic α_1 adrenoceptor agonist, similar in structure to adrenaline
 - Boluses or infusion at rates of 40 – 180 mcg/min
 - Metabolism not well described, longer than naturally occurring catecholamines (but still minutes)
- **Isoprenaline:** Current international guidelines do not recommend isoprenaline as the first line agent to treat any condition. \uparrow Myocardial O₂ requirements while \downarrow effective coronary perfusion (due to \downarrow SVR \rightarrow \downarrow diastolic BP) although causes coronary vasodilation. May paradoxically worsen heart block. Start low.

Catecholamine sparing inotropes/vasopressors

- See Studies Comparing Inotropes, page 45
- **Vasopressin:**
 - Acts on a number of receptors:
 - V1: potent vasoconstriction
 - V2: anti-diuresis – renal receptors
 - V3: pituitary
 - OTR: oxytocin receptor subtypes
 - P2: purinergic receptors – not yet well characterised – plasma membrane receptors involved in vascular reactivity, apoptosis and cytokine secretion
 - 0.01 – 0.04 U/min for sepsis via central line.
 - Seems to potentiate the action of other vasoconstrictor agents and increases both urine output and creatinine clearance

- In catecholamine resistant shock, may respond to small doses that have no pressor effect in healthy people
- Rapidly inactivated by trypsin and peptidases
- Improved outcomes from low dose vasopressin (over noradrenaline) in the less severe septic shock subgroup. See VASST Trial, Studies Comparing Inotropes, page 45
- Potential adverse effects:
 - Ischaemia: heart, GI, skin
 - ↓CO
 - Liver abnormalities
 - Platelet dysfunction
- Terlipressin: synthetic analogue. Longer half-life, can be given by bolus. 0.25 – 0.5 mg bolus, repeated at 30 min intervals to max of 2 mg
- Other uses of vasopressin and its analogues:
 - Varices: vasopressin (with GTN to counteract myocardial and mesenteric ischaemia) or terlipressin. See Variceal Bleeding, page 169
 - Desmopressin/DDAVP: in Von Willebrand's and following post-cardiac surgical bleeding to improve platelet dysfunction (but may cause myocardial ischaemia). See DDAVP/Desmopressin, page 297
 - Diabetes insipidus: IM, IV or IN. See Changes During Brain Death, page 358
- **Milrinone:**
 - Phosphodiesterase III inhibitor → non-receptor mediated competitive inhibition of phosphodiesterase isoenzymes → ↑cAMP → ↑contractility independent of β stimulation. Also vasodilation → hypotension so may need noradrenaline
 - Patients on long term β-blockers: develop tolerance with ↓ catecholamine receptor responsiveness → ↓ intracellular cAMP
 - Usually loading dose given. Long half-life ~ 4- 6 hours. Be alert to deterioration as it wears off. Only licensed for 24 hours use
 - Arrhythmogenic
 - Decreased excretion in renal failure – follow manufacturers recommendations for dose reduction
 - Better effect on lusitropy – postulated benefits in diastolic failure
 - Only real benefit is in cardiac patients, especially with diastolic dysfunction
 - Little or no role in sepsis.
- **Levosimendan:**
 - Intracellular Ca sensitiser: Binds to troponin C → ↑myocyte sensitivity to Ca → ↑contractility. Bypasses other receptors
 - Also opens ATP-dependent K⁺ channels in vascular smooth muscle → dilates smooth muscle → coronary, systemic and pulmonary vasodilation (which may → hypotension)
 - → ↓afterload, ↓preload and ↑contractility without impairing relaxation
 - Doesn't ↑O₂ consumption compared to dobutamine
 - First trial in Lancet 2002, Follath et al. LIDO study. Levosimendan had mortality benefit over dobutamine, n = 203. Subsequent studies (RUSSLAN, CASINO, REVIVE ½ and SURVIVE) have been conflicting – early haemodynamic improvements but no long term difference cf dobutamine.
 - Good with load induced RV failure as it ↓pulmonary artery resistance
 - Main use is in chronic failure – its role in acute failure and shock is uncertain but promising. No trials in ICU
 - Loading dose 12 – 24 mcg/kg/min over 10 mins (avoid if hypotensive) followed by 0.1 mcg/kg/min for 24 hrs. In severe failure no loading dose and low dose infusion: 0.05 µg/kg/min. If tachycardia consider low dose of short acting β-blocker
 - Pharmacokinetics are complicated, in patients with multiple organ dysfunction they are unclear: short acting drug with long acting metabolites converted in the ?gut, kidney and bowel clearance
 - Has a long-lasting metabolite which results in any improvement being sustained for several weeks
 - In canine models is associated with less infarct size than milrinone, and some suggestion that pre-bypass administration limits peak troponin. However, given the cost (\$1,500 - \$3,000 per day) only used as a rescue therapy
 - SE: hypotension and headache. Contraindicated in LV outflow tract obstruction, severe renal or hepatic failure, severe hypotension/tachycardia, or history of torsade
- For pressor resistant high output shock resistant to noradrenaline and hydrocortisone, consider terlipressin or methylthioninium chloride (**methylene blue** - inhibits NO-cAMP pathway. Use only reported in a few small case series. Dose 1 – 2 mg/kg over 15 – 30 mins)

- Digoxin: See Antiarrhythmic Drugs, page 148

Vasodilators

- Glyceryl Trinitrate:
 - Needs non-PVC giving sets (although studies used PVC sets so may overestimate doses)
 - Start at 5 ml/hr and titrate, 0.5 – 10 mg/hr of 1 mg/ml
 - Causes vasodilation and greater venodilation. Reduces preload and afterload
 - May worsen oxygenation due to ↑shunting
 - Increased effect in severe AS and with sildenafil
- Nitroprusside:
 - Nitric oxide generating → potent vasodilation
 - 0.3 – 1.5 µg/kg/min
 - Cardiac output and contractility usually stable
 - May ↓PaO₂ due to changes in pulmonary vasculature
 - Causes cerebral dilatation → ↑ICP. May cause ileus
 - Risk of cyanide toxicity ↑ by hypothermia, malnutrition, B12 deficiency and renal or hepatic impairment. Signs are ↑HR, dysrhythmias, hyperventilation, sweating, metabolic acidosis. Treatment: stop the infusion and give sodium thiosulphate. See Specific Therapy for Poisons, page 264
 - Not compatible with anything else ⇒ don't piggy back. Protect from light
 - Small changes can have large effects ⇒ go slow

Management of Sepsis

- See also Sepsis in Pregnancy, page 321
- Models of Sepsis over time:
 - Bad bugs... to
 - It's all about the host response... to
 - Wide variation between host responses (due to genetics). We have no predictors of favourable response to sepsis, only bio and genetic markers of poor outcome. Perhaps it's about using biomarkers to target management
- Pathophysiology:
 - Is incredibly complex and variable
 - Receptors (such as Toll-like receptors) initiate cellular responses. Can respond to microbial ligands and sterile injury
 - Cytokine release + complement + activation of coagulation → vasodilation + ↑CO (despite ↓contractility and hypovolaemia due to ↑capillary permeability)
 - Mediated by:
 - Activated ATP sensitive K channels → K efflux → membrane hyperpolarisation → ↓Ca entry into vascular smooth muscle
 - ↑NO synthase in vascular smooth muscle and endothelium → ↑nitric oxide
 - Relative deficiency of endogenous vasopressin
 - Relative adrenocortical deficiency
 - DO₂ is supra-normal but outweighed by increased VO₂
 - Genetic determination of host defences correlates to mortality

Definitions of Sepsis

- Usual definitions:
 - Based on Bone et al, Chest 1992 (ie old).
 - SIRS: Two or more of:
 - Temp < 36 or > 38
 - Pulse > 90
 - RR > 20, PaCO₂ < 32 or ventilator dependence
 - WBC > 12, < 4 or >10% band forms
 - Sepsis = strongly suspected or proven source of infection, and SIRS
 - Severe sepsis = Sepsis and dysfunction of one end organ (eg hypotension) – one of CVS, respiratory, renal, neurological, hepatic or coagulation. Gut and endocrine are more difficult to objectively assess
 - Septic shock = Hypotension after fluids (or on inotropes) + sepsis. Mortality 30 – 50%. Outcomes in Australia and NZ in severe sepsis, 27% died in ICU, 37% died in hospital. See Finer et al, ICM 2004

- Problems with these definitions:
 - Not specific: lots of non-infectious conditions cause SIRS. Infection may be present but not the cause
 - Not sensitive: Minor infection (eg flu) can cause SIRS
 - What we are still looking for is a definition that encapsulates a dysregulated host response in which the immune response is causing disproportionate organ damage
- Surviving Sepsis criteria for sepsis: Infection, and “some of the following”:
 - General variables: fever > 38.3 , hypothermia (core temp < 36), pulse > 90 or more than 2 SD above normal for age, tachypnoea, altered mental state, significant oedema or positive fluid balance > 20 ml/kg over 24 hr, hyperglycaemia (glucose > 7.7) in the absence of diabetes
 - Inflammatory variables: WBC > 12 or < 4 or $> 10\%$ immature forms, CRP or procalcitonin > 2 SD above normal
 - Hemodynamic variables: Hypotension: SBP < 90 , MAP < 70 , or an SBP decrease > 40 or less than two SD below normal for age. ~ 80 are peripherally vasodilated (peripherally warm), 20% are “cold” sepsis. Opposite in kids – they’re more commonly shut down.
 - Organ dysfunction variables:
 - Hypoxaemia: PF ratio < 300
 - Acute Oliguria: urine output < 0.5 ml/kg/hr for at least 2 hours despite adequate fluid resuscitation
 - Creatinine increase > 44.2 $\mu\text{mol/L}$
 - Coagulopathy: INR > 0.5 or aPPT > 60
 - Ileus (absent bowel sounds)
 - Thrombocytopenia: platelets < 100
 - Hyperbilirubinaemia: total bilirubin > 70
 - Tissue perfusion variables: hyperlactataemia > 1 mmol/L
 - Decreased capillary refill or mottling
- Surviving Sepsis criteria for severe sepsis: Any of the following thought due to infection
 - Sepsis-induced hypotension
 - Lactate above upper limits or normal
 - Urine output < 0.5 ml/kg/hr for 2 hours despite adequate fluid resuscitation
 - Acute Lung Injury: P/F < 250 in the absence of pneumonia, < 200 in the presence of pneumonia
 - Creatinine > 176.8 $\mu\text{mol/L}$ (2.0 mg/dl)
 - Bilirubin > 34.2 2 mg/dl
 - Platelets < 100
 - INR > 1.5

Framework for Managing Sepsis

- Recognise sepsis
- Obtain appropriate specimens
- Commence antibiotics
- Look for signs of organ dysfunction
- Resuscitate
- Drain collections
- Set targets
- Monitor for improvement
- Escalate if needed

Surviving Sepsis Guidelines

- Strengths:
 - Compiled by an international panel of experts
 - Uses GRADE process for guideline development (assessing quality and strength of recommendations separately)
 - Draws together all relevant literature
 - Focuses future research
- Criticisms of the original guidelines include:
 - Strength of evidence: more than 50% of recommendations level E, only 5 level A
 - Sepsis is very broad – can you have a guideline for all cases?
 - Still includes a subjective judgement on what’s important
 - Extrapolation of evidence from non-sepsis studies (eg tight glycaemic control extrapolated from a study of surgical patients)

- Includes bundles (eg for resuscitation) where the evidence for components of the bundle is scant
- Early goal directed therapy based on Rivers Study which is controversial
- Steroid recommendations controversial
- Vasopressor preference grade D. Doubts over inclusion of Dopamine
- Significant omissions: eg selective digestive decontamination
- Industry sponsorship may bias recommendations
- Concern that recommendations become the “standard of practice” exposing clinicians to litigation if they deviate from them
- See Hicks et al, Surviving Sepsis Campaign: An assessment by the Australian and New Zealand Intensive Care Society, Anaesthesia and Intensive Care, Mar 2008

2012 Guidelines

- CCM Feb 2013, Dellinger et al, developed using GRADE system
- Surviving Sepsis Care Bundles:
 - To be completed within 3 hours:
 - Measure lactate level
 - Obtain blood cultures prior to ABs
 - Administer broad spectrum ABs
 - Administer 30 ml/kg crystalloid for hypotension or lactate > 4
 - To be completed within 6 hours:
 - Apply vasopressors for MAP < 65 not responsive to fluids
 - If persistent MAP < 65 or lactate > 4 measure CVP and ScvO2
 - Remeasure lactate if originally > 4

Bold = Strong recommendation. Normal = weak recommendation

Level (Quality of Evidence)	A (High)	B (Moderate)	C (Low)	D (Very Low)
Initial Resuscitation			Protocolised, quantitative resuscitation if hypotension after fluid challenge or lactate > 4, targeting CVP 8 – 12, MAP > 65, UO > 0.5 and CV sats > 70%	
Infection Management		Antibiotics within 1 hour of recognition of septic shock or severe sepsis without shock. Empiric combination therapy for 3 – 5 days only. Oral chlorhexidine to reduce VAP. SOD and SDD to reduced VAP “where this methodology is found to be effective”	Blood cultures before ABs with 1 drawn percutaneously and 1 from each vascular access device (unless inserted < 48 hours previously)	
Fluid Therapy		Crystalloids as the initial fluid. Not HES fluid	Albumin when patients require “substantial amounts” of crystalloids	
Vasopressors/ Inotropes	Don’t use dopamine for renal protection	Noradrenaline is first choice of vasopressor, Adrenaline when a 2 nd agent is needed	Target MAP > 65. Dopamine as an alternative vasopressor only in highly selected patients (low risk of tachyarrhythmias or bradycardia). Dobutamine to 20 mcg/kg/min in	

			addition to vasopressors if myocardial dysfunction or hypoperfusion despite adequate filling and MAP	
Steroids		Not using ACTH stimulation to identify patients to receive steroids	200 mg hydrocortisone/day only if fluids and vasopressors are able to restore haemodynamic stability	No steroids if no shock
Blood Products		Transfuse for Hb < 70, targeting 70 – 90. No IVIg		Prophylactic platelets if < 10, < 20 with high risk of bleeding, < 50 for active bleeding or procedures
Sedation		Minimise sedation		
Ventilating ARDS	Tidal volume 6 ml/kg (vs 12 ml/kg). Use a weaning protocol with regular spontaneous breathing trials. No Pulmonary artery catheter for SEPSIS induced ARDS	Plateau pressure < 30. Use PEEP. Head of bed 30 – 45°. Prone positioning if PF ratio < 100	Higher rather than lower PEEP for moderate or severe ARDS. Recruitment manoeuvres. Conservative rather than liberal fluid strategy for established sepsis induced ARDS who do not have tissue hypoperfusion	
Glucose control	Protocolised management of BSL > 180 mg/dl		Monitor BSL every 1 – 2 hours till stable, then every 4 hours	
Renal		Continuous and intermittent renal replacement are equivalent		
VTE prophylaxis	If CrCl < 30 use Dalteparin or UFH	Patients should receive prophylaxis with LMWH or UFH BD	Treat with a combination of drugs and pneumatic compression devices	
Stress Ulcer Prophylaxis		H2 or PPI for those with bleeding risk facts. Those without risk factors should not receive prophylaxis		PPIs are better than H2RA

Early Goal Directed Therapy in Sepsis

- See also:
 - Fluid Resuscitation, page 40
 - Threshold for **Red Blood Cells**, page 301
- NEJM 2001: Manny Rivers trial
 - 263 patients in single centre
 - Protocolised resuscitation with lots of patients with diabetes and poor hearts
 - Treatment arm cared for by Rivers (who worked for Edwards Life Sciences), control arm standard treatment
 - Endpoint was in-hospital mortality
 - Aggressive replacement within 6 hours + targeting ScvO₂ > 70% + Hb > 10 + UO > 0.5 – 1 ml/kg/hr

- Targeting fluids to CVP of 8 – 12, ↓MAP then noradrenaline, ↑MAP then GTN
- 28 day mortality from 46.5 to 30.5% - NNT to prevent death 6 - 8
- Issues:
 - High Hb level contradicts TRICC Study (in young healthy adults)
 - An ScvO₂ value > 70 is not necessarily reassuring in patients with established hyperdynamic shock as this may reflect an inability of the tissues to extract and utilise oxygen. ScvO₂ may be more useful in cardiac surgery where the problem may be more obviously ↓CO rather than dysoxia
 - Issue is generalisability: poor population, mainly normotensive with high lactate (very unusual) with a high mortality baseline with multiple interventions tested at the same time. (Aust/NZ ~ 20% for sepsis)
 - MAP > 65 is poorly established as an appropriate target (based on Le Doux, Crit Care Med 2000, 10 patients in each arm)
- Incorporated into surviving sepsis guidelines, current recommendation IC. Supported by a Chinese multicentre study
- The problem: no one does EGDT as described by Rivers. Use of the protocol leads to more fluids, more vasoactives and more blood transfusion than otherwise
- Recent trials:
 - ARISE (Australasian Resuscitation of Sepsis Evaluation): CTG trial. NEJM, Oct 2014. RCT of 1600 patients in 51 centres, treated as standard practice or goal directed therapy (which involved insertion of a central line and ICU care). EGDT group received more fluid, more vasopressors (66 vs 58%), more transfusion (13 vs 7%), more dobutamine (15 vs 3%). No difference in mortality – 18.6 vs 18.8%
 - PROMISE: UK
 - ProCESS: US, NEJM 2014. Patients in 31 US ED departments randomised to protocolised EGDT meeting sepsis criteria after 1 litre fluid, protocolised standard therapy without CVL, inotropes or transfusion, or stand care. N = 1341. 60 day mortality 21 vs 18.2 vs 18.9%. EGDT got more fluid and vasopressors and meet MAP targets earlier. Change in enrolment size mid-course from 1950 to 1350 due to observed mortality less than predicted aimed to preserve the same relative risk reduction. Odd!
 - 1500 patients each. Protocols aligned. Using continuous ScvO₂ monitoring
- TOE guided assessment of fluid loading vs “standard” fluid resuscitation protocols suggests poor agreement between echo and standard haemodynamic surrogates (CCM 2012)
- Single centre RCT in Boston showed equivalence of ScvO₂ and lactate clearance (targeting ↓10% in lactate every 2 hours) guided resuscitation. Is it attention to and completion of resuscitation that’s important, not how it’s measured?

MAP targets in Sepsis

- See Russell’s editorial, NEJM 2014. Gut O₂ delivery falls first with ↓MAP. Cerebral blood flow reaches a critical point at ~ 50 mmHg. Chronic HTN shifts cerebral autoregulation up, anti-hypertension treatment shifts it back toward normal. Need to balance ischaemia from ↓MAP with ischaemia from too much vasoconstriction
- MAP > 65 is poorly established as an appropriate target (based on Le Doux, Crit Care Med 2000, 10 patients in each arm)
- Beloncle et al, CCM 2013. Trial in pigs given faecal peritonitis induced shock, target of Map 50 – 60 vs 75 – 85. The lower group had ↑AKI, the higher group required ↑fluid and noradrenaline
- SEPISPAM Study, Asfar et al, NEJM 2014. French study n = 776 with septic shock randomised to MAP 80 – 85 vs 65 – 70. No difference in 28 day mortality (36.6 vs 34%). More AF in the high target group. In those with prior HTN, more RRT in the low group but not ↑mortality (Powered at 45% 28 day mortality)
- Prospective, observational study of the association between MAP and progression of AKI in 423 patients found progression of AKI was associated with ↓MAP, Poukkanen, Crit Care 2013

Antibiotics in Sepsis

- Influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting, Ibrahim et al, Chest Jul 2000
- Roberts, Kumar, Time to Appropriate Antibiotic Administration is a critical determinant in pneumonia-associated septic shock, Chest 2004
- Kumar, Roberts, Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock, Crit Care Med, 2006. Retrospective Cohort study of 2731

patients in 14 ICUs treated for septic shock. Each hour of delay in antibiotics was associated with ↓ in survival of 7.6%

- Kumar et al, Chest 2009, Initiation of inappropriate antimicrobial therapy results in a five-fold reduction of survival in human septic shock. Key message: start empiric ABs broad and then de-escalate

Corticosteroids in Septic Shock

- Possible mechanisms of action:
 - Treatment of deficiency
 - Effect on immune system (eg via nuclear factor kappa β)
 - Up-regulation of receptors for vasopressors such as nor-adrenaline
 - Possible interaction with vasopressin
- *Summary:*
 - Reduces shock duration – no clear improvement in mortality
 - Adverse effects: ↑glucose, ↑fungal infection, myopathy, poor wound healing
 - No observed increase in: GI bleeding, super-infection, acquired neuromuscular weakness
- A while back, large doses (eg 30 – 120 mg/kg of methylprednisolone) were used → haemodynamic improvement but ↑mortality (?due to ↑infection)
- Relative adrenal insufficiency (RAI):
 - Now replaced by term Critical Illness Related Steroid Insufficiency (CIRST)
 - Controversial concept
 - Increase in plasma cortisol of ≤ 9 mcg/dl 60 mins after 250 mcg of corticotropin. Doubts about validity of using plasma cortisol and the Synacthen test. Most cortisol is bound to corticosteroid binding protein. Usual test is total cortisol. Free varies considerably in critical illness. Need to assess free cortisol vs outcome (hard to do). Unknown how this correlates with intracellular levels
 - Insufficient cortisol for presumed requirements of stress – but patients with higher cortisols have higher mortality
 - Low response to stimulation test → worse mortality
 - Does it correlate with outcome or contribute to it?
- JAMA Aug 2002: Annane et al: Effect of treatment with low doses of hydrocortisone (50 mg QID) and fludrocortisone on mortality in patients with septic shock. Multicentre trial with 300 patients with > 1 hour fluid or vasopressor refractory shock in the last 8 hours. No difference in treatment vs placebo, but 10% mortality reduction in patients with RAI ($p = 0.02$). Complicated by use of etomidate
- CORTICUS (Corticosteroid Therapy of septic shock, NEJM 2008, Sprung et al):
 - Multi-centre trial. 499 patients with > 1 hr fluid or vasopressor refractory septic shock (SBP < 90) in the last 72 hours. 50 mg hydrocortisone for QID for 5 days then taper.
 - Faster resolution of shock in those whom shock reversed. More hyperglycaemia, infection and hyponatraemia
 - No difference in 28 day mortality in whole group, or in the subgroup (46%) with no response to a corticotropin test. Shock reversed more quickly, more super-infections, hyper-glycaemia, hypernatraemia
 - Criticisms: Under-powered (only recruited 500 of planned 800 patients). Low death rate in control group – was there selection bias (patients only entered if they weren't too sick, cause if they were the docs wanted to give them steroids)
 - Annane et al had sicker patients by SAP II score – the ones most likely to benefit
- COITSS (Corticosteroids and intensive insulin), JAMA 2010
- ADRENAL trial by ANZICS starting 2012
- Steroids in Pneumonia: Dexamethasone and Length of Hospital Stay in Patients with community acquired pneumonia, Meijvis et al, Lancet 2011. ↓LOS but no change in survival or other outcomes with addition of steroids to antibiotics
- Of benefit in pneumococcal meningitis

Selective Gut Decontamination

- A prophylactic strategy to prevent or minimise nosocomial infection from endogenous organisms.
- Definitions:
 - SDD: Selective Digestive Tract Decontamination
 - SOD: Selective Oral Decontamination (no IV or non-absorbable Abs)
- Introduced in 1984
- Aims to eradicate potentially pathogenic aerobic microbes from the mouth and stomach while preserving the indigenous anaerobic flora to prevent overgrowth of resistant bacteria or yeasts

- Targets include Staph aureus, E Coli, C albicans, and G-ives (Klebsiella, Pseudomonas, Acinetobacter) that colonise individuals when critically ill
- Hypothesised that gut hypoperfusion promotes bacterial translocation → system infection with pathogenic G-ive bacteria
- Two components to most regimes:
 - Topical non-absorbed antibiotics given orally and/or NG: eg polymyxin E, tobramycin, amphotericin B
 - Parenteral antibiotics: eg cefotaxime or cefuroxime for 4 days
- Evidence:
 - Conflicting evidence –60 RCTs to date and 11 meta-analyses (most showing benefit). Some meta-analysis support it, but concern it will promote resistance (Meta-analysis of 64 studies shows no ↑ in resistance, Daneman et al, Lancet Infectious Diseases 2013)
 - A large trial (of oral colistin, tobramycin and amphotericin B, de Jonge et al, Lancet 2003) showed reduced G-ive infection and ↓mortality
 - de Smet, NEJM 2009. Cross-over trial using cluster randomisation in 13 ICUs in the Netherlands of selective oral decontamination (SOD) vs SDD (Selective decontamination of the digestive tract) involving 5939 patients with expected ventilation > 48 hours. IV cefotaxime and oral tobramycin, colistin and amphotericin B in the stomach and mouth, vs only drugs in the mouth. Reduced mortality by 3.5% without no emergence of resistant or ↑rate of C difficile
 - Meta-analysis: BMJ April 2014: SDD 0.74 odds ratio of mortality, SOD: 0.85 odd ratio of mortality, Oral chlorhexidine 1.25 odds ratio of mortality
 - Oostdijk et al, JAMA Oct 2014, Cluster randomised cross over trial in 16 Dutch ICUs, comparing 12 months SOD and 12 months SDD in ~ 12,000 patients with an expected ICU LOS > 48 hours. Both regimes had colistin, tobramycin and amphotericin B. SDD also have 4 days of IV broad spectrum cephalosporin. No difference in 28 day mortality. SDD had lower rectal carriage of antibiotic resistant bacteria and ICU acquired bacteraemia (5.6 vs 11.8%), but a greater gradual increase in amino-glycoside resistant G-ive bacteria
- Efficacy and safety is only shown in ICUs with a low prevalence of MRSA and VRE (eg in the Netherlands). In these settings, SDD may decrease G –ive colonisation, pneumonia and ICU/hospital mortality
- ANZIC CTG planning a very large cluster RCT in Australia, NZ, UK and Canada randomising ~ 100 ICUs using a protocol similar to the Dutch protocol of oral Tobramycin & colistin, with nystatin instead of amphotericin, and with 4/7 of an IV AB (which most are already on for therapeutic reasons)

Other Treatments for Sepsis

- See also:
 - Nutrition and Specific Diseases, page 345
 - Intensive Insulin Control, page 313
- High Volume Haemofiltration: Suggestion that cytokine removal (in ultrafiltrate and sticking to the filter) improves outcome at high doses (eg 45 ml/kg/hr) but no RCT.
- Some evidence of continuation of **statins**:
 - See Tieyeh et al, Arch Int Med, 2009. Meta-analysis suggests benefit but heterogeneity of trials and infections and ?publication bias. ICU retrospective studies suggest benefit (Gao et al, Brit J or Anaesthesia, 2008)
 - STATInS Trial of atorvastatin in severe sepsis. Phase 2B RCT with IL-6 as surrogate outcome. Prior statin use → ↓inflammation. De novo use did not affect IL-6 (Am J Resp & Crit Care Med 2013)
 - Papazian, JAMA 2013, Simvastatin as adjuvant treatment for VAP, 300 patients in French ICUs. Stopped early for futility, de novo statins may be harmful
 - NEJM May 2014, RCT of rosuvastatin vs placebo in mechanically ventilated patients with ARDS. Stopped at 645 of 1000 patients for futility
 - McAuley, NEJM Oct 2014, RCT N = 540 or simvastatin or placebo in patients with severe ARDS. No difference in ventilator free days or organ-failure free days
- Meta-analysis of small studies suggests evidence for IVIg. Large trial needed
- 70 odd studies of TNF and other blockers – none positive
- B blockade: Esmolol for heart rate control in septic shock in patients on noradrenaline after 24 hours (ie sick). Open label phase 2 trial of 77 patients → ↓noradrenaline, ↑CI, ↑pH, ↓lactate. Mortality 49 vs 84%
- Telactaferon is an anti-inflammatory molecule found in secretions, breast milk etc. Morality benefit in phase 2 trial given enterally in sepsis (?effect on translocation).....
- Activated Protein C/Xigris:

- In sepsis, inflammatory cytokines → ↓thrombomodulin. Normally thrombomodulin bound to thrombin converts inactive to activated protein C.
- Recombinant endogenous component of the anti-coagulation system
- Possible mechanisms include:
 - Improved microcirculation via effects on anticoagulation (Inhibits factors Va and VIIIa, promotes fibrinolysis by indirectly inducing plasmin activity)
 - Anti-inflammatory effects
 - Inhibition of endothelial cell apoptosis
- PROWESS: Bernard et al, NEJM 2001. Multicentre trial. 6.1% ARR in 28 day mortality in severe sepsis and MODS, but ↑ risk of bleeding. Quicker resolution of cardiovascular and respiratory organ dysfunction. No benefit in APACHE < 25 or kids
- ADDRESS and RESOLVE: no mortality benefit and no improvement in organ failure. ↑risk of intra-cerebral bleeding
- Cochrane Review: insufficient evidence to support its use and ↑risk of internal bleeding
- PROWESS SHOCK (2012): negative trial of Xigris vs placebo with non-significant ↑ in mortality for treatment arm – drug withdrawn
- Last indication before being withdrawn was in adult sepsis with APACHE > 25
- SE bleeding, expensive

Inflammatory markers

- Over 170 biomarkers of sepsis have been proposed for diagnosis and prognosis (incl IL-6)
- Potential benefits:
 - ↓antibiotic use, ↓resistance
 - ↓LOS
 - ↓Cost
- Disadvantages:
 - Lack of availability, non-standardised assays and cut-off value limit their practical use
 - Biomarkers don't tell you about the site of infection/inflammation, and cannot replace a good history, exam, and investigations
 - Tests are expensive and assays are not standardised
- Perhaps of most help when you're confused
- Suggested to differentiate infectious from non-infectious fevers:
 - CRP
 - Procalcitonin:
 - Synthesised by thyroid C cells, but in sepsis has extra-thyroidal origin from inflamed/infected tissue
 - Rapid and easy test to perform. Result in 30 mins compared to 24 hours for blood cultures
 - Also rises in non-septic SIRS, and immediately after surgery and trauma
 - Doesn't rise in viral infection, autoimmune disorders and immunocompromised patients
 - Data comparing to CRP are conflicting
 - Several trials show trend to ↓antibiotic exposure by monitoring procalcitonin in ICUs (eg stop if daily measurements drop below 0.25):
 - ProRata Trial, Lancet Jan 2010 (~ 600 patients in *unblinded* 8 centre RCT, usual care vs protocol driven cessation of ABs, trend to ↓mortality in procalcitonin group, significantly less days of ABs)
 - Proguard Trial (CCM 2011): Meta-analysis, not yet sufficient data to exclude a rise in mortality from biomarker guided therapy
 - Hochreiter et al, Critical Care, 2009, showed ↓duration of ABs with no ↑adverse effects
 - Use caution in European Studies: standard AB courses are up to 14 days. Therefore there is lots of scope to stop early. In Australasia where standard courses are 5 – 7 days, there may not be enough unnecessary length of treatment to justify biomarker testing
 - Many studies in this area of how to guide therapy and differentiate between viral and bacterial infection. Need further research to define different patient groups, which testing kits, and the risks of adverse outcomes in false negative tests
- Lipopolysaccharide binding protein
- Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1)
- Expression of the high-affinity immunoglobulin-Fc fragment receptor I (FcγRI) CD64 on neutrophils (polymorphonuclear [PMN] CD64 index)

- Various composite bio-scores of these have been proposed to detect sepsis – but none have measured how many cases of sepsis would otherwise be missed
- Troponin: Correlates with LV and RV dysfunction in sepsis, and correlates with mortality (CCM April 2014)

Multiple Organ Dysfunction Syndrome

- MODS = presence of altered function involving two or more organ systems in an acutely ill patient such that homeostasis cannot be maintained without intervention
- Didn't exist 50 years ago – patients couldn't be kept alive long enough for sequential organ failure to occur
- Downward spiral: SIRS → Frank organ failure → death
- “Dysfunction” preferred to “failure”: organ is not capable of maintaining homeostasis
- Differential:
 - Infectious
 - Non-infectious:
 - Mechanical ventilation
 - Aspiration
 - Surgery
 - Burns
 - Reperfusion syndromes
 - Visceral ischaemia
 - Pancreatitis
 - Hepatic failure
 - Cardiopulmonary bypass
 - Massive transfusion
 - Transfusion reactions
 - Hyperthermia
 - Malignancy

Pathophysiology of MODS

- Tissue injury 2nd to hypoxia, due to:
 - acute lung injury
 - ↓cardiac output due to:
 - ↓preload
 - ↓contractility mediated by NO, IL-1 β and TNF- α
 - Microcirculatory dysfunction due to abnormal distribution of blood due to:
 - NO-mediated vasodilation
 - Functional shunting
 - Obstruction by microthrombi (+/- endothelial oedema): Activation/amplification of tissue factor pathway → ↑thrombin → ↑fibrin
 - Mitochondrial defective oxygen utilisation (“tissue dysoxia”):
 - NO and reactive oxygen species inhibit the mitochondrial respiratory chain
 - Mitochondria also modulate Ca levels and synthesise haem and sulphur centres
 - MODS outcome has strong inherited component. ?Due to variations in mitochondrial DNA
- Inflammation: activation of circulating immune cells (especially natural killer, T and B cells and macrophages), endothelium, multiple mediator cascades releasing cytokines
- Molecular mechanisms: cell/antigen products → activate toll-like receptors (evolutionary conserved receptors of innate immune system expressed by monocytes and macrophages) → intracellular signalling (notably through nuclear factor κ B)
- Endothelial dysfunction:
 - Triggered by antigen, hypoxia, hypoperfusion, ↑temperature, acidosis, ↑glucose
 - Alters cell function and transcription → ↑cell surface adhesion molecules → leukocyte rolling/adhesion/transmigration, cytokine mediated positive feedback and cellular recruitment
- Regional maldistribution of blood flow:
 - Following restoration of normal arterial blood pressure, there may still be significant maldistribution of blood flow in vital organs (“Cryptic Shock”)
 - Inhomogeneity in the regional circulation and microcirculation plays a crucial role in the pathogenesis of organ dysfunction

- Measures of regional circulation have shown useful prognostic value, data that using it to guide therapy is sparse

Commonly Affected Organs

Organ	Clinical features	Physiological/Biochemical changes
Neurological	↓LOC	Abnormal EEG suggesting metabolic encephalopathy
Cardiovascular	SBP < 90 or < 40 from baseline, tachycardia > 90, arrhythmia, oedema	↓SVR, myocardial depression
Respiratory	RR > 20, desaturation, cyanosis	PaCO ₂ < 32, ↓PaO ₂ /FiO ₂ , ↑work of breathing, ↑lung water
Renal	UO < 0.5 mg/kg/hr	↑creatinine, urea
GI	Abdominal discomfort and distension, large NG losses, haemorrhage	↑intestinal permeability (may → translocation of endotoxin, bacteria, other mediators), splanchnic ischaemia, ileus, acalculous cholecystitis, pancreatitis, stress ulceration
Hepatic	Jaundice, encephalopathy	↑bilirubin, ↑lactate, ↑ or ↓ glucose (↑ or ↓gluconeogenesis, ↓clearance)
Haematological	Haemorrhage, rash	↑ or ↓WBC, DIC (coagulopathy and platelets < by 50% over 3 days or < 80)

Management of MODS

- Early identification of organ dysfunction
- Good supportive care (all ↓mortality):
 - Fluid resuscitation +/- inotropes/vasopressors
 - Mechanical ventilation with lung protective strategies
 - Renal replacement
- Prevention of secondary insults:
 - Nosocomial infection
 - Prevent over-sedation
 - Pressure area care
 - Head up
 - Early enteral nutrition
 - Stress ulcer and DVT prophylaxis
- Research findings:
 - No therapeutic interventions specifically directed at MODS have altered outcome
 - Most research in MODS due to sepsis and unclear whether it can be extrapolated to non-septic MODS
 - Making a normal or supra-normal physiologic state the therapeutic target when the homeostasis is profoundly disrupted may be detrimental
- Other strategies:
 - See Intensive Insulin Control, page 313
 - Low dose glucocorticoids: interest in “replacement doses” of steroids in SIRS with some evidence of benefit. Steroids inhibit NF-κB and iNOS induction. See Corticosteroids in Septic Shock, page 54
 - Manipulation of Coagulation Cascade: No benefit from antithrombin III treatment or Activated Protein C
 - Nutrition: ω3 fatty acids may reduce release of pro-inflammatory mediators. See Nutrition and Specific Diseases, page 345
 - High volume haemofiltration: see High Volume Haemofiltration, page 195

Outcome

- Number of organs affected and the duration of dysfunction stratifies mortality

- Likely better outcomes over time – attributed to better supportive care (not treatments targeted at MODS)
- After 7 days, illness (& SOFA score) on admission becomes less important, compared with day 6.
Cardiovascular dysfunction the strongest independent predictor of death
- MODS → ↓return to work, ↓ADLs, and ↓living at home at 1 year

- For A-a gradient see Oxygen Cascade, page 25

Acid Base Disorders

- Anions = -ive, cations = +ive
- Intracellular pH is 6.8 at 37°C, extracellular pH is 7.4
- $\text{pH} = 6.1 + \log_{10} (\text{HCO}_3^- / 0.03 \times \text{PCO}_2)$

Stuart Theory

- Fluid compartments have varying concentrations of non-CO₂ generating (non-volatile) molecules with weak acid properties. In plasma they consist mainly of albumin.
- Non-volatile weak acids can be modelled as having a single anionic form (A⁻) and a single conjugate base form (HA)
- $\text{Atot} = [\text{HA}] + [\text{A}^-]$. A change in pH will shift the balance from HA to A⁻
- Strong ions:
 - Certain elements are always ionised in body fluids including: Na, K, Ca, Mg, Cl
 - This includes anions with $\text{pK}_a < 4$, eg sulphate, lactate, β -hydroxybutyrate
 - There are more strong cations than anions
 - Strong Ion Difference (SID) = [strong cations] – [strong anions] mEq/l
 - When calculated from measured strong ions in normal plasma ~ 42 mEq/l
 - $\text{SID} + \text{H}^+ - \text{HCO}_3^- - \text{CO}_3^{2-} - \text{A}^- - \text{OH}^- = 0$ (due to law of electrical neutrality)
 - Hence, in arterial blood, **pH is defined by PaCO₂, extracellular SID and extracellular Atot**
- Weak ions:
 - Total net charge of H⁺, OH⁻, HCO₃⁻, CO₃²⁻, A⁻ must always equal SID
 - However, only HCO₃⁻ and A⁻ are material – the others only exist in minute concentrations – they are the “buffer base”
 - So $\text{SID} = \text{HCO}_3^- + \text{A}^-$
 $= (\text{Na} + \text{K} + \text{Mg} + \text{Ca}) - (\text{Cl}^- + \text{Lactate} + \text{SO}_4)$ [NB organic acids are also strong ions eg ketones, alcohol metabolites, but are not usually present]
 - Rule of thumb: simply SID to Na – Cl. If < 38 then metabolic acidosis
 - A⁻ is principally Albumin (g/l) and Phosphate (mmol/l). Atot = total concentration of weak acid (an acid that doesn't completely dissociate)
- Changes in Acid-base balance:
 - At a given PaCO₂, a *falling SID or a rising Atot reduce pH*. Ie low albumin increases pH
 - Acute respiratory disturbances move data points along the prevailing PaCO₂/pH curve
 - Metabolic disturbances (altered extracellular SID or Atot) shift the entire curve up or down
 - H⁺ and HCO₃⁻ are dependent variables, responsive exclusively to PCO₂, SID and Atot
 - If **SID decreases** → ↓HCO₃⁻ → ↓pH (SID and pH move in the same direction) – effect of giving fluid with SID of 0 (either NaCl or dextrose)
 - If **SID increases** → ↑HCO₃⁻ → ↑pH – giving NaHCO₃ has a very high SID due to the Na, not the HCO₃, leading to alkalosis
- Renal involvement in acid-base:
 - Without renal function there is a progressive metabolic acidosis
 - About 60 mEq of strong anions (especially SO₄) are produced daily
 - Kidney's regulate extracellular SID via urinary SID, the principle means being tubular NH₄⁺ - which is an adjustable cation partner for tubular Cl⁻ and other strong anions
 - Kidney's also modify Atot via phosphate excretion
- Base excess:
 - = zero at pH = 7.4 and PCO₂ = 40 mmHg
 - = concentration of titratable hydrogen ion required to return the pH to 7.4 while maintaining PCO₂ at 40 mmHg
 - In vivo, BE loses its CO₂ invariance, as ions are driven between intravascular and interstitial compartments. A primary change in CO₂ shifts BE in the opposite direction
 - Standardised Base Excess (SBE) = BE calculated at Hb concentration of approximately 50 g/l, replicating the mean extracellular compartment. Hb is the predominate extracellular weak acid
 - SBE quantifies the increase in extracellular SID needed to shift the curve back to the normal position
 - Morgan's approach: standard base excess is the best metabolic index as it integrates extracellular SID and Atot, irrespective of PaCO₂

Measuring Acid-Base

- pH: glass electrode. Tube is made of pH sensitive glass across which a potential difference is generated. Measures potential difference across the electrodes
- PCO₂: Modified glass electrode. Glass pH electrode which is in contact with a thin film of NaHCO₃ solution separated from the sample by a CO₂ permeable membrane. CO₂ diffuses into the NaHCO₃ and alters the pH
- PO₂: Clark electrode or polarographic electrode. Measures current generated or the current flow across the Clark electrode, which changes with PO₂ concentration

Basic Approach

- ALWAYS CALCULATE AG, Aa, δ/δ for each question if the data is available – they put it there for a reason....
- Initially ignore derived values: HCO₃, SBE
- Is it acidosis or alkalosis
- Is it respiratory or metabolic
- Is compensation appropriate: PaCO₂ and HCO₃ will move in the same direction
- Extent of compensation. Note absent or inappropriate respiratory compensation (eg ketoacidosis with pH = 7.2 and PaCO₂ of 40 implies a respiratory acidosis as well – PaCO₂ should be 20, this person is tiring)

Compensation

- See also Normal Values in Late Pregnancy, page 317
- A normal PaCO₂ combined with an abnormal pH always represents 2 disturbances
- Metabolic compensation:
 - In respiratory disturbances, kidneys adjust extracellular SID by regulating urinary SID, primarily urinary chloride
 - Over the PaCO₂ range of 25 – 80, full compensation is possible but may take up to 5 days
 - HCO₃ compensation rules ignore the A- component of the buffer base (effective SID) concentration:
- Respiratory compensation:
 - Faster but less effective – normal pH is never regained
 - Maximal response takes 12 – 24 hours – initially driven by peripheral chemoreceptors, CSF equilibration of SID with plasma takes time
- **Respiratory :**

Δ HCO ₃ for every 10 CO ₂	Acute	Chronic
Acidosis	↑1	↑4
Alkalosis	↓2	↓5

- **Acidosis:**
 - Acute:
 - Expected $[\text{HCO}_3^-] = 24 * 0.1 * (\text{PaCO}_2 - 40)$
 - ↑1 HCO₃ for every ↑10 CO₂
 - Limit of compensation: HCO₃ = 38
 - Chronic:
 - Expected $[\text{HCO}_3^-] = 24 * 0.35 * (\text{PaCO}_2 - 40)$
 - ↑4 HCO₃ for every ↑10 CO₂
 - Limit of compensation: HCO₃ = 45
- **Alkalosis:**
 - Acute:
 - Expected $[\text{HCO}_3^-] = 24 - 0.2 * (40 - \text{PaCO}_2)$
 - ↓2 HCO₃ for every ↓10 CO₂
 - Limit of compensation: HCO₃ = 18
 - Chronic:
 - Expected $[\text{HCO}_3^-] = 24 - 0.5 * (40 - \text{PaCO}_2)$
 - ↓5 HCO₃ for every ↓10 CO₂
 - Limit of compensation: HCO₃ = 15
- **Metabolic**
 - **Acidosis:**
 - Expected $\text{PaCO}_2 = 1.5 * [\text{HCO}_3^-] + 8 \pm 2$
 - ↓12.5 CO₂ for every ↓10 HCO₃
 - Short cut: PaCO₂ = last 2 digits of pH (ie pH 7.23 ⇒ PCO₂ of 23)

- Limit of compensation: $PCO_2 = 15$
- **Alkalosis:**
 - Expected $PaCO_2 = 0.6 * [HCO_3^-] + 40$
 - $\uparrow 7 CO_2$ for every $\uparrow 10 HCO_3$
 - Short cut: $PaCO_2 = \text{last 2 digits of pH}$
 - Limit of compensation: $PCO_2 = 55$
- SBE rules: (SBE in mmol/l)
 - Acute respiratory acidosis and alkalosis: $\Delta SBE = 0 * \Delta PaCO_2$
 - Chronic respiratory acidosis and alkalosis: $\Delta SBE = 0.4 * \Delta PaCO_2$
 - Metabolic acidosis: $\Delta PaCO_2 = \Delta SBE$
 - Metabolic alkalosis: $\Delta PaCO_2 = 0.6 * \Delta SBE$

Anion Gap

- Anion gap (mEq/L) = $Na - (Cl + HCO_3)$. Normal 10, range 6 – 15 mmol/L
- Its primary purpose is scanning for unmeasured strong anions; its sensitivity and specificity is low. Quantifies unmeasured anions – unmeasured cations
- Normally, most of the AG consists of the negative charge on albumin and PO_4
- Severe pH disturbances act via the A- component
- Hypoalbuminaemia may mask an increased concentration of gap anions by lowering the value of the anion gap. Albumin corrected anion gap (Figge et al, CCM, 1998):
 - Devised to correct for variations in plasma albumin
 - $AGc = AG + 0.25 * (40 - \text{albumin})$ [Compared to a coefficient of 0.025 for corrected Ca]

Osmolal Gap

- Scans for unmeasured osmotically active molecules
 - \Rightarrow diagnosis of intoxication as a cause of $\uparrow AG$ acidosis
 - Measured osmolality is calculated via the depression in freezing point of the sample
- Calculated osm gap = $2 * (Na + K) + \text{urea} + \text{glucose}$ [or $1.86 * (Na + K) + \text{urea} + \text{glucose}$]
- Osmolal gap = measured osm – calculated osm
- Normal is < 10
- High gap due to:
 - Normal anion gap and high osmolar gap (ie non-ionic compounds)
 - Sorbitol
 - Mannitol
 - Toluene
 - Maltose (eg Intragam, immunoglobulin)
 - Pseudohyponatraemia
 - Hypertriglyceridaemia
 - High anion gap and high osmolar gap
 - Alcohols:
 - Methanol and Ethylene glycol: see Specific Therapy for Poisons, page 264
 - Alcoholic ketoacidosis: measure ethanol and plasma β -hydroxybutyrate
 - Acetone
 - Glycerol in ketoacidosis
 - Glycine (eg TURP syndrome)
 - Radiocontrast media
 - Unknown solutes in lactic acidosis and renal failure (but not lactate itself)

Metabolic Acidosis

- Severe acidosis < 7.2
- SID is low relative to Atot
- Either:
 - Narrowing of difference between Na and Cl (relative, not absolute value of Cl is what matters) – normal AG
 - Accumulation of other anions (elevated AGc)
- Interpretation:
 - Acidosis and base deficit of < -2 may detect inadequate DO_2 , but only reflects global perfusion
 - Lactate is unreliable: measures balance between DO_2 and VO_2
- Adverse effects of metabolic acidosis:
 - \downarrow myocardial contractility, arrhythmias, vasoconstriction

- Pulmonary vasoconstriction, hyperventilation
- ↓Splanchnic and renal blood flow
- ↑metabolic rate, catabolism, ↓ATP synthesis, ↓2,3DPG synthesis (offsets ↑O₂ availability from Bohr effect)
- Confusion, bone loss, muscle wasting
- If intubation, a sudden reduction in minute volume can be lethal (removing respiratory compensation)
- Differential of severe acidosis in a 48 year old unconscious alcoholic:
 - Ischaemic bowel
 - Pancreatitis
 - Metformin induced acidosis
 - Thiamine deficiency
- Differential of a respiratory and metabolic acidosis in an unconscious person:
 - Post-arrest
 - Post-seizure
 - Near-drowning
 - Near-hanging

Working out a Metabolic Acidosis

- Calculate AG or **AGc**, if:
 - High:
 - Unmeasured anions likely → **measure osmolality**.
 - If there is no obvious cause for an elevated AGc, perform specific assays (glucose, renal function, rhabdomyolysis, L-lactate, β-hydroxybutyrate, D-lactate, salicylate)
 - Calculate osmolar gap. If high AG and high OG then ketones, lactate, ethanol, ethylene glycol, methanol, mannitol
 - Normal: measure urinary anion gap.
 - = Urine Na + Urine K – Urine Cl, normally – 20 to – 50 mmol/L
 - Cl⁻ in urine matches unmeasured NH₄⁺ (the body's way of excreting H⁺)
 - Extra-renal cause of acidosis → ↑NH₄⁺ in urine to compensate → UAG more negative
 - Renal cause of acidosis → kidney is not excreting NH₄⁺ → UAG less negative
 - Low:
 - Lab error: chloride overestimation (especially when HCO₃ is very high), Na underestimation
 - ↓Anions (other than HCO₃ and Cl): Low albumin if not corrected for this
 - ↑Cations other than Na: lithium, Ca, Mg, IgG, myeloma
- Compare AGc elevation with SBE or [HCO₃]. A rise in AGc should be accompanied by a fall in [HCO₃]. If not, then dual disorders. Confirm with δ/δ ratio

Normal AGc Metabolic Acidosis

- ie excludes ↓albumin in renal insufficiency
- H⁺ gain
 - Saline infusions: SBE rarely falls below -10. Causes acidosis as plasma tends to the effective crystalloid SID, and a metabolic acidosis by diluting Atot
 - Acid loads: TPN and NH₄Cl administration
- HCO₃ loss:
 - GI losses of SID enteric fluid:
 - More negative urinary anion gap
 - HCO₃ in diarrhoea, ascites, fistulae
 - Renal loss of HCO₃ or failure to excrete NH₄:
 - More positive urinary anion gap
 - Renal tubular acidosis: Urinary SID is inappropriately high. Disturbance in tubular Cl handling, due to ↓NH₄ production proximally (type 4, ↑K), distally (type 1, ↓K, caused amongst many other things by Toluene) or ↑proximal Cl resorption. Type 1 and 2: give HCO₃ or citrate and give K-citrate to treat hypokalaemia. Type 4: stop offending agents, treat adrenal insufficiency and/or alkali supplements of frusemide
 - Acetazolamide (carbonic anhydrase inhibitors)
 - Hypoaldosteronism (eg Addison's) → ↓H⁺ excretion. Also ↓Na, ↑K, may have renal injury send to ↓BP
 - Drug induced ↑K with renal insufficiency
- Li toxicity (ie unmeasured cations, such as Li, and hyperglobulinaemia, will ↓AG)

Raised AGc Metabolic Acidosis

- Anagram: **Left Total Knee Replacement**
- Lactic Acidosis:
 - L-lactic acidosis (types A and B)
 - D-lactic acid acidosis
 - See Lactic Acidosis, page 64
- Toxins (see Specific Therapy for Poisons, page 264):
 - Ethylene glycol (also $\rightarrow \downarrow \text{Ca}$)
 - Methanol
 - Salicylates
 - Iron
 - Paraldehyde
- Ketoacidosis:
 - Diabetic: acetoacetate
 - Alcoholic: β -hydroxybutyrate. Clues: normal sugar, high ketones (too high for starvation ketosis) and abnormal liver enzymes (less likely with DKA)
 - Starvation
 - Inborn errors of metabolism
- Late Renal failure: sulphate and other organic anions, $\uparrow \text{PO}_4$
- Others:
 - Pyroglutamic acidosis: history of paracetamol ingestion in liver dysfunction. Measure pyroglutamic acid levels
 - Myeloma IgA bands

δ/δ ratio: $\delta \text{AG} / \delta \text{HCO}_3$

- Done in high AG disorders to check for a concurrent non-anion gap component
- Rise in AG (numerator) should be matched by a fall in $\text{HCO}_3 \Rightarrow$ ratio should be $\sim 1 - 2$:
 - Eg: AG 18 (6 above 12, ie $\delta \text{AG} = 6$), expect decrease of HCO_3 to 16 (6 below 22, $\delta \text{HCO}_3 = 6$), so $\delta/\delta = 1 \Rightarrow$ no non-anion gap component
 - Not all acid gets buffered by HCO_3 in ECF so there tends to be a bigger \uparrow in AG than decrease in HCO_3 – so a value up to 2 can be normal
- Additional loss of HCO_3 (eg an additional normal AG acidosis, or concurrent respiratory acidosis) \rightarrow greater loss of HCO_3 than expected $\rightarrow \uparrow$ denominator \rightarrow lower ratio
- Unrelated gain in HCO_3 (eg a metabolic alkalosis offsetting the loss from the acidosis) \rightarrow lower denominator $\rightarrow \delta/\delta > 2$

δ/δ ratio	
< 0.4	Hyperchloraemic normal AG acidosis
0.4 – 0.8	Consider combined high AG and normal AG acidosis, but note that the ratio is often < 1 in acidosis associated with renal failure
1 – 2	Usual for uncomplicated high-AG acidosis. Lactic acidosis: average value 1.6. DKA more likely to have a ratio closer to 1 due to urine ketone loss (esp if patient not dehydrated)
> 2	High anion gap metabolic acidosis + metabolic alkalosis. Suggests a pre-existing elevated HCO_3 so consider a concurrent metabolic alkalosis or pre-existing compensated respiratory acidosis

- Can also be calculated as a gap rather than a ratio:
 - $\delta \text{AG} - \delta \text{HCO}_3$ (difference between the rise in AG and the fall in HCO_3)
 - $> 6 \Rightarrow$ metabolic alkalosis + \uparrow AG metabolic acidosis
 - $< -6 \Rightarrow$ normal AG + raised AG metabolic acidosis

Lactic Acidosis

- Blood lactate $> 5 \text{ mmol/L}$ and $\text{pH} < 7.35$
- May be masked by concurrent alkalosis
- Anion gap is only 50% sensitive to detecting lactic acidosis. Compounded by many things, especially \downarrow Albumin
- Clinical use:

- Even small increases associated with worse outcomes. \uparrow Lactate predicts mortality; 83% mortality if lactate > 10 – although completely depends on underlying condition (severe lactic acidosis is a normal finding in healthy athletes during exercise)
- Not just absolute level, but also rate of fall predictive (fast is good, slow is bad)
- In general, we don't understand lactic kinetics, nor how to respond
- Lactate gap: bedside lactate (lactate oxidase method) – laboratory lactate (lactate dehydrogenase method). Seen with ethylene glycol toxicity, due to interference with the bedside (blood gas machine) assay but not the laboratory test
- Pathophysiology:
 - Lactate produced at 0.8 mmol/kg/hr and metabolised in liver (up to 700 mmol per day), kidneys, muscle, brain and red blood cells
 - Pyruvate + NADH + H⁺ \leftrightarrow Lactate and NAD⁺ (catalysed by lactate dehydrogenase)
- Lactic acid:
 - L-Lactate acidosis (more common type in ICU): hypoxia, dialysate, liver failure, sympathomimetics, thiamine deficiency
 - D-lactate: short bowel syndrome, jejunio-ileal bypass, ischaemic bowel, small bowel obstruction
- Classification (Cohen and Woods) of L-Lactate:
 - **Type A:** due to tissue hypoxia - evidence of impaired tissue oxygenation, circulatory compromise:
 - Shock, poor tissue perfusion
 - Acute hypoxaemia
 - Severe anaemia
 - CO poisoning
 - **Type B:** no hypoxia, either \uparrow production (Drugs eg SNAP, congenital d-lactic acidosis) or \downarrow clearance (hepatic impairment, hypothermia):
 - B1 (underlying disease):
 - Sepsis: Tissue hypoxia may not be the major mechanism – more due to severity of inflammatory response and hyper-metabolic state, regional microvascular and *mitochondrial dysfunction*, *excess catecholamines* \rightarrow \downarrow uptake by reducing regional hepatic flow and \uparrow production due to \uparrow glycogenolysis. (If you β -block an animal before inducing shock, the rise in lactic acid is significantly reduced)
 - Inhibition of pyruvate dehydrogenase by endotoxin \rightarrow impairment of mitochondria
 - Lung injury: pulmonary release of lactate proportional to severity of lung injury, due to anaerobic metabolism in hypoxic regions of the lung, altered glucose metabolism and direct effect of cytokines on pulmonary cells. Metabolic and respiratory acidosis may protect the lung against injury, and interventions aimed at correcting acidosis (eg hyperventilation) may be bad
 - Asthma: could be due to respiratory muscles – but severe acidosis can also occur in paralysed ventilated patients. ?Principally due to β agonists \rightarrow \uparrow gluconeogenesis, glycogenolysis, etc. Lactic acidosis does not affect prognosis
 - Cardiac bypass patients: lactic acidosis common and associated with \uparrow morbidity. ?Due to \downarrow DO₂ on pump (~ cardiogenic shock). Severity may be related to polymorphisms in cytokine genes. Worsened by adrenaline – but – as in asthma – lactic acidosis due to adrenaline doesn't alter prognosis.
 - Mesenteric ischaemia: \uparrow Lactate within an hour of induced intestinal ischaemia, correlates with mortality. Lactate is sensitive (100%) but not specific (42%) for gut ischaemia.
 - Liver failure
 - Thiamine deficiency: essential cofactor for pyruvate dehydrogenase. Test red cell transketolase
 - Malignancy: Leukaemia, lymphoma, large tumours
 - Pheochromocytoma
 - Diabetes: ketoacidosis ketones may inhibit hepatic lactate uptake
 - Hypermetabolic states (trauma, burns)
 - Increased muscle activity: seizures – no prognostic significance as rapidly cleared
 - B2 (drug or toxin): *adrenaline, salbutamol, propofol, reverse transcriptase inhibitors, ethanol* (\rightarrow \uparrow conversion of pyruvate to lactate), *methanol, ethylene glycol, paracetamol, nitroprusside, salicylates, biguanides, fructose, sorbitol, cyanide, isoniazid*
 - B3: including G6PD deficiency, deficiency of enzymes of oxidative phosphorylation, fructose 1,6 diphosphatase deficiency, pyruvate carboxylase deficiency
 - Exogenous administration: *lactate buffered fluid*
 - Management:

- Lactate is a question not any answer: exclude occult sepsis, inadequate resuscitation, localised ischaemia or cardiovascular failure
- Cardiac dysfunction is associated with, but unlikely to be caused by, lactic acid
- Stop NRTIs in HIV: hyperlactataemia in 8.3%
- Trial of titrating cardiovascular management to 2 hourly lactate showed no benefit
- Dialysis/haemofiltration
 - Peritoneal dialysis reported as effective at removing lactate
 - Bicarbonate-buffered haemofiltration is ineffective
 - If lactate already high (eg shock or liver disease) lactate-based dialysis may overload metabolic clearance \Rightarrow use bicarbonate based dialysis

Bicarbonate for Treatment of a Metabolic Acidosis

- Possible rationale for HCO_3^- use:
 - Severe acidaemia: various authorities threshold varies from 6.9 to 7.1 but no hard data and lots of variation in thresholds
 - Life-threatening hyperkalaemia an undisputed indication
 - Renal or GI loss
- In general, correction of acidaemia is achieved through correcting the underlying physiology (fluids and insulin)
- Dose of HCO_3^- to reverse a metabolic acidosis in ml = Weight (kg) * 0.3 * -SBE (mmol) [0.3 = proportion of weight that is extracellular fluid, 1 ml 8.4% HCO_3^- is 1 mmol]
- 1 mmol/kg increases SBE by approximately 3 mEq/l. It is the Na that increases SID
- Bicarbonate therapy for acidosis is controversial:
 - Evidence:
 - Never shown to be beneficial in any clinical trial
 - No evidence of use of HCO_3^- to treat acidaemia or improve cardiac contractility
 - Some evidence for use in hyperkalaemia as a temporising measure
 - Theoretical advantage for use in renal or GI loss if delta ratio is < 1
 - In paediatrics, some evidence that use associated with worse outcomes, in generally sicker patients
 - Not all studies have demonstrated \uparrow pH after HCO_3^- administration
 - Complications include:
 - Acute hypercapnea $\rightarrow \uparrow$ intracellular acidosis as CO_2 crosses cell membranes rapidly. If ventilation severely limited (eg ARDS) HCO_3^- may \downarrow pH
 - Hypokalaemia and hypernatraemia
 - Ionised hypocalcaemia ($\rightarrow \downarrow$ heart contractility)
 - Hypertonic \rightarrow acute \uparrow in intravascular volume
 - Left shift of oxygen dissociation curve $\rightarrow \downarrow$ O_2 delivery
 - Reduced complications by slow infusions, \uparrow minute volume, correct ionised hypocalcaemia
 - Consider if:
 - TCA or Aspirin overdose (see Specific Therapy for Poisons, page 264)
 - Treatment of hyperkalaemia (no trials)
 - Pulmonary hypertension and heart failure: pulmonary vasoconstriction may be exacerbated by acidosis
 - Arrhythmias in the setting of ischaemic heart disease may be worsened by acidosis
 - Consider slow bicarbonate infusion to keep pH > 7.15
- Formulations of bicarbonate:
 - Sodabcarb 8.4% (or 4.2%) solution. 8.4% solution has pH 7.8, 1000 mmol/L Na, Osmolality of 200. Hyperosmolar. Generates high CO_2 . Can cause paradoxical acidosis in the presence of a low output state. Also hypokalaemia, alkalosis and left shift of the curve. Phlebitis when given peripherally. Improves vasopressor responsiveness (but don't run in the same line as inotropes/vasopressors)
 - Carbicarb: equiosmolar combination of sodium carbonate and sodium bicarbonate. Less rise in CO_2 . More consistently increases intracellular pH. Inconsistent effects on haemodynamics. Not commonly used clinically
 - THAM: Commercially available weak alkali. Buffers H^+ ions. No CO_2 rise. Side effects include \uparrow K, \downarrow glucose, extravasation related necrosis and hepatic dysfunction

Metabolic Alkalosis

- Severe > 7.60 , $\text{HCO}_3^- > 45$ mmol/L
- High SID relative to Atot

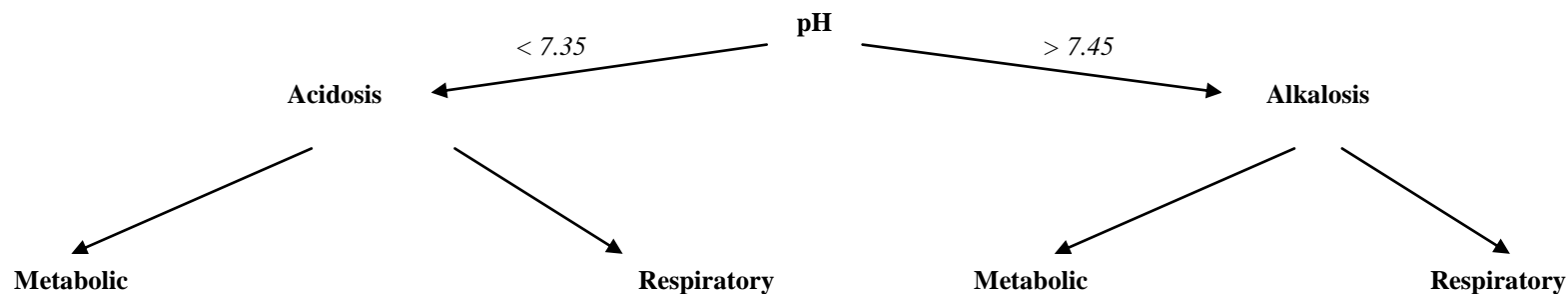
- Causes:
 - Loss of H^+
 - GI: vomiting, suctioning
 - Renal:
 - Loop or thiazide diuretics, liquorice: $\downarrow ECF \rightarrow \uparrow aldosterone + \text{high distal flow rates of Na} \rightarrow K \text{ resorption/H loss}$
 - Steroid excess: Corticosteroids, Cushing's, Conn's \rightarrow loss of H^+ in addition to Na/K effects
 - Gain of HCO_3^- :
 - Resolution of a metabolic acidosis with delayed correction of metabolic compensation (ie recently but now corrected hypercapneic alkalosis)
 - Hypercalcaemia, Milk Alkali syndrome ($\uparrow Ca$ ingestion $\rightarrow \uparrow Na$ excretion + $\downarrow PTH \rightarrow HCO_3^-$ retention)
 - Gain of high SID fluid: $NaHCO_3$ administration, Na citrate (> 8 units stored blood, plasma exchange), renal replacement with high SID fluid
 - Redistribution: Refeeding syndrome: (\rightarrow hypokalaemic alkalosis)
- Treatment:
 - Stop precipitants
 - Hydrate with NaCl (concept of saline responsive vs non-responsive, urinary Cl <20 if responsive). Turns off aldosterone stimulation due to hypovolaemia \rightarrow provides Cl for absorption and allows excretion of HCO_3^-
 - +/- correct albumin ($\uparrow Atot \rightarrow \downarrow SID$)
 - Correct KCl (Cl most helpful, K disappears into depleted intracellular space)
 - More difficult where CCF, CRF, liver disease lead to $\uparrow aldosteronism$ in presence of $\uparrow ECF$. Prefer K sparing diuretics
 - Acetazolamide: increase urinary SID. Carbonic Anhydrase inhibitor. 250 - 500 mg bd
 - Dialysis

Respiratory Acidosis

- Causes:
 - Hypoventilation (think anatomically):
 - CNS depression
 - Spinal chord
 - Chest wall: neuromuscular weakness, myopathy, flail segment, abdominal distension, obesity
 - Parenchyma: asthma, pneumonia, ALI,
 - Airway difficulty
- Compensation (over time) with $\uparrow HCO_3^-$ reabsorption

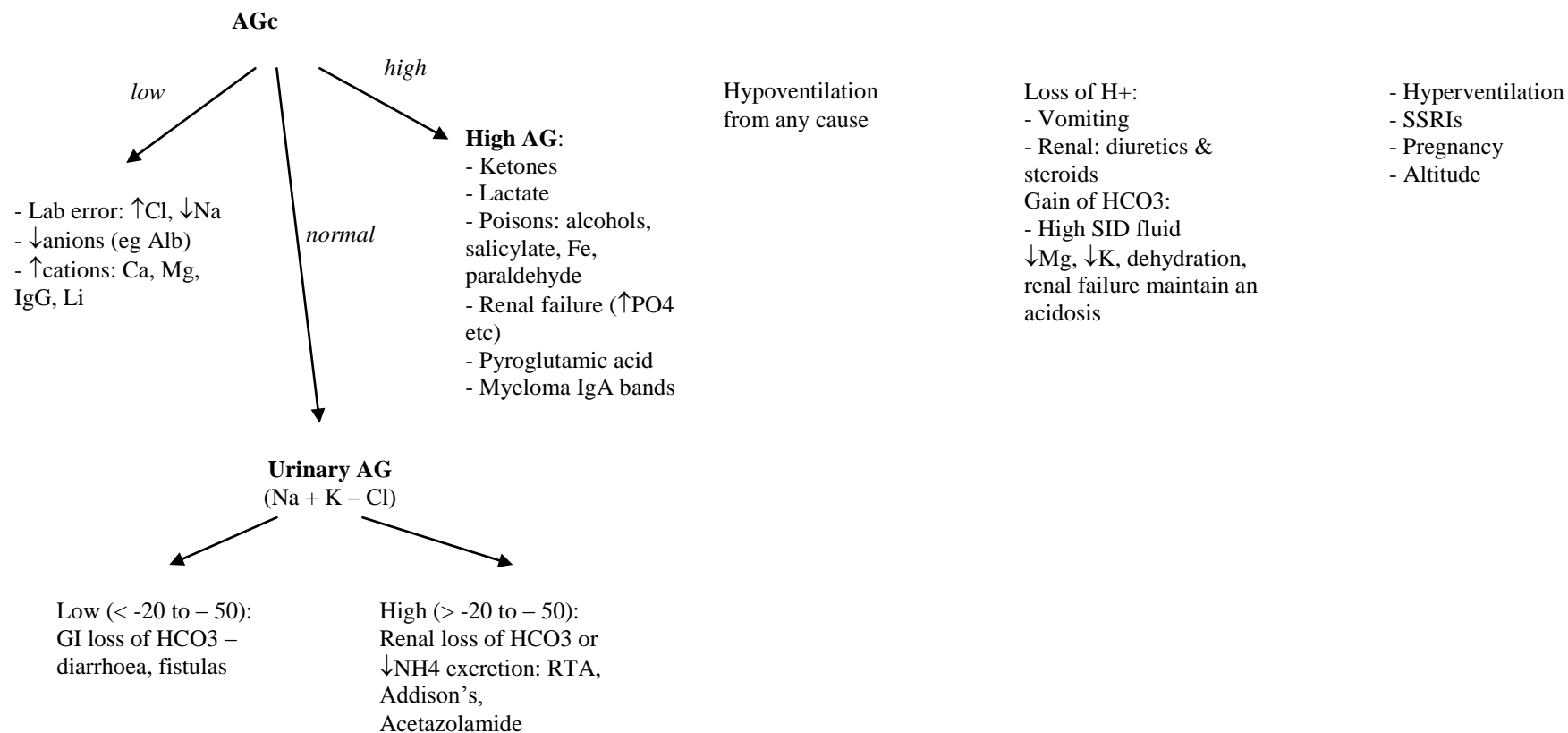
Respiratory Alkalosis

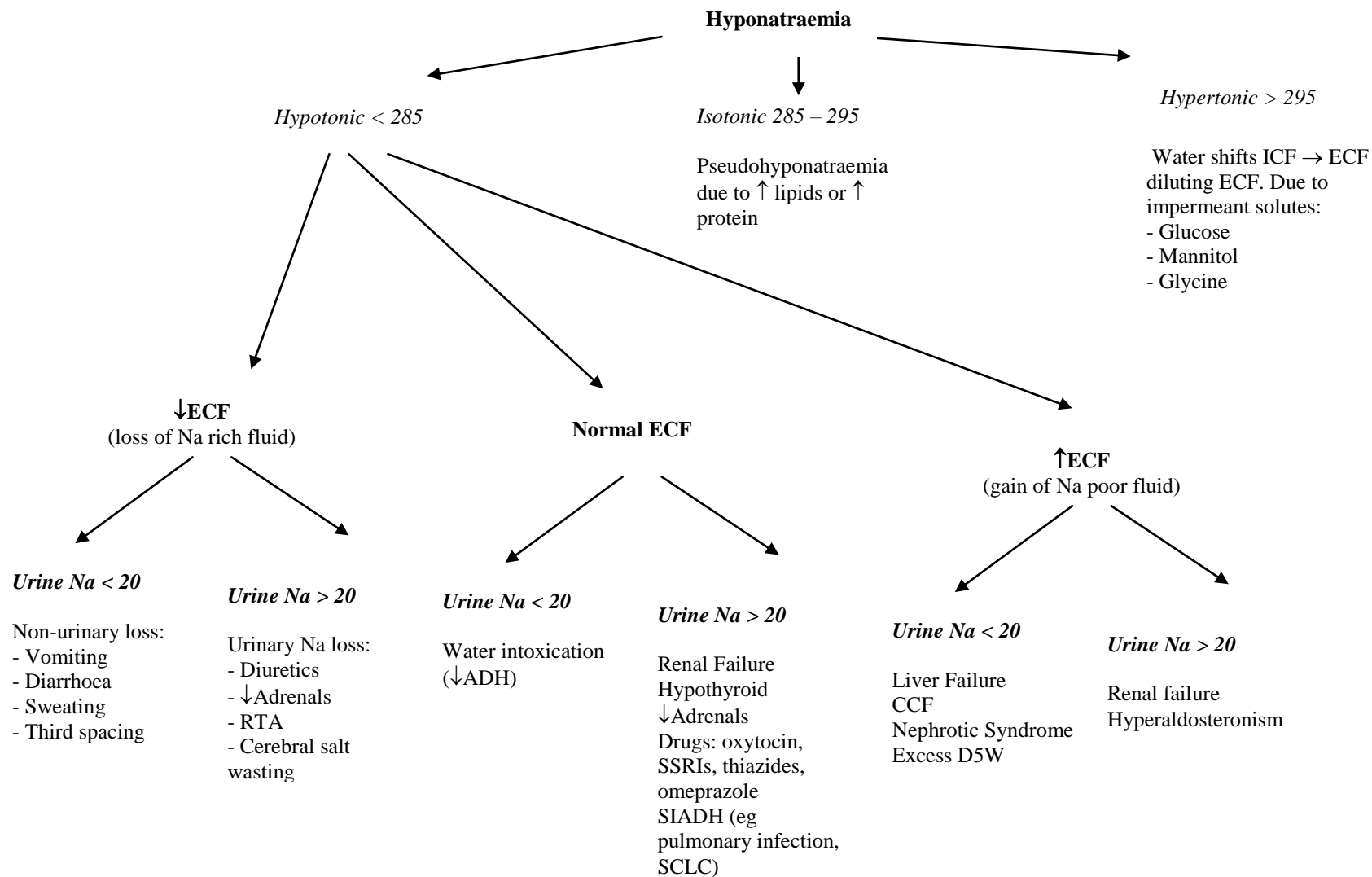
- Acute:
 - Hypoxaemia
 - Sepsis
 - PE
 - Asthma
 - Drugs: SSRIs
 - Pain, anxiety
 - Central: stimulate respiratory centre – progesterone in pregnancy, theophylline, salicylates, amphetamines
- Chronic:
 - Pregnancy
 - Altitude
 - Chronic lung or liver disease
 - Compensation (over time) with $\downarrow HCO_3^-$ reabsorption



Compensation:

	PaCO ₂ = last 2 digits of pH	Acute: ↑1 HCO ₃ for ↑10 CO ₂ Chronic: ↑4 HCO ₃ for ↑10 CO ₂	↓12.5 CO ₂ for ↓10 HCO ₃	Acute: ↓2 HCO ₃ for ↓10 CO ₂ Chronic: ↓5 HCO ₃ for ↓10 CO ₂
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SIADH: Urine osmolality > plasma, Urine Na > 20. Diagnosis of exclusion: normal kidney, liver, heart, pituitary, adrenal, thyroid. No hypotension, oedema, drugs

Electrolytes

Basic Approach

- Assess:
 - Intake
 - Output:
 - Urine
 - Non-urine (GIT top, GIT bottom, GIT middle, skin)
 - Redistribution
- Pattern analysis: start with the most unusual or uncommon abnormality in blood results (it will focus the options)
- Odd electrolyte patterns:
 - $\uparrow K$, $\downarrow Na$, $\uparrow Ca$, $\downarrow Glucose$, $\uparrow Urea$: hypoadrenalism
 - $\downarrow Na$, $\downarrow glucose$, $\uparrow cholesterol$: consider myxoedema coma

Water

- Water Metabolism:
 - Intake controlled by thirst
 - Excretion controlled by ADH:
 - Osmolality < 280 mOsm/kg suppresses ADH to level of maximal urinary dilution
 - Maximal ADH > 295 (greatest action by \uparrow thirst)
 - An increase in osmolality caused by permeant solutes (eg urea) doesn't \uparrow ADH
 - \uparrow in ADH in response to hypovolaemia/hypotension (extremely marked when $\uparrow 30\%$ plasma volume lost)
 - ADH secretion and drugs:
 - \uparrow with narcotics, barbiturates, carbamazepine, amitriptyline
 - \downarrow with ethanol, phenytoin
- For every 1 litre of water lost in a 70 kg man, $\uparrow 7 - 8$ mOsm/kg, $\uparrow 3.5 - 4.0$ Na
- Tonicity:
 - Effects of \uparrow solute depend on whether solute distributes through:
 - Total body water (eg alcohol or urea)
 - ECF only: mannitol or glucose. In which case hyperosmolality \rightarrow shift from ICF to ECF. = Hypertonicity
- Water content of tissues varies from adipose (10%) to brain (84%)

Sodium

- Total body content 4,000 mmol
- Average intake 150 mmol
- Daily around 25,000 mmol of Na is filtered by the kidney, only 150 excreted. Energy intensive
- If ADH homeostasis is normal, urine and serum osmolality always go in the same direction, eg dilute serum \rightarrow dilute urine
- Serum: centrifuged from clotted blood \Rightarrow no clotting factors/fibrinogen. Is 93% water, 7% solids. If Na is 140 mmol/L, the concentration of Na in the serum was is 150 mmol/L ($140 * 100/93$) –which is why normal saline is 150 mmol/L
- Plasma: centrifuges from anti-coagulated blood \Rightarrow has fibrinogen, factors and anti-coagulant

Hyponatraemia

- $Na > 135$, severe > 120
- Measure: Plasma osmolality, urinary osmolality and urinary Na
- Isotonic hyponatraemia (285 – 295 mOsm/kg): \uparrow lipids or \uparrow protein \rightarrow pseudohyponatraemia (error of measurement). Raised osmolar gap but not anion gap
- Hypertonic hyponatraemia (> 295 mOsm/kg):
 - Hypertonicity \rightarrow water shifts from ICF \rightarrow ECF \Rightarrow dilutes ECF Na. When you correct the problem, the Na will return to its normal value (ie treat the problem not the sodium)
 - Usually no action required other than reversing cause
 - Due to \uparrow permeate solutes:
 - \uparrow Glucose: For every 3 mmol \uparrow in glucose, Na \downarrow by 1
 - Hypertonic infusions: mannitol
 - TURP syndrome

- Absorption of glycine from irrigation solution
 - → Confusion, due to glycine being an inhibitory neurotransmitter, ↑ plasma ammonia may contribute. Encephalopathy is not due to ↑ in brain water
 - → visual impairment and even fixed pupils which resolves over hours
 - Test for ↑ ammonia and metabolic acidosis
 - Only give hypertonic saline if measured osmolality < 260 osmol/kg
 - Rapid glycine elimination → rapid correction of Na – OK if osmolality constant
- Hypotonic hyponatraemia: excess total body water (<285 mOsm/kg)
 - Either:
 - Water retention: urinary Na > 40: SIADH, hypovolaemia, cardiac failure, pain, post-operative, renal failure, polydipsia
 - Salt depletion: urinary Na < 20: adrenal failure, diuretic excess
 - ↑ECF (ie ↑NaCl, ↑H₂O): Gain of Na-poor fluid
 - Urinary sodium > 20:
 - Acute and chronic renal failure
 - Hyperaldosteronism from any cause (eg Steroids, Cushing's)
 - Urinary sodium < 20:
 - Liver failure/cirrhosis
 - CCF (→ 2ndary hyperaldosteronism)
 - Nephrotic syndrome
 - Excess 5% dextrose (Factitious hyponatraemia)
 - Normal ECF: ⇒ ↑ADH
 - Urinary Na < 20 mEq/L:
 - Water intoxication (dietary ↓solute intake, psychogenic polydipsia, water overload) this is appropriate – they've got too much water and they're trying to lose it
 - Pain (eg post-operative)
 - Urinary Na > 20 mEq/L:
 - Renal failure
 - Hypothyroidism
 - Adrenal insufficiency
 - Medications: oxytocin for induced labour, SSRIs in the elderly, thiazides, omeprazole
 - SIADH (eg pulmonary infections, SCLC)
 - ↓ECF (hypovolaemic): Loss of Na rich fluid
 - Urinary Na < 20 mEq/L ⇒ non-urinary loss. Treat with slow resuscitation
 - Vomiting
 - Diarrhoea, fistulas/stomas
 - Skin losses (sweating, Cystic fibrosis)
 - Third spacing (eg burns, pancreatitis)
 - Urinary Na > 20 ⇒ urinary loss (salt wasting states):
 - Diuretics
 - Adrenal insufficiency
 - Renal tubular acidosis
- Cerebral salt wasting: see Hyponatraemia, page 208. ↑Urinary Na → ↓ECF (cf SIADH when ECF is normal or ↑). Treatment replace sodium and water, maybe fludrocortisone

Syndrome of Inappropriate Antidiuretic Hormone (SIADH)

- Diagnosis:
 - Hypotonic hyponatraemia
 - Urine osmolality > plasma osmolality
 - Urine Na > 20 mmol/l
 - Diagnosis of exclusion:
 - Normal renal, hepatic, cardiac, pituitary, adrenal and thyroid function
 - Absence of hypotension, hypovolaemia, oedema and drugs affecting ADH secretion
 - Correction by water restriction
- Severe:
 - If Na < 120 or neurological manifestations
 - Balance between cerebral oedema from low Na and pontine myelinolysis/Osmotic Demyelination Syndrome from rapid correction (irreversible damage with symptoms from 3/7 to 3/52 later). Risks are alcoholism, malnourishment, prolonged diuretic use and liver failure
- Treatment:

- Water restriction – especially if chronic onset
- Active intervention:
 - If Na < 100 or symptomatic (confusion, coma, seizures)
 - Limited evidence
 - Aim for correction from 0.5 – 2 mmol/l/hr (slower better if possible)
 - V2 receptor antagonists – prevent ADH mediated aquaporin mobilization. Trialled in CHF, cirrhosis and SIAHD. Their place in the critically ill is uncertain
- Seizures:
 - Aim to raise Na by ~ 2.5 - 5 mmol
 - Na dose:
 - = total body water * desired change in Na Level (3 ml/kg 3% saline will raise Na by 2.5 mmol – enough to help without hurting)
 - = weight * 0.6 * change in Na in mmol. [Don't know why it's total body water – not ECF – maybe that ↑osmolality of ECF causes water to redistribute from ICF → ECF so affects total body water – no references round. NB formula for HCO has coefficient of 0.3]
 - With either:
 - 10 – 20 ml 20% Na
 - 100 – 150 ml 3% Na
 - Want to give NaCl not water
 - Through central line (hyperosmotic) over ½ an hour with careful monitoring
 - May need desmopressin (↓water excretion) or even sterile water to slow the correction if too fast

Hypernatraemia

- Na > 145, symptoms with Na > 155 - 160
- Indicates ICF volume concentration ⇒ cellular dehydration → neurologic symptoms: lethargy, weakness, cerebral oedema if too rapidly corrected (limit to 0.5 mmol/L/hr)
- Usually not due to ↑ total body Na. Total body Na is low, normal or high
- Don't see it unless thirst mechanism impaired
- Causes:
 - Water depletion:
 - Dehydration
 - GIT losses with excess Na replacement
 - Renal loss: neurogenic or nephrogenic (eg Li), diuretics
 - Salt gain: hypertonic saline or NaHCO₃
 - Cushing's/steroids

Potassium

- Total body K = 3500 mmol in a 70 kg male
- ECF K ranges from 3.1 to 4.2 mmol/l – 55 to 70 mmol
- Less efficient renal mechanisms to retain K even when depleted (compared to Na)
- ↑K → ↑insulin → intracellular K shift independent of glucose
- β-agonists:
 - → ↑cellular uptake via a cyclic AMP-dependent activation of the Na/K pump
 - → shift of K from ECF → ICF
- Aldosterone and glucocorticoids → ↑K excretion

Hypokalaemia

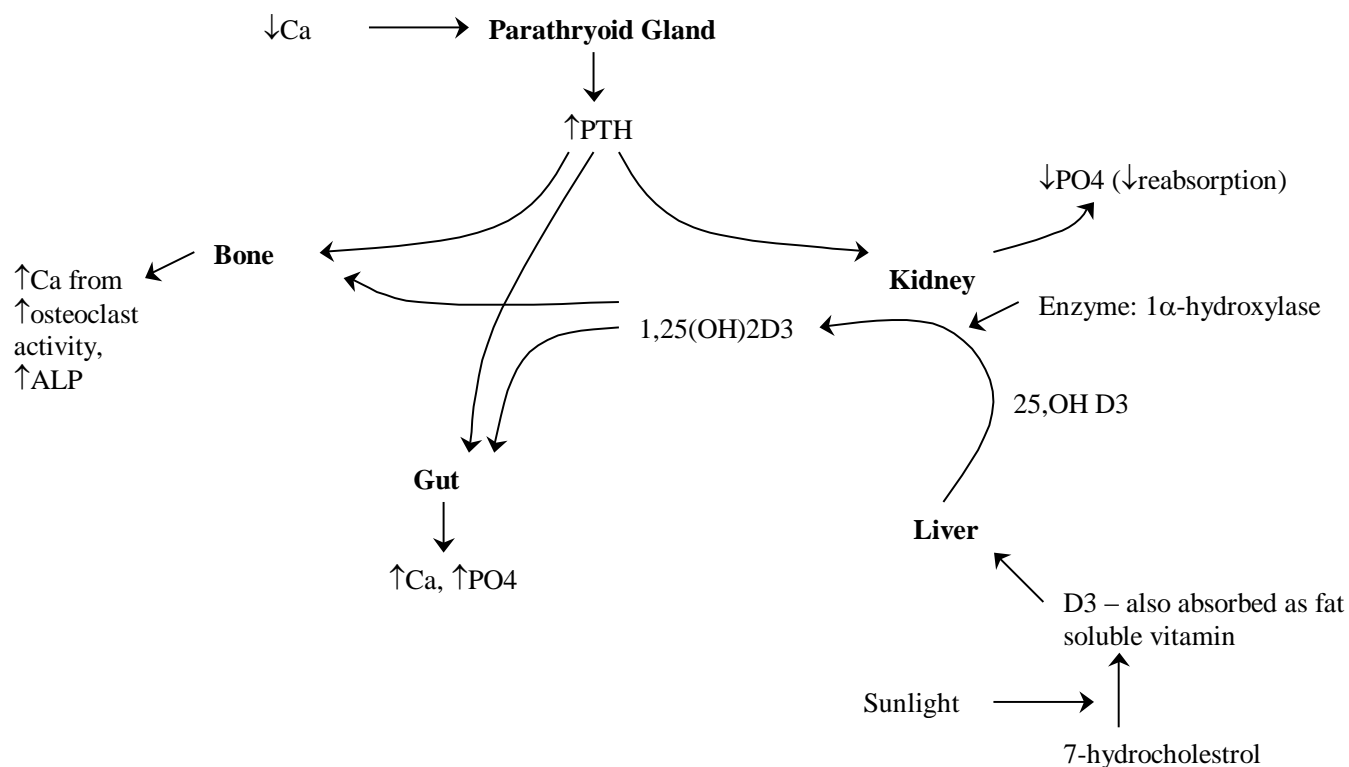
- Serum K < 3.5 (plasma K < 3.0)
- PC: weakness, depression, constipation, ileus, VT (esp torsades), PR prolongation, TWI, prominent U waves
- Treatment: IV or oral (especially if metabolic alkalosis). No more than 40 mmol/hr. If RTA and ↓ K, then K citrate may be better than KCl
- Causes:
 - ↓Intake: anorexia, malabsorption
 - ↑Excretion:
 - Renal:
 - Steroids: Conn's, Cushing's, Ectopic ACTH
 - Drugs: diuretics, corticosteroids, carbapenems, gentamicin, lithium
 - RTA
 - Vomiting: loss of HCl → metabolic alkalosis

- Diarrhoea, laxatives: Loss of $\text{HCO}_3^- \rightarrow$ metabolic acidosis
- Redistribution:
 - Insulin
 - Alkalosis
 - β_2 adrenergics
 - Delayed following blood transfusion
 - Refeeding syndrome
- If severe, causes rhabdomyolysis

Hyperkalaemia

- PC: tingling, paraesthesia, weakness, hypotension, bradycardia, peak T waves, flattened P wave, wide QRS, deep S wave, progressing to sign wave and asystole ($\text{K} > 7$)
- Causes:
 - Artefact: haemolysis
 - \uparrow Intake:
 - Blood transfusion
 - Exogenous
 - \downarrow output:
 - Renal:
 - Failure
 - K sparing diuretics
 - Hypoaldosteronism, including drug induced (ACEI, ARB)
 - Redistribution:
 - Cell lysis – crush injury, tumour lysis, rhabdomyolysis
 - Acidosis
 - Digoxin overdose
- Treatment:
 - Aggressive rehydration with non-K containing fluids
 - CaCl_2 5 – 10 mmol to reduced cardiac effects
 - NaHCO_3 , 50 – 100 mmol (added to 1 litre $\frac{1}{2}$ normal saline at 100 ml/hr to maintain a urine pH > 6.5 and prevent development of ARF. Alkalinisation can exacerbate hypocalcaemia. No controlled trials)
 - Glucose 50 ml 50% with 20 units soluble insulin
 - Inhaled beta-agonists
 - Ca Resonium (oral phosphate binders)
 - Diuresis with frusemide 40 or 80 mg or mannitol

Calcium



- Normal intake 15- 20 mmol, only 40% absorbed
- ECF Ca is in three forms:
 - 40% bound to albumin – correct Ca 0.025 mmol/l for every 1g/l albumin varies from 40
 - 47% ionized – the active form, reduced in alkalosis
 - 13% complexed with citrate, sulphate and phosphate
- Ca, Mg and PO_4 :
 - Mainly intracellular and bone
 - Protein bound \Rightarrow affect by acid/base

Hypocalcaemia

- For review of assessment and clinical course see Steele et al, Crit Care 2013
- PC:
 - Neuro: paraesthesia, tetany, cramps, seizures, psychosis
 - CVS: arrhythmia, hypotension, inotrope unresponsiveness, $\uparrow\text{QT}$
 - Resp: apnoea, laryngospasm, bronchospasm
- Causes:
 - Artfactual 2nd to low albumin
 - \downarrow Intake:
 - \downarrow intake
 - \downarrow fat absorption (eg steatorrhoea) or \downarrow sunlight or renal failure or liver failure $\rightarrow \downarrow$ Vitamin D
 - \uparrow Excretion:
 - \downarrow Vitamin D (dietary, malabsorption, liver disease)
 - \downarrow PTH, 2nd to \downarrow Mg, sepsis. Common post parathyroidectomy (Hungry bone syndrome – rebound absorption of Ca by bone in sudden absence of PTH). Treat with bolus or infusion of calcium. Check and replace Mg
 - Loop diuretics
 - Redistribution:
 - Chelation:
 - Tumour lysis
 - Rhabdomyolysis
 - Citrate from transfusion
 - Alkalosis $\rightarrow \uparrow$ protein binding
 - \downarrow PTH $\rightarrow \uparrow$ bone uptake
 - Drugs: bisphosphonates, phenytoin

- Treatment: 1 ml CaCl has 3 times as much Ca as Ca gluconate. Via central line given risks if extravasation

Hypercalcaemia

- **Correct for albumin** (see above). Ionized Ca more accurately reflects serum Ca. Ionized Ca decreases with alkalosis (decreased competition for protein binding from H)
- Physiology:
 - PTH → ↑bone resorption, ↑renal calcium absorption and PO₄ excretion, ↑conversion of Vit D to active form (Calcitriol)
 - Calcitriol → ↑intestinal Ca absorption, and small ↑ in bone resorption
- PC:
 - Kidney: polyuria, polydipsia, oliguria, renal failure
 - GIT: anorexia, nausea, vomiting, constipation, abdominal pain, pancreatitis
 - Neurological: weakness, mental disturbance, depression
 - CVS: Hypertension, prolonged PR, QT shortening, ST elevation (may mimic STEMI), widened T waves, arrhythmias including Brady arrhythmia and VF
 - Musculo-skeletal: bone pain
- Causes:
 - ↑intake (rare):
 - Vitamin D intoxication
 - Milk-alkali syndrome
 - ↓excretion:
 - Renal failure
 - Thiazides, Li
 - ↑Vitamin D
 - Altered redistribution (generally ↑resorption from bone):
 - Any cause of ↑Vitamin D (eg granulomatous disease - sarcoid)
 - Any cause of ↑PTH: primary hyperparathyroidism, PTH secreting tumours, hyperthyroidism
 - Bony infiltrates by infection, Paget's, malignancy
 - Immobilisation
 - Sarcoid
 - Hyperthyroidism
 - Dehydration
 - Recovery stage of pancreatitis or rhabdomyolysis
 - In massive transfusion, citrate binds Ca ⇒ need to measure ionised Ca
- In cancer:
 - Half of all patients with malignancy associated ↑Ca die within a month of diagnosis
 - Mechanisms:
 - Humoral effect from PTHrH (80%): non-small cell lung Ca, prostate, breast, myeloma
 - Ectopic PTH production
 - Local osteolysis from bone metastasis due to IL-1, IL-6, etc.)
 - Vitamin D mediated (<1%): lymphoma, [also TB, sarcoid] (steroids only help in this class – but may also cause tumour lysis syndrome)
- Management:
 - Volume expansion with N Saline (200 – 500 ml/hr unless cardiac or renal disease, aiming for brisk urine output). Fluids alone correct Ca in only about 1/3
 - Loop diuretics once euvoalaemic. Not thiazides otherwise ↑ distal tubular reabsorption of calcium. [NB no role for diuretics in malignant hypercalcaemia in multiple RCTs. Aggressive diuresis has a limited potential to remove calcium and may lead to renal dysfunction if inappropriate negative balance ensues]
 - Bisphosphonates: block osteoclastic bone resorption, take 2 – 4 days to work, normalise levels for 1 – 4 weeks (time to treat underlying malignancy)
 - Calcitonin: inhibits bone resorption and ↑renal excretion. Rapid onset, short duration, potential for tachyphylaxis, and generally abandoned in favour of newer drugs
 - Corticosteroids
 - Oral phosphate repletion if hypophosphatemia
 - Dialysis if desperate, and if CHF/CRF

Magnesium

- Mainly an intracellular ion, role in transfer, storage and utilisation of energy
- Causes of ↓Mg:

- ↓intake:
 - GI:
 - Diarrhoea
 - NG suction
 - Malabsorption
 - Alcohol
 - TPN
- ↑loss:
 - Renal tubular acidosis
 - Drugs: amphotericin, aminoglycosides, diuretics, omeprazole, cisplatin
 - Redistribution: insulin, hungry bone
- Pathophysiology:
 - ↓Mg →:
 - K disturbance:
 - Mg is a co-factor of Na/K ATPase in the renal tubule. ↓Mg → ↑K loss in the urine
 - ↓intracellular K and ↑ intracellular Na → ↑resting membrane potential → irritability (arrhythmias, tetany, seizures)
 - ↓PTH → ↓Ca
- Treatment: MgSO₄ 5 – 10 mmol, given slowly. If rapid → hypotension, heart block, bradycardia
- Used in:
 - Eclampsia: RCT in over 10,000 women
 - AF: 2nd line rate control and/or reversion
 - IV or nebulised in Asthma
 - Preliminary trials for vasospasm in SAH
- Hypermagnesaemia: renal failure. Usually iatrogenic. PC areflexic weakness. Treatment:
 - Ca (functional antagonist)
 - Diuretics
 - Dialysis

Phosphate

- Causes of hypophosphataemia:
 - ↑PTH
 - ↓Vitamin D
 - RTA
 - Alkalosis
 - Alcoholism
 - Refeeding Syndrome
 - Haemodialysis
- Causes of hyperphosphataemia (which always → ↓PTH):
 - Rhabdomyolysis
 - Renal failure
 - Vitamin D toxicity
 - Acidosis
 - Tumour lysis
 - ↓PTH

Cell Necrosis Syndromes

- Any cell necrosis causes: ↑K, ↑LDH, ↑PO₄, ↓Ca, ↑Urate
- Cell necrosis syndromes:
 - Haemolysis: ↑K, ↑LDH, ↑bilirubin, ↑unconjugated bilirubin, ↓Hb
 - Rhabdomyolysis: ↑K, ↑LDH, ↑CK, ↑Cr, ↓urea:Cr ratio, ↑PO₄, low to normal Ca
 - Tumour Lysis Syndrome: ↑K, ↑LDH, ↑PO₄, ↑urate, low to normal Ca

Airway Management

- See also:
 - Adult Cardiopulmonary Resuscitation, page 163
 - Swallow Assessment, page 350
 - Weaning from Mechanical Ventilation, page 95
 - Can you Extubate this Patient, page 376
- Aims:
 - Secure unobstructed gas exchange
 - Protect the lungs from soiling
- Bag mask ventilation: Problems: Inadequate ventilation, gastric insufflation, pulmonary aspiration
- Airways: nasopharyngeal airway is better tolerated by a semiconscious patient than the OPA but risks epistaxis, aspiration and rarely laryngospasm or oesophageal placement
- ILMA: contraindications include inability to open the mouth, pharyngeal pathology, airway obstruction at or below the larynx, low pulmonary compliance or high airway pressure

Endotracheal intubation

- Indications for intubation:
 - Unconscious
 - Severe maxillofacial fractures
 - Risk for aspiration
 - Risk of obstruction (neck injury, haematoma, oedema)
- Excessively vigorous suctioning should be avoided as it can cause laryngospasm, vagal stimulation, mucosal injury and bleeding
- Maintaining oxygenation:
 - Critical desaturation on intubation occurs with sats < 70 %
 - Is much faster in ICU than healthy adults
 - High incidence of difficult intubation in ICU, and therefore prolonged intubation times
 - Pre-oxygenation is the standard of care, but its efficacy alone has been questioned in ICU
 - Some advocate “apnoeic oxygenation”:
 - Delivering 100% O₂ to the airways (eg via nasal cannula) during intubation. The theory being that O₂ continues to be drawn into the blood stream at ~200 ml/min, creating passive gas flow into the lungs
 - In elective patients, this extends the desaturation time from 7 to 10 minutes, and in obese patients for bariatric surgery from 2.5 to 4 minutes
 - As the shunt fraction increases (as it does in ICU), the benefit will reduce
- Laryngoscopy:
 - All FIRST attempts should have ideal positioning (tragus of ear horizontal with suprasternal notch), use of external laryngeal manipulation, etc. (get everything right first time). If repeat attempts, then max 30 secs without ventilation
 - If obese, 25° head up → 30 – 60 secs longer pre-hypoxic time
 - Cricoid force: 10 N awake, 30 N asleep
 - Bougie: Gum elastic bougie, aka Eschmann Tracheal Tube Introducer.
 - Tracheal position confirmed by:
 - Clicks from tracheal rings (65 – 90%)
 - Bougie rotates to left or right on entering a bronchus
 - Bougie is held up at the bronchial tree (~ 50 cm mark). No of these occur with oesophageal passage
 - If ET tube held up at arytenoids or aryepiglottic folds, withdraw slightly, turn 90° and advance
 - Alternative laryngoscope blade: long blade, McCoy
 - Large ET tube to reduce resistance and facilitate sputum clearance
 - No nasal intubation in base of skull fractures
 - Video laryngoscopes: In the anaesthetic literature clearly reduce intubation time and attempts in Grade 3 and 4 airways. Still need good laryngoscopy skills to get it in the right place. Shouldn't be first line. Potential important role in trauma/spinal cases

- Safety features of an ET tube: clear, non-toxic plastic, single use, radio-opaque line, high volume low pressure cuff with pilot tube, murphy's eye, bevelled tip to aid insertion, centimetre markings to assess depth, standard 15 mm connector, size labelling
- Types of ET tube:
 - Multiple lumen oesophageal airway: Distal lumen may go into the oesophagus (usually), two balloons inflate and the other lumen vents through holes in between the balloons
 - Laryngeal tube airway: Extra-glottic airway. Inflates above and below the glottis and vents in between
 - Double Lumen Endobronchial Tube
 - For anatomical or physiological lung separation
 - Indications:
 - Massive haemoptysis from unilateral lesion
 - Whole lung lavage eg alveolar proteinosis
 - Copious infected secretions with risk of soiling unaffected lung (eg bronchiectasis, abscess)
 - Unilateral parenchymal injury: aspiration, contusion, pneumonia
 - Single lung transplant
 - Bronchopulmonary fistula
 - Unilateral bronchospasm
- Complications:
 - Capnography may be false positive for a few breaths in oesophageal placement if gastric insufflation has occurred or carbonated drinks. False negative (little or no CO₂) in arrest or low output states
 - During intubation: incorrect placement, laryngeal trauma, ↓CO, ↑intracranial pressure, hypoxia, aspiration
 - While tube in place: blockage, dislodgement, tube deformation, damage to larynx
 - Following extubation: airway obstruction, laryngeal and tracheal stenosis
- High risk for hypotension following induction:
 - Due to drug effects (myocardial depression and ↓peripheral vascular resistance), ↓ venous return/preload with positive pressure ventilation, removal of sympathetic drive from anxiety
 - Prevent with adequate hydration, having inotropes and pressors available, low positive pressure if possible, and close monitoring before and after
- Laryngeal Mask Airway. Possible uses include:
 - Use in a failed intubation algorithm (especially an intubating LMA)
 - Part of cardiac arrest team by practitioners not familiar with ETT
 - Maintain airway during a percutaneous tracheostomy

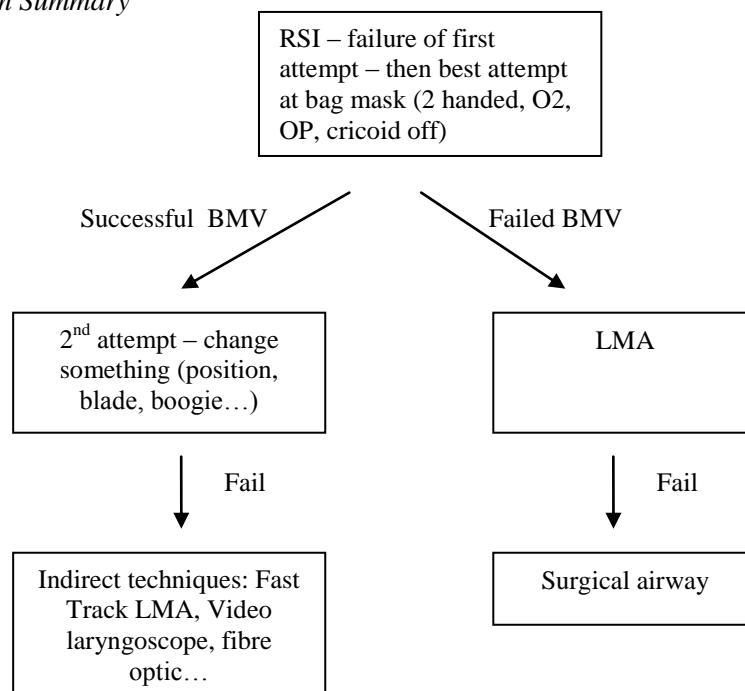
Awake Fibre Optic Intubation

- Procedure is clearly explained to the patient
- Good local anaesthetic and vasoconstriction
 - Failure is usually due to excessive secretions/bleeding
 - Aids cooperation, ↓cardiovascular responses and ↓laryngospasm
- Options are:
 - Glycopyrolate 3 – 5 µg/kg iv 15 mins prior: prolongs LA contact time and effect and assists visualisation
 - A small dose of midazolam may help (beware those with sleep apnoea who obstruct and lose your view)
 - Nasal cavity and nasopharynx: 10% lignocaine spray with phenylephrine spray, or cotton tipped pledgets soaked in 4% cocaine or nebuliser filled with 5 ml of 4% lignocaine or 5 ml Lignocaine 2% gel
 - Oral cavity and oropharynx:
 - 10% lignocaine spray (5 – 10 sprays = 50 – 100 mg)
 - Gargle with 5 ml 4% lignocaine viscous
 - Nebulise with 2 * 3 – 4 ml 4% lignocaine – expect cough and voice change
 - Nerve block of internal branch of superior laryngeal nerve
 - Allow adequate time to act
- Positioning: Lawn chair position, get the patient to hold their tongue forward with gauze (or assistant with Magills) and advance scope with inspiration to optimise air space volume
- Parker tip tubes are much less likely to get obstructed at the chords
- Consider use of Burman split OPA
- Suction port of fibrescope can be used to insufflate 100% O₂ or apply local anaesthetic

Can't Intubate, Can't Ventilate

- Laryngoscopy: Routine no more than 4 attempts, RSI no more than 3 attempts (maintaining O₂ with face mask and anaesthesia and cricoid if RSI)
- If RSI no ILMA or LMA (normally not more than 2 insertions + 1 attempt at fibreoptic) as doing RSI due to aspiration risk as LMA not advised unless benefit > risk
- Optimal bag masking: maximum head extension, maximum jaw thrust, 2 handed, NP airway
- Failed oxygenation: SpO₂ < 90% with FiO₂ 100% ⇒ can't ventilate, can't intubate
- Call for help
- Supraglottic rescue: LMA: 2 attempts at insertion, ↓ cricoid force if necessary
- Infraglottic Rescue techniques:
 - Goal is oxygenation, not ventilation
 - Cannula Cricothyroidotomy: Kink resistant cannula through cricothyroid membrane eg Manujet, confirm position with aspiration. If ventilation fails, or surgical emphysema convert immediately to surgical cricothyroidotomy
 - Surgical Cricothyroidotomy: Stab incision with no 20 Scalpel through cricothyroid membrane, enlarge with blunt dissection (eg scalpel handle), caudal traction with tracheal hook, insert tube
 - Tubes of outer diameter of 8.5 mm or less should be used to avoid laryngeal or vocal cord damage
 - Complications: subglottic stenosis (1.6%), thyroid fracture, haemorrhage and pneumothorax
 - Contraindicated age < 12

Algorithm Summary



Difficult Airway

- ~10% of ICU cases
- Predicted by:
 - History: snore/OSA, wheeze, surgery/radiotherapy, beard
 - Examination findings:
 - Short neck especially obese or muscular with a thyro-mental distance < 6 cm
 - Limited neck (flexion < 35°) or jaw movement (mouth opening < 3 cm)
 - Protruding teeth and receding lower jaw
 - Mallampatti classification: class > 2 predicts possible difficult airway
- Cormack and Lehane classification of glottis views
- Issues in ICU:
 - Emergency: often little time for history and exam
 - Physiologically unstable → little reserve
 - Remote sites (ICU, CT), often after-hours

- Not fasted
- See De Jong 2013, Am J Resp Crit Care, for predictive scoring for difficult airway

Upper airway obstruction

- Sites of obstruction:
 - Supraglottic: above the true vocal chords
 - Glottic: involving the true vocal chords
 - Infraglottic: below chords and above carina
- Mechanisms of obstruction
 - Functional: CNS, PNS, neuromuscular
 - Mechanical: foreign body, infection, oedema, haemorrhage/haematoma, trauma, burn, neoplasm, congenital
- Management of obstruction:
 - Extrinsic compression:
 - Haematoma: immediate evacuation – remove sutures if post-surgical. If coagulation abnormalities then intubation preferred over surgical airway
 - Retropharyngeal abscess: drainage under local anaesthetic
 - Burn/Ingestion injury:
 - Suspect if large burn (> 40%), facial burn, soot in nostrils, burns of tongue and pharynx, stridor or hoarseness
 - At risk of progress supraglottic oedema over 24 – 48 hours ⇒ early prophylactic intubation, or close watch with 2 – 4 hourly awake fibre-optic laryngoscopy
 - Adult epiglottitis:
 - Common causes: H influenzae, H parainfluenzae, T pneumoniae, St aureus
 - Sudden onset sore throat in excess of findings, muffled voice, dysphagia, stridor, dyspnoea, sepsis
 - Gentle fibreoptic laryngoscopy or lateral neck xray to confirm diagnosis. Don't transport a patient with an unsafe airway for imaging
 - Controversial whether to electively intubate or not – at risk of sudden obstruction later. Avoid RSI. Tracheostomy under local a safe alternative. No evidence of benefit from steroids
 - Angio-oedema:
 - Characterised by sub-epithelial swelling
 - Common causes: stings, shellfish ingestion, drugs
 - Treatment: adequate airway, O2, adrenaline and steroids
 - Hereditary angioedema: functionless or low levels of c1 esterase inhibitor. Acute attacks don't respond to adrenaline, antihistamines or corticosteroids. Secure airway, infuse C1 esterase inhibitor concentrates (onset 30 – 120 mins) or FFP (2 – 4 units). Stanazolol or Danazol effective in decreasing frequency of attacks
- Post-obstruction pulmonary oedema:
 - Occurs in up to 10% of upper airway obstruction
 - Caused by marked decreased intra-thoracic pressure from inspiration against a close airway
 - Occurs from mins to 2 hours after obstruction
 - Treat with airway maintenance, O2, diuretics, morphine, fluid resuscitation +/- CPAP or PEEP

Post-extubation Stridor

- Aka post-extubation laryngeal oedema
- Risks:
 - Patient factors:
 - Female sex
 - High BMI
 - Older age group
 - Illness factors:
 - Trauma, surgery or infection of upper airways
 - Traumatic or difficult intubation
 - Elevated APACHE
 - Duration of IPPV > 5 days
 - Low GCS
 - History of agitation
 - Tube factors:
 - Over inflated cuff

- Large ETT
- Occurs in 20% but not usually severe enough to require reintubation
- Treatment:
 - Usually conservative: humidified O₂, nebulised neat adrenaline every 30 – 60 mins (constricts arterioles, reduces oedema)
 - Steroids: May be more useful in prevention rather than treatment, commenced 12 hours prior to extubation. Multi-dose parenteral steroids prevent laryngeal oedema and reduce reintubation (Meta-analysis in BMJ 2008, Fan et al). Likely applicable to only a small number in ICU as laryngeal oedema is only one cause of failed extubation
 - CPAP: relief of symptoms, ↓work of breathing (be cautious)
 - Heliox: improved patient comfort, shown to reduce the need for intubation
 - If all this fails: reintubate

Physiology of Ventilation

Objectives of Ventilation

- Manipulate alveolar ventilation and PaCO₂: eg reverse respiratory acidosis, ↓cerebral blood flow and intracranial pressure
- ↑PaO₂: by ↑FRC, ↑end-inspiratory lung volume, ↑FiO₂
- ↓Work of breathing: eg to overcome respiratory muscle fatigue
- ↑FRC: eg ↑PaO₂, ↓VILI
- To stabilise chest wall in severe chest injury

Measurement of Lung Mechanics

TLC Total Lung Capacity	(S)VC (Slow) Vital Capacity	IC: Inspiratory Capacity	Vt: Tidal Volume
	RV: Residual Volume	FRC: Functional Residual Capacity	

- VC:
 - Normal VC is 70 ml/kg, a reduction to 12 – 15 ml/kg suggestive of possible need for ventilation
 - Factors that ↓ VC:
 - ↓muscle strength: myopathy, neuropathy, spinal cord injury
 - ↑lung elastance: pulmonary oedema, atelectasis, pulmonary fibrosis, loss of lung tissue
 - ↑chest wall elastance: pleural effusion, haemothorax, pneumothorax, kyphoscoliosis, obesity, ascites
 - ↓functional residual capacity: atelectasis, premature airway closure (eg COPD)
- FRC:
 - Rarely measured in ICU, although some ventilators use nitrogen wash-in and wash-out to estimate FRC
 - When FRC < closing volume (lung volume at which airway closure collapse is present during expiration) there is a marked ↑ in V/Q mismatch ⇒ use PEEP to elevate FRC
 - ↑FRC puts diaphragm at a mechanical disadvantage (eg in severe airflow limitation, dynamic hyperinflation and in loss of elastic recoil)
- Chest wall compliance can markedly affect lung mechanics: so think of the respiratory system as lung + chest wall
- Pressure across the lung (what generates gas flow) = Pao (pressure at the airway opening) – Ppl (mean pleural pressure, estimated as oesophageal pressure Pes from balloon in lower third of the oesophagus in a supine, intubated, spontaneously breathing patient)
- Compliance = $Tv / (P_{plat} - PEEP)$
- Elastance
 - = slope of V-P relationship (= inverse of compliance)
 - $E_{rs} = E_l + E_{cw}$ (normal 10 – 15 cmH₂O/l)
 - $1/C_{rs} = 1/C_l + 1/C_{cw}$ (normal 60 – 100 ml/cmH₂O)
 - Factors increasing elastance: small body size, female, lung resection, ↓aerated lung (fibrosis, oedema, ↓surfactant)
 - Measurement using end-inspiratory occlusion method:

- Constant flow breath, muscles relaxed
- Plateau introduced at end inspiration: sudden initial pressure drop due to dissipation of flow resistance ($P_{peak} \rightarrow P_1$ due to airways resistance) followed by a slower secondary pressure drop to plateau pressure ($P_{dif} = P_1 - P_2$ due to tissue resistance) due to stress relaxation. Takes at least 1 – 2 secs
- $E_{rs,static} = (P_2 - P_0)/V_t$
- $E_{rs,dynamic} = (P_1 - P_0)/V_t$
- Where P_0 = total PEEP (iPEEP + extrinsic PEEP)
- Difference between $P_{el,dyn}$ and $P_{el,st}$ is the effective recoil pressure during mechanical ventilation
- Static Volume-Pressure curve:
 - Incremental volume and pressure points are made after a sufficient period of no flow has allowed Pres to be dissipated. Done by either:
 - “Super-syringe method”: paralysed patient progressively inflated from FRC to a predetermined pressure limit in 100 ml steps, with pause after each step. May become hypoxic
 - Randomly inserting a range of single volume inflations followed by a prolonged pause, during mechanical ventilation in a paralysed patient with PEEP of 0
 - Defines a sigmoidal-shaped curve with upper (above this \Rightarrow lung over-inflation) and lower (\Rightarrow recruitment) inflection points, and a mid-section with relatively linear V-P relation, the slope of which is the elastance
 - Curve has an advantage over end-inspiratory elastance since you don’t know what part of the V-P curve is being measured
 - Ventilation between upper and lower inflection points should minimise shear forces from repeated opening and closing, and alveolar over-stretch. This may be too simplistic – in ALI recruitment happens over the entire V-P curve
- Dynamic V-P curve:
 - Collected during normal ventilation \rightarrow “functional” description of lung mechanics
 - Volume is not referenced to FRC
 - Always shows Hysteresis due to airways and tissue resistance
 - Can draw a line from the “no flow” point at end-inspiration and end-expiration to determine elastance but inaccurate as these points can be hard to identify
- Resistance:
 - RL (Lung resistance) = R_{aw} (Airway resistance) + R_{ti} (tissue resistance)
 - Resistance is flow, volume and frequency dependent
 - $R_{aw} = (P_{pk} - P_1)/V_t$
 - Endotracheal tube contributes to R_{aw} , so best to measure P_{ao} distally with an endotracheal catheter
- Respiratory effort to achieve a desired minute volume = sum of forces needed to be overcome to generate inspiratory flow = Work (respiratory muscles) = :
 - elastic work
 - + flow-resistive work (airflow obstruction) – will include ventilator circuit
 - + threshold work: iPEEP. Must be overcome before inspiratory flow can commence. Will also impede triggering of inspiratory support
- Ventilatory failure occurs when forces opposing inspiration (elastic, resistive and threshold work) exceed the respiratory muscle effort to maintain minute volume
- On controlled mechanical ventilation (ie $P_{[muscles]} = 0$): P (at airway) = P (elastic) + P (resistive)

Variables in Mechanical Ventilation

- See also:
 - Invasive Ventilation in ARDS, page 113
 - Ventilation in COPD123
 - Ventilation of Asthma in 126
- **FiO₂:**
 - In ARF usually start at 100% and titrate down
 - High FiO₂ damaging to lung (see Hazards of O₂ Therapy, page 85) and nitrogen washout may exacerbate atelectasis
- **Respiratory rate:** sufficient expiratory time must be allowed to minimise dynamic hyperinflation and PEEP_i
- **Inspiratory flow pattern:**

- Volume controlled = constant flow rate (CMV – Controlled Mechanical Ventilation)
- Constant inspiratory pressure = pressure controlled ventilation (PCV). Pres is dissipated during inspiration so Ppk and Pplat are the same.
- Although peak airway pressure is lower in PCV, alveolar distending pressure (inferred from Pplat) is no different provided Ti and Vt are the same
- In ARDS, no difference between VCV and PCV in haemodynamics, oxygenation, recruited lung volume but:
 - PCV may dissipate elastic strain earlier
 - High Vi in PCV may exacerbate VILI
- **End inspiratory pause:**
 - Allows measurement of Pplat
 - Allows dissipation of total energy → less force driving expiration → potential for ↑gas trapping
- **I:E Ratio:**
 - With severe airflow limitation, use high inspiratory flow rates to prolong Te and minimise DHI
 - Inverse-ratio ventilation: I:E ratio is > 1 supposedly to improve recruitment, with ↑gas trapping → desirable ↑ in PEEP from PEEPi. Does reduce PaCO2 but doesn't improve oxygenation, and may be worse haemodynamics and exacerbate regional over-inflation
- **Positive end-expiratory pressure:**
 - Elevation in end-expiratory pressure on which all forms of ventilation can be imposed
 - When PEEP is maintained throughout the respiratory cycle ⇒ CPAP
 - Created by placing a resistance in the expiratory circuit – ideally one that offers minimal resistance to flow once it's opening P is reached, to minimise expiratory work and avoid barotraumas during coughing
 - Maintains recruitment of collapsed lung, ↑FRC and minimises intra-pulmonary shunt
 - May redistribute water from alveoli to interstitium (but doesn't ↓ extravascular lung volume – although may do in CHF due to ↓venous return)
 - Inadequate PEEP may contribute to VILI by ↑ tidal opening and closing of alveoli
 - Haemodynamic effects of PEEP: ↑intrathoracic pressure →
 - ↓venous return → ↓preload
 - ↓transmural gradient → ↓afterload
- **PEEPi:**
 - Total PEEP = PEEPe + PEEPi
 - PEEPi =
 - Elevation in the static recoil pressure of the respiratory system at end-expiration. Arises due to inadequate Te
 - = that PEEP which is present in alveoli above and beyond applied (extrinsic) PEEPe
 - FRC increases as gas trapping occurs until a new equilibrium point is reached
 - Distribution of PEEPi is likely to be less uniform than an equivalent PEEPe
 - Absent in healthy lung. Present in:
 - States of slowed expiration:
 - Airflow obstruction: bronchospasm, kinked ETT, secretions, clogged HME filters
 - Dynamic hyperinflation
 - States of short expiratory time:
 - Tachypnoea
 - May be a desired endpoint in IRV, HFOV
 - Leads to:
 - Gas trapping due to inadequate expiratory time to return to FRC
 - ↑lung volume: risks of barotraumas (→ pneumothorax, pneumomediastinum)
 - ↑lung pressure:
 - ↑Work of breathing: adds an elastic load to inspiratory work during partial ventilatory modes, large positive pressure gradient to overcome for inspiration to commence. → increased O2 demand and respiratory muscle fatigue
 - ↓spontaneous triggering (which may be reduced by small amounts of PEEPe)
 - Cardiovascular effects: ↓venous return, ↓cardiac output, hypotension, more marked with hypovolaemia
 - ↑ICP
 - V/Q mismatch
 - Falsely raised CVP despite hypovolaemia

- Some evidence of \uparrow PEEP \rightarrow diaphragmatic shortening \rightarrow quicker atrophy
- Diagnosis: Expiratory flow does not return to zero prior to initiation of next breath
- Measured by:
 - Occlusion pressure in a prolonged end-expiratory pause (~ 5 secs) in a paralysed patient (average static iPEEP across all lung units). Surrogate measure of dynamic hyperinflation
 - Fall in oesophageal pressure during inspiration prior to initiation of inspiratory flow in a spontaneously breathing patient, or change in Pao prior to inspiratory flow in a paralysed patient (dynamic). Changes from breath to breath, and active expiration in airflow obstruction falsely increases PEEPi
- Management:
 - Reversible factors: bronchospasm, secretions
 - Prolong expiratory time: \downarrow Vf, \uparrow inspiratory flow, \downarrow inspiratory time
 - \downarrow tidal volume
 - Exogenous PEEP (to 50 – 80% of accurately measured PEEPi) can improve triggering and may improve distribution of inspired gas

Management Issues in Ventilation

- See also Invasive Ventilation in ARDS, page 113

Tidal Volume

- Meta-analysis of low tidal volume trials in non-ARDS patients in 20 studies, Neto, JAMA 2012: Mortality benefit with protective vs conventional tidal volume (4.2% vs 12.6%). Also less pulmonary infection, shorter LOS, shorter duration of mechanical ventilation, higher PaCO₂, lower pH. PEEP and plateau pressure did not influence the results. Heterogeneous populations (surgical and critical care, and short duration of treatment of ventilation median $\sim 6 - 7$ hrs)
- Low tidal volume (6 – 8 ml/kg) vs high (10 – 12 ml/kg) at risk of pulmonary complications after major abdominal surgery \rightarrow low Vt had \downarrow complications and \downarrow LOS (Futier, IMPROVE study, NEJM 2013)

Recruitment

- = opening and maintaining unstable lung units. Can only be accurately measured on CT scan
- Unrecruited lung \rightarrow \uparrow pressures and \downarrow PaO₂
- Evidence of PEEP:
 - \uparrow transient increases in oxygenation
 - No effect found on mortality
 - High PEEP after recruitment improves survival in case series
 - High vs Low PEEP trials:
 - ALEVOLI, LOVS, EXPRESS
 - All negative, but didn't distinguish between recruitable and non-recruitable lung
 - Other studies have used pressure-volume loop to assess recruitability
 - May need higher PEEP (eg 25) and for longer (eg 3 days)
 - PROVHILO Trial, RCT of high (median 12) vs low (median 2) PEEP in 900 patients having open abdominal surgery and at risk of pulmonary complications. No difference in post-op complications (40 vs 39%) but more hypotension and vasopressor with high PEEP
- Recruitability depends on:
 - Type of ARDS: pulmonary, non-pulmonary
 - Stage of disease: early or later
 - Pressure applied
 - Chest wall compliance
 - Consolidation won't recruit, atelectasis may
- To minimise VILI want to:
 - Minimise Pend-inhalation: don't want to over-stretch open lung
 - Keep PEEP-exhalation $>$ Pclosing: don't want to allow alveolar to close
 - \Rightarrow how do you find opening and closing pressure
- All strategies limited:
 - No single pressure can open all airspaces. 45 cm should get 95%+ of alveoli (depending on pathology)
 - No single PEEP can prevent all airspace closure
 - There are long time constants for airspace opening

- Paralysis/sedation are bad for the diaphragm
- Recruitment methods:
 - PEEP
 - V_t , P_{peak}
 - Sigh breath:
 - Ability of ventilator to deliver intermittent breaths at least twice V_t to reduce atelectasis (in part through release of pulmonary surfactant)
 - Can cause excessive lung stretch
 - Applied for varying times
 - Hamilton's solution: Pressure ramping method: assess recruitability and find closing pressure
 - If expiratory P-V loop is higher than inspiratory look during a pressure ramping manoeuvre then the lung is recruitable
 - Optimal duration: if you're going to recruit you'll do most of it in 10 seconds - \uparrow haemodynamic compromise if much larger
 - Aim to set PEEP at δ volume (point of greatest vertical distance between inspiratory and expiratory loops) rather than the lower inflection point (lots of variations on PEEP setting described)
 - PEEP lower than the δ volume \Rightarrow derecruitment and greater expiratory flow
 - Recommendation: if the lung is recruitable, do a ramping manoeuvre up to 40 (even 60 cm) for 10 sec. Set PEEP > 10 cm up to 25 cm
 - In theory, titrating according to transpulmonary pressure (P_{aw} – Poesophagus measured with an oesophageal probe) is more appropriate, aiming for P_{tp} to be always > 0 ($< 0 \Rightarrow$ collapse in expiration \rightarrow atelectatic trauma)

Permissive hypercapnea

- Side effects: respiratory acidosis, peripheral and cerebral vasodilation, tachycardia, sweating, CNS depression at high levels
- Avoid if high intracranial pressure
- If severe:
 - Check tube and exclude complications (atelectasis, pneumothorax)
 - $\uparrow V_t$, $\uparrow RR$
 - Treat dyssynchrony
 - Consider paralysis
 - \downarrow Dead space: recruitment and reduce dead space in circuit
 - Oscillation
 - Extracorporeal CO₂ removal

Hazards of O₂ Therapy

- Myths about O₂ treatment:
 - We confuse low sats as a marker of disease with a life-threatening episode requiring treatment
 - Supplemental O₂ does not give you a "safety margin". It delays recognition of a deterioration
 - Role of oxygen therapy is to increase DO₂ not PaO₂. If $\uparrow PaO_2 \rightarrow$ vasoconstriction then $\uparrow FiO_2$ may be counterproductive. Lactate is one measure of adequacy of delivery
- O₂ toxicity:
 - Not yet in a position to know the balance of risks of O₂ toxicity vs hypoxia
 - Specific toxicities:
 - Lung toxicity: Old data suggests high FiO_2 is harmful to the lung – with high FiO_2 cellular damage (?by O₂ free radicals over whelming normal scavenging systems) \rightarrow progressive reduction in compliance + interstitial oedema \rightarrow fibrosis. The safe concentration/duration is unknown. "Safe" periods above 50% vary from 16 to 30 hours.
 - $\uparrow PaO_2 \rightarrow \downarrow$ coronary artery blood flow
 - $\uparrow PaO_1 \rightarrow$ pulmonary vasoconstriction \rightarrow worse V/Q mismatch $\rightarrow \uparrow$ dead space ventilation $\rightarrow \uparrow PaCO_2$
 - It's been uncertain whether this causes net harm:
 - In a number of small trials (stroke, MI, resuscitation) less O₂ is better than unlimited O₂. PROXY study of post-surgery O₂ suggests less is better. Cohort study in 2,894 ventilated *stroke* patients: adjusted OR 1.4 for mortality with $\uparrow PO_2$ (Rincon, CCM 2014)
 - Early $PaO_2 > 300$ or < 60 is associated with \uparrow mortality in *TBI* (Rincon, J Neurol Neurosurg Psychiatry, 2013)

- Hyperoxia (> 300 mmHg) in the first 24 hours post *cardiac arrest* may increase mortality (Kilgannon et al, JAMA 2009)
- Asthma: Pre-hospital 6 litres O₂ vs O₂ titrated 88 – 92% with air driven nebs → ↓mortality in later (Austin, BMJ 2010). Titrated vs high flow O₂ in severe asthma → ↑PaCO₂ in high flow (Perrin, Thorax, 2012)
- ↑O₂ associated with ↓surgical site infection (11.4 vs 14.1%) but not ↓atelectasis (Meta-analysis, Hovaguiman, Anaesthesiology 2013)
- Hypoxia associated with worse outcome in terms of infection in RCT in abdominal surgery. Other studies showing ↑infection in hypoxia. PROXI Trial: Meyhoff et al, JAMA 2009, RCT of 1400 adults undergoing laparotomy, randomised to FiO₂ 0.8 vs 0.3 during and for 2 hours after surgery. No change in surgical site infection, 1.5% ↑in 30 day mortality (p = 0.13)
- Neonates: Bronchopulmonary dysplasia (reduced by surfactant and maternal steroids) and retinopathy of prematurity (vasoproliferative disorder reduced with tighter O₂ control)
- Other potential physiological harms of O₂:
 - CNS effects (incl seizures) with O₂ > 3 atmospheres
 - ↓innate immunity in lab studies
 - Alters tracheal flora in favour of pseudomonas and Proteus
 - Pre-existing mild lung injury may increase the susceptibility to oxygen-induced lung damage
- Other risks associated with O₂:
 - High O₂ → ↑atelectasis and Bronchoalveolar distension on post mortem studies. Absorption atelectasis occurs at FiO₂ as low as 0.3 – 0.5 and will ↑V/Q mismatch
 - Pressure: wall supply is usually 4 bar (3040 mmHg). Cylinder supply when full is 137 bar (104,120 mmHg)
 - Fire risk: turn off O₂ when defibrillating – sparks cause fires

Management of Hypoxia

- Check tube position, exclude atelectasis or pneumothorax
- ↑FiO₂
- ↑Mean airway pressure: use pressure control mode, ↑PEEP, ↑inspiratory time including inverse ratio ventilation
- Recruitment manoeuvre
- Treat dyssynchrony
- Consider paralysis
- Pulmonary vasodilators: Nitric oxide or inhaled prostacyclin: see RV dysfunction after Cardiac Surgery, see 153
- Oscillation: see Newer Ventilation Strategies, page 92
- Extracorporeal Membrane Oxygenation, page 162

Management of alarm for high peak pressure

- Immediate assessment: ABC
- Consider:
 - Ventilator problems
 - Circuit problems
 - Blocked or kinked tube
 - Patient problems

Patient-Ventilator Interaction

- Dyssynchrony:
 - Patient fails to achieve respiration in synchrony with the ventilator in the timing and duration of inspiration, inspiratory flow demand, and switch to expiration
 - → agitation, diaphoresis, tachycardia, HTN and weaning failure
- Triggering of inspiration:
 - PEEP_i hinders triggering as inspiratory muscles must first reduce Pao below ambient pressure. So Pmus must exceed PEEP_i. Extra load may add up to 40% of total inspiratory work in ARF with DHL. Helped by low levels of CPAP
 - Auto-triggering: Oversetting the pressure sensitivity to improve trigger function risks problems from cardiac oscillations, hiccups, circuit rainout (condensation) and mask leak in NIV (can even trigger ventilation in brain dead patients)
- Cessation of inspiration:

- Mechanical Ti shorter than neural Ti: prolonged inspiratory muscle effort during early expiration which may trigger an early breath
- Mechanical Ti longer than neural Ti: → passive inflation
- Management:
 - Exclude:
 - Airway complications eg tube impinging on the carina or obstruction, sputum
 - Pathology: pneumothorax, pulmonary oedema
 - Choose appropriate mode
 - Select sensitivity not too low or too high
 - Choose an appropriate ventilator and flow rate
 - Sedation
- NAVA: Neurologically Adjusted Ventilator Assist. Senses diaphragmatic contraction via an oesophageal probe → more accurate triggering. Particularly helpful at times when it's hard for the ventilator to get it right (eg large ET leak, NIV with mask leak). No trial data yet

Complications of invasive ventilation

- Equipment: malfunction, disconnection, contamination
- Pulmonary:
 - See Mechanisms of Ventilator Associated Lung Injury, page 112
 - Intubation: trauma to teeth, airway, etc.
 - VAP: See Ventilator Associated Pneumonia, page 120
 - VILI (eg diffuse lung injury due to regional over distension or from inadequate PEEP causing tidal recruitment and de-recruitment). See Mechanisms of Ventilator Associated Lung Injury, page 112
 - Overt barotrauma eg pneumothorax
 - Ventilator Induced Diaphragmatic Dystrophy (VIDD): small studies repeatedly show reduction in diaphragmatic thickness in controlled modes. Pressure support modes may increase thickness. Don't know how much patient work is enough to maintain it
 - O₂ toxicity: see Hazards of O₂ Therapy, page 85
 - Asynchrony: wasted respiratory work, impaired gas exchange and respiratory distress
- Circulation:
 - ↓RV preload → ↓CO
 - ↑RV afterload if the lung is over-distended
 - ↓Splanchnic blood flow with high levels of PEEP or mean Paw
 - ↑intracranial pressure with high levels of PEEP or mean Paw
 - Fluid retention due to ↓CO → ↓renal blood flow
- Other:
 - Gut distension
 - Mucosal ulceration
 - Peripheral and respiratory muscle weakness
 - Sleep disturbance, agitation and fear (may be prolonged after recovery)
 - Neuropsychiatric complications

Oral Decontamination

- See also:
 - Selective Gut Decontamination, page 54
 - Ventilator Associated Pneumonia, page 120
- Chlorhexidine:
 - The most commonly studied agent and it has been suggested this should be added to ventilator bundles (Wip et al, Current Opinion in Infectious Diseases, 2009)
 - JAMA April 2014: Meta-analysis of 16 studies, n = 3,630) of daily oral chlorhexidine. Differences between cardiac and non-cardiac studies in terms of outcomes – associated with ↓VAP in cardiac but not non-cardiac surgical patients. But combined no difference in VAP, LOS, mortality.
- Also trials of teeth cleaning vs sterilisation vs topical antibiotics

Malignant Hyperthermia

- Rare genetic disorder – usually autosomal dominant. Mutations of the calcium channel found in the sarcoplasmic reticulum of skeletal muscle
- Triggered by suxamethonium and volatile anaesthetic agents (usually within an hour) → uncontrolled calcium efflux → tetany and ↑↑ muscle metabolism

- Diagnosis: susceptible patient, exposure to triggering agent, signs of ↑metabolic rate (↑pulse, ↑tone, ↑O₂ consumption, ↑CO₂, marked hyperthermia)
- Complications: rhabdomyolysis, shock, DIC, mixed lactic and respiratory acidosis
- Treatment:
 - Remove triggering agent
 - Specific antidote: dantrolene 20 mg/vial, diluted to 60 ml with water, 2.5 mg/kg up to 10 mg/kg, repeated every 10 – 15 hours for 3 days)
 - Active cooling and supportive care
 - Muscle biopsy and family screening

Sedation in Ventilated Patients

- See also Delirium, page 352
- Original ventilators couldn't synchronise, so deep sedation was the standard of care
- Over-sedation prolongs ventilation and over sedation is common. Under sedation is uncomfortable, risks line or tube dislodgement, and ↑nursing workload
- Reduced sedation may lead to:
 - Reduced vasoactive drugs and fluids (which may also improve enteral nutrition tolerance)
 - Reduced duration of ventilation and ICU stay
 - Reduced psychological sequelae eg PTSD (eg Am J of Resp and Crit Care Med 2003, 168: 1457 – 61)
 - Choice of drugs is important to ↓delirium (BZDs are bad)
- Sedation scores: there are a number. Richmond Agitation-Sedation Scale (RASS) have been validated and is widely used, ranges from -5 to + 4, ideal is -2 to 0
- Observational study found early deep sedation negatively associated with LOS and 180 day mortality

Sedation Holds

- Studies on sedation holds:
 - Complex area to study – sedation and ventilation inter-related
 - An early trial was **Kress et al, NEJM 2000**, single centre trial of 128 mechanically ventilated patients with daily interruption vs only at the discretion of physician with no sedation target or protocol in the control group (?over-sedated). Medical ICU (no surgery, trauma), long placebo arm of NZ. Reduced LOS with interruption (6.4 vs 9.9 days). Long ventilation time in placebo arm
 - Girard et al, **Awakening and Breathing Controlled Trial (ABC Trial)**, Lancet **2008**, unblinded RCT in non-surgical patients in 4 centres in North America (presence of respiratory technician → ?generalisability), found a paired daily spontaneous awakening and breathing trial reduced LOS, one-year mortality and tracheostomy rates. ↑Self extubation in the intervention arm but no harm from this. Other studies less convincing
 - Daily Interruption of Sedation in Patients Receiving Mechanical Ventilation, Am J Crit Care, July 2011, Weisbrodt et al (CTG publication). Pilot study for test of protocol for blinded sedation
 - Early deep sedation is associated with longer ventilation and increased mortality in regression modelling in 251 patients. Is it causative or just a sign of being sicker? (Shehabi et al, SPICE Study Investigators and the ANZICS Clinical Trials Group, Am J Resp Crit Care Med, 2012)
 - Comparison of Sedation protocol + sedation protocol with daily interruption of sedation showed no difference in duration and more bolus sedatives in the daily interruption group. MRCT in 430 Canadian patients, Mehta et al, JAMA 2012
 - JAMA 2012, MRCT of sedation protocol (at historically low levels) or sedation protocol + daily interruption showed no difference, plus less work & bolus sedatives in the protocol only arm. Higher total doses of sedatives in daily interruption arm. Excluded OHCA and TBI.
- Studies on sedation holds generally show:
 - ↓duration in ventilation, ICU stay
 - Fewer CNS investigations
 - ↓Complications, including VAP, upper GI haemorrhage, bacteraemia, VTE and sinusitis
 - Single observation studies suggest no ↑ in psychological outcomes
- Potential risks of regular sedation interruption in those with:
 - Poorly controlled ICP
 - Difficult ventilation (eg dyssynchrony) → hypoxia
 - Particular risks from self-extubation (eg intubated for airway obstruction), or where there were not sufficient skilled staff to manage an unprotected airway
 - Therapy that is likely to be particularly distressing (burns, permissive hypercapnia)

Sedation Drugs

- **Morphine:**
 - See also Opioid Poisoning, page 269
 - Opioid analgesic activation predominantly μ (and some κ) opioid receptors, also anxiolytic and sympatholysis
 - Pharmaceutics: clear liquid in ampoule with 10 mg/ml
 - Dose: 1 – 5 mg/hr (+ loading dose)
 - Pharmacokinetics: initial rapid redistribution, elimination phase $T_{1/2}$ of ~ 2 hours. 35% protein bound. V_d 3.3 L/kg. Hepatic metabolism to active metabolite morphine-6-glucuronide which has longer half-life. 90% renal excretion.
 - Dynamics: effect prolonged with hepatic or renal dysfunction
 - SE: hypotension, sedation, respiratory and GI depression, rarely biliary spasm
 - Antagonist: naloxone
- **Midazolam:**
 - Pharmaceutics: colourless isotonic but acidic solution (pH3.3) as 1 or 5 mg/ml
 - Dose: bolus 1 – 5 mg, infusion 1 – 5 mg/hr
 - Kinetics: onset in minutes, elimination half-life 1 – 3 hours, but may be much longer in the critically ill, especially elderly or renal failure. 97% protein bound, metabolised by P450-3A to active metabolite 1-OH-methylmidazolam and then renally excreted
 - Dynamics: ICU dose of 0.03 – 0.2 mg/kg/hr. Action via activation of the benzodiazepine receptor which augments the inhibitory effect of the GABA receptor.
 - SE: cardiorespiratory depression, withdrawal if rapid cessation. Compatible with many drugs and infusions (except Hartman's)
- **Propofol:**
 - Pharmaceutics: white isotonic aqueous emulsion containing soya oil and egg lecithin. Supports bacterial growth so syringes/bottles should be changed every 12 hours. 1 kcal/ml
 - Dose: 1 – 3 mg/kg/hr
 - Kinetics: Hydrophobic with high lipid solubility that allows it to cross the BBB rapidly. Rapid redistribution to tissues (2 – 8 minutes) → short duration of action, but terminal elimination of 3 – 20 hours – context sensitive half-life. May influence waking after days of infusion. 98% protein bound
 - Dynamics:
 - Dose 1 – 3 mg/kg/hr (higher rates have been associated with rhabdomyolysis)
 - GABA receptor action (although different from benzodiazepine receptor)
 - Effective anticonvulsant
 - Compatible with dextrose, but not with many other solutions or drugs
 - Complications:
 - Hypotension from vasodilation → ↓preload, and mild myocardial depression
 - Hyperlipidaemia possible. Monitor triglycerides. Adjust TPN
 - Propofol Infusion Syndrome
 - Risk factors:
 - Large doses (> 4 mg/kg/hr for > 48 hours in adults), high concentrations (2% vs 1%)
 - Age
 - Acute neurological injury
 - Low carbohydrate intake
 - Catecholamine and/or corticosteroid infusion
 - Findings:
 - Unexplained lactic acidosis
 - Increasing inotrope requirement and/or cardiovascular collapse
 - Arrhythmia, heart block
 - Lipaemic serum
 - Brugada-like ECG (convex-curved ST elevation in V1 – V3)
 - Rhabdomyolysis, with ↑CK and ↑K
 - Renal failure
 - [Green urine a side effect of propofol, not the infusion syndrome]
 - Management:
 - High index of suspicion
 - Stop propofol!
 - Standard cardio-respiratory support

- Consider pacing (although may be resistant to pacing)
 - Adequate carbohydrate intake (6 – 8 mg/kg/min)
 - Haemodialysis and haemoperfusion used but unproven
 - ECMO: case reports of success
- Thiopentone:**
 - Pharmaceutics: Powder, dissolved in water giving an alkaline solution with a final concentration of 25 mg/ml
 - Kinetics: Onset of action in minutes. 80% protein bound. Very large volume of distribution. Elimination $T_{1/2}$ 3 – 8 hours (presumably longer after prolonged infusion). Metabolised in liver to inactive metabolites that are renally excreted
 - Dynamics: Dose 25 – 100 mg/hr (0.5 – 1.5 mg/kg/hr) with boluses of 25 – 100 mg as required. Effective CNS depressant including resultant isoelectric EEG and fixed dilated pupils. Incompatible with many solutions (especially if acidic). Discard after 24 hours. Time to waking delayed (up to days) after lengthy infusion and/or liver dysfunction
- Dexmedetomidine:**
 - Relatively selective α_2 agonist with sedative and analgesic properties. 8 times greater α_2 affinity than clonidine
 - Sedated but arose easily, allowing neurological examinations. Useful in agitation
 - Pharmaceutics: clear liquid in ampoule with 200 μ g/2 ml. Expensive
 - Pharmacokinetics: initial rapid redistribution (6 mins) followed by elimination $T_{1/2}$ of ~ 2 hrs. 94% protein bound. Vd 1.5 l/kg. Near complete hepatic metabolism to inactive metabolites that are excreted in urine
 - Administration: only by iv infusion, load of 1 μ g/kg then 0.2 – 0.7 μ g/kg/hr (or higher)
 - Dynamics: effects prolonged with hepatic or renal dysfunction
 - Dexmedetomidine vs midazolam for sedation of critically ill patients, JAMA 2009, Riker et al. In patients expected to be ventilated for > 24 hours, Dexmedetomidine 0.2 – 1.4 μ g/kg/hr vs midazolam 0.02-0.1 mg/kg/hr titrate to a RASS of -2 to + 1. Fentanyl analgesia, midazolam rescue in both groups. No difference in percentage of time within target RASS (primary outcome). *More delirium and longer time to extubation with midazolam but no change in ICU stay.* More bradycardia in dexmedetomidine group. Trial problems: lack of intention to treat analysis, no analgesic effect of dexmedetomidine seen, control arm did not cease midazolam well before expected extubation (standard practice)
 - Non-inferior to propofol in PRODEX trial (not deep sedation). See review in Crit Care, 2013 17:320
 - Complications:
 - Cardiovascular: bradycardia and hypotension
 - Not well studied for long term administration to the critically ill. Licensed for use for 24 hours only in Australia, though utilised in trials up to 120 hours
- Ketamine:**
 - Dissociative anaesthetic with profound analgesia, NMDA receptor antagonist. Also bronchodilation
 - Pharmaceutics: clear liquid in ampoule with 200mg/2 ml
 - Pharmacokinetics: initial rapid redistribution ($T_{1/2}$ 10 – 15 mins), followed by β -phase $T_{1/2}$ of about 2.5 hours. 2 – 50 % protein bound, Vd 1.8 L/kg, 90% excreted in urine after extensive hepatic metabolism to less active metabolites
 - Action: onset in 30 secs, duration of analgesia approximately 30 minutes (profound analgesia of shorter duration)
 - Dose: Anaesthetic dose 1 – 2 mg/kg, analgesia can be achieved with lower doses (10 – 20 mcg or 0.1 – 0.3 mg/kg) or low dose infusion (0.1 mg/kg/hr)
 - SE: Relative preservation of respiratory reflexes except at higher doses, can increase BP and ICP, emergence reactions, \uparrow airway secretions, \uparrow uterine tone
- Small trial of **melatonin** in tracheostomised patients failed to increase amount of sleep (Ibrahim and Bellomo, Critical Care and Resuscitation, 2006)

Traditional Ventilation Modes

Ventilation Terminology

- Mechanical breath description:
 - Control variable: eg set pressure or volume
 - Trigger variable: the thing that starts inspiration, eg the patient (changes in pressure or flow), or set rate

- Limit variable: the maximum value during inspiration
- Cycle variable: that which ends inspiration (time, volume, pressure, flow):
 - Volume controlled: inspiration ends when pre-set volume is reached \Rightarrow volume-cycled
 - Pressure Controlled: inspiration ends after pre-set inspiratory time \Rightarrow time-cycled
 - Pressure Support Ventilation: inspiration ends when flow rate reaches certain percentage of peak flow \Rightarrow flow-cycled
- Type of control or targeting:
 - Set point: the ventilator delivers and maintains a set, constant goal
 - Servo: ventilator adjusts its output to a patient variable (eg in proportional assist ventilation inspiratory flow follows the patient)
 - Adaptive: ventilator adjusts a set point to maintain a different operator-selected set point
 - Optimal: ventilator uses a model to calculate the set points to achieve a goal

Controlled Mechanical Ventilation (CMV)

- Characteristics:
 - Relaxed patient, constant flow during inspiration
 - Volume delivered depends on inspiratory time
 - Airway pressure depends on lung and chest wall elastance and respiratory system resistance
 - Expiration is passive decline in volume to FRC
 - At end of inspiration, inspiratory flow stops, and lung resistance dissipates from peak to plateau pressure
 - Minute ventilation = fixed respiratory rate (f) * tidal volume (V_t)
- Useful for:
 - Alveolar hypoventilation (eg respiratory muscle weakness)
 - PaCO_2 needs to be in a fixed range (eg \uparrow ICP)
 - When work of breathing needs to be minimised (eg cardiorespiratory failure)
- Can't match respiratory effort – so spontaneous, supported or assisted breaths not possible

Assist Control Ventilation

- In addition to standard set f, patient can trigger a standard CMV breath
- May be little reduction in respiratory work compared to an unassisted breath as muscles will still contract throughout breath

Synchronised Intermittent Mandatory Ventilation (SIMV)

- T_i is partitioned into patient-initiated and true spontaneous breaths to avoid breath-stacking
- During spontaneous breaths, the \uparrow work imposed by the ET tube, circuit and ventilator must be overcome
- In weaning trials, SIMV is slower than T-piece and PSV

Pressure Support Ventilation

- Each patient-triggered breath is supported by gas flow to achieve a pre-set pressure (above PEEP_e)
- Leads to reduction in P_{mus} and work of breathing
- Ventilator usually detects a fall in the inspiratory flow rate to either 25% of the initial flow rate or less than 5 L/min
- Disadvantages: variable V_t , excessive V_t and patient-ventilator dyssynchrony

Adaptive Pressure Control

- = Pressure Regulated Volume Control, Adaptive Pressure Ventilation, Volume targeted pressure control
- Pressure-control can't guarantee a tidal volume
- APC delivers pressure-controlled breaths with an adaptive targeting scheme – adjusting inspiratory pressure to deliver a set minimum tidal volume
- Flow of gas varies to maintain constant airway pressure. Allows a patient who generates an inspiratory effort to receive flow as demanded, which is more comfortable (as opposed to volume controlled, in which flow is fixed, and if the patient's effort is big enough \rightarrow flow asynchrony in which the patient doesn't get the flow they asked for)
- If patient effort is large enough, the T_v will increase in spite of \downarrow respiratory pressure
- Not appropriate for patients who have an inappropriate increased respiratory drive (eg metabolic acidosis) since the inspiratory pressure will \downarrow to maintain the targeted average tidal volume, shifting the work of breathing onto the patient

Proportional Assist Ventilation

- Inspiratory P is applied in proportion to patient effort
- Requires normal or elevated respiratory drive
- Contra-indicated in respiratory depression and large air leaks (eg broncho-pulmonary fistula). Caution in hyperinflation, when the patient may still be exhaling but the ventilator doesn't recognise it
- Leads to elastic and resistive unloading
- → ↓work of breathing and ↑*patient-ventilator synchrony* → ↓sedation and improved sleep
- More difficult to use and no outcome studies showing improving yet

Adaptive Support Ventilation (ASV)

- Ventilator supplies mandatory minute volume, if the patient would otherwise generate a lower minute ventilation
- Delivers pressure controlled breaths according to an algorithm designed to minimise the work of breathing – selecting a T_v and f
- Normal M_v is based on patients ideal weight and estimated dead space
- Adjusts I:E ratio to avoid air trapping

Bilevel Ventilation

- In a patient without spontaneous breaths is equivalent to PSV plus PEEP, or pressure controlled intermittent mandatory ventilation
- Ventilator maintains a constant pressure (set point) even in the face of spontaneous breaths
- Time in each airway pressure called Thigh and Tlow
- V_t depends on respiratory compliance and the difference between the CPAP levels
- Levels should be titrated to prevent end-expiratory alveolar collapse and tidal over-distension
- Spontaneous ventilation can be achieved at any point in the cycle (cf above modes where synchrony is critical):
 - Patients contributes 10 – 40% of the M_v
 - Potentially reduces need for sedation (not clear from the limited evidence)
 - Maintaining spontaneous breathing has haemodynamic and ventilatory benefits. Some machines still attempt synchronisation with the two levels to avoid asynchrony
- Biphasic:
 - Main goal is synchrony
 - Other names: BiLevel, BIPAP, DUOPAP – don't confuse with BiPAP which is non-invasive
 - Uses conventional I:E ratios (not usually exceeding 1:1)
 - In a patient with poor drive or paralysed, this is the same as pressure controlled ventilation

Newer Ventilation Strategies

- Standard mode for patients with ARDS is volume-controlled ventilation with a low T_v lung protective strategy (6 ml/kg ideal body weight). May require heavy sedation and even paralysis
- Consider a rescue strategy if:
 - $FiO_2 > 70\%$ and $PEEP > 14$ cm or
 - $pH < 7.25$ with a tidal volume > 6 ml/kg and a $P_{plat} > 30$

Summary of Initial Ventilator Settings

HFOV	APRV
Frequency: pH < 7.1 4Hz pH < 7.2 5 Hz pH < 7.35 6 Hz pH > 7.35 7 Hz Amplitude (power): 70 – 90 cm H ₂ O Paw: 5 cm H ₂ O > plateau pressure on CV to max of 35 cm H ₂ O Bias flow: 40 L/min Inspiratory time 33% FiO ₂ 100 %	Thigh: 4- 6 secs Tlow: 0.6 – 0.8 seconds based on T-PEFR Phigh: Same as plateau pressure on CV or Paw + 2 – 4 cm H ₂ O if transition from HFOV Plow 0 FiO ₂ 100%

- Change ventilator settings depending on blood gas:

	HFOV	APRV
↓O ₂	↑FiO ₂ ↑Paw by 2 cm H ₂ O to max of 40 Recruitment manoeuvre Increase bias flow	↑FiO ₂ ↑Phigh to max 40 cm H ₂ O Recruitment manoeuvre ↑Thigh Adjust Tlow to keep T-PEFR > 50%
↑CO ₂ /↓pH	↓frequency to minimum of 3 Hz ↑Power to max 90 cm H ₂ O ↑Inspiratory trapping (but ↑ air trapping) Introduce endotracheal cuff leak	Ensure patient is spontaneously breathing ↑Tlow ↑Phigh and Thigh to increase minute ventilation

Airway Pressure Release Ventilation

- = APRV
- Biphasic and APRV are conceptually similar – except APRB spends less time at low pressure
- Description:
 - Minute ventilation and CO₂ excretion augmented by brief (0.5 – 1.5 s) periodic cycling to a lower level of CPAP (usually 0)
 - An extreme form of pressure controlled, time cycled, inverse ratio ventilation, with I:E ratio of ~ 4:1
 - Effectively using autoPEEP to ↑FRC and ↑area for gas exchange
- Physiology:
 - P_{low} is usually 0 – collapse is prevented by iPEEP during the short expiration phase
 - T_v determined by Phigh and respiratory compliance. Significantly lower peak/plateau pressures for a given tidal volume than conventional ventilation → unloads inspiratory muscles → lower work of breathing
 - Conventional ventilation preferentially fills and distends compliant alveoli, rather than fibrotic alveoli with a longer time constant for filling. APRV aims to fill the latter without over-distending the former
- Settings:
 - Phigh and Thigh: main determinants of Paw and therefore oxygenation/gas exchange
 - (Phigh – P_{low}), T_{low}, and the patient's spontaneous M_v determine ventilation and therefore CO₂
 - Set initial Phigh at most recent plateau pressure (usually 20 – 35 cm), P_{low} at 0, Thigh 4 – 6 seconds, T_{low} 0.6 – 0.8 secs
 - If obstructive lung disease the T_{low} 0.8 – 1.5
- Benefits:
 - Main goal is to maximise mean airway pressure → ↑Oxygenation and ↑recruitment. Occurs slowly over 24 hours
 - Can spontaneously breath through the whole cycle → decreased need for sedation (→ shorter ventilation and ↓delirium) and benefits in ventilation and haemodynamics in animal and clinical trials
 - Lowers peak airway pressure
- Weaning:
 - Lower Phigh and extend Thigh → ↓minute ventilation by machine → forces patient to breathe more. Equivalent of a progressive spontaneous breathing trial with a smooth transition to CPAP
 - Phigh should be ↓ in increments of no more than 3 cm H₂O no more often than 8 – 12 hourly otherwise derecruitment
 - Back to conventional ventilation when Phigh < 20, T_{high} > 6 and FiO₂ < 40%
- Has been used in trauma patients with ARDS, limited data in medical patients. Speculation that it may be helpful in morbid obesity
- Contraindicated in:
 - Severe COPD or asthma
 - When deep sedation is required – best for spontaneously breathing patients – can work without spontaneous breathing but patient breaths contribute a significant amount to minute ventilation
 - Intravascular volume may require augmentation to offset ↓venous return

High Frequency Ventilation

- Small V_t (1 – 3 ml/kg) delivered at high f (100 – 300/min)
- “Experimental”, used in ARDS to minimise lung injury, as an EMCO sparing strategy
- **High Frequency Jet Ventilation (HFJV):**

- Dry gas from a high pressure source delivered into an intratracheal catheter of special ET tube
- Used with improvement in gas exchange in ARDS
- Risks:
 - Inadequate humidification
 - Gas trapping if severe airflow limitation
- **High Frequency Oscillation Ventilation (HFO):**
 - How it works:
 - Superimposes very small mandatory breaths at rates of 3 – 7 Hz (oscillations) on top of spontaneous breaths
 - Ventilator delivers a constant flow (bias flow), a valve creates resistance to maintain airway pressure, and a piston pump oscillates a 3 – 7 Hz
 - Tidal volumes are not measured but are approximately the volume of the anatomic dead space
 - Mechanism of effect unknown. Postulated reasons include:
 - Gas transport in the proximal airway is by convection (bulk flow) with transition into diffusion deeper down
 - Coaxial flow with gas in the middle of the ET tube and large airways flowing inwards, and periphery flowing outward
 - Augmented molecular diffusion in the alveolar due to → kinetic energy
 - Asymmetric filling of adjacent alveoli (pendelluft) due to differing emptying times
 - What it achieves:
 - Small tidal volumes allow higher end expiratory lung volumes with less over distension → greater lung recruitment with less risk of over distension
 - High respiratory rate lowers CO₂
 - Smaller early studies show ↑oxygenation and improved ventilation
 - Oscillate Trial (Canada) in early ARDS, n = 548, stopped early for ↑mortality. See editorial by Young, NEJM 2013
 - Oscar Trial (UK), RCT of n = 795 in 29 ICUs, in ARDS after 48 hours. Used Novalung R100 oscillator. No difference in mortality (~41%) or ventilatory free days
 - Possible that the benefit of ↑O₂ offset by haemodynamic compromise
 - Why did Canadians oscillating do worse? Did Oscillate look after the control arm better (6 vs 8 ml/kg V_t)
 - Parameters:
 - Frequency: lower than 3 Hz is not recommended as → ↑oscillator depth → ↑barotrauma. Max of 7 in adults (higher in kids). Slowing the frequency → ↑PaO₂ due to increased time for gas exchange. T_v is not constant with increasing rate, so faster rate → smaller tidal volume → ↑proportion of dead space ventilation
 - Power: is the voltage that drives the piston, generating tidal volumes. Expiration is active. Adjusted to obtain a slight wiggle at the patients thigh, alternatively PCO₂ + 20
 - Bias flow: max is 60 L/min. Increasing it → ↑Paw → ↑oxygenation
 - Mean airway pressure is adjusted in increments of 2. Increase if recurrent hypoxic events that resolve with recruitment
 - Inspiratory time: should always < 50% to minimise air-trapping (ET tube contributes > 50% of the total airway resistance during expiration). 33% optimal haemodynamically. Increasing it will → ↑Paw → ↑O₂, and → ↑T_v → ↓CO₂
 - Adjustments:
 - Target pH > 7.25 – 7.35
 - Aim for saturations > 88% or PaO₂ > 55 to minimise risk of O₂ toxicity
 - Utilise the highest possible frequency to minimise the tidal volume and only decrease for CO₂ control if delta P maximal
 - PO₂ determined by mean airway pressure and FiO₂
 - CO₂ adjusted first by ↑amplitude then by ↓frequency, then by ↑inspiratory time, and finally by reducing anatomic dead space (by deflating the cuff enough to ↓Paw 5 – 8 cm and then increasing Paw by this amount. Risk of aspiration)
 - Spontaneous breaths:
 - Patients sedated to level required to suppress deep breaths or cough as deep spontaneous breath will trigger alarms and affect ventilator performance
 - A significant spontaneous inspiration can exceed the ventilator flow rate

- Spontaneous breaths on HFOV help maintain end-expiratory alveolar expansion in dependent lung regions → better V/Q distribution
- Weaning:
 - No consensus on who to wean to conventional ventilation
 - Suggested protocol:
 - Decrease O₂ to < 60%
 - Decrease P_{aw} in 2 cm increments to 30 cm
 - Wean O₂ to 40% as long as sats > 88%
 - Wean P_{aw} to 20 – 25 cm (any lower → derecruitment)
 - Back to HFOV if sats < 88% in first 48 hours after transition
- Complications:
 - Low familiarity
 - Can't auscultate lungs
 - Over/under distension of the lung
 - Pneumothorax
 - ET occlusion from secretions
 - Haemodynamic compromise
 - No transport ventilator and can't nebulise medications
 - Contraindicated in severe airflow obstruction or intracranial hypertension
 - ↑work of breathing in spontaneously breathing patients
- Benefits in neonates and children with ARDS, data in adults inconclusive
- Several studies show oxygenation improves after switching to HFOV but mortality benefit hasn't been demonstrated in randomised trials – may not have been powered to detect small changes in mortality

Weaning from Mechanical Ventilation

- See:
 - Respiratory Hot Cases, page 375
 - McConville, NEJM review article
- = Gradual process of improving strength to load ratio of the respiratory system
- 40% of ICU time is taken by weaning
- Criteria for commencing weaning:
 - Reversal of original insult
 - Neuromuscular state: ability to initiate a spontaneous breath
 - Adequacy of oxygenation: low PEEP (5 – 8 cm H₂O) and FiO₂ < 0.4 – 0.5
 - Cardiovascular stability
- Also consider whether an artificial airway is required for airway protection
- Optimising patient for weaning:
 - ↓Work of breathing:
 - ↑compliance: treat infection
 - ↓resistance: treat bronchospasm; physio, bronchoscopy or mini-trac to mobilise sputum
 - Optimise position
 - ↓CO₂ production: treat fever, agitation, pain, over-feeding
 - ↓dead space
 - ↑Power:
 - preserve muscle strength: nutrition, maximise spontaneous breathing
 - improve muscle strength: avoid fatigue, normalise electrolytes (esp Mg, Ca, K)
 - Optimise drive to breathe: ↓ sedation, agitation
- Predicting success of weaning:
 - Increased risk of failure (up to ~ 20%) if:
 - Elderly
 - Prolonged ventilation
 - COPD
 - Positive fluid prior to extubation
 - Failure due to:
 - ↑rate → ↓V_t → ↑PCO₂
 - Central depression

- A number of indices have been proposed as predictors of failure – rarely used alone. Rapid shallow breathing index (f/V_t) > 105 breaths per litre per minute on a T piece for one minute predictive of failure, one large study reported increasing risk from 57. subsequent studies report varying results
- Risk factors for reintubation in small studies:
 - Medical/neurological over surgical patients
 - ↑secretions
 - ↓mental state
 - Inadequate cough
 - Positive fluid balance
 - Pneumonia
 - Failure of 2 or more SBTs
 - Comorbidities, including heart failure
 - Computerised systems for continuously assessing and reducing ventilatory support have conflicting results
- Spontaneous breathing trial algorithm. Failure defined as:
 - RR > 35
 - Sats < 90
 - HR > 140
 - Sustained change in HR > 20%
 - ↑anxiety or diaphoresis
- Ventilatory approach to weaning:
 - Brochard et al, Am J of Resp and Crit Care Medicine, 1994. RCT in 3 ICUS of 109 ventilated patients ready for weaning. Those who failed 2 hours on a T piece were randomised to SIMV, PSV or further T piece sessions. PSV best at 21 days
 - Esteban et al, NEJM 1995, 4 methods trialled. Once daily spontaneous breathing trial equally as effective as multiple daily trials and led to extubation 3 times more rapidly than SIMV and twice as quickly as PSV
 - Automated weaning: Cochrane Review (Rose 2013) of 15 trials (high quality evidence) showed ↓ duration of ventilation (17%), ↓ICU LOS but not hospital LOS or mortality
- Use of NIV in weaning:
 - Survival benefit in COPD, no overall benefit in other groups in controlled studies (Burns et al, BMJ 2009)
 - NEJM 2004, Esteban et al: Early extubation to NIV better than prolonged ventilation, as long as you do it in the right group. Failed extubation was randomised to re-intubation vs NIV. NIV did worse except the 10% with COPD who did better. But ~12 hr delay to reintubation of NIV – floundered for too long first?
 - Better in those electively weaned to NIV due to high risk of failure, than as a rescue therapy for failed extubation (Nava et al, Crit Care Med 2005; Esteban et al, NEJM 2004)
 - Meta-analysis (n = 1211) of NIV post-extubation in cardiothoracic surgery round ↓ reintubation, ↓ mortality with greatest benefit in high risk and no benefit in low risk. Opler 2013 Crit Care & Resus.
- Strategies to reduce the need for ventilation at all that have RCT evidence:
 - EGDT in sepsis (Rivers et al)
 - NIV in COPD or cardiogenic oedema (Brochard et al, NEJM 1995)
- Strategies to ↓ the duration of ventilation with RCT evidence:
 - Low tidal volume ventilation (ARDSNet)
 - Daily interruption of sedation (Kress et al)
 - Interruption of sedation before spontaneous breathing trial (Girard et al)
 - Early physical and occupational therapy (Schweickert et al, Lancet 2009)
 - Conservative fluid management in ARDS (ARDSNet, NEJM 2006)
 - Strategies to reduce VAP (Dezfulian, Meta-analysis Am J Med 2005)
 - Use of a BNP guided diuresis protocol (vs physician guided diuresis) reduced ventilator days but not other outcomes (n = 304, Am J Resp Crit Care Med, 2012). Effect strongest in LV systolic dysfunction

Tracheostomy

- See also:
 - ANZICS Consensus Statement on Percutaneous Dilatational Tracheostomy (on website)
 - Ventilation in COPD, page 123

- Early tracheostomy has become more common due to:
 - Ease of percutaneous technique
 - Growth of other care settings which can manage a trachy → earlier ICU discharge
 - Not due to evidence of benefit. Medicare reimbursements in the USA are high for tracheostomy patients. “Wait and see” may lower repayments

Indications for Tracheostomy

- Indications for a tracheostomy:
 - No reliable prediction tool
 - Airway maintenance: upper airway obstruction or inability to protect the airway
 - Prolonged ventilation: prolonged dependence on mechanical ventilation, secretion management, permanent access in traumatic or neurological diseases
 - Griffiths et al, BMJ 2005, Meta-analysis of the timing of tracheostomy in adult patients. Huge number of papers screened, 5 selected of 406 patients. No difference in mortality or the risk of pneumonia. Reduced length of artificial ventilation and LOS
 - TracMan study subsequently reported: day 1 – 4 (if expected to require > 7 more days ventilation) vs after day 10 in 909 patients in a MRCT in the UK. Under recruited. No difference in 30 day or 2 year mortality. Only 45% of patients allocated to late tracheostomy actually got one. May be benefit from waiting. Very little reduction of sedatives after tracheostomy (unclear what this means or whether it masked any benefit).
 - Early percutaneous tracheostomy vs prolonged intubation of mechanically ventilated patients after cardiac surgery: a RCT, Ann Intern Med 2011, Trouillet et al. Early percutaneous tracheostomy didn’t alter clinical outcomes or survival in post-cardiac surgery patients requiring prolonged ventilation – but better sedation, comfort, autonomy and nutrition
 - Meta-analysis, 13 RCTs, n = 2,434, 800 deaths, trachy < 1 week vs > 1 week found lower ICU mortality but not 1 year mortality. Siempos, Lancet, Resp Med 2014
 - Studies have been in respiratory failure, not neurological injury
- In safe hands, percutaneous is at least as safe as a surgical tracheostomy and associated with lower incidence of infection. Ciaglia technique simplified from multiple to single graduated dilator, but this may cause more tracheal wall injuries and ring fractures
- Contraindications:
 - Absolute contraindications: Need surgical approach if:
 - High risk of active bleeding
 - Unstable patient or emergency airway required
 - Child < 16: small, mobile and compressible airway
 - Infection over the site
 - Anatomical anomalies: eg mass or goitre
 - Relative:
 - Known or suspected difficult airway
 - Difficult landmarks, including 1st and maybe 2nd tracheal rings being retrosternal (short neck), previous tracheostomy
 - Unstable cervical injury
 - INR > 1.5 or platelets < 50 or therapeutic clexane
 - Compromise respiratory function: FiO₂ > 0.6 or PEEP dependence > 10 cm

Complications of Tracheostomy

- Overall complication rates of 4 – 9%, minor bleeding and desaturation being the most common. Obesity increases complication risk 2.7 fold in one study
- During insertion:
 - Loss of airway in ~ 1 in a 1000
 - Haemorrhage:
 - Minor bleeding: minimise bleeding with rectifying coagulopathy, adrenaline with local and head up. If bleeding, continue with tracheostomy as it provides compression
 - Major bleeding: secure the airway by translaryngeal intubation with the cuff below the stoma so the lungs are protected. Urgent referral to a senior surgeon (ENT, cardiothoracic, vascular). Check and correct FBC and coags, send cross match.
 - Aspiration: ensure starved or aspirate stomach
 - Damage to local structures:
 - Worst complication is splitting posterior tracheal wall

- Surgical emphysema
- Pneumothorax
- Cricoid cartilage damage
- Misplacement in pre-tracheal tissues, oesophagus or right main bronchus
- Occlusion of the tip against the carina or tracheal wall
- Complications following insertion:
 - Accidental decannulation:
 - Be cautious of heavy attachments (eg in-line suction)
 - Material mortality risk. Must handle as an airway emergency for which staff must be trained
 - Biggest problem is attempted recannulation and bagging → massive surgical emphysema.
 - Try passing suction catheter
 - Can't recannulate within 3 days of insertion – must intubate, backup is LMA. Basically ignore the trachy and manage airway as if there were no tracheostomy
 - > 3 – 7 days attempt recannulation with capnography before bagging
 - Blockage with secretions
 - Infection
 - Tracheal damage: mucosal ulceration, tracheo-oesophageal fistula
 - Late bleeding: erosion of a vein/artery. Especially serious is the right brachio-cephalic artery (innominate artery) → massive bleeding. Finger pressure to the root of the neck in the sternal notch. Slowly and steadily inflate balloon to maximum pressure (but without popping it). Urgent surgical referral. Sometimes needs cardiothoracic bypass to repair.
 - As with any surgical procedure, follow-up is critical
- Late complications of a tracheostomy:
 - Tracheal dilation and persisting fistula
 - Tethering (Cosmetic)
 - Tracheomalacia: increasing flaccidity of the trachea following prolonged intubation leading to expiratory stridor
 - Tracheal Stenosis (>15% reduction in tracheal diameter) – rare
 - Polyps, ulcers, aspiration, swallowing difficulty

Anatomy of the Trachea

- Trachea is attached superiorly to the cricoid cartilage, by the cricotracheal membrane
- Trachea is covered anteriorly by skin, superficial fascia, strap muscles (sternohyoid, sternothyroid) and deep (pretracheal) fascia
- 2nd to 4th rings of the trachea are covered by isthmus of the thyroid anteriorly. Branches of the superior thyroid artery run along the superior aspect of the thyroid isthmus, anterior to the trachea. Lateral lobes of the thyroid lie between the trachea and the carotid sheath and its contents
- Inferior thyroid veins lie anterior to the lower part of the cervical trachea, posterior to the strap muscles
- Oesophagus lies posterior to the trachea
- Carotid sheath containing carotid artery, jugular vein, and vagus nerve lie posterolateral to the trachea
- Recurrent laryngeal nerves lie posterolaterally in the groove between the trachea and the oesophagus
- Anterior jugular veins are often connected by a vein that runs superficially across the lower neck.

Procedure for Bronchoscopy

- Risk/benefit assessment, including:
 - Review of absolute and relative contraindications
 - Thorough exam of neck anatomy
 - Airway assessment (including review of intubation records)
- Informed consent
- Fasted, or if large bore NG then aspirate
- Minimise other distractions, during normal working hours with suitable skill mix
- Skill airway doctor to manage the airway
- Have difficult airway equipment available and fibre-optic scope
- Routine use of bronchoscope is controversial:
 - Uses include checking guide wire placement, followed by withdrawal, and rechecking for clots/placement before cuff inflation
 - Risks include partial occlusion of the ETT tube, ↑complexity and cost of the procedure, distraction from airway management, damage to bronchoscope by needle

- ANZICS recommends a bronchoscope should always be available, and its use should be considered for every procedure
- Ultrasound guidance is an alternative in trained hands. The first marker of an anterior jugular vein under the stoma site is uncontrolled bleeding!, also visualise thyroid, but not within the trachea, and limited usefulness in the cannulation itself due to small field
- Monitoring: must include capnography for confirming placement
- Pre-oxygenate with FiO₂ of 100% and continue through procedure
- Position with rolled towel or pillow under scapulae
- Withdraw ET so cuff is at or just below cords. LMA use has also been described
- Ideal placement is between 2nd and 3rd rings, failing that between 1st and 2nd. Placement between the cricoid cartilage and 1st ring may → long term sequelae.
- Secure carefully. Do not remove ETT until secured
- Post procedure CXR to ensure correct placement and exclude pneumothorax, pneumomediastinum and lung collapse

Types of Tracheostomy Tube

- Tube sizing:
 - Tubes are sized according to their function internal diameter (ID) at the narrowest point (ISO 5366-1:2004). This may not take account of the inner cannula in some types
 - Need to limit the outside diameter to approximately $\frac{3}{4}$ of the internal diameter of the trachea (in order to allow airflow when the cuff is deflated). For females an OD of 10mm, males 11 mm, is usual
 - If the tube is too small → have to over inflate the cuff → mucosal damage
- Obese patients: may require a tube with an extended proximal length
- If problematic airway may be useful to consider options such as downsizing, changing to an uncuffed or fenestrated tube, or a tube with the option for sub-glottic aspiration
- Fenestrated tube:
 - Fenestration in the posterior wall of the intra-tracheal component of the shaft above the cuff
 - Aim is to allow airflow through as well as around a capped tube
 - Not recommended at the time of percutaneous tracheostomy. Should not be used while still requiring mechanical ventilation because of the risk of surgical emphysema (even if a non-fenestrated inner is in place)
 - Fenestrations are frequently poorly positioned within the trachea and may promote development of granulation tissue in the tracheal mucosa
 - In practice, downsizing or switching to an uncuffed tube is sufficient to improve flow of air through the upper airway in most patients
- Cuffed tubes:
 - Cuff pressure should be checked regularly and not exceed 25 cmH₂O. Causes of excessive pressure are:
 - Use of a tube that is too small
 - Poor tube positioning in the trachea
 - Tracheal dilation
 - Over-inflation of the cuff
 - Small trial evidence of benefit of uncuffed over cuffed tubes in T piece trials (Hernandez et al, ICM 2013)
- Adjustable flange tubes: Distinct angulation limiting maximum proximal length to 40 mm. Constructed using thermosensitive PVC that softens at body temperature. No inner cannula. Not specifically designed for compatibility with percutaneous introducer kits
- Speaking valves: should only be used with an uncuffed tube, a cuffed tube with the cuff deflated, or a fenestrated tube with the cuff deflated
- Occlusion or decanulation cap: blocks of tracheostomy. Hard for the patient and ↑airways resistance (higher than when the tube is removed). Best with fenestrated tube and fenestrated inner

Routine tracheostomy care

- Is eating with a tracheostomy tube possible: Tracheostomy cuff does not prevent aspiration. See Swallow Assessment, page 350
- Inner tubes should be changed regularly
- Entire tube should be changed every 30 days:
 - Have appropriate emergency equipment
 - Explain procedure to patient

- Nil by mouth for 4 hours
- Position patient – semi-recumbent position
- Monitor oxygen sats. Pre-oxygenate if oxygen dependent
- Check the new tube: check for cuff leaks and that the introducer is easy to remove
- Lubricate the new tube
- Remove old tracheostomy dressing and clean around the site
- Suction the oropharynx and deflate cuff while suctioning trachea
- Two techniques for exchange:
 - Using introducer: remove the old with a down and out movement. Insert new one initially 90° to cervical axis then rotate down the trachea. Remove introducer immediately
 - Using airway exchange device: railroad the new one over it during expiration
- Insert inner cannula and check the cuff pressure
- Confirm normal chest movement, air entry, O₂ sats. Palpate for surgical emphysema
- Clean the stoma site, secure and dress the tracheostomy
- Document: tube size, type and complications
- Cuff pressure should not exceed 25 cmH₂O
- Humidification is essential
- Any difficulty with passing a suction catheter requires immediate attention

Weaning and Decanulation

- A tracheostomy should be removed as soon as it is no longer required
- Passy Muir Speaking Valve:
 - Inhale through the valve, exhale via vocal chords: permits speaking
 - Contraindications:
 - Unconscious patient
 - Inflated tracheostomy tube cuff
 - Limitation to exhalation, eg severe upper airway obstruction
 - Excessive secretions
 - Severe COPD with gas trapping
 - ET tube
- Risks during decanulation:
 - Airway obstruction
 - Aspiration
 - Ventilatory failure
 - Sputum retention
 - Difficulty in oral reintubation
- Decanulation should be performed:
 - Using objective criteria:
 - The process necessitating the insertion has resolved
 - Patient is able to cough, swallow and protect their airway
 - Ventilatory reserve is adequate (decanulation increases the anatomical dead space → ↑work of breathing)
 - Secretions are not excessive
 - Nutritional status is adequate
 - Patient is comfortable with the cuff deflated
 - The airway is patent above the level of the stoma
 - By competent staff
 - In an appropriate environment
 - With appropriate monitoring
 - With a range of emergency equipment and drugs commensurate with the risk (eg LMAs, tubes, bag/mask...)
- Process:
 - Do it in the morning when the patient is rested and can be monitored through the day
 - Slowly deflate the cuff completely
 - Occlude tube with a gloved finger to check airflow around the tube
 - Cover with an occlusive dressing
 - Get the patient to hold their fingers on the dressing when coughing
 - Observe for signs of respiratory distress

- Review prior to hospital discharge, for wound healing, infection, stridor, SOBOE

Non-Invasive Ventilation

- See also:
 - Non-Invasive Ventilation in Heart Failure, page 138
 - NIV in ARDS, page 113
 - Ventilation of Asthma, page 126
 - Weaning from Mechanical Ventilation, page 95
- Dramatic increase in use over last 10 years
- Either:
 - Positive airway pressure (Pao) or
 - Negative pressure to the chest (eg iron lung): induces OSA, doesn't control FiO₂, is bulky but no oral or nasal prosthesis
- Supports respiratory failure through:
 - ↑alveolar ventilation → ↓CO₂
 - Alveolar recruitment and ↑FiO₂ → ↑oxygenation. Using closed circuit is an important way to improve oxygenation
 - ↓work of breathing → ↓respiratory muscle insufficiency
 - Stabilisation of chest wall in trauma or surgery
 - ↓LV afterload (↓LV transmural pressure) may → ↑cardiac function
- Modes: 3 common modes
 - Continuous positive airways pressure (CPAP):
 - ↓work of breathing by:
 - ↑alveolar recruitment → ↑elastic work
 - ↓threshold load in the presence of iPEEP
 - alveolar recruitment and ↓intrapulmonary shunt → ↑oxygenation
 - ↓afterload
 - Inspiratory positive airway pressure (IPAP):
 - ↑V_t → ↓PaCO₂
 - ↓in P_{mus} → ↓respiratory muscle insufficiency
 - induction of pulmonary surfactant release through alveolar ventilation above tidal volume
 - Bilevel positive airway pressure (BPAP): conceptually similar to PSV + CPAP
- Patient-ventilatory interaction: the only aspect specific to NIV are mask leaks → ↓ability to sense the end of expiration because there is continued expiratory gas flow
- Technical requirements:
 - High gas flow that can match peak inspiratory flow
 - Expiratory resistor that can maintain PEEP with low resistance to flow
 - Ability to humidify gases and provide apnoea backup support
- Complications:
 - Contraindications:
 - Respiratory arrest
 - Unprotected airway/↓LOC
 - Inability to clear secretions or large sputum load
 - Untreated pneumothorax
 - Marked haemodynamic instability (NIV delays intubation and worsens outcome)
 - Oesophageal or maxillofacial surgery/pathology
 - Complications:
 - Mask discomfort
 - Abrasions
 - Nasal congestion, sinus pain
 - Oro-nasal dryness
 - Aspiration pneumonitis
 - ↑intraocular pressure (esp if glaucoma)
 - ↑intracranial pressure (esp in neurotrauma)
 - ↓BP if hypovolaemic
 - Aerophagy and gastric distension (uncommon)
- Indications:

- Caution with old studies due to rapid improvement in ventilators
- Established in multiple studies in COPD and acute pulmonary oedema
- Remainder of potential indications (eg pneumonia, asthma) based on small trials, especially if COPD patients excluded from mixed cohorts
- ARDS: ↑ NIV usage but controversial. Opponents would say ↑ mortality 2nd to delay in delivering adequate PEEP via intubation
- As an alternative to intubation: can delay intubation, and in these settings leads to worse outcomes. We not good at predicting who will fail NIV
- Following extubation: data is mixed. Key problem is the temptation to delay reintubation in persistent respiratory failure
- In post-operative general surgery and cardiothoracic patients CPAP improves oxygenation and RR and ↓ risk of re-intubation in mild hypoxic respiratory failure. No data on outcome.
- Mask CPAP is superior to MV in isolated severe chest trauma. Contraindicated in neuro-trauma, intracranial hypertension and untreated pneumothorax
- Prospective Observational Study in 54 ICUs with patients admitted with a do not intubate order. High mortality, but amongst survivors 90 day quality of life similar to intubated. Ie if they survived, did well rather than slow death. Azuli, Int Care Med 2013

Oxygen Delivery Devices

- Wall pressure O₂ is 415 kPa. Full O₂ cylinder is 12,000 – 17,000 kPa
- Most simpler devices (eg NP, masks) deliver O₂ at significantly lower rates than peak inspiratory flow rates (25 – 35 L/min normally, up to 100+ in critical illness) ⇒ final FiO₂ heavily influenced by entrainment of environmental air
- As the respiratory rate rises, the effective inspired O₂ concentration (EIOC) deteriorates
- Reservoir bags don't seem to add much extra O₂ delivery ability
- Unidirectional valves aid in stopping rebreathing of expired gas
- CPAP may actually help oxygenation by eliminating environmental air, rather than by CPAP
- Variable performance systems:
 - Nasal cannula use naso-pharynx as a reservoir
 - Masks: rebreathing CO₂ can occur if flow rates < 4 l/min. Maximum FiO₂ of 0.6 – 0.7, less if respiratory distress
 - T-piece system: flow rate needs to be high enough to match the patient's PIFR so as to prevent rebreathing of expired gas
- Fixed-performance systems: Venturi-type masks, anaesthetic circuits, NIPPV systems

High Flow Nasal Canuale

- Mechanisms of potential benefit:
 - ↑FiO₂ using anatomic reservoir of nasopharynx and rinsing of airway dead space with O₂
 - CPAP: ↓atelectasis → ↓VQ mismatch, ↑compliance, ↓work of breathing
 - Warmed and humidified O₂ more comfortable
- Adverse effects: Pressure areas in nose, epistaxis, gastric distension
- Relative contraindications: nasal fracture, upper airway haemorrhage, base of skull fracture, recent upper airway surgery
- Int Care Med 2013, Review of HFNP in neonates, infants adults:
 - No data to support benefit over CPAP in neonates
 - Possible benefit in bronchiolitis – other indications in kids unknown
 - Limited data in adults

Humidification

- When nasopharynx is bypassed, artificial humidification is necessary
- Humidity can be expressed as:
 - Absolute humidity: total mass of water in a volume of gas at a given temperature (g/m³). Respiratory care requires > 30 g/m³. 100% at 37°C is 43 g/m³
 - Relative humidity: mass of water (per volume of gas) as a percentage of saturated water vapour at a given temperature
 - Partial pressure
- Physiology:
 - Cilia beat in a watery layer over which is a viscous mucous layer

- Moves superficial mucous layer from deep in lung to glottis at 10 mm/min
- Cilia function and mucus composition affected by temperature and humidification. Mucus flow markedly reduced below 75% relative humidification and ceases < 50%. Also ↓surfactant → ↓compliance
- Air is isothermic and saturated by just below the carina
- β-agonists → ↑mucus clearance by ↑cilia beat frequency and mucus and water secretion
- Metaplasia of tracheal epithelium occurs over weeks to months in patients with a permanent tracheostomy
- Ideal humidification device is unaffected by a large range of fresh gas flows, including high flows
- Heat and Moisture Exchange Filter (HME):
 - Passive humidifier traps and returns heat and moisture to patient
 - Hydrophobic pleated filter for heat and moisture exchange
 - Bacterial and viral filtration properties: filter protects against liquid and airborne contamination
 - Although theoretically a microbial filter, no difference in VAP compared with water baths, as VAP usually due to aspiration followed by tubing colonisation
 - Minimal resistance to flow
 - Luer lock gas sampling port to connect to ETCO₂ monitoring
 - 15 mm/22 mm ISO standard connectors
 - Disposable single patient use
 - Cheap, increased risk of occlusion, ↑resistance, ↑dead space, difficult to deliver aerosol medications
 - Cannot match the humidification of water baths, especially at high flows
- Wet circuit:
 - Active humidifier: pass inspired gas either through (bubble) or over (passover, wick) a heated bath
 - Is very efficiency, more costly and labour intensive, has no effect on resistance or dead space
 - Need heated hose
 - Is associated with ↑risk of VAP (but decision to use a passive humidifier should not be based solely on infection control considerations: Grade A evidence, AARV Clinical Practice Guidelines 2003)
 - Rare to culture bacteria from humidifiers. Contamination increases with frequent changes

- See also Monitoring Oxygenation, page 25

Bits and Pieces

Haemoptysis

- Massive: = life-threatening, defined variously as 100 – 600 mls/24 hours
- Vascular supply to lungs:
 - Low pressure pulmonary circulation to alveolar
 - Fewer high pressure bronchial arteries, including to the airways \Rightarrow more important source for haemoptysis despite being a small proportion of pulmonary flow
- Differential of haemoptysis:
 - Airways disease:
 - Bronchitis
 - Bronchogenic carcinoma
 - Bronchiectasis
 - Fistulas: eg aorto-bronchial fistulas 2nd to aortic aneurysms
 - Parenchymal disease:
 - Infection: TB, abscess, aspergilloma
 - Immune mediated: Goodpasture's, Wenger's, Diffuse alveolar haemorrhage
 - Malignancy: primary or secondary
 - Pulmonary vascular disease:
 - PE
 - \uparrow pulmonary capillary pressure, eg mitral stenosis or LVF
 - Perforation by PA catheter
 - Any severe coagulopathy
 - Trauma: blunt or penetrating trauma, including tracheo-innominate artery fistula, ruptured bronchus
 - Upper respiratory tract
 - GI tract
- Diagnosis: CTPA or bronchoscopy
- Management:
 - ABC
 - Correct any coagulopathy
 - Secure airway with large size tube if necessary. Consider double lumen if there is unilateral pathology and sufficient time
 - Nurse in lateral Decubitus position, bleeding lung down
 - Antibiotics or immunosuppressives as indicated
 - Surgical control:
 - Bronchoscopy – balloon tipped catheter
 - Bronchial artery embolisation
 - Lobectomy

DLCO

- 0.3% CO is inspired, held for 10 secs then expired. The difference between inspired and expired \rightarrow DLCO. Measures gas diffusion of CO from alveoli to pulmonary capillaries
- \uparrow DLCO:
 - Pulmonary haemorrhage
 - Polycythaemia
 - Asthma
 - L \rightarrow R intra-cardiac shunt
 - Obesity
 - High altitude
 - Hyperthyroidism
- \downarrow DLCO:
 - Interstitial lung diseases
 - Emphysema

- Congestive heart failure
- PE
- Severe anaemia
- Hypothyroidism
- Hypothermia

Differential of Wheeze

- Differential of wheeze and dyspnoea:
 - LV failure
 - Aspiration
 - Obstruction/inhaled foreign body
 - PE
 - Hyperventilation syndromes

Causes of Cyanosis

- See also Pulse Oximetry, page 28
- Severe methaemoglobinaemia
- Sulfhaemoglobinaemia
- Haemoglobin mutation
- Polycythaemia
- Hypothermia
- High Altitude

Causes of Clubbing

- Common:
 - Cardiovascular:
 - Congenital cyanotic heart disease
 - Infective endocarditis
 - Respiratory
 - Lung carcinoma (usually not small cell)
 - Chronic pulmonary suppuration: bronchiectasis, lung abscess, empyema
 - Idiopathic pulmonary fibrosis
- Uncommon:
 - Respiratory: Cystic fibrosis, asbestosis, pleural mesothelioma (benign fibrous type)
 - Gastrointestinal:
 - Cirrhosis (especially biliary cirrhosis)
 - Inflammatory bowel disease
 - Coeliac disease
 - Thyrotoxicosis
 - Familial or idiopathic
- Rare: pregnancy

Hiccups

- Causes:
 - Irritation of the diaphragm: subphrenic abscess, cholecystitis, pneumonia, pericarditis
 - Irritation of the stomach wall: distension, ulcer, ileus
 - Phrenic nerve stimulation/irritation: neoplasia, goitre
 - Brainstem lesion: neoplasm, ischaemia, surgery
 - Metabolic: uraemia
- Management is often unsatisfactory:
 - Diagnose and treat underlying cause
 - Medications have poor efficacy: chlorpromazine, metoclopramide, haloperidol, phenytoin
 - Physical stimulation of the posterior pharynx by NG tube may interrupt the reflex arc
 - If desperate, phrenic nerve block has been tried

Obstructive Sleep Apnoea

- Frequent apnoea during sleep, snoring, day-time somnolence, pathophysiological changes (\downarrow PaO₂, \uparrow CO₂, systemic and pulmonary vasoconstriction)

- Oropharyngeal patency is maintained by paired sets of upper airway muscles, stopping otherwise floppy tissues from being sucked into the airway. Obstruction may occur in sleep due to:
 - ↓Airway size: large tonsils, macroglossia, myxoedema, acromegaly...
 - ↓neuromuscular tone: especially in REM sleep
 - ↓neuromuscular coordination: ↓ coordination between upper airway tone and inspiration
- Long term complications:
 - Cardiac: HTN, nocturnal angina/arrhythmias
 - Respiratory: respiratory failure, pulmonary HTN, cor pulmonale (→ RHF)
 - Neurological: headache, somnolence
 - Psychiatric: depression, poor concentration
 - Other: impotence, polycythaemia, glaucoma, trauma due to somnolence

Inhalation Therapy

- Particles of:
 - 40 µm deposit in the upper airway
 - 8 – 15 µm deposit in the bronchi
 - 3 – 5 µm deposit in the peripheral conducting airways
 - 0.8 – 3.0 µm deposit in the lung parenchyma
- Nebulisers: Gas flow may add to tidal volumes unless compensated for by the ventilator, and may impair ventilator triggering. Ultrasonic nebulisers (typically 1MHz) create an aerosol with uniform small droplets (< 5 µm). A significant amount of aerosol deposits in the circuit and large airways
- MDI: Aerosol delivery increases from 4 – 6% to 11% with a spacer. Increased delivery from humidification, lower and long inspiratory flow rate and minimised turbulence (eg no elbow connector).
- Dry powder: little experience in ventilated patients
- Applications:
 - Mucolytics: role to reduce viscosity in critically ill patients is unknown
 - Response to bronchodilators judged by changes in peak-to-plateau pressure gradient and PEEPi. Optimal dosing in NIV unknown
 - Aerosolised antibiotics contentious. Good evidence in cystic fibrosis, and also in bronchiectasis. May be clinical benefit when inhaled gentamicin or vancomycin inhaled antibiotics added to systemic therapy for VAP.
 - Nebulised 3% saline safe in patients with severe airflow limitation, and is effective in sputum induction for diagnosis P carinii pneumonia in AIDS.

Hyperbaric O2

- Physiology:
 - Measures: 1 atmosphere =
 - 14.7 lbs/in²
 - 101.3 kPa
 - 760 mmHg
 - 1030 cm H₂O
 - Hyperbaric O₂ is delivered at 2 – 3 atmospheres absolute (ie 1 – 2 atmospheres above normal atmospheric pressure)
 - → Elevation of partial pressure of gases (↑O₂ carried in blood rather than bound to haemoglobin). Boyles and Dalton's Law ⇒ ↑ partial pressure in blood. For each 100 mmHg ↑ pressure in the alveolar, can dissolve 0.3 mmHg further O₂ in blood
 - At rest metabolic demands of an average person can be met by dissolved O₂ alone when breathing 100% O₂ at 3 atmospheres (yields at PaO₂ of 1000 – 1400)
- Discuss with a hyperbaric unit on a case by case basis. Commence other supportive/adjunctive therapy
- Indications:
 - Decompression illness – most accepted indication. Decompress up to 6 atmospheres
 - Arterial gas embolism: precipitation of gas or direct vascular entry of gas (trauma, surgical...) – usually iatrogenic, eg air flush during angiogram, air in bypass circuit, venous air and PFO. CT and MRI not sensitive to finding bubbles. Usually clinical diagnosis
 - Aggressive soft tissue infections: Clostridial myonecrosis (gas gangrene), necrotising fasciitis, Fournier's gangrene. Anaerobic bacteria can't defend themselves against high O₂ tension
 - Carbon monoxide poisoning:
 - Usually half-life of CO in air is 320 mins, reduced to 90 mins by giving 100% O₂, or 23 mins at 3 atmospheres of O₂

- High O₂ pressure displaces CO from Hb
- 8 RCTs with variable results, Scheinkestel MJA 1999, Weaver NEJM 2002, generally of poor quality, no statistical reduction in sequelae at 1 month
- Likely greatest benefit with age > 35, LOC and COHb levels > 25% (all associated with ↑ risk of neurological sequelae)
- Crush injury
- Thin evidence for other effects:
 - Anti-infective at partial pressure > 1500 mmHg. Anti-infective impacts on anaerobic bacteria. Improved phagocytosis 2nd to ↑ free radical O₂
 - Indications of ↑ fibroblasts, etc.
 - Benefit in ischaemic reperfusion (eg diabetic wound healing, necrotising fasciitis)
 - Insufficient evidence in burns, non-diabetic wounds, some evidence in traumatic wounds
- Complications:
 - Risks of transport
 - Claustrophobia
 - Barotrauma (middle ear and sinuses, GI distension, tooth displacement/pain, gas embolism on decompression). Fill ET cuff with saline
 - Acute O₂ toxicity (→ seizures, pulmonary toxicity)
 - Visual problems (acute myopia, cataracts)
 - Fire danger: Can't defibrillate
 - Ventilators unreliable

Chest Imaging

- See also Chest Injuries, page 245

Chest Xray

- Systematic assessment of CXR
 - Technical aspects: correct patient, AP/PA, position, rotation, adequacy of inspiration, exposure
 - Lungs and pleural cavity
 - Heart and mediastinum
 - Bones
 - Soft tissues
 - Indwelling devices
- Parenchymal change:
 - Interstitial oedema: peribronchial cuffing, Kerley B lines, intraparenchymal reticular pattern
 - Air space change: will usually see air bronchograms
- Anatomy:
 - R superior mediastinal border: R brachiocephalic vein and superior vena cava. Can be widened by mediastinal fat
 - L mediastinal border above the arch: L carotid and L subclavian arteries and veins
 - L cardiac border: L atrial appendage merging with L ventricle inferiorly
 - In an older patient trachea may be displaced by a dilated aortic arch
 - Carinal angle is usually < 80°. Splaying of the angle is an insensitive sign of subcarinal disease (lymphadenopathy of very enlarged LA)
 - R dome of the diaphragm is usually higher than the left by up to 2 cm when erect
- Mechanisms for collapse:
 - Relaxation or passive collapse
 - Pressure from fluid or air in the pleural space
 - Because of volume loss, eg fibrosis, adhesive collapse in ARDS
- Mediastinal abnormalities;
 - Acute mediastinitis: usually perforation of the oesophagus, pharynx or trachea. Widened mediastinum +/- pneumomediastinum
 - Mediastinal haemorrhage from venous or arterial bleeding. Consider aortic rupture
- Pneumothorax: pleural adhesions may cause a loculated or encysted pneumothorax

Daily routine chest radiographs

- Controversial
- Hard to study due to investigation bias, blinding problems and outcome assessment

- Generalisability an issue: often single centre specialty European or American ICUs – relevance to Australasia Units?
- American College of Radiology: routine daily CXRs indicated in mechanically ventilated patients
- Comparison of routine and on-demand prescription of chest radiographs in mechanically ventilated adults: a multicentre, cluster-randomised two-period crossover study. Hejblum et al. Lancet 2009;374: 1687-93. Fewer xrays were done and no difference in the duration of mechanical ventilation, LOS or ICU mortality
- Lakhal et al, Intensive Care Med 2012, prospective observational study on 1225 patients in 104 French ICUs, ‘On demand’ reduced regular morning CXR number, did not lead to more outside this time. The lower the P/F ratio the higher the value of the “on-demand” and the lower the value of the “daily routine”. Authors argue for a restrictive strategy
- Current evidence:
 - Doesn’t suggest that these lead to changes in therapeutic management
 - LOS and duration of mechanical ventilation not adversely affected by elimination of daily routine CXR
 - On demand reduces number of CXRs by ~ 30%

Pulmonary Infiltrate on CXR

- Diffuse pulmonary infiltrate on a CXR:
 - Infection:
 - VAP
 - Immunocompromised:
 - G +ive: Strep, staph epidermidis
 - G –ive: E Coli, pseudomonas, klebsiella
 - Atypical: Legionella, Mycoplasma
 - Viral: CMV, HSV, RSV, influenza, H1N1, VZV
 - Fungal: aspergillus (advanced), candida, Cryptococcus (uncommon)
 - PCP, toxoplasmosis
 - TB
 - Oedema:
 - High pressure pulmonary oedema:
 - Fluid overload
 - Heart failure
 - Low pressure pulmonary oedema: ARDS
 - Pulmonary contusion
 - Diffuse Alveolar Haemorrhage (see page 109)
 - Pulmonary fibrosis: NSIP
 - Aspiration
 - Pleural fluid
 - Drug reaction
 - Transfusion Related Acute Lung Injury
 - Malignancy
 - Radiation
 - Autoimmune/vasculitis

Post-Operative Chest Complications on CXR

- Complications of general surgery:
 - Atelectasis
 - Pleural effusions
 - Pneumothorax: usually a complication of PPV or CVL insertion
 - Aspiration pneumonia: patchy consolidation within a few hours. Clearing occurs within a few days unless there is super-infection
- Thoracic complications of cardiac surgery:
 - Widening of the cardiac silhouette is usual and represents bleeding or oedema. Pneumopericardium may also be present
 - Progressive or marked widening suggests haemorrhage
 - L basal atelectasis is invariable and settles over a week or two. Small effusions are common
 - Pneumoperitoneum is sometimes seen if the peritoneum was involved in the sternotomy incision
 - Lymph vessels can be damaged
 - 1st or 2nd rib may be fractured by sternotomy → post-operative pain

Line and Tube Positions

- End of CVC is ideally in the superior vena cava. Look for complications of pneumothorax and mediastinal haematoma (perforation of the subclavian vein)
- Pulmonary artery catheters: ideally 5 – 8 cm beyond the bifurcation of the main pulmonary artery in either the R or L pulmonary artery. See Pulmonary Artery Catheter, page 33
- ET tube: neck extension and flexion can make a tube move up to 5 cm. In neutral position tube should be 5 – 6 cm above the carina
- Tracheostomy tube: Tube tip should be at the level of T3. Exclude complications of pneumothorax, pneumomediastinum and subcutaneous emphysema
- Pleural tubes: check all side holes are within the thorax
- Intra-aortic balloon pump: ideal position of the tip is just distal to the origin of the L subclavian artery on TOE, or tip in 2nd intercostal space just above the left main bronchus. If advanced too far it may occlude the left subclavian artery and if too distal may occlude branches of the abdominal aorta. See Intra-aortic balloon counterpulsation, page 160

Computed Tomography

- Contrast enhancement:
 - Optimal enhancement of pulmonary arteries occurs 10 – 15 seconds after the start of injection for PE
 - Optimal timing of an inflammatory lesion may be 30 – 40 seconds to allow contrast to diffuse
- HRCT: images usually 1.5 mm thick every 1 cm – less radiation with this sequential technique
- Patterns of lung infiltrates:
 - Alveolar/consolidation: rounded, ill defined, obliterates vessel. Caused by something filling the alveolar sacs (fluid, blood, pus, tumour)
 - Interstitial: Linear infiltrates, Kerley B lines or peribronchovascular lines
 - Ground glass: can see vessels running through it. Is interstitial or early alveolar
- Artery and bronchus should be the same size. If the bronchus is dilated → signet ring sign

Diffuse Alveolar Haemorrhage

- A syndrome of bleeding due to disruption of the alveolar-capillary basement membrane
- Usually – but not always – presents with haemoptasis and rapid progression of SOB
- Imaging: (usually) bilateral air space opacity and ground glass (increasing in density to frank consolidation) on CT
- Investigations:
 - Pulmonary function tests: sequential *increase* in DLCO due to absorption of CO by Hb within the alveolar compartment
 - Bronchoalveolar lavage: sequential lavages of 50 – 60 ml of saline are progressively *more* haemorrhagic
- 3 clusters of causes:
 - Pulmonary Vasculitis:
 - Due to neutrophil infiltration of the lung interstitium and loss of capillary integrity
 - See also Autoimmune Markers, page 293
 - With renal impairment can be one of the following (pulmonary-renal syndrome):
 - Wegner's granulomatosis: positive C-ANCA and anti-PR3
 - Microscopic Polyarteritis: positive P-ANCA and anti-MPO
 - Goodpasture's Syndrome: anti-GBM antibodies
 - Other potential autoimmune causes include SLE: ↓complement, anti-ds-DNA
 - Lung biopsy gives further clues (although if required, kidney biopsy is possible less invasive)
 - Treated with pulse steroids (methyl prednisolone 500 to 2000 mg) +/- other immunosuppressives (eg cyclophosphamide) +/- plasma exchange
 - Bland pulmonary haemorrhage:
 - No inflammation
 - Due to ↑LVEDP, mitral disease and coagulopathy/anticoagulants
 - Diffuse alveolar damage:
 - Synonymous with ARDS – oedema of the alveolar septum

Acute Respiratory Distress Syndrome

- Acute hypoxaemic respiratory failure due to bilateral and diffuse alveolar damage

- New Berlin Definition (JAMA 2012):
 - Timing: Must be acute: within 1 week of insult or respiratory deterioration
 - Chest imaging: Bilateral opacities not fully explained by effusions, collapse or nodules
 - Origin: Respiratory failure not fully explained by cardiac failure or fluid overload
 - Oxygenation:
 - Mild: $\text{PaO}_2/\text{FiO}_2$ from 201 – 300 with PEEP or CPAP ≥ 5 (27% mortality)
 - Moderate: $\text{PaO}_2/\text{FiO}_2$ from 101 – 200 with PEEP ≥ 5 (32% mortality)
 - Severe: $\text{PaO}_2/\text{FiO}_2$ from ≤ 100 (45% mortality)
 - 4 other variables not included as they didn't contribute to predictive ability:
 - Radiographic severity
 - Respiratory compliance ≤ 40 ml/cm H₂O
 - PEEP ≥ 10 cm H₂O
 - Expired minute volume > 10
 - PAOP removed given decline in the use of PACs. Can have ARDS as long as the clinical setting is not fully explained by cardiac failure. If there is no ARDS risk factor, oedema must be excluded (eg with echo)
 - AUC ROC for mortality of 0.577 compared to 0.526 for AECC definition
- Old Criteria:
 - American-European Consensus Conference definitions AECC (most common criteria, broad):
 - Definition:
 - Acute
 - $\text{PaO}_2/\text{FiO}_2 < 300$ mmHg (ALI) or < 200 (ARDS)
 - CXR: bilateral infiltrates consistent with pulmonary oedema usually sparing the costophrenic angles
 - PAOP: < 18 mmHg or no clinical evidence of elevated LAP
 - Weaknesses were:
 - The lack of definition of acute, and the effect of PEEP \rightarrow variations in $\text{PiO}_2/\text{FiO}_2$ ratio
 - Fail to specify an acute cause
 - Use a $\text{PaO}_2/\text{FiO}_2$ ratio independent of respiratory support
 - Not specific about radiologic criteria
 - Lung Injury Score (LIS): Four point score derived from ranges of $\text{PaO}_2/\text{FiO}_2$, PEEP, compliance and the number of quadrants affected on CXR
 - Delphi definition: $\text{PaO}_2/\text{FiO}_2 < 200$ with 10 cmH₂O PEEP
 - Last two have better sensitivity when matched with autopsy evidence of diffuse alveolar damage
- Causes:
 - Direct (ie alveolar insult): Pneumonia (46%), aspiration of gastric contents (29%), lung contusion (34%), fat embolism, near drowning, inhalational injury, reperfusion injury
 - Indirect (ie capillary insult): non-pulmonary sepsis (25%), multiple trauma (41%), massive transfusion (34%), pancreatitis (25%), cardiopulmonary bypass
 - Risk increased by low pH, chronic alcohol, chronic lung disease
- Differential:
 - Fluid overload
 - Cardiogenic pulmonary oedema
 - Pulmonary fibrosis (idiopathic, radiation, dust, allergic, histoplasmosis)
 - Lymphangitis carcinomatosa
- Imaging:
 - CXR: considerable inter-observer variability
 - CT:
 - Demonstrates heterogeneity of lung inflation, early on there is dorsal dependent increase in lung density (= "gravitational gradient" which reverses with a shift from supine to prone). Ground-glass appearance suggests fibrosis
 - By 2nd week there may be altered lung architecture and cysts or pneumatoceles
 - Abscess formation, empyema and non-dependent consolidation all \Rightarrow superadded infection
 - Mediastinal and interstitial emphysema as well as pneumothorax suggest barotraumas

Epidemiology of ARDS

- Australian data imply 1 in 10 cardiothoracic ICU patients develop ARDS \Rightarrow clinicians tend to underestimate prevalence

- Australian mortality 32% for ALI and 34% for ARDS
- Lower risk in trauma, higher risk for chronic liver disease, non-pulmonary organ dysfunction, sepsis, and age > 70
- Long term outcomes:
 - Respiratory function usually returns to normal by 6 - 12 months. Impaired diffusing capacity is the most common persisting abnormality
 - Compared to non-ARDS patients, more severe long term reduction in pulmonary and general health related quality of life. ↓ Exercise tolerance may be attributable to critical illness neuropathy and myopathy. Depression, anxiety and PTSD are common
 - Most survivors have cognitive impairments (eg impaired memory or concentration) correlated to the period and severity of desaturation < 90%
 - All this cautions against permissive hypoxaemia
 - Neurophysiological outcomes assessed by Mikkelsen et al, Am J of Respiratory and CCM 2012, and outcome study from the FACTT study (conservative vs liberal fluid management in ARDS). Only 25% followed up, 50% had definable deficits in executive function at 1 year

Pathogenesis of ARDS

- Sequence is uncertain and likely depends on both the insult and host factors. Basic stages are:
 - Injury
 - Exudative: alveolar capillary membrane disruption with inflammatory cell infiltrate
 - Proliferative: Type 2 alveolar cells and inflammatory cells
 - Fibrotic: infiltration with fibroblasts
 - Resolution: slow and incomplete repair
- Oedema is arguably a significant component, and possibly the most treatable
- Alveolocapillary barrier:
 - 50 – 100 m² surface area of alveolar is 90% alveolar type 1 and 10% type 2 cells
 - Covered in 20 ml fluid, of which 10% is surfactant
 - In ALI, the barrier is damaged with bidirectional leakage of fluid
- Neutrophils in ALI:
 - Most abundant cell type in early ALI
 - When activated by adherence to endothelium release a variety of reactive O₂ species, cytokines and proteases that contribute to tissue damage
 - However, ALI occurs in neutropenic patients
- Other cell types:
 - Pulmonary endothelial cells, platelets, interstitial and alveolar macrophages and alveolar type 2 cells (proliferate and cover denuded epithelium before differentiating into type 1 cells) involved
 - Microvascular thrombosis common in ALI, and contributes to pulmonary hypertension
 - Alveolar macrophages may amplify lung injury and also modulate fibrosis (via TGFα and platelet derived growth factor)
- Biological markers:
 - Numerous proteins (eg IL-1, TNF-α, IL-10) are elevated in ARDS but are not predictive
 - TNF-α, IL-1β, IL 6 and IL 8 are the most important. However increases in their receptors and in counter-regulator cytokines mean absolute levels don't correlate to biological impact. Measurement of cytokines is not predictive of ALI or mortality
 - In small studies, ferritin (non-specific O₂ free radical response) and serum surfactant protein B (lung-specific) appear predictive
- Histological evidence of fibrosing alveolitis not found until 5 days after onset
- The result:
 - Stiff lungs (→ ↓compliance), prone to trauma with ventilation, impaired ventilation (↑CO₂) and V/Q mismatch
 - Changes are not uniform
- Mortality up to 40% is due to:
 - Multiorgan failure second to infection, haemodynamic compromise or VALI, and/or
 - Severe hypoxaemia: predominantly due to alveoli that are perfused but not ventilated (shunt)
- Some argue ARDS is largely a hospital acquired iatrogenic injury secondary to delayed Abs, too much fluid and poor ventilation

Mechanisms of Ventilator Associated Lung Injury

- Hypoxia does kill patients with ARDS – ventilators do. The risk is iatrogenic ventilator associated lung injury → constant search for strategies to “rest the lung” while maintaining sufficient PaO₂
- Volutrauma:
 - = End inspiratory alveolar over-distension
 - Non-homogenous lung injury due to over-distension of normal alveolar units to transpulmonary pressures above ~ 30 cm
 - Leads to gross physical disruption of the lung architecture, ↑ alveolar-capillary permeability due to over distension of the lung, activation or stretch responsive inflammatory pathways, and stress on intracellular junctions
 - Exacerbation of acute lung injury is detectable on analysis of BAL fluid, but is difficult to distinguish from inflammation arising from the initial insult
 - Causes:
 - Alveolar rupture → extra alveolar air: interstitial emphysema, mediastinal emphysema, pneumothorax, pneumoperitoneum and subcutaneous emphysema
 - → haemodynamic and respiratory compromise
 - Treatment:
 - Lung protective strategies: lower tidal volumes, lower respiratory rates, lower mean airway pressures (by reducing PEEP 6 → 5 → 4), avoidance of auto-PEEP
 - Drain collections of gas
 - Double lumen tubes/differential lung ventilation
- Barotrauma: increasing the trans-pulmonary pressures above 50 cm → disruption of the basement membrane → gross air leaks
- Biotrauma: mechano-transduction and tissue disruption → up-regulation and release of chemokines and cytokines → WBC attraction and activation → pulmonary and systemic inflammatory response
- “Atelectrauma”: Recruitment/de-recruitment injury: the weight of oedematous lung contributes to collapse of the dependant portions of the lung → repeated opening and closing with tidal ventilation
- Shearing injury: Occurs at the junction of the collapse lung and ventilated lung, with ventilate lung moving against the relatively fixed collapsed lung with high shearing force and subsequent injury
- Oxygen toxicity: see Hazards of O₂ Therapy, page 85

Summary of Management of ARDS

- General:
 - Diagnose and treat infection/sepsis (reduces O₂ demand)
 - Drain collections
 - Recognize and resuscitate shock
 - Sedation +/- paralysis: ↓ O₂ requirements, ↓ CO₂ production, improve dys-synchrony
 - Optimise fluid balance: balance of ↓ interstitial oedema and ↑ CO
 - Optimise haemoglobin: balance between improving O₂ carriage and minimising immune and volume effects of transfusion
- Respiratory support:
 - Physio
 - Suctioning
 - Prone positioning
- Ventilation measures:
 - ↓ Tidal volume
 - Limit plateau pressure
 - Slow respiratory rate
 - Increase FiO₂, aim for < 60%
 - Optimise recruitment:
 - Increase PEEP: ↑ surface area for gas exchange, ↓ atelectasis, redistribute lung water
 - Lung recruitment
 - Increase I:E ratio towards 1:1
 - Inverse ratio ventilation: use autoPEEP to increase FRC and area for gas exchange
 - Permissive hypercapnea as long as pH > 7.1 (problematic in head injury and pulmonary hypertension)
 - Spontaneous ventilation
 - Transpulmonary pressure monitoring
- Optimise blood flow to ventilated alveoli: Inhaled NO or prostacyclin

- Last resorts:
 - Decrease circuit dead space (lower CO₂)
 - HFOV
 - ECMO
- No drugs are of benefit

Management of ARDS

NIV in ARDS

- Role of NIV uncertain – more complications, delays intubation. Current data do not support the routine use of NIV in undifferentiated hypoxaemic ARF
- NIV vs intubation in haematological malignancy and ARDS. Chest 2004, Depuydt et al. Non-randomised retrospective study in a single centre. No difference in mortality between non-invasive and matched intubated patients. 71% mortality overall.

Invasive Ventilation in ARDS

- Tidal Volume:
 - Traditionally 12 – 15 ml/kg to reduce atelectasis which → intrapulmonary shunt
 - Especially in ARDS → ventilator induced lung injury (VILI)
 - ARDS Network study (NEJM 2000):
 - 861 patients from 75 ICUs. Entry with bilateral infiltrates, P/F ratio < 300 in the first 36 hours
 - Strict PEEP and FiO₂ protocol (but PEEP dictates FRC not oxygenation), and patients were ventilated with assist-control mode to avoid excessive spontaneous Vt (can happen with SIMV in supported breaths). Average rate was ~ 30/min in low mortality group. However, more PEEP required
 - Pplat target was < 30
 - Showed 6 ml/kg LBW (with plateau pressures < 30) better than 12 ml/kg LBW (with plateau pressures < 30) - mortality reduced by 22% from 40% to 31%. However, 12 ml/kg is large – standard treatment arm was not really standard – did all it show was that over-distension is bad?
 - Meta-analysis showed Vt < 7.7 ml predicted body weight was protective.
 - Now called “Lung Protective Ventilation”
- Avoidance of overstretch: Vt need to be reduced in proportion to the reduction in aerated lung otherwise aerated lung will over stretch. It is lung stretch, not Paw, that leads to volutrauma
- Lab studies show repeat opening and closing of airspaces by tidal recruitment → diffuse alveolar damage – not supported by clinical data
- Normal lung fully inflated at a transpulmonary pressure of ~30 cmH₂O. Pplat, the elastic distending pressure, should not exceed 30 – 35. Patients may show evidence of over-inflation at elastic distending pressures as low as 18 – 26 cm H₂O. Vt limitation is more practical than PSV or measurement of transpulmonary pressure with an oesophageal balloon. However oesophageal pressure monitoring permits measurement of transpulmonary pressure, excluding effect of the chest wall. Of greater use when the chest wall pressures are abnormal (marked obesity, chest wall trauma, etc.)
- Other ventilation modes:
 - Pressure controlled has theoretical advantage that Ppk ~ Pplat (decelerating flow pattern dissipates Pres before end-inspiration) but haemodynamic stability and mean airway pressure are no different, and a moderate sized RCT found no difference
 - Inverse ratio ventilation: small decrease in CO₂ but higher mean airway pressure and ↑risk of haemodynamic consequences
 - HFOV: early studies showed no benefit. Controversial meta-analysis reported potential benefit (Sud et al, BMJ 2010). OSCAR trial in progress
- ACURASYS, Papazian, NEJM 2010, MRCT of 340 patients within 48 hours onset of ARDS treated with muscle relaxants for 48 hours vs placebo. Raw 90 day mortality not different, but adjusted for baseline differences showed improved mortality.... Meta-analysis (Alhazzani et al, Critical Care, 2013) showed 48-hour infusions of cisatracurium reduced mortality and barotrauma, with no effect on ICU-acquired weakness

Permissive Hypercapnea

- CO₂ target:
 - Low Vt → ↑PaCO₂ unless rate is increased
 - ARDS Net aimed at normocapnea with RR up to 35 to minimize acidosis. Leads to more tidal stretch and possibly DHI

- Raised PCO₂ may not be that harmful as – if it occurs slowly – intracellular acidosis is well compensated. May have small detrimental effect on pulmonary hypertension and arrhythmias
- CO₂ may have a role in reducing inflammatory response (↓neutrophil function, ↓proinflammatory cytokines). In animal models, this benefit is lost if acidosis is reversed (acidosis may help mitochondria harness O₂). Increases the risk of sepsis (but you've got antibiotics). So, don't ↑ RR to ↓ CO₂ (controversial)
- Small studies in the early 90s low tidal volume regardless of PCO₂. ARDSNET tried to avoid hypercapnea by ↑RR and administering NaHCO₃
- Augmenting RR to combat rises in CO₂ may augment mechanical and bio-trauma to the lung

PEEP in ARDS

- Aim is to improve oxygenation and minimise VILI (contributed to by tidal opening and closing of alveoli).
- Improves PaO₂ by increasing FRC and recruiting alveoli but may impair venous return
- However in ALI recruitment occurs along the entire curve
- But PEEP may:
 - ↓ venous return, so CO falls even though O₂ rises
 - Lead to over-inflation of non-dependent alveoli (in addition to recruitment of dependent alveoli). Less likely if alveolar distending pressure is < 30 – 35 cmH₂O, or change in driving pressure is < 2cmH₂O when V_t is constant
- The ARDSNet protocol titrates PEEP to PaO₂/FiO₂ – but this results in tidal over-inflation in about one third. Lower inflection point of a volume-pressure curve has been used to set PEEP as it was thought this reflected recruitment
- Key papers:
 - ALEVOLI, ARDSNET, NEJM 2004: Higher vs lower PEEP, tidal volume of 6 ml/kg and end-inspiratory plateau pressure limit of 30: High not better than low PEEP (protocol changed half way through) – or could say high PEEP is at least no worse than low PEEP
 - High levels of PEEP may improve survival in ARDS: a meta-analysis. Oba et al, Respiratory Medicine 2009. Reduction in hospital mortality with high PEEP amongst those with ARDS (ie only helped the sickest). Similar findings in Briel et al, JAMA 2010
 - Mercat et al: strategy of maximum PEEP while maintaining P_{plat} of 28 – 30 → ↓ in ventilator free days
 - Meade et al: “Open Lung ventilation strategy” – high PEEP and recruitment manoeuvres – trend to improvement
 - Clinical heterogeneity in studies. Remains unclear whether PEEP has an independent mortality benefit in ARDS. Cochrane Review 2013 found no difference in mortality or ventilator free days but ↑PEEP → ↑O₂
 - CT analysis has not been shown to influence outcome
- Reasonable approaches:
 - Use a scale similar to the ARDS Network protocol
 - Titrate PEEP to PaO₂, aiming for a maximum PEEP of ~15 cmH₂O, levels up to 25 cm H₂O have been advocated in severe ARDS
 - Measure elastic mechanics at the bedside: the delta-PEEP technique indirectly assesses excess stress as PEEP is increased at a constant V_t

Recruitment manoeuvres in ARDS

- See Recruitment, page 84
- Recruitment is not homogenous – will preferentially distend normal lung
- Unclear whether they add anything to PEEP – largest trial showed no effect. ?Only effective in early ARDS when lower levels of baseline PEEP used
- Apply 30 – 40 cm continuous positive pressure in an apnoeic patient for 30 – 40 seconds
- May lead to improved oxygenation. May also cause hypotension in an under-filled patient
- Stretch above resting V_t powerful stimulus for surfactant release

Oxygenation in ARDS

- Balance between damage from ↑airway pressure and ↑FiO₂ is unknown – generally FiO₂ regarded as less damaging
- No prospective trial of O₂ targets in ARDS
- Start at FiO₂ of 1 and titrate down to < 0.6
- SaO₂ > 90% and PaO₂ > 60 reasonable targets

- $DO_2 = CO \times \text{arterial } O_2 \text{ content}$. Cellular hypoxia therefore significantly worsened by \downarrow CI in presence of hypoxaemia

Prone Position in ARDS

- For persisting severe hypoxia
- Prone position \rightarrow \downarrow chest wall compliance. So in PCV should have \uparrow recruitment at same levels of pressure
- 5 larger RCTs:
 - MRCT in 466 patients in French ICUs used to proning, early in illness, 16 hours prone at a time vs supine, in PF ratio of < 150 persisting > 24 hours. 28 day mortality 16% vs 32%. Complications the same. PROCEVA Trial. Guerin et al, NEJM 2013. Very dramatic result – is it true? Influenced by number of H1N1 patients?
 - MRCT in 304 patients comparing supine with prone position for 6 hours per day. Improved PaO₂ in 70%, with a modest increase sustained in supine position. Recruits dorsal lung, ventral lung collapses, but perfusion more evenly distributed. No improvement in mortality – but possibly improvement in the most hypoxic \Rightarrow use as a rescue therapy
 - Gattinoni et al, NEJM 2001. Similar results in a trial of 791 patients half randomised to mean of 8.6 hrs per day for 4 days
 - Guerin et al, JAMA 2004
 - Other equally powered negative trials (eg Taccone et al, JAMA 2009)
 - Meta-analysis of $n = 2,246$ in 11 RCTs found proning associated with \downarrow mortality (especially with > 10 hour prone sessions), \uparrow pressure ulcers and airway problems (Lee, CCM 2013). Also further meta-analysis NEJM May 2014: Odds ratio of 0.77 for mortality with proning.
- Theoretically improve secretion drainage (dorsal ventral orientation of large airways)
- Debate over who should be prone, when in their course, duration of proning, how many days to persist
- Small case control study suggests it may be of greater benefit in the obese (De Jong, Chest 2013)
- Disadvantages: requires expertise, manpower, potential for dislodgement of tube/lines, problems with airway access, \uparrow new pressure sores, \uparrow ICP, \downarrow enteral feed tolerance, difficult or contraindicated in spinal trauma/abdo surgery/pelvic fractures/pregnancy
- Advantages in rest-and-dress dorsal soft tissue injuries (eg back)

Pulmonary Vasodilators in ARDS

- See also Management of Right Ventricular Dysfunction, page 138
- May reduce pulmonary shunt and \downarrow RV afterload (although an \uparrow in CO is unusual). Delivered to well-ventilated lung. Vasodilate pulmonary circulation and redistribute blood away from poorly ventilated lung
- Technically easier than proning and HFVO
- Monitor PO₂ for effectiveness. Risk of opening up circulation to poorly aerated lung \rightarrow \uparrow shunt \rightarrow \downarrow PO₂.
- iNO/ Nitric oxide:
 - “Routine use should be discontinued”, at least until trials indicate any subgroup that may benefit
 - Evidence: meta-analysis of 9 studies, $n = 1142$, of NO in severe ARDS, no difference in mortality. Adhikari CCM 2013
 - Smooth-muscle relaxant via cAMP \rightarrow local pulmonary vasodilation \rightarrow potentially improving VQ mismatch and \downarrow pulmonary artery hypertension, plus potential immuno-modulation (\downarrow neutrophil adhesion and platelet aggregation)
 - Conventional vasodilators produce excessive systemic vasodilatation
 - RCTs in ARDS show short term oxygenation benefits up to 72 hours, but no change in length of ventilation or mortality (eg. Adhikari et al, BMJ 2007). Cochrane Review
 - Physiological improvement also demonstrated in pulmonary artery hypertension and heart transplantation but no longer term benefits
 - Monitoring of efficacy:
 - Should be performed with PAP/PaO₂ and/or Pulmonary Vascular Resistance (via pulmonary artery catheter or TOE)
 - \uparrow PaO₂ of 20% a positive response – continue iNO at the minimum effective dose
 - May be no fall in PA pressure (though PVR has fallen). Positive response may be seen in CO, SvO₂ and/or CVP
 - For temporary rescue only
 - Requirements:
 - Cylinders contain 800 ppm + nitrogen. Need complex equipment to monitor PO₂, pulmonary artery pressure, methaemoglobin and NO and nitrogen dioxide
 - Delivery via mixed NO/N₂ – measure inspiratory concentrations of each

- Commonly used doses are 1 – 60 ppm
- Safe management: includes knowledge of spill emergency procedure. Needs waste gas evacuation, including at the least adequate air conditioning and possibly passive and active scavenging
- Lots of money! Costs \$2,000 per day
- Advantages: Binding to Hb inactivates NO so systemic complications modest
- Side effects:
 - Toxicity with NO₂ and possibly methaemoglobin
 - Risk of pulmonary haemorrhage
 - May have rebound PAH with discontinuation
 - Reports of ↑renal failure and nosocomial infection
- Inhaled prostaglandins/Inhaled PGI₂:
 - Up to 50 ng/kg/min improves oxygenation as effectively as iNO. Continuously jet nebulised due to short half life
 - Iloprost:
 - Is a derivative of PGI₂ with similar activity, longer duration of action, and without the alkaline buffer (which can cause airway inflammation). May be better than iNO.
 - Given via ultrasonic nebuliser. Doesn't cause systemic hypotension that IV administration would. Benefit demonstrated in surrogate endpoints (PAH and RV function)
 - Neither has been shown to improve outcomes.
- Sildenafil. Different pathway from prostaglandins. Currently only oral form available. Can't use concurrently with GTN

Other Measures in ARDS

- Fluid management:
 - Limit CVP to PEEP + 2 maximum. Consider furosemide if CVP > PEEP + 5
 - ARDSNET, NEJM 2006, detailed protocol of fluid, diuretics and vasoactive infusions to achieve CVP of 10 – 14 mmHg or < 4. Only 10% of screened patients randomised. No difference in 60 day mortality. ?reduced duration of ventilation in dry/conservative group.
- Heavy sedation +/- paralysis:
 - Minimise O₂ consumption/CO₂ production and eliminate dyssynchrony
 - Improved (or worsened) ventilation/perfusion relationships
 - ACURASYS Study (Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome), Papazian et al NEJM 2010, MRCT in 340 patients with ARDS (PF < 150), either 48 hrs NMBA or placebo, within 48 hrs of presentation, adjusted (but not raw) mortality improved at 90% (31% vs 40%), mortality separated late (after 12 days), no difference in weakness
- No pharmacological agents found effective (although lack of protective ventilation strategy may have masked a drug effect):
 - Recombinant surfactant improves O₂ but not mortality
 - Steroids in ARDS:
 - Menduri Study (JAMA): cross-over trial showed a reduction in lung injury score and ↓mortality (small sample)
 - More recent Menduri study: ↓Lung injury score, ↓LOS, ↓duration of IPPV
 - ARDSNET, NEJM 2006.RCT with n – 180 randomised after 7 – 28 days to placebo vs methylprednisolone (ie late in the disease process). Showed no change in 60 day mortality but ↑O₂, ↑in ventilator free days and shock free days, offset by neuromuscular complications and ↑reintubation
 - Another study showed initiation after 2 weeks was associated with ↑mortality
 - Possible reasons for no positive trials despite experimental evidence:
 - Given too late. Does it need to be early to ↓inflammation. Trials have often started after ARDS established
 - Side effects outweigh benefits
 - ARDS not one disease entity
 - Overall, not recommended
 - β₂ agonists → ↓ventilator free dys but no mortality, meta-analysis of 3 RCTs (n = 646) with ALI (Singh, Respir Care 2014)

Pneumonia

- Causative organisms:
 - *Strep pneumoniae*
 - *Haemophilus influenzae*
 - Atypicals: *Legionella*, *Chlamydia*, *Mycoplasma*
 - *Moraxella catarrhalis*
 - Enterobacteriaceae species (including *Klebsiella pneumoniae*)
 - *Staphylococcus aureus*
 - *Pseudomonas* species
 - Viruses:
 - Influenza A & B
 - Parainfluenzae 1, 2, 3
 - Adenovirus
 - Respiratory Syncytial virus
 - Varicella Zoster virus
- Risk factors for peculiar bugs:
 - Exposure to animals, birds, insect bites
 - Geographical: immigration, North America (*Histoplasma capsulatum*)
 - Host factors: Diabetes, alcohol, COPD, Whooping cough, nursing home residency (treat as health care associated), large volume aspiration, lung abscess
- Severe Acute Respiratory Syndrome (SARS):
 - WHO/CDC Case definition of a suspected case:
 - Fever > 38
 - Cough or difficulty breathing
 - Either close contact with a person diagnosed with SARS or travel within 10 days in a SARS area
 - Management:
 - SARS RNA assay or antibodies to SARS virus
 - Prevention of transmission
 - Health care workers excluded from work for 10 days if they develop symptoms
 - No specific antiviral effective

Investigations in Pneumonia

- Sputum:
 - Debatable efficacy due to contamination by upper respiratory tract commensals. Heavy growth of single organism likely diagnosis. Cannot be processed for anaerobes due to upper airway contamination
 - The following are almost always pathogens when recovered from respiratory secretions: *Legionella*, *Chlamydia*, TB, viruses, *Strongyloides*, *Toxoplasma Gondii*, PCP....
 - Heyland et al, NEJM 2006, MRCT, n = 740, no difference in treatment or outcomes between BAL and tracheal aspirates. Other conflicting studies
- Urinary *Legionella* antigen: sensitive and specific for serogroup 1 (the most common)
- Urinary pneumococcal antigen: 50 – 80% sensitivity, high specificity (> 90%)
- Serology for *Chlamydia pneumoniae* IgM
- HIV
- Bronchoalveolar lavage in immunocompromised patients who fail to respond to antibiotics or in whom sputums couldn't be obtained
- Some advocate routine surveillance sputum cultures in all patients so if a VAP develops you have recent information on colonisation and sensitivities. Little hard evidence
- H1N1 diagnosis:
 - Pre-test probability: season, prevalence, history
 - rRT-PCR most sensitive and specific
 - Rapid antigen tests and immunofluorescence antibody testing are not specific for different flu A subtypes
 - Serology only useful post infection

Prognosis in Community Acquired Pneumonia

- Major criteria:
 - Invasive mechanical ventilation

- Septic shock with the need for vasopressors
- Minor criteria:
 - RR \geq 30 (or need for non-invasive ventilation)
 - Low PaO₂/FiO₂ ratio
 - Multilobar infiltrates
 - Confusion/disorientation
 - Uraemia
 - Leukopenia (WBC $<$ 4)
 - Thrombocytopenia (Platelets $<$ 100)
 - Hypothermia $<$ 36°C
 - SBP $<$ 90
- Other potential criteria: hypoglycaemia (in non-diabetic patients), alcoholism/alcohol withdrawal, hyponatraemia, \uparrow lactate, cirrhosis, asplenia

Management in Pneumonia

- Antibiotic issues:
 - Quinolones less appropriate in high prevalence TB areas as it may mask TB infection
 - Changing to narrower spectrum Abs may inadequately treat the 5 – 38% with polymicrobial infection
 - Interest in aerosolised ABs as potentially able to achieve much higher local AB concentration and thus overcome the MIC of resistant organisms
 - Role of zanamivir and oseltamivir in severe influenza is not clear but early treatment in those with less severe symptoms resulted in a reduction of the duration of symptoms if started within 48 hours of symptoms
- Risk of pseudomonas:
 - In COPD/bronchiectasis, recent hospitalisation, recent antimicrobial therapy, gross aspiration
 - If no β -lactam allergy: Tazocin or carbapenem or (cefepime + ciprofloxacin) or (aminoglycoside + advanced macrolide)
- Duration: No clinical trials have addressed this. Recommended continued until afebrile for 48 – 72 hours and organ dysfunction has largely resolved. Short courses suboptimal for Staph Aureus, less common organisms, or pseudomonas
- Response:
 - Defervescence varies with organism, severity and age:
 - 7 days in elderly patients
 - 6 – 7 days in bacteraemia pneumococcal pneumonia
 - 1 – 2 days in M pneumoniae
 - 5 days in Legionella
 - Pseudomonas and M pneumoniae may persist in the sputum despite effective therapy
 - Sieve:
 - Does the patient have pneumonia?
 - Has a complication developed: empyema, abscess, super-infection, BOOP
 - Right drug with right dose and right route?
 - Resistance
 - Polymicrobial infection
 - Drug fever
- Referral to ICU if three of:
 - SBP $<$ 90
 - Multilobar disease
 - PaO₂/FiO₂ $<$ 250
 - Confusion
 - Urea $>$ 7 mmol/l
 - Leukopenia
 - Thrombocytopenia
 - Hypothermia
- Nebulised Heparin: Trial on-going. Sputum thinning properties. Improves mucociliary escalator clearance. Demonstrated in CF patients. ?Antibiotic. ?Anti-inflammatory topically. No impact on systemic coagulation. Range of doses (average 5,000 u nebulised QID). Unclear whether it needs to be just nebulised (targeting airways) or ultrasonic nebulised (targeting alveolar)

Tuberculosis

- Multiple sputum samples. If not available then bronchial washings or gastric lavage (neutralised immediately on collection). Pleural biopsy sensitive. PCR on sputum equally sensitive to culture in smear negative patients and quicker – but high false negative rate
- Normal CXR excludes pulmonary TB except in HIV infected patients (but early apical lesions can be missed)
- Treatment: 6 months rifampicin 600mg/day + isoniazid 300 mg/day + 2 months pyrazinamide 2 g/day + ethambutol 15 mg/kg/day (also long as good vision and baseline testing)
- Infection control: Manage in isolation with negative pressure. Non-resistant TB is non-infectious after 2 weeks. Aerosol spread \Rightarrow N95 mask
- In HIV with CD4 < 350, extrapulmonary disease is more common. < 100 may present with systemic sepsis. Caution: Rifampicin and protease inhibitors and NNRTI interact.

Pneumonia in the Immunocompromised

- Incidence highest in haematological malignancy, bone marrow transplants and AIDS
- Bacterial pneumonias progress quickly (1 – 2 days). Fungal and protozoal pneumonias are slower
- Bronchoscopy usually important. Fagon et al, Annals of Internal Medicine 2000. Subsequent trial in 740 immunocompromised patients (Canadian Critical Care Trials Group, NEJM 2006) found no difference between BAL and endotracheal aspirates. Remains unclear which is best – recommend using BAL for complicated patients not responding to conventional treatment
- CXR:
 - Diffuse infiltrate: CMV, PCP, bacteria, aspergillus (advanced), Cryptococcus (uncommon), non-infectious (drugs, NSIP, radiation, malignancy)
 - Focal infiltrate: G-ive rods, Staph aureus, Aspergillus, cryptococcus, nocardia, TB, Legionella, non-infectious
- NIV: mechanical ventilation associated with high mortality. May benefit from NIV but unclear if this translates into improved survival. Reasonable on the basis of current data to consider NIV. See Non-Invasive Ventilation, page 101
- Pneumocystis Jiroveci Pneumonia (PCP):
 - Insidious onset dry cough, SOB, fever, on background of fatigue and weight loss
 - CXR: initially normal in 10%. Non-specific changes. Effusions and lymph nodes uncommon (consider TB, Kaposi's sarcoma, lymphoma)
 - Induced sputum: ultrasonically nebulised hypertonic saline \rightarrow sputum with cysts and trophozoites. Less sensitive than bronchoscopy but less invasive. Bronchoscopy with lavage diagnostic in 90%
 - Consider delaying start of HIV treatment given risk of reconstitution syndrome
 - Treatment: cotrimoxazole (SE common – nausea, vomiting, skin rash, myelotoxicity) + prednisone
 - Response time of 4 – 7 days
- Cytomegalovirus:
 - Highest risk in allogeneic stem cell transplantation (depending on whether recipient is seropositive), followed by lung transplant, pancreas transplant, liver, heart then renal and AIDS
 - Difficult to distinguish between CMV infection and CMV disease (demonstrated by CMV-pp65 antigen in peripheral WBCs and CMV DNA or RNA in the blood by PCR)
- Fungal Pneumonia:
 - Rare
 - Require cell mediated immunity for control
 - Candidiasis: cell-mediated immunity predisposes to mucosal overgrowth, but impaired phagocytosis is required for deep invasion
 - Pulmonary lesions usually imply disseminated candidiasis
- Invasive Aspergillosis:
 - Quickly lethal in immunocompromised
 - Requires both histological and culture evidence from biopsies of infected organs

Hospital Acquired Pneumonia

- Difficult diagnosis: features non-specific and CXR findings non-specific (atelectasis, PE, aspiration, CHF, Ca...)
- Thought to result from micro-aspiration of bacteria colonising the upper respiratory tract
- Diagnosis:
 - > 48 hours since admission
 - CXR changes

- Consistent clinical features or lab findings (including micro)
- Controversy over the value of bronchoscopic sampling. Blood cultures positive in 8 – 20%
- Duration: 7 days (except for pseudomonas and staph) provided clinical response
- For uncomplicated pneumonia < 5 days since admission, cefuroxime usually OK
- Response: improvement not usually apparent for 48 – 72 hours and therapy should not be changed in this time. CXR improvement often lags clinical improvement. Significant CXR progression should raise concern
- Prevention: CDC measures include:
 - Hand washing
 - 30° head up
 - Subglottic aspiration of secretions
 - Orotracheal rather than nasotracheal intubation
 - Changing the breathing circuit only when visibly soiled
 - Preferential use of non-invasive ventilation

Parapneumonic Effusion

- Complicated effusions tend to develop 7 – 14 days after initial fluid formation
- Suggested by ↑fluid volume, continued fever and pH < 7.3 with large numbers of neutrophils
- Empyema:
 - Anaerobic bacteria, usually streptococci or G – ive rods, responsive for 76% of cases
 - CT may be required to differentiate between abscess and an empyema
 - US useful in guiding drainage

Ventilator Associated Pneumonia

- Definition:
 - ETT for > 48 hrs, then new and sustained change for > 48 hrs on CXR of a ventilated patient with a consistent clinical picture (↑ or ↓temperature, WBC, purulent secretions, worse gas exchange)
 - Agreement between clinicians in studies based on vignettes is nearly random
 - Pneumonia is usually in dependent lung
- Epidemiology:
 - Risk factors: Duration of MV, prior lung disease, trauma
 - Prevalence varies from 9 – 27% of MV patients
 - Attributable mortality varies by study. → ↑cost, LOS and duration of MV
- Surveillance definitions:
 - Are subjective, making benchmarking and research problematic
 - Pay for performance leads to measurable under reporting against surveillance criteria
 - Autopsy series show 1/3 – 1/2 of patients meeting surveillance criteria don't have it
 - New CDC surveillance paradigm (NEJM 2013). From VAP surveillance to complications of mechanical ventilation or infection related ventilator associated complications (IVAC):
 - Ventilator associated condition
 - Ventilator associated ventilator complication
 - Possible pneumonia
 - Probably pneumonia
 - Don't include radiographic criteria (subjective)
- Prevention – variable evidence of reduced VAP rates in:
 - Physical therapies:
 - Angle of the bed: Trial of supine vs semi-recumbent position in 86 mechanically ventilated patients, stopped early for benefit. Drakulovic et al, Lancet 1999. Angle of the bed is not predictive of the angle of the patient. Magic level is 45%. But this high → ↑lumbosacral pain especially in the elderly
 - Regular chest physio
 - Proning
 - Equipment:
 - Possible benefit from ET tubes permitting continuous subglottic suctioning (eg Damas, CCM 2014, single centre trial n = 352 with ↓VAP and ↓ABs)
 - Soft evidence that oral tubes is better than nasal
 - Evidence awaited for new cuffs which don't form vertical creases (which then permit passage of secretions)

- In-line suctioning devices have not been convincingly shown to make a difference
- Regular cuff pressure monitoring
- HME vs hot water bath humidification – which wins depends on which meta-analysis you read (see Humidification, page 102)
- Infection control:
 - VAP correlated to pharyngeal colonisation, biggest cause is ET tube. Best prevention is extubation
 - Antibiotic impregnated tubes: very expensive, more studies needed
 - 2% chlorhexidine mouthwash (best defined in cardiothoracic population). See Oral Decontamination, page 87
 - Disposable circuits, sterilised equipment
 - Systemic decontamination effective (but ↑cost and concerns but not evidence about ↑resistance)
 - Old data that early infection is significantly reduced by a single dose of ceftriaxone at induction
- Feeding:
 - Enteral nutrition an independent risk factor for VAP
 - Probiotics don't help
 - Nasojejunal tubes (cf NG tubes) have not been associated with reductions in VAP
 - Pro-kinetics to ↓residuals: Scant, small studies
- Other:
 - Sedation holds → earlier extubation → ↓VAP
 - Regular staff education and infection control practices beneficial (Hand washing, especially alcohol based gels, reduce incidence)
- Accidental extubation is bad (→ aspiration). Elective extubation followed by reintubation is not associated with ↑VAP
- Diagnosis:
 - Ongoing debate about diagnosis, thresholds and surveillance definitions. Do you monitor for bugs, inflammation, ↓ventilatory parameters...
 - The dilemma: delayed diagnosis (→ ↑mortality) vs wrong or over diagnosis
 - Xray change and clinical criteria have very poor sensitivity and specificity on post mortem studies
 - Inflammatory markers are non-specific and not sensitive, so can't be used for diagnosis. Biomarkers (eg STRENGTH-1) so far show poor discriminatory ability
 - Blood culture only positive in 8 – 20%
 - Most commonly on organism in bronchial aspirate. Treat if positive Gram stain. Balance between early treatment and antibiotic stewardship. Surveillance cultures (ie routine sampling of patients without VAP) correlates poorly with VAP. Pneumonia (and pulmonary infiltrates) may precede purulent sputum
 - Whether to use tracheo-bronchial aspirates, blind BAL, bronchoscope guided BAL +/- quantitative culture is controversial. Quality of BAL taking is often poor. Washings don't tell you about the tissue burden
 - Treatment may not eliminate bronchial carriage even if clinical improvement. Colonising bacteria (eg pseudomonas) may overgrow and obscure a fastidious infection
 - Generally BAL only in the immunocompromised, otherwise tracheal sample is generally sufficient
- Treatment:
 - Empiric treatment will depend on local prevalence. Early infection will be the usual suspects (strep, haemophilus, moraxella) which cefuroxime will cover
 - Later will need to consider staph and G-ives
 - Targeting treatment: Multicentre study of 413 patient with suspected VAP. Invasive management (BAL samples with culture and stopping ABs if negative) vs clinical criteria, endotracheal aspirates and empiric antibiotics. Invasive group had ↓ 14 and 28 day mortality and lower AB use
- Non-resolution. Consider:
 - Host factors: alcoholism, pre-existing respiratory disease
 - Severity of CAP:
 - Pathogens resolve at different rates
 - Resistance or unusual bug
 - Complications:
 - Infectious: empyema/abscess
 - Non-infectious: DAH, BOOP, Wegner's, sarcoid, SLE, heart failure

Chronic Obstructive Pulmonary Disease

- Most precipitating factors are reversible and the outcome is often good \Rightarrow justifies aggressive management in the majority of patients
- FEV1, 6 minute walk, and inverse BMI correlate with mortality
- Hypercapnic COPD has inpatient mortality of 11%, 80% 12 month readmission and 50% 1 year mortality
- Presentation:
 - 50% infective cause: *S pneumoniae* or *H influenzae* in 80%, also *S viridans*, *Moraxella* (previously *Branhamella*) *catarrhalis*, *Mycoplasma pneumoniae*, *Pseudomonas aeruginosa*. Viruses in 20 – 30%. Not clear if these are pathogens or colonisers
 - Pink puffers: normocapnea, emphysema predominant, thin, pursed-lip breathing, hyperinflated
 - Blue bloaters: bronchitis predominant, obese, CNS depression (retention, ETOH, sedatives, analgesics)

Pathophysiology of COPD

- Reduced expiratory airflow due to:
 - \uparrow airway resistance: mucosal oedema and hypertrophy, secretions, bronchospasm, airway tortuosity and turbulence, \downarrow lung parenchymal elastic tissues that support the small airways
 - \downarrow lung elastic recoil
- Result: prolonged expiration, pulmonary hyperinflation, inspiratory muscle disadvantage (suboptimal muscle length-tension relationships), \uparrow work of breathing and dyspnoea \rightarrow fatigue and respiratory failure (compounded by myopathy from steroids or electrolyte disturbances)
- May be:
 - Triggered by small changes in lung function from infection or cardiac failure \rightarrow decompensation
 - Compounded by central hypoventilation
 - \uparrow work of breathing \rightarrow \uparrow blood flow to respiratory muscles \rightarrow \uparrow demand on cardiac output
- Hyperinflation has two components:
 - Static: loss of parenchymal elastic recoil and chest wall adaptation \rightarrow volume of gas left after an expiratory period long enough for all expiratory airflow to cease (30 – 120 secs)
 - Dynamic: Slow expiration \rightarrow lungs don't empty before next inspiratory breath (changes with airflow obstruction, but also CO₂ production and amount of dead space)
- Early COPD often dominated by bronchitis leading to emphysema dominant pathology

Diagnosis of COPD

- FEV1:
 - 50 – 70% predicted: mild
 - 30 – 50% predicted: moderate – signs of hyperinflation (eg loss of cardiac silhouette, liver ptosis)
 - < 30%: severe: accessory muscle use, SOB at rest, pulmonary hypertension, hypercapnea (dilated veins, blurred vision, flap, confusion)
- Bronchodilator response > 12% or 200 ml \rightarrow in FEV1 \Rightarrow asthma
- TLCO (Total lung carbon monoxide) uptake predicts total alveolar surface area and approximates amount of emphysema
- CXR: hyperinflation (10 posterior or 6 anterior ribs) and large airspace anterior to sternum, pulmonary hypertension (enlarged pulmonary veins, RV enlargement)
- Check ECG for right hypertrophy or strain: P pulmonale, RAD, dominant R waves in V1-2, ST depression
- Blood gas: renal compensation for chronic hypercapnea \rightarrow \uparrow HCO₃ 4 mmol/L for each 10 mmHg of chronic CO₂ rise
- Differential:
 - Asthma: check history, triggers, response to β agonists
 - Bronchiolitis obliterans: fixed airflow obstruction following virus, inhalation of toxic fumes, bone marrow or heart/lung transplant or drugs (eg penicillamine). Insult follows several weeks later by cough and insidious SOB. Diagnosis by biopsy
 - Bronchiectasis
 - CHF

Treatment of COPD

- PO₂ to target of 90 +/- 2% - will avoid \uparrow CO₂ in the majority. Hypoxia < 85% suggests additional problem (pneumonia, pulmonary oedema, embolus, pneumothorax)
- Antibiotics
- Bronchodilators:

- Small amount of reversal is common and \uparrow mucociliary clearance. Anticholinergics may be better than β_2 -agonists (with fewer side effects and no tachyphylaxis) \Rightarrow ipratropium 0.5 mg two hourly then 4 – 6 hourly
- Aminophylline: weak bronchodilator, improves diaphragm contractility, mucociliary transport, RH function. Some studies show benefit, others don't. Loading dose 5 – 6 mg/kg over 30 mins, then infuse at 0.5 mg/kg/hr. Monitor serum theophylline levels and target low therapeutic range (55 – 85 mmol/l) to reduce side effects
- Steroids equivalent to oral prednisone at 0.5 mg/kg for up to 10 days. Leuppi et al, JAMA 2013, 5 days of 40 mg pred the stop non-inferior to 14 days, and \downarrow LOS (best dose finding study)
- Secretion clearance:
 - Chest physio: encouraging coughing and deep breathing. Bubble positive expiratory pressure (PEP) assists sputum clearance
 - Nebulised mucolytic agents: Benefit never established
 - Fibre-optic bronchoscopy: to clear sputum plus if suspected or for lavage for diagnosis
- Don't fluid overload. Diuretics + digoxin if failure. Care in severe pulmonary hypertension where \downarrow RV preload can \rightarrow low output.
- Pulmonary vasodilators have not been shown to improve outcome but have physiological benefit...
- Aspiration of pneumothoraces may be as good as intercostal drains
- Supportive care: DVT prophylaxis, electrolytes (\downarrow phosphate, Mg, Ca or K may impair respiratory muscle function), exclude hypothyroidism
- Nutrition: avoid excessive carbohydrate calories \rightarrow \uparrow CO₂ production by 15%
- Of no benefit: respiratory stimulants (central drive not usually the limiting factor)
- Follow-up:
 - Pulmonary rehab, vaccination
 - Lung volume reduction surgery (unless FEV1 < 20% - too bad). Improvements in quality of life, peaking at 1 – 2 years
 - Lung transplantation: age < 65, < 10 mg prednisone per day, free of significant coexistent disease. Survival at 1, 2 and 5 years is 75, 66 and 50%. Not widespread due to limited supply of lungs

Ventilation in COPD

- Most patients with COPD presenting with ARF do not have end-stage disease – short term outcome is sufficiently good to justify active treatment
- Non-invasive:
 - Celikel, Chest 1998
 - Esteban, NEJM 1995
 - RCTs show reduced mortality (95% CI RR 0.35 – 0.76, NNT 10), intubation, LOS and fewer iatrogenic complications. Improved O₂ and CO₂ compared with medical treatment. Confirmed in 8 RCTs: Lightowler et al, Cochrane systematic review, BMJ 2003
 - Indications (entry criteria for most trials):
 - Acute SOB
 - Respiratory rate > 28
 - PaCO₂ > 45 and 7.25 < pH < 7.35 (although more recent data shows benefit for even worse pHs)
 - Following extubation – reduces re-intubation rates significantly
 - Predictors of success: pH and PaCO₂ in first 2 hours, but not the PaO₂
 - Predictors of failure of NIV: mask intolerance, pH < 7.25, RR > 35, \downarrow LOC, poor clinical response to initial therapy
 - Less successful in hypoxaemic respiratory failure
 - Side effects: discomfort, nasal skin necrosis, gastric distension, aspiration
 - Anxiolytics may be helpful if anxiety precipitates tachypnoea but extreme caution recommended
 - All modes of NIV effective, no comparative trials to address optimal mode or pressure level
- Invasive:
 - Hospital survival up to 80% but 30% 12 month survival
 - Being previously house-bound (or worse still chair or bed bound) indicate poor outcome and quality of life
 - Indications:
 - Fatigue and impending respiratory collapse
 - Deteriorating consciousness (due to fatigue or hypercapnea)
 - Hypoxia refractory to high FiO₂
 - Deterioration due to failure of secretion clearance

- Aims:
 - Support ventilation while reversible factors improve
 - Allow rest while preventing wasting
 - Avoid dynamic hyperinflation (DHI): causes circulatory compromise and barotrauma
 - \Rightarrow Low level respiratory support
- Technique:
 - Start on 8 – 15 cmH₂O with 3 – 8 cm PEEP
 - If exhausted, post-arrest or comatose, then SIMV
 - Low minute ventilation to avoid DHI – 115 ml/kg
 - Adequate time for expiration \Rightarrow small tidal volume (8 ml/kg) and rate < 14
 - If excessive DHI then \downarrow MV and accept hypercapnic acidosis. Sedate to avoid spontaneous ventilation worsening DHI. Avoid relaxants unless essential
 - If DHI OK then encourage spontaneous ventilation to avoid respiratory muscle wasting
- Assess DHI by:
 - Measuring plateau pressure by applying end inspiratory pause of 0.5 s following a single breath. If > 25 then DHI present \Rightarrow reduce rate. Pplat may be high if poor compliance
 - PEEPi: Measure with prolonged expiratory pause. If > 8 – 10 then further prolongation of expiratory time likely to be necessary. May need to \uparrow inspiratory flow rate (controversial) to lengthen I:E ratio
- Weaning:
 - Predictive value of numerous individual criteria limited
 - Respiratory rate/tidal volume < 100 (shallow breathing index) reasonable
 - Small retrospective trial of extracorporeal CO₂ removal (Novalung) showed \downarrow ventilation, \downarrow LOS but no difference in 6 month mortality
- Tracheostomy:
 - See Tracheostomy, page 96
 - After 10 days risk of trauma and sepsis increases
 - Tracheostomy allows long-term ventilatory support, sputum clearance, protection of the upper airway, less sedation and reduced dead space/upper-airway resistance
 - Unable to prevent enough upper airway seal to cough \rightarrow ongoing atelectasis
 - NG feeding usually required
 - Cuff pressure < 20cm. Must be humidified otherwise dried secretions block tube
 - Remove when:
 - Suctioning less than 2 - 4 hourly
 - Can cough (eg has sufficient respiratory muscle strength)
 - Can protect airway from aspiration
 - FiO₂ < 40% and non-invasive pressures would be sufficient

Asthma

- Majority of adverse outcomes are attributed to underestimation of severity with delayed and/or inadequate treatment
- Asthma:
 - Reversible airway obstruction
 - Airway inflammation
 - Increase airway responsiveness to a variety of stimuli

Pathophysiology of Asthma

- Genetic and environmental factors
- IgE-dependent mechanisms important
- Triggers are non-specific (eg cold, exercise) or specific (dust mites, pollen, animal danders), stress or emotion
- Two patterns:
 - Acute severe asthma, symptoms over hours/days on background of poor control. Slower to respond to treatment, ?due to greater contribution from mucous and bronchial wall inflammation
 - Hyperacute: very quick, less common, younger male patients, high bronchial reactivity to triggers responding quicker to bronchodilators
- Respiratory impact:

- ↑work of breathing from ↑airways resistance and ↓compliance (due to hyperinflation). Mechanical disadvantage due to lung volume close to TLC → respiratory muscle failure with ↓ventilation
- V/Q mismatch due to airway narrowing: further increases MV requirements → ↑work of breathing
- Haemodynamic effects:
 - Inspiratory pleural pressures as low as -35 cmH₂O → ↑ venous return → ↑RV volume → ↓LV volume
 - Hypoxic pulmonary vasoconstriction, acidosis, ↑ lung volume → ↑RV afterload → ↓LV preload
 - Negative intrapleural pressures → ↑LV afterload
 - → Pulsus paradoxus: ↓ in systolic blood pressure during inspiration of > 10 mmHg (typically 15 – 25 mmHg, normal = 5 mmHg)

Severity Assessment of Asthma

- History: prior intubation, multiple presentations, poor psychosocial circumstances
- Vitals: RR > 30, pulse > 120, pulsus paradoxus > 15 mmHg specific but not sensitive for severe attack
- Exam: Declining conscious state, single words, accessory muscle use
- LFT: FEV₁ < 1.0 litres of PEF < 100 l/min ⇒ very severe
- ABG: Initially hypocapnea but ↑work of breathing, ↑V/Q mismatch and ↓haemodynamics all → ↓alveolar ventilation and PCO₂ > 45. May also be a metabolic acidosis – usually due to lactic acidosis from β-agonists
- Response to first 2 hours of treatment predicts outcome

Management of Asthma

- Oxygen:
 - Humidified O₂ so sats > 90%
 - Emerging evidence of harms of hyperoxia in some: → pulmonary hypoxic vasoconstriction, worsening V/Q mismatch → ↑PCO₂. See Hazards of O₂ Therapy, 85
- Short acting β-agonists:
 - Salbutamol (relatively β₂ selective), terbutaline, isoprenaline, epinephrine
 - Cause smooth-muscle mediated bronchodilation and may ↓ mucosal oedema
 - MDIs with spacer may be better than nebuliser (< 10% reaches the lungs even under ideal conditions)
 - IV Salbutamol
 - Bolus: 10 mcg/kg to max 500 mcg (~adults try 250 mcg) slow push
 - Little evidence to support IV β-agonists – they have a theoretical advantage of reaching less ventilated lung
 - Typical dose is 5 – 20 µg/min. Infusion 5 mg in 50 mls (0.1 mg/ml) at 0 – 10 ml/hr (approx. 5 – 20 µg/min)
 - SE include: tachycardia, arrhythmia, hypertension, hypotension, tremor, hypokalaemia, hyperglycaemia, and lactic acidosis (in 70% after 2 – 4 hours, reaching 4 – 12 mmol/l and may significantly add to respiratory acidosis and distress. Settles 4 – 6 hours after cessation)
- Anticholinergics:
 - ↓ parasympathetic-mediated cholinergic bronchomotor tone → bronchodilation
 - Ipratropium is a quaternary derivative of atropine. Clear evidence of incremental benefit and few extra side-effects
 - Optimal dose unknown – recommended 0.5 mg every 2 – 6 hours (although more frequent initial dosing has been used)
- Corticosteroids:
 - → ↑β responsiveness, ↓inflammatory cell response, ↓mucus secretion
 - Effects within 6 – 12 hours, oral as effective as IV, no benefit from > 800 mg hydrocortisone/day. If IV, convert to declining oral dose of prednisone 0.5 mg/kg within 4 – 7 days
 - Use inhaled steroids from day 1
 - SE: hyperglycaemia, ↓K, hypertension, acute psychosis, myopathy, ↑infection risk (including legionella, PCP and varicella)
- Aminophylline:
 - Conflicting studies. Inferior bronchodilator with narrow therapeutic range and frequent side-effects (headache, nausea, vomiting, restlessness; arrhythmias and seizures at serum levels > 0.2 mmol/l or 40 mg/l). Structural and pharmacological similarity to caffeine
 - Cochrane Review 2012 (Travers et al) of 11 studies comparing 350 patients getting IV β-agonists or aminophylline. No difference in outcomes. More side effects with aminophylline

- Initial loading dose of 3 mg/kg (omitted if already taking theophylline) and infuse at 0.5 mg/hour. Reduce if cirrhosis, CHF, COPD or if on cimetidine, erythromycin or antiviral vaccines. Check drug levels every 24 hours (30 – 80 $\mu\text{mol/l}$)
- Magnesium Sulphate: blocks Ca^{2+} channels \rightarrow smooth-muscle relaxation. 5 – 10 mmol slowly over 20 mins. SE: hypotension, flushing, sedation, weakness, areflexia, respiratory depression and arrhythmias at high levels
- Non-established rescue treatments:
 - Adrenaline: No benefit found over salbutamol. Really need central access
 - Heliox: 70% helium, 30% oxygen. Mixed results from trials. Reduces gas density and turbulence with \downarrow airflow resistance
 - Volatile anaesthetic
 - Ketamine: may cause some bronchodilation. Useful induction agent (1 – 2 mg/kg). SE \uparrow secretions, hyperdynamic cardiovascular response and hallucinations (reduced with benzodiazepines)
 - Leukotriene Antagonists: evidence in chronic asthma. Only some evidence in acute asthma
 - Inhaled mucolytics: no benefit and may worsen obstruction
 - Antibiotics: not unless there is evidence of infection
 - Sedation: clear association with avoidable deaths

Ventilation of Asthma

- Dynamic Hyperinflation:
 - Incomplete exhalation traps gas \Rightarrow lungs don't return to FRC \rightarrow progressive accumulation of trapped gas
 - Equilibrium reached when small airway calibre and lung elastic recoil increase enough to allow tidal volume to be exhaled
 - Adaptive in mild obstruction as allows desired V_t to be achieved
- Trapped gas exerts a positive pressure on the alveoli = PEEPi or autoPEEP. Measured PEEPi underestimates true PEEPi as less obstructed airways only remain in communication with major airways during exhalation. See Measurement of Lung Mechanics, page 81
- As airway obstruction worsens, static hyperinflation rises (due to airway closure)
- NIV:
 - Theoretical advantages:
 - External PEEP overcomes PEEPi and therefore reduces the inspiratory threshold work of breathing
 - Augmentation of inspiration with NIV \rightarrow \downarrow work of breathing
 - Shorter inspiratory time \rightarrow less DHI
 - Inspiratory augmentation + PEEP \rightarrow airspace opening \rightarrow $\downarrow V/Q$ mismatch
 - Experimental works suggest main effect is to unload inspiratory muscles
 - No large RCTs
 - Contraindications: \downarrow LOC, haemodynamic instability, inability to protect airway and clear secretions and high risk of aspiration
 - Start at CPAP of 5 and IPAP of 13 – 15 aiming for respiratory rate < 25 and exhaled tidal volume of 7 ml/kg. Favourable response is usually apparent within the first hour
 - Complications: nasal bridge ulceration, mask discomfort, nasal congestion, gastric insufflation, aspiration, hypotension and pneumothorax (lower risk than with intubation)
- Invasive Ventilation:
 - A patient who complains of exhaustion is likely to need intubation
 - Intubate with largest tube possible and bag slowly (8 – 10 /min)
 - Initial settings:
 - Minute ventilation < 115 ml/kg/min (< 8 l/min in a 70 kg patient), eg V_t of 5 – 7 ml/kg and RR of 8 – 12, I:E ratio $> 1:3$, short inspiratory time to ensure expiratory time > 4 secs (requires volume-controlled inspiratory flow rate of 70 – 100 l/min)
 - Results in a high peak airway pressure but will lower DHI and Pplat and reduce barotrauma
 - PEEP will further increase lung volume and should not be used initially
 - This will cause hypoventilation \rightarrow respiratory acidosis \rightarrow respiratory distress so will need heavy sedation
 - If significant hypotension treat by reducing the respiratory rate (\rightarrow \downarrow DHI) and \downarrow intravascular loading
 - Assessing DHI:

- Measure Pplat: airway pressure after transient expiratory pause at the end of inspiration. The best measure of DHI. Pplat reflects gas trapping. Measure at end inspiration with a 2 s pause. Pressure falls from peak (static plus resistive) to Pplat (static). Must be no leaks in the system and patient generally sedated/paralysed to get reliable measure. Aim < 25 – 30 cmH₂O.
- Intrinsic PEEP is the airway pressure during occlusion of expiratory flow at the end of expiration. May underestimate end expiratory alveolar pressure – marked DHI may occur despite low levels of PEEPi, especially at low respiratory rates
- If transient rate reduction to 4 – 6 breaths/min for 2 – 4 min or during apnoea of 60 seconds → significant increase in BP and ↓ in CVP then DHI has been suppressing circulation
- Adjusting ventilation:
 - Use minimum amount of hypoventilation to achieve a safe level of DHI in association with less sedation and minimal of no use of NMBAs
 - Adjust ventilation based on DHI, not on PaCO₂ or pH. If Pplat > 25 then reduce rate. If Pplat is low then ↑rate or reduce sedation and allow spontaneous breathing
 - Hypercapnea is usually well tolerated. No evidence of benefit from bicarbonate but some recommend for PCO₂ < 7.1 to reduce acidaemia induced respiratory distress
 - Pressure support of 10 – 16 cmH₂O when obstruction improves. CPAP of 3 – 7 will assist ventilator triggering and ↓work of breathing
- Complications of invasive ventilation:
 - Risks pulmonary hyperinflation and aggravation of bronchospasm
 - Hypotension cause by sedation, DHI, pneumothoraces, arrhythmias or hypovolaemia
 - PEA arrest: a small number of patients can rapidly develop excessive DHI during initial uncontrolled mechanical ventilation. Immediately disconnect from the ventilator (apnoea) for 60 seconds or hypoventilate 2 – 3 breaths/min to diagnose and improve
 - Pneumothorax: as soon as it is suspected, reduce RR to protect the other lung from over-inflation. Always insert intercostal catheter by blunt dissection.
 - Acute necrotising myopathy: in patients who also receive NMBAs or very deep sedation (exacerbated by steroids). Weakness, EEG evidence of myopathy, and ↑CK. Muscle biopsy diagnostic

Pulmonary Embolism

- See:
 - NEJM, Dec 25 2008
 - 2014 ESC Guidelines on the diagnosis and management of acute PE
- Aetiology:
 - Most PE results from DVT of the lower limbs, pelvic veins or inferior vena cava
 - Risk factors: venous stasis, vein wall injury, hypercoagulable, immobility, surgery, trauma, malignancy and pregnancy
 - Hypercoagulable states:
 - Activated protein C resistance mediated by factor V Leiden most common
 - Antithrombin III, Protein S or Protein C deficiency
 - Lupus anticoagulant
- Pathophysiology:
 - Pulmonary artery obstruction → release of vasoactive agents → ↑pulmonary vascular resistance and acute pulmonary hypertension → ↑RV afterload → ↑RV wall tension and dilatation + coronary ischaemia → RV dysfunction
 - V/Q mismatch → hypoxaemia + ↑dead space ventilation → wider end-tidal to arterial CO₂ gradient
- Diagnosis:
 - Clinical assessment is not sensitive nor specific
 - Haemoptysis → late presentation where pulmonary infarction has occurred
- Investigations:
 - Pulmonary angiography the traditional gold standard
 - Multi-slice CT now compares well with angiography. Also can assess severity: RV/LV ratio (> 0.9) and clot in the proximal branches of the pulmonary artery correlated with severity. Can detect an alternative diagnosis, and assess DVT in legs, pelvis or abdomen. Detects alternative diagnoses. Issues of transport, radiation, contrast. PIOPED II suggested that CTPA requires concomitant pre-test probability assessment (Wells) to be effective.

- D-dimer: degradation product of cross-linked fibrin detected in serum. Negative d-dimer highly predictive of absence of DVT and PE. Multiple causes of a raised D-dimer \Rightarrow not at all specific
- BNP and Trop of no use for diagnosis, but add to risk stratification. Troponin elevated in 30 – 50% with moderate/large PE. NT-terminal Pro-BNP a better predictor of outcome than troponin
- ECG normal in one third. Most common findings are tachycardia, and non-specific S-T depression and TWI in anterior leads. S1Q3T3 infrequent
- CXR identifies alternative diagnoses
- Echo: Rapid, bedside test, avoiding transport, radiation and contrast. Poor at excluding a PE – can miss up to 50%. Useful for unstable patient. Most common findings are RV dilation, RV hypokinesis (especially if apical sparing), paradoxical interventricular septal motion toward the LV, TR and pulmonary HTN
- V/Q scanning: looking for mismatched perfusion defects. Low probability scan with high clinical suspicion \Rightarrow 40% chance of a PE
- Risk stratification:
 - Massive: Hypotension (SBP < 90 or cardiogenic shock) \Rightarrow 25 – 30% mortality. Urgent removal of clot
 - Submassive: Normotension but RH dysfunction: Thrombolysis appears to improve outcomes but more bleeding. No mortality reduction but less escalation (eg to ICU) or clinical deterioration. Controversial over whether thrombolysis appropriate
 - Mild: low risk of death or recurrence. LMWH. Consider outpatient treatment
- Management:
 - For non-massive PE, LMWH as good as unfractionated heparin. Quinlan et al, meta-analysis, Annals of Internal Medicine 2004
 - For venous thromboembolism, apixiban non-inferior to heparin, then warfarin, Agnelli NEJM 2013
 - Unfractionated heparin if had thrombolysis or embolectomy. Need to get to therapeutic levels quickly. Complications of bleeding and Heparin-induced thrombotic thrombocytopenia syndrome
 - IVC Filter: if anticoagulation contraindicated or ineffective. See Meta-analysis in JAMA Surg, Haut 2013. Filter placement associated with RR of fatal PE of 0.09 (CI 0.01 – 0.81) and no \uparrow in DVT. NNT to prevent on additional PE ranged from 109 - 962
 - Thrombolysis:
 - Similar degree of resolution with heparin after days to weeks. Best within 48 hours, but benefit up to 14 days
 - Cerebral haemorrhage in 1.8%, major bleeding in 13%.
 - Evidence is not strong. Oh: No studies have found mortality difference from thrombolysis – but ??What about:
 - Significant reduction in mortality in massive in meta-analysis – 9.4% vs 19% with heparin alone, NNT 10, if arterial hypotension
 - Submassive PE:
 - Konstantinides et al, NEJM 2002 which showed \downarrow in-hospital mortality in RCT of 256 patients with PE with RV dysfunction but not shock
 - PEITHO Trial, Meyer, NEJM 2014, RCT, n = 1006, median age 70, tenecteplase (30 – 50 mcg single dose) + heparin vs placebo + heparin, in normotensive PEs with RV dysfunction (CT or echo) and myocardial injury (\uparrow trop). No difference in day 7 death (1.2 vs 1.8%) or day 30 (2.4 vs 3.2%). Less CVS decompensation in tenecteplase group but \uparrow intracranial bleeding (6.3 vs 1.2%), stroke (2.4 vs 0.2%)
 - Don't know about long term outcomes in terms of pulmonary HTN or RV dysfunction – which is what treatment in this group is theoretically aimed at preventing
 - No studies definitively favour one thrombolytic over another. Useful up to 14 days after symptom onset
 - Surgical embolectomy: Results vary widely. Perioperative mortality of 25 – 50%. Consider if contraindication to thrombolysis or as rescue
 - Percutaneous embolectomy: including catheter guided thrombolysis: mortality still about 20 – 30%
- Supportive care:
 - Volume loading can improve haemodynamics but also worsen RV function – be cautious
 - Intravenous vasoactive agents:
 - Coronary ischaemia an important part of haemodynamic instability
 - RV coronary perfusion pressure = MAP – RVP
 - If < 30, myocardial blood flow falls substantially \rightarrow RV failure \rightarrow shock
 - Raising MAP and \downarrow PAP will improve coronary blood flow

- Noradrenaline the best vasopressor to raise MAP. Care with anything that vasodilates even if CO might improve (eg dobutamine, GTN, milrinone)
- Beneficial effects with aortic balloon pumps in animal studies
- iNO as adjunctive, rescue therapy
- O₂: high flows may be required due to hyperventilation and ↑ dead space
- If shocked then consider PA catheter to titrate treatment – ?risk of haemorrhage outweighed by benefits of better monitoring
- Prophylaxis:
 - LMWH and fondaparinux (factor Xa inhibitor) as efficacious as UFH and less HITTS
 - Graduated compression stockings and intermittent pneumatic compression devices

Broncho Pulmonary Fistula

- See J of Critical Care, 2010, 25: 47 – 55
- Formal definition: leak of inspired air into the pleural space for > 24 hours
- Causes:
 - Pulmonary resection, ↑risk with incomplete tumour resection, steroids, haemophilus influenza...
 - Persistent spontaneous pneumothorax, including ruptured bullae
 - Necrotising lung infection
 - Inflammatory lung diseases
 - Malignancy
 - Trauma, iatrogenic (CVL placement)
- Diagnosis (if not obvious): reduced level of an effusion on CXR, CT, methylene blue in the chest drain after putting it down the ET tube
- Complications:
 - Incomplete expansion of affected lung
 - Derecruitment, volutrauma or barotrauma of unaffected lung
 - Inability to maintain PEEP
 - Ventilator auto-triggering
 - Inaccurate calorimetry
 - Empyema
- Management:
 - Supportive:
 - Aim: decrease sedation (maintain spontaneous breathing) and minimise airway pressure (low Tv, low PEEP, permissive hypercapnea, short Tinsp)
 - Intercostal catheter, large bore if large leak (flow of turbulent moist gas described by the Fanning equation). May require multiple catheters. However, suction on chest tube may increase flow through the chest tube and ↑auto-triggering which may be treated with ↑sedation...
 - No randomised trials of different ventilator strategies
 - Independent lung ventilation via double-lumen tube is theoretically attractive, requires double lumen tube, two ventilators, and may not be tolerated in hypoxic patients
 - High frequency jet ventilation may provide adequate gas exchange at lower airway pressures. No better than conventional ventilation on case series. Data in ARDS suggests increased mortality. No data in HFOV
 - Application of PEEP to intercostal catheter – may decrease leak but compromises drainage and risk of tension
 - Echo. Little experience
 - General ICU care, consider ABs, attention to nutrition
 - Definitive:
 - Bronchoscopic occlusion: can be definitive but is technically challenging and not feasible with multiple leaks
 - Surgical repair (the latter if large proximal fistula > 0.8 mm), oversown with omentum or muscle flaps. Need to be able to tolerate surgery.

- See also Heart Disease in Pregnancy, page 321
- Causes of myocarditis:
 - Infection: TB, enterovirus, echovirus, coxsackie virus, HIV, HSV6, HCV, parvovirus
 - Rheumatic fever
 - Haemochromatosis
 - SLE, Sarcoid
 - Alcohol
 - Drugs (eg doxorubicin)

Echocardiography

- Includes:
 - Two dimensional anatomical imaging
 - M-mode echocardiography (usually obtained with 2-D guidance). Beam is not scanned but stays in a fixed position displaying the structures along the beam (depth on the vertical axis) over time (on the y axis). Rapid sampling makes identification of thin moving structures, such as valve leaflets, relatively easy
 - Doppler techniques:
 - Doppler shift is the difference between frequencies transmitted and reflected off red blood cells
 - Calculated from $V = C * \Delta f / 2f_t * \cos(\theta)$ where V = velocity of blood flow, C = speed of sound in soft tissue (1540 m/s), Δf = Doppler (frequency shift) and θ = angle between ultrasound beam and the direction of blood flow
 - It is very important that the beam is nearly parallel with the direction of blood flow
 - Velocities can be converted to pressure gradients using the simplified Bernoulli equation $\Delta P = 4V^2$
 - Flow towards the probe is read, away is blue
- Not (yet) an efficient technique for ongoing haemodynamic monitoring
- Principles:
 - Sound in the frequency 1 – 10 MHz
 - No known adverse biologic effects
 - No RCTs specifically test the impact of echocardiography on outcome
 - Evaluation of valvular stenosis requires:
 - Imaging the valve to define the morphology and mobility of the valve cusps
 - Quantification of the degree of stenosis
 - Effect of pressure overloading on the relevant chambers
 - Note: in conditions of low cardiac output, pressure gradients will be low and therefore underestimate the severity of stenosis
- TTE:
 - May be inadequate images in mechanically ventilated or obese patients, or those with chronic lung disease, obesity, chest trauma or surgical wounds
 - In ICU may be limited by inability to position
- TOE:
 - Compared to TEE provides additional information in 32 – 100% of ICU examinations and new diagnoses in 38 – 59%. Approximately 20% of patients with unexplained hypotension require surgery on the basis of TOE findings
 - Is more sensitive and specific for endocarditis than TEE, and required (over TTE) to diagnose prosthetic valve endocarditis, aortic dissection, aortic trauma, LA appendage clot and localised tamponade (post cardiac surgery)
 - Contraindicated in oesophageal stricture or neoplasm
 - Relative contraindication in oesophageal varices, severe coagulopathy and significant cervical spine abnormalities
 - Routine AB prophylaxis not required

Echo Abnormalities to Look For

- Pericardial effusion/tamponade: variable amount of “black” fluid possibly with echo-dense fibrin strands
- Aortic dissection: TOE best – allows visualisation of ascending and descending aortic defects, false lumens, AR, tamponade, and regional wall motion abnormalities suggesting coronary artery occlusion

- LV wall thickness: systolic > 1.5 cm → hypertrophy, < 0.6 cm suggests scarring, dilated cardiomyopathy
- LV systolic function: M mode can calculate:
 - Fractional shortening: change in LV internal dimensions between systole and diastole (normal = 30 – 45%)
 - Ejection fraction
 - Stroke volume
- LV diastolic dysfunction: Abnormal LV stiffness and impaired relaxation → altered motion of the anterior mitral valve leaflet → a number of sensitive but not specific markers....
- Aortic valve: Nature of leaflets and:
 - Stenosis: pressure gradient (calculated from $4 \times \text{peak velocity}^2$). Normal < 10 mmHg, severe > 60. Valve area: normal 2.5 – 5.5 cm, severe < 1.0. Look for complications: dilation, ventricular dysfunction, post-stenotic aortic dilatation
 - Regurgitation: Features of severity: LVEDD > 5.5 cm, LV jet reaching the apex, regurgitant orifice > 60% width at cusps, reversal of diastolic flow in the aortic arch
- Mitral valve: nature of leaflets and:
 - Stenosis: M-mode pattern of abnormal opening and closing, LA dilatation, severe = valve area < 1 cm (normal 4 – 6), pressure gradient > 10, pulmonary hypertension
 - Regurgitation: Wide jet at the leaflet tips, reversal of systolic flow in the pulmonary veins, pulmonary HTN, dilated LV and LA
- Endocarditis: Vegetations – usually mobile echo-reflective masses
- Cardiomyopathy: dilated, restrictive, hypertrophic obstructive (with systolic anterior movement [SAM] of the mitral valve)
- RV dysfunction: RV > LV size. Bulging of the interventricular septum and pulmonary hypertension

ECG Interpretation

- Axis:
 - LAD = left of -30
 - RAD = right of + 100
- Inverted P waves:
 - Swapped limb leads
 - Low atrial focus
 - Dextrocardia
- Normal Q waves: < 2 mm or < 25% of R wave height
- Tall R wave in V1 (> 25% of S wave and duration < 0.04s):
 - RBBB
 - RV hypertrophy
 - Posterior MI
 - Acute right heart strain (R ventricular dilation)
 - WPW Type A
 - Dextrocardia
 - Reversed anterior chest leads (eg V1 & V3)
 - Duchenne's Muscular dystrophy
 - Normal variant in 1%
 - Incorrect lead placement
- Blocks:
 - Left anterior hemiblock:
 - Anterior (anterosuperior division) bundle of His more vulnerable due to long course and thinner dimension.
 - LAD: I positive, II and III predominantly negative with initial R wave in II, III, aVF
 - No Q in II or aVF
 - QRS 0.1 – 0.12
 - Left posterior hemiblock
 - RAD: I negative, II and III predominantly positive. Exclude other causes of RAD, including RV hypertrophy
 - QRS 0.1 – 0.12
 - Left Bundle Branch Block
 - QRS > 0.12
 - M pattern in V6. Primary and secondary R wave (RR')

- Always of significance – reflects IHD or hypertrophy
- Right Bundle Branch Block:
 - QRS > 0.12
 - Activation of the free wall of the RV is delayed → wide M shaped QRS in V1/2 (right ear bigger than left). Can be normal variant, massive PE, RV hypertrophy, IHD and congenital heart disease
- Trifascicular block:
 - Important to distinguish from AV node disease, ie is the long PR interval due to AV delay or more distal conduction delay:
 - AV node: if it fails an escape rhythm from the Bundle of His takes over
 - Trifascicular block: Diffuse disease. IF AV fails the escape rhythm may be ventricular and therefore dangerously low
 - Criteria: Prolonged PR interval, RBBB and either L anterior or posterior fascicular block
- ST elevation:
 - Pericarditis – generalised concave up
 - AMI – concave down
 - Ventricular aneurysm: persistent ST elevation
- Ventricular Tachycardia:
 - Need to distinguish VT from SVT with aberrant conduction: Don't give adenosine or verapamil to VT – can lead to collapse. Often AV dissociation → cannon waves and fusion beats (Ps buried in QRS). If in doubt assume VT. Characteristics of VT:
 - QRS > 140 ms
 - Bizarre QRS complex, concordance of QRS complex in all precordial leads
 - Slurring of the initial portion of the QRS
 - Large S wave in V6
- J waves:
 - Aka Osborne waves
 - Secondary deflections at the end of the QRS
 - Due to hypothermia. Also bradycardia and TWI
 - Said to occur < 28°C, but can occur in low 30s
- U waves: ↓K, ↑Ca, thyrotoxicosis, digitalis, Long QT syndrome
- PE:
 - RAD
 - P pulmonale
 - RSR in V1
 - S1Q3T3
- Heart block:
 - 2nd Degree Mobitz Type 1 (Wenckebach): progressive prolongation. Conduction ↑ with each atrial impulse until it fails to conduct
 - 2nd Degree Mobitz type 2: intermittent failure of conduction without preceding ↑ in PR interval. More likely to be associated with structural heart disease. More likely to progress to 3rd degree block
 - 3rd degree block: most commonly caused by idiopathic fibrosis of the conduction system, also MI, valvular heart disease, cardiac surgery and congenital forms of block
 - Sick sinus syndrome: atropine or low dose-isoprenaline if unstable as a bridge to pacing

Acute Cardiac Syndromes

- See also Adult Cardiopulmonary Resuscitation, page 163
- Pain of recent origin, is more frequent, severe or prolonged than any usual angina, occurring at rest
- Caused by:
 - activated macrophages attracted to intimal injury incorporating blood stream lipids into connective tissue causing plaque. Original stenotic lesion is < 50% in 70%
 - plaque rupture or fissuring → platelet aggregation (limited by antiplatelet agents) via glycoprotein IIb/IIIa receptors with cross link fibrinogen (white thrombus)
 - thrombin activation (inhibited by antithrombin agents eg heparin) → fibrin clot with enmeshed red cells (red thrombus) – lysed by fibrinolytic agents
 - recent thrombus formation on pre-existing coronary artery plaque (originally caused by) → ↓myocardial O2 supply.
 - In time, fibrosis of infarcted muscle causes decreased compliance, expansion of the infarcted segment, and compensatory hypertrophy of unaffected myocardial cells (ventricular remodelling)

- Anatomy:
 - RCA is “dominant” as opposed to circumflex if it gives rise to the posterior descending coronary artery
 - Infarct size determines:
 - LV systolic function impairment
 - Stroke volume decrease
 - Ventricular filling pressure rise
 - LV diastolic dysfunction
- Definition of MI: ↑ in troponin above 99th percentile with a least one of:
 - New ST & T change or new LBBB
 - New Q waves
 - Cardiac imaging or angiography consistent with MI
- Divided into:
 - STEMI:
 - Usually due to complete occlusion of an artery ⇒ indication for reperfusion therapy
 - Always Trop rise
 - Height of initial ST-segment elevation is modestly correlated with degree of ischaemia
 - 8% of patients with MI will only display ST-elevation in posterior leads (V7 – V8, true posterior) or in the right pre-cordial leads V3R – V6R (RV)
 - ECG localisation may differ from anatomical blockage if there is collateral circulation or previous CAGB
 - Acute resolution correlates with re-perfusion
 - Tak-Tsubo syndrome is also characterised by precordial ST-segment elevation
 - NSTEMI/UA:
 - NSTEMI: ↑ biomarkers.
 - Unstable angina: normal biomarkers
 - Treatments directed at platelet inactivation and “plaque stabilisation”. Thrombolytic therapy is not beneficial and is associated with worse outcomes
 - ST-segment depression has lesser early mortality and similar or higher 6 month and 10 year mortality than ST-elevation
- Clinical presentation:
 - 20 – 60% of non-fatal infarctions are unrecognised at onset
 - Signs:
 - Autonomic activation: pallor, sweating, agitation
 - LV failure: gallop rhythm, ↑RR, 4th heart sound.
 - Differentials include:
 - Dissection
 - Pericarditis

Investigations for Acute Coronary Syndromes

- Troponins:
 - See Review, JAMA 5 June 2013
 - TnT and Tin are two of the three isoforms of cardiac troponins (part of the thin filament of the myocyte contractile apparatus)
 - They are more sensitive than CK and Ck-MB
 - 50% release by 4 hours, peak at 12 – 24 hours, persist in serum up to 7 – 10 days
 - Predict short and long term risk
 - AUC correlates to extent of MI
 - Washout and peak altered by reperfusion
 - Incomplete understanding of elevation after cardiac and non-cardiac surgery
 - Are frequently elevated in critical illness – and in this setting do not correspond to adverse outcomes. Associated with ↑ morbidity and mortality in surgical ICU outcomes
 - Are elevated in:
 - Other cardiac conditions: pericarditis, AF, cardioversion
 - Non-cardiac conditions: renal failure, sepsis
 - Are a risk stratification tool in conjunction with other tests (ECG, echo...)
- Other bio-markers:
 - CK: also found in skeletal muscle

- CK-MB: used to diagnose reinfarction within 14 days
- AST: also found in skeletal muscle
- LDH
- CRP, hs-CRP, ESR: non-specific, added prognostic information
- BNP/B-type Natriuretic peptide:
 - Released in response to ventricular wall distension
 - ↑ in heart failure. Useful to guide therapy
 - Diagnostic marker in presentations to ED with SOB
 - Can be ↑ in sepsis, ALT, PE, intracranial haemorrhage
 - Place in ICU unclear
- Novel biomarkers: Copeptin, Heart-type Fatty Acid Binding Protein (H-FABP), myeloperoxidase.... None shown to be superior to Troponin
- Echocardiography:
 - Primary goal is assessing regional and global LV dysfunction
 - Exclude differentials (aortic dissection, pericardial effusion)
 - TOE may help in cardiogenic shock as a guide to fluid therapy
 - Dobutamine stress echo at 2 – 10 days can distinguish non-viable myocardium from stunned myocardium (superiority to ETT not proven)
- Should you do a head CT on someone presenting with an arrest? Issues:
 - Arrests due to intra-cerebral events are a small percentage of the total (2 – 3 % in an audit in Wellington)
 - Arrest due to an intracerebral event is nearly uniformly fatal in case series data
 - Therefore, would only consider a head CT in non-routine settings:
 - On warfarin – with a potentially drainable lesion
 - Young – where the balance of risks shifts from cardiac toward neurologic causes
 - Other situations: eg prior headache, no malignant rhythm captured at any point
 - Other than this, head CT does not help management – it only allows earlier prognostication in a very small group

Management of Acute Coronary Syndromes

- 50% of deaths from MI occur within the first hour (usually VF)
- Pre-hospital compared to in-hospital thrombolysis → ↓ 17% in 30 day mortality
- Indications for reperfusion therapy: presentation ≤ 12 hours, unrelieved by GTN with ↑ST in 2 or more contiguous leads (> 2 mm in v2 – v6 or > 1 mm in limb leads) or new onset LBBB or posterior infarct (dominant R wave and ST depression > 2 mm in v1 – v2) or presentation 12 – 24 hours after onset of ACS with continuing pain and evidence of evolving infarction
- Percutaneous Coronary Intervention :
 - Superior to thrombolysis if door-to-needle time < 90 mins, survival benefit of 20 patients per 1000 treated (better outcomes in higher risk patients)
 - Consider:
 - If (Door-to-balloon) – (door-to-needle) < 1 hour
 - High risk from STEMI: Age > 75, extensive anterior infarct, high risk of bleeding, previous MI or CABG
 - Also consider if:
 - Contraindications to thrombolysis
 - Cardiogenic shock to 36 hours (high mortality, thrombolysis ineffective)
 - Failed thrombolysis
 - Previous CABG
 - Caution in risk of contrast-associated renal failure
 - In comatose patients with arrhythmia due to NSTEMI who were cooled, early cardiac catheterisation → ↓ risk of death in an observational study (Hollenback, Resuscitation 2013)
- Thrombolysis:
 - Critically dependent on door to needle times. Can still thrombolyse with benefit from 6 – 12 hours
 - Peak benefit is in 65 – 75 year old group
 - Thrombolysis promotes conversion of plasminogen to plasmin → lyses fibrin
 - Lower mortality despite ↑ cerebral haemorrhage (fatal in 40 – 60% of cases) – risk for which is significantly increase with age, recent stroke and hypertension (exclusion criteria for many trials, consider PCI)
 - As good as PCI in early presentations (< 3 hours) as fresh clots more likely to be lysed

- Thrombolysis alone does not improve the appalling mortality of cardiogenic shock 2nd to MI (55% at 30 days)
- Cooling: see Induced hypothermia After Cardiac Arrest, page 136
- Adjunctive therapy:
 - Key driver of improved outcomes (regardless of choices over PCI/thrombolysis)
 - Necessary because underlying artery remains unstable
 - Aspirin (if necessary rectally) + clopidogrel (significant additional benefit) unless contraindicated. Does not appear to ↑bleeding
 - Abciximab (GP IIB/IIIA inhibitors) with primary PCI, little benefit in thrombolysis and ↑ bleeding
 - Heparins: do not lyse clot, decrease rethrombosis. LMWH probably superior to UFH. Fondaparinux (Xa factor inhibitor) has less bleeding complications
 - β-blockers: oral within 24 hours unless contraindicated by bradycardia, heart block and hypotension. Benefit from IV pre-thrombolysis, less now? (↓reinfarction, ↓VF, ↑shock, no net benefit). Non-randomised trial of 664 patients showed improved mortality from immediate over delayed β-blockers in STEMI (Hirschl, CCM 2013)
 - ACEI
 - If LV dysfunction and heart failure the spironolactone or eplerenone
 - Recommend SBP of 100 mg in STEMI, but no clinical studies have investigated the best level
- Transfusion thresholds:
 - Target of Hb to 100 is without RCT evidence
 - Retrospective registry analysis in elderly patients with MI (Wu, NEJM 2001) showed transfusion in those with a haematocrit of < 30 was associated with reduced 30 day mortality compared with those with the same haematocrit who were not transfused
 - Focus trial: MRCT of 2016 patients aged > 50 following hip surgery with high risk for cardiovascular disease. Targeted Hb 100 vs 80 or symptoms of anaemia. No difference in mortality, ability to walk at 60 days, or cardiovascular morbidity

Complications of Acute Coronary Syndromes

- Rhythm disturbance:
 - In nearly all patients, most likely in the first few hours and during reperfusion
 - Correct hypoxia, hypovolaemia and acid-base disturbances
 - Maintain serum K in the range 4 – 5
 - Maintain serum magnesium level – no benefit from prophylactic or routine use
 - Prophylactic lignocaine increases mortality – reserve for life-threatening ventricular arrhythmias
- Failed thrombolysis: further thrombolysis not associated with ↑survival. Rescue PCI didn't help survival but did ↓heart failure
- Heart failure:
 - When abnormally contracting segment > 30% of LV circumference; shocked if > 40%
 - ACEI limit dilatation, and preserve LV function in those with reduced function
 - RV failure: important to maintain preload, may benefit from volume loading
- Reinfarction within 10 days in 5 – 10%. Post-infarction angina unresponsive to medical therapy → early PCI
- Severe mitral regurgitation 2nd to papillary muscle rupture
- Cardiac rupture: Interventricular septum in 1 – 2 % of MIs. May have new long systolic murmur with progressive clinical deterioration. Untreated mortality > 50% at 1 week. Prompt surgery +/- balloon pump as a bridge
- Systemic Emboli: 1% during admission, and in 2% by 12 months – mainly in extensive anterior MI (mural thrombi in 30 – 40% of anterior Q wave MIs)
- Pericarditis: rub in 10 -1 5% of anterior MIs at 24 – 72 hours, may mimic ischaemia. Dressler's syndrome = fever, ↑ESR, rub, pain and arthralgia

MI in the ICU

- Few RCTs to guide therapy in post-operative infarction or in MI in the critically ill (usually excluded from trials of ACS therapy)
- Pathophysiology is probably different to ACS – ischaemia is due to O2 supply and demand problems rather than isolated thrombus
- Invasive management usually necessary – thrombolysis usually precluded by bleeding risk and uncertainty about cause

Induced hypothermia After Cardiac Arrest

- Aka “Targeted Temperature Management”
- See:
 - Out of Hospital Cardiac Arrest, page 165
 - Holzer, NEJM Sept 2010
- Not supported in children post-arrest, other than new-borns, nor in pregnancy (no data)
- Hypothermia considered in lots of settings (eg cardiac surgery). Reduces brain metabolism, ↓release of glutamate and dopamine, ↓oxidative stress, ↓apoptosis
- For treatment of “post-cardiac arrest syndrome”, second to both hypoxia and substrate depletion, and subsequent reperfusion injury
- 2 RCTs in Feb 2002 NEJM:
 - Bernard, Melbourne: 77 patients with VF or pulseless VT (age > 18 for men, > 50 for women, no cardiogenic shock, “persistent coma”) randomised by day of month to control or cooling to 33o within 2 hours for 12 hours with ice packs. Non-blinded. Outcome was discharge to home/rehab (good) or otherwise. 49% of cooled who survived had a good outcome, cf 26% in control. After adjustment for baseline differences, OR of 5.25 for a good outcome if cooled. Hypothermia had complications of ↓cardiac index, ↑SVR, and hyperglycaemia
 - Hypothermia After Cardiac Arrest – HACA Study (Austria): 253 patients (with “no response to voice”) randomised to cooling to 32 – 34o for 24 hours with cold air. 55% vs 39% had a favourable outcome. Mortality at 6 months 41 vs 55%. Only 8% of screened patients admitted
 - No data from these studies to guide how long is too long before cooling. Animal models suggest sooner is better
- Subsequent papers:
 - ICE Study: Italian Cooling Experience, Resuscitation 2012: < 2 hours vs > 2 hours from arrest to cooling, prospective observational trial, ICU mortality and 6 month mortality higher in the early cooling group (potential confounders)
 - Retrospective case series analysis suggests active and passive re-warming equivalent
 - Targeted Temperature management (TTM Trial) at 33oC vs 36oC after Cardiac Arrest, Nielsen et al, NEJM 2013:
 - Asking the question was the benefit due to hypothermia or to avoiding fever
 - Included protocolised withdrawal of treatment: prognosticate 72 hours after rewarming unless brain death, myoclonus or negative SSNP
 - Targeted to 33 for 28 hours then warm by 0.5o per hour. Both arms had temperature target < 37.5 in unconscious patients from 36 – 72 hours
 - N = 939, assessed at 180 days. Included shockable and non-shockable rhythms (as opposed to 2002 studies), and anyone with GCS 3 – 8. VF/VT initial rhythm in 80%. Average ROSC 25 mins. Bystander CPR in 70%
 - Death in 50% (33oC) vs 48% (36oC), further 4% in each arm had poor neurological outcome
 - Result may demonstrate the benefit of active treatment of hyperthermia
 - In contrast to a decade ago, one half compared to one third of patients with ROSC can expect to survive to hospital discharge
 - Observational study in n=270 found temperature > 38.5 oC within 36 hours after rewarming was associated with ↑mortality (36% vs 22%) and poorer neurological outcome (Bro-Jeppese, Resuscitation 2013)
 - Pre-hospital induction of mild hypothermia, JAMA 2013, RCT n = 1364 in OHCA with ROSC but intubated, randomised to standard care or pre-hospital cooling to 34o, then standard in hospital care (most cooled). Survival to discharge (in VF group) 64% in both arms
- Lots of variation in international practice about whether it’s applied to VF/VT only or any arrhythmia, OHCA or in-hospital only, other hypoxic injuries (eg hanging) etc.
- Australian and NZ Resuscitation Council Recommendations (Pre-TTM):
 - Who to cool: sustained “coma” after ROSC. Various definitions range from GCS ≤8 or “not responding to verbal commands” (Level of evidence 1)
 - Non-RCT studies general support cooling after other non-shockable rhythm arrests
 - No studies address cardiac arrests due to non-cardiac causes. “It is reasonable to assume that these patients might also benefit from induced hypothermia” (Expert Consensus Opinion)
 - Methods of cooling studied include ice-cold fluids, intravascular heat exchanger, ice packs and cooling blankets. All safe and effective
 - Five studies indicated that PCI while cooled is safe
- Not proven in non-VT/VF arrests or in-hospital arrests

- Physiological benefits:
 - ↓cerebral O₂ consumption
 - ↓excitatory amino acids (esp glutamate) and free radical formation
 - ↓cerebral oedema and intracranial pressure
 - ↓neutrophil migration to ischaemic tissue
- Management:
 - Core temperature and invasive blood pressure should be monitored
 - Shivering should be suppressed with sedation +/- muscle relaxants
 - Methods vary in terms of ease and speed:
 - Surface cooling: slow and titration of temperature can be difficult
 - Circulating cold water blankets
 - Force cold air convective blankets
 - Ice packs to the axillae and groin: risk of burns
 - Immersion in ice bath: effective for children, commercial devices under development, limited practical use
 - Cooling garments, helmets, etc.: faster (up to 3 °C per hour) but costly
 - Large volume ice cold IV fluid: 30 ml/kg crystalloid cooled to 4°C and infused over 30 mins: easy, cheap, ↓ temp by 1.6°C, initial study by Bernard showed no adverse effects. Contra-indicated in pulmonary oedema. Needs additional method to maintain hypothermia
 - Body cavity lavage: Gastric 500 ml/10 min, bladder 300 ml/10 min, peritoneal: cheap, time-consuming, invasive
 - Extra-corporeal circuits: may be part of CRRT, invasive
 - External heat exchange control devices via indwelling central line: cool by 0.8°C/hr. Will achieve and maintain target temperature. Invasive and expensive
 - Rewarm slowly at 0.3 to 0.5 °C per hour
- Risks:
 - Cardiovascular: bradycardia, vasoconstriction, arrhythmias uncommon at 33°C
 - Haematological: ↓WBC, ↓number and function of platelets, ↑clotting times
 - ↑infection risk
 - GI: ↓gut motility, hyperglycaemia
 - Renal: renal dysfunction, *diuresis*
 - Metabolic: ↓K, ↓Mg, pancreatitis
 - MS: shivering → lactic acidosis
 - Neurological: non-convulsive status
- Note:
 - As the patient is cold and paralysed, more complex techniques for measuring CO are invalidated and bedside assessment of circulation and interpretation of acid-base and lactate are difficult
 - Limited data suggests cooling reduces the predictive value of motor responses and of absent N2O responses

Acute Heart Failure

- ICU patients with acute heart failure often have one or both of:
 - Underlying coronary artery disease
 - Significant other organ dysfunction
- Difficult balance between the best interests of myocardium and other vital organs
- Aim: minimum necessary DO₂ and arterial pressure to maintain other organ function at maximum cardiac efficiency (eg optimum fluid resuscitation)
- For exacerbations of chronic heart failure see NICE guidelines. These include not routinely offering nitrites or opioids, and CPAP only if the person has pulmonary oedema and acidaemia. The role of dopamine, thiazides, ultrafiltration and IABP are recommendations for research to confirm or deny efficacy

Investigations for Heart Failure

- Echo. Useful for identifying:
 - Effusions, whether ventricular filling is impaired, and whether drainage is necessary. It is the rate of accumulation, not the amount of fluid, that determines the degree of cardiac compromise
 - Volume preload of LV when preload pressures are raised
 - Primary valvular disease (urgent surgery may be required), cf functional valvular disease 2nd to ventricular dysfunction (surgery may be fatal)

- Regional abnormalities from acute or old infarcts
- Intracardiac thrombus
- Contractile failure (\uparrow end-diastolic and end-systolic dimensions), although EF can be misleading if on inotropes
- Diastolic dysfunction. \uparrow pre-load measurements fail to reflect true volume preload and extra volume may be indicated
- Pulmonary hypertension with TR \Rightarrow an estimate of pulmonary artery pressure can be made
- TOE: good views of aorta, atria and L heart valves. R heart valves and LV less well imaged
- Troponins: see page Investigations, page 133
- Brain-Type Natriuretic Peptide (BNP)
 - First isolated from porcine brain
 - Main source is ventricular myocardium, released when wall is stressed
 - Cut off below 100 pg/ml has sensitivity of $\sim 90\%$ and specificity of $\sim 80\%$ for excluding heart failure
 - A marker of myocardial dysfunction and prognosis in severe sepsis

Management of Heart Failure

- Correct abnormal metabolic factors:
 - Hypoxaemia
 - pH < 7.20 . Contractility increases linearly with \uparrow pH to > 7.40
 - K > 5.5
 - Mg < 0.9
 - Ca < 1.0
 - PO₄ < 0.8
 - Hb < 90 . Trial showing benefit of 70 – 90 rather than 10 – 12 did not admit the elderly or those with IHD
 - Thiamine deficiency (malnutrition, excess alcohol, chronic frusemide or digoxin treatment) – oral thiamine of 200 mg/day improves LV function
- Consider revascularisation for ischaemia
- Treat arrhythmias
- Inotropes see page 44, Levosimendan see page 47
- β -blockade (rather than stimulation) if still tachycardic after fluid resuscitation – although surgical patients with low CO and DO₂ and pulse < 100 then β -agonist. No β -blockade superior to another in RCTS in chronic heart failure. Likely class effect (Chatterjee, BMJ 2013)
- Ventilation:
 - CPAP and invasive positive pressure ventilation
 - Improved oxygenation, and reduced work of breathing \downarrow O₂ consumption by up to 30%
 - If intubating will need volume and adrenaline to counter-act \downarrow effect of endogenous catecholamines from sedation/analgesia
- Mechanical Augmentation: See page 160
- Lancet 1998, Cotter et al, trial of 110 patients randomised to ISMN 3 mg every 5 minutes or frusemide 80 mg every 15 mins + ISMN 1 mg/hr, in patients with pulmonary oedema and sats $< 90\%$. Low dose frusemide, high dose ISMN did better
- Constanzo et al, 2007, UNLOAD Trial, 200 patients with heart failure LCEF $\sim 40\%$ to veno-venous ultrafiltration or IV diuretics. Ultrafiltration group had greater fluid loss at 48 hours and fewer rehospitalisations within 90 day, no significant difference in Cr or mortality
- Bart et al, 2012, NEJM, RCT of 188 patients with decompensated HF, showed stepped pharmacological therapy superior to ultrafiltration

Non-Invasive Ventilation in Heart Failure

- $\rightarrow \uparrow$ elastic workload (Pel) and to lesser extent resistive workload (Pres)
- \downarrow hypoxia, recruits alveoli, \downarrow intrapulmonary shunt, \downarrow LV afterload
- RCTs have consistently demonstrated \downarrow hypoxia, \downarrow hypercapnea, \downarrow intubation, \downarrow LOS and \uparrow survival. Eg Masip et al, JAMA 2005, Meta-analysis of 15 trials of CPAP vs BiPAP. \downarrow Mortality in the BiPAP group
- Optimal mode appears to be CPAP alone. Addition of BiPAP may \uparrow MI without additional outcome benefit
- Optimal level unresolved, but Pao of 10 cm H₂O appears safe and effective in the majority of subjects
- Cochrane Review 2013: 32 studies, n = 2916, \downarrow hospital mortality, \downarrow intubation, \downarrow ICU but not hospital stay. No \uparrow MI

Management of Right Ventricular Dysfunction

- The right side of the heart:
 - Responds to preload, contractility, and afterload like the L heart
 - Is affected by sepsis, inflammation, coronary disease, arrhythmias
 - Is high compliant. ↑volume but ↓muscle mass compared to the left
 - Can't handle ↑pressure
 - Coronary perfusion also occurs in systole
- Much harder to diagnose and monitor dysfunction:
 - All clinical signs relate to preload
 - Echo can measure afterload, but complicated by complex geometry and by intraventricular dependence. Most echo measures are load dependent
 - MRI may be helpful for RH function
- Things that make RV dysfunction worse:
 - ↓PO₂, ↑PCO₂ and ↓pH all → ↑RV afterload
 - Ventilation → ↓preload and ↑RV afterload (opposite to LV) → bigger risk on intubation
- Specific RH management considered in RH ischaemia or pulmonary HTN:
 - Treat LVF, lung disease, RV infarct, PE, endocarditis, sepsis
 - Treat confounding factors: ↓O₂, ↑CO₂, ↓pH without high ventilatory pressures (good luck!)
 - Optimise preload: give or remove fluid. CVP not that helpful. If fluid doesn't help then stop
 - Contractility: Inotropes to maintain MAP/RV perfusion. dobutamine, milrinone ↑contractility and ↓PVR. Noradrenaline and vasopressin to protect SVR
 - Vasoconstrictors → maintenance of RV perfusion pressure, but will increase the work of the LV
 - Afterload reduction in PAH:
 - If PAP > 25 mmHg or MPAP/MAP > 0.4
 - Pulmonary Vasodilators: NO, prostacyclins, Bosentan, Sildenafil (see Pulmonary Vasodilators, page 115)
 - Conventional vasodilators produce excessive systemic vasodilatation
 - GTN also → ↓PVR but has systemic effects and can't give with Sildenafil
 - May be no fall in PA pressure (though PVR has fallen). Positive response may be seen in CO, SvO₂ and/or CVP
 - IABC: maintain coronary artery perfusion and ↓RV afterload
 - Bivad, ECHO, heart transplant

Therapy	Advantages	Disadvantages
Volume	↑filling pressure. PA catheter may help guide therapy	RA pressure may not accurately predict preload.
Inotropes or vasopressors	May help in RV infarction by increasing coronary perfusion pressure. Some suggestion that Levosimendan may improve RV overload in ARDS	No large scale data on any inotrope or vasopressor in isolated RV failure
Afterload manipulation: control of hypoxia, ↑CO ₂ and acidosis	↓PA pressure	Optimal targets unclear
Prostaglandins	↓PA pressures. Iloprost has longer T _{1/2}	May cause systemic hypotension, flushing
NO	Improved VQ matching, ↑O ₂ , ↓PVR	Met Hb, platelet dysfunction, requires special equipment, not shown to improve mortality
Bosentan	↓PA pressures.	No large scale data. Long T _{1/2} and hepatotoxicity
PDE Inhibitors (eg Sildenafil – currently oral only)	↓PA pressures	No large scale data
Pacing to improve AV dyssynchrony	Improves RV preload	
Mechanical ventilation	Improved O ₂ and CO ₂ may → ↓pulmonary hypertension	Deleterious effects of IPPV

- If already on medication for pulmonary hypertension then don't stop otherwise rebound pulmonary hypertension

Valvular Heart Disease

Rheumatic Fever

- Cross reaction following Group A β -haemolytic streptococci
- Presents with:
 - Polyarthrititis
 - Carditis: murmurs (most commonly mitral or AR), cardiomegaly, CHF
 - Subcutaneous nodules
 - Rash (erythema marginatum)

Infective Endocarditis

- Delay in diagnosis \rightarrow \downarrow survival: fever + murmur = endocarditis until proven otherwise
- Causes:
 - Community acquired (staph, coagulase-negative staph, viridians, less commonly enterococci)
 - Increasingly post-procedure in hospital (staph now more common than streptococcus viridans, MRSA in line infections)
 - Prosthetic valve endocarditis is a disaster. Infection involves the sewing ring \rightarrow paraprosthetic leak or abscess, may not have vegetations. May require TOE or cardiac MRI or CT to visualise
 - Tricuspid valve in drug abuse. Frequently misdiagnosed as pneumonia
 - If a cardiac redo within 12 months, always cover MRSA
- Common pathogens:
 - Staphylococci
 - Streptococci viridans and sanguis
 - Enterococci
 - HACEK Organisms:
 - Oral gram negative bacilli: Haemophilus parainfluenzae, Actinobacillus, cardiobacterium, Eikenella, Kingella.
 - Fastidious to grow – may need prolonged culture up to 10 days, so a differential in culture negative endocarditis
 - Their significance is that they need G-ive cover with a 3rd generation cephalosporin, which is not part of the usual empiric treatment, so the correct antibiotic may be started late...
 - Q Fever: Coxiella Burnetti. Rickettsial infection. Difficult to culture. Prolonged treatment
- Symptoms: vague ill health, night sweats, weight loss, mild fever
- Clinical features of endocarditis:
 - New murmur
 - Purpura fulminans
 - Osler's nodes: tender nodules on pulps of fingers and toes
 - Janeway lesions: non-tender haemorrhagic macules in the peripheries
 - Roth spots: retinal haemorrhages with a pale centre
 - New neurological signs
 - Tender and swollen joints
 - Mainly in chronic:
 - Nail and conjunctival splinter haemorrhages
 - Clubbing
 - Splenomegaly
 - Anaemia
 - Signs of heart failure
- Diagnosis:
 - Modified Duke's Criteria. Major criteria include 2 positive blood cultures, evidence on echo, new regurgitant murmur
 - 3 sets of blood cultures before antibiotics – don't wait for a temperature spike – probably don't need to take from different sites
 - Can't be diagnosed or excluded by echo
 - \uparrow CRP. $\uparrow\uparrow$ WBC if staph, may be normal in less virulent organisms – check for fastidious bacteria and fungi (eg Q fever – Coxiella burnetti)

- Echo: vegetations if they're > 3 mm. Degree of regurgitation, intramyocardial spread and LV function. TOE better for MR endocarditis and abscess detection.
- Histology of replaced valve
- Differential of subsequent renal failure:
 - Pre-renal: hypovolaemia, heart failure
 - Intra-renal: nephrotoxic agents, sepsis, *immune mediated GN*
- Treatment:
 - Try and be specific. Will need prolonged treatment. If subacute may elect to wait for cultures
 - Antibiotics:
 - Penicillin sensitive: Penicillin G or amoxicillin or ceftriaxone
 - If complicated or prosthetic valve add gentamicin. If acute then cover staph. If a risk of MRSA add vancomycin to flucloxacillin (don't drop the flucloxacillin as it is more effective than vancomycin for sensitive staph aureus)
 - If allergic to penicillin then vancomycin or teicoplanin +/- gentamicin
 - Could do cephalosporin +/- quinolone
 - Surgery:
 - If indicated, do it early, not necessary to wait for antibiotic treatment to take effect (Kang, NEJM 2012). 2 centre RCT of acute L sided native valve endocarditis and vegetations > 10 mm – surgery within 48 hours or surgery only if complications during medical treatment. No difference in mortality but ↓ embolic events
 - Indications: haemodynamic deterioration with increasing AR or MR or abscess
 - Fungi and Q fever usually require surgery
 - Vegetations > 10 mm → ↑ embolism risk but not known if surgery reduces this

Mitral Stenosis

- Mainly caused by RF, also left atrial myxoma, calcification of the annulus, SLE, ball-valve thrombus
- Causes ↑ LA pressure, pulmonary venous and arterial hypertension
- Associated AF is associated with marked symptomatic deterioration and ↑↑ risk of LA thrombus
- Clinical signs:
 - Mitral facies (peripheral cyanosis on the cheeks)
 - Small volume pulse – may be irregular
 - Tapping apex due to a palpable first heart sound
 - Loud first heart sound, and an opening snap 0.04 – 0.1 s after S2 with rumbling diastolic murmur
- Investigations:
 - Broad P wave in lead 2 due to LA hypertrophy
 - Prominent upper-lobe pulmonary veins
- Severe stenosis if valve area < 1 cm²
- Treatment:
 - β-blockers to slow the rate → ↑ diastolic filling time
 - Diuretics
 - Anticoagulation
 - Mitral balloon valvuloplasty compares well with surgical treatment. Contraindicated if significant MR or heavy calcification

Mitral Regurgitation

- Chronic MR:
 - Causes: mitral valve prolapse, RF, LV dilatation of any cause, prosthetic heart valves
 - Time for LV and LA to adapt
 - Treatment: initially medical (ACEI to reduce afterload, diuretics and digitalis). However, severe CHF or death after valve replacement increase abruptly when LV end-diastolic diameter > 4.5 mm or EF < 60%. If no stenosis, repair preferable to replacement
- Acute:
 - Causes: ruptured chordae, ruptured papillary muscle, prosthetic valves
 - Sudden pressure on LA → severe pulmonary oedema without change in LV dimension
 - Treatment: pre- and after-load reduction and urgent surgery

Mitral Valve Prolapse

- Myxomatous degeneration of the valve → redundancy of the leaflets → as LV pressure rises during systole a portion of the valve prolapses into the LA → regurgitation

- Usually mild. Can progress to severe
- Exam: mid-systolic click and late systolic murmur, louder with valsalva and on standing

Aortic Stenosis

- Causes: degeneration of a bicuspid aortic valve (→ soft A2)
- Leads to: ↑LV systolic pressure, LV hypertrophy, ↓LV compliance
- Investigations:
 - ECG: LV hypertrophy
 - CXR: post-stenotic dilatation in the ascending aorta
- Treatment: Valve replacement as soon as symptomatic, or if LV dysfunction or jet velocity > 4 m/s

Aortic Regurgitation

- Chronic causes:
 - RF
 - CTDs (AS, Reiter's, RA)
 - Syphilitic aortitis
 - Cystic Medial Necrosis (Marfan's)
 - Hypertension → aortic root dilation
 - Congenital bicuspid aortic valve
 - Endocarditis
- Leads to LV dilation and LV hypertrophy
- Symptoms: fatigue and dyspnoea
- Exam: enlarged apex, early diastolic blowing murmur from left sternal edge to the apex. Austin Flint (Mid diastolic) murmur due to regurgitant aortic jet hitting the anterior mitral valve leaflet
- Investigations:
 - ECG: LV hypertrophy, with strain pattern
- Treatment:
 - Medical: vasodilation, eg ACEI
 - Surgery before LV end-systolic diameter > 55 mm or ejection fraction < 60%
- Acute causes:
 - Endocarditis (Staph or pneumococcus) → acute LV diastolic pressure and volume overload severe pulmonary oedema without LV dilation

Tricuspid Regurgitation

- Causes:
 - 2nd to RV dilatation/hypertrophy 2nd to pulmonary hypertension
 - Infective endocarditis (usually *S aureus*) in drug addicts
- Large V waves in jugular venous pressure

Congenital Heart Disease

Ostium Secundum Atrial Septal Defect

- Often unrecognised due to subtle symptoms
- May develop AF and CHF. Paradoxical emboli rare
- Exam: pulmonary ejection systolic murmur with wide and fixed S2
- Investigations:
 - ECG: RBBB, and LAD with a primum defect
 - Echo: (especially TOE) shows defect and gives estimate of pulmonary artery pressure
- Increased risk of Eisenmenger's syndrome but no risk of endocarditis
- Closure is now usually by an occluder for larger defects only
- Non-cardiac surgery:
 - Low risk
 - If ↑peripheral vascular resistance → ↑L to R shunting
 - Systemic paradoxical emboli possible ⇒ early mobilisation after surgery

Patent Ductus Arteriosus

- Endocarditis risk increases from age 20
- By age 30, sizeable L to R shunts develop → heart failure

Fallot's Tetralogy

- Features: VSD, over-riding aorta, RVOT narrowing (subvalvular or valvular level – eg pulmonary stenosis or atresia), RVH. Requires patent ductus for survival
- Pre-cordial findings: ESM or PSM, RV heave, loud single second heart sound
- Pulmonary stenosis usually sufficient to prevent excessive pulmonary blood flow, but not big enough to cause R to L ventricular shunting
- Late health status good – 30 year survival is 90%
- In some RV fibrosis → ventricular arrhythmia and sudden death

Eisenmenger's syndrome

- Fixed pulmonary vascular resistance ⇒ not able to respond rapidly to haemodynamic change ⇒ sudden fall or rise in systemic vascular resistance dangerous

Cardiac Arrhythmias

- See ECG, page 131

Electrophysiology

- Highly selective ion channels determine the rate of ion flux → magnitude and rate of change of myocyte membrane potential. Ion channel function can be affected by:
 - Genetic mutations
 - Changes in functional expression
 - Acute ischaemia
 - Autonomic tone
 - Myocardial scarring
 - Electrolyte concentration
- Spectrum includes:
 - Fast response cells (conducting and contracting myocytes) and slow-response cells (pacemaker cells in SA and AV nodes)
 - They also differ in refractoriness – determined by the voltage-dependent recovery of Na channels
 - Fast response myocytes lose their early loss of refractoriness in ischaemia or Na channel-blocking drugs and behave like slow response myocytes with slow conduction
- Phases:
 - Phase 0: rapidity of depolarisation determines speed of conduction. Fast uses Na channels, slow uses Ca channels
 - Phase 1: early incomplete repolarisation due to K channels (not in slow myocytes)
 - Phase 2: prolonged plateau repolarisation, Ca balanced then overcome by K flux
 - Phase 3: rapid repolarisation as outward K current of the delayed rectifiers increases
- Basis for arrhythmia:
 - Genetics: Primary electrical disease is associated with mutations in ion channels eg LQTS. Inheritable structural heart disease (eg hypertrophic and dilated cardiomyopathies) are associated with atrial arrhythmias and SCD
 - Molecular: structural and electrical remodelling in response to myocardial injury, changed haemodynamics and neurohumoral signalling → heterogeneous slowing of conduction velocity and prolonged refractoriness. Heart failure is associated with:
 - Down regulation of depolarising K currents → prolonged repolarisation → susceptible to early after-depolarisation (EAD). Heterogeneous change → substrate for re-entrant arrhythmias
 - ↓Na channel density → ↓conduction velocity
- Arrhythmogenic mechanisms:
 - Abnormalities of impulse
 - Impulse generation:
 - Enhanced normal automaticity or triggered activity (oscillations in the membrane potential that are initiated or triggered by a preceding action potential)
 - Early after-depolarisations are sub-threshold humps occurring during phase 2 or 3 – on reaching the threshold single or multiple action potentials are induced – especially with prolonged action potential in bradycardia
 - Delayed after-depolarisations – depend on previous rapid rhythm for initiation due to Ca induced Ca release
 - Conduction

- Structural influences: MI, hypertrophy, dilation, fibrosis
- Transient influences: ischaemia/reperfusion, systemic factors (hypoxia, acidosis), neurophysiological (autonomic tone, catecholamines), toxicity
- Re-entry:
 - Re-excitation of an area by a circulating impulse
 - Requires: conduction block in one limb of the circuit, slowed conduction in the other limb, impulse returning back along the limb initially blocked to re-excite the initial limb. Required cardiac wavelength to be shorter than the potential re-entrant pathway
 - Can be abolished by: \uparrow conduction velocity, \uparrow refractory period, \downarrow slowing conduction (convert a unidirectional block into a complete block)
- Electrolyte Abnormalities:
 - K: Both \uparrow and \downarrow K \rightarrow arrhythmia due to changes in RMP. Ischaemia $\rightarrow \uparrow$ extracellular K $\rightarrow \downarrow$ RMP \rightarrow abnormal automaticity and inactivation of fast inward Na channels which slows conduction velocity. During MI the incidence of VF/VT is 15% at 4.5 mmol/l, 38% at 3.0 and 67% at 2.5
 - Antiarrhythmic properties of Mg are clearly established, but relationship between \downarrow Mg and arrhythmia is circumstantial. \downarrow Mg by itself has little effect on myocytes or the ECG. Product of K and Mg best predicts arrhythmia in thiazide use
- Proarrhythmic effects of anti-arrhythmic drugs:
 - Correlated with the degree of drug-induced QT prolongation or characteristics of Na channel blockade
 - Slowing of conduction – which may block a re-entry circuit – may create the substrate needed for re-entry
 - Increasing conduction velocity would be antiarrhythmic – but no antiarrhythmics do this
 - Prolonging the refractory period is an ideal antiarrhythmic property – potency of class IA and II drugs depend on this
 - However, as drugs \uparrow refractory period and slow conduction they may have no effect, \downarrow proarrhythmia, or \uparrow proarrhythmia depending on the properties of the potential re-entrant circuit
 - Risk of arrhythmia increased by toxic levels of drugs, severe LV dysfunction, pre-existing arrhythmia, digoxin, \downarrow K, \downarrow Mg, bradycardia, combination anti-arrhythmics
- Management:
 - History, including thyrotoxicosis, EOTH and family history if young
 - Vagal manoeuvres:
 - $\rightarrow \uparrow$ vagal tone \rightarrow prolong AV conduction and \uparrow refractoriness
 - VT not affected
 - Valsalva, iced water on face, or carotid sinus massage (head extended and turned away, exclude bruits, rub carotid bifurcation anterior to SCM just below angle of the jaw, contraindicated in cerebrovascular disease)

Supraventricular Tachycardias

- Anything that requires atrial or AV nodal tissue for initiation and maintenance
- Can be broad complex if concurrent BBB or pre-excitation

AV Node Dependent

- Diagnose with Adenosine, see page 150
- Treatment includes vagal manoeuvres and adenosine (slow AV conduction). Verapamil an option but hypotension a problem (especially if concurrent β -blockers). Rapid atrial pacing works but is rarely needed. Cardiovert if unstable
- AV nodal re-entry tachycardia: re-entry within the AV node. Not usually associated with structural heart disease
- AV re-entry tachycardia:
 - One limb is an accessory pathway, the other the AV node
 - In 25% of cases the pathway only conducts retrogradely so pre-excitation (the δ wave) is buried in the QRS complex. Orthodromic AVRT has an antegrade nodal and retrograde accessory pathway circuit. Because the circuit is longer, a retrograde P may be seen after the QRS (cf AVNRT)
 - Type A Wolf-Parkinson-White Pre-excitation syndrome: upright QRS deflections in the right precordial leads (tall R wave) \rightarrow accessory pathway on the left \rightarrow pre-excitation of the LV
 - Type B: dominantly negative QRS in V1 (Deep S wave) \rightarrow accessory pathway on the right \rightarrow pre-excitation of RV

- Type A/B “old” terminology predating EPS
- Treatment:
 - Unstable: shock
 - Drugs that prolong refractory period of the accessory pathway: sotalol, amiodarone, flecainide (β -blockers have no effect on refractory period)
 - Drugs that shorten the refractory period are contra-indicated (eg digoxin)
 - Avoid verapamil as it may block the AV node and, if AF, \rightarrow very rapid conduction to the ventricles via the accessory pathway
 - Radio frequency ablation is curative
- AF uncommon in WPW but may be life-threatening as most impulses are conducted via the accessory pathway (\rightarrow wide complexes)
- Accelerated idionodal rhythm/accelerated junctional rhythm: increased automaticity of the AV node above the usual inherent rate of 40 – 60, often to 60 – 99. May see independent atrial activity. Consider digoxin toxicity. Junctional tachycardia exceeds 100/min

AV Node Independent

- Blocking the AV node will slow the ventricular rate but not terminate the rhythm
- See 2014 AATS guidelines for the prevention and management of perioperative atrial fibrillation and flutter for thoracic surgical procedures, Journal of Thoracic and Cardiovascular Surgery, 148:3, 2014 – good review covering monitoring, drugs,
- **Atrial flutter:**
 - Single re-entry confined to the atria, most commonly anticlockwise. Type 1 (240 – 320 bpm) entrained with overdrive pacing, type 2 (340 – 430 bpm) not terminated by pacing.
 - Saw-tooth pattern in V1 – can be unmasked by vagal manoeuvres.
 - Rarely 1:1 conduction occurs – associated with sympathetic overactivity or class 1 antiarrhythmics.
 - Check electrolytes
 - Not reliably terminated by any drug treatment.
 - Slow ventricular rate: Digoxin (as long as not MFAT), β -blocker, amiodarone, overdrive pacing
 - Low energy cardioversion usually effective. Prevention with sotalol, low dose amiodarone or flecainide (if no structural heart disease)
- **Atrial fibrillation:**
 - Multiple re-entry circuits confined to atria. Paroxysmal AF appears to originate primarily at the junction of the left atrium and pulmonary veins
 - LV dysfunction \rightarrow atrial stretch and fibrosis \rightarrow electrical and ionic channel remodelling
 - Idiopathic AF has good prognosis, AF developing after cardiac surgery \rightarrow \uparrow stroke, arrhythmias and LOS
 - Consider \uparrow TFTs and ETOH
 - \rightarrow \uparrow pulmonary capillary wedge pressure, \downarrow stroke volume and CO, embolism and tachycardiomyopathy
 - Is it AF:
 - Slow the recording speed and check for P waves
 - Connect the ECG to an atrial pacing and look for P waves
 - Treatment:
 - Unstable: shock
 - Stable, symptomatic and \downarrow LV function: Shock or digoxin, amiodarone to control rate (target < 110)
 - Stable, symptomatic and normal LV function: β -blockers, diltiazem, digoxin (poor control with exercise and \uparrow sympathetic tone), Mg (short term), amiodarone, sotalol
 - Stable, no structural heart disease, minimal symptoms: Single dose flecainide (greatest LV depression and high risk of arrhythmia)
 - Check it's NOT multifocal atrial tachycardia – digoxin may worsen this
 - Conversion to sinus rhythm more important if young or heart failure
 - Critically ill patients are likely to relapse
 - Newer antiarrhythmics (eg ibutilide and dofetilide) may \uparrow reversion, but \uparrow arrhythmia risk
 - AF ablation possible eg isolating all four pulmonary veins
 - Anticoagulate according to CHADS2 score with aspirin or warfarin

Other

- Unifocal atrial tachycardia: usually due to ↑automaticity. Consider digoxin toxicity, especially if AV block present. Consider digoxin, β-blockers or amiodarone to control ventricular rate
- Multifocal Atrial Tachycardia: ↑automaticity or triggered activity. At least 3 different P wave morphologies. Uncommon. Often misdiagnosed as AF. Usually in critically ill elderly with concurrent chronic lung disease, cor pulmonale, high mortality from underlying disease. Consider theophylline toxicity. Spontaneous reversion the rule. Magnesium best for acute control. β-blockers work but often contra-indicated by lung disease

Ventricular Tachycardias

- > 30 secs ⇒ sustained VT
- Monomorphic VT the most common. Due to slow conduction through scar tissue from previous MI
 - May → arrest due to rhythm itself or degeneration to VF
 - VT suggested by concordance, profound LAD
 - Is it VT: Brugada and Williams criteria:
 - Is an RS complex present in any precordial lead? If not, it's VT
 - If an RS is present, if the duration of the R-to-S nadir (lowest part of the S wave) > 100 ms in any chest lead then it's VT
 - If RS < 100, then if there is any evidence of AV dissociation (independent P waves, capture or fusion beats) then it's VT
 - If V1 and V6 are typically of a RBBB or LBBB then it's supraventricular
 - Treatment:
 - Termination by adenosine suggests SVT – but this can destabilise VT and is *not* recommended
 - Unstable: shock
 - Stable:
 - Amiodarone – less negative inotropy
 - Sotalol and procainamide effective but negative inotropy
 - Lidocaine – once advocated but not significant doubts
 - NOT digoxin or verapamil
- Polymorphic VT and Torsades:
 - Torsade de pointes usually has a prolonged QT during sinus rhythm and U-waves are often present
- Accelerated Idioventricular rhythm (AIVR) – incorrectly known as slow VT. Benign arrhythmia due to ↑automaticity. Common in inferior MI. May → haemodynamic deterioration due to loss of atrial systole
- VF: amiodarone is the drug of choice for DC shock-resistant VF (300 mg, or 5 mg/kg followed by 2.5 mg/kg both studied)

Long QT Syndrome

- QTc = QT/ square root (RR interval). Can be adjusted for age and gender
- Prolonged repolarisation → substrate for random re-entry → polymorphous VT (classically torsades) especially if acute adrenergic arousal or bradycardia
- Due to enhancing Na driven depolarisation or delayed rectifier K currents, causing either:
 - Extended plateau phase → susceptible to early after-depolarisations
 - Heterogeneity of prolonged action → spatial dispersion of repolarisations → substrate for re-entry
- Less capacity to respond to other stressors impairing repolarisation: ↓K, ↓Mg, class 3 drugs
- Causes:
 - Acquired:
 - Drugs: Class 1A, III, TCAs, macrolides
 - Myocardial pathology: MI, cardiomyopathy, myocarditis
 - Hypokalaemia
 - Acute cerebral injury
 - Idiopathic: Mutation in 7 gene loci, each with a known rate of SCD. 30% present with unexplained syncope, the remainder found on family screening. Degree of QTc prolongation is not predictive of syncope or SCD
- Treatment:
 - VT: DC shock.
 - Mg is the anti-arrhythmic of choice
 - Overdrive pacing
 - Atropine

- Prevention: If past history of syncope, 5% risk of SCD per year. β -blockers first line to reduced exercise heart rate to $< 130/\text{min}$. Pace if bradycardic. Stellate sympathetic ganglionectomy if malignant. ICD

Premature Ventricular Ectopic Beats

- Not associated with \uparrow SCD in asymptomatic healthy adults
- \uparrow SCD if:
 - Exercised induced
 - A marker of risk for VT/VF in AMI – (prophylactic lidocaine \rightarrow \uparrow mortality)
- VEB following each sinus beat is ventricular bigeminy
- Long term suppression of VEB with class IC drugs (eg flecainide) \rightarrow \uparrow mortality

Critically Ill patients and Arrhythmia

- See also Arrhythmia after Cardiac Surgery, page 153

Supraventricular Arrhythmias

- See Supraventricular Tachycardias, page 144
- SVT the most common that require treatment – AF, Aflutter and unifocal atrial tachycardias. Result in:
 - Adverse myocardial O₂ supply-demand balance
 - \downarrow BP, CO and DO₂
 - Impaired end-organ function: oliguria and worsening gas exchange
- SVT in an ICU patient is associated with \uparrow mortality, especially in sepsis and respiratory failure. Incidence increases with:
 - Elderly
 - History of IHD
 - Diastolic failure with \uparrow PAOP
 - Catecholamine infusion (dose does not appear to be important) – if elderly, IHD and catecholamine infusion should almost consider SVT prophylaxis given high incidence
 - \downarrow K and Mg are not important predictors of SVT
- Rate control is difficult:
 - Digoxin results often poor due to endogenous and exogenous sympathomimetic tone. Inotropic and vasopressor effects of digoxin beneficial
 - Mg effective at rate control, regardless of plasma level. In one study it was at least as effective as amiodarone in rate control and time to reversion. Hypotension due to vasodilation may be a problem
 - Amiodarone \rightarrow reliable rate control over days
 - Cardioversion best reserved for rhythm control once drugs have achieved rate control
 - Diltiazem, sotalol and procainamide associated with prohibitive myocardial depression and hypotension

MI and Arrhythmias

- Most common arrhythmias during reperfusion are VEB, AIVRs and non-sustained VT, rather than sustained VT or VF
- \uparrow risk of VF during reperfusion, but \downarrow risk during hospital stay
- Dipyridamole (inhibits cellular uptake of adenosine) is effective in preventing and treating reperfusion ventricular arrhythmia
- No benefit in larger trials from Mg – may have a role if β -blockers or thrombotic therapy contraindicated
- K following AMI negatively correlated to VEB and VT, with probability of VT falling until K > 4.5 . ILCOR recommends K > 4.0 and Mg > 1.0
- Bradyarrhythmia:
 - Due to \uparrow vagal tone or occlusion of R coronary artery in inferior MI
 - Asymptomatic bradycardia with type 1 block don't need treatment. Treat if \downarrow CO or hypotensive
 - Mobitz 1: may require treatment \rightarrow atropine. 0.5 – 1.0 mg every 3 mins until resolution to a maximum of 0.03 – 0.04 mg/kg
 - Mobitz 2: atropine has little impact on infranodal block, and may \rightarrow 3rd degree block by increasing sinus rate and enhancing block. Consider pacing
- AF:
 - In 15%. Later in course is related to post-infarct pericarditis
 - Treatment with β -blockers if fast rate causing compromise or further ischaemia
- Ventricular arrhythmia:

- VT/VF most common cause of pre-hospital mortality from MI (in hospital due to failure)
- In hospital 5% develop VF, usually in the first 4 hours
- Primary VF → ↑in-hospital complications but not long term mortality
- Lignocaine decreases VF but causes other complications – so does not change mortality
- Trials of prevention in the setting of frequent VEBs have showed:
 - Class 1 agents – no benefit (Class 1C increased mortality) despite arrhythmia suppression
 - Class 2 (β -blockers) show significant benefit
 - Class 3: no class effect. Sotalol → ↑mortality. Amiodarone → ↓mortality (CAMIAT trial, EMIAT trial in EF < 40% showed ↓arrhythmias but same mortality)

Sudden Cardiac Death

- Three causes:
 - Primary VT/VF (most common)
 - Primary SVT with rapid ventricular rate: usually AF in the presence of an accessory pathway
 - Bradycardia or asystole: high AV block or sinus node dysfunction + inadequate escape response
- Due to one of three causes:
 - IHD: old or new infarct
 - Non-ischaemic heart disease: cardiomyopathy, valvular disease, congenital disease, ventricular hypertrophy, cardiac trauma
 - No structural disease: primary electrical disease, electrolyte abnormalities, drugs
- Investigations should include:
 - Plasma levels of arrhythmogenic drugs
 - Toxicology screen
 - Holter monitor
 - EPS
- Prevention:
 - Revascularisation: RCT in survivors of SCD with critical stenosis strongly favours surgery over medical management
 - CAST study: poor results from antiarrhythmic drugs alone. Consider amiodarone if suppression of inducible VT at repeat EPS following introduction of amiodarone and EF > 30 – 40%
 - Ablation often not sufficient on its own
 - ICD: significant survival benefit – except in high risk patients following CABG. Usually combined with low dose amiodarone (despite mild cardiac depression) to improve arrhythmia control and prolong battery life

Antiarrhythmic Drugs

- Vaughan-Williams Classification:
 - Class 1: sodium channel blockers – depresses rate of rise of phase 0
 - 1A: prolongs repolarisation, eg procainamide
 - 1B: shortens repolarisation, eg lignocaine, phenytoin
 - 1C: minimal effect on repolarisation: flecainide
 - Class 2: β receptor blockers: propranolol, atenolol, metoprolol, esmolol
 - Class 3: prolongation of repolarisation via K channel blockers: amiodarone, sotalol
 - Class 4: Ca channel blockers: verapamil (negative inotropic effects off set by after load reduction), diltiazem (cleared by liver, bioavailability 40%). Depress slope of diastolic depolarisation in the SA node, the rate of rise of phase 0, slow conduction and prolong refractoriness of AV node. Don't change sinus rate as peripheral vasodilation → sympathetic stimulation of SA node
 - Incomplete: does not include cholinergic agonists, digoxin, Mg and adenosine
- An alternative classification classifies drugs by their varied impact on Na channels (fast, medium and slow), receptors (Ca, K, α , β , M2, P) and Na/K ATPase pump

Digoxin

- See also:
 - Specific Therapy for Poisons, page 264
 - (Apparent) Volume of Distribution, page 334
- Muscarinic subtype 2 receptor (M2) agonist and Na/K ATPase blocker → ↑intracellular Ca
- Produces ↑contractility, ↑myocardial automaticity, ↓AV conduction
- → PR prolongation and altered ventricular repolarisation (reverse tick in ST segments)
- Therapeutic levels are 0.5 – 2.0 ng/ml, measured 6 – 8 hours after dose

- Well absorbed orally. Elimination half-life 36 hours with normal renal function
- TI narrowed in ↓K, ↓Mg, ↑Ca, hypoxia, cardiac surgery and ischaemia
- Lots of interactions: ↑plasma level by competition with P-glycoprotein-mediated transport
- Contraindications due to:
 - Ischaemia/infarction: positive inotropic effects of Na/K ATPase blockade are bad in setting of ischaemia and diastolic dysfunction
 - Diastolic failure due to hypertrophy/ischaemia
 - Renal failure, ↑K
 - Caution with other drugs that affect AV node conduction (β and Ca blockers)
- Adverse effects:
 - Inward Ca current → DAD initiated arrhythmia
 - Poisoning of Na/K ATPase → ↑K → pacemaker refractory bradycardia
 - Nausea, altered cognition, blurred/yellow vision
 - Treat toxicity with K, Mg or antibodies (Digibind)
- Evidence:
 - In AF with CHF: control heart rate, ↓mortality, ↑exercise tolerance and ↓symptoms
 - In SR with CHF unresponsive to other therapy → may improve symptoms but not mortality or hospital admission rate

β-blockers

- Differ by:
 - Relative cardioselectivity: atenolol (renal elimination), metoprolol (liver elimination)
 - Non-cardioselectivity: propranolol
 - Lipid solubility (→ central activity): metoprolol, propranolol
- Antiarrhythmics are a class effect, no β-blockers has been shown to be superior
- Survival post-MI may related to central modulation of autonomic tone of the more lipid soluble agents
- Reduce phase 4 slope of the action potential of pacemaker cells → prolongs refractoriness and slows AV conduction
- Labetalol: see Eclampsia, page 318
- Esmolol:
 - Ultra-short acting cardio-selective β-blocker
 - Useful for rapid ventricular rate control in AF
 - Distribution half-life 2 min, elimination half-life is 9 min
 - Rapidly metabolised by esterases in red blood cells
 - Mix 100 mg in 10 ml (10 mg/ml)
 - Loading dose IV: 500 µg/kg over 1 min, then 50 µg/kg for 4 mins. If adequate rate not achieved then reload followed by 100 µg/kg for 4 mins. Repeat with 50 µg/kg increments till 300 µg/kg
 - Maintenance: 50 – 200 mcg/kg/min
 - Relative contraindications: reversible airways disease and poor LV function

Magnesium

- Many effects, including blocking L-type Ca channels and cofactor for Na/K ATPase providing energy for Na/K channels
- Deficiency leads to:
 - ↓intracellular K and ↑intracellular Na → ↓RMP
 - ↑intracellular Na → Na/Ca counter-transport → ↑intracellular Ca → DAD triggered activity
- Giving K won't correct ↓intracellular K if ↓Mg. ⇒ consider Mg as a Na/K pump agonist
- Mg → ↓vulnerable period (↑absolute refractory period and ↓relative refractory period) and more synchronous conduction
- Most helpful in setting of ischaemia where ↓intracellular K is a consequence
- Indications:
 - As effective as amiodarone for acute control of AF: 0.15 mmol/kg as slow IV push
 - Acute control of MAT
 - Ventricular arrhythmia associated with Torsades and digoxin toxicity
 - Drug induced VT triggered by class 1 agents (eg flecainide)
 - Transient ventricular arrhythmia in ischaemia (eg post infarct and post-cardiac surgery): 10 mmol as slow IV push, repeat if required (or follow with infusion)
- Observational data suggests plasma level of 1.8 mmol/l required for potent antiarrhythmic action

- Duration of action 30 mins, filtered by kidneys, most is reabsorbed
- Adverse effects:
 - If too rapid → peripheral vasodilation → flushing, nausea, hypotension
 - If excessive dosing → skeletal muscle weakness, problematic in acute-on-chronic respiratory failure
 - If already ↑K then brady-arrhythmias/heart block

Flecainide

- Rate dependent Na channel blockade → marked slowing of conduction in all tissue with little prolongation of refractoriness
- Suppression of VEBs after MI → ↑mortality
- Depresses contractility → contraindicated in ↓LV function and also → proarrhythmia
- ↑pacing capture threshold
- CNS effects: visual disturbance, dizziness and nausea

Amiodarone

- Complex profile: includes prolonged AP and ↑refractoriness of all cardiac tissue, QT prolongation
- Given IV its main effect is on the AV node and causes some cardiac depression (depending on rate of administration). Acute administration → mainly class 1 & 2 effects. Class 3 effect due to a metabolite and may take some days to achieve (control of ventricular arrhythmia)
- Haemodynamically stable → frequently used in critically ill
- Oral bioavailability 40 – 70%, delayed onset reduced by loading dose
- Highly protein bound with very high apparent volume of distribution. Terminal half-life after long term treatment: 50 days. Excreted by liver and bile
- Indications:
 - Slowing AF/AFL: 3 – 5 mg/kg IV over 10 – 60 min depending on blood pressure and myocardial function, followed by 0.35 – 0.5 mg/kg per h
 - Post-op AF prophylaxis: 200 mg TDS for 5 days
 - Terminating AVRNT and AVRT (but adenosine better for acute reversion and verapamil better for termination and prophylaxis): 3 – 5 mg/kg IV over 10 – 60 min depending on blood pressure and myocardial function, followed by 0.35 – 0.5 mg/kg per h
 - DC shock resistant VF: 5 mg/kg, further 2.5 mg/kg if required
 - Stable VT: 5 – 7 mg/kg over 30 – 60 min, followed by 0.5 – 0.6 mg/kg/h
 - Adverse effects:
 - Short term: hypotension, bradycardia, sinus arrest, nausea
 - Long term photosensitivity of skin, corneal micro-deposits (?significance), thyroid dysfunction (including increased peripheral conversion T4 to T3), liver dysfunction (stop if LFTs > 3 * normal), pulmonary toxicity 10% at 3 years
 - Potentiates warfarin, digoxin and other antiarrhythmics

Lignocaine

- Class 1 membrane stabilising anti-arrhythmic agent
- Na channel blockage → ↓action potential duration and shortened refractory period
- Rapidly redistributed. Approximately 65% protein bound. Elimination half-life 1.6 hours
- SE: light-headed, hypotension, heart block, confusion, seizure
- Dose in VT: 1 – 1.5 mg/kg with subsequent boluses (up to 3 mg/kg total), followed by infusion (1 – 4 mg/min, at decreasing dose, up to 24 hours)

Adenosine

- Stimulates A1 receptors on cardiac cells, influencing adenosine-sensitive K⁺ channels
- → slower AR and high degree AV node block
- Half-life 2 mins
- Don't give to asthmatics → may potentiate bronchospasm
- If giving adenosine for ?SVT, potentiated by some drugs → prolonged half-life. Don't give if on:
 - PDE inhibitors such as Milrinone
 - Dipyridamole
 - Carbamazepine
 - Antagonised by methylxanthines (esp theophylline and caffeine)
- Prolonged effects in patients denervated transplanted hearts

Intensive Care after Cardiac Surgery

- See Post Cardiac Patient Hot Case, page 378
- Ideal environment for standardisation of care across investigations, fluid and electrolyte management, vasoactive and other drug administration, and mechanical ventilation
- Sameness of patients can obscure their particularity
- On arrival:
 - Transport with head up. Otherwise pooling of blood which then “dumps” later and can’t be differentiated from new bleeding
 - Confirm integrity and position of ET, NG tube and lines/catheters
 - Switch to ventilator – check both lungs
 - CXR to assess lung expansion and catheter placement
 - ECG to check for acute ischaemia
- Monitoring:
 - PA Catheters:
 - In at least low-risk patients, surgery is safe without PA catheter
 - Soft evidence of benefit in more complicated cases
 - Cardiac Output measurement:
 - Pulse contour analysis and US techniques becoming more commonplace
 - Role not established
 - Doppler enabling windows may be difficult in a post-surgical patient
- Fluids:
 - Despite intraoperative fluids, hypovolaemia is common especially with warming-related vasodilation
 - Can be exacerbated by polyuria in the early post-operative period – possible related to hypothermia, haemodilution and after-effects of bypass
 - Fluid must be isotonic. No benefit for any particularly fluid has been found
 - Larger volumes of crystalloid than colloid are required
- Electrolytes:
 - ↓Mg and ↓K frequent, exacerbated by polyuria. Maintain in high normal range, especially in atrial or ventricular ectopy, or tachydysrhythmias
 - Late ↑K common, especially if renal impairment – usually only treat if significant renal impairment
 - Consider Ca if massive transfusion

Off-pump or on-pump CABG

- Balancing:
 - Easy, bloodless surgical field, with
 - Risks of bypass and embolic events from clamping and cannulating the aorta
- No difference between off-pump vs on-pump CABG in RCT of 4752 patients in terms of composite of 30 day death, stroke, MI or new renal failure (CORONARY study, NEJM April 19, 2012). Off-pump had significant lower rates of blood-product transfusion, return to theatre for bleeding, acute kidney injury and respiratory complications, but more early repeat revascularisations (0.7 vs 0.2%). Only surgeons familiar with off-pump involved (and no trainees as primary surgeons), and ?a higher risk group of patients ⇒ ?greater benefit from off-pump approach. Follow-up study (NEJM 2013) showed no difference in cognition at 1 year
- Elective CAGS in > 75 years showed no difference between on pump and off pump CAGS (NEJM 2013)
- Evidence of higher long term risks of off-pump, in terms of repeat revascularisation, MI, stroke and death

Post-Operative Hypotension

- Many of the usual signs are obscured by anaesthesia and surgery, eg reduced tachycardia due to drugs, hypothermia and heart disease. Lactic acidosis not necessarily reliable
- Causes:
 - Artefact
 - LV Preload:
 - Hypovolaemia, including haemorrhage
 - Tamponade: Signs: Hypotension, tachycardia, distended neck veins, ↑JVP, exaggerated x descent, pulsus paradoxus, muffled heart sounds, absent apex, low voltage on ECG and electrical alternans
 - Pericardial constriction
 - Pulmonary hypertension
 - RV failure

- Medication: propofol
- Anaphylaxis
- Vasoplegia
- Afterload:
 - Excessive vasoconstriction
 - Aortic stenosis
 - Functional LV obstruction
 - Obstructive cardiomyopathy
 - Systolic anterior motion of the mitral valve
- Myocardial function:
 - Arrhythmia, pacing wire problem
 - Mechanical: VSD, valve pathology
 - Cardiomyopathy
 - Ischaemia, may be due to graft failure. Remedial options include angiography or re-operation
 - Transient myocardial depression following acute ischaemia - “stunning”
 - Metabolic, electrolyte abnormalities, pharmacological depression
- Associated with ↑GI, renal and neurological complications
- If O₂ delivery OK, initially low CO may be OK. Don’t overdo β-agonists – given it’s known beta-blockade is beneficial in postoperative cardiac patient
- Treatment is urgent if a spiral of ischaemia and heart failure is to be averted:
 - Rules of thumb:
 - Well preserved ventricular function, no obvious ischaemia ⇒ responds well to fluid
 - Vasoconstrictors can break the cycle of hypotension-ischaemia-hypotension but take care in impaired ventricular function and in vascular or aortic pathology
 - Poor LV function and ↑inotropes ⇒ something more sinister
 - Establish diagnosis. Imaging to distinguish tamponade from CHF. May not see tamponade on TTE early after surgery – so use it to exclude other causes
 - Correct hypovolaemia, tamponade, acute ischaemia, electrolyte abnormalities and dysrhythmia
 - If hypertension and ventricular dilatation → vasodilators
 - Inotropes (see also Inotropic/Vasopressor Support, page 44):
 - Dobutamine: pure β₁ agonist ⇒ inotropic, lusitropic (decreased relaxation 2ndary to ↑contractility) and some chronotropic effects
 - Noradrenaline, metaraminol, vasopressin and high-dose dopamine are vasoconstrictors ⇒ hazardous in hypovolaemia and shouldn’t be used alone in the presence of low cardiac output
 - Adrenaline: use in cardiac patients problematic especially due to lactic acidosis. Potent vasoconstrictor
 - Milrinone: effective inotropic agent, especially in β-receptor down-regulation. Potent vasodilator and long duration of action ⇒ difficult to titrate and wean.
 - Levosimendan: promise both perioperatively and as rescue treatment
 - Ventricular assist devices: expensive and technically demanding. Indications not well established, but include intractable heart failure and failure to wean from bypass
 - Delayed sternal closure: ↑CO and ↓inotrope requirements
 - Continue mechanical ventilation → ↓cardiac workload 2nd to ↓work of breathing

Post-Operative Hypertension After Cardiac Surgery

- Complications include:
 - Bleeding
 - Heart failure
 - Vascular (especially aortic) injury
 - Myocardial ischaemia
- Treatment:
 - Check catheter not blocked
 - Adequate sedation and analgesia
 - Vascular resistance declines over first few hours so use short acting agents
 - GTN theoretically better than Nitroprusside (risk of coronary steal) but this is very rare and nitroprusside appears to be more effective
 - Too great a reduction risks dropping cardiac O₂ supply more than demand

Post-Operative Bleeding after Cardiac Surgery

- Causes:
 - Incomplete surgical haemostasis
 - Residual heparin effect
 - Platelet abnormalities: anti-platelet agents, bypass
 - Clotting factor depletion
 - Haemodilution
 - Hypothermia
 - Postoperative hypertension
- Management:
 - Re-transfusion reduces autologous transfusion requirements
 - Reducing transfusion threshold to 80 g/l ↓exposure to blood transfusion without adverse effects in stable patients
 - Reversal of residual heparin (“heparin rebound”) and correction of coagulopathy with blood products
 - Correct temperature and acidosis
 - Correct ionised calcium
 - Tranexamic acid: evidence is mainly intra-operative, not post-operative. Aprotinin and desmopressin associated with side effects. See Procoagulants, page 297
 - Factor 7a: off-label usage but commonly used in post-cardiac surgical bleeding. Dosage controversial. Discuss with haematologist. See Recombinant Activated Factor 7a (rFVIIa), page 297
 - Mixed evidence for application of PEEP

Diastolic Dysfunction after Cardiac Surgery

- Diagnosis: demonstration of small ventricular volumes despite ↑filling pressures
- Causes:
 - Diastolic dysfunction most common
 - ↓LV volume despite ↑filling pressures:
 - Myocardial ischaemia
 - RV dilation
 - Pericardial abnormalities
- Management:
 - Correct correctable causes
 - Maintain blood volume, including with transfusion
 - Maintain sinus rhythm
 - Atrial pacing at a faster rate, as SV is fixed
 - β-agonists and milrinone improve diastolic relaxation and hence ventricular compliance

RV dysfunction after Cardiac Surgery

- Common causes include:
 - RV ischaemia/infarction
 - Poor myocardial perfusion
 - Anteriorly placed RV
 - By-pass related pulmonary hypertension
- See Management of Right Ventricular Dysfunction, page 139. Consider delayed sternal closure

Arrhythmia after Cardiac Surgery

- Atrial Fibrillation:
 - Incidence varies from 10 – 50%, highest in some valvular procedures
 - Usually self-limiting
 - Risks include prior AF, mitral valve disease, ↑ age, ↑p wave duration, post-operative withdrawal of β-blockers
 - Most common on day 2 – 3, but may occur weeks later
 - Of greatest significance if poor LV
 - Major risk is thromboembolic complications:
 - Stroke in 1 – 6% post CABG – increases 3 fold if SVT
 - May cause haemodynamic compromise
 - Anticoagulate if longer than 48 hours. Some advocate waiting till 72 hours
 - Prevention:

- Continue pre-op β -blockers
- Prophylactic β -blockers (even small doses) prevent AF – found in a number of RCTs
- Amiodarone prophylaxis reduced post op AF from 53 to 25%
- Diltiazem effective, esmolol more effective, verapamil not effective
- Sotalol effective but more bradycardia and hypotension
- No correlation with magnesium. Digoxin not effective for prevention
- Management options:
 - Aim: control ventricular rate, prevent VTE, cardioversion
 - Do nothing – spontaneous reversion common
 - Rate control: β -blockage best established. Digoxin not more effective than placebo at reversion, and may be poorer rate control in the presence of catecholamine stimulation. Also consider amiodarone, sotalol or Ca Channel blocker (if LV OK)
 - Cardioversion:
 - Early DC cardioversion ineffective (arrhythmogenic factors remain and recurrence is common) and potentially harmful. Only if haemodynamic compromise
 - Consider amiodarone or Mg
- Prophylactic AV pacing: transient heart block common
- Ventricular arrhythmia:
 - Keep K > 4
 - If hypertensive, Mg useful as it vasodilates
 - VF/pulseless VT: defibrillate before compressions (may cause mechanical injury post-sternotomy). If no output then open cardiac massage. See Cardiac Arrest, page 154
 - If VT/VF cardioverted, give prophylaxis with Mg, amiodarone or sotalol until sympathetic adrenergic stimulation associated with waking and weaning is past
 - Low output \rightarrow catecholamines \rightarrow ischaemia \rightarrow \uparrow rate of polymorphous VT/VF. Treatment with:
 - High dose amiodarone and antiarrhythmic levels of Mg (1.8 – 2.0)
 - Aortic balloon pump to protect coronary artery perfusion pressure
 - Pacing, given antiarrhythmics may cause bradycardia. Faster rate (90 – 100) may not be ideal for CO, but may protect against abnormal automaticity and is better than recurrent DC shocks
 - Complex ventricular dysrhythmias: look for causal ischaemia and graft malfunction

Cardiac Arrest after Cardiac Surgery

- Post cardiac surgery arrests have a relatively good outcomes given high incidence of reversible causes
- Detection:
 - VF or asystole on ECG
 - Other rhythm but arterial and other pressure wave forms pulseless
 - Check central pulse
- Exclude reversible causes:
 - Monitoring fault
 - Arrhythmia
 - Pneumothorax
 - Hypovolaemia
- Principles:
 - Defer adrenaline while reversible causes detected and corrected – severe hypertension can disrupt the aortotomy site with severe consequences
 - External chest compressions in someone with a recent sternotomy are associated with risk of trauma, and worsening bleeding, and reduced efficacy. Defer until after defibrillation or pacing
 - Most serious complication of chest opening is inadvertent disruption of grafts
- Management:
 - Arrest alarm
 - Exclude reversible causes
 - Identify arrest team leader
 - Airway: FiO₂ 100%, check bilaterally for breath sounds and expansion, check ventilation (bag patient, can you pass suction catheter down tube)
 - Defibrillation: VF – 3 sequential shocks without CPR. For asystole or extreme bradycardia set pacemaker to DDD at 90 bpm with maximum atrial and ventricular output. If PEA, turn off pacemaker to exclude underlying VF
 - External cardiac massage: commence immediately unless defibrillation or pacing appropriate. Don't be over vigorous. Aim for SBP on arterial trace of 60 mmHg

- Drugs: Stop and check all infusions. 1000 mls crystalloid stat. If VT or VF then 300 mg amiodarone
- Prepare for emergency re-sternotomy
- Redo Sternotomy / Chest opening
 - Main aim is relief of tamponade – don't rush to perform internal cardiac massage
 - Maintain strict aseptic technique (→ shown to reduce mediastinitis): gloves and gown
 - Apply sterile all-in-one adhesive drape. Don't use antiseptic (drape won't stick)
 - Commence sterile external cardiac massage
 - Cut sternotomy incision deeply down to the sternal wires – remove sutures
 - Untwist wires – assistant cuts them, then sustained pull
 - If tamponade not yet relieved carefully insert a sternal spreader
 - Clear excessive clot but be careful not to disrupt grafts
 - Internal cardiac massage should only be performed by a non-cardiac surgeon where a patient would die without it:
 - Carefully remove any clot and identify at-risk structures such as grafts (especially internal mammary artery)
 - Don't lift apex if MVR given risk of posterior ventricular rupture
 - Pass R hand over apex and round to the back with palm up and hand flat. Place left hand on anterior surface. Squeeze hands together aiming for systolic pressure > 60
 - Sterile internal defibrillation at 10 – 50 J

Respiratory Management After Cardiac Surgery

- Immediate extubation appears to offer little patient benefit
- Re-intubation is rare, but more likely in older patients with pre-existing lung and vascular disease and impaired ventricular function
- Hypoxia common:
 - Mainly due to atelectasis. Responds well to PEEP, prolonged inspiration and recruitment manoeuvres
 - Sinister causes: CHF and ARDS (2nd to shock, blood transfusion or bypass itself)
 - Patent foramen ovale with R → L shunt and pulmonary hypertension decompensated by atelectasis
 - PE rare given bypass induced platelet dysfunction
- Incentive spirometry and chest physio common, but no strong evidence. Early mobilisation most beneficial, facilitated by adequate analgesia
- COX2 appear to ↑risk of complications

Renal Injury following Cardiac Surgery

- AKI highly associated with poor prognosis
- Multi-factorial: intra-operative hypotension, inflammation, micro-emboli 2nd to bypass, medications, oxidative stress, haemolysis...
- Occurs in 1.1 % of normal pre-op creatinine, 16% of ↑pre-op creatinine
- Risk factors for RRT:
 - Premorbid:
 - Female sex
 - Chronic kidney disease
 - LV dysfunction
 - DM
 - PVD
 - COPD
 - Surgery specific:
 - Emergency surgery
 - Intra-aortic balloon pump
 - Bypass time
- Prevention:
 - Avoid nephrotoxins
 - Hydration (avoid pre-op fluid restriction)
 - Optimal management of low cardiac output
 - No evidence for dopamine, mannitol, ACEI, CCB
 - Small trial evidence for pre-op clonidine
- Pre-op NaHCO₃ possibly harmful (Haase et al, PLoS 2013), MRCT, n = 350, with trend to ↑AKI and ↑NGAL in NaHCO₃

Other Postoperative Complications

- Protamine reactions:
 - 1 mg protamine to neutralise 100 u heparin if just given, declines over hours
 - Hypersensitivity reactions: hypotension
 - Pulmonary vasoconstriction and hypertension
- Immune mediated after bypass:
 - ARDS
 - SIRS
- Renal failure:
 - Seen in 1 – 5% depending on definition
 - Risk factors: age, heart failure, prolonged bypass, diabetes, prior renal impairment, post-operative shock
 - No established preventative strategies beyond haemodynamic management and avoiding nephrotoxic agents
- Shivering:
 - Common and complex. Not entirely related to core temperature
 - Causes significant increase in metabolic rate → increases O₂ demand and ICP
 - Prevention with dexamethasone, clonidine, high-dose morphine, pethidine and external warming
 - Pethidine 25 mg effective in one out of two normothermic post-op shiverers
 - If severe, paralyse and sedate during warming
- Deep sternal infection:
 - Uncommon: 0.5 – 2.5%
 - Risks: diabetes, obesity, use of internal mammary artery (especially bilateral)
- Neurological:
 - Neuropsychiatric deterioration, delirium, peripheral neuropathies (most common is unilateral phrenic nerve palsy)
 - Paraplegia a recognised complication of thoracic aortic surgery
 - Cerebral infarction:
 - 1 – 5 %
 - Mainly embolic
 - Risks: carotid artery stenosis, hypertension, AF, aortic atheroma, ↓LV EF, PVD
- GI complications: Uncommonly (< 1%) include: Peptic ulcer, pancreatitis, cholecystitis, gut ischaemia, ileus, hepatic dysfunction

Heart-Lung Transplant Patient Representing to ICU

- Opportunistic infections: including atypicals, pneumocystis, aspergillus and CMV
- Immunosuppression: Needs to keep going – issues with dose adjustment if dialysed, renal failure
- Cardiac issues. Heart is denervated:
 - Only responsive to directly acting drugs – no autonomic reflexes
 - Doesn't respond so well to changes in intravascular volume – more difficult to assess
 - Altered ECG/rhythm strip
 - Premature diffuse obliterative coronary atherosclerosis → ↓ventricular function
- Respiratory issues:
 - Impaired cough and secretion clearance
 - Impaired lung function due to Obliterative Bronchiolitis (from chronic rejection)
 - Bronchial or tracheal stenosis from anastomotic site
- Renal: altered renal function 2nd to immunosuppressive drugs
- Altered adrenal function 2nd to steroid use

Perioperative Complications after non-Cardiac surgery

- POISE Trial, Lancet 2008, Effects of Metoprolol CR in patients having non-cardiac surgery. 8351 patients randomised to metoprolol 2 – 4 hours before surgery and continuing 30 days. Fewer MIs but more strokes and death in the metoprolol group (?dose too high)
- Stopping anticoagulation: see Perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, 2008
- Less than 10 mg per day of prednisone does not require replacement peri-operatively (Nicholson, Anaesthesia 1999)

DC Cardioversion

- Indications:
 - Haemodynamically unstable VT and sustained SVT that precipitate angina, heart failure or hypotension
 - Haemodynamically stable VT following trial of antiarrhythmic drug therapy
 - AF/AFL once potential precipitants eliminated. Thromboembolism in up to 6% without anticoagulation. Anticoagulation for 3 – 4 weeks prior reduces risk by 80%
- Depolarises a critical mass of myocardium leaving insufficient myocardium to maintain re-entry
- Biphasic waveform provides equal efficacy at lower electrical energy
- Avoid placement over pacemakers and ICDs: may cause malfunction or block current to the heart. Some current will go down the leads – need to check pacing threshold post-shock. Use AP position with paddles > 10 cm from the unit. Check pacemaker afterwards
- In atrial tachycardias and VT, synchronised shock with R wave reduces risk of induced VF should the shock be delivered on the relatively refractory portion of the T wave. Unsynchronised shock if pulseless or hypotensive VT (may not detect R wave → delay)
- Energy > 400 J reported to cause myocardial necrosis
- Need preoxygenation. If poor myocardial output need reduced dose of sedation and longer onset
- Digoxin toxicity → much lower energy levels necessary (10 J MDS – monophasic damped sinusoidal)

Pacing and Implantable Defibrillators

- Electrodes:
 - Unipolar: needs a skin electrode for return current pathway. Rarely used for temporary pacing
 - Bipolar: if one limb fails, can be converted to a unipolar system
- Placement:
 - Transvenous endocardial: via a vein to R ventricle (sometimes atria)
 - Epicardial: following cardiac surgery
 - Transcutaneous: high impedance patches (better current density and less pain) with adjustable current outputs (50 – 150 mA)
 - Transoesophageal rarely used. Pacing Swan-Ganz is unstable
- Leads:
 - Ventricular leads: relatively stiff
 - Atrial leads: preformed J tip to hook into the R atrial appendage → lead stability with low pacing threshold and good sensing capacity
- North American and British Group (NABG) pacemaker code:
 - Position 1: Chambers **paced** - O = none, A = Atrium, V = ventricle, D = dual
 - Position 2: Chambers **sensed** - O = none, A = Atrium, V = ventricle, D = dual
 - Position 3: response to sensing:
 - O = none
 - T = triggered: discharge is triggered by sensed signal
 - I = inhibited: pacemakers discharge is inhibited (ie switched off) by a sensed signal. Eg VVI – ventricle pacing is inhibited by spontaneous ventricular activity
 - D = dual: both T & I can occur. Reserved for dual chamber pacing. Depolarisation in the atrium inhibits atrial output but triggers ventricular pacing with a delay mimicking the normal PR interval. Spontaneous ventricular depolarisation inhibits ventricular pacing
 - Position 4: **rate modulation**: O = none, R = rate modulation. Incorporates a sensor to vary the pacemaker independently of intrinsic cardiac activity. Uses either:
 - Vibration detectors, but may respond to non-physiological stimuli, eg an electric drill
 - Minute ventilation sensors: measures impedance differences between the pacing electrode and pacemaker, but may pace too fast eg in a mechanically ventilated patient requiring a large minute volume
 - Newer ones can be a combination of both
 - Position 5: **multi-site pacing**: O = none, A = one or both atrium, V = one or both ventricle, D = dual. Eg DDDRv is dual-chamber, rate-adaptive, biventricular pacing
- Resynchronisation: → improved LVEF, CO and haemodynamics, ↑exercise tolerance, decreased NYHA class, ↓hospitalisation and ↑quality of life

Specific Modes

- Single chamber:

- **AOO** and **VOO**: asynchronous atrial and ventricular pacing. No sensing, almost obsolete except in pacing emergencies
- **AAI**: atrial demand pacing: for sinus bradycardia with intact AV conduction
- **VVI**: ventricular demand pacing: most commonly used mode in life-threatening bradycardias. AV synchrony is lost, and there is no “speed-up for need”
- Dual chamber:
 - **DVI**: AV sequential pacing. Indicated for atrial bradycardias – of no value for atrial tachycardias. Atria and ventricles are paced in sequence. Only ventricle sensed. If AV conduction is successful, ventricular output is inhibited. To maintain AV synchrony without atrial sensing the pacemaker discharge rate must be greater than the spontaneous atrial rate. Asynchronous atrial pacing can precipitate AF. Self-inhibition (“cross-talk”) can occur
 - **DDD**: pacing and sensing in both chambers. Atrial impulse will trigger a ventricular output and simultaneously inhibit an atrial output. Upper rate-limiters prevent excessive atrial activity from causing high ventricular rate. Function depends on the underlying rhythm:
 - Atrial bradycardia with intact AC conduction → atrial pacing
 - NSR with AV block → synchronised ventricular pacing
 - Sinus bradycardia with AV block → sequential AV pacing
 - NSR and AV conduction → inhibits both atrial and ventricular pacing
- Problems with pacemakers:
 - DDD and VDD: re-entry pacemaker-mediated **endless-loop tachycardias**: a VEB conducts retrogradely to the atria, is sensed by the pacemaker, and triggers a ventricular beat. Pacemaker forms the anterograde limb. Stopped by converting to asynchronous (non-sensing) mode or DDI or ↑ the post-ventricular atrial refractory period
 - RV pacing → LBBB pattern → dyssynchrony
 - If not rate adaptive, the arbitrary back-up rate of 70 – 80 beats/min may need to be increased if DO2 is inadequate. Rate adaptive pacemakers may not sense increased CO requirements of, for example, septic shock
 - Loss of AV synchrony in VVI and VVIR pacing may → “**pacemaker syndrome**”. Suggested by fall in BP with onset of ventricular pacing → ↓BP, SV and CO. For long term pacing, DDD or AAI is superior to VVI and has lower incidence of AF
 - **Cross-talk**: in dual chamber pace-makers, a pacemaker generated current in one chamber is sensed in the other chamber as native activity → inhibition. : Inappropriate detection of the atrial pacing stimulus by the ventricular channel → asystole if there is no escape rhythm. Turn down output or duration of atrial pulse, or ↓sensitivity of ventricular pacing
 - In dual chamber pacemakers, AV interval needs to be as close as possible to the normal P-R interval (140 - 200 ms). If intra-atrial conduction time is prolonged, the LV may contract before the LA → **DDD pacemaker syndrome**. Increase the AC interval
 - Diathermy: use bipolar wherever possible. If pacemaker dependent, it may be safer to switch to an asynchronous mode first. In an emergency, placing a magnet over a permanent pacemaker will normally result in a fixed rate mode. Modern pacemakers are less likely to be magnet responsive, but are less likely to be diathermy responsive
 - ICDs should be switched off before diathermy is used: placing a magnet over the ICD will deactivate the unit but not change pacing functions. In a pacemaker, a magnet will make it default to a fixed rate

Mode	Advantages	Disadvantages
AAI	Single lead AV synchrony Can assess ST changes	Ineffective in AF Risk of asystole if AV block Relies on single lead
VVI	Single lead Useful in AF Useful in high grade AV block	Higher risk of perforation than ventricular lead AV dys-synchrony (→pacemaker syndrome) Can't assess ST change Loss of atrial kick
DDD	AV synchrony Useful if AV block Rate responsive	Abnormal contraction Pacemaker-re-entry tachycardia Cross-talk Abnormal contraction

Temporary Pacing

- Indications:

- Bradycardia leading to:
 - Symptoms and failure of medical treatment
 - Malignant ventricular arrhythmia
- After high risk cardiac surgery (aortic or mitral valve replacement): DDD epicardial pacing → ↑ CO at any heart rate over VVI. Optimising AV delay and occasionally multi-site pacing may also help
- Patients with 2nd or 3rd degree block should be paced prior to surgery
- Tachyarrhythmias. Use rapid pacing for:
 - SVTs: start atrial pacing at slow rate (60 – 80) and increase to 10 – 20% faster than spontaneous atrial rate. Avoid inadvertent rapid ventricular pacing. Hold for 30 seconds then switch off pacemaker.
 - AVNRT and AVRT: don't usually need pacing as adenosine or verapamil usually effective. Pacing with a short PR interval can prevent drug-resistant AVNRT and AVRT
 - Atrial flutter: may be resistant to drugs, and pacing usually reverts
 - Unifocal atrial tachycardia
 - Ventricular tachycardia.
 - Don't use for rates > 300 or if severe haemodynamic compromise – they need DC cardioversion
 - Only monomorphic VT can be reverted with rapid ventricular pacing. Torsades can usually be prevented by pacing the atrium or ventricle at 90 – 100 beats/min, as it's onset is invariably preceded by a pause or bradycardia
 - Ventricular burst pacing: pace at 120% of spontaneous rate for 5 – 10 beats. NSR should ensue. May precipitate VF. Have defibrillator handy
 - Overdrive atrial pacing may work if there is 1:1 AV conduction and the ventricular rate is slow (120 – 180)
 - No value in sinus tachycardia, AF and VF
- Insertion technique:
 - RIJ has least complications with ease of manipulation and stability of the lead. Antecubital veins associated with lead instability and thrombophlebitis
 - Atrial J lead placement requires experience. Right atrial appendage is anterior and medial. Confirm placement on lateral CXR or fluoroscopy
 - If acute MI and thrombolysis avoid central venous cannulation – use femoral vein if necessary but associated with problems with sterility and DVT
 - Lead manipulated under fluoroscopic control to the apex of the RV
 - CXR to exclude pneumothorax and confirm adequate lead positioning
 - Transvenous RV pacing may be impossible (eg artificial tricuspid valve or congenital anomaly)
- Testing an external pacemaker:
 - Pacing threshold (minimum current required to initiate depolarisation of the paced chamber): distal electrode connected to the negative pacemaker terminal. Pace at 5 – 10 beats/min faster than the patient heart rate and slowly decrease output (at a pulse duration of 0.5 – 1.0 ms) until consistent capture is lost. Ideally ventricular threshold is 1.0 mA and atrial is 2.0 mA. Pacing threshold is set at 2 – 3 times pacing threshold and always > 3 mA to allow sufficient safety margin.
 - Sensing (ability of the pacemaker to detect the patients intrinsic cardiac activity so the pacemaker doesn't compete inappropriately with the patient – preventing R on T etc.): Amplitude of the ventricular signal is 5 – 15 mV, atrial is 2- 5 mV. Set output to zero. Set pacing rate lower than the spontaneous rate of the chamber being tested. Decreased pacemaker sensitivity until there is competition between paced and spontaneous rhythms. Set sensitivity at twice that value (changing sensitivity from 2.0 to 1.0 mV will double the sensitivity). Don't test sensitivity in pace-maker dependent patients
- Complications:
 - Associated with central venous line insertion: pneumothorax, haemothorax, arterial puncture, AV fistula, perforation of the RV (rarely results in tamponade)
 - Under-sensing → pacemaker-induced arrhythmias
 - Oversensing → pacemaker inhibition → loss of pacemaker stimuli
 - Failure to capture: due to device defects, unstable lead position, acid base abnormalities, hyperglycaemia, drugs (eg β-blockers)
 - Extracardiac stimulation: usually diaphragmatic
 - Occasionally thrombus formation and infection
- Emergency failure to pace response:
 - Check pacemaker is switched on and connected

- Increase output to maximum (20 mA or 10 V)
- Select asynchronous mode (DOO/VOO) to prevent over-sensing
- Connect pacemaker directly to the pacing lead; the connecting wires may be faulty
- Unipolar pacing with a cutaneous pacing stitch
- Replace the unit or change the batteries
- Switch to transcutaneous pacing
- CPR and/or positive chronotropic drugs
- Open chest and replace wires

Permanent pacing

- Usual indications: chronic, symptomatic 2nd or 3rd degree block, SA node dysfunction
- Other indications:
 - HOCM: symptomatic patients with high LVOT gradient. DDD pacing with short PR interval → early apical activation → ↓LVOT gradient and ↓systolic anterior motion (SAM) of the mitral valve
 - Heart failure: CRT (Resynchronisation) of left ventricular wall with septal wall → improved symptoms and survival in class III/IV CHF with dilated or ischaemic cardiomyopathy with QRS > 130 ms, LVEDD > 55 mm and LV Function < 35%. Biventricular pacing usually reserved for permanent pacing

Implantable Cardiac Defibrillator

- Proven survival benefit in patients who have had a VT/VF arrest not due to transient or reversible cause, and in patients with recent MI and low LV EF (< 30%)
- Programmable graded response:
 - Slow VT (160 – 180) → Antitachycardia pacing: pace faster than the intrinsic rate
 - Biphasic DC shock: synchronised for VT, asynchronised for VF at low then high energy
 - Backup pacing (single or dual chamber) available if there is a significant bradycardia after cardioversion/defibrillation
- Complications:
 - If DC shocks are unsuccessful, re-programme to deliver higher energy
 - Arrhythmia storm: deactivate, transthoracic defibrillation and drug therapy. Saves battery and allows device to be checked
 - Inappropriate shocks (usually AF or another SVT): switch off at once
 - Infection (it's a foreign body)
 - Electromagnetic interference – can't have MRI
 - Caution with CVL and PACs interfering with leads

Mechanical Cardiac Augmentation

- Principles of Mechanical circulatory support:
 - Intervention in the highest risk patients is most effective if done early
 - IABP is usually the first line treatment for cardiogenic shock

Intra-aortic balloon counterpulsation

- Intra-aortic balloon pump:
 - Bridge to surgery in papillary rupture and ischaemic ventricular septal defect
 - Ultimate effect on CO is limited to an increase of 0.5 – 1.0 l/min, so insufficient in profound cardiogenic shock
 - Use as supportive therapy in other patients with MI → ↓1 year mortality → Class 1 recommendation, based on registry data. Only used 25% of the time for this
 - However, IABP-SHOCK 2 Trial, NEJM 2012, RCT in 600 patients of IABP vs no IABP in cardiogenic shock requiring revascularisation, no difference in 30 day mortality of 40 vs 401%, with no difference in major bleeding, sepsis or leg ischaemia. Unblinded. Previous mortality in this group 45 – 50%. 1 year follow up showed no difference except a trend to ↑reinfarction in the balloon pump arm (RR 2.6, p = 0.05)
 - RCT of pre-op balloon pump in ↓LV Fn for CABG. Single centre RCT in EF < 0.35% in elective surgery. Stopped at 110 patients for futility (31% mortality in control, 40% in IABP)
- Inflates with 30 – 50 ml helium during diastole and deflated at end diastole. Helium used as excellent laminar flow characteristics
- Can be ECG timed (T wave or diastolic notch)
- Improves outcomes in:

- High risk cardiac surgery
- Support of infarct-related, non-surgical coronary reperfusion
- Actions:
 - Augmentation of diastolic coronary perfusion pressure → coronary perfusion (Diastolic augmentation/peak diastolic pressure > systolic pressure)
 - Left ventricular afterload reduction → ↓LV filling pressure (assisted peak systolic pressure [after the IAB deflation] should be lower than unassisted systolic)
 - ↑Cardiac index
 - ↓myocardial lactate production
- Prophylactic indications:
 - Cardiac surgery: two of:
 - left main > 70%
 - LV ejection fraction < 0.4
 - Unstable angina
 - Re-operation
 - Failure to wean from bypass
 - Cardiogenic shock:
 - Reversible myocardial depression. Not helpful in irreversible cases except as a bridge to transport
 - Support for reperfusion/revascularisation
 - Non-cardiac procedures: Severe LV impairment, unstable angina
- Contraindications:
 - Aortic incompetence
 - Aortic aneurysm, dissection, or graft
 - Severe PVD
 - Uncontrolled bleeding or sepsis
 - Won't work so well in a compliant aorta (eg a young person) even if large (eg 50 cm³) balloon
- Complications:
 - Failure to advance on insertion (due to PVD, aortic dissection or perforation)
 - Limb ischaemia (6 – 16%) 2nd to clots: requires early recognition based on routine systematic observation. Use to be systemically heparinised. Not routine now
 - Vascular trauma, dissection
 - Infection (cutdown > percutaneous)
 - Balloon rupture: blood in helium tubing. Stop pump. Remove catheter. Head down.
 - Bleeding, especially after removal
 - Thrombocytopenia
 - Malposition → vascular obstruction of abdominal viscera or spinal chord
 - Malfunction → failure to unwrap
 - Early inflation → ↑LV wall stress and ↑myocardial O₂ consumption, ↑LVEDV and LVEDP, worsening of mitral regurgitation, worsening of pulmonary oedema
- Timing of inflation/deflation is critical. Best achieved using the pressure waveform and 1:2 ratio
- Inflation with the aortic notch
- Weaning:
 - Down to 1:2 for 8 hours then out (or further down to 1:4 for 8 hours)
 - Risk of clots if left in but not pumping
 - Usually < 3 days, max 7 days
- Always check:
 - Machine:
 - Helium bottle level
 - Triggering, and appropriate inflation/deflation times (ask if you can put it onto 1:2)
 - Pulses on affected leg
 - Pulse in L arm
 - Insertion site for bleeding
 - CXR: want the tip to be just distal to the left subclavian artery – on CXR just above the left main bronchus in the 2nd intercostal space
 - Whether it can be removed

Ventricular Assist Devices

- Usually require anaesthetic and surgical placement (percutaneous insertion technically possible)

- Can be used as a bridge to transplant
- More complex, and more difficult to transport than IABP
- Needs anticoagulation
- Greater control of cardiac output
- Options:
 - Percutaneous left ventricular assist device
 - Percutaneous right ventricular assist device
 - Surgically place devices
 - Devices range in the amount of CO they provide from 2.5 to 10 l/min, and have varying maximum lengths of use
- Complications: bleeding, infection, haemolysis, graft failure

Extracorporeal Membrane Oxygenation

- See ECMO Hot Case, page 378
- Extracorporeal life support where blood is oxygenated and CO₂ removed
- First used in 1972
- Established in:
 - Neonates: Bartlett trial in the US (back the winner design) and in the UK trial 93 – 95
 - Adults: JAMA trial 1979 reported harm, JAMA 1986 reported benefit in case series with VV ECMO
 - Now 1600 cases per year worldwide
- Recent papers:
 - Cesar Trial: Lancet 2009, Conventional ventilation vs *referral for* ECMO for severe respiratory failure. Only the ECMO patients were transferred to one specialist centre – only 75% of these got ECMO. Patients transferred for ECMO +/- actually getting it did better (63 vs 47% 6 month survival). Difficult to interpret. Didn't answer the question as to whether other local measures could be as good as ECMO (eg HFO)
 - 2009 H1N1 ANZ ECMO: JAMA 2009, observational study of 68 patients, compared with 133 ventilated but not ECMOed patients. 21% mortality in ECMO, 13% in non-ECMO
- Bottom line: May improve survival in patients with severe acute respiratory failure, impact in cardiac failure is uncertain
- Types of ECMO:
 - Venous-Venous (VV):
 - Drainage usually from femoral vein, return to SVC
 - For severe respiratory failure: usually pneumonia, ARDS, acute lung graft failure post-transplant, pulmonary contusion
 - Advantages: normal lung blood flow, pulsatile blood pressure, oxygenated blood to root of aorta
 - Disadvantages: no cardiac support, local recirculation through circuit at high flows, reversed gas exchange in lung in FiO₂ low
 - Ventilation: must maintain alveolar volume: high PEEP, low RR, Tv 3 – 4 ml/kg
 - Low flow: one drainage cannula, efficient CO₂ removal but weaker oxygenation
 - High flow: may need drainage cannula in femoral and RIJ, with return to proximal IVC. Better oxygenation
 - Can now get Bicaval lines – one line into SVC that drains from RIJ and IVC and returns to SVC
 - Advantages of VV over VA ECMO:
 - If adequate cardiac function, then V-A ECMO → significant native blood pulmonary blood flow → relatively hypoxic perfusion of upper body compared with lower half
 - Avoids risk of serious arterial injury
 - Less severe consequences in case of air or clot embolization
 - Low pressure system may prolong circuit life
 - Venous-Arterial (VA):
 - For severe cardiac failure with or without respiratory failure, eg:
 - Graft failure post heart/heart-lung transplant
 - Non-ischaemic cardiogenic shock
 - Post cardiac surgery CPB weaning failure
 - Cardiomyopathy bridge to LVAD
 - Drug overdose
 - Sepsis (eg with EF < 25%)

- Central VA: Drainage from large central vein (eg SVC), return to aorta (or to subclavian artery). Requires sternotomy. Predisposes to severe post op bleeding. Usually just for failure to wean from CPB
- Peripheral VA: drain from proximal IVC, return to femoral artery with distal leg reperfusion cannula. Creates high O₂ in blood, relative lung ischaemia, no pulsatile flow, preferential perfusion of lower body (especially if native cardiac output is high) and hypoxic coronaries
- High flow peripheral VA is best option for long term ECMO in severe heart failure. Usually requires proximal IVC and RIJ drainage with femoral return + distal limb reperfusion cannula
- Indications:
 - For acute, severe, reversible respiratory or cardiac failure when risk of dying despite conventional treatment is 50 – 100%
 - Institutional experience plays a large role in patient selection
- Contraindications:
 - Absolute:
 - Progressive and non-reversible condition (except as bridge to cardiac transplant only – not lung)
 - Chronic severe pulmonary HT
 - Advanced malignancy
 - GVHD
 - Body size < 20 kg or > 120 kg
 - Unwitnessed cardiac arrest
 - Relative:
 - Age > 70
 - Multiple trauma with multiple bleeding sites
 - CPR duration > 60 minutes
 - Multiple organ failure
 - CNS injury
- The circuit:
 - Requires anticoagulation with ACT 180 – 200 secs
 - Pump: minimal haemolytic index
 - Oxygenator: integrated heat exchange, heparin bonded
 - SaO₂ determined by total flow through the circuit – only one control → increase or decrease flow rate. Set flow rate to deliver desired O₂
- Weaning:
 - VA: ↑pulsatility → increasing native heart function. TOE to assess function. Can cease O₂ flow to oxygenator to assess respiratory function
 - VV: Don't reduce flow, just turn off O₂ to oxygenator to assess
 - All arterial cannula removed by open surgery. If venous cannula inserted percutaneously can be removed with site compression
- Problems:
 - Flow limitation: if cannula drains too much, vein collapses causing 'kicking' of line (especially if high abdominal pressure)
 - Can't maintain flow:
 - Check cannula and tubing position
 - Compression: constipation, ileus, pneumothorax, tamponade
 - Obstruction: clot in circuit, hypovolaemia
 - Air embolism on insertion of second RIJ line if CVP < 10
 - Recirculation at high flows in VV
 - In VA, ↑pO₂ may be improving lung function, ↓native CO, ↑ECMO flow rate
 - ↑pressure gradient before and after pump → thrombosis

Adult Cardiopulmonary Resuscitation

- See also Out of Hospital Cardiac Arrest, page 165
- 'Chain of survival': key links in the chain of resuscitation process – early recognition and summoning help, early basic life support, early access to defibrillation and early ALS, post-resuscitation care
- Family presence during out-of-hospital cardiac arrest is associated with ↓ symptoms of PTSD, with no effect on medical team emotional stress, resuscitation or patient outcome (Jabre et al, NEJM 2013)
- Basic Life Support:

- Optimal rate of compression unknown: < 80 associated with worse outcomes, > 120 with more fatigue but no benefits
- Ideal depth of compression unknown – recommended 1/3rd of chest depth. Rib fractures associated with ↑survival
- Minimise interruptions to compressions
- Compression – ventilation ratio: minute ventilation requirement during cardiac arrest are less than non-arrest state. Recommend 30:2. Hyperventilation in some studies is associated with ↓survival. Rate < 10 min with volume just sufficient to achieve chest rising. Mechanical chest compressions confer no benefit (Rubertsson, JAMA 2013)
- Monitoring quality of CPR. Hard and fast. Consider ETCO₂:
 - Falls immediately at onset of arrest
 - Increases immediately with chest compressions
 - Linear correlation with cardiac index
 - Early detection of return of spontaneous circulation (sudden increase)
 - Assessment of ET tube placement
 - Absolute value predicts successful resuscitation
- Compression only CPR:
 - Animal studies and human case series in out-of-hospital arrests suggest ventilation doesn't add much
 - Human RCTs in which telephone dispatcher gave advice for compression only or usual CPR where it had not commenced:
 - Svensson et al, NEJM 2010: 1276 patients analysed, no difference in 30 day survival
 - Rea et al, NEJM 2010: 1941 patients, no difference in survival to discharge. Trend to better outcomes with compression only in arrests from cardiac causes (70% of cases)
 - CPR alone → some passive ventilation
- Timing of defibrillation:
 - In recent-onset VF immediate defibrillation (best outcomes if its within 3 minutes)
 - For VF persisting longer than 3 minutes, initial CPR may improve shock success
- Single-shock: as long as it is quality CPR, single shock then immediately recommence CPR. 3-shock strategy if first defibrillation attempt in witnessed arrest and they can all be given in 30 seconds
- Duration of CPR: No RCT evidence. Goldberger et al (Lancet 2012), large registry observational study of inpatient arrest. ROSC in 48%. 15% survived to discharge. Longer duration of CPR (15 – 30 mins as opposed to 0 – 15 mins) gives small increase in survival to discharge (14.5% to 16.2%). Neurological outcome is similar between people with ROSC < 15 mins and from 15 – 30 mins. ie this suggests keeping going saves a few without worse neurological outcome
- Advanced Life Support:
 - Not demonstrated to improve outcomes
 - Precordial thump if witnessed and monitored arrest with shockable rhythm if defibrillation not immediately available
 - Chest compressions should restart immediately after shock without rhythm check, and continue for 2 minutes or until signs of life. Return of rhythm is not usually associated with immediate return of circulation
 - Airway management: no data supports any approach. ET is “gold standard” but not shown to improve outcomes. Hasegawa, JAMA 2013, large Japanese registry study, supraglottic airway or ET, vs bag mask, worsened neurological outcome
 - Hyperventilation is associated with ↑intrathoracic pressure, ↓coronary and cerebral perfusion, and in animals a ↓rate of ROSC. Recommended rate is 8 – 10/min. Tidal volume is on that results in a visible chest rise
 - ECMO during CPR. For in hospital arrest may increase survival, if available. Only case series data. Roughly extends point of no return from 30 mins to 60 mins. Makes no difference in out-of-hospital or unwitnessed arrests
- Drugs during CPR:
 - No RCT show the routine use of *any* drug increases survival to hospital discharge
 - No vasopressor has been shown to improve survival. Adrenaline is recommended. Vasopressin is an alternative. Adrenaline use was associated with worse survival in both Swedish and Japanese retrospective cohort studies (2012 JAMA), despite increased ROSC in the Japanese study. Associated with increased myocardial O₂ consumption and ventricular arrhythmias. Meta-analysis of 13 observational studies (n = 2,381 to 421,459) showed no significant effect on survival to discharge

(Atkissawedparit, Crit Care 2014). Animal models show beneficial short term effect and ↑cerebral and coronary perfusion

- No antiarrhythmic has been shown to improve long term survival. Amiodarone (300 mg or 5 mg/kg) for shock refractory VF → ↑survival to discharge compared with placebo. After third cycle.
- Dorian et al, NEJM 2002: trial of amiodarone or lignocaine for pre-hospital VF arrest persisting after one cycle. 22 vs 12% survived to hospital, no change in hospital discharge morality (?underpowered). Previously lignocaine was preferred.
- No atropine
- Other possible drugs:
 - Magnesium: hypomagnesaemia, hypokalaemia, ↑Ca, TCA overdose, torsade
 - Calcium: ↓Ca, ↑K, β blocker/ca blocker toxicity
 - NaHCO₃: ↑K, TCA toxicity
- Post resuscitation care:
 - Induced hypothermia (see below)
 - Other factors have limited data. Hyperventilation harmful (→ cerebral vasoconstriction). Tight glucose control controversial. Good supportive care important
 - BP recommendation: target patient's usual BP, or SBP > 100
 - Consider coronary reperfusion
- Causes of a PEA arrest (guidelines now recommend consider for both PEA and VT/VF arrest):
 - Tension pneumothorax
 - Thrombosis: PE
 - Tamponade
 - Toxins: TCAs, digoxin, CCBs, β-blockers
 - Hypothermia
 - Hypovolaemia
 - Hypoxia
 - Hypokalaemia/hyperkalaemia/Acidosis

Out of Hospital Cardiac Arrest

- See also:
 - Brain Death, page 358
 - Induced hypothermia After Cardiac Arrest, page 136
 - Prognostication in Comatose Survivors of Cardiac Arrest: An advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine, IC 2014. Quality of evidence of 73 included studies was generally low or very low.
- In a large Japanese cohort study of 209,577 patients, adrenaline was associated with (Goto, Crit Care 2013):
 - Worse survival (27 vs 15%) and worse neuro recovery (18 vs 7%) in initially shockable rhythms at 1 month
 - Worse survival but not change neuro outcomes in non-shockable rhythms at 1 month
- Family presence during CPR for adult out-of-hospital (NEJM 2013). 570 relatives randomised to be present vs usual practice. PTSD at 90 day worse in the control group (OR 1.7). No difference in duration or treatment received ⇒ family presence beneficial
- Prognostication in Anoxic Coma:
 - After cessation of sedation, probability of awakening decreases with each day of coma
 - Average outcomes: Long term outcome in elderly survivors of in-hospital cardiac arrest, observational study of 6972 patients > 65 years. 1 year survival 58%, older and female patients higher mortality risk (NEJM 2013)
 - Multi-modal prognostication approach is recommended – can't put all your weight on one measure
 - No neurophysiological study reliably predict outcome at < 24 hours:
 - EEG findings of diffuse suppression, burst suppression, generalised seizures or diffuse periodic complexes indicate poor prognosis. ↑false positive predictive for poor outcome after induced hypothermia
 - SSEP: bilaterally absent cortical N20 wave of short-latency somatosensory evoked potentials to median nerve stimulation at 72 hours after cardiac arrest highly accurate (100% specificity), not studied after hypothermia. Requires neurologist to interpret. Not interfered with by sedative drugs. Inappropriate in spinal injury
 - Clinical findings:

- Clinical examination not reliable before 24 hours and norm of 72 hours is from data pre-hypothermia era. May need to wait longer than 72 hours in cooled patients
- Bilaterally absent pupillary reflexes at 72 hours a robust predictor – 0%FPR, low sensitivity. Absent corneal reflexes less specific (more affected by residual sedatives/NMBA)
- Absent or extensor motor response at 72 hours to pain 74% sensitive, but high FPR ~27%
- Generalised myoclonus status:
 - Not a single seizure or sporadic myoclonus – no consensus on duration to be called status – but 30 mins a reasonable guide
 - Single jerks (not status) FPR 5% and sensitivity of 33% for poor outcome
 - Status starting within 48 hours a predictor of very poor outcome with reported false positive rate of 0% (0-4) and sensitivity 15% in non-cooled patients. However, there are case reports of severe myoclonus developing functional outcome. Early or severe myoclonus is, however, generally really bad
- Investigations:
 - CT may reveal catastrophic intracerebral cause for the arrest. Diffuse swelling is common but predictive power is unknown. Role of MRI/PET unclear
 - Biomarkers: serum neuron-specific enolase levels > 33 µg/L at days 1 – 3 associated with poor outcome
- Best prognostic estimates come from absence of pupillary response or motor response to pain on day 3, somatosensory evoked potentials and EEG
- Predictors of unfavourable outcome (see Zandbergen et al, Lancet 1998, Systematic review of early prediction of poor outcome in anoxic ischaemic coma):
 - Initial rhythm: VF better than asystole
 - Duration of anoxia (collapse to CPR): 8 – 10 mins
 - Duration of CPR (CPR to ROSC): > 30 mins
 - Duration of post-anoxic coma: > 72 hours
 - Absent pupillary reaction on day 3
 - Motor response worse than withdrawal on day 3
 - Roving spontaneous eye movements absent on day 1
 - Elevated neuron specific enolase > 33 µg/l
 - Absent N20 on SSEPs with median nerve stimulation within 1 – 2 days of CPR
- A Meta-analysis of outcome predictors at 72 hours post-OHCA with hypothermia showed (Kamps, Int Care Med 2013):
 - GCS motor score 1 – 2 had a false +ive rate of 0.21
 - Bilaterally absent corneal reflexes had a false positive rate of 0.02
 - Bilaterally absent SN20 had a false positive rate of 0.007
 - Bilaterally absent papillary reflexes had a false positive rate of 0.004
- The above may not correlate with individual outcome. Co-morbidities and pre-arrest performance status may determine overall survival
- Confounders to prediction:
 - Induced hypothermia – extent unclear
 - Time of assessment – 72 hours post arrest recommended
 - Sedatives, NMBA
 - Shock/organ failure

Changes to CPR Guidelines

- 2006 Life Support Guidelines
 - Basic Life Support:
 - Basic life support = unresponsive, not breathing, not moving
 - Pulse check **not** required to commence CPR. If not responding or not breathing then immediate CPR. Rescue breathing first in kids
 - Rescue breathing now called expired air resuscitation
 - Compression ventilation ratio is 30:2 for all adults and children
 - Same ratio regardless of number of rescuers
 - Site of chest compressions is the “centre of the chest” – no need to measure and re-measure
 - 2 initial breaths not 5
 - Chest compressions occur at rate of 100/min for all groups
 - Advanced Life Support
 - Minimise interruptions to chest compressions

- If unwitnessed arrest and VF/pulseless VT, **single shock** instead of stacked shocks
- If witnessed arrest, up to 3 shocks at first attempt
- If Monophasic then 360 for all shocks, biphasic, 200J for all shocks, if unsure use 200J
- 2 min CPR after each shock before checking rhythm and pulse
- International Liaison Committee on Resuscitation (ILCOR), consensus guidelines
 - 2005 Update. Major changes:
 - Breath-to-compression ratio change to 2:30
 - 100 compressions for adults and children (not neonates)
 - Unless arrest is witnessed, “stacked” DC cardioversion * 3 before giving CPR became one shock
 - In subsequent cycles, only one shock before continuing CPR
 - 2010 update of 2005 (Circulation 2010). Minor changes to :
 - Simply the algorithm
 - Promote lay person effectiveness, eg de-emphasise ventilation
 - Reduce interruptions to chest compressions
 - Add therapeutic cooling to post-arrest care
 - No atropine for asystole
- Changes to NZ Resuscitation Council Guidelines 2011 (included harmonising with Australia):
 - Depth of compression has increased to at least 5 cm, or one third of the depth of the chest, with evidence suggesting that 6 – 7cm compression is better
 - Signs of life only checked under circulation. Pulse checks only if confident in finding them
 - Precordial thump only delivered if you are at the patient’s side when they collapsed and the patient is on a monitor showing VT. No longer recommended for VF, or if the time to collapse is > 30 – 40 secs
 - Chest compressions start before ventilation in an adult unless a clear hypoxaemia precedes the collapse
 - Single shock should be used for witnessed and unwitnessed collapses except in specific circumstances (eg electrophysiology labs and angiography suites)

- See also Abdominal and Pelvic Injury, page 253
- Schema for reading an abdominal CT:
 - Scroll down through solid organs (retroperitoneal):
 - Liver/Spleen: are they homogenous and equal attenuation. If the veins are bright, it is a porto-venous phase scan
 - Pancreas: find portal vein, follow to splenic vein, follow to SMV, pancreas is draped on top. Is it homogenous. May see duct down the middle
 - Adrenals: y shaped anterior and superior to kidneys
 - Kidneys: cortex on outside, medulla on inside
 - Bladder: check for free fluid in utero-vesicle pouch (Pouch of Douglas) in female and recto-vesical pouch in male
 - Check bowel on way back up
 - Flip to lung window, check for free air
 - Look at lymph nodes from the bottom: inguinal, pelvic (lateral wall of pelvis either side of bladder), periaortic/aortocaval nodes – just above bifurcation
 - Abdominal aorta should be < 2.5 cm diameter
 - Check lung bases
 - Look at sagittal view, bone windows, check spine for alignment

Acute Gastrointestinal Bleeding

- See also Stress Ulcer Prophylaxis, page 351
- Differential:
 - Upper:
 - Peptic ulcer disease – 75%. DU:GU 3:1. Mortality fallen substantially to ~ 5%
 - Varies: mortality ~ 30%. Oesophageal: gastric varices 9:1
 - Oesophagitis, gastritis and duodenitis
 - Mallory-Weiss syndrome
 - Portal hypertensive gastropathy
 - Lower:
 - Diverticular bleeding
 - Angiodysplasia and AVM
 - Colonic polyps or tumours
 - Meckel's diverticulum
 - Inflammatory bowel disease
- Risk factors: old age, comorbid conditions, coagulopathy, magnitude of bleeding
- Transfusion thresholds: Villanueva NEJM 2013, MRCT of 921 patients with severe upper GI bleed (massive bleeding excluded, as was Rockall score of 0, ie low risk of rebleeding). Threshold of 70 better than 90 for survival (95% vs 91%) and rebleed. On subgroup analysis, the improved mortality was in peptic ulcer and Child Pugh A & B cirrhosis, but not in Child Pugh C. Excess mortality in the liberal transfusion group (primarily CP A & B) was due to uncontrolled bleeding. This correlated with an ↑ in hepatic pressure gradient – postulated due to ↑ fluid resuscitation

Non-variceal Upper GI bleed

- Endoscopy preferred to barium x-rays: more precise identification, can give treatment, barium unreliable in prior gastric surgery
- Angiography uncommon. If there is sufficient haemorrhage to obscure vision, then should be considered for surgery not angiography to identify source
- Significant bleed suggested by SBP < 100, postural drop, > 4 units in 12 hours
- High risk ulcer suggested by: active bleeding, adherent clot, protuberant vessel or flat pigmented spot on ulcer base. Predict rebleeding
- Management:
 - Use of prognostic scales to risk stratify patients is recommended
 - Correct coagulopathy from anticoagulation, but this should not delay endoscopy if indicated
 - Resuscitate:
 - Plasma expanders and blood (target Hb > 70)
 - If shocked then central venous pressure and hourly urine
 - Control bleeding

- Most stop bleeding spontaneously
- Pre-endoscopy PPIs may downstage lesions, but should not delay endoscopy if indicated
- Endoscopy if high risk of persistent or recurrent bleeding. Haemostasis through:
 - Adrenaline: unclear whether action is by local tamponade or vasoconstriction. Little systemic effect of adrenaline
 - Coaptive coagulation: heater probe or bipolar coagulation probe
 - Haemoclips: no tissue injury, but in some sites can be technically difficult
- Surgery: little agreement on best indications or timing. Percutaneous embolisation should be considered. Indicators for surgery include:
 - Failure to achieve endoscopic haemostasis
 - Massive transfusion (> 6 – 8 units of blood)
 - Recurrent clinical bleeding after initial control
 - Evidence of GI perforation
- PPIs/H2-receptor antagonists:
 - Acidic environment impairs platelet function and haemostasis
 - IV bolus followed by continuous infusion PPI should be used as an adjunct to endoscopy in high risk patients
 - Antifibrinolytics (eg tranexamic acid) ineffective
- Prevent recurrence:
 - H Pylori eradication if they test positive
 - If requiring an NSAID, COX-2 + PPI is recommended (still ↑risk with COX2 alone)
- Not recommended:
 - Routine second-look endoscopy
 - Somatostatin and octreotide are not routine

Variceal Bleeding

- Drugs affecting portal pressure:
 - Splanchnic vasoconstrictors: vasopressin and somatostatin (and their analogues). IV only so only used acutely
 - Non selective β -blockers (propranolol, nadolol):
 - → ↓portal flow due to β_1 action (↓cardiac output) and β_2 action (splanchnic vasoconstriction). Oral so used for chronic control.
 - Not used for compensated cirrhosis (ie no varices) as they don't prevent progression
 - Carvedilol at low dose is better than endoscopic variceal ligation for early variceal haemorrhage
 - Intrahepatic vasodilation induced by:
 - ↑nitric oxide delivery to intrahepatic circulation: nitrates, simvastatin
 - Blocking adrenergic activity: prazosin, clonidine
 - Blocking angiotensin: ACEI and ARBs
 - However, venodilators may also cause systemic vasodilation → Na retention and vasoconstriction
 - None of these drugs licensed for the treatment of portal hypertension – all off-label use
- Risk stratification:
 - At a minimum, stratify into:
 - Compensated cirrhosis
 - Uncompensated cirrhosis: ascites, variceal haemorrhage, encephalopathy or jaundice
 - Child Pugh class
 - Measurement of portal pressure with hepatic venous pressure gradient (HVPG) > 5 mmHg (but clinically significant above 10) best classifies risk. Obtained by catheterisation of the hepatic vein with a balloon catheter through the jugular or femoral vein. Invasive. Not widely used
- Resuscitation:
 - Fluid + blood. May need FFP and platelets
 - Over-transfusion may → rebound in portal pressure
 - Careful insertion of an NG tube to aspirate blood
 - Lactulose 15 – 30 ml QID to prevent hepatic encephalopathy
- Control:
 - Portal hypertension can → bleeding from oesophageal or gastric varices, peptic ulcers and portal hypertensive gastropathy
 - Pharmacological control (should be first line):
 - Formerly vasopressin: 0.2 – 0.4 U/min to reduce portal pressure (the most potent splanchnic vasoconstrictor) but cardiac ischaemia in 10%, limb and bowel ischaemia, hypertension and

worsening coagulopathy (release of plasminogen activator). Safety improved somewhat by adding GTN

- Terlipressin: analogue of vasopressin with long T_{1/2}, fewer cardiac side effects and more effective (↓mortality, Cochrane review 2009). 2 mg IV every 4 hours, 1 mg after bleeding controlled
- Somatostatin (or its analogue octreotide) → ↓portal pressure and azygous blood flow. Effective as an adjuvant to endoscopy with ↓re-bleeding and transfusion. Safe – so can be used for 5 days. Doubts about its effectiveness from meta-analysis.
- Terlipressin might be the vasoactive drug of choice given no other drug has shown mortality benefit (Cochrane Review 2009)
- Should be continued for 3 – 5 days
- Do not use β-blockers acutely – they ↓BP and blunt ↑pulse rate compensating for bleeding
- Minimise trauma (eg NG tubes)
- Endoscopic injection sclerotherapy: either intravariceal or paravariceal. Controls 80 – 90% of acute variceal bleeds. Complications of ulcer formation, fever, chest pain and mediastinitis are common
- Endoscopic variceal ligation: as effective as sclerotherapy without the complication of tissue irritation → often the first choice
- Balloon tamponade: Sengstaken-Blackmore tube (or Minnesota Tube):
 - Inflation of gastric balloon may be sufficient to occlude gastric feeding veins and stop bleeding. Otherwise inflate oesophageal balloon to 50 – 60 mmHg
 - Allows aspiration of gastric and oesophageal contents
 - Limit to 24 hours otherwise necrosis
 - Contraindications:
 - Known oesophageal stricture
 - Unidentified source of bleeding
 - Unprotected airway
 - Complications:
 - Aspiration pneumonia
 - Cardiac arrhythmias
 - Oesophageal perforation
 - Acute airway obstruction
- TIPS: See Other Supportive Care in Liver Failure, page 178
- Supportive care: prophylactic antibiotics for 7 days has mortality benefit. Oral norfloxacin, IV ciprofloxacin, or IV ceftriaxone if high levels of ciprofloxacin resistance

Lower GI Bleeding

- Arises from a source distal to the ligament of Treitz
- Massive bleeding suggests ischaemia or inflammatory bowel disease
- Painless bleeding is common in diverticulosis, angiodysplasia or Meckel's diverticulum
- Portal hypertension may present with haemorrhoids causing massive haematochezia
- Investigations:
 - Colonoscopy difficult in active bleeding. Much better yield with adequate bowel preparation
 - Radionucleotide study: 99mTc labelled red cells (prolongs life in the body of 99mTc) detects source in 80% cases
 - Angiography helpful if active bleeding obscures endoscopic view and in defining abnormal vasculatures (eg angiodysplasia, AVM, inherited vascular anomalies)
- Management:
 - Endoscopy: electro-coagulation, heater probe, laser photocoagulation or polypectomy
 - Angiography: intra-arterial infusion of vasopressin or embolic agents. Frequent recurrence of bleeding with diverticular disease
 - Surgery

Acute Pancreatitis

- Mild, interstitial, oedematous pancreatitis most common but acute necrotising pancreatitis (ANP) accounts for most mortality – dropping from 25 – 35% to 15% over the last 20 years in best centres
- Many therapeutic interventions tried, little evidence of benefit
- Causes:
 - Alcohol
 - Biliary tract disease
 - Idiopathic

- Metabolic: hyperlipidaemia, hyperparathyroidism, diabetic ketoacidosis, end-stage renal failure, pregnancy, post renal-transplant
- Mechanical: post traumatic, postoperative, post-ERCP, duodenal obstruction
- Infection: HIV, mumps, EBV, Mycoplasma, legionella, campylobacter, Ascariasis
- Vascular: necrotising vasculitis, SLE, TTP
- Drugs: azathioprine, thiazides, frusemide, tetracyclines, oestrogens, valproic acid, metronidazole, erythromycin
- Toxins: scorpion venom, organophosphates, methyl alcohol
- Pathophysiology:
 - Necrosis develops within 96 hours
- Severity assessment:
 - Main determinant of outcome is the extent of pancreatic necrosis
 - Ranson's score: originally from 100 cases of mainly alcohol induced pancreatitis:
 - On admission:
 - Age > 55
 - WBC > 16
 - Glucose > 11
 - LDH > 400
 - AST > 250
 - After 48 hours:
 - ↓ in haematocrit > 10%
 - Increase in urea > 1.8 mmol/L
 - PaO₂ < 8 kPa
 - Base deficit > 4 mmol/l
 - Fluid deficit > 6 litres
 - 0 – 2 risk factors < 1% mortality, 3 – 4 15%, 5 – 6 40%, > 6 100%
 - Glasgow or Imrie score excludes LDH, base deficit and fluid deficit as the least contributory

Diagnosis of Pancreatitis

- Contrast CT:
 - When to scan:
 - If clinical diagnosis is in doubt
 - Signs of severity: ↑analyse, abdominal distension, tenderness, high fever, ↑WBC
 - Ranson score > 3 or APACHE II > 8
 - No improvement after 72 hours of initial conservative therapy
 - Acute deterioration after initial improvement
 - Lack of normal enhancement due to necrosis which presents with diffuse or focal areas of non-viable parenchyma.
 - Two prognostic factors are:
 - the extent of necrosis. Necrosis in the head of the pancreas is as bad as the whole pancreas, distal portion of the gland has more favourable outcome
 - the grade of peripancreatic inflammation
 - Grades of peripancreatic inflammation (as per Blathazar score):
 - A: Normal pancreas
 - B: Focal or diffuse pancreatic enlargement
 - C: Pancreatic gland abnormalities associated with peripancreatic inflammation
 - D: Single fluid collection
 - E: Two or more fluid collections and/or gas present in or adjacent to the pancreas
- US less helpful. Obscured by bowel gas, extent of necrosis can't be assessed. Useful for detecting stones and guiding FNA of potentially infected pancreas
- Differential of ↑lipase: pancreatitis, perforated duodenal ulcer, intestinal obstruction, cholecystitis, gut ischaemia

Management of Pancreatitis

- Good housekeeping: vigorous fluid replacement, correction of electrolytes and glucose, respiratory, cardiovascular and renal support as necessary
- ERCP: Data not uniformly consistent
 - Mainly for severe biliary pancreatitis
 - In mild biliary pancreatitis risks possibly outweigh benefits
- Surgery:

- used to be common. Now as an adjunct to conservative management for infection only:
 - Trial in 88 patients with necrotising pancreatitis found benefit from step up approach (percutaneous drainage → retroperitoneal necrosectomy if needed) over open necrosectomy (NEJM 2010, van Santvoort et al)
 - Laparotomy for acute abdomen when diagnosis is in doubt. If a chance finding of pancreatitis, put a T-tube in the common bile duct and place a feeding jejunostomy
- Sterile pancreatic necrosis: Can survive without surgery – which exposes them to risk of infection. Currently conservative approach is recommended. Prophylactic ABs probably indicated
- Infected pancreatic necrosis:
 - CT documents necrosis, FNA of localised fluid collection proves infection
 - Undisputed indication for urgent surgery – but what surgery is not proven. Options include debridement and drainage, continuous closed lavage of the lesser sac, staged repeated laparotomy or open packing
- Pancreatic abscess: Circumscribed collections of pus containing little or no necrosis. Commonly occur late – 3 - 4 weeks after onset. CT scan most accurate. Percutaneous catheter drainage successful in 70%. Open drainage may be required, especially in yeast infection
- Controversial indications for surgery are stable but persistent necrosis, deterioration in clinical course, organ failure, abdominal compartment syndrome
- Drugs:
 - None of proven benefit
 - As autodigestion is, at least in theory, a significant contributor, “resting the pancreas” (to stop it secretion lipases etc.) is of possible benefit. However, secretion suppressing drugs (eg H2 blockers, atropine, calcitonin, glucagon and fluorouracil) don’t alter the course of the disease
 - Somatostatin and octreotide (a long acting analogue):
 - Potent inhibitors of secretion
 - Somatostatin blocks the release of tumour necrosis factor and interferon γ
 - Both agents are powerful splanchnic vasoconstrictors which may → hypoperfusion which may → ↑necrosis
 - Insufficient evidence at present to recommend them
 - Protease inhibitors: stop autodigestion by proteases. Aprotinin and gabexate mesylate inhibit serine proteases. No mortality reduction from 2 RCTs
 - Anti-inflammatory therapy: Limited human data. Small numbers in a subgroup of the PROWESS Trial (APC) showed benefit. No published trials of corticosteroids
- Prophylactic Antibiotics:
 - The problem: Bacterial infection of necrotic pancreatic tissue occurs in 40 – 70% of ANP, but can be difficult to distinguish from non-infective SIRS, or infection at other sites
 - Early studies of prophylaxis showed variable results (some with benefit), but were mostly unblinded, included mild cases and used antibiotics with poor penetration. Cochrane meta-analysis of 3 RCTs of prophylaxis in CT proven ANP show ↓sepsis by 21% and ↓mortality by 12.3%
 - No difference in 2 recent large RCTs, Isenmann 2004 and Delinger 2007 (100 patients randomised to meropenem or placebo)
 - No benefit in mild pancreatitis
 - Carbapenems (eg meropenem) preferred over cefuroxime/metronidazole (better penetration into flamed tissue)
 - Prophylactic antifungals: Antifungals correlate with extent of necrosis on admission. High mortality. One small study of fluconazole showed no benefit on mortality
- Selective gut decontamination:
 - Conflicting evidence. See Selective Gut Decontamination, page 54
 - Hypothesised that gut hypoperfusion promotes bacterial translocation → infection of pancreatic tissue
 - Only trial showed reduced G-ive infection – but unclear whether this was a topical or systemic effect

Nutritional Support in Pancreatitis

- See also Nutrition, page 339
- Patients are nutritionally depleted and have increased metabolic demands
- Severe pancreatitis was considered a contraindication to EN in order to “rest the pancreas” → TPN was standard. Several retrospective and prospective evaluations of TPN show no conclusive survival benefit
- *Evidence now clearly supports enteral feeding.* A number of EN vs TPN trials have shown EN is well tolerated with fewer total and septic complications (Cochrane Review 2010 of 8 RCTs). However, EN may not be tolerated (eg due to an ileus or slowed transit time). Australasian observational studies still show high use of TPN: Nutritional therapy in patients with acute pancreatitis requiring critical care unit

management: A prospective observational study in Australia and NZ, Crit Care Med 2011, Davies et al, CTG Publication

- EN is recommended to be given distal to the ligament of Treitz, distal to the 3rd part of the duodenum, below the cholecystikinin (CCK) cells which stimulate exocrine secretion. 3 small studies suggest it is safe to feed into the stomach with no increase in complications ⇒ Suggestion to try gastric feeding and only go post-pyloric if this fails (Chang, CCM 2013)
- Elemental feeds and pancreatic enzymes if absorption is a problem
- Role of lipids in TPN:
 - Induction of pancreatitis by endogenous circulating triglycerides is well documented, and has led to caution in some to lipid administration in TPN
 - Various studies have concluded that lipids in TPN do not cause stimulation of exocrine pancreatic function
 - Lipid emulsions can safely be used as a source of calories and essential fatty acids if serum triglyceride levels remain below 400 mg/dl during infusion
- Recommendations:
 - Mild uncomplicated pancreatitis do not benefit from nutritional support
 - In moderate to severe pancreatitis, let hyperacute inflammation settle then start a trial of EN via a jejunal tube:
 - Use a feeding protocol to maximise the chances of achieving nutritional target rates
 - Determine the rate for enteral nutrition. Can use either indirect calorimetry, predictive equations (eg Harris-Benedict equation) or simplistic formulae (25 – 30 kcal/kg/day with at least 1.2 – 3 g/kg/day protein))
 - Commence at 30 ml/hr and increase as tolerated
 - Consider prokinetics if large aspirates
 - Avoid probiotics (the only multi-centre RCT showed ↑mortality and incidence of MOF in the treatment group)
 - If surgery at any stage, place a jejunal tube
 - TPN (enriched with glutamine) only if 5 – 7 day trial of EN is not tolerated
 - Strict glycaemic control is required either way

Acute Liver Failure

- See also
 - Liver Failure Related Syndromes, page 182
 - Peritonitis, page 185
 - Liver Dysfunction In Pregnancy, page 319

Differential of Acute Liver Failure

- A heterogeneous condition, a number of classifications, O'Grady definition divides into Hyperacute, acute and subacute
- **Hyperacute:** onset of encephalopathy with 7 days of the development of jaundice
 - Paracetamol: paracetamol level may be negative by day 3 or 4, AST and ALT may be > 10,000. See Paracetamol toxicity, page 179
 - Vascular: Ischaemic (dilated HV on US, transaminases > 5000), veno-occlusive
 - Viral
 - Toxins: carbon tetrachloride, Amanita phalloides (mushroom, present with diarrhoea)
 - Heatstroke: myoglobinuria, rhabdomyolysis
 - Acute alcoholic hepatitis: prednisone of probably benefit, pentoxifylline not (Mathurin, JAMA 2013)
- **Acute:** encephalopathy within 8 – 28 days after the onset of jaundice
 - Causes:
 - Sero-negative/idiopathic – diagnosis of exclusion. Worse prognosis than those with an identifiable virus/drugs
 - Drug related (15 – 25% of cases of ALF):
 - Dose related, eg paracetamol – see below. Role of NAC in non-paracetamol ALF not clear
 - Idiosyncratic: TB drugs (rifampicin/isoniazid), statins, recreational drugs (ecstasy, cocaine), anticonvulsants (phenytoin/valproate), NSAIDs. Diagnosis usually based on temporal relationship
 - Can be a genuine hypersensitivity reaction with ↑eosinophils, fever, rash, sensitisation over 1–5 weeks, symptoms recur promptly with re-challenge
 - Pregnancy related: usually good prognosis

- Fatty liver: ↑uric acid, ↑neutrophils, often first pregnancy. CT may show rupture or veno-occlusive disease
- HELLP Syndrome: haemolysis (microangiopathic haemolytic anaemia) elevated liver enzymes and low platelets, DIC prominent
- Liver rupture: in association with pre-eclampsia, fatty liver and HELLP
- Trauma
- Autoimmune: diagnosis: autoantibodies, immunoglobulins. Steroids for autoimmune hepatitis are beneficial. For autoimmune ALF it is less clear – steroids may be detrimental
- Presentation:
 - Less pronounced rise in transaminases
 - May have established ascites ⇒ difficult to distinguish from chronic liver disease
 - Encephalopathy often late, and lower risk of cerebral oedema and intracranial hypertension
 - Once they develop poor prognostic criteria, recovery without liver transplant is rare
- **Subacute:** encephalopathy 4 – 26 weeks after the onset of jaundice
 - Wilson's disease: urinary copper, cerulo-plasmin (although low in many cases of liver failure), low ALP, Kayser-Fleischer rings
 - Lymphoma
 - Carcinoma: Diagnosis with imaging and biopsy. ↑ALP and LDH
 - Budd-Chiari Syndrome: Diagnosis with US showing no HV signal, reverse flow in portal vein. Often capsular pain from congestion and ascites. Either anatomical abnormality (Asia) or thrombosis (Europe & USA). Thrombolytics may be helpful early in the course. TIPS increasingly used to decompress the liver.

Diagnosis of Liver Failure

- Ultrasound: nature of liver (nodularity ⇒ CLD), vascular pattern, presence of ascites and hepatomegaly
- Histology: Usually transjugular route. Controversy around place in ALF. Can be specific (eg Wilson's disease, malignancy). Confluent necrosis is the most common finding and is not specific. > 50% necrosis ⇒ poor prognosis, but subject to sampling error
- Causes of altered liver function tests:
 - Bilirubin:
 - Unconjugated/indirect: neonatal, Gilbert Syndrome, haemolysis, haematoma resorption
 - Conjugated:
 - ICU jaundice: MODS
 - Cholestasis: flucloxacillin, obstruction
 - TPN
 - Liver congestion: CHF
 - Hepatitis
 - AST: liver, heart, skeletal muscle, brain
 - ALT: liver, muscle
 - ALT & AST: massive rises ischaemic and toxic hepatitis. Alcoholic hepatitis AST > ALT, and AST rarely > 500
 - GGT: ETOH, liver, pancreas, kidneys
 - ALP: Liver and bone, late pregnancy
 - LDH: ischaemic/necrotic tissue in any part of the body (MI, pneumonia, haemolysis, rhabdomyolysis, ischaemic gut)
- Causes of ↑ammonia:
 - Liver failure
 - Porto-systemic shunts
 - ↑protein load: TPN, GI bleed
 - Gastric bypass
 - Cancer: myeloma
 - Infection with urease splitting organisms: proteus
 - Inherited disorders of the urea cycles
 - Drugs: valproate, carbamazepine, glycine, chemotherapy

Prognosis in Liver Failure

- Kings College Hospital Prognostic Criteria/O'Grady criteria (not validated for Wilson's, Budd-Chiari or pregnancy related):
 - Paracetamol related (based on case series in the 1970s):
 - Acidosis (pH < 7.3) or

- Prothrombin time > 100 seconds (INR > 6.5), and creatinine > 300 mmol/l and grade 3 - 4 encephalopathy all within 24 hr time frame
- Non-paracetamol:
 - Encephalopathy + one of:
 - Age < 10 or > 40
 - Bilirubin > 300 mmol/l
 - Time from jaundice to encephalopathy > 7 days
 - Either non-A non-B (ie seronegative hepatitis) or drug induced
 - Prothrombin time > 50
 - Or, prothrombin time > 100/INR > 6.5
 - Or, pH < 7.3 following volume resuscitation
- Child-Pugh score:
 - Hepatic encephalopathy
 - Ascites
 - Serum Albumin
 - Total bilirubin
 - INR
 - → Score 5 to 15. A 5-6, B 7-9, C 10-15, corresponds to 1 year mortality of 29%, 38% and 88%. Originally used for prognostication for surgery, also used for prognostication in chronic liver disease and prediction of likelihood of complications of cirrhosis
- Biopsy Scoring:
 - Grade: inflammatory activity by Histologic Activity Index (HAI): 0 – 18
 - Stage: progression by degree of fibrosis (0 – 6)
- MELD Score: uses bilirubin, creatinine and INR. Initially developed to predict 3 month mortality post TIPS. Now used for prognosis of liver disease and prioritising liver transplant recipients
- Once a patient hits intensive care, global scores are more accurate than a liver specific score (eg SOFA better than Child Pugh) or MELD. Still not accurate enough for individual prognostication

Acute Viral Hepatitis

- 40 – 70% of ALF worldwide
- Hep A:
 - Rarely leads to ALF, but is common, so contributes 10% of cases
 - Diagnosis: IgM antibody to HAV
 - Relatively good prognosis, but worse with age
- Hep B:
 - Majority of viral hepatitis
 - Immunologically mediated with active destruction of infected hepatocytes
 - Diagnosis: HBcAb to core antigen. HBsAg may be negative by presentation. DNA
 - If steroids or chemotherapy consider reactivation of Hep B – consider prophylactic antivirals
 - May be Hep D super-infection
- Hep C:
 - Usually chronic liver disease. Rarely results in ALF
 - Hep E: Diagnosis IgM antibody
- Others: CMV, herpes simplex 1 and 2, zoster, EBV, measles. Rare for these to cause ALF, more likely if immune compromised

Acute on Chronic Liver Disease

- Commonest scenario presenting to ICU
- Chronic liver failure needing ICU care is a very heterogeneous group in terms of outcomes – don't put them in the same basket:
 - Sepsis + CLF + 2ndary organ failure has high mortality
 - Variceal bleeding generally does well
 - Bad encephalopathy only does even better
- Acute deterioration more likely to be rescuable than someone who's been languishing on the ward for weeks. Specific reversible causes should be considered (sepsis or alcoholic hepatitis). Cases unlikely to benefit include:
 - Multiple alcoholic relapses
 - Very malnourished
 - Chronic on-going decompensation

- Common presentations:
 - Encephalopathy
 - Sepsis, including spontaneous bacterial peritonitis (albumin on day 1 and 3 → ↑survival and ↓RF, NEJM 2000, is this just due to volume resuscitation or to specific properties of Albumin?)
 - Renal failure
 - Variceal bleeding
 - Cardiorespiratory failure
- Try and find a cause of decompensation:
 - Sepsis
 - Dehydration
 - Drugs (eg opiates/sedatives)
 - Hepatocellular carcinoma: check α -feta-protein. Therapies have improved significantly, transplant can be curative
 - Portal vein thrombosis
 - Alcoholic hepatitis: high risk patients benefit from steroids. No benefit from antioxidants
- Do not usually develop ↑ICP with encephalitis. Aim to ↓ ammonia levels with bowel cleansing (eg lactulose). Little evidence base for any particular option.
- Protein restriction no longer supported – RCT of early vs slow introduction of protein showed no ↑ in encephalitis.

Encephalopathy in Liver Failure

- Encephalopathy required for diagnosis of ALF
- Spectrum from mild confusion to deep coma, cerebral oedema and ↑ICP
- Modified Parsons-Smith scale:

	Clinical	Neuro signs	GCS
0	Normal	Only on formal testing	15
1	Trivial lack of awareness	Tremor, apraxia, incoordination	15
2	Lethargy, disorientation, personality change	Asterixis, ataxia, dysarthria	11-15
3	Confusion, somnolence, responsive to stimuli	Asterixis, ataxia	8-11
4	Coma	Decerebration	<8

- Can progress quickly (anticipate if transporting and tube)
- Pathophysiology:
 - Presumed build-up of toxins, particular ammonia
 - Leads to glutamine intracerebral accumulation → cerebral oedema
 - Development of encephalitis is associated with ↑inflammatory markers. No yet clear whether anti-inflammatory treatments will help encephalitis
- Cerebral blood flow:
 - Marked variability in patients with ALF
 - Hyperventilation has no proven role, except in ↑ICP. Difficult balance in acute lung injury
- Adding rifaximin (1,200 mg/day) to lactulose in RCT of 120 patients → ↓encephalopathy, ↓mortality, shorter LOS (Sharma, Am J Gastro 2013)
- Evidence by extrapolation from neurosurgical literature:
 - Prophylactic tubing for Grade 3/4 coma. Sedate with opiod and propofol
 - Aim for cerebral perfusion pressure > 60. May not autoregulate, so ↑BP may → ↑cerebral blood flow may → ↑cerebral oedema
 - Treat sustained rises in ICP above 25 with bolus mannitol 0.5 g/kg with an appropriate diuresis, NaCl and propofol. Maintain osmolarity at < 320 mosmol to avoid damage to the blood brain barrier
 - Once study showed hypothermia → ↓cerebral blood flow, ↓ICP and ↓ammonia uptake – contentious – controlled studies awaited. Avoid fever
 - IV indomethacin (0.5 mg/kg) beneficial in one trial
- Measurement of ammonia:
 - Normal values can't exclude encephalopathy
 - Levels > 150 – 200 μ mol/L and the failure for this level to fall with treatment are poor markers
 - Very high levels may indicate cerebral herniation
 - Also elevated in TPN, GI bleed, steroid use, porto-systemic shunts, inborn errors of metabolism

Coagulopathy in Liver Failure

- ↑prothrombin time and to lesser extent activated partial thromboplastin ratio (APTR)
- May small response to IV vitamin K – usually tried
- Consumptive thrombocytopenia
- Bleeding only in severe coagulopathy with low fibrinogen and ↓↓thrombocytopenia
- Coagulation factors not routinely given (compromises monitoring of INR), but use for major bleed and prophylactically before major procedures. Plasma products + platelets and recombinant factor VII both used

Cardiovascular Support in Liver Failure

- Frequently have hyperdynamic circulation with peripheral vasodilation and central volume depletion
- Volume responsiveness can be difficult to assess – dynamic better than static assessment
- If requiring pressors, consider adrenal dysfunction. Short Synacthen test with 250 µg ACTH and test at 30 and 60 minutes. If subnormal, hydrocortisone replacement for 10 days
- In cardiovascular failure, the preference between noradrenaline vs vasopressin vs terlipressin is unclear – should use ICP monitoring (although hasn't been shown to improve outcome – like most monitoring devices in isolation. Complication rate ~ 10%)

Renal Support in Liver Failure

- Liver failure → ↑risk of AKI, due to eg portal hypertensive bleeding and sepsis, medications
- Renal failure common (up to 50%), especially in paracetamol poisoning
- Early dialysis to control fluid and limit acidosis. Use bicarbonate buffers as the liver can't metabolise lactate or acetate.
- Optimal filtration 35/ml/kg/hr
- Ultrafiltration effective at clearing ammonia (Clearance highly correlated with urea clearance). (Slack, Liver Int, 2013)
- Difficult balance between anticoagulation and coagulopathy: ?regional heparin or citrate, low dose systemic heparin
- Hepatorenal syndrome:
 - In severe acute or chronic liver dysfunction in the absence of other causes; other causes are still more common:
 - Acute tubular necrosis 2nd to sepsis or paracentesis-induced or diuretic-induced hypovolaemia
 - ↑intra-abdominal pressure
 - alcoholic cardio-myopathy or alcoholic hepatitis
 - These can directly cause AKI due to hypovolaemia, HRS can't then be diagnosed. So accurate fluid assessment important
 - Exclude normal prerenal, renal and post-renal causes.
 - Diagnosis based on history of deteriorating renal function in the presence of severe liver disease, low urinary Na (< 10 mmol/l), oliguria, unremarkable urinalysis and sediment, absence of obstruction and exclusion of intravascular depletion
 - ?2nd to severe renal vasoconstriction and Na retention. Hypovolaemia and ↑intra-abdominal pressure 2nd to ascites may also contribute
 - Two types:
 - Type 1: rapidly progressive renal failure with a Cr doubling time < 2 weeks, poor prognosis, median survival < 1 month without transplant
 - Type 2: moderate, steady deterioration in renal function, better prognosis
 - Treatment of type 1:
 - Avoid known precipitating causes
 - Avoid nephrotoxins
 - **Maintain volume:**
 - Volume expansion
 - Discontinue diuretics
 - **Vasoconstriction** to ↑MAP → ↑renal perfusion:
 - Drugs with varying degrees of evidence: α agonists (midodrine orally, 7.5 – 12.5 mg tds), noradrenaline, vasopressin analogues, and octreotide
 - Recent data to suggest that terlipressin (1 – 2 mg IV bd) may → ↑GFR (vasopressin derivative)
 - Small trial evidence to suggest terlipressin = noradrenaline and noradrenaline much cheaper (Gosh, Liver Int, 2013)

- ↑Intra-abdominal pressure may ↓renal perfusion. Consider large volume paracentesis with plasma expansion with albumin (8 gm Albumin per litre)
- RRT has not been shown to alter outcomes except as a bridge to liver transplantation
- TIPS may offer a survival benefit in those unsuitable for transplant or with a long wait for a donor

Nutrition in Liver Failure

- Commence early
- If large aspirates (> 200 ml/4 hours) use a prokinetic agent (erythromycin 250 mg iv 6 hourly likely more effective than metoclopramide)
- Consider post-pyloric feeding tube in refractory aspirates (but delay if ↑ICP)
- If profound coagulopathy, avoid nasal bleeding with oral placement
- Optimal nature of feed unclear, but likely to have ↑caloric requirements
- Usually have peripheral and hepatic insulin resistance, tight glucose control reasonable not proven

Other Supportive Care in Liver Failure

- Very few specific treatments except NAC in paracetamol poisoning
- Acidosis may be due to:
 - Lactic acidosis: either due to hypovolaemia or inability of liver to metabolise. Failure of lactate to resolve with fluid loading a poor prognostic sign
 - Hyperchloraemic acidosis
 - Renal failure
- Pancreatitis is common – look for it
- Respiratory:
 - Ventilatory support is usually for coma rather than hypoxia (at least initially)
 - Respiratory complications include pleural effusion and intrapulmonary shunts. ARDS may be precipitated by sepsis or inflammation
 - Hepato-pulmonary Syndrome: Liver Failure Related Syndromes, page 182
- Sepsis is common. ALF → functional immunosuppression due to ↓cell mediated immunity, complement and phagocytosis. Avoid nosocomial infection. Consider prophylactic antifungals, especially if listed for transplant
- Hyponatraemia is detrimental. RCT showed benefit for Na between 140 and 150, using boluses of 30% hypertonic saline for episodes of ICP > 25
- TIPS Procedure - Transjugular Intrahepatic Portosystemic Shunt:
 - Stent placed via the jugular from the hepatic to a branch of the intra-hepatic portal vein. → ↓portal pressure
 - Indications: Varices and ascites resistant to medical therapy
 - Uses guide wire and dilators to place a stent. Usually successful in > 90%. → significant ↓ in variceal bleeding
 - Unlike shunt surgery, TIPS does not reduce the chance of future liver transplantation
 - Complications:
 - Intra-abdominal haemorrhage
 - Thrombosis
 - Stent occlusion
 - Capsular puncture
 - Bleeding
 - Hepatic encephalopathy in 25 – 60%
 - Stent migration
- Molecular Absorbents Recirculation System (MARS):
 - = “Liver Dialysis”
 - Albumin is dialysed against blood, removing albumin bound toxins (eg ammonia, bile acids, bilirubin, copper, iron and phenols)
 - This albumin is then “cleaned” and recirculated
 - ?No additional benefit compared to simple dialysis against albumin (Single Pass Albumin Dialysis) with respect to bilirubin. Haemodialysis is better at removing ammonia
 - RELIEF Trial, Hepatology 2012, in acute on chronic liver failure, RCT of 189 patients, no difference in mortality over standard treatment
 - Saliba (Annals of Int Med 2013) – no difference in 6 month survival between MARS and standard treatment in 102 patients

Paracetamol toxicity

- Paediatric dose: 15 mg/kg 4 hourly to a max of 90 mg/kg/day for 48 hrs then 60 mg/kg/day following
- Blood levels correlate with severity of hepatic injury – levels > 300 µg/ml 4 hrs after predict severe injury, levels < 150 suggest significant injury unlikely
- Mechanism:
 - Predominantly metabolised by a phase 2 reaction to sulfate and glucuronide metabolites. These pathways become saturated in toxicity
 - Small amount metabolised by CYP450 2E1 forming toxic metabolite is NAPQI (N-acetylbenzoquinone-imine). The amount of NAPQI will vary according to genetic profile
 - This is detoxified by binding to glutathione which is then renally excreted. This continues until glutathione is depleted
 - If ↑NAPQI or ↓glutathione then accumulation → hepatic injury
- Increased risk in chronic alcohol (→ enzyme induction → ↑NAPQI production, also alcohol → ↓glutathione production), enzyme inducing agents (phenytoin, carbamazepine, rifampicin) and glutathione-deplete patients (eg anorexics)
- Increased risk of chronic toxicity in:
 - Unintentional multiple overdosing
 - Fasting/dehydration/vomiting
 - Renal or hepatic failure
 - Enzyme inducing or hepatotoxic drugs
- Management:
 - Lavage, activated charcoal – rarely helpful
 - NAC:
 - No RCTs in paracetamol toxicity, although there are early vs late studies
 - Acts by providing a reservoir of sulfhydryl groups to bind toxic metabolites or by stimulating synthesis of glutathione (ie acts as a glutathione surrogate)
 - No harm from waiting 4 hours to commence treatment. So safe to do a 4 hr level then treat.
 - May help up to 36 hours
 - Value of NAC in people presenting after 24 hours with transaminitis controversial
 - 150 mg/kg in 5% dextrose over 15 mins (slower if hypotension), 50 mg/kg over 4 hours, 100 mg/kg over 16 hours – total 300 mg/kg. Repeat last dose until INR < 2
 - Side effects are generally rare and minor. Rash, angio-oedema, bronchospasm on bolus treated with slowing infusion, antihistamines and bronchodilators
 - Also trialled in alcoholic hepatitis in addition to steroids with trend to benefit (Nguyen NEJM 2011)
 - Cysteamine and methionine have also been used to prevent hepatotoxicity but less effective and more adverse events
- Transplant:
 - Melbourne practice no to transplant – to be of benefit need to do it early – so you will transplant people who actually don't need it, and this carries the harm of transplant for those who would have survived without it. On balance, no benefit
 - Biochemical indicators for transplant are:
 - pH < 7.3 or lactate > 3.0 after adequate resuscitation, or
 - If all of the following occur within a 24 hour period: Cr > 300, Pt > 100 (INR > 6.5), Grade 3 – 4 encephalopathy

Liver Transplant

- See Transplant Hot Case, page 373
- 1 year survival > 90%
- Indications have widened and contraindications decreased. Portopulmonary and hepatopulmonary syndromes are now an active indication for transplantation as opposed to a contraindication – but likely to have a more complex post-operative course
- Patients in acute failure in ICU already on vasopressors have 1 year survival < 50%. Average is ~90%
- Sicker patients:
 - Long waiting times ⇒ patients usually critically ill before a transplant
 - Once multiorgan failure has developed in a debilitated patient awaiting transplant, survival rates decrease to 20 – 30%
 - Acute liver failure the riskiest: very sick, and more likely to be given marginal organs or even ABO blood incompatible organs. Use King's College Hospital prognostic criteria to identify those at high

risk and spare those in whom spontaneous recovery will otherwise occur (see Prognosis in Liver Failure, page 174)

Anatomical considerations

- Operative Technique:
 - Vena Cava preservation: piggyback technique. Haemodynamically stable during the anhepatic phase, ↓ transfusion requirements, shorter anhepatic time
 - Portal bypass: internal, temporary portocaval shunt or external veno-venous bypass
 - Split liver if anatomy and size match allow. ↑ rate of bile leaks and haematoma/collections at the cut surface
 - Auxiliary liver transplant: subtotal hepatectomy and implantation of a reduced sized graft. Technically difficult. But may allow regeneration of the native liver allowing withdrawal of immunosuppression
 - Radiologist needs to be aware of the technique used, and the type of grafts used (end to end, right or left split, auxiliary, etc.)
- DCD donation: survival is approaching that for brain dead donor. Prolonged cold ischaemia, and warm ischaemia > 30 mins, is associated with poor graft function and biliary complications
- Living donor-related transplantation is now routine in paediatric liver transplantation. Morbidity rates for donors higher with right lobe donation compared with left. Survival in recipients 80% at 12 months
- 'Small for size' syndrome: also a feature of liver resection. Portal flow passing into a small remnant or graft → arteriolar constriction. ↑ Bilirubin, graft dysfunction, ascites, and portal HTN

Intraoperative Haemodynamics

- Surgery associated with massive blood loss: pre-operative coagulopathy portal hypertension, surgical technique, intraoperative changes in haemostasis, activation of fibrinolytic system, platelet dysfunction, ↓ Ca due to citrate intoxication, acidosis, hypothermia...
- Supported by cell salvage techniques common, antifibrinolytic drugs
- Some patient groups are pro-thrombotic: those with pre-op portal venous thrombosis have a higher incidence of prothrombotic mutations, those with biliary cirrhosis and primary sclerosing cholangitis are frequently pro-thrombotic
- Post-reperfusion syndrome: after reperfusion of the portal vein through the donor graft. Release of vasoactive substances and cold potassium rich preservation fluids → hypotension, bradycardia, vasodilation, ↑ K. Usually settles over 5 mins

Post-operative care

- Early complications:
 - Technical complications
 - Conditions associated with pre-existing liver disease
 - Immunosuppression
 - Graft function
 - Massive transfusion
 - Coagulopathy: target INR < 2, APPT < 50, plts > 30
 - Overload: attempt negative fluid balance on the first day → ↓ pulmonary complications and ↓ graft congestion
- Cardiovascular:
 - End stage liver disease has hyperdynamic circulation with low SVR, high CI, and low circulating volume
 - Cirrhotic cardiomyopathy is often revealed: abnormal myocardium in the presence of liver failure (unrelated but additional to effects of alcohol).
 - Liver transplant → severe cardiovascular stress: haemorrhage, 3rd space loss, impaired venous return due to caval clamping, hypocalcaemia, acidosis....
 - Post-transplant:
 - HTN from ↑ SVR due to restoration of liver function and portal pressure
 - HTN from calcineurin immunosuppressants
 - ↑ afterload may unmask cardiac dysfunction
 - → diuretics, afterload reduction and positive pressure ventilation
- Pulmonary:
 - Complications occur in 40 – 80%
 - Early weaning (if possible) associated with better outcomes but not possible if unstable, pulmonary oedema, severe encephalopathy, primary graft dysfunction

- Preoperative impairment (pleural effusions, hypoxaemia, pulmonary HTN, poor muscle bulk/weakness) associated with post-operative problems
- Specific complications: R hemidiaphragm palsy, pleural effusions, ongoing shunting 2nd to hepatopulmonary syndrome, atelectasis and infection
- De novo ARDS uncommon
- Management of porto-pulmonary syndrome if R sided pressures elevated to ensure that liver congestion (→ graft dysfunction) is minimised
- Neurological:
 - Most commonly persistent encephalopathy in those with pre-transplant encephalopathy
 - Multifactorial: hepatic, metabolic, infectious, vascular and pharmacological (eg high dose steroids for rejection, sedatives, analgesics, calcineurin inhibitors → seizures, etc.)
 - Consider intracerebral haemorrhage. Infectious complications usually later
- Renal dysfunction:
 - Acute kidney dysfunction common post-operatively
 - Multifactorial:
 - Pre-op dysfunction: HTN, diabetes, hepatorenal syndrome
 - Intraoperative instability
 - Blood product requirement
 - Drug toxicity
 - Graft dysfunction
 - Intra-abdominal hypertension
 - Mycophenolate may be substituted in the post-transplant course to limit renal dysfunction
- Primary non-function:
 - Poor graft function from the time of reperfusion, with ↑lactate, coagulopathy, metabolic acidosis, ↓glucose, ↑K and a rapid rise in transaminases
 - Major contributor is ischaemic injury to the graft: depends on preservation fluid, and duration of warm and cold ischaemic time
- Surgical problems:
 - Abdominal bleeding:
 - Anastomosis
 - Graft surface if cut down
 - General ooze 2nd to coagulopathy
 - Pseudo-aneurysm formation
 - Vascular complications:
 - Anastomotic thrombosis uncommon. Small vessel calibre is a risk factor. Ultrasound is routine post-operatively and if there is a sudden rise in LFTs. If the vessel is not visualised → CT angiography
 - Venous complications: portal thrombosis even more uncommon. Also consider inferior vena-caval obstruction
 - Biliary complications relatively common:
 - Bile duct normally receives 2/3rds of its supply from the gastroduodenal artery. Post-transplant it is all from the hepatic artery → vulnerable to ischaemic injury
 - Strictures are more common than leaks
- Acute rejection:
 - A risk from 5 – 7 days post-transplant
 - Signs non-specific: include fever, ↓graft function, rapid ↑ in LFTs
 - Liver biopsy the only reliable diagnostic tool – but may be contraindicated due to coagulopathy (may use trans-jugular approach)
 - Treatment: Pulsed methylprednisolone 1 g for 3 days
 - Differential: sepsis, problems with vascular integrity. Procalcitonin may be of use in the differentiation
- Sepsis and fever:
 - Uniquely vulnerable to bacterial infection: pre-operative colonisation, prolonged surgery, large wounds, lots of lines
 - Changing epidemiology:
 - G+ive bacterial infection (enterococci and staph) now more common than G-ive sepsis
 - Emergence of multi-resistance bacteria: MRSA, VRE, ESBL
 - Decline in pneumocystis jiroveci and CMV due to better immunosuppressive regimes and prophylaxis

- Still at risk from HSV, CMV and opportunistic fungal infections. Aggressive recurrent HCV cirrhosis a late complication in 20%
- Fever:
 - Usually infectious, exclude acute rejection
 - Immunosuppression → not always a febrile response to infection
- Immunosuppression:
 - Immunosuppression, especially steroids → ↑HCV viral load. Convert to single-or double agent immunosuppression as soon as possible. Role of antiviral therapy (interferon and ribavirin) unclear
 - Acute rejection after 5 – 7 days → resembles delayed-type hypersensitivity syndrome
 - Chronic rejection over months to years → “vanishing bile duct syndrome”
 - Mainstay of drugs:
 - Steroids
 - Calcineurin inhibitors: cyclosporin and tacrolimus. Limited by neuro and nephro toxicity
 - Switching to azathioprine or mycophenolate
 - Antilymphocyte antibodies (ALA) for 10 - 14 days post-transplant may allow the delay of introduction of calcineurin inhibitors in renal failure
 - IL-2 monoclonal antibodies increasingly used: bind to IL-2 receptors which are only present on activated T-cells
 - Sirolimus: substitute for tacrolimus. Structurally similar, different mechanism, but same result (↓IL-2 dependent proliferation). Also an antifungal and antiproliferative agent. No neuro or renal toxicity. However, can potentiate cyclosporin toxicity, ↑lipids, ↓platelets, ↓WBC, ↓RBC, poor wound healing
- Housekeeping: analgesia, nutrition

Liver Failure Related Syndromes

- Hepatopulmonary syndrome:
 - Due to vascular dilation at the pre- and post-capillary level → decreased VQ ratios
 - Intrapulmonary vasodilation with R → L shunting, mainly affecting lung bases, so worsens with sitting up due to ↑basal blood flow → ↑shunt
 - Diagnostic criteria:
 - Chronic liver disease +/- cirrhosis
 - Arterial hypoxaemia
 - $\text{PaO}_2 < 75$ or Aa gradient > 20
 - Intrapulmonary vascular dilation
 - Diagnose with contrast echo. Agitated saline injected IV. Immediate visualisation in L heart ⇒ intracardiac shunt. Delayed visualisation ⇒ intrapleural shunt
 - Medical management disappointing → indication for transplant with resolution usual in the months afterwards. However, the more hypoxic the greater the perioperative risk
- Porto-pulmonary hypertension:
 - Diagnostic criteria:
 - Portal hypertension
 - Mean pulmonary artery pressure > 25
 - Pulmonary artery occlusion pressure < 15
 - Pulmonary vascular resistance $> 120 \text{ dynes/s/cm}^5$
 - Usually due to increased pulmonary flow, not increased resistance – these patients do well
 - In $< 4\%$, pulmonary hypertension is due to ↑pulmonary vascular resistance 2nd to pulmonary vasoconstriction. More serious. Trials of post-transplant treatment with epoprostenol (a PGI₂ analogue) encouraging

Abdominal Surgical Catastrophes

- See also Procoagulants, page 297, for control of bleeding
- Often in elderly patients with comorbidities and reduced physiological reserve
- Often associated with sepsis and subsequent multi-organ failure
- Few controlled trials
- Potential for conflict between intensivists and surgeons who occupy “different moral economies”!
- OPTIMISE Trial, NEJM May 2014, MRCT, n = 734, undergoing major abdominal surgery and aged > 65 at high risk of cardiac or respiratory disease. Standard care vs fluid/inotrope regime using CO LiDCO monitor to 6 hours post-op. Fluids included colloids. 43 vs 36% rate of “minor or major complications” at 28 days. Non-significant. Incorporated into a meta-analysis which showed benefit.

Abdominal Aortic Aneurysm

- M:F = 6:1 (although women's grow quicker). Disease of the elderly
- AAA = infra-renal aorta > 30 mm. 1% in 50 year olds, 10% in 80 year olds
- Expansion ~ 0.3 cm/year < 5 cm and 0.5 cm/year > 5 cm
- Risk of rupture < 1% per annum < 50 mm and 17% per annum > 60 mm
- Elective open repair perioperative mortality is ~ 5%, endovascular repair ~ 1.5, but 2 year survival the same
- Urgent non-leaking repair → 15% mortality, rupture repair → 50% mortality
- Endovascular vs open repair compared in the EVAR-1 and DREAM Trials (NEJM 2010), also OVER Trial (JAMA 2009). In general, endovascular repair has early mortality benefit that disappears at 2 years. Trials started over 10 years ago – experience and technology have improved.... Tight selection criteria in the studies may reduce generalisability of the results
- EVAR-2 Trial (Endovascular Aneurysm Repair 2 trial, NEJM 2010): RCT in 33 UK hospitals of 404 patients comparing endovascular repair with no treatment for those at too higher risk for open surgery ⇒ reduced aneurysm related death, but no difference in all-cause mortality. Prophylactic repair is designed to prolong life – those at high risk due to comorbidities should not be treated. However, not clear who is high risk – likely to be a small group
- Ruptured AAA or iliac aneurysm:
 - Typically over 70
 - Sudden onset shock and back or abdominal tenderness. Pulsatile abdominal mass is not common
 - Initially usually retroperitoneal, extension to intraperitoneal → ↑physiological disturbance
 - Bedside US may introduce delay in vascular referral without benefit. Only half of those with suspected rupture are CT'ed before laparotomy given risk of sudden deterioration in the scanner
 - A small number have infection of the aneurysm with staph or salmonella
 - ICU care aims at rapid ventilator weaning +/- thoracic epidural (if coagulopathy allows)
 - Common post-operative complications include:
 - Hypothermia
 - Dilutional coagulopathy
 - Circulatory shock
 - Pre-renal failure (→ leads to persistent renal failure more commonly than other ICU patients)
 - Rhabdomyolysis in legs 2nd to ischaemia (↑LDH, ↑AST, ↑K, ↓Ca)
 - Severe or progressive multi-organ failure, or limb or organ infarction at 24 – 48 hours should prompt consideration of treatment withdrawal

Other Intra-abdominal Vascular Pathology

- Aortic dissection:
 - Risk factors:
 - Age
 - Hypertension
 - Connective tissue disorders (Marfan's syndrome, Ehlers Danlos)
 - Pregnancy
 - Cocaine use
 - Aortic coarctation
 - Aortic valve defects (eg congenital bicuspid valves)
 - PC: pain in a distribution corresponding to the site of dissection
 - Classification:
 - Stanford A: origin of the dissection in the ascending aorta before the R brachiocephalic artery (some references say proximal to L subclavian artery..?). Requires surgery as damage to the ascending aorta usually leads to AV incompetence due to loss of suspensory support
 - Stanford B: Origin distal to the subclavian artery
 - Acutely, BP control critical to prevent propagation:
 - Ensure adequate analgesia
 - Control heart rate: aim for 60 – 70/min with β-blocker (Ca blocker if β-blocker intolerant) and/or clonidine. Aim is to control rate, more than blood pressure. Progression is related to shear stress, which is worsened by frequent changes in pressure (systolic → diastolic → systolic)
 - Complications:
 - Occlusion of vascular branches: MI, stroke, paraplegia due to spinal cord ischaemia, anuria or acute abdomen
 - Acute aortic valve incompetence
 - Tamponade

- External aortic rupture
- L main bronchial compression
- Left recurrent laryngeal nerve palsy
- Acute aortic occlusion: Uncommon. Usually thrombotic. Present with painful lower limb paresis or paraplegia and absent distal circulation. Needs emergency revascularisation
- Mesenteric infarction: acute abdomen, often in critically ill patients, due to non-occlusive arterial ischaemia, embolism or atherosclerotic thrombosis. Despite surgery, mortality is high
- Spontaneous retroperitoneal haemorrhage: associate with vascular or malignant disease of the kidney or adrenal gland, rupture of retroperitoneal veins or with anticoagulation. Usually present with acute abdominal pain and shock. CT for diagnosis. Sometime radiologic embolisation can control bleeding

Intraabdominal Sepsis

- Very common in the ICU (Oh's author reports it as their most common site of sepsis)
- Common causes:
 - Faecal peritonitis
 - Diverticular disease or colonic malignancy
 - After prior anterior resection
 - Perforated upper abdominal viscus (usually GU or DU)
 - Biliary obstruction: ultrasound followed by ERCP and sphincterotomy. Cover enterococci and aerobic G-ive bacilli
 - Acalculous cholecystitis
 - Intestinal infarction
 - Appendicitis (more often presenting with perforation in the elderly)
- Management:
 - Support oxygen transport
 - Remove septic source – usually involves surgery. If shocked and peritonitis indication for urgent surgery without further investigation.
 - Initial surgery involves:
 - Removal of all peritoneal contamination
 - Drainage of abscesses
 - Resection of devitalised tissue
 - Defunctioning of the gut to prevent ongoing contamination
 - Abdomen may be left open to control intra-abdominal hypertension or facilitate repeat laparotomy
 - Failure to improve suggests ongoing contamination or ischaemia or abscess.
 - Early failure: repeat laparotomy
 - Late failure: CT scan ? abscess with positive radiologic drainage or directed laparotomy
 - Appropriate antibiotics:
 - Intestinal contamination or infarction → mixed aerobic and anaerobic infection (enterococcus, gram negatives and anaerobes) → combination triple therapy with amoxicillin + gentamicin + metronidazole (or clindamycin), or a carbapenem, or tazocin. Vancomycin, gentamicin and metronidazole if penicillin allergic
 - May consider empiric fluconazole if fungus on two non-sterile sites or one sterile site. See Fungal Infection, page 281
 - Peritonitis following gastric or duodenal perforation: consider adding staph cover

Acalculous cholecystitis

- Rare but serious
- Half the cases in ICU develop insidiously in patients ill for another reason, and can go unrecognised until gangrene, perforation or abscess develop
- Pathophysiology: bile stasis + increased viscosity → gall bladder contraction with wall ischaemia. Atherosclerosis and shock contribute
- High incidence of gangrene → perforation
- High index of suspicion required in a patient with new abdominal pain or sepsis. Variable clinical signs
- Risks include critically ill, HIV, TPN, DM, major surgery, vasculitis
- Investigations:
 - FBC, LFTs, ↑bilirubin, blood cultures
 - CT, US and laparoscopy are not uniformly reliable → low threshold for exploratory laparotomy/laparoscopy
- Treatment: early broad-spectrum coverage (eg triple cover). If too sick for surgery, could consider percutaneous drainage

Peritonitis

- Spontaneous Bacterial Peritonitis:
 - Usually a single bug: E coli, Klebsiella pneumoniae, pneumococci or enterococci, rarely anaerobes
 - In end stage liver disease:
 - SBP is a grave sign – hepatic decompensation and multi-organ failure often develop
 - Early albumin supplementation shown to ↓ renal failure and mortality
 - Treat with broad spectrum beta-lactam antibiotics, followed by prophylactic orals
- CAPD-associated Peritonitis:
 - Not uncommon in CAPD, but infrequently leads to ICU
 - Development of non-renal organ failure reflects delay in treatment, abscess formation, an unusual bug (eg fungi) or an unrecognised gastrointestinal septic source
- Tertiary peritonitis:
 - = peritonitis of the critically ill patient that persists or recurs at least 48 hours after adequate management of primary or secondary peritonitis (eg after prior laparotomy)
 - Commonly due to: enterobacter, pseudomonas, candida albicans
 - Empiric therapy should include: amoxicillin, gentamicin, metronidazole until culture results back
 - If Candida, stop other antibiotics, remove foreign bodies, and treat with amphotericin B for > 4 weeks

Toxic Megacolon

- Dilated, inflamed colon with systemic toxicity
- Presentation: diarrhoea and distension (an odd combination)
- Causes:
 - Usually inflammatory bowel disease
 - Infection: clostridium difficile, CMV (if HIV or immunosuppressed), rarely others
- Management:
 - Limited colonoscopy (despite risk of perforation) and biopsy may yield important information (eg microbiology)
 - Surgery common. May observe medical management for several days, but ↑ dilation, perforation, bleeding or ↑ toxicity → surgery with subtotal colectomy + end-ileostomy
 - Supportive care:
 - ICU
 - Antibiotics for colonic perforation
 - Steroids: equivalent of ~ 300 mg/day hydrocortisone
 - Other immunosuppression (tacrolimus, anti-TNF mabs) have been used
 - TPN in Crohn's, but doesn't reduce LOS or surgery in ulcerative colitis

Abdominal Compartment Syndrome

- Uncommon but high morbidity (~ 50%). Unclear the degree to which IAH is a cause of morbidity or an indicator of severity of underlying disease
- Unresolved about the extent to which ↓ an elevated IAP → reversal of ACS
- Definitions (disparate reported definitions):
 - Intra-abdominal hypertension: IAP > 12 mmHg
 - Abdominal compartment syndrome as IAP > 20 mmHg with associated organ dysfunction (use or a strict cut-off value is not recommended – it varies from patient to patient)
 - Abdominal perfusion pressure = MAP - IAP
- Consider if:
 - Surgery for trauma or sepsis and associated with excessive crystalloid administration
 - Abdominal trauma, pancreatitis, liver transplantation, bowel obstruction, tense ascites....
 - Tense or distended abdomen and haemodynamic instability, ↓ urine output, ↓ LOC or ↑ lactic acidosis
- Measured via intravesical pressure – normally 5 – 7 mmHg. Supine paralysed patient. Inject 25 ml into catheter via side port, wait 30 – 60 secs for relaxation of detrusor, attached pressure transducer. Measure pressure at end-expiration. Pitfalls include:
 - Increased with ↑ BMI
 - Using wrong zero point. Measure with a pressure transducer attached to a freely flowing Foley's catheter, zeroed at the level of the pubic symphysis
 - Leak in the system → falsely ↓ reading
 - Small contracted bladder (eg chronic or radiation cystitis) → low compliance and falsely ↑ IAP
 - Pelvic haematoma → tight pelvic compartment with falsely ↑ IAP
- Impacts:

- Renal: capillary and venous compression, ↓GFR, UO
- Bowel: decreased blood flow (Abdominal perfusion pressure < 50 mmHg is critical), ↓pH, bowel ischaemia, congestion 2nd to ↑mesenteric pressure, ↑translocation of bacteria
- Hepatic: ↓portal flow, ↓lactate clearance
- Cardiac: ↓venous return → ↓cardiac output, elevated afterload
- Respiratory: hypoxia from: ↑Paw, ↓FRC, atelectasis, V/Q mismatch, ↑work of breathing
- Cerebral: ↑ICP, ↓CPP
- Management:
 - Physiologic changes with IAP > 12 but expert opinion is that decompressive measures should be pursued for IAP > 20
 - Urgent decompressive laparotomy
 - Avoidance of prone position
 - Gastric and colonic decompression
 - Neostigmine and other prokinetic agents
 - Sedation or neuromuscular blockage → ↑abdominal wall compliance
 - Diuresis or ultrafiltration or draining of intraperitoneal fluid
- Crit Care Medicine 2010, Cheatham et al, prospective observational single-centre study of 478 consecutive patients into a pathway for management of abdominal compartment syndrome. ↓mortality and ↑rate of primary closure in patients with more aggressive intervention (early opening of abdomen, prophylactic opening in high-risk patients) See wsacs.org

Complications of Abdominal Catastrophes

- Open abdomen and staged abdominal repair:
 - Synthetic materials permit temporary fascial closure to facilitate repeat laparotomy and staged repair
 - Mesh for < 1 week open; for > 1 week non-adherent material to prevent adherence and minimise the risk of perforation during removal
- Enterocutaneous fistulas: intestinal, biliary and pancreatic
 - Rare but difficult complications
 - Usually associated with severe intra-abdominal pathology (IBD, malignancy, pancreatitis) +/- sepsis
 - Complex fistulas and multiple collections often present
 - Management:
 - Drainage of abscess
 - Control of fistula by drainage
 - Proximal defunctioning
 - Protection of skin from fistula fluid
 - Nutritional support: TPN for proximal small bowel fistulas, EN probably OK for the rest
 - Replacement of fluid and electrolyte losses
 - Somatostatin analogues can reduce high output small-bowel fistula losses, and H2-blockers are used in intestinal or pancreatic fistulas, efficacy in achieving closure is unclear
- Colonic pseudo-obstruction:
 - Severe form of colonic ileus
 - Leads to:
 - Ventilatory difficulty
 - Intra-abdominal hypertension
 - Failure of enteral feeding
 - Small risk of perforation
 - Conservative management:
 - NG drainage
 - IV fluid replacement
 - Avoidance of opioids and anticholinergics
 - Neostigmine effective but may → bradycardia

- See: An Official ATS/ERS/ESICM/SCCM/SRLF Statement: Prevention and Management of Acute Renal Failure in the ICU Patient, An International Consensus Conference in Intensive Care Medicine, Am J Respir Crit Care Med, 2010
- Renal dysfunction occurs in 15 – 20% of ICU patients. Even a small rise in Cr is associated with ↑ mortality
- Preferred term is *Acute Kidney Insufficiency* (AKI)

Acute Kidney Insufficiency

Physiology

- Kidney and oxygen:
 - Kidney is one of the bodies key O₂ sensing organs (⇒ EPO)
 - Kidney gets 25% of CO for only 1 % of body weight – this is a huge O₂ load. Needs protective mechanisms (like the lung)
 - Glomerular can shunt blood past glomeruli or through segments of it. If you try and deliver more O₂, kidney is well able to send it away. At the same time, the medulla is at risk of hypoxia....
- Sepsis:
 - Abnormal state
 - Renal blood flow is dissociated from GFR ⇒ intra-renal shunting
 - We have no idea how to manipulate kidney blood flow – or if this would be desirable
- Decline of renal function characterised by:
 - ↑ End products of nitrogen metabolism (eg urea and creatinine) – insensitive markers, modified by nutrition, steroids, presence of GI blood, muscle mass, age, gender, muscle injury. Only start becoming abnormal when > 50% of GFR is lost. Use of creatinine clearance measurement doesn't usually change management, radio-nucleotide tests are cumbersome in ICU
 - Urine output as a predictor of ↑Cr tomorrow has a sensitivity of ~ 60% (basically a toss of a coin)
 - Accumulation of non-volatile acids
 - ↑K and PO₄ concentration
- Acute tubular necrosis is increasingly being challenged as a clinical diagnosis in the setting of prerenal azotaemia –the two cannot be connected clinically, and doubt exists in animal studies. Pre-renal hypoperfusion is associated with a wide range of innate, vascular and immune mediated insults to the kidney falling on a continuum from sublethal injury to apoptosis to necrosis

Classification of Acute Renal Insufficiency

- See:
 - KDIGO Clinical Practice Guideline for Acute Kidney Injury, March 2012
 - Bellomo et al, Crit Care 2004 for criteria
- RIFLE criteria (use the worst of GFR or UO):

	GFR	Urine Output
• Risk (highest sensitivity)	• ↑Cr * 1.5 or ↓GFR > 25%	• < 0.5 ml/kg/h for 6 hrs
• Injury:	• ↑ Cr * 2 or ↓GFR > 50%	• < 0.5 ml/kg/hr for 12 hrs
• Failure (highest specificity):	• Increased Cr * 3, ↓GFR by 75% or Cr ≥ 4 mg/dl (350 μmol/l) if acute rise ≥ 0.5 mg/dl (44 μmol/l) (denoted RIFLE-Fc for acute on chronic)	• < 0.3 ml/kg/h for 24 hrs or anuria for 12 hrs

- Loss: Persistent ARF = complete loss of kidney function > 4 weeks
- ESKD = end-stage kidney disease > 3 months
- Progression down the RIFLE criteria is associated with a higher length of stay in ICU and a higher mortality
- Has been prospectively validated for classification of renal failure for research purposes
- Weaknesses of RIFLE:

- Are not specific so are not useful for predictions in individual ICU patients
- Don't include any measure of time course (for example a rise in Cr over 1 day is likely to be worse than the same rise over 4 days)
- Dependence on urine and creatinine measurement:
 - Urine output measurement can be inaccurate, and affected by diuretics
 - A number of factors other than renal function affect Cr
 - It is uncertain how to weight Cr and urine but they are given equal weighting
- Recovery is defined as complete (return to baseline) or incomplete (persistent abnormality of RIFLE criteria but discontinuation of RRT)
- Other criteria include the Acute Kidney Injury Network (AKIN) criteria and Sequential Organ Failure Assessment (SOFA) renal sub-score
- Ralib, CCM 2013, in 725 prospectively studied ICU patients < 0.5 ml/kg/hr for 6 hours \rightarrow \uparrow in renal injury in 72% (> 26 mol or 50% increase). Urine output of 0.3 ml/kg/hr best associated with mortality and dialysis

Risk Factors for Acute Renal Insufficiency

- Pre-existing conditions:
 - Age
 - Pre-existing renal disease
 - Diabetes
- Acute insults:
 - Sepsis
 - Hypovolaemia
 - Shock
 - Cardiac surgery
 - Rhabdomyolysis
 - Infusion of contrast medium
- Critical illness associated ARI requiring RRT is associated with higher in-hospital mortality (OR 3.9) compared to ESRF patients admitted to ICU. Ie don't be too harsh on people with CRF

Oliguria

- In most ICU patients, there is no "fluid depletion"
- Good evidence that more fluid will not lead to \uparrow renal blood flow
- Creatinine:
 - \downarrow Cr may just be dilutional
 - PPV of oliguria for \uparrow Cr next day is low
- Misconceptions:
 - AKI is due to renal under perfusion. Wrong. Animal and human studies show kidneys are very resistant to ischaemia from renal artery clamping
 - Giving fluids (in animal studies) to \uparrow DO₂ actually \downarrow DO₂ (from ?haemodilution). In septic animals, fluid does not \uparrow renal DO₂
- Giving fluid to \uparrow UO if euvolaemic is unhelpful:
 - \uparrow Literature that \uparrow fluid balance \rightarrow \downarrow kidney outcomes. Possible reasons include gut and kidney oedema
 - FACTT Trial of liberal vs conservative fluid in AKI
 - Brandstrup (Annals of Surg 2003): liberal vs conservative in major abdo surgery \rightarrow more fluid not helpful
- Frusemide: Frusemide "stress test". 1 mg/kg stat dose – cumulative UO at 2 hours predicts progression to AKIN III with sens 87% and spec 84% (Crit Care 2013, 17: R207)

Causes of Acute Renal Insufficiency

- See Causes of Reduced Urine Output Hot Case, page 379
- Prerenal:
 - By far the most common in ICU
 - Due to loss or intravascular volume or an obstruction of renal flow
 - Systemic factors which \downarrow GFR:
 - \downarrow Cardiac output
 - Hypovolaemia
 - Distributive shock 2nd to sepsis
 - Pathogenesis includes (no studies to show which is most important):

- Ischaemia of outer medulla
- Tubular obstruction from casts of exfoliated cells
- Interstitial oedema secondary to back-diffusion of fluid
- Humorally mediated afferent arteriolar vasoconstriction
- Inflammatory response → local release of mediators
- Disruption of normal cellular adhesion
- Treatment: treat cause while resuscitating patient using invasive monitoring to guide therapy
- If treatment delays, injury becomes “established” and may take days or weeks to recover
- Parenchymal renal failure:
 - Typical structural changes seen on microscopy
 - Pathogenesis is typically immunological. Sepsis and inflammatory response → medullary ischaemia, tubular obstruction and vasoconstriction
 - Nephrotoxins (particularly important): 20% of the most commonly prescribed ICU medications have nephrotoxic potential. Half are anti-infective agents
 - **Radiocontrast agents**: see Contrast nephropathy, page 192
 - Antibiotics:
 - Aminoglycosides: interstitial nephritis
 - Amphotericin B → renal vasoconstriction
 - β -lactam antibiotics: interstitial nephritis
 - NSAIDs
 - Cisplatin
 - Cyclosporin A
 - Tacrolimus
 - Associated with tubular precipitation of crystals:
 - Acyclovir
 - Methotrexate
 - Sulphonamides
 - Glomerulonephritis
 - Vasculitis
 - Interstitial nephritis
 - Malignant hypertension
 - Pyelonephritis
 - Amyloidosis
 - Malignancy
 - Hepatorenal syndrome: see Renal Support in Liver Failure, page 177
 - Rhabdomyolysis-associated ARF: see Rhabdomyolysis-associated ARF, page 193
- Post-renal failure
 - ↑Intra-abdominal pressure. Pressure > 25 – 30 mmHg ⇒ consider decompression
 - Bladder neck obstruction due to enlarged prostate
 - Ureteric obstruction (pelvic tumours, retro-peritoneal fibrosis, papillary necrosis, large calculi)
 - Obstruction of urinary catheter
 - Intra-renal obstruction due to crystals
 - Not all cases have abnormal ultrasound

Diagnosis of Acute Renal Insufficiency

- Post renal causes: ultrasound
- Pre-renal causes: Urine analysis is important for separating pre-renal and renal failure (eg excreted fractions of Na) - although the scientific basis for the use of urinary chemistry indices in patients with septic AKI is weak
- Intra-renal causes:
 - Check urine for infection
 - Check for nephrotoxins
 - Rhabdomyolysis: creatinine kinase and free myoglobin
 - vasculitis or GN: CXR, blood film, inflammatory markers and antibodies (anti-GBM, ANCA, anti-DNA, anti-smooth-muscle)
 - If TTP possible: LDH, haptoglobin, unconjugated bilirubin and free haemoglobin
 - Myeloma: Bence Jones proteins
 - Possibly renal biopsy
- Urine sediment may represent an additional surrogate for structural injury to tubular epithelial tissue. A Urine Microscopic Score (UMS) is proposed

- Bio-markers:
 - Creatinine is recommended as the primary guide. Need to consider factors affecting creatinine: body size, catabolic state, rhabdomyolysis, and dilutional effects. Impact of sepsis on kinetics of creatinine is unclear
 - Blood urea nitrogen (BUN): affected by even more factors but correlates better with uraemic complications
 - Cystatin-C: undergoing evaluation. Produced by all cells. Is filtered across the glomerulus but not secreted by renal epithelial cells (creatinine is). Rises earlier than Cr in patients with AKI
 - Urinary Neutrophil Gelatinase (NGAL): a polypeptide that is rapidly upregulated in renal epithelial tissue in response to distal nephron injury. Levels are measured in urine and plasma; concentration \uparrow in dose-dependent fashion with severity and duration of acute tubular injury. Observational studies suggest it is a sensitive biomarker for anticipating (by 24 – 48 hrs) the occurrence of conventionally diagnosed AKI. Findings not universal. Difficult to study given a suboptimal surrogate marker (Cr) is the “gold standard”
 - Other markers assessed for ability to discriminate pre-renal from renal failure. Discriminating ability not high. Includes, kidney injury molecule-1 (KIM) and interleukin-18. Need further assessment
- Urea-Creatinine Ratio (in mmol/L to mmol/L [not μ mol], as opposed to American units mg/dl to mg/dl):
 - Normal is 50 – 100: 1
 - Ratio $> 100:1$ suggests pre-renal problem. Urea reabsorption is increased so ratio moves in favour of creatinine
 - Ratio $< 40:1$ suggests intra-renal problem (intra-renal damage lowers urea reabsorption $\rightarrow \downarrow$ ratio)
 - Increased: dehydration (excretion of urea is dependent not only on GFR, but also on the urine flow rate. GRF decrease $\rightarrow \downarrow$ urine flow rate $\rightarrow \uparrow$ urea absorption), GI bleeding, high protein diet, corticosteroids, severe catabolism, tumour lysis, low muscle mass
 - Decreased: low protein diet, malnutrition, severe liver dysfunction, pregnancy (haemodilution), SIADH, rhabdomyolysis, high muscle mass
- Random notes on urine analysis:
 - Fractional excretion of sodium (FeNa) and fractional excretion of urea correlate poorly with development of worsening AKI
 - Specific gravity of urine = weight of solution over weight of the same volume of water. A proxy for concentration or osmolality (although osmolality measures only number, not weight of particles).
 - Urine osmolality also includes all osmotically active particles, including mannitol, radiocontrast and glucose

Complications of Acute Kidney Insufficiency

- Acid base disturbances:
 - \downarrow Chloride excretion
 - Accumulation of organic anions such as phosphate
 - Decreased albumin
- High K
- Volume overload:
 - Pulmonary, cerebral and peripheral oedema
 - GI \rightarrow compartment syndromes, bleeding, poor absorption
- Acute lung injury: neutrophil activation and sequestration in the lung \rightarrow ALI
- Uraemia
- Haematological/immunological: WBC dysfunction, \downarrow erythropoietin, \downarrow von Willebrand's factor
- Patients with AKI are more likely to have future chronic renal disease, even if the AKI resolves

Prevention of Kidney Insufficiency

- Reduce nephrotoxic drugs:
 - Choose the least nephrotoxic drug
 - Reduce duration
 - Dose adjust according to Cr clearance (note – formula are only useful when Cr is in steady state – eg advanced renal disease. In ICU will be potentially confounded by \uparrow clearance if hyperdynamic state and volume expansion ($\rightarrow \uparrow V_d$))
 - Monitor serum levels (eg antibiotics) and reduce dose if high
 - Give aminoglycosides once daily
- Fluid resuscitation:
 - AKI involves multiple mechanisms: correction of hypovolaemia will not always prevent renal failure
 - Maintain intravascular volume, oxygenation and haemoglobin (> 70 g/L)

- Complicated by the absence of practical tests to quantify renal blood flow
- No studies specifically designed to test the impact of resuscitation strategies on renal function. A study of the impact of pulmonary artery catheters found more AKI in the treatment group on day 3 despite more fluids. FACTT Trial of PAC in ARDS with conservative and restrictive fluid strategies found conservative strategy lead to less RRT (although patients with overt renal failure excluded from enrolment)
- No benefit for hypo-oncotic colloids (gelatins and 4% albumin) over crystalloids for protecting kidneys, except in liver disease. Hyper-oncotic colloids (dextran, HES and 20% albumin) carry a risk of renal dysfunction
- MAP:
 - It is unknown whether the current recommendation to maintain a MAP ≥ 65 in critically ill patients is sufficient for preventing AKI
 - \uparrow MAP to near normal levels may \uparrow GFR (but requires vasopressors). If hypertension or renovascular disease 75 – 80 may not be sufficient. Titration of vasopressors to MAP of 85 vs 65 tested in two small trials (one of 10 patients). Increased cardiac output but no difference in urine output or CrCl.
 - Impact on renal blood flow is inferred from changes in urine output, serum creatinine and/or creatinine clearance
 - Which vasopressor: No recommendation can be made. VASST study (800 patients with sepsis) showed vasopressin compared to noradrenaline may reduce progression to AKI only in those with less severe shock, but no difference in need for RRT. Studies Comparing Inotropes, page 45
- Benefits of “nephroprotective drugs” unclear:
 - Bellomo et al, Low dose dopamine in patients with early renal dysfunction, DOPAMINE Trial, Lancet 2000, no place for “renal-dose” dopamine in patients with SIRS and early acute renal dysfunction. First major ANZICS CTG study. Is a tubular diuretic and may \uparrow UO (which may be incorrectly interpreted as an \uparrow GFR)
 - Mannitol: No controlled human data
 - Diuretics:
 - Not recommended for the prevention or treatment of AKI, except for management of fluid overload
 - Hypothesised that they protect the loop of Henle from ischaemia by \downarrow transport related workload. Encouraging animal data, no RCTs in humans. May decrease need for dialysis by inducing polyuria \rightarrow less overload, acidosis and hyperkalaemia (the 3 major triggers for RRT)
 - POISE-2 A cardiovascular trial with pre-defined renal endpoints in non-cardiac surgical candidates (JAMA 2014) showed no benefit from aspirin or clonidine, and potential harm (aspirin \rightarrow bleeding, clonidine \rightarrow hypotension)

Management of Emerging or Established AKI

- General care:
 - Address underlying causes
 - Avoid hypovolaemia. If urine output not restored after large fluid volumes then stop otherwise overload
 - Diuretics: do not \downarrow mortality or morbidity, nor improve renal outcome, but may facilitate fluid management
 - Stop nephrotoxic drugs
 - Maintain MAP: kidney autoregulation is blunted. Maintain MAP > 65 mmHg
- Nutrition:
 - CVVH \rightarrow loss of 10 - 15 g/day or protein
 - Usual formulae may under-estimate actual energy needs
 - Giving too much protein will \rightarrow accumulation of end products given \downarrow renal clearance
 - Early nutritional support with adequate calories (30 - 35 kcal/kg/day) with adequate protein (at least 1 – 2 g/kg/day)
 - No evidence that specific renal nutritional solutions are useful
- Prompt treatment of hyperkalaemia (> 6 mmol/l) with insulin and dextrose, bicarbonate if acidosis, and /or salbutamol. CaCl if K > 7
- Metabolic acidosis on its own is almost always present but rarely requires treatment
- Marked azotaemia ([urea] > 40 mmol/L or [creatinine] > 400 μ mol/l) probably requires RRT unless likely to normalise within 24 – 48 hours. No RCTs guide optimal time for starting RRT
- Growing evidence that better uraemic control improves survival by perhaps 30%
- No evidence of benefit from pharmacological treatment. Trial of fenoldopam (an anti-inflammatory) negative (JAMA 2014)

Contrast nephropathy

- Definition: rise in Cr > 44 or 25% above baseline within 48 hours
- Risks:
 - Main ones:
 - Pre-existing renal impairment
 - Volume of contrast
 - Others:
 - Age > 75
 - Anaemia
 - Proteinuria
 - Dehydration
 - Hypotension
 - Intra-aortic balloon pump
 - Nephrotoxic drugs
 - Comorbid conditions: diabetes, sepsis, multiple myeloma, nephrotic syndrome, cirrhosis, CHF, pulmonary oedema
 - Contrast media:
 - High-osmolar worse than low or iso-osmolar – supported by RCTs and meta-analysis
 - Non-ionic have been reported better than ionic, ?difference dubious
 - Risks greater if intra-arterially as opposed to intravenous
- Prevention:
 - Stop Metformin: ↑lactic acidosis with renal impairment
 - Minimise use of contrast
 - Fluid:
 - Saline infusion to maintain intravascular volume superior to mannitol or frusemide. Solomon et al, NEJM 1994. 78 non-ICU patient with chronic renal failure and ionic contrast. Saline alone had the greatest effect. Subsequently shown that normal saline better than .45% (Mueller; Arch Int Med 2002)
 - Bicarbonate solutions may be better than saline (JAMA 2004;291:2328). One study in favour, two with no difference (Brar, JAMA 2008). KDIGO recommend either saline or bicarbonate for volume expansion prior to contrast.
 - Safety not assessed in ICU patients, especially those at risk of pulmonary oedema
 - N-Acetylcysteine (NAC)
 - Inconsistent results across multiple studies with considerable heterogeneity. Evidence not sufficient for recommending its use. 19 RCTs, 11 meta-analyses, most small single centre trials – an example of how not to do research! (See Bagshaw et al, Arch Intern Med, Jan 2006)
 - Trials only used Cr as an outcome. Heterogenous groups (eg cardiac angiography, CT studies, etc.)
 - 600 mg bd with 2 doses before and 2 after with IV saline and non-ionic contrast in 83 patients with chronic renal insufficiency, Tepel et al, NEJM 2000. Significant reduction in Cr in the treatment group at 48 hours.
 - Little risk. Serious complications (hypotension, angio-oedema, bronchospasm, hyponatraemia, seizure, volume overload) appear dose related
 - Effectiveness in ICU patients who are already resuscitated remains unknown
 - Bicarbonate: Heterogeneity in outcomes, with benefit more likely with lower quality studies. 150 ml 8.4% HCO₃ plus 850 mls 5% dextrose, 3 ml/kg/hr for 1 hour, and 1 ml/kg/hr for 6 hours post. ANZICS CTG 2013 Phase 2B RCT in 417 patients after cardiac surgery showed alkalinisation of urine but no change in renal outcomes.
 - CRRT: No protective effect? Studies show benefit of post, and pre and post contrast haemofiltration (eg Marenzi NEJM 2003). Contrast removed by dialysis. High inter-trial heterogeneity. Not accepted into clinical practice
 - Small RCTs have not shown evidence that vasodilators help (dopamine, fenoldopam, ANP, Ca blockers, PGE1, endothelin receptor agonist)
 - Theophylline and aminophylline may limit the rise in Cr, the clinical significance of this is unclear
 - Need multicentre head to head studies – or some have recommended it's been done to death and we should be content with pre-hydration
 - RCT in 2,998 patients with T2DM and CRF, comparing 10 mg/day rosuvastatin from 2 days before to 3 days after contrast and found ↓incidence of AKI (2.3% vs 3.9%, p = 0.01) and ↓heart failure at 30 days (2.6 vs 4.3%, p = 0.02). Han, J of Am College of Cardiology, 2013

AKI in Specific Disease States

- See:
 - Tumour Lysis Syndrome, page 290
 - Abdominal Compartment Syndrome, page 185
 - Renal Support in Liver Failure, page 177
 - Renal Injury following Cardiac Surgery, page 155

Lung injury

- Little is known about the relationship between respiratory failure and AKI
- ARDSNET study with low tidal volume ventilation had less renal failure in that arm.

Rhabdomyolysis-associated ARF

- Contributed to by pre-renal, renal and post-renal factors
- In response to muscle injury:
 - Direct Trauma: crush, burns, pressure
 - Exertional: excessive exercise, seizures, tetanus
 - Ischaemia: ischaemic necrosis (vascular, compression)
 - Hyperthermia: heat stroke, neuroleptic malignant syndrome, malignant hyperthermia
 - Systemic: metabolic disorders (eg profound ↓K or ↓PO₄), polymyositis
 - Drugs: cocaine, neuroleptics, statins
 - Toxins: snakes, spiders
- Cr > 150 or CK > 5,000 associated with ↑risk of AKI or need for RRT
- Myoglobinuria occurs when serum myoglobin > 1,500 to 3,000 ng/ml
- No RCTs conducted for treatment – practice based on retrospective analysis and small series:
 - Eliminating cause
 - Prompt and aggressive fluid management (damaged muscle cells → massive uptake of fluid → hypovolaemia)
 - Correction of compartment syndrome
 - Alkalinisation of urine (pH > 6.5). Little evidence. Enough N Saline may achieve this on its own
 - Maintenance of polyuria (> 300 ml/h)
 - Mannitol controversial
- Prognosis: renal recovery within 3 months

Renal Replacement Therapy

- Term is not accurate: not possible to replace all functions of the kidney
- Ongoing controversies: when to start RRT, modes of anticoagulation, optimal membrane composition

Principles

- Water removal, by a process called **ultrafiltration** (colloquially abbreviated to filtration) – requires driving pressure to move fluid across a semipermeable membrane. Achieved by:
 - Generating a transmembrane pressure (HF, IHD) which is greater than oncotic pressure
 - Increasing the osmolarity of the dialysate (as in PD)
- Solute removal:
 - Creating an electrochemical gradient across the membrane with a flow-past system with toxin-free dialysate moving solutes from a higher concentration to a lower concentration (**Diffusion** - IHD and PD). The mass transfer of solute depends on:
 - The solute (size, charge, protein binding)
 - The dialysis membrane (type, porosity, thickness, surface area)
 - Flow rates of blood and dialysate
 - The concentration gradient
 - Degree of protein binding
 - Best for molecules < 20 kDa
 - Creating a transmembrane pressure-driven ‘solvent drag’ where solute is swept together with solvent (**convection**) across a porous membrane, is discarded and then replaced with toxin-free replacement fluid (HF). Convective transport is independent of the concentration gradient across the membrane, and depends on the force of the transmembrane fluid flux. Better for middle sized molecules (> 600, <50,000 kDa)
- Fear of early dialysis arises from IHD with cuprophane membranes (especially haemodynamic instability). Continuous RRT or SLEDD minimises these effects

- **Filtration Fraction:** The fraction of plasma that is removed from blood during haemofiltration. Determined by the transmembrane and oncotic pressure. The optimal fraction at a haematocrit of 30% is of the order of 20 – 25%. A higher fraction leads to haemoconcentration and an ↑risk of filter clotting
- **Sieving coefficient:** ratio of concentration of solutes in the ultrafiltrate compared to that of plasma. SC = 1 describes complete permeability, SC = 0 implies no permeability. A high sieving coefficient is good for middle sized molecules but undesirable for albumin.

Types of RRT

- Intermittent Haemodialysis. Needs special plumbing
- SLEDD: slow (or sustained) low-efficiency daily dialysis – slow haemofiltration. An adaptation of IHD to mimic benefits of CRRT, usually runs 8 – 12 hours overnight every night. Less nursing cost. Can double up machines, transfer patients to CT or OT during the day etc. Fast compared with CVVHF. Needs special plumbing
- Continuous:
 - SCUF: slow continuous ultrafiltration 100 – 300 ml/hr (ie no added filtrate and no dialysate)
 - CVVH: Continuous veno-venous haemofiltration (ie no dialysate counter-current, just convection). Effective for clearing mid-sized molecules such as inflammatory cytokines
 - CVVHD: Continuous veno-venous haemodialysis (ie no filtrate, just counter-current dialysate). Fluid not removed. Mostly small molecules. Solute removal directly proportional the dialysate flow rate
 - CVVHDF: Continuous veno-venous haemodiafiltration. Combines convective and diffusive dialysis. Small and middle sized molecules cleared
 - CAVH: Continuous anterior-venous haemofiltration – no longer used

Indications for RRT

- Consider if one, strongly recommended if two:
 - Urine output: only a relative indication
 - Oliguria: UO < 200 ml/24 hr
 - Anuria: UO 0 – 50 ml/12 hr
 - Pulmonary oedema unresponsive to diuretics
 - Creatinine > 400 µmol/l
 - Electrolyte disorders:
 - K > 6.5 mmol/l or rapidly rising. Continue medical measures until K is normalising
 - Na < 110 and > 160 mmol/l
 - Uncompensated metabolic acidosis: pH < 7.1, to prevent mental state changes, cardiac depression, hypotension
 - Uraemia:
 - Urea > 35 mmol/l. Optimal level unknown. Uncontrolled studies suggest early CRRT better than late
 - Uraemic complications a better target?: encephalopathy/myopathy/neuropathy/pericarditis
 - Temperature > 40
 - Overdose with a dialyzable toxin: low molecular size, low protein binding, unionized and water soluble, eg lithium, Fe, heavy metals, salicylates, alcohols, valproate, theophylline, barbiturates
- When to start:
 - Traditional thresholds in stable patients may be inappropriately high in ICU as they don't take into account:
 - the interaction with other failing organs (eg lungs, brain)
 - Increase catabolism → ↑urea
 - Difficult to restrict fluid given infusions
 - Critically ill patients may be more sensitive to metabolic derangements
 - Wide variability in clinical practice
 - PICARD Trial: early vs late start of RRT: Early did better. Only one RCT has tested effect of RRT on outcomes in the critically ill, with no difference in 28 days survival. Underpowered.

Management and Titration of RRT

- Mechanisms to improve urea clearance:
 - ↑blood flow
 - ↑dialysate flow
 - Use of filters with larger membrane surface areas
 - Change filter if failing
 - Maximising time on CRRT by ensuring good vascular access, optimising filter life and rationalising time out of ICU for imaging, surgery, etc.

- Replacement fluid pre-filter: may increase urea clearance by elution from red cells. Replacement fluid post-filter increases concentration gradient across membrane
- Mode:
 - Controversial given no RCTs.
 - Judge modes by:
 - Haemodynamic side-effects
 - Ability to control fluid status
 - Biocompatibility
 - Risk of infection
 - Uraemic control
 - Avoidance of cerebral oedema
 - Ability to allow full nutritional support
 - Ability to control acidosis
 - Cost
 - CRRT and SLEDD offer many advantages over PD and IHD – including absence of fluid, protein and diet restrictions required between dialysis making nutritional support difficult
- Drug prescription:
 - ARF and RRT profoundly affect drug clearance
 - Penicillins, carbapenems, vancomycin and metronidazole require dose adjustment (see table in Oh)
- Complications:
 - Infection
 - Vascular access complications
 - Fluid volume deficit (dehydration)
 - Hypotension
 - Electrolyte imbalances
 - Acid/base imbalance
 - Blood loss
 - Air embolus
 - Reaction to AN69 haemofilter (can be due to ethylene oxide sterilizing agent or ACEI)

Renal Replacement Therapy Variables

- Blood flow rate:
 - IHD can do 400 – 450 ml/min due to high flow access through AV fistula
 - CRRT at 150 ml/min
 - Lowest reasonable rate for SLED is 200 – 250
- Dialysis rate. Dialysis rate (may not dialyse at all on CRRT – ie CVVHF):
 - IHD: 36 – 50 litres per hour
 - SLED: 15 – 25 litres per hour (ie “low efficiency” compared to IHD, but hugely efficient compared with CRRT). Can’t see effluent bags (straight down the sink)
 - CRRT: 1 – 5 litres per hour
- Buffer:
 - IHD: bicarbonate at point of care. Added to ionised water just before it goes into the patient
 - SLED: same as IHD
 - CRRT:
 - Lactate: Bear in mind if raising lactate in patient
 - Can use bicarbonate – but needs to be added to bags. Better for outcomes but ↑ cost
 - K or PO4 added to anything

High Volume Haemofiltration

- Goal is to remove soluble mediators of sepsis in the absence of AKI
- The theory is that a higher solute clearance of middle sized molecules with → more rapid settling of inflammatory milieu
- Lacks scientific rationale (according to international consensus conference):
 - Mediator removal is non-selective
 - Clearances are trivial compared with production and the large pool of cytokines and other mediators bound to tissue
 - Potent anti-inflammatory therapies haven’t improved therapy in septic shock, the effectiveness of cytokine removal seems implausible and could be harmful
 - Observed cardiovascular benefits could be due to control of hyperthermia, correction of fluid overload, metabolic acidosis or electrolyte abnormalities

- Typical filtration rate 6 – 10 L/hr. Best dose unknown. Requires high blood flow (> 300 ml/min) to avoid excess pre-dilution or excessive haemoconcentration
- More costly and more labour intensive
- ↓PO₄ a big problem
- Small studies suggest possible benefits. Eg Bellomo Lancet 2002 shows improved 15 day survival with 20 vs 35 ml/kg/hr in a single centre study. Not replicated in multi-centre RCTs, including RENAL, 2009, multicentre RCT in critically ill patients with AKI, 25 vs 40 ml/kg/hr dose of CVVHF made no difference to 90 day mortality
- Meta-analysis of 4 trials (n = 470) of high volume (effluent > 50 ml/kg/hr) haemofiltration vs standard found no difference in outcomes and more adverse events (Clark, Crit Care 2014)

CRRT vs IHD

- CVVHDF vs IHD for acute renal failure in patients with MODS: a multicentre randomised trial. Vinsonneau et al. Lancet 2006. 360 medical and surgical patients. No difference in 60 day mortality, equivalent efficacy (urea concentrations and fluid removal). No more hypotension in IHD. More hypothermia in CVVHDF. No difference in duration of RRT
- Single centre RCT in 252 ICU patients comparing IHD and CRRT with no difference in any outcomes (Scheffold, CONNINT Trial, Crit Care 2014)
- A number of other studies and a Cochrane review have not found a difference (except a higher MAP on CRRT)
- However, these modes have a number of differences that may constrain options → may not be interchangeable:
 - Rate of solute flux (speed)
 - Patient mobility
 - Ability to safely achieve large fluid removal goals
 - Vascular access (IHD requires higher flows). Remember access issues in any renal question
- Advantages of IHD:
 - Rapid clearance of acidosis, uraemia, K and toxins (small molecules)
 - Removes less amino acids, endogenous hormones and cofactors (large molecules). Doesn't take off β₂-microglobulin etc. → renal osteodystrophy
 - Don't need continuous anticoagulation
 - ↓exposure to artificial membrane
 - Less blood lost from clotting
 - Lower costs: low flux/permeability cellulose based membranes → ↑SIRS response
- Advantages of CRRT:
 - Less rapid solute and fluid shifts (less disequilibrium syndrome, less brain oedema, more haemodynamic stability)
 - High flux membranes, synthetic → less inflammatory response
 - Allows for continuous dose adjustment
 - Removes more "middle" molecules
- Disadvantages of CRRT:
 - Masks fever
 - Increased removal
- Meta-analysis of observational studies of long term outcomes of AKI in ICU: those initially dialysed with IHD had a 1.7 times risk of CRRT of remaining dialysis dependent (Int Care Med 2013)

Continuous Renal Replacement Therapy

- Originally arterio-venous, but now veno-venous due to ↓morbidity of avoiding arterial cannulation
- Ultrafiltration rates of 2 l/h yield urea clearances > 30 ml/min
- Delivering dialysate counter current to blood flow converts haemofiltration to haemodiafiltration
- Predictable outcomes – fulfils all above criteria but is expensive – requires trained nurses and medical availability 24 hours. Continuous circuit anticoagulation may be an issue
- Greatest solute clearances are achieved with CVVHDF with both replacement and dialysate solutions at maximum flow rates
- Solutions: Dialysate and replacement
 - Standard solutions contain lactate. Not suitable if liver failure or severe metabolic acidosis
 - Bicarbonate buffered solutions can be used instead – caution with citrate/calcium anticoagulation as CaHCO₃ can precipitate
- Dose:
 - Optimal dose (effective effluent per kg per hour) is unknown – assessed in 5 RCTs to date

- Ronco's Lancet 2000 single centre unblinded study of CVVHD with post dilution, showed 35 and 45 were better than 20 ml/kg/hr (although this group had more elderly patients with sepsis), endpoint mortality 15 days after dialysis ceased. Similar finding to Saudan (Kid Int 2006)
- Bouman (CCM 2002) and Tolwani (J Am Soc Nephrol, 2008) found no survival difference with higher effluent rates
- ATN Study, NEJM 2008, no difference at 60 days between standard (IHD or SLED three times weekly at 20 ml/kg/hr) vs intense (IHD or SLED 6 times a week at 35 ml/kg/hr)
- RENAL (Randomized Evaluation of Normal vs Augmented Level Replacement Therapy): High dose vs standard dose haemofiltration in Acute Renal Failure, NEJM 2009, ANZICS CTG. 1508 ICU patients on post-dilution CVVHDF with ultrafiltration rates of 40 ml/kg/hr or 25 ml/kg/hr. No difference in 90 day mortality. More hypophosphataemia in higher group. Over 90% recovered renal function
- For the moment a typical dose is 25 ml/kg/hr
- Choice of membranes:
 - No controlled studies. AN 69 most common in Australia. Allows removal of solutes with a molecular weight up to 50,000 Daltons for a high flux membrane
 - No RCTs have compared membrane size. If high-volume haemofiltration is planned, membrane surface needs to be 1.6 – 2 m² range

Anticoagulation on Renal Replacement Therapy

- No anticoagulation with IHD (or SLED) due to higher flow rates
- Activation of coagulation cascade → clotting of circuit → anticoagulation to prolong circuit life
- Ideal anticoagulant would stop clotting and not induce systemic bleeding. None exists
- Studies are scarce, clear definitions of bleeding are lacking
- Systemic options:
 - Limited data suggests Warfarin with INR 2 -3 is insufficient to prevent clotting
 - Heparin:
 - See also:
 - Anticoagulation, page 296
 - Heparin Induced Thrombocytopenia, page 308
 - Heparin coated filters: evidence limited to chronic IHD
 - In most, low-dose pre-filter heparin (< 500 IU/h) is sufficient, and has no effect on patients coagulation tests
 - Medium-dose pre-filter heparin (500 – 1000 IU/h)
 - Full heparinisation: higher dose may be necessary, or given for another indication (PE, MI)
 - LMWH: can accumulate in AKI – long half-life. Effect more predictable than UFH. Lower risk of HITTS. Monitor anti-Xa levels
 - Non-heparin systemic anticoagulation:
 - Heparinoids: danaparoid - Limited availability, risk of cross-reactivity with heparin-induced antibodies, hard to monitor
 - Prostacycline and analogues: SE: hypotension, and if HITTS present still requires anti-coagulant treatment for that
 - Direct thrombin inhibitors: Good relationship between levels and APPT
 - Bivalirudin most common in NZ, Hirudin (accumulates in renal failure), Lepirudin (accumulates in renal failure), argatroban (hepatic metabolism, falsely raises INR/PT)
 - No antagonist
 - No accurate assessment of anticoagulation: APTT and ACT not very accurate
 - May also raise INR
 - Expensive
 - NB Dabigatran is an oral DTI. Renal half-life dependent (from 8 hrs to 72 hrs, contraindicated if CrCl < 30)
 - Serine proteinase inhibitors (nafamostat mesylate): limited experience, high cost, not available in Australasia. SE: anaphylaxis, agranulocytosis
 - Fondaparinux: not readily available (lots in the UK – used for DVT prophylaxis). Limited evidence supporting its use
 - None: in 10 – 20% can't anticoagulate (eg coagulopathy or recent surgery) → keep flow up (200 ml/min) and reliable vascular access.
- Regional anticoagulation:
 - Regional pre-filter citrate/post-filter calcium anticoagulation:
 - Chelates Ca → inactivates clotting cascade as Ca is necessary for IX → IXa and PT → thrombin

- Ca-citrate complex is partially removed by filter, some enters circulation and is metabolised in the liver. Generates 3 bicarbonate for 1 citrate.
- Soft evidence of benefit over systemic heparin. Method of choice if high risk of bleeding
- Is very effective but requires a special calcium free dialysate or replacement fluid (caution with bicarbonate buffers, can precipitate with calcium).
- Potential side effects of:
 - Requires Ca infusion outside of circuit (access issues). If inadequate replacement then anxiety, paraesthesias, carpopedal spasm, tetany, arrhythmias
 - ↑Na (may → ↑alkalosis)
 - Citrate accumulation if ↓liver function (so inability of liver to clear the citrate load) → metabolic acidosis with high anion gap. Raised ratio of total to ionised Ca (normal 1.9 – 2.2%, toxic > 2.5:1)
 - Labour intensive
 - Still need DVT prophylaxis
- Regional pre-filter heparin/post-filter protamine anticoagulation (usually at a 100 IU: 1 mg ratio) is more complex but helpful in filter clotting where anticoagulation is dangerous. Cumbersome. Side effects of long-term protamine infusion unknown
- Pre-dilution (pre-filter infusion of the replacement fluid) may prolong filter life at the expense of treatment efficacy
- If filter clotting, always check catheter flow, position, etc., don't just increase anticoagulation. Smaller catheters (eg 11.5 Fr subclavian double lumen catheters) worse than 13.5 Fr.

Filter Problems

- Filter should last for > 24 hours in CRRT. Change regardless at 72 hours
- Preventing clotting:
 - Circuit preparation
 - Good access
 - Appropriate blood flow rate
 - Appropriate membrane size and type
 - Pre-dilution
 - Post-dilution into the air-bubble trap
 - Training and education of staff
 - Anticoagulation
- Low arterial pressure alarm:
 - Kinked or clamped line
 - Malpositioned patient (eg sitting up with femoral line)
 - Clotted line
 - Access device against vessel wall
 - Hypovolaemia
- High venous pressure alarm:
 - Kinked or clamped line
 - Clotted line
 - Positional vascular access obstruction
- Disconnection alarm:
 - Line disconnection
 - Circuit kinked or clamped before pressure sensory
 - Blood pump speed relatively too slow with respect to catheter performance
- Air in the circuit alarm:
 - Presence of small bubbles (often due to bicarbonate – CO₂ coming from filter bags)
 - Line disconnection at arterial access
 - Turbulence close to sensor
- Fluid balance error:
 - Effluent or haemofiltration/dialysis bags moving or incorrectly hung
 - Kinking in effluent or haemofiltration/dialysis bags
 - Machine occasional error
 - Machine systematic error (if more than 10 times without reason in 3 hours) ⇒ service it

Intermittent Haemodialysis

- Access, circuit and use of counter-current dialysate is the same as CVVHD
- Fluid removed by ultrafiltration, solutes removed by diffusion

- Blood flow is 350-450 ml/min, ultrafiltration rate is 300 – 2000 ml/hr
- Standard IHD uses high dialysate flows (300 – 800 ml/hr), generates dialysate by mixing purified water with concentrate, and is applied intermittently (eg 3 – 4 hours every 2 days)
- Limitations in ICU:
 - Volume has to be removed quicker – which may → hypotension → may delay renal recovery
 - Solute removal is episodic → inferior uraemic and acid-base control → unnecessary limitations on nutritional support
 - Rapid solute shifts → ↑brain water content → ↑ ICP
 - Membrane bioincompatibility: standard low flux cuprophane membranes trigger inflammatory pathways compared to high-flux synthetic membranes. Given similar costs, biocompatible membranes (eg polysulfone) are used

Peritoneal Dialysis

- Uncommon in adult ARF
- Possible value in 3rd world (it's cheap) and in children (peritoneal membrane has a greater relative surface area)
- Shortcomings:
 - Limited solute clearance
 - High risk of peritonitis
 - Unpredictable peritonitis (dialysate is glucose rich)
 - Fluid leaks
 - Protein loss
 - Interference with diaphragm function
- An RCT shows PD is associated with worse mortality than CVVH

Other Blood purification Techniques

- Haemoperfusion: See Decontamination, page 261
- Plasmapheresis or Plasma Exchange: see Plasma Exchange, page 305

- See also:
 - Neurology Hot Cases, page 380
 - Delirium, page 352

Cerebral Physiology

- Energy requirements:
 - Needs:
 - 45 – 75 ml O₂/min
 - 75 mg glucose/min
 - Can't store precursors so needs constant supply
 - Reduced precursors for any reason a major contributor to brain injury
- Cerebral blood supply:
 - Anterior circulation (carotids): 70%
 - Posterior circulation (vertebrobasilar) 30%
- Cerebral blood flow (CBF):
 - CPP = arterial pressure in feeding arteries – pressure in draining veins, approximated by MAP – ICP
 - As CPP rises, cerebral vessels constrict so that flow is constant over a wide range of CPP (~50 – 150 mmHg – range varies, especially with age). This autoregulation is controlled by local myogenic response to intra-arterial pressure. Outside this range pressure increases/decreases in direct proportion in changes to CPP.
 - Very high CPP can → oedema 2nd to ↑ hydrostatic pressure
- O₂/CO₂:
 - Hyperoxaemia causes no change in CBF
 - Hypoxia causes ↑ in CBF
 - Dramatic response to changes in PaCO₂:
 - Doubling PaCO₂ doubles CBF
 - Halving PaCO₂ halves CBF
 - Increases in CBF → ↑ ICP
- Cerebral injury:
 - Global hypoxic/ischaemic insults:
 - Usually sudden, short and severe (eg cardiac/respiratory arrest)
 - After 4 – 6 minutes histological damage in selective neuronal populations and the beginnings of deficits in survivors
 - Focal hypoxic/ischaemic insults:
 - More prolonged duration
 - Periphery of the area is the ischaemic penumbra – the focus of therapeutic intervention
 - Irreversible damage in 30 – 60 minutes
 - Effects of declining CBF:
 - Normal CBF of 50 ml/min per 100gm (750 ml/min for 1500 gm brain) delivers 2 -3 times the usual O₂ needed
 - CBF of 15 – 25 ml/min per 100 g → loss of electrical activity
 - CBF 10 – 15 ml/min per 100 g is sufficient to support ATP levels necessary to maintain ion pump function despite lack of electrical activity
 - Below 10 ml/min per 100 g pump function fails → membrane failure
 - Effects of ischaemia:
 - Anaerobic glycolysis → lactic acidosis
 - Ion pump failure → efflux of K, influx of Na, Ca and Cl → release of excitatory amino acid neurotransmitters → depolarisation of neighbouring cells and distal parts of brain
 - ↑ free radicals
 - ↑ leukocytes → plug small capillaries if low flow + ↑ free radicals

Brain Stem Anatomy

- Brain stem blood supply:
 - Superior cerebellar artery
 - Anterior and posterior inferior cerebellar artery (AICA and PICA)

- Rule of 4s:
 - There are 4 medial structures:
 - Motor pathway (corticospinal tract)
 - Medial Lemniscus (contralateral loss of vibration and proprioception in the arm and leg)
 - Medial longitudinal fasciculus: ipsilateral inter-nuclear ophthalmoplegia (failure of adduction of the ipsilateral eye and nystagmus in the opposite)
 - Motor nuclei (3, 4, 6 or 12 – all those that divide into 12 except 1 and 2)
 - There are 4 “side” (lateral) structures. Damage leads to Lateral Medullary Syndrome:
 - Spinocerebellar pathway: ipsilateral ataxia of the arm and leg
 - Spinothalamic pathway: contralateral pain and temperature of limbs (not trunk)
 - Sensory nucleus of the 5th nerve
 - Sympathetic pathway: ipsilateral Horner’s syndrome (partial ptosis and miosis). See Horner’s Syndrome, page 382
 - These medial and side structures generally pass the length of the brain stem. To find the lesion, think about where these longitudinal pathways intersect with transverse pathways:
 - 4 Cranial nerves in the medulla:
 - CN9: Glossopharyngeal (ipsilateral loss of pharyngeal sensation)
 - CN 10: Vagus (ipsilateral palatal weakness)
 - CN11: Spinal Accessory (ipsilateral weakness of the trapezius and sternocleidomastoid)
 - CN12: Hypoglossal: ipsilateral weakness of the tongue (only motor nerve in the medial medulla)
 - 4 Cranial nerves in the pons:
 - CN5: Trigeminal: pain, temperature and light touch on the face as far back as the anterior two-thirds of the scalp but sparing the angle of the jaw
 - CN6: Abducens: weakness of the lateral rectus (only motor nerve in the medial pons)
 - CN7: Facial: facial weakness
 - CN8: Auditory: ipsilateral deafness
 - 4 Cranial nerves above the pons:
 - CN1: Olfactory
 - CN2: midbrain
 - CN3: Oculomotor: eye turned out and down, with or without a dilated pupil
 - CN4: Trochlear: weakness of superior oblique
 - A medial brainstem lesion will consist of the 4 Ms, and a lateral syndrome will consist of the 4 S’s. If there are both medial and lateral signs then consider basilar artery occlusion

Brain Imaging

Head CT

- Interpretation:
 - Cerebrum, cerebellum and brain stem:
 - Density differences, grey/white matter differentiation
 - Brain herniations: tonsillar (>5 mm below foramen magnum), transtentorial, subfalcine (cingulate gyrus)
 - CSF containing spaces: Ventricles, basal cisterns and sulci
 - Calvarium and scalp
 - Review areas: paranasal sinuses, nasopharynx, mastoid air cells and orbits
- Abnormalities on Head CT

↑Intracranial pressure	<ul style="list-style-type: none"> • Effacement of basal cisterns • Loss of grey-white differentiation • Midline shift • Herniation of cerebellar tonsils into the foramen magnum • Herniation of uncus: shift of brainstem, distortion of adjacent cisterns, dilation of contralateral temporal horn
Traumatic brain injury	<ul style="list-style-type: none"> • Coup and countercoup injuries • Skull fractures, with intracranial air, opacification of sinuses from blood • Contusions • Haemorrhage: extradural, subdural, subarachnoid, intracerebral • Punctate white matter haemorrhages
Cerebral Infarction	<ul style="list-style-type: none"> • Vascular territory: anterior cerebral artery, middle cerebral artery, posterior cerebral artery • Watershed distribution (hypotensive infarct) • Basal ganglia (hypoxic injury)
Cerebral haemorrhage	<ul style="list-style-type: none"> • Extradural: lens-shaped, convex, confined within suture lines • Subdural: concave, blood follows contour of brain surface • Subarachnoid: within CSF spaces • Intracerebral
Non-traumatic subarachnoid haemorrhage	<ul style="list-style-type: none"> • Blood outlining the brain surface, Sylvain fissure and in CSF spaces (ventricles, aqueduct and cisterns: pontine, quadregeminal, ambient, supra-sellae) • Non-obstructive hydrocephalus • Potentially intracerebral haemorrhage or infarction in a vascular distribution (most commonly anterior cerebral artery distribution complicating a ruptured anterior communicating artery aneurysm)
Mass Lesions	<ul style="list-style-type: none"> • Tumours: 2ndary deposits most common in adults. GMB is a complex lesion with loss of architecture and necrosis • Cerebral abscess: ring enhancement, single or multiple lesions

MRI of the Brain

- Sequences:
 - T1: CSF is black, fat is white. Good images of anatomy – especially fat containing structures
 - T2: CSF and fluid are white (hyperintense). [World War 2 – Water is White in 2]
 - Flair (Fluid Attenuated Inversion recovery): CSF is black, pathological fluid is white, fat is intermediate
 - DWI (Diffusion Weighted Images) and ADC (Apparent Diffusion Coefficient) go together. For infarcts and abscesses. Motion of water is restricted in cytotoxic oedema (inflammation) and abscess – but moves freely in normal tissues
 - GRE (Gradient Echo): for blood
 - MRA: Angiography
 - MRV: Venography

The Unconscious Patient

- See ICM April 2014 for a superb review of the assessment of the unconscious patient
- Wakefulness:
 - Requires interaction between cerebral hemispheres and reticular activating system – in particular the areas of the RAS between the rostral pons and the diencephalon
 - In the cerebral hemispheres, consciousness is not focal, but related to the mass of functioning cortex
- Disorders of consciousness:
 - Confusion: inability to think clearly, inattentiveness, ↓awareness and disorientation
 - Delirium: confusion with agitation and hallucination
 - Stupor: unresponsiveness with arousal only and deep and repeated stimuli
 - Coma: unarousable unresponsiveness
- Prognosis:
 - Coma following head injury has a better outcome than non-traumatic (medical) coma
 - Non-traumatic coma:
 - > 6 hours (excluding anoxic coma), only 15% return to their pre-morbid state of health
 - Coma due to infection, metabolic causes and MODS has a better outcome than anoxic coma

- Outcome scales have been developed to assess neurological recovery:
 - Bathel index
 - Rankin scale
 - Glasgow outcome scale (widely used for trauma): see Traumatic Brain Injury, page 235
- For prognosis after anoxic brain injury, see Out of Hospital Cardiac Arrest, page 165

Coma like syndromes

- Locked in syndrome: alert and aware, able to blink, vertical eye movements. Medial and lateral gaze palsies, no other voluntary movement, due to bilateral anterior pontine lesion transecting descending pathways but sparing ascending sensory and RAS pathways. EEG and metabolism normal
- Persistent Vegetative State: Previously comatose patient who now appears to be awake. Spontaneous non-purposeful limb movements, non-purposeful eye movements, yawning. No speech or awareness. Bilateral cortical damage with preservation of brainstem. EEG has polymorphic delta or theta waves, sometimes alpha. Metabolism 40 – 60% of normal. Persistent = longer than 4 weeks
- Akinetic Mutism (coma vigile): Partially or fully awake, immobile and silent. Due to bilateral frontal lobe lesion, hydrocephalus or 3rd ventricular masses. Diffuse slowing on EEG
- Catatonia: Awake, maybe fixed posture, mute, decreased motor activity. Psychiatric origin. Non-specific EEG patterns
- Minimally Conscious State: globally impaired responsiveness, discernible evidence of self and environment. Due to global neuronal damage. EEG has theta and alpha waves

Differential of Coma

- *Coma with focal signs:*
 - Trauma: extradural, subdural and parenchymal haemorrhage, concussions. Exclude drugs/ETOH. Anterior basal skull fracture suggest by periorbital haematomas (Raccoon eyes), Battle's sign and cerebrospinal fluid
 - Vascular: intracerebral haemorrhage. Consider secondary causes of hypertension if young
 - Vascular: thromboembolic. Consider echo for embolic source
 - Brain abscess: subacute, look for ENT and dental sources. Endocarditis and suppurative lung disease may be a source
- *Coma without focal signs but with meningeal irritation:*
 - Infection: meningitis, encephalitis. Petechial rash points to meningococcaemia, rickettsial infection or endocarditis. Nuchal rigidity may not be seen in the elderly or deeply comatose. Abnormal CSF. Consider underlying immunosuppressive states
 - Subarachnoid haemorrhage. Check for sub-hyaloid haemorrhages on fundoscopy. Consider polycystic kidney disease
- *Coma without focal signs and no meningeal irritation:*
 - Metabolic causes:
 - Hyponatraemia
 - Hypoxia
 - Hypercapnea
 - Hypo- and hyperthermia
 - Hyper- and hypo-osmolar states
 - Organ failure: hepatic and uraemic foetor are rare
 - Hepatic: look for peripheral stigmata
 - Renal
 - Endocrine causes n(may have more than one):
 - Hypoglycaemia
 - Hyperglycaemia: ketones on breath
 - Myxoedema (puffy faces in hypothyroidism)
 - Adrenal insufficiency
 - Hypopituitarism
 - Seizure Disorders: abnormal EEG, check anticonvulsant levels, exclude underlying space occupying lesion
 - Toxic/Drugs:
 - Sedatives
 - Narcotics
 - Alcohol: telangiectasia, clubbing
 - Psychotropic
 - Carbon monoxide: cherry red discolouration of skin

- Poisons
- Behavioural, sleep deprivation, pseudocoma

Eyes in Coma

- Pupillary responses:
 - Pupils of normal size and response to direct and consensual light reflexes confirms integrity of retina, optic nerve, optic chiasm and tracts, midbrain and 3rd cranial nerve nuclei and nerves

Miosis (< 2mm in size)	Cause	Basis
Unilateral	Horner's syndrome Local pathology	Sympathetic paralysis Trauma to sympathetics
Bilateral	Pontine lesions Thalamic haemorrhage Metabolic encephalopathy Organophosphate Barbiturate Narcotics	Sympathetic paralysis Cholinesterase inhibition Central effect
Mydriasis (>5 mm in size)		
Unilateral fixed pupil	Midbrain lesion Uncial herniation	3 rd nerve damage Stretch of 3 rd nerve against petroclinoid ligament
Bilateral fixed pupils	Massive midbrain haemorrhage Hypoxic cerebral injury Drugs Atropine/anticholinergics Tricyclics Sympathomimetic	Bilateral 3 rd nerve damage Mesencephalic damage Paralysis of parasympathetics Prevent reuptake of catecholamines Stimulation of sympathetics

- Ophthalmoscopy:
 - Never dilate pupils without documenting prior size and response
 - Papilloedema → ↑intracranial pressure, frequently absent when acute
 - Sub-hyaloid and vitreous haemorrhage with subarachnoid haemorrhage
- Eye movements:
 - Horizontal eye movements:
 - To look left, the right frontal lobe co-ordinates with the left pontine region
 - Frontal lobe lesion: eyes deviate to the side of the lesion
 - Pontine lesion: eyes deviate away from the lesion
 - Vertical eye movements are under bilateral cortical and upper midbrain control
 - Spontaneous roving eye movements excludes brainstem pathology
 - Ocular bobbing: pontine lesion – loss of horizontal gaze and unopposed vertical gaze activity
 - Skew deviation (vertical separation of the ocular axes) with pontine and cerebellar disorders
 - Full response to oculovestibular stimuli ⇒ functional integrity of a large part of the brain stem

Limb Movements in Coma

- Mild depression on consciousness: restlessness, swallowing, yawning, localising
- Basal ganglion lesion: choreoathetotic or ballistic movements
- Myoclonic movements: usually post anoxic
- Asterixis: metabolic encephalopathies
- Decerebrate rigidity: stiff extension, uni- or bilateral, spontaneous or in response to noxious stimuli, in midbrain lesions, hypoglycaemia, anoxia, hepatic coma, drugs
- Decorticate posturing: flexion of elbows and wrists, extension of lower limbs. Lesion usually above the midbrain in the cerebral white matter

Respiratory System in Coma

- Failure can result from hypoventilation, aspiration pneumonia, neurogenic pulmonary oedema
- Bradypnoea: drugs, hypothyroid coma
- Tachypnoea: central neurogenic hyperventilation (midbrain lesion)
- Cheyne-Stokes respiration: Deep cerebral lesions, metabolic encephalopathy
- Ataxic breathing: medullary lesions (usually progresses to agonal gasps and terminal apnoea)

Body Temperature

- Hypothermia (< 35) in ETOH, barbiturates, sepsis, drowning, hypoglycaemia, myxoedema, hypothermia
- Hyperthermia: pontine haemorrhage, intracranial infections, heat stroke, anticholinergic drug toxicity

Brain herniation

- Results from downward displacement of the upper brainstem (central herniation) with or without involvement of the uncus (lateral herniation)
- Clinical progression including:
 - Progressive obtundation
 - Cheyne-Stokes respiration
 - Small pupils → medium fixed sized pupils
 - Extensor posturing
- If uncus herniation then pupillary dilation occurs early because of third nerve compression
- Cushing's response (hypertension, bradycardia) is not always present and any heart rhythm may be present

Investigations in Coma

- Bloods: glucose, electrolytes, ABG, liver, renal, osmolality, blood film
 - FBC: polycythaemia, infection, thrombocythaemia
 - CRP: infection, Vasculitis, carcinoma
 - Coags, cholesterol, TAGs, syphilis
 - If Venous thrombosis, thrombophilia screen: protein C & S, Factor V Leiden, Antithrombin III
 - Overdose: toxicology, alcohol, paracetamol, salicylates, TCAs. Store serum for uncommon drug investigations
- Cardiac investigations: ECG (arrhythmias), TTE or TOE (if event in internal carotid artery territory)
- Neuroimaging:
 - CT:
 - Including to exclude cerebral oedema prior to LP
 - Differentiates infarction, haemorrhage, tumour, abscess or subdural
 - In the first 24 hours may only show minor loss of grey/white matter differentiation
 - After several weeks, can't distinguish between infarct or haemorrhage
 - Limitations include transfer, frequent need for sedation, poor sensitivity for early stroke, IV contrast (death in 1 in 40,000)
 - MRI:
 - More sensitive for acute ischaemia, diffuse axonal injury, and cerebral oedema, tumour and abscess. Brain stem better visualised. No xrays.
 - Multimodal MRI with diffusion and perfusion-weighted MRI with angiography much more sensitive in demonstrating small areas of ischaemia
 - MRA best for venous thrombosis
 - Disadvantages of long imaging times and no metal allowed
 - PET and SPECT (single photon emission with computer tomography) scans: assessment of cerebral blood flow and oxygenation and in prognostication of neurotrauma. Little role in acute disorders. Research tools only.
- LP.
 - Requires CT prior if:
 - New onset seizures
 - Focal neurological signs (suspicion of a space occupying lesion)
 - ↓LOC
 - Immunocompromised
 - History of CNS disease (mass lesion, stroke, focal infection)
 - Papilloedema
 - CSF analysis:
 - Normal WBC < 5 cells
 - RBC/WBC ratio – approximately 750:1
 - CSF pleocytosis: consider infection, blood, foreign body
- Electroencephalograph (EEG): useful for:
 - Seizures and non-convulsive seizures
 - Hepatic encephalopathy: paroxysmal triphasic waves
 - Severity of hypoxic encephalopathy: presence of theta activity, diffuse slowing, burst suppression (when severe), alpha coma (severe forms)
 - Herpes encephalitis: periodic sharp spikes

- Poor sensitivity and specificity for prognostication after cardiac arrest
- Widespread use of bi-spectral analysis in anaesthetics for awareness in high risk patients (B-Aware Study) may have relevance in ICU – not yet assessed
- EEG patterns possible in the critically ill:
 - Generalised suppression/isoelectric
 - Generalised burst suppression accompanied by epileptiform activity
 - Epileptiform and generalised periodic discharges, especially myoclonus
 - Alpha pattern coma
- Evoked potentials:
 - Visual, brainstem and somatosensory evoked potentials
 - Test integrity of neuroanatomical pathways within the brain and the spinal cord
 - Useful for assessment of blindness in comatose patients, assessment of locked-in states
 - Some data to suggest better prognostic value than clinical judgement in patients with anoxic coma
- Bio-markers:
 - Include neurone specific enolase (cytoplasm of neurons, cut off levels vary in small studies), S-100 B protein (astroglial cells), CK-BB fraction (astrocytes), glial fibrillary acidic protein (glial origin)
 - Concerns remain about sensitivity and specificity for assessment of severity and prediction of outcome

Management of Coma

- See also Brain-Specific Monitoring, page 238
- Airway, oxygenation, maintain circulation, secure access. Avoid hypoxia and hypercapnia (PaO₂ > 80 and PCO₂ 35 – 40)
- Assumed cervical trauma until excluded on history or imaging
- Consider and treat:
 - Give 50% glucose after taking bloods – benefits for hypoglycaemia outweigh potential risks of glucose on augmentation of brain lactate production
 - Thiamine + dextrose
 - Naloxone if suspected narcotics with respiratory depression
 - If hypertension, bradycardia and fixed dilate pupils then consider tentorial herniation → give 20% mannitol at 0.5 – 1 g/kg and consider external ventricular drain
 - Antibiotics for meningitis
 - Treatment of seizures
 - Treat extremes of body temperature

Encephalopathy

- Describes alteration in level or content of consciousness due to a process extrinsic to the brain
- Features:
 - Waxing and waning (structural causes usually fixed)
 - Fundoscopy, pupil response, eye movements are usually preserved
 - Motor findings usually symmetrical
 - Involuntary movements include asterixis, tremor, myoclonus (rare in structural causes)
- Sepsis-associated encephalopathy:
 - If impaired mental function, extracranial infection, and absence of other pathologies
 - Multifactorial cause: alteration in cerebral blood flow, breakdown of blood-brain barrier resulting in oedema, reduced brain O₂ consumption 2nd to endotoxins and cytokines, neuronal degeneration and ↑aromatic amino acids → alteration in neurotransmitter function. Hypotension may contribute
 - Asterixis, tremor and myoclonus usually absent (more common in metabolic encephalopathies)
 - Therapy directed at the underlying septic process
- ICU encephalopathy or ICU syndrome:
 - Agitation, restlessness and frank delirium arising 5 – 7 days after admission
 - Multifactorial causes: prolonged ventilation, sleep deprivation, loss of day night cycles, immobilisation, noisy environment, monotony, multiple sedations, underlying disease
 - A diagnosis of exclusion
 - Supportive care: sedation, improved sleep quality, reduced boredom

General Management of Acute Cerebrovascular Events

- See Investigations in Coma, page 205

Supportive Care and monitoring in Cerebral Insult

- Nursing/supportive care:

- Eye and mouth care
- Regular changes in limb position + limb physiotherapy
- Bronchial suction
- Stress ulcer prophylaxis
- DVT prophylaxis
- Early NG feeding (exclude basal skull fracture before insertion of an NG tube)
- Early rehabilitation under specialist teams
- Specific Treatment:
 - Monitoring
 - Early treatment of hypotension, hypoxia, hyperthermia and intracranial hypertension
 - Maintenance of CPP

Hypertension in Cerebral Insult

- Blood pressure is often high, mechanisms and effects not well understood
- Benefits of intervention debated
- Specific indications in each condition – generally only treat if > 220 , or > 180 if bleed or given thrombolysis (that's what was done in the trials)

Hyperglycaemia in Cerebral Insult

- Associated with increased mortality after a stroke
- Possible reasons include:
 - Direct cytotoxicity
 - Marker of dysglycaemia which is associated with vascular disease and endothelial dysfunction
- Insulin is directly neuroprotective – and is the subject of a number of current trials

Hyperthermia/Hypothermia in Cerebral Insult

- \uparrow temperature \rightarrow :
 - \uparrow brain metabolism
 - O₂ requirements
 - CBF and ICP
 - Neurotransmitter and free radical production
 - BBB failure
- \uparrow temperature following stroke $\rightarrow \uparrow$ severity, infarct size, functional outcome and mortality
- Treat by cooling to normothermia and early treatment of infection
- Hypothermia:
 - See Induced hypothermia After Cardiac Arrest, page 136
 - Prolongs survival in drowning, used extensively in cardiac surgery...
 - Study in head trauma of cooling to 33°C for 48 hours was stopped due to no improvement in 6 month functional outcome, and worse outcomes for older than 45 (NEJM 2001)
 - No randomised trials in stroke to date – Nordic Cooling Stroke Study (NOCSS) in progress
 - In cardiac arrest: unconscious adults with spontaneous circulation after witnessed cardiac arrest should be cooled to 32 – 34°C for 12 – 24 hours, when the initial rhythm is VF (NEJM 2002). No evidence for other rhythms or in-hospital arrest. Insufficient evidence for a recommendation in children
 - Cooling is associated with \uparrow VAP

Haemodilution in Cerebral Insult

- \downarrow haematocrit with hypervolaemic haemodilution may \rightarrow better flow \rightarrow better O₂ delivery to areas with impaired supply
- Traditionally part of the treatment in SAH (especially vasospasm), not tested against concurrent controls
- Benefit in animal models not replicated in stroke, and trials have had complications in patients with heart failure

Intracranial Pressure Management in Cerebral Insult

- See also Intracranial Pressure Management in Brain , page 239
- $CCP = MAP - ICP$
- = the pressure gradient driving cerebral blood flow
- 3 compartments within fixed cranium contribute to ICP:
 - Blood
 - Non-compliant brain tissue
 - Cerebrospinal fluid (CSF)

- Initially, rises in ICP are compensated by ↓blood and ↓CSF, but if ↑ICP persists even small increases in blood can ↑↑ICP
- Poor correlation between ICP and cerebral blood flow
- Does not allow for differential autoregulation in the normal and injured brain
- Monitoring ICP:
 - Ranked by accuracy, stability, and ability to drain CSF
 - Most favourable:
 - Intraventricular:
 - Most accurate
 - Can be re-zeroed (recalibrated) after insertion
 - CSF drainage possible, and therefore dynamic testing of pressure-volume relationship
 - But more technically difficult
 - High infection rates, increase significantly after 5 days
 - Difficult to insert in patients with collapsed ventricles
 - Coagulopathy an absolute contraindication
 - Cheap
 - Intraparenchymal: good when lateral ventricles have already collapsed, low infection rates, can't be recalibrated in-vivo, can't drain CSF and may not reflect global ICP
 - Fibre-optic or strain gauge tipped catheters can be placed intraparenchymally or intraventricularly. Small calibre, can be inserted at bedside. Can't zero calibrate after insertion and baseline drift that may be clinically significant after 5 days. Coagulopathy a relative contraindication. Expensive
 - Followed by subdural, subarachnoid and epidural devices. Subdural do not accurately reflect global intracranial pressure, especially after craniectomy
 - Can also use transcranial Doppler (see Complications of Subarachnoid Haemorrhage, page 213)
 - MAP and ICP should be referenced to the external auditory meatus (equivalent to the external auditory meatus)
- General management:
 - ICP monitoring if GCS < 8, evidence of herniation or hydrocephalus
 - Exclude hypovolaemia, head to 30°, analgesia/sedation, neuromuscular blockage reduces ICP by reducing intrathoracic pressure (and → ↑venous return). However, can't assess GCS

Decompressive Craniectomy

- Proven (by Meta-analysis): malignant MCA infarct. See Management of Cerebral Infarction, page 209
- Somewhat disproven:
 - TBI: DECRA (for diffuse oedema only). See Decompressive Craniectomy in Brain Trauma, page 241
 - SAH: Sydney retrospective audit. See Subarachnoid Haemorrhage, page 212
- Also considered in:
 - ICH
 - Cerebral venous thrombosis
 - Encephalitis

Hyponatraemia in Cerebral Insult

- See Hyponatraemia, page 70
- Cerebral salt wasting: Excessive natriuresis (?due to ↑atrial natriuretic peptide) → hyponatraemia dehydration – ie should be hypovolaemic. Aetiology unclear. Diagnosis controversial. Occurs in first week and resolves after 2 – 4 weeks. Treatment: N saline (which should restore volume, remove the stimulus to ↑ADH → dilute urine – unless they also have SIADH), if not responding the fludrocortisone
- SIADH: Treatment: fluid restriction – although risks cerebral infarction due to hypovolaemia. Isotonic saline may worsen hyponatraemia as Na is excreted and water retained. Mild hypertonic saline can be used (low quality evidence, strong recommendation). Limit free water intake. Consider mineralocorticoids
- Differentiating:
 - Elevated urine osmolality in both – this is appropriate in CSW (they are dry ⇒ ↑ADH), and inappropriate in SIADH (due to inappropriate ↑ADH)
 - Urine sodium concentrations usually elevated in both SIADH and CSWS (> 40 mmol/l)
 - Urinary sodium excretion (urinary Na concentration * volume l/24 hours) is high in CSWS and normal in SIADH
 - Signs of hypovolaemia despite a urinary Na that is not low is the best pointer to CSW

Drugs for Neuroprotection

- Propofol:
 - Neuroprotective in focal and global models of cerebral ischaemia
 - ↓cerebral metabolic rate → ↓CBF
 - Side effects: hypotension and hyperlipidaemia with infusion of 200 µg/kg/min for burst suppression (reduced with more concentrated form)
- Calcium antagonists:
 - Influx of calcium is a common mediator for cell death from a variety of causes
 - Trials of IV nimodipine in acute stroke terminated early due to worse outcomes – worse outcome correlated with ↓BP
- Steroids: CRASH trial of effect of methylprednisolone after head trauma showed worse outcomes. Controversial benefit in spinal injury.

Cerebral Infarction

Aetiology of Cerebral Infarction

- Stroke = acute focal neurological deficit, caused by cerebrovascular disease, which lasts for more than 24 hours
- Main causes: thromboembolism and spontaneous intracranial haemorrhage (either intra-cerebral or subarachnoid haemorrhage)
- Risks: age, HTN, IHD, AF, smoking, obesity, some oral contraceptives, ↑cholesterol, ↑haematocrit
- Prognosis:
 - One month mortality 30%, haemorrhagic worse than infarction
 - At one year, haemorrhagic better than infarction
 - 30% of survivors dependent on others
- The challenge for ICU is to identify potential survivors
- Aetiology:
 - Cerebral thrombosis:
 - Atherosclerosis the main culprit: progressive plaque formation leading to platelet aggregation and thrombus
 - Any disease resulting in vasculitis, vertebral or carotid artery dissection
 - Venous thrombosis (< 1% of strokes) in hypercoagulable states
 - Embolism:
 - Originates from thrombus overlying arterial atherosclerotic plaques
 - 30% from left atrium or ventricle
 - No clinical sign reliably differentiates thrombosis from embolism (although embolism may have more rapid onset)
- Brain thromboplastin (?aka tissue thromboplastin) is a membrane protein released from damaged blood cells that activates the extrinsic coagulation pathway causing local clotting. In excess it can cause DIC. This is a differential of disordered coagulation due to thrombolysis

Management of Cerebral Infarction

- Stroke Unit: 28% reduction in mortality and disability at 3 months
- A & B:
 - If GCS ≤8 or absent gag then intubation
 - If hypercarbia the ventilating to normocarbica → better outcome
- C:
 - Hypertensive patients may have impaired autoregulation, regional perfusion may depend on BP
 - High blood pressure after stroke is associated with worse outcome
 - Control of even very high BP (> 220/120) is not without risk (NB Don't generalise trials in major strokes to minor CVA or TIA – there early initiation of antihypertensives is of benefit):
 - CHHIPS Trial (Lancet 2009) – small numbers suggest no harm and perhaps 3 month mortality benefit from early lowering with labetalol and/or lisinopril. Further research needed
 - RCT in 4,071 non-thrombolysed ischaemic strokes, with elevated BP within 48 hours of onset. Two arms: no antihypertensive treatment and lowering BP 10% to 25% within the first 24 hours and to less than 140/90 within 7 days. Found no difference in composite outcome of death or major disability at 14 days (2013)
 - SCAST Trial – potential harm from acute candesartan
 - ENOS Trial (Lancet 2014), n = 4011, of GTN patch for 7 days showed no benefit or harm. Half patients had regular anti-hypertensives stopped with benefit in terms of Barthel index at 60 days

- Avoid drugs which cause cerebral vasodilation as they may aggravate oedema
- Haemodilution may improve flow, but trials have shown no clinical benefit
- Metabolic: Hypo and hyper-glycaemia worsen prognosis
- Anticoagulation: reduction in thromboembolism offset by increased haemorrhage. Only anticoagulate if high risk of recurrence (prosthetic heart valves, AF with known thrombus, thrombophilic disorders)
- Specific treatment:
 - Thrombolysis:
 - Contraindications:
 - Stroke or head trauma < 3 months
 - Past or present intracranial haemorrhage
 - Major surgery in the last 14 days
 - GI or urinary bleeding in last 21 days
 - MI in last 3 months
 - Non-compressible arterial puncture in previous 7 days
 - Thrombocytopenia
 - Persistent, severe HTN
 - NINDS trial showed improvement with alteplase within 3 hours. Not replicated in 2 European trials and Atlantis trial. Cochrane recommends it. Treat hypertension > 180 if thrombolysing as this is what was done in the trials
 - Also ECASS3 Trial
 - These RCTs don't differentiate between anterior and posterior circulation strokes – however the NIHSS score of 4 – 22 which may trials used as an inclusion criteria does not favour the inclusion of many POCs (Basilar artery thrombosis tends to score > 22, minor brainstem and occipital lobe events often score < 4)
 - No RCTs in Basilar Artery Thrombosis (see Brain Stem Anatomy, page 200). Case series supports use and suggests rough equivalence of intra-venous and intra-arterial approaches
 - Large registry study of real world patients shows faster thrombolysis → better mortality and functional outcomes (JAMA 2013)
 - Intra-arterial thrombolysis:
 - No clear benefit over IV thrombolysis, but of benefit in recent surgery. Could change in the future with improving technology or quicker treatment
 - PROACT study, JAMA 1999, showed benefit from intra-arterial pro-urokinase with an improvement in 90 day outcome, but more haemorrhagic transformation
 - IMS3 and SYNTHESIS Trials (NEJM 2013) showed intra-arterial therapy (intra-arterial thrombolysis or embolectomy) in addition to IV thrombolysis was *not* superior to IV thrombolysis alone. Favourable penumbral pattern did not predict benefit.
 - Embolectomy: shown to be safe and effective MERCI trial, Stroke 2005. Not compared to thrombolysis
 - Small trials and meta-analysis support the use of sonothrombolysis (ultrasound enhanced lysis) in addition to tPA (Ricci et al, Stroke 2013)
- Cerebral Protection: No agent effective in phase 3 trials.
- Decompressive Craniectomy and durotomy:
 - An option in malignant hemispheric infarction (~ 10% of infarcts). Mortality otherwise as high as 78%. Higher risk in the younger (less atrophy to compensate for swelling)
 - > 50% hypodensity of MCA territory on CT predictive of fatal cerebral oedema
 - Pooled evidence from 3 RCTs in Europe
 - In younger patients with large MCA infarcts. Reduces mortality from 78 to 29% but with more moderate residual neurological deficit. Those living independently increased from 6 to 14%. Neither group had survivors with no residual deficit. Trials excluded people over 55 and 60. Case series suggest some benefit in older patients but generally worse survival
 - Originally just in non-dominant hemisphere strokes. Now routine in either side. Dominant may do better as able to participate in rehab despite dysphasia. Large non-dominant strokes often have severe neglect with may preclude effective rehab
 - Surgery is not precluded by thrombolysis (although should wait perhaps 24 hours)
 - Generally recommended for age < 50, over this on a case by case basis
 - Over 61 year olds, symptoms <48 hrs, > 2/3 MCA territory infarct: better severe disability survival I large hemicraniectomy. Stopped after enrolment of 112 patients due to efficacy – mainly converted patients from 5 or 6 (death) to 4 (unable to walk). No patients in either arm had scores in Rankin Score 0 – 3 (normal through to less severe disability). DESTINY 2 Trial 2014
 - Other decompressive options include drainage of secondary hydrocephalus with EVD or evacuation of haemorrhage into infarcted areas

- Brain stem strokes: management options may include EVD for hydrocephalus, decompressive posterior fossa craniectomy, risk of locked in syndrome
- Watch for complications: aspiration pneumonia, DVT, UTI, pressure sores, contractures and depression

Intracerebral Haemorrhage

- Causes:
 - Most commonly chronic hypertension → rupture of microaneurysms/penetrator arteries
 - Also 2nd to malignancy, vasculitis, mycotic aneurysms, amyloidosis, sarcoidosis, malignant hypertension, over-anticoagulation, primary haemorrhagic disorders
 - In younger patients, most commonly underlying vascular abnormality
- Presentation:
 - sudden onset focal neurology and ↓LOC
 - Headache and neck stiffness in conscious patients if there is extension into ventricles, which may → secondary hydrocephalus → ocular palsy's including sunset eyes
- Investigations:
 - LP if mycotic aneurysm suspected (after CT to exclude ↑ICP)
 - Digital subtraction angiography
- Management:
 - Presentation with GCS < 8/15 almost universally poor outcome. Intraventricular extension worsens prognosis
 - Reverse anticoagulation. See Warfarin, page 296
 - Hypertension:
 - If chronic hypertension then target $90 < \text{MAP} < 130$, using vasopressors if low.
 - INTERACT trial suggests early aggressive blood pressure control is not harmful and may reduce size. Treat extremes (SBP > 180 mmHg)
 - INTERACT 2 Trial (Anderson et al NEJM 2013), target pf < 140 compared with 180 within 1 hour, with physicians choice of agent → death or disability in 52 vs 55.6% (p = 0.06). ↓modified Rankin score
 - If secondary hydrocephalus (from intraventricular extension) then EVD, set so it drains at CSF > 10 mm Hg. If sudden decrease suspect blocked drain. Small phase II trial evidence of possible benefit from intraventricular tPA in selected patients
 - No:
 - steroids
 - hyperventilation to PaCO₂ of 30 to control ICP – which it does quickly - as it will have detrimental effects on cerebral blood flow in other areas of the brain
 - prophylaxis for seizures
 - Surgery:
 - Sub-occipital craniotomy and evacuation for cerebellar bleed if brain stem compression or hydrocephalus, on the basis of case series showing benefit
 - Non-statistically significant benefit from early surgical decompression in spontaneous supratentorial intracerebral haemorrhage vs medical management with rescue decompression if needed (STICH Trial, International Surgical Trial in Intracerebral haemorrhage, Lancet 2005 n - 1033). Excluded patients with suspected aneurysm. “Early” surgery had mean of 30 hours from onset – so didn't really test genuinely early surgery. Type of surgery was at discretion of the surgeon – most was craniotomy (as opposed to less invasive methods). 26% of conservative group crossed over to surgery. Best results if < 1 cm from the cortical surface – in which case clot evacuation within 6 hours
 - STITCH II Trial, Mendelow, Lancet 2013. 601 patients randomised to initial conservative management or early evacuation in lobar bleeds. No difference
 - Due to variable evidence, best for refractory ↑ICP, in non-dominant hemisphere, in patients who are not obtunded (who have a poor prognosis regardless), and who are deteriorating
 - One phase 2 trial of with rFVIIa showed reduced haematoma growth, mortality *and* disability, but small increase in thromboembolic events (NEJM 2005, Mayer et al). Larger phase three trial (NEJM 2008, Mayer et al) → no change in functional outcome. Best dose remains unclear. See Intracerebral Haemorrhage, page 211

Subarachnoid Haemorrhage

- See Critical Care Management of Patients Following Aneurysmal Subarachnoid Haemorrhage: Recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference, Neurocritical Care, 20 July 2011
- = bleeding occurring principally into the subarachnoid space and not into the parenchyma, 85% caused by ruptured saccular (berry) aneurysms (which develop later in life – not congenital)
- Epidemiology:
 - Same risk factors, but usually younger patients (peak in 6th decade) with female: male of 1.6:1
 - 5 – 20% have positive family history with first degree relatives having 3 – 7 fold risk
 - Overall mortality 50%, up to 50% survivors having residual deficit → dependency
- Presentation: thunderclap headache, ↓LOC for < 1 hour in 50%, with focal neurology in ~ 30%. Meningism and vomiting in those with higher GCS
- Investigations:
 - CT is false negative in 2% due to small volume of blood → LP for xanthochromia after at least 6 hours (for blood to lyse)
 - Difficult to distinguish between trauma leading to post-traumatic SAH and primary aneurysmal SAH causing a fall/crash
 - Angiography the gold standard, MRI and CT becoming more sensitive
 - CTA should be used if endovascular repair is not planned at the time. CTA preferred over digital subtraction angiography in this setting.
 - Transcranial Doppler to estimate MCA blood velocity shows velocity of > 120 cm/s correlates with vasospasm on angiography – allows monitoring in the ICU and response to treatment. Needs thin window of temporal bone (absent in 15%) and is very user dependent
- Scoring
 - World Federation of Neurological Surgeons Grading:

	Signs	GCS	Motor deficit
I	Conscious, no meningism	15	Absent
II	Drowsy, no significant deficit	13 – 14	Absent
III	Drowsy with neurological deficit – probably intracerebral clot	13 – 14	Present
IV	Deteriorating with major deficit – because of large intracerebral clot	7 – 12	Present or absent
V	Moribund with extensor rigidity and failing vital centres	3 – 6	Present or absent
 - Hunt and Hess clinical classification: Clinical score grading from 1 (70% survival) to 5 (10% survival)
 - Fisher Score grading severity on CT:
 - 1: none evident
 - 2: < 1 mm thickness of blood
 - 3: > 1 mm thick
 - 4: Diffuse, intraventricular haemorrhage or parenchymal extension
- Major problems to manage:
 - Effects of the haemorrhage itself
 - Early rebleeding
 - Hydrocephalus
 - Vasospasm/delayed cerebral ischaemia – often used as surrogate markers of each other but can occur independently. *Vasospasm should only be used as a descriptor of radiological findings.*
- Only on intervention (nimodipine) has been proven to improve outcome in prospective randomised controlled trials

Management of Subarachnoid Haemorrhage

- Supportive Care:
 - Should be treated at high volume centres
 - Neurological observation
 - Intubation if required for airway protection,
 - Analgesia
 - Stress ulcer prophylaxis
 - DVT prophylaxis with sequential compression devices. No heparin in unprotected aneurysms or within 24 hours before or after intracranial procedures

- Fluid management: no specific modality recommended over clinical assessment and vigilant fluid balance management. Should target euvolaemia (evidence of harm from hypervolaemia). If persistently negative fluid balance, consider fludrocortisone or hydrocortisone
- Hypo and hyper glycaemia should be avoided
- Temperature management: look for infection if ↑temperature, lower temperature during the risk period for delayed cerebral ischaemia (antipyretics and surface/intravascular cooling if required)
- Statins: continue prior statins, trials are pending for acute statin therapy in statin-naïve patients for prophylaxis of delayed cerebral ischaemia
- Avoid hypomagnesium, trials pending for induced hypermagnesium – not currently recommended
- Anaemia: General medical thresholds not appropriate. Target Hg above 8 – 10 g/dl (moderate quality evidence)
- Surgical Intervention:
 - Decompressive Craniectomy associated with poorer outcomes (Sydney Retrospective Audit)
 - Clipping preferred, wrapping, ligation or bypass grafting if inaccessible
 - Timing debated. Early (within 3 days) → fewer deaths from rebleeding but more friable tissues. Opposite with day 10 – 12. No RCTs.
 - Endovascular coiling:
 - Not all aneurysms can be coiled (eg wide necks)
 - Risks: aneurysm rupture or occlusion of adjacent vessel causing ischaemia
 - Requires anticoagulation
 - If major complications, still need neurosurgical procedure
 - Coiling easier than clipping in posterior fossa
 - ISAT Trial (International Subarachnoid Aneurysm Trial), Lancet 2005, Molyneux et al. Clipping vs coiling in 2143 patients with ruptured aneurysms. Multicentre study comparing craniotomy and endovascular coiling where both were appropriate (ie > 90% of aneurysms < 10 mm and in the anterior circulation). Coiling had more independent survivors at 1 year. Risk of rebleeding low, but higher in coiling. Problems with wide neck aneurysm. Technology continues to advance
 - Other advantages of coiling over clipping:
 - Reduced cost
 - No need for craniotomy and associated neuro-anaesthetics
- Blood Pressure Control:
 - Reduced bleeding but higher rates of infarction with BP lowering
 - Hypotension should be avoided
 - Recommended to reduce BP > 200/100 with unclipped aneurysms - β and Ca channel blockers recommended. Vasodilating agents may → cerebral vasodilation which may → ↑ICP
- No neuroprotective strategies have shown benefit
- Statins: Conflicting meta-analyses. Needs further research. STASH Trial recruiting

Complications of Subarachnoid Haemorrhage

- **Acute hydrocephalus:**
 - Characterised by one-point drop in GCS, sluggish papillary responses and bilateral downward deviation of the eyes (“sunset eyes”)
 - Confirm with CT
 - Treat with EVD – complications of bleeding and infection (no RCTs)
- **Raised ICP:** see Intracranial Pressure, page 207
- **Seizure control:** little evidence for prophylaxis, if used should be short course and not phenytoin. Consider continuous EEG monitoring for neurological deterioration of uncertain cause - ↑sensitivity vs traditional snapshot EEG. Permits early detection of NCSE (which is often missed). Most people who have fits have them early (eg if you’re monitoring do it for the first 24 hours)
- **Rebleeding:**
 - Risk dependent on site of aneurysm, presence of clot, degree of vasospasm, age and sex
 - 5 – 10% over the first 72 hours, 20% in first 2 weeks, the 1.5% per day for following 2 weeks
 - Immediate repair markedly reduces the risk of rebleeding (clipping or coiling)
 - An early short course of anti-fibrinolytic therapy prior to repair (but no longer than 72 hours) should be considered (weak recommendation)
- **Delayed Cerebral Ischaemia (DCI):**
 - Definition: neurological deterioration presumed related to ischaemia that persists for > 1 hour.
 - Most commonly caused by vasospasm. May lead to infarction. Most common 3 – 14 days after event
 - Assessment: repeated clinical exam. CT with contrast accurate and less invasive. DSA gold standard. Transcranial Doppler high specificity but only moderate sensitivity.

- Management:
 - Aim: prevent secondary injury
 - Consider a saline bolus to increase CBF in ischaemia as a prelude to other interventions
 - Haemodynamic strategies: trial a period of induced hypertension titrated to neurologic function. No benefit from hypervolaemia over euvolaemia. No place for haemodilution
 - Drugs: only evidence is for Ca channel blockers. Some centres use intra-cisternal thrombolytics
- **Cerebral vasospasm** related delayed cerebral ischaemia:
 - Tends to occur day 4 – 14 post bleed
 - Angiographic evidence in 70% of SAH, only 30% symptomatic → a dilemma
 - *Prophylactic oral nimodipine* 60 mg QID for 21 days reduces risk of ischaemic stroke by 34%. BMJ 1989, Pickard et al. IV nimodipine needs titration (higher incidence of hypotension) and no robust evidence. If hypotension then more regular, smaller doses. Benefits appear to be due to an effect on the smaller penetrating vessels, or neuroprotective effects, rather than cerebral vasodilation identifiable by angiography
 - Diagnosis/monitoring for vasospasm:
 - Clinical exam, new neurology or drop in GCS in a conscious patient. Lack of specificity and sensitivity often necessitates a CT. Non-invasive, repeatable, performed at bedside
 - EEG: Focal areas of slowing correlate with angiographic vasospasm and a ↓ in alpha to delta ratio strongly correlates with ischaemia. Sensitivity and specificity high. Not readily available and requires skilled interpretation. Potential role for continuous EEG
 - Digital subtraction 4 vessel angiography the gold standard for detection of large artery vasospasm. Detects narrowing but not necessarily ↓ distal flow. May allow therapeutic intervention (angioplasty) at the same time. Invasive, risks of bleeding, embolism, contrast exposure and transport, 1% risk of stroke, requires skilled interventionist
 - High quality CTA can be used for screening for vasospasm. May be combined with perfusion allowing characterisation of both vascular anatomy and associated perfusion abnormalities. Image clarity will be affected by clips or coils. Requires contrast load. Diagnostic capability remains unclear
 - MRI: Diffusion weighted accurately identifies brain tissue at high risk of infarction. Perfusion weighted reveals asymmetry in regional perfusion.
 - Transcranial doppler:
 - Low risk, performed at the bedside, non-invasive and able to be repeated daily enabling trend analysis
 - Operator dependent with high inter-observer variability
 - Debate about the correlation between flow and vasospasm. High velocity (> 200 cm/sec) is bad, but what about lower velocity. May be more accurate when MCA velocity is indexed to the ipsilateral extracranial carotid artery (Lindgaard index, > 3 strongly predictive)
 - SPECT/PET: Show variable correlation with vasospasm as assessed by more conventional methods.
 - Measures of tissue oxygenation with parenchymal sensors, and microdialysis for monitoring biochemical indices of ischaemia, are largely research tools
 - If ↓LOC but no rebleeding, hydrocephalus or metabolic disturbance, and evidence of vasospasm on TCD or angiogram, then treat:
 - Intra-arterial vasodilators and/or angioplasty
 - Timing is unclear, but generally rescue therapy when medical treatment has failed
 - Tried without clear positive benefit:
 - Nicardipine reduced vasospasm but didn't improve outcome
 - Statins: Conflicting evidence. Awaiting results of STASH trial
 - Mixed studies with MgSO₄. MASH Trial of 1204 patients in MRCT showed no benefit. Neither did Bradford et al, CCR 2013 (Australian study of 162 patients)
 - Tried or ongoing studies with NO donors, endothelin-1 antagonists, dapsone...
 - Angiographically directed vasodilators (eg verapamil, nimodipine) may show short term reversal but sustained effect has not been confirmed
 - Small trial of lumbar CSF drainage post clipping → ↓ vasospasm (30 vs 63%) and higher GCS at 1 & 3 months
 - Triple H therapy:
 - The theory is that vasospasm is due to loss of effective autoregulation. CBF is then dependent on perfusion pressure and viscosity
 - Hypertensive (with vasopressors), hypervolaemia (with fluid loading) haemodilution for 21 days

- Not used as a strict protocol, no RCTs, but fluid loading, and vasopressors if ↓GCS are common. See Treggiari et al, J of neurosurgery 2003 for systematic review
- Acute management of vasospasm in *traumatic* SAH *not* recommended. See Brain Specific Therapy, page 240
- **Parenchymal haematoma:**
 - In 30%
 - Worse prognosis than SAH alone
 - If compressive symptoms then haematoma evacuation and simultaneous clipping may improve outcome
- **Hyponatraemia:** See Hyponatraemia in Cerebral Insult, page 208, page
- **Medical Complications:** Mortality due to these almost the same as due to initial bleed, rebleed and vasospasm combined
 - Arrhythmias: 35%. Baseline cardiac assessment with enzymes, ECG and echo is recommended if evidence of myocardial dysfunction
 - Liver dysfunction: 24%
 - Neurogenic pulmonary oedema: 23%
 - Pneumonia: 22%
 - ARDS and atelectasis: 20%
 - Renal dysfunction: 5%

Cerebral Venous Thrombosis

- Precipitants:
 - Infection eg meningitis, epidural or subdural abscess
 - Facial or dental infection
 - Prothrombotic states: diabetic ketoacidosis, ecstasy abuse, OCP, hereditary
 - Idiopathic
- PC: headache, focal neurological deficits (esp cranial nerves), seizures, papilloedema
- Treatment: anticoagulate, even if surrounding intracerebral haemorrhage

Status Epilepticus

- = > 30 mins of a single seizure or intermittent seizures without regaining consciousness
- Operational definition of 5 mins: promotes earlier treatment and diagnosis, and seizures less likely to stop spontaneously after this
- Refractory SE = failure of initial therapy
- Two categories of SE:
 - Generalised convulsive: generalised tonic clonic with LOC
 - Non-convulsive status epilepticus (NCSE):
 - Altered consciousness without convulsive movements but EEG evidence of seizures
 - Group of syndromes with a wide range of responses to anti-convulsants
 - Includes absence SE, complex partial SE (twilight state – confusion, agitation, bizarre behaviour) and GCSE with loss of motor manifestations (they become more and more subtle with time, up to 14% who do not recover after cessation of overt convulsive activity have NCSE)
 - No universal definition. Difficult to diagnose due to:
 - Differentiating from post-ictal state
 - Differentiating from non-ictal symptoms (eg underlying encephalopathy)
 - EEG may be non-specific between epilepsy and encephalopathy
 - Under diagnosed with frequent delays in treatment
 - Due to an acute medical disorder is associated with ↑mortality cf pre-existing epilepsy (27% vs 3%)
 - Treat aggressively as for convulsive status
- Major inhibitory mechanism in the brain is γ -aminobutyric acid A (GABA-A) receptor mediated inhibition. Glutamatergic excitatory synaptic transmission is important in sustaining SE
- Causes of SE:
 - Structural:
 - Previous cerebral insult: stroke, trauma, tumour, meningitis
 - Stroke
 - CNS tumours
 - Head trauma
 - Non-structural:

- Low antiepileptic levels
- Cerebral hypoxia/anoxia
- Metabolic: electrolyte abnormalities, uraemia, $\uparrow\downarrow$ glucose
- ETOH: withdrawal or intoxication
- CNS infection
- Systemic infection
- Idiopathic
- Drug toxicity: TCAs, phenothiazines, theophylline, isoniazid, cocaine, amphetamine
- For SE starting in the ICU consider:
 - Drug withdrawal: narcotics, benzodiazepines, omitting anticonvulsants
 - Metabolic disturbance: hyponatraemia, hypocalcaemia, $\uparrow\downarrow$ glycaemia, uraemia, hepatic encephalopathy
 - Drug toxicity: pethidine, theophylline, cyclosporin, tacrolimus, antibiotics (penicillin, cephalosporins, ciprofloxacin, imipenem in renal failure)
 - Vascular: occlusion or haemorrhage
- EEG:
 - Predictable sequence of EEG changes during untreated GCSE – waxing and waning seizure activity → monomorphic discharges → increasing periods of electrographic silence
 - Some encephalopathies have epileptiform patterns on EEG but aren't traditional NCSE. Unclear whether the abnormal discharges contribute to the altered mental state (eg myoclonic discharges after hypoxic insult)
- Endocrine and metabolic effects of GCSE:
 - \uparrow catecholamines initially → then hypotension + hypoglycaemia → given cerebral metabolic activity remains high falling CPP → hypoxic injury
 - Don't forget: aspiration, rhabdomyolysis, cardiac arrhythmias
 - Hyperthermia due to both muscle activity and central sympathetic drive (ie can persist even when paralysed)
- Pseudoseizures:
 - Suggestive features: variation from event to event, 'on-off' appearance, \uparrow movement if restrained, resistance to eye opening, absence of pupillary dilation, normal tendon reflexes and plantars immediately after convulsion, no metabolic change despite prolonged fitting
 - EEG monitoring only certain way of differentiating pseudoseizure
- Investigations:
 - Initial:
 - Glucose, electrolytes, urea, LFTs
 - ABG or oximetry
 - Anticonvulsant drug levels
 - FBC (eg consider TTP)
 - Urinalysis
 - After stabilisation:
 - LFTs, lactate, CK
 - Toxicology
 - LP: if suspicion of infection. Meningitis is an uncommon cause of SE in adults
 - EEG and response on EEG to BZD
 - Brain imaging: CT or MRI
- Outcome:
 - Worsens with age: 3% in children, 30% in those over 65
 - SE precipitated by hypoxia is usually fatal. NCSE found in critically ill comatose patients is bad
 - Neurone-specific enolase (NSE): marker of brain injury. Increases in serum NSE correlate with duration and prognosis of GCSE

Management of Status Epilepticus

- The longer it goes, the harder it is to treat with drugs
- Approach:
 - Termination and prevention of recurrent seizures
 - Treat precipitating causes
 - Avoid complications
- Little evidence: the main RCT showed lorazepam, Phenobarbital, or diazepam followed by phenytoin are all acceptable initial treatment. Phenytoin alone is not as good as lorazepam
- EEG:

- Goal controversial: either background suppression (iso-electric) or seizure suppression regardless of background
- Indications for EEG monitoring:
 - Refractory status – to aid titration of AEDs (minimising dose and toxicity) and ensuring suppression – continuous or intermittent monitoring
 - If receiving neuromuscular blockade
 - Poor conscious state after apparent suppression of seizures
 - Suspected pseudoseizures
- Particularly in the elderly, aggressive treatment (eg anaesthesia) may be associated with more risk than benefit
- Protocol:
 - Assess: A, B, C, GCS
 - IV access and bloods
 - If hypoglycaemic or if not glucose measurement available, give glucose: in adults thiamine 100mg iv and 50 ml of 50% glucose
 - **Benzodiazepines:**
 - Enhance inhibition of GABA. Effect may reduce with prolonged use due to ↓ receptor affinity
 - **Lorazepam:** 0.1 mg/kg iv at 2 mg/min to 10 mg. Less lipid soluble, but equivalent in RCT to diazepam, and lower incidence of seizure recurrence due to longer action (ie best agent)
 - **Diazepam** 0.2 mg/kg at 5 mg/min up to 20 mg. If it terminates seizure give phenytoin prophylaxis. Highly lipid soluble but short duration of action
 - **Midazolam:** short duration allows earlier neurological assessment. Can be administered buccal, intranasal and intramuscular (rapidly absorbed compared to im diazepam and lorazepam) routes. Intranasal midazolam as effective as iv diazepam in kids and buccal is as effective as rectal diazepam in prolonged seizures
 - Repeat dose every 2 – 5 mins if required
 - Anti-epileptics for benzodiazepine resistant status:
 - See Meta-analysis in Yasiry, Seizure 2013
 - **Phenytoin:**
 - 90% Protein bound. Hepatic elimination. Half-life 22 hours (ie several days in steady state). Zero order metabolism in therapeutic range. Enzyme inducer (see Phase 1 Metabolism, page 336)
 - 15 – 20 mg/kg at < 50 mg/min. 1 gm may be insufficient in some adults. Never IM. 85% bioavailability (ie oral and iv doses ~ the same)
 - Efficacy 50%
 - Monitor BP (hypotension in 50% at 50 mg/min) and ECG (arrhythmias in 2%) during infusion. If hypotension or arrhythmias then stop or slow infusion
 - Dose related neurotoxicity (nystagmus, ↓coordination, confusion)
 - Blood dyscrasias (eg megaloblastic anaemia) respond to folate supplementation
 - Rare hypersensitivity (eg SJS)
 - Carrier may contribute to side effects – fosphenytoin may be preferable
 - **Valproate:** has been used but insufficient data to recommend its use before phenytoin. Non-sedating, generally well tolerated, few reports of hypotension or respiratory depression. 25 – 35 mg/kg at a maximum rate of 6 mg/kg per min
 - **Levetiracetam** (Kepra) is increasingly used. Efficacy 68%
 - **Phenobarbital:** Potent anticonvulsant barbiturate with long duration. Equal efficacy to BZDs and phenytoin as first line, but greater depression of respiration, BP and LOC. Likelihood of phenobarbital controlling seizures when these other agents have failed is small.
 - If persisting (refractory SE) intubate with either of the following targeting EEG suppression of seizures or EEG background suppression. Maintain BP by reducing infusion rate, fluids or pressors:
 - See Sedation Drugs, page 89
 - **Thiopental:** Barbiturate. Slow bolus 3 – 4 mg/kg (rapidly redistributed into peripheral fat, once saturated prolonged action of hours or days) followed by infusion 1 – 5 mg/kg/h.
 - **Propofol:** slow bolus 1 – 2 mg/kg followed by infusion 2 – 5 mg/kg/h. Controls seizures more effectively than barbiturates, and short duration allows earlier assessment. Seizures tend to recur with sudden discontinuation.
 - **Midazolam:** slow bolus 0.1 – 0.2 mg/kg followed by infusion 0.1 – 1.0 mg/kg/h. Wide variation in recommended infusion rates. Tachyphylaxis may develop
 - Useful adjuncts may include ketamine, topiramate, and inhalational agents

- Insert NG and administer usual AED
- Continue seizure monitoring – continuous till 2 hours after stopped then half an hour for every 2 hours.
- Avoid muscle relaxants unless problems with ventilation or severe lactic acidosis. Only use with continuous EEG monitoring
- 12 hours after resolution start reducing propofol or discontinue midazolam
- Surgery is very occasionally used (eg focal resection, corpus callosotomy, vagus nerve stimulation)
- Reverse factors that lower seizure threshold: ↓drugs, (cefepime), fever, hypoxia, ↓glucose, ↓Na

Meningitis and Encephalomyelitis

- Definitions:
 - Meningitis: Infection/inflammation of the meninges and subarachnoid space
 - Aseptic Meningitis: bacteria not isolated from CSF. Due to viral meningitis, partially treated bacterial meningitis, TB, fungal, lymphoma, sarcoidosis...
 - Encephalitis: infection of the brain parenchyma: may present with seizures, cognitive or behavioural symptoms
 - Subdural empyema: suppurative process between the pia and dura mater
 - Brain abscess: puss within the brain parenchyma
- Differential:
 - Infection:
 - Bacteria:
 - Streptococcus pneumoniae
 - Neisseria meningitidis
 - Haemophilus influenzae
 - Listeria monocytogenes (age extremes)
 - Neonates: Streptococcus agalactiae, E. Coli
 - TB, Brucellosis, Borrelia, Leptospirosis, Treponema pallidum (Syphilis)
 - Skull trauma/surgery: Staph aureus, G – ive bacilli
 - Virus: CMV, EBV, HCV, echovirus, enterovirus, HSV, Arboviruses (eg Ross river and Dengue)
 - Fungi: Candida, Cryptococcus
 - Protozoa: Malaria
 - Multisystem inflammatory or malignant disease:
 - Lupus
 - Sarcoid
 - Lymphoma
 - Micro-metastasis
 - Inflammation from other causes:
 - Haemorrhage
 - Vaccination
- Drugs

Diagnosis of Meningitis/Encephalomyelitis

- Lumbar Puncture:
 - For good paper on the complications of LP, see Williams et al, Internal Medicine Journal 2008
 - Bed rest following LP → non-significant trend to worse post-LP headache. Longitudinal bevel orientation → ↓post LP headache
 - No evidence that wearing a mask reduces post-LP meningitis
 - Aspirin is not a contraindication to emergent LP. Clotting abnormalities/warfarin should be corrected/reversed before emergent LP
 - No reports of a neurologically normal person deteriorating post LP
 - Clinical exam predicts findings on CT (NPV 97%, no complications from missed abnormalities). Indications for CT prior to LP (any signs of raised ICP):
 - Focal neurology
 - Significantly reduced LOC (Swedish guidelines have removed this, saying LP should be performed immediately if meningitis suspected)
 - Seizures
 - Immunocompromise
 - Papilloedema

- Concern about herniation post-LP is only reported in 7 adults, 6 of whom had signs of imminent herniation before LP. Not doing a CT → ↓door-to-antibiotic time and ↓mortality. Mortality increases 3% per hour of antibiotic delay (Glimaker, BMJ 2013)
- 50 – 60% sensitivity, even shortly after empirical antibiotics.
- PCR

	Normal	Bacterial	Viral
WBC	< 5 per mm ³ mononuclear	200 – 10 000 per mm ³ predominantly polymorphs	< 500 per mm ³ mainly lymphocytes
Protein	0.2 – 0.4 g/l	0.5 – 2.0 g/l	0.4 – 0.8 g/l
Glucose	= blood	<= blood	

- Throat swab

Bacterial Meningitis

- Presentation: usual presentation (fever, headache, photophobia, neck stiffness, seizures, Kernig's, ↓ LOC) may be muted in immunocompromised, elderly or infant. Classic signs in < 50%
- Droplet or saliva spread. Usually haematogenous spread to meninges. Check for dental, sinus, pharynx and ear infection
- Significant inflammatory response leading to vasculitis, thrombosis, cell damage → vasogenic and cytotoxic oedema
- Organisms:
 - Streptococcus pneumoniae: Pneumococcal meningitis has worse outcomes than meningococcal
 - Neisseria meningitidis
 - Haemophilus influenzae: reduced significantly by vaccination
 - Listeria monocytogenes
 - Nosocomial infections: E Coli, Pseudomonas, Klebsiella, Acinetobacter
 - Immunocompromised: fungal, viral and cryptococcal
 - Following neurosurgical or trauma: staph aureus and S epidermidis

Management of Bacterial meningitis

- Delays in ABs a significant risk factor
- ABs:
 - Penicillin G, ampicillin (covers listeria), 3rd generation cephalosporins modified for local resistance
 - Drug resistance Strep pneumoniae: Ceftriaxone + rifampicin or vancomycin. Repeat LP after 48 hours to check for improvement
 - Recent head injury/shunts: vancomycin + aminoglycoside (gent 5 – 7 mg/kg)
- Dexamethasone treatment:
 - Trials:
 - European trial (de Gans et al, NEJM 2002), 301 patients, overall benefit, but on subgroup analysis benefit confined to those with S pneumoniae, with presenting GCS 8 – 11, and benefit seemed to be from reducing in systemic complications, not neurological complications
 - Malawi, n = 465, 95% had HIV, no benefit from dexamethasone
 - Vietnam, n = 435 in suspected meningitis, no benefit, but in the subgroup with culture positive meningitis (ie confirmed bacterial), mortality improved. 39% had Strep suis, these did better than the rest
 - Meta-analysis of all trials: suggests only mortality benefit in S pneumonia, and improved neurological outcome (eg ↓sensorineural hearing loss) in developed not developing countries
 - 0.15 mg/kg every 6 hours for 4 days. Stop dexamethasone if subsequently demonstrated to be not S Pneumococcus
 - Benefit in Haemophilus in kids
 - In animal models, dexamethasone may reduce BBB penetration of vancomycin → high doses recommended
- If seizure (risk factor for poor prognosis):
 - IV BZD then phenytoin load
 - Exclude raised ICP, cerebritis, cerebral abscess, venous thrombosis
- Raised ICP: hyperventilation, mannitol infusion, CSF drainage
- Cooling: MRCT in 49 French ICUs with GCS < 8 targeting 32 – 34°C stopped early for potential harm
- General management:
 - IV fluids to maintain cerebral perfusion pressure ~ 70 mmHg
 - Respiratory support

- Public health: 2 day course of rifampicin 600 mg 12 hourly

Pneumococcal meningitis

- Treatment:
 - ABs within 30 mins
 - Ceftriaxone 2 gm bd + vancomycin 1 gm BD (stop if sensitive to ceftriaxone). Then penicillin 1.8 gm 4 hourly if MIC < 0.125 gm/l
 - Dexamethasone 0.15 gm/kg max 10 mg QID for 4 days (risks altering vancomycin penetration)
- Predisposing factors:
 - Extremes of age: < 2 or > 65
 - Chronic lung disease, sinusitis, otitis media
 - Asplenia (functional and anatomic)
 - Immunosuppression
 - Transplant
 - CSF leaks/head trauma
 - Cochlear implants/shunts
 - Alcoholism
 - Diabetes
 - Hypo-Ig conditions
- Prevention in asplenic patient:
 - Vaccination 14 days before or after splenectomy
 - Revaccinate 5 yearly (no consensus)
 - Antibiotics empirically if febrile
 - If previous problems then oral ABs for life

TB Meningitis

- Varied presentation
- Risk factors include: HIV, diabetes, recent steroids
- Diagnosis:
 - CSF can be normal in HIV
 - Cultures can take up to 6 weeks
 - Imaging: basal meningitis and hydrocephalus (non-specific)
- Treat with isoniazid (bactericidal and good CNS penetration), pyrazinamide, rifampicin, and ethambutol. Monitor kidneys, liver and eyes. Some evidence of steroids in some populations

Viral Meningitis

- Presentation: less severe than meningitis
- Usually self-limiting enterovirus or coxsackie infection
- Also echoviruses, mumps, polio, HIV
- HSV 1 is a common cause of encephalitis but rarely of meningitis
- Treatment: HSV1 or 2 → acyclovir 10 mg/kg TDS

Encephalitis

- Intellectual impairment, focal neurology or seizures suggests parenchyma involved
- Diagnosis:
 - T2 weighted MRI
 - EEG showing slow waves
 - PCR of CSF
- Pathogens:
 - HSV 1:
 - Most common cause of focal encephalitis (usually frontal or temporal lobes)
 - IV acyclovir 30 mg/day for 14 days reduces mortality from 70 → 25%. Monitor renal function
 - If cerebral oedema then empirical steroids but no trials to support this
 - CMV: ganciclovir/valganciclovir
 - Arboviruses: can cause epidemics via mosquitoes and ticks. West Nile virus most common. Test with CSF antibodies
 - Chronic JC virus → progressive multifocal leukoencephalopathy (PML). Subacute confusion, weakness, visual symptoms in immunocompromised. No treatment
 - Chronic infection: HIV 1, measles, rubella

Subdural Empyema

- Pus between the dural and arachnoid space, usually due to ear or sinus infection
- Need head CT and surgical drainage
- With treatment 20% mortality and neurological sequelae common

Epidural Infection

- Infection between skull and dura, often as a result of osteomyelitis or malignancy
- Fever, local tenderness, rapid progression
- Often staph aureus
- CT or MRI
- Decompression and drainage urgent
- Often nosocomial infection → resistance common

Brain Abscess

- Predisposing factors: cranial trauma, neurosurgery, chronic ear or sinus disease, suppurative lung disease, congenital heart disease
- PC: headache, vomiting, ↓LOD, seizures, focal neuro signs
- Investigations:
 - LP potential dangerous
 - CT scan: ring enhancing lesion
 - Assessment of immune status (eg HIV)
 - Specific blood tests, eg Toxoplasma serology
- Indications for surgery: large single lesions, relief of ↑ ICP, tissue diagnosis
- Empirical antibiotics

Lyme Disease

- Tick-borne spirochete *Borrelia burgdorferi*
- Presentation:
 - GI upset and fever
 - Neuro symptoms: cranial neuropathy (eg facial palsy), meningoencephalitis, radiculopathy
- CSF may not be remarkable. PCR may be helpful. Characteristic MRI appearances
- Treatment: 10 - 21 days of β-lactam
- Vaccine preventable

Other

- Cerebral malaria
- Legionella and mycoplasma pneumonia may → headache, coma, encephalopathy
- Septic encephalopathy: multifactorial: changes in cerebral blood flow, oedema, disruption of BBB, inflammatory mediators, deranged renal and liver function. EEG ↑ slow waves

Tetanus

- Caused by exotoxins produced by *Clostridium tetani*, obligate spore forming G+ve anaerobic rod. Spores in soil and animal faeces. Not invasive – requires portal of entry. Infects necrotic wounds/burns/ulcer. Incubation of 2 – 12 days
- Pathology:
 - Tetanospasmin toxin: potent (0.01 mg lethal dose), concentrates in the anterior horn and is preferentially bound by inhibitory inter-neurons, blocking inhibitory pathways. Binding is irreversible so recovery depends on formation of new nerve terminals
 - Tetanolysin: causes haemolysis, myocardial dysfunction
- Epidemiology: US 0.04 per 100,000, Africa 5 in 1,000 live births
- Presentation:
 - Pain and stiffness → rigidity, difficulty mouth opening (trismus/lock jaw) → moves down the body. Spasms life threatening when they involve larynx or diaphragm.
 - Non-muscular manifestations if severe:
 - Autonomic: loss of inhibitory control of spinal cord sympathetic tracts → sympathetic overactivity. Tachycardia, bowel and bladder dysfunction, HTN, fever, sweating, cyanosis of digits
 - Cardiac arrhythmias: sudden arrest from tetanolysin. Turns or suctioning may precipitate bradycardia or arrest
- Diagnosis: no lab tests (non-specific). Culture *C. tetani* from wound in 30%

- Differential:
 - Dystonic reaction to TCAs
 - Strychnine poisoning
 - Convulsions
 - Tetany
- Prevention and treatment:
 - Active immunity from tetanus toxoid, non-toxic derivative of the toxin:
 - Used for vaccination
 - Immunisation with toxoid confers protection for the *next* injury – not the current one. A completed primary immunisation confers lifelong immunity (although booster recommended at 65). No deaths have been reported in the US among those who have completed primary vaccination
 - Trauma patients who cannot communicate their vaccination status are often given a “routine booster”. Risks are pain (50%), swelling (25%), rare anaphylaxis and GBS. No evidence of benefit exists, and there is evidence of no benefit if primary vaccination was completed (Rhee et al, Journal of Trauma, 2005)
 - Antitetanus toxin at best neutralises only circulating toxin – not toxin already fixed in CNS. Single dose human anti-tetanus immunoglobulin (5,000 – 10,000 units). FFP is a cheaper substitute. Should be reserved for those who have never received primary immunisation (mainly those born pre-WW2)
 - Wound care: debridement. It is not possible to clinically determine if a wound is tetanus prone. Can occur with minor injuries. Is rare after major injuries
 - Antibiotics: destroy spores. Depends on antibiotic concentration at wound site. Options include metronidazole (good penetration of necrotic tissue) and penicillin (penicillin may worsen spasms as a GABA antagonist)
 - Muscle spasms settle over 1 – 3 weeks
- Infection does not confer immunity. If infected then tetanus toxoid at a separate site to TIg injection
- Supportive care:
 - Darkened room with minimal external stimulation
 - Secure airway, ventilate if necessary, any muscle relaxant if needed. Consider early tracheostomy
 - Heavy sedation may prevent spasm and lessen autonomic dysfunction – mega doses of morphine and diazepam (up to 3400 mg/day)
 - Short acting α (eg chlorpromazine) and β (eg esmolol) blockers for autonomic dysfunction – never unopposed β blocker alone (otherwise congestive cardiac failure). Labetalol (dual α and β -blockade has been used)
 - Mg confirmed in a large trial. Infuse 20 mmol/hr to serum 2.5 – 4.0 mmol/l – blocks catecholamine release, ↓receptor responsiveness to catecholamines
 - Potential role of dantrolene, baclofen
- Prognosis: 50% mortality in over 60s. Those who survive are likely to make a full recovery

Neuromuscular disorders

- See Weakness Hot Case, page 382
- Presentations:
 - Catastrophic weakness → IUC admission. Often primary neurologic illness (eg GBS, etc.)
 - Admitted with non-neurologic illness who develop weakness (more likely to be Critical illness myopathy/neuropathy or iatrogenic)
- Differential of weakness in ICU:
 - Cerebral cortex:
 - Vascular event
 - Metabolic or ischaemic encephalopathy
 - Brainstem: Lower pontine haemorrhage or infarction (locked in state)
 - Spine:
 - Transverse myelitis/MS
 - Compression (tumour, abscess, haemorrhage)
 - Ischaemia
 - Infection: CMV, mycoplasma, legionella, herpes
 - Spinal anterior horn cells:
 - Motor neuron disease
 - Poliomyelitis
 - West Nile Virus

- Spinal muscular atrophy
- Peripheral nerve condition:
 - *Guillain-Barre* (progressive bilateral paralysis)
 - *Critical illness polyneuropathy* (symmetrical weakness in association with critical illness, especially in severe sepsis. May have muscle tenderness and ↓ distal sensation)
 - Lambert-Eaton syndrome
 - Toxins: arsenic, thallium, cyanide
 - Uraemia 2nd to renal failure (esp acute on chronic)
 - Mononeuropathies or plexopathies: 2nd to ischaemia, pressure palsies, compartment syndromes, etc.
- Neuromuscular junction:
 - *Myasthenia gravis*
 - Botulism: see Other Causes of Weakness in ICU, page 227
 - *Delayed reversal of neuromuscular blockage* (prolonged by acidosis and ↓K)
 - Toxins: pesticide poisoning
 - Tick paralysis. Rare. US and Australia. Resembles GBS but with complete ophthalmoplegia. Look for tick in skin/hair. Removal → improvement
- Muscle contraction:
 - *Steroid myopathy*
 - Severe ↓K, ↓PO₄, ↑Mg or ↑Ca
 - *Critical-illness myopathy*:
 - Severe catabolism and disuse atrophy
 - Acute alcoholic myopathy
 - Polymyositis/dermatomyositis
 - Toxic: colchicine, statins, amiodarone....
 - Porphyria: abdo pain, seizures/neuropsychiatric symptoms, dark urine, ↓Na, rapid onset motor neuropathy. Starvation and anticonvulsants are triggers. Test urine for porphyrins
 - Periodic paralysis
- Consider nutritional deficiency and cachexia

Guillain Barre Syndrome

- Major cause of rapid-onset flaccid paralysis now that polio is largely eradicated
- Aetiology:
 - Antecedent campylobacter jejuni infection (25 – 40%, more severe course), viral infection (CMV, influenza A, zoster, EBV, chickenpox, mumps, HIV), vaccination
 - Cell-mediated peripheral nerve demyelination
 - May be secondary Wallerian degeneration
 - Subtypes:
 - Acute motor axonal neuropathy (AMAN) and Acute Motor Sensory axonal neuropathy (AMSAN): associated with antibodies to GD1a and GQ1b gangliosides
 - Miller-Fisher syndrome: cranial nerves predominate: ataxia, areflexia and ophthalmoplegia. Strongly associated with recent C jejuni infection and GQ1b antibodies
- Presentation:
 - Initial paraesthesia common
 - Ascending relatively symmetrical motor weakness
 - Loss of tendon reflexes
 - Cranial nerve involvement in 45%, especially bilateral weakness of facial muscles
 - 1/3 require ventilatory support
 - Autonomic dysfunction is common: orthostatic or persistent hypotension, paroxysmal hypertension and bradycardia, ventricular tachyarrhythmias. Sometimes paralytic ileus, urinary retention and sweating
- Risk factors for poor prognosis:
 - Older age
 - Rapid onset (< 7 dys prior to presentation) or severely weak at presentation
 - Need for ventilation
 - EMG with average distal motor response < 20% normal
 - Proven campylobacter
- Differential:
 - CIDP
 - Structural: disc herniation

- Other acute neuromuscular conditions: botulism, myasthenia, polio, toxic neuropathy eg lead poisoning
- Abnormal porphyrin metabolism
- Recent diphtheria
- Critical illness polyneuropathy
- Investigations:
 - Identification of infection with campylobacter, mycoplasma, EBV, varicella, CMV
 - CSF protein > 0.4 g/l in 90%
 - Elevated CSF IgG levels
 - Nerve conduction studies: reduced conduction velocity and prolonged distal latencies. Reduced distal motor amplitude if severe
- Management:
 - Nadir in 2 – 4 weeks
 - Specific therapy:
 - Plasma exchange (plasmapheresis) – in 2 RCTs improved functional outcomes not mortality. 3 – 5 exchanges of 1 – 2 plasma volumes each over 1 – 2 weeks then stop (cf TTP, where continued until remission, and FFP better). FFP has more side effects than albumin as replacement fluid
 - Immunoglobulin therapy – as effective as plasmapheresis. 0.4 g/kg iv daily for 5 days. ~ 10% relapse, most respond to a further course
 - High or low dose steroids of no value (Cochrane Review)
 - Supportive therapy:
 - Meticulous housekeeping: pressure area care, maintenance of joint mobility and pulmonary function. Prevent corneal ulceration and faecal impaction. May not need venous access
 - Respiratory:
 - Chest physiotherapy
 - Regular monitoring of vital capacity better than regular ABGs. < 15 ml/kg or 30% of predicted level suggests intubation likely. Needs intubation by vital capacity < 10 ml/kg (less than predicted tidal volume)
 - Watch for bulbar involvement: aspiration reflex, inadequate cough
 - Consider early tracheostomy
 - Cardiovascular:
 - Sinus tachycardia the most common autonomic manifestation. Usually not treated
 - Drugs which → exaggerated hypotensive response: GTN, morphine, furosemide...
 - Drugs which → exaggerated hypertensive response: phenylephrine, ephedrine, dopamine, isoprenaline
 - Arrhythmics: suxamethonium, ET suctioning
 - Cardiac arrest: GA – can induce serious arrhythmias
 - GI:
 - Paralytic ileus can occur shortly after intubation
 - Energy and fluid requirements considerably reduced
 - Sedation/analgesia:
 - If not ventilated, take care of respiratory depression/loss of airway
 - Night sedation may help preserve diurnal rhythms
 - Limb pain with passive movement very common – quinine, NSAIDS, antidepressants all tried but may need opioids
- Prognosis:
 - 2.5 – 5% in hospital mortality
 - 15% with functional disability at 1 year

Myasthenia Gravis

- PC: weakness or fatigability on sustained effort
- ICU needed because of severe bulbar or respiratory involvement due to:
 - Spontaneous exacerbation
 - Complication of drug therapy
 - Intercurrent illness
 - Following surgical thymectomy
- PC:
 - Ptosis and diplopia (ocular the only site affected in 20%)
 - Bulbar weakness
 - Asymmetric limb and trunk weakness

- Peak incidence in young females
- All symptoms exaggerated with tiredness (eg worst at end of the day), and improve with rest
- Aetiology:
 - Auto-antibodies to ACh receptors in skeletal muscle detected in 90% - work by competitive inhibition, immune mediated destruction of receptors or binding to parts of the receptor molecule which prevent ACh binding
 - Thymic hyperplasia in the majority, thymoma in 10%
 - Associated with other auto-immune disorders: thyroid, also RA, SLE and pernicious anaemia
- Investigations:
 - Positive 1 mg edrophonium (Tensilon) test – high sensitivity, poor specificity. Atropine 0.6 mg first to prevent muscarinic side-effects
 - EEG has characteristic changes in 90%
- Management:
 - Symptomatic treatment: Drugs which potentiate ACh – pyridostigmine, initially 60 mg QID, but with lots of dose adjustment
 - Steroids: Initially high dose (50 – 100 mg/day prednisone). Transient exacerbation on starting is common
 - Azathioprine and cyclophosphamide – effective in 80% but may take months
 - Thymectomy: best chance of long term remission. Need preoperative optimisation of neuromuscular function. Improvement may take months or even years
 - Plasma exchange, especially in severe respiratory failure secondary to conventional therapy. 5 exchanges of 3 – 4 litres over 2 weeks, *or* IV γ -globulin 400 kg/kg/day for 5 days (mechanism of action unknown)
- Myasthenic Crisis:
 - Life threatening deterioration affecting bulbar and/or respiratory function
 - Due to intercurrent infection, pregnancy, surgery, or drugs (eg gentamicin, suxamethonium, morphine, pethidine...)
 - Need ICU care due to high risk of respiratory failure, pneumonia from inability to cough or from aspiration
 - Identify and correct reversible causes (incl \downarrow K, \uparrow Ca, \downarrow Mg)
 - Monitor respiratory function, ABGs may only deteriorate late
 - High dose steroids and plasma exchange simultaneously
- Cholinergic Crisis:
 - Excessive doses of anticholinesterase drugs, eg > 120 mg every 3 hours
 - PC: abdominal cramps, diarrhoea, excessive pulmonary secretions, sweating, salivation, bradycardia (but this can also occur in MG on high doses of pyridostigmine)
- Perioperative Management:
 - High dose steroids and/or plasma exchange to improve the patients fitness for surgery
 - Avoid non-depolarising muscle relaxants (vecuronium and atracurium probably OK in reduced dose). Suxamethonium is safe
 - 1/3rd need post-op ventilation: predictive factors long pre-operative duration of MG, coexistent chronic respiratory disease, high anticholinesterase requirements, low pre-operative vital capacity (< 2.9 litres)

Motor Neuron Disease

- Most common form is amyotrophic lateral sclerosis
- Affects upper and lower motor neurons, affecting cerebral cortex and anterior horn cells → muscle denervation → atrophy, but sparing of sensory and autonomic function
- PC: limb weakness, muscle wasting (esp small muscles of the hand), fasciculation, spasticity and hyperreflexia (ie upper and lower motor neuron signs)
- Diagnosis: clinical + EMG findings of denervation in at least 3 limbs.
- Differential:
 - Multifocal motor neuropathy
 - Post-polio syndrome
- Management supportive. Centrally acting glutamate antagonist riluzole slightly slows progression

Weakness Syndromes

- Poorly understood, diagnosis of exclusion
- Exclude:
 - Residual paralysis from NMBA: nerve stimulator
 - Residual sedation: consider antidotes: naloxone/flumazenil

- Cranial nerve abnormalities: consider GBS
- Electrolyte abnormalities (\uparrow Ca, abnormal K)
- Deconditioning
- Underlying neuromuscular problem: alcohol, B12 deficiency
- Rhabdomyolysis (eg statins, infection)
- Upper neuro lesions yet to progress to hypertonias: watershed infarcts, acute myelitis
- Evidenced by weaning difficulty: RR > 35, tidal volumes < 5 ml/kg and respiratory acidosis on discontinuing ventilation
- Various names, lack of clear classifications or diagnostic tests make it a confusing area
- Critical illness neuropathy or myopathy now 2 – 3 times more common than primary neuromuscular disorders (GBS, MND, etc.). Affects half of adults in ICU > 1 week, and 70% with sepsis with MOD, ? associated with hyperglycaemia (Crit Care Med 2005 33:4)
- Risks:
 - Severity of illness (eg APACHE)
 - Dialysis
 - Steroids
 - Hyperglycaemia
 - Drugs: aminoglycosides
 - Age
- Examination:
 - Normal higher functions, normal cranial nerves and symmetrical features favour a critical illness neuromyopathy or peripheral neuropathy
 - Reflexes profoundly decreased in neuropathies and decreased in myopathies. Essentially normal in deconditioning or persisting sedative effect
 - Plantars may suggest upper or lower cause
 - Myopathies are often worse proximally and also involve the face
 - Muscle wasting suggests myopathy or pre-existing problem
 - Fasciculation suggests severe neuropathy or myopathy
- Investigation:
 - Bloods:
 - ESR/CRP
 - Electrolytes: K, Ca, PO₄, Mg
 - CK
 - Antibody panel
 - MRI of head and spine to exclude cerebral and spinal causes
 - LP for GBS
 - Nerve conduction studies. Neuropathy shows \downarrow amplitude, \downarrow sensory amplitude, latency preserved (myelin intact)
 - EMG: Myopathy shows retained nerve action potentials, needle EMG with short-duration, low amplitude muscle potentials without decremental response of repeated testing
 - Nerve or muscle biopsy
- No specific therapies. Recovery usual with supportive care. Growth Hormone associated with \uparrow hand grip strength but \uparrow mortality

Critical Illness Polyneuropathy

- Most common
- Acute, diffuse, mainly motor neuropathy
- Presents in recovery phase (> 1 week after onset) with persistent quadriparetic weakness and atrophy, hyporeflexia, loss of peripheral sensation to touch and pin prick and difficulty in weaning, but relative preservation of cranial nerve function
- Specific association with sepsis and MODS
- Difficulty in diagnosis probably means it's often missed
- Histology: axonal degeneration of motor and sensory nerves, and denervation atrophy of muscles
- Prognosis: underlying illness often carries high mortality. Of those who survive, 70% make a complete recovery over 4 – 5 months

Critical Illness Myopathy

- Linked with high use of corticosteroids, neuromuscular blocking agents and perhaps aminoglycosides and β -agonists
- Reflexes and sensation generally preserved

- May have ↑ CK, in severe cases may progress to rhabdomyolysis
- Histology: muscle necrosis and loss of thick filaments
- Subtypes:
 - Tick-filament (myosin) loss: common with steroids, NMBAs and sepsis
 - Cachectic or disuse myopathy: normal EEG
 - Acute rhabdomyolysis: rare, near normal EMG, ↑↑CK
 - Acute necrotising myopathy of intensive care: rare ↑↑CK, poor prognosis
- Functional recovery common

Other Causes of Weakness in ICU

- Periodic paralysis: rare, inherited, episodic weakness presenting before 25 years, resulting from a defect of skeletal muscle ion channels. Hyper and hypokalaemic forms
- Botulism:
 - Cause by exo-toxins of the anaerobic, spore-forming G +ive Clostridium botulinum
 - Prevents ACh release at neuromuscular junction
 - The toxin is produced in vitro and then ingested. May be infection of surgical wound ~ 10 days post op. Presents 3 days after ingestion with nausea, vomiting, diarrhoea or constipation, dryness of eyes and mouth, dysphagia, generalise weakness, bulbar palsy, diplopia, pupillary involvement, normal sensation, normal GCS, often afebrile → progressive symmetrical descending weakness
 - Treatment generally supportive. US Defence Department has an antitoxin not publicly available!

- See Paediatric Trauma, page 328
- See Trauma Hot Case, page 372

Trauma Overview and Basic Management

- Priorities:
 - Rescue the rescuer: ensure your own safety, personal protective equipment
 - Treat the greatest threat to life
 - Definitive diagnosis not immediately important, but anticipate injuries from mechanism
 - Time is of the essence
 - Do no further harm
- All trauma involves transfers of care. Need a common language. Handover: MIST - specify:
 - Mechanism
 - Injuries
 - Status
 - Treatment so far
- Time course of death: trimodal distribution
 - First peak: seconds to minutes, from severe brain or high spinal injury, rupture of heart or large vessels. Generally can't be saved. Only prevention will reduce deaths
 - Second peak: minutes to several hours from injury, due to subdural or epidural haematomas, haemopneumothorax, ruptured spleen, liver lacerations, pelvic fractures, other major blood loss
 - Third peak: days to weeks, due to sepsis or multiorgan dysfunction
- Physical injury from mechanical energy:
 - Blunt: more difficult – injuries often internal, multiple, and not obvious. Bleeding diffuse and venous
 - Penetrating: bleeding often arterial and easier to locate and control
- Triage: Severity determined from
 - ↓LOC: related to brain injury, hypoxia, shock, alcohol/drugs, precipitating neurological or cardiac events
 - Respiratory distress: Common with upper body injuries. Consider airway obstruction, laryngeal injury, pulmonary aspiration, lung and chest wall injury
 - Shock:
 - May be cold and pale. May not be tachycardic. Hypotension may be a late sign
 - Usually haemorrhagic:
 - From external loss, major fractures (detected clinically or via xray), pleural cavity (urgent CXR), peritoneal cavity (detected by laparotomy, diagnostic peritoneal lavage or CT/US), retroperitoneum
 - If exsanguination secondary to penetrating thoracic injury, then emergency room thoracotomy. No place in blunt trauma – needs intubation, volume, bilateral intrapleural drains, chest and pelvic xray and rapidly to OT if bleeding is intrathoracic or intra-abdominal
 - Cardiogenic: distended neck veins ⇒ consider tension pneumothorax, MI, tamponade or MI
 - Neurological: spinal cord injury → ↓BP and warm dilated peripheries
 - Septic: not usual at initial presentation
 - “Golden hour” reflects the longer the patient is shocked the worse the outcome, but has no real validity
 - Alcohol, neurological injury and distracting injuries can make absence of pain unrealistic
- Other needs:
 - Meticulous record keeping, given lots of different people involved
 - Issues around consent – who and when
 - Often the need to preserve or acquire forensic evidence
 - “Stable” is a place full of horse shit – they are either normal or abnormal
 - To operate or not is a surgical decision. Refer to them for this – don't decide for them

Organisation of Trauma Treatment

- Lots of organisational problems. The reality is often junior doctors in charge of resuscitations, delays in urgent operations, and preventable deaths
- Good trauma care requires:
 - Advanced care at the site of injury
 - Rapid transport
 - Sound, clear policies on which hospital's trauma patients should go to

- Systems for rapid evaluation within hospitals
- Patient transfer:
 - Regionalisation has become an accepted concept – means ambulances bypass hospitals
 - Patient outcome is directly related to the time from injury to definitive care \Rightarrow systems to assemble appropriate staff, transfer early, etc.
 - A trauma centre requires rapidly available experience surgeons, anaesthetists and neurosurgeons, and a minimum number of patients annually
- Definitions:
 - Multiple-casualty incident: number and severity of patient do not exceed the ability of the facility to render care. Patients with life-threatening problems and those with multiple system injuries treated first
 - Mass-casualty incident: exceeds the capability of the facility and staff. Patients with the greatest chance of survival and requiring the least expenditure of time, equipment, supplies and personnel are treated first

Trauma Scoring Systems

- Abbreviated Injury Scale (AIS) – anatomy of injury:
 - Divides body into 6 regions: head and neck, face, thorax, abdomen, pelvis, extremities and external
 - Rates injuries in each area as 1 (minor), 2 (moderate), 3 (serious), 4 (severe, survival probably), 5 (critical, survival uncertain), 6 (unsurvivable)
 - Designed for MVAs, validated for blunt and penetrating trauma
 - No variables for physiology or chronic health status
 - Injury Severity Score (ISS) based on AIS grades for three worst body regions, score between 0 – 75. ≥ 16 indicates major trauma and gives mortality $> 10\%$, death below 24 rare, high mortality over 50
- Revised Trauma Score: physiological field based score based on GCS, RR, SBP, cap refill, chest expansion at admission
- TRISS severity index is based on revised trauma score, ISS and patient age. Correlates well with outcome
- APACHE and other physiological scoring systems *don't* work well for trauma
- Comorbidity has a profound effect on trauma outcome

Assessment of Trauma

- According to Advanced Trauma Life Support guidelines
- **Primary Survey:**
 - Do log roll to inspect back where it is appropriate. Usually at E, but if B isn't working you need to do it there to eg exclude posterior penetrating chest injury
 - A:
 - Talk to patient – a verbal response is a good indicator of airway patency and level of consciousness
 - Recognise potential for progressive airway loss \rightarrow frequent reassessment
 - B:
 - Assess and ensure adequate oxygenation and ventilation.
 - Assess for and treat critical injuries: tension pneumothorax, flail chest, massive haemothorax, open pneumothorax
 - C:
 - Assess for organ perfusion: LOC, skin colour, pulse and character, BP
 - Haemorrhage is the primary cause of preventable death after injury. Compounded by coagulopathy (dilutional, depletion) and hypothermia
 - Identify and control external haemorrhage during the primary survey. Resuscitating with on-going bleeding is a waste of time
 - Consider occult haemorrhage: chest, pelvis, abdomen, long bones
 - D (Disability – neurologic status). GCS and pupillary response. Can deteriorate quickly (eg acute epidural haematoma where the patient “talks then dies”). Reassess regularly
 - E (expose the patient). Prevent hypothermia
 - Beware: children, the elderly, athletes either have abundant reserve or none – visible decompensation may be a terminal sign
- **Resuscitation:** Follows ABC
 - A:
 - Chin lift not a head tilt
 - If they can tolerate an OPA they are likely to need intubation
 - Manual in-line stabilisation (MILS) from below

- If there is any doubt about a patient's ability to maintain an airway, or they are restless or uncooperative, then RSI
- B: High flow oxygen for all trauma patients
- C:
 - ↓BP is a sign of decompensation – spot shock before this
 - Clinical signs following blood loss:
 - Class I shock: Up to 750 ml in adult (15%), BP normal, pulse normal: crystalloid
 - Class II shock: 800 – 1500 ml in adult (15 – 30%), BP normal, pulse ↑, respiratory rate ↑: colloid unless pre-existing anaemia, ↓cardiopulmonary reserve or if blood loss continues
 - Class III shock: 1500 – 2000 ml (30 – 40%): rapid volume replacement with RBC probably required
 - Beware special cases where normal values may not apply: extremes of age, pregnancy, athletes, medications (eg β-blockers, anticoagulants), pacemakers
 - Do blood cross-match and other blood tests (including glucose, ethanol and pregnancy test)
 - Purposeful (not “aggressive”) fluid resuscitation via large bore cannula. Often bolus of 1 – 2 litres warmed saline, 20 ml/kg in child. See Fluid Resuscitation in Trauma, page 231
 - With blunt injury, blood loss may continue for 24 – 48 hours
- Resuscitation adjuncts:
 - ECG monitoring: dysrhythmia may indicate blunt cardiac trauma
 - Other monitoring: pulse oximetry, EtCO₂, Sats, BP
 - Xrays
 - Monitor urine output:
 - Urinary catheter unless ruptured urethra suspected (blood at urinary meatus, severe fracture pelvis or abnormal prostate position on PR) in which case SPC
 - If ?pelvic injury can do inject contrast into the meatus and xray to check patency of the urethra
 - Adults want at least > 0.5 ml/kg/hr, children over 1 > 1.0 ml/kg/hr
 - Acceptable urine output may not be due to adequate resuscitation, but to ethanol, mannitol, nephrogenic or neurogenic diabetes insipidus, or non-oliguria renal failure
 - Naso-gastric tube: ↓distension and ↓aspiration (and ↓vomiting in the CT scanner)
 - Analgesia
- **Secondary survey:** once resuscitation is underway
 - History:
 - A: Allergies
 - M: Medications
 - P: Past illnesses/pregnancy
 - L: Last meal
 - E: Events/environment related to injury. Ejection from a motor vehicle greatly increases risks
 - Top to toe, exam front and back
 - Head:
 - Include ears and nose for CSF and blood, and examine scalp thoroughly
 - Check bleeding into airway and jaw for mobility
 - Eyes: check acuity, pupillary size, haemorrhage, penetrating injury, remove contacts, dislocation of lens, ocular entrapment
 - Maxillofacial structures: definitive management often safely delayed
 - Neck: blunt injury can cause injury with delayed signs (eg carotid dissection)
 - Spine: C spine fracture or dislocation assumed until proved otherwise. Signs of spinal cord injury include warm peripheries (loss of vasomotor tone), diaphragmatic breathing, paralysis, priapism, loss of anal tone. Inspect and palpate whole spine
 - Thorax:
 - Rib fractures of themselves minor, but can → haemothorax, pneumothorax, lung contusion and flail chest
 - Less common but severe injuries to heart and great vessels
 - Abdomen:
 - Spleen, liver and mesentery damage and retroperitoneal haemorrhage common
 - Injuries to pancreas and hollow viscera less common
 - Retroperitoneal injuries may not be obvious
 - Normal exam does not exclude significant injury
 - Pelvis:

- Fractures difficult to detect clinically. Look for bruising over iliac wings, labia, and scrotum. Pain on palpation in an awake patient, or movement on gentle AP pressure if unconscious, is significant. Only check once – manipulation can ↑bleeding. Check distal pulses
- Can have massive blood loss, especially with posterior fractures involving sacroiliac dislocation. Urgent management.
- Ruptured bladder/urethra with anterior fractures
- Extremities:
 - Can lose > 1 litre blood from long bone fractures, especially when open, comminuted or displaced
 - Watch for compartment syndrome: especially tibia and forearm fractures, due to vascular, bony or crush injuries. Gives pain to passive stretch or disproportionate pain if awake. Tissue pressures > 34 – 45 mmHg. ↓pulse is a late sign
 - Check distal pulses for vascular compromise (check with doppler)
 - Reduce and splint fractures
 - Military antishock trousers not recommended
- Regular reassessment to ensure new findings are not overlooked
- Remember tetanus toxoid:
 - See Tetanus, page 221
 - Can't predict risk of tetanus from nature of the wounds. However, it is less likely in linear uncontaminated wounds less than 6 hours old
 - Consider human tetanus immune globulin (TIG) if tetanus prone wounds and < 3 previous tetanus toxoid doses

Fluid Resuscitation in Trauma

- See Fluid Resuscitation, page 40 and Fluid Resuscitation in Trauma, page 231
- 2 * large bore cannulas in the ACF. Convert one to a rapid infusion catheter (RIC). Central lines are long and thin ⇒ slow flow. Gauge = number of needles side by side in an inch (↑gauge = ↓size). French = internal diameter)
- If hypotensive or vasoconstricted because of blood loss will usually require transfusion
- Transfusion of large volumes of blood wasteful while bleeding uncontrolled
- In penetrating trauma, extensive fluids prior to haemostasis may be detrimental (?↑BP, displacement of clot, dilutional coagulopathy). Single centre study of 598 patients with penetrating torso trauma randomised to pre-hospital fluids, or none till operating theatre (Bickwell et al, NEJM 1994). Delayed fluid resuscitation showed ↓in-hospital mortality, fewer complications (eg pneumonia, ARDS, coagulopathy, wound infection, acute renal failure). Study has not been replicated. Risk of SIRS and MODS with increased duration of uncorrected shock. Continued controversy.
- No such evidence in blunt trauma. Often dealing with hard to control venous ooze rather than arterial bleeding
- Prolonged hypotension is bad for injured brains ⇒ don't deliberately under resuscitate
- Target a MAP of 40 mmHg until bleeding is controlled in uncontrolled haemorrhage due to trauma
- Meta-analysis of red cell transfusion in trauma, adjusted for confounders → mortality (OR 1.07), MOR and ALI for each additional unit of RBC (Patel, Injury 2014)
- Options:
 - Balanced salt solutions
 - Platelets/FFP for documented or suspected coagulopathy
 - Little evidence of hypertonic saline as small-volume resuscitation fluid pre-hospital (Cooper et al, JAMA 2004). Received either 250 ml 7.5% saline or 250ml Ringers Lactate *in addition* to normal resuscitation protocols. Patients with multi-trauma → diverse cohort
- Not options:
 - Albumin contraindicated – SAFE study showed higher mortality in trauma subgroup, especially those with traumatic brain injury
 - Glucose and glucose-saline solutions not effective

Damage Control Resuscitation

- *Permissive hypotension:*
 - Avoiding over-aggressive resuscitation in order to keep the SBP low enough to avoid exsanguinations but high enough to maintain perfusion. High pressures lead to the disruption of unstable clot and therefore worse bleeding
 - Limited evidence extrapolated from animal studies. Only human evidence is in penetrating trauma, no blunt
 - Trials of volume replacement during active bleeding show better outcomes with lower volume resuscitation

- *Haemostatic Resuscitation:*
 - Correct **hypothermia**: hypothermia → ↓platelet function, ↑platelet sequestration in liver and spleen, ↓ function of factors (eg XI and XII), and altered fibrinolysis. But weak in vitro effect if temperature > 32
 - Correct **acidosis**: pH strongly effects activity of factors V, VIIa and X. Acidosis inhibits thrombin generation. Cardiac contractility and CO fall with pH < 7.2. Impact if pH > 7.2 is likely to be small
 - Treat **coagulopathy** early and aggressively: Many coagulopathic changes occur after trauma. Present at admission and not the product of resuscitation. Use higher FFP to RBC ratios than previously (associated with improved survival). See Massive Bleeding, page 303
 - Limit crystalloid fluids: A large volume fluids can lead to dilutional coagulopathy (> 3 litres of crystalloid → measurable coagulopathy), have no O2 carrying capacity, and contribute to tissue and organ oedema.
 - Hypertonic saline is another potential option
- *Damage Control Surgery:*
 - Management of the metabolic derangement of ongoing bleeding is more important than definitive surgery. Survival given preference over morbidity
 - 4 phase approach to abdominal surgery after trauma:
 - Recognise patients at risk
 - Shortened operations that control haemorrhage and contain spillage from the alimentary tract and urogenital tracts only
 - Rapid transfer to ICU to restore normal physiology: cardiovascular resuscitation, correct acidosis, coagulopathy and hypothermia
 - Repeat laparotomy at 24 – 36 hours with removal of packs, definitive surgery and formal abdominal closure if possible
 - Risks of this approach:
 - New onset or uncontrolled bleeding
 - Abdominal compartment syndrome
 - Inability to wake and wean: open abdomen, planned return to theatre
 - Missed injuries in the multiply injured patient

Imaging of Trauma

- If unstable, don't send to a radiology department distant from skilled resuscitation facilities
- ED xrays:
 - CXR: erect is better for showing intrapleural air or fluid, rupture diaphragm, free abdominal gas or for an abnormal mediastinum
 - Lateral cervical spine: screening only. Does not "clear the spine"
 - Pelvis: not needed in awake patients with no pelvic abnormalities
 - Abdomen: of limited value in the initial evaluation of trauma
- FAST scan: see Abdominal and Pelvic Injury, page 253
- CT
 - Neck
 - Chest
 - Abdomen and pelvis
 - "Pan-man" scan associated with significant radiation exposure. In children will cause an measurable increase in fatal cancers

DVT prophylaxis in Trauma

- Weigh risks vs benefits
- Differential of sudden hypoxia:
 - PE
 - Pneumothorax
 - Lobar collapse
 - VAP
- Investigations if ?PE:
 - CTPA
 - Echo for haemodynamic significance
 - USS for evidence of a DVT
- Management:
 - IVC filter placement:
 - Complications related to duration of placement:

- Chronic lower limb venous insufficiency
- Need for long term anticoagulation
- Local erosion – vena cava or adjacent organ perforation
- Migration
- Thrombosis: IVC thrombosis, sub-filter thrombosis, recurrent DVT
- Risk of infection: temporary filters are attached to a guide wire that protrudes externally
- Retrievable filters need replacement every 14 days due to associated thrombosis
- LMWH or IV heparin with close APTT monitoring. Meta-analysis (Jamjoom et al, J Neurotrauma 2013) found pharmacological prophylaxis < 72 hours (n = 713) cf > 72 hours (n=911) was associated with ↓VTE but no statistically significant progression of intra-cerebral haemorrhage
- Not thrombolysis
- Brain Trauma Foundation guidelines: Level 3 recommendation for:
 - Graduated compression stockings or intermittent pneumatic compression
 - LMWH or unfractionated heparin:
 - insufficient evidence for agent, dose or timing, although efficacy (and adverse effects) may be increased with LMWHs
 - More efficacious than mechanical prophylaxis
 - Increased risk of intracranial haematoma expansion if given within 24 hrs of arrival or surgical intervention
 - Most studies are mixed populations of neurosurgical patients rather than TBI
 - Limited number of RCTs – most studies are case series with historical controls

Steroids in Trauma

- HYPOLYTE, Roquilly et al, JAMA 2011, Hydrocortisone Therapy for Patients with Multiple Trauma. ↓In hospital acquired pneumonia in ventilated trauma patients, ↓duration of ventilation, no change in survival. Requires further studies

Analgesia in Trauma

- Local anaesthetic:
 - Lignocaine: max 3 mg/kg
 - Lignocaine with adrenaline: max 6 mg/kg
 - 1% lignocaine = 10 mg/ml ⇒ 70 kg person max safe dose of lignocaine with adrenaline is 42 ml
- Epidurals (eg for chest or abdo injuries):
 - Advantages:
 - Excellent analgesia
 - Opioid sparing: less delirium, constipation, itch, respiratory depression
 - Good analgesia ⇒ improved respiratory function
 - Lower incidence of DVT
 - Reduced interactions from systemic analgesia
 - Disadvantages:
 - More hypotension → more fluid given
 - Require more expertise, staff less familiar
 - Risks of epidural insertion: epidural haematoma (esp if coagulopathic)
 - Risk of incomplete or high block
 - May mask other injuries
 - Elderly patients have increased risks either way. Older patients may be harder to get an epidural in

Trauma in Pregnancy

- Difficult due to:
 - Altered physiology
 - risk to the gravid uterus and fetus
 - Conflict of priorities between mother and fetus (although in general what's good for the mother is good for the baby)
 - Multidisciplinary involvement
 - ↑Anxiety by patient and family
- Assessment:
 - Position to avoid aortocaval compression
 - Maternal compensation for blood loss can lead to a profound ↓uterine blood flow (uterus is not autoregulated) ⇒ fetal hypoxia despite normal maternal vital signs
 - Because of ↑blood volume may not see decompensation (eg ↓BP) until 35% blood lost

- Primary survey of mother first, then assessment of fetus, then secondary survey
- Secondary survey should include vaginal exam
- Be alert to the possibility of domestic violence
- Minimise xrays, consider US
- Normal values in pregnancy:
 - Haematocrit: 32 – 42%
 - WBC: 5 – 12
 - Arterial pH: 7.40 – 7.45
 - Bicarbonate: 17 – 22 mEq/L
 - PaCO₂: 25 – 30 mmHg
 - BP: SBP and DBP falls 5 to 15 mmHg in 2nd trimester, back to nearer normal in 3rd
 - CVP: variable, but response to volume is same as non-pregnant state
 - GFR and renal blood flow ↑, Cr and urea ↓
 - Pituitary gland increases in size by 30 – 50% (still on the same blood supply, so susceptible to shock)
- Risks:
 - A: difficult airway
 - B: aspiration, high diaphragm, reduced FRC
 - C: Failure to recognise decompensation
- Treatment:
 - Early engagement of obstetrics
 - Give high flow O₂ until maternal hypoxaemia, hypovolaemia and fetal distress excluded
 - ↓Respiratory reserve requires earlier intervention. PaCO₂ of 35 – 40 may indicate impending respiratory failure
 - Place chest drains higher – 3rd or 4th intercostal space
 - IV access in the arms
 - Cardiotocographic monitoring essential. CTG monitoring is the most sensitive test of fetal distress, for 6 hours if no risk of loss, for 24 hours if risks for loss or abruption or abnormalities detected
 - Don't use vasopressors → further reduce uterine flow
 - Transfusions should be Rhesus compatible
 - All Rhesus-negative mothers should receive immune globulin, unless injury is remote from the uterus, because of the immunological risk of even minor feto-maternal haemorrhage
 - Pelvic binders may not work
- Imaging:
 - Minimise xrays (or shield), especially under 20 weeks. CXR delivers less than 5 mGy to the lungs and very little to the shielded abdomen. Greatest risk in 1st trimester where exposure to more than 50 – 100 mGy is a concern
 - US is safe, accurately detects free fluid, confirms fetal well-being and identifies placental abnormalities
 - DPL is safe if open method used above the fundus, otherwise contra-indicated
 - CT may miss injuries due to abdominal crowding
- Types of injuries:
 - Main causes of fetal death:
 - Maternal shock or death
 - Placental abruption: vaginal bleeding in 70%, uterine tenderness, contractions/tetany, uterine irritability (contracts when touched). Ultrasound may demonstrate the lesion, but not 100% sensitive. Late in pregnancy, minor injury may precipitate abruption
 - Blunt trauma:
 - Abdominal wall, uterus and amniotic fluid generally protect fetus
 - Uterine rupture is unusual, but possible with a lap belt. Suggested by abdo tenderness, guarding, rigidity or rebound, abnormal fetal lie (eg transverse), easy palpation of extra-uterine fetal parts
 - Placental abruption or fetal loss are rare
 - Premature contractions are common
 - Retroperitoneal haemorrhage is more common

Trauma in Obesity

- Differences in the pattern of injury in the obese:
 - Lower injury severity scores overall
 - More severe extremity injuries
 - More thoracic injury

- Less brain injury (controversial)
- Longer extraction times (?higher risk of crush injury)
- Considerations during initial assessment:
 - Airway: ↑risk of obstruction when not tubed, risk of more difficult bag-mask ventilation and intubation
 - Breathing: ↑difficulty of inserting chest drains, risk of obesity hypoventilation, ↑atelectasis
 - Circulation: needs appropriately sized cuff, IV access difficult (early inter-osseous)
 - Other: Clinical signs harder to detect (eg pneumothorax). Log rolling harder. FAST scanning less sensitive than in non-obese and false positive pericardial effusions more common.

Geriatric Trauma

- General considerations in the elderly:
 - Older patients are more likely to have a fatal outcome
 - Common injuries include falls, MVAs, burns
 - Minor mechanisms can → significant injury or complications (especially with anticoagulants)
 - Decreased ability to treat normally due to comorbidities, including arthritis, osteoarthritis, emphysema, heart disease...
 - Many elderly return to their previous level of function. Attempts to identify which elderly trauma patients are at greatest risk of dying have not found utility in clinical practice
- Airway:
 - Leave intact well fitted dentures in place until airway control achieved
 - OA affecting C-spine and TMJ can make intubation harder
- Breathing: Loss of respiratory reserve. Chest wall injury and pulmonary contusion not well tolerated
- Circulation: “normal” blood pressure and heart rate don’t indicate normovolaemia. Metabolic acidosis predicts mortality
- Brain injury: fewer cerebral contusions but more subdural and intraparenchymal haematomas
- C-spine injuries: more difficult to diagnose given pre-existing OA complicating symptoms and images
- Hypothermia may be due to pre-existing sepsis
- Susceptible to fractures of long bones – especially femur, hip, humerus and wrist
- Drug interactions more common. Antihypertensives may contribute to shock. Psychotropics compound delirium or cause problems when discontinued abruptly
- Elderly abuse: injury may be deliberately inflicted. Note significant delay in seeking treatment
- End of life decisions

Traumatic Brain Injury

- See:
 - Head Trauma Hot Case, page 383
 - Early Management of Severe Traumatic Brain Injury, Lancet 22 Sept 2012
 - Outcome calculators:
 - www.crash2.lshtm.acu.uk/risk%20calculator/index.html
 - www.tbi-impact.org/?p=impact/calc
- Spectrum of injury includes:
 - Primary insult
 - Secondary insult: the following independently worsen outcome:
 - Hypotension SBP < 90
 - Hypoxia: sats < 90% or PaO₂ < 50
 - Hypoglycaemia
 - Hyperpyrexia: temp > 39
- Physiology:
 - Brain is a poorly compliant organ that can’t accommodate pathological ↑ in ICP
 - Inflammatory response → disruption of BBB and alterations in regional and global cerebral blood flow
 - Phases:
 - Hypoperfusion phase: reduced CBF for first 72 hours → risk of ischaemia. Disrupted autoregulation → CBF directly dependent on systemic BP. Target CPP ~ 60 – 70
 - Hyperaemic phase: recovering autoregulation → better CBF. Inflammation → hyperaemia → ↑ICP ⇒ vasogenic cerebral oedema. Occurs in 25 – 30%. Persists for 7 – 10 days. Can tolerate slightly lower ICPs (> 50)

- Vasospastic phase: in 10 – 15%, especially if severe with significant traumatic SAH → hypoperfusion 2nd to arterial vasospasm, post-traumatic hypometabolism and impaired autoregulation
- Potential bio-markers:
 - Initial enthusiasm for S100B and neuron-specific enolase, but I's unclear if they add value beyond traditional predictors
 - Glial fibrillary acidic protein and ubiquitin carboxy-terminal hydrolase L1
- Outcome scores:
 - Extended Glasgow Outcome Score:

	Rating	Definition
5	Good Recovery	Resumption of normal life despite minor deficits
4	Moderate Disability	Disabled but independent. Can work in a sheltered setting
3	Severe Disability	Conscious but disabled. Dependent for daily support
2	Persistent vegetative	Minimal responsiveness
1	Death	
- SF-36 Quality of Life questionnaire
- For good prognostic calculator, see www.tbi-impact.org/?p=impact/calc or Crash TBI calculator
- Recovery rule of thumb: 60% of eventual function at 6 weeks, 90% at 6 months, 100% at 2.5 years
- Bad prognostic signs:
 - Main factors:
 - Severity of injury
 - Low GCS on presentation
 - Pupillary abnormalities
 - Hypotension/hypoxia. One episode of hypotension → doubling of mortality in observational studies (No trials of whether resuscitation helps this)
 - Advanced age (> 60 years)
 - Comorbidities
 - Other factors:
 - Penetrating has higher mortality than blunt
 - Raised ICP is usually an indicator of severity
 - CT scan abnormalities: eg traumatic subarachnoid haemorrhage
 - Non-evacuable mass lesions (especially in critical parts of the brain such as posterior fossa)
 - Admission variables of age, clinical severity, pupillary reactivity, CT abnormalities, and lab values (Hb, glucose) are the best, but only explain about 35% of variability in outcome
- Risk factors for post-traumatic seizure disorder:
 - GCS < 10
 - Cortical contusion
 - Depressed skull fracture
 - Subdural, epidural or intracerebral haematoma
 - Penetrating head wound
 - Seizure within 24 hours of injury

Resuscitation in Traumatic Brain Injury

- According to Advanced Trauma Life Support (ATLS)
- ABC have priority: direct association between hypotension, hypoxia and adverse outcome
- A: tube with RSI, cricoid pressure and in-line mobilisation if GCS < 8, agitated or significant extracranial trauma. Assume C-spine injury → put in hard collar
- B: ventilated on 100% with 6 – 10 ml/kg tidal volumes till blood gas available. Aim for PaO₂ ≥ 100 and PaCO₂ 35 – 40
- C:
 - Control shock
 - Fluids:
 - Fluid Resuscitation in Trauma, page 231 and Fluid Resuscitation, page 40
 - Normal saline recommended
 - Albumin associated with worse outcomes – subgroup analysis of SAFE Study
 - Hypertonic saline:
 - See also Brain Specific Therapy, page 240
 - Out of hospital hypertonic saline, hypertonic saline with dextran or normal saline, in traumatic brain injury, did not alter outcome at 6 months (Bulger et al, JAMA 2010)

- Some small trials suggest benefit in ↓ICP
- Place arterial line and CVL (but must not delay volume expansion)
- Inotropes if needed
- Brain Trauma Foundation (SBP target) differs from European guidelines (MAP target). Based on observational studies. No comment on targets if other active haemorrhage
- If BP cannot be brought up to > 100 mmHg despite aggressive fluid resuscitation, the priority is to establish the cause of the hypotension, with neurosurgical evaluation taking 2nd priority
- D: Disability:
 - Know mechanism of injury. High velocity injuries associated with greater degree of axonal injury.
 - LOC: initially assess with Awake, Verbal, Pain, Unresponsive (AVPU)
 - Glasgow Coma Score: GCS (1974):
 - Skewed toward motor score – most reliable measure of prognosis in TBI
 - Best score, in the absence of sedation:
 - 14 – 15 ⇒ mild
 - 9 – 13 ⇒ moderate
 - ≤8 ⇒ **severe**
 - Fails to:
 - Incorporate brain stem reflexes
 - Identify the heterogeneity and complexity of severe injuries
 - Unreliable in the middle range of 9 – 12
 - Variable inter-rater reliability
 - Difficult for untrained staff to apply properly, especially between M = 3, 4, 5
 - M score doesn't factor in unilateral pathology
 - Not applicable if age < 5
 - Minimise the real burden of mild brain injury
 - Little evidence demonstrating the reliability of the GCS
 - Numerous other scoring systems that have greater validity and reliability, eg FOUR score
 - Debate in the literature about at which point following injury is the best time to use GCS for prognostic purposes
 - Pupils: abnormality ⇒ compression of 3rd nerve, may suggest ↑ICP or pending herniation, especially when associated with lateralising signs
 - Papilloedema is uncommon in the acute phase of head injuries
- Secondary survey:
 - Target MAP to likely pre-morbid BP
 - “Damage-control” surgery in Traumatic Brain Injury (compared with damage control resuscitation, for trauma in general, page 231): over first 24 – 48 hours only do life- or limb-saving surgery to minimise secondary insults. Semi-urgent surgery (eg fixation of closed fractures) can wait. If having surgery, ICP monitoring should be considered
- Most measures to care for patients with brain injury increase ICP, eg intubation, lying flat for CT scan, etc. Be slick.

Imaging in Traumatic Brain Injury

- See also Brain Imaging, page 201
- CT:
 - Only when initial assessment and resuscitation are complete
 - Required in anyone with witnessed LOS, definite amnesia or witnessed disorientation and any of:
 - Age > 65 years
 - GCS < 15 at 2 hours post injury
 - Suspected skull fracture or basal skull fracture
 - Vomiting 3 or more times
 - Combative patients where clinical assessment is masked by ETOH/drugs or other injuries
 - Amnesia of > 30 minutes before injury
 - Dangerous mechanism (ejected from motor vehicle, pedestrian, fall from > 1 metre...)
 - Benefits:
 - Detects mass lesions which can be drained
 - Baseline
 - Prognostication (eg subarachnoid bleeding bad)
 - Types of oedema:
 - Vasogenic oedema:
 - Extra-cellular fluid, BBB disrupted, spreads along white matter tracts

- → Accentuates grey-white matter differentiation. Seen in infections and tumours
- Cytotoxic oedema:
 - Cellular oedema, BBB intact, involves grey and white matter
 - → Loss of differentiation between grey and white matter. Seen in trauma and ischaemia. Causes DWI restriction in MRI
- Brain Trauma Foundation scoring (compare with scoring in Subarachnoid Haemorrhage, page 212)

Diffuse Injury I	No pathology on CT	
Diffuse injury II		Lesion densities present and or midline shift < 5 mm, may include bony fragments
Diffuse Injury III (Swelling)	No high or mixed density lesion > 25 mm, and	Cisterns compressed with midline shift < 5 mm
Diffuse Injury IV (Midline shift)		Midline shift > 5 mm
Evacuated mass lesion	Any lesion surgically evacuated	
Non-evacuated mass lesion	High or mixed density lesion > 25 mm	

- Cerebral angiography:
 - Consider if eg carotid artery dissection suspected
 - Indicated by:
 - Large isodense lesion on CT scan
 - Condition not consistent with CT, eg dense hemiparesis in the absence of a mass lesion
- MRI:
 - Not sufficiently more helpful in the acute phase to warrant routine use
 - Increased risks in unstable patient
 - Useful for later prognostication in mild and moderate head injury

Brain-Specific Monitoring

- Deterioration in GCS or new lateralising signs should be regarded as ↑ICP, possible herniation or new mass lesion till proven otherwise and prompt a CT
- *Intracranial pressure monitoring:*
 - See Intracranial Pressure Management, page 207
 - Contraindicated by coagulopathy
 - ICP is a strong predictor of outcome after severe TBI
 - Numerous studies have shown that patients who respond to ICP lowering therapies have a lower mortality than those that don't, allowing some prognostication
 - BEST TRIPPS study showed no difference in outcome
 - No RCTs trials have demonstrated that ICP-guided therapy improves patient-centred outcomes. Meta-analysis of 2 RCTs and 7 cohort studies found no benefit in mortality or functional outcome from ICP monitoring (Su et al, PLoS ONE, 2014 9(2))
 - Some observational studies have noted an association between ICP guided management and prolonged length of stay (Carmer 2005) and worse outcome (S[C?]hafi, 2008). Others have not
 - Trial of ICP monitoring vs clinical exam and imaging to guide therapy in 324 patients, NEJM 2012 in Bolivia and Ecuador (where equipoise between clinical and ICP directed therapy exists). No difference in outcomes at 6 months. Didn't argue against ICP management – but how we monitor it. Both arms received treatment for ↑ICP. Questions about external validity given 45% of patients weren't transported to hospital by ambulance (eg significant differences to US in pre-hospital transport). ?Underpowered to detect improvement in GCS
 - *BTF Guidelines recommend ICP monitoring* in patients with GCS ≤ 8 (ie can't assess clinically) following non-surgical resuscitation with either:
 - Abnormal CT scan:
 - Diffuse injury II – IV or
 - High or mixed density lesions > 25 mm
 - Normal CT scan with two or more of:
 - Age > 40
 - Unilateral or bilateral motor posturing
 - Significant extracranial trauma with systolic hypotension (< 90 mmHg)
 - Or in a moderate head injury (GCS 9 – 12) with both abnormal CT scan and requiring sedation
 - *ie DON'T monitor:*
 - GCS > 12 or

- GCS > 8 unless abnormal scan *and* sedated
- Management of Extra-Ventricular Drain EVD:
 - Attach flushed transducer to fluid-filled catheter – do not flush
 - Set transducer to reference level (external auditory meatus)
 - Attached drainage manometer and set at 10 – 20 cm H₂O at level of EAM
 - Monitor ICP continuously with intermittent drainage (hourly) unless clinically indicated, for which drainage may be more frequent or continuously
 - Daily CSF:
 - Volume of drainage
 - RBC/WBC ratio
 - Microbiology
 - Target for monitoring is controversial. 1995 guidelines said 70 mmHg, but lowered to 60 given no difference in neurologic outcomes and higher risk of ARDS in patients treated with pressors to maintain CPP (with ARDS → worse outcomes of TBI). Hypotension is associated with worse outcome, so together with clinical evidence it assumed that a low CPP is bad (eg < 50)
 - Continue pressure monitoring until:
 - Patient can be assessed clinically
 - ICP has stabilised (< 20 – 25 cmH₂O)
 - Cerebral oedema has resolved on CT scan
 - Occurs in the majority within 7 days
 - *Cerebral blood flow*: currently no method of routinely measuring cerebral blood flow at the bedside. Qualitative measures with jugular bulb oximetry and intermittent or continuous transcranial doppler – insufficient data on both to make recommendations
 - *Cerebral hypoxia monitoring*: via fibre optic implant. Not established. Difficulties of regional variation in O₂
 - *Cerebral function*:
 - EEG: accuracy and reliability questionable due to electrical interference from monitors and ventilators
 - Bispectral index has not been validated
 - Evoked potentials: reliance on one variable to predict outcome is not recommended

Intracranial Pressure Management in Brain Trauma

- See Intracranial Pressure Management in , page 207
- Defence of cerebral perfusion pressure:
 - Target CPP > 60 and ICP < 20, but may not be applicable over the entire time course
 - Hypoperfusion phase (0 – 72 hrs): Hypoperfusion is present in most with GCS ≤ 8. Maintaining CPP paramount. Target haemodynamic management before Osmotherapy or hyperventilation
 - Hyperaemic phase (3 – 7 days): 25 – 30% will have ↑ICP, persistent oedema on CT +/- high jugular venous saturations. Either due to intracranial inflammation or vasopressors used to augment CPP. Suspect the latter if ↑doses required as tachyphylaxis develops. If CT is unchanged, lower CPP targets to ↓vasopressors can be used
- Reduction of ICP:
 - Target ICP < 25
 - Most effective interventions are removal of mass lesions, drainage of CSF (5 – 10 cm above the head and opened every 1 – 4 hours) or decompressive craniectomy. Little evidence for medical therapies
- Emergency Surgical Decompression (Burr Holes): May be life-saving in a clear history of expanding subdural or extradural haematoma, eg in low velocity injuries to the temporal region and associated skull fracture, with deterioration
- Hyperventilation:
 - Aggressive hyperventilation → ↓PCO₂ → ↓global CBF → ↓in blood volume in brain → ↓ICP
 - Hypoperfusion may be worsened by hyperventilation → don't do it, despite theoretical ↓in ICP. Prolonged hypocapnea → ↓cerebral blood flow and eventually becomes ineffective as CSF pH returns towards normal and may → ischaemia
 - If unequivocal signs of ↑ICP or impending herniation (pupillary dilatation, lateralising signs, ↓LOC) then PaCO₂ ≤ 30 may be considered as a bridge to surgery
 - Brain trauma foundation recommends avoiding even PaCO₂ of 35 in the first 24 hours after a traumatic brain injury – although down to 35 probably OK
- Blood compartment:
 - Small but most compliant compartment of the intracranial volume
 - MAP should be raised to a level at or above the patient's usual pressure
 - ↑BP → ↓vascular diameter (if in autoregulation zone) → ↓blood volume

- CSF compartment: CSF drainage via ventriculostomy – no RCTs
- Osmotherapy:
 - Remove either free water or the lesion causing the \uparrow ICP
 - Only if euvoelaemic, haemodynamically stable with osmolality < 320 mOsm/L
 - Net efflux of fluid from oedematous brain $\rightarrow \downarrow$ ICP + plasma expanding effect with \downarrow haematocrit \rightarrow better CBF (this may contribute more than cerebral dehydration)
 - Meta-analysis of 6 heterogenous RCTS comparing mannitol and concentrated saline showed no statistical difference in lowering ICP, Rickard, Emerg Med J, 2014
 - **Mannitol:**
 - Moves free water across the BBB by raising osmolarity. May also have anti-oxidant effects
 - Introduces an osmol gap – need regular measurements of osmolality to monitor it
 - Mannitol 0.5 g/kg over 15 mins. Repeat up to 4 hourly. **Stop** when plasma osmolality reaches 310 – 320 mOsm/kg. No benefit and higher mortality in case-control studies at higher osmolality
 - Adverse effects:
 - Osmotic effect over a narrow range (290 – 330 mOsm/l)
 - ETOH will also increase this gap \rightarrow possible confusion
 - Can theoretically enter the brain if there is BBB damage and \uparrow brain osmolality
 - May cause excess diuresis \rightarrow hypovolaemia (especially if vasopressors \rightarrow squeezing a
 - If one or both dilated and unreactive pupils, not due to hypoxia or shock, then mannitol 1 g/kg to relieve brainstem compression. Only after adequate fluid, otherwise hypovolaemia
 - **Hypertonic saline:**
 - See also Resuscitation in Traumatic Brain Injury, page 236
 - Little evidence
 - Target Na of 145 – 155
 - Advantages:
 - Rapid effect: peaking in 10 mins, waning after an hour
 - Easy to monitor, doesn't need osmolality monitoring
 - Less risk of hypovolaemia than mannitol
 - May have a better effect on cerebral blood flow for a given reduction in ICP. The BBB is less permeable to Na than mannitol, making it a potentially more potent osmotic agent
 - Theoretical benefit in modulating the inflammatory response, including reducing adhesion of leucocytes to the endothelium
 - Cheap
 - Disadvantages:
 - No outcome data
 - Needs central venous access
 - May \rightarrow hypokalaemia and hyperchloraemic acidosis, volume overload/pulmonary oedema
 - May \rightarrow osmotic demyelination
 - Coagulopathy: may affect APTT, INR and platelet aggregation
 - Rapid changes in serum Na may \rightarrow seizures and encephalopathy
 - May affect normal brain more than injured brain. Theoretically may worsen herniation
 - May \rightarrow rebound \uparrow ICP but unclear whether the hypertonic saline is responsible
 - Hypothermia:
 - What's known:
 - Hypothermia $\rightarrow \downarrow$ ICP and hyperthermia \rightarrow worse outcomes
 - Hypothermia is not benign - \uparrow rates of VT and hypoglycaemia
 - Controls ICP but no reduction in mortality in conflicting studies
 - POLAR trial looking at hypothermia in TBI
 - Barbiturate coma (targeting burst suppression) to \downarrow metabolism is not recommended

Brain Specific Therapy in Brain Trauma

- See also General Management of Acute Cerebrovascular Events, page 206
- Little evidence. High quality reviews show no evidence of benefit of 22 possible interventions, except for adverse effect of steroids (Lei et al, J or Neurotrauma 2013)
- No consistent benefit for therapeutic hypothermia (in traumatic brain injury has been found in high quality trials (Georgiou et al, Brit J Anaesthesia 2013). MRCT in paediatric neurotrauma terminated early for futility (Adelson et al, Lancet Neurology 2013). See also Hyperthermia/Hypothermia in Cerebral Insult, page 207
- No therapies for modulating intracranial inflammation have been successful

- Steroids associated with worse mortality at 14 days and 6 months and ↑risk of severe disability: CRASH trial, Lancet 2004 and 2005, n = 10,000, all severity of head injury, 48 hours of IV steroids vs placebo. A number of methodological criticisms – heterogeneous ICU units, very high doses of steroids
- CRASH2: Tranexamic acid in trauma (consider external validity): see Tranexamic Acid, page 297
- Vasospasm:
 - In approximately 10 – 15%, especially in traumatic subarachnoid haemorrhage
 - Nimodipine, chemical angioplasty and triple H therapy have not been shown to be effective in traumatic SAH ⇒ not recommended
- Amantadine: single centre trial in minimally conscious patients for 4 weeks from 4 weeks showed faster improvement but no long term change (NEJM 2012, 1 March)
- Drugs currently being evaluated: erythropoietin, statins, ciclosporin-A, tranexamic acid, progesterone

Decompressive Craniectomy in Brain Trauma

- DECRA Trial:
 - Early decompressive craniectomy (< 72 hours, mean time to randomisation was 35 hrs) vs medical therapy in medically refractory ICP > 20 mmHg due to diffuse brain injury (ie *not due to mass lesion* – for which craniotomy would be standard) in patients < 60 years old (mean 25)
 - Showed ↓ICP but no change in mortality and worse functional outcomes. Mortality in both arms historically low (~ 20%)
 - Trial ran from 2002 to 2010 and recruited 155 of 3478 eligible patients. Mean age 24 years – mainly MVAs
 - Groups not balanced for unreactive pupils. Control group – some had early decompression. Standard therapy included barbiturate coma
 - Questions over threshold for ↑ICP and how long to wait for medical management to work – DECRA aimed for early intervention – was it too early (ie not yet refractory)? Also questions about which sort of craniotomy is best.
 - Conclusion: it's not just about pressure. Craniotomy to relieve pressure may also be bad (permits axonal stretch, metabolic change, etc.)
- RESUCE-ICP trial underway with decompression as rescue treatment, aiming for larger numbers
- Still has a role, but threshold is raised. Often performed for clot evacuation if significant bleeding
- Paediatric data suggests better outcome in paediatric head injuries
- Complications:
 - Infection
 - Collections: sub-galeal and subdural collections usually on the ipsilateral side
 - Bleeding
 - Brain herniation through the craniotomy
 - Venous thrombosis due to occlusion of venous circulation by herniation
 - Sinking flap syndrome
 - Paradoxical subtentorial herniation with LP or CSF drainage (due to atmospheric pressure: intracranial pressure gradient)
 - Hydrocephalus
 - Bone flap resorption
 - Worsening of brain injury

Base of Skull Fractures

- Clinical signs of base of skull fracture:
 - CSF otorrhoea
 - CSF rhinorrhoea
 - Haemotympanum
 - Raccoon/Panda eyes (suggests *frontal* base of skull)
 - Cranial nerve abnormalities
 - Battle's sign
- Life threatening complications of base of skull fractures:
 - Panhypopituitarism
 - Basal meningitis
 - Carotid artery trauma or pseudoaneurysms
 - Cavernous sinus thrombosis
- Diagnosis:
 - Glucose in clear fluid from nose, ear or orbit strongly suggests CSF

- $\beta 2$ Transferrin is specific for CSF. $\beta 1$ Transferrin is an iron binding protein made in the liver and found in serum. It is converted to the $\beta 2$ analogue only in the brain
- Prophylactic antibiotics:
 - Both base of skull fractures and CSF leak predispose to meningitis due to direct contact with bacteria in the paranasal sinuses, nasopharynx and middle ear
 - Few RCTs exist, the primary end point was a reduction in meningitis
 - No role for prophylactic antibiotics, whether there is a CSF leak or not
 - Treat infection specifically

Supportive Therapy

- As per guidelines of the Brain Injury Foundation of the American Association of Neurological Surgeons, and the European Brain Injury Consortium
- Take priority over brain-specific therapies, which are of inclusive efficacy
- Haemodynamic Management:
 - Arterial monitoring. Consider femoral is unstable as radial may underestimate the true pressure in shocked patients. Non-invasive not recommended
 - Set target in light of pre-morbid blood pressure
 - PA catheters not recommended on current evidence
- Fluid management:
 - Monitor according to CVP, urine output, pulse, electrolytes
 - Target euvoelaemia
 - No evidence to recommend crystalloids over colloids. Glucose containing fluids only if hyperosmolar > 320 mOsm/l
 - Haematocrit of $\sim 30\%$ and transfuse to maintain Hb 85 – 100
- Inotropes:
 - Only when volume resuscitation complete/underway
 - Earlier use being advocated during hypo-perfusion phase
 - No conclusive trials to recommend one of noradrenaline, adrenaline or dopamine. Dopamine may have direct effects on cerebral vasculature. Noradrenaline usually recommended
 - Lower pressure targets (eg 50 – 70) may be better if oedema develops
- Neurogenic hypertension:
 - Common later ($> \text{day } 5$)
 - Centrally mediated
 - May be associated with ECG changes and/or SVTs
 - Usually self-limiting and correlates with injury severity
 - β -blockers or centrally acting agents (eg clonidine) effective. Vasodilators relatively contra-indicated
- Ventilation:
 - Aim for normocapnea. Permissive hypercapnea (eg in ALI) ‘does not have a role’
 - Use PEEP > 10 cm with caution – may compromise BP especially in hypovolaemic patients. Levels > 15 may reduce cerebral venous return
 - Ensure they won’t be hypoxic after extubation
 - Early tracheostomy
 - Neurogenic pulmonary oedema:
 - Related to severity of injury
 - Sympathetic overactivity \rightarrow sudden pulmonary oedema, hypoxia, poor lung compliance, usually within 2 – 8 hours of injury
 - Treat with PEEP, sedation to ablate sympathetic activity (β -blockers usually unnecessary), diuretics if necessary but caution in case of hypovolaemia
 - In patients with cardiac disease, treat as cardiogenic until proven otherwise
 - Phase 2 trials show \downarrow mortality and \uparrow outcome in hyperbaric O₂ treatment (Rockswold, J Neurosurgery 2013)
- Sedation:
 - See Sedation in Ventilated Patients, page 88
 - No standards
 - Initially agents with least haemodynamic effect, eg short acting opioids (eg fentanyl) – also temper sympathetic surges. Document papillary responses before giving them
 - During ICU phase, want to sedate as lightly as possible to assess neuro function. Don’t want agents which accumulate or are associated with \uparrow delirium
 - Propofol now more popular than narcotics/benzodiazepine infusions.
 - Benefits: Controls sympathetic swings, short acting, doesn’t affect pupils

- Downsides: negative inotrope, prolonged use → tachyphylaxis, calories ++ from lipid
- Prolonged use of muscle relaxants associated with adverse outcome
- Thiopentone effective at ↓ICP but is associated with ↑infection risk (inhibits macrophages, etc.)
- Nursed at 30 – 45o to facilitate ventilation and ↓aspiration
- DVT prophylaxis in Trauma: see page 232
- Physiotherapy for lungs (May need sedation to temper rises in intracranial pressure) and contracture prevention
- Metabolic:
 - Watch for SIADH and diabetes insipidus
 - Centrally mediated high glucose common. Role of tight glucose control not determined and hypoglycaemia is a secondary insult
 - Maintain normothermia
- Nutrition:
 - Early enteral feeding
 - Not nasogastric till injury to the anterior cranial fossa (→ fractured cribriform plate) is excluded
 - Gastroparesis common ⇒ post-pyloric feeding may be helpful
- Gastric stress ulceration prevention: risk is less now with more aggressive resuscitation and early enteral feeding. Antacid therapy as for other intensive care patients till feeding established, or for duration of ICU stay if previous PUD
- Thromboprophylaxis: tricky. No standards. Usually not used in intracranial haemorrhage until they have resolved on CT. TEDs and pneumatic compression stockings unproven. If DVT then vena caval filters

Polyuria in Brain Injury

- Differential:
 - Diabetes Insipidus: ↑Na, ↓urine Na, ↑serum osmolality, ↓urine osmolality, normal osmolar gap
 - Mannitol: normal, hypo or hypernatraemia, ↑urine Na, ↑serum osmolality, ↑urine osmolality, ↑osmolar gap
 - Cerebral salt wasting: ↓Na, ↑urine Na, ↓serum osmolality, ↑urine osmolality, normal osmolar gap
 - Also consider polyuria due to diuresis and due to hypertensive therapy (→ ↑renal perfusion)

Maxillofacial and Upper-airway Injuries

Types of Injury

- Main issues amongst both blunt and penetrating trauma are:
 - Life-threatening haemorrhage
 - Airway obstruction
- Common fractures:
 - Maxilla (23%)
 - Orbital region (22%)
 - Zygoma (16%)
 - Nasal bones (15%)
 - Mandible (13%). Airway obstruction may occur after bilateral fractures given posterior displacement of the tongue
- Midfacial fractures:
 - Facial skeleton acts as a “crumple zone” on impact ⇒ isolated fractures rare
 - Le Forte Classification:
 - Le Forte 1: Only maxilla
 - Le Forte 2: Most common, maxilla, nasal bones and medial aspect of the orbit
 - Le Forte 3: Separates midfacial skeleton from the cranium
 - Airway problems arise from:
 - Posterior movement of the soft palate
 - Oral secretions and bone/blood
 - Most injuries causing blindness are due to globe perforation rather than optic nerve injury
 - Traumatic occlusion of the internal carotid is a rare complication. CT angiography if suspected
- Haemorrhage:
 - Severe haemorrhage mainly associated with mid-facial fractures
 - Vascular supply is from the internal and external carotids, the internal maxillary artery is usually the major source
 - Swallowing may conceal size of fracture

- Associated injuries:
 - Anterior cranial fossa/base of skull. Can cause dural tears → CSF leak, which can → fistula (most presenting within the first week). Meningitis is uncommon
 - C-spine injuries more common in MVA than assault or sporting injuries

Examination

- Things not to miss:
 - Septal deviation or haematoma
 - CSF rhinorrhoea ⇒ assay for β 2-transferrin (more useful than traditional glucose leak). Antibiotic prophylaxis is controversial
 - Extent of jaw opening
 - Signs of basal skull fracture: haemotympanum, Battle's sign, raccoon eyes
 - Corneal integrity, papillary reflexes
 - Bruit over the orbit may ⇒ carotido-cavernous fistula

Management

- Airway management:
 - Assess and monitor for signs of obstruction
 - Clear airway
 - Definitive airway intervention if required
- Airway problems:
 - Haemorrhage/debris: suction, volume replacement, head down, haemorrhage control
 - Oedema: is progressive ⇒ an unobstructed airway may become compromised. Monitor closely, head at 30°, maintain spontaneous ventilation during airway manipulation
 - Bilateral mandibular fracture leading to posterior displacement of tongue: anterior traction on tongue or jaw, clip or suture through tongue
 - TMJ impairment: NT intubation or surgical airway
 - Midfacial fracture: ⇒ poor mask seal. Anterior traction on mobile segment
 - Basilar skull: avoid nasal intubation, HG tube
 - Cervical spine injury: OT intubation with in-line stabilisation; fiberoptic intubation; surgical airway
- Intubation:
 - RSI if difficulty not anticipated
 - If laryngoscopy likely to be difficult must maintain spontaneous respiration → awake fibre-optic. Sprayed or nebulised lignocaine (4%) to posterior pharynx + transcrioid injection of 2 – 4 ml lignocaine (2%)
 - Excessive bleeding ⇒ fiberoptic techniques useless
- Haemorrhage: Topical vasoconstrictors may not be sufficient within ongoing nasal haemorrhage. Anterior nasopharyngeal packs may help. Foley catheters passed into the posterior nasopharynx with balloons filled with air may stem blood loss, especially with anterior traction
- Surgery:
 - Usually delayed 4 – 10 days to allow swelling to subside
 - Earlier if optic nerve compromise
 - Debridement and closure of facial wounds within 24 hours

Direct Airway Trauma

- Relatively rare
- Mechanisms:
 - Extended neck vs steering wheel in MVA
 - “Clothesline injuries” – eg cyclist/horse rider vs wire
 - Assaults/strangulation
 - → Associated C-spine injury
- Resulting problems:
 - Tracheal transection
 - Oedema, fluid and air dissecting down the layers of the mucosa
 - Vascular injury
 - Pharyngeal or oesophageal injury
 - Nerve injury (spinal cord or brachial plexus)
- Management:
 - Often delayed diagnosis

- Stable laryngeal tenderness → CT scan or fiberoptic laryngoscopy, consider angiography and contrast studies
- Cricoid pressure can → laryngotracheal separation and is contraindicated
- Try to maintain spontaneous breathing until tube is placed distal to the injury

Chest Injuries

- Causes:
 - Blunt injury (most common): usually MVA
 - Penetrating: stab or gunshot
- Only the minority require surgery – most can be managed conservatively with good primary and secondary survey and management

Immediate Management

- A, B, C, D, analgesia
- Causes of loss of output on induction of a chest trauma patient:
 - Too much anaesthetic agent
 - Hypovolaemia
 - Oesophageal intubation
 - Tension pneumothorax
 - Pericardial tamponade
 - Anaphylaxis
 - Systemic air embolism
 - Severe blunt cardiac injury
- Cardiac arrest:
 - CPR is unsuccessful in trauma patient – and may cause further injury and obstruct access for more useful interventions (eg intercostal tubes)
 - ED thoracotomy if witnessed loss of vital signs after penetrating chest trauma. This allows:
 - Release of tamponade
 - Control of bleeding
 - Control of air embolism or bronchopleural fistula
 - Cross-clamping of the descending aorta
 - Internal cardiac massage

Critical injuries to Spot During Primary Survey

- **Tension pneumothorax:**
 - Suggested by:
 - ↑RR and ↑HR
 - Hyperinflation
 - Contralateral tracheal deviation
 - Hyper-resonance to percussion
 - Reduced breath sounds
 - Hypotension and ↑JVP
 - If in extremis then needle decompression in midclavicular line, 2nd intercostal space then intercostal tube drainage
 - Subcutaneous emphysema following blunt chest trauma is always associated with pneumothorax → insert an intercostal tube
 - Simple pneumothorax
 - Can tension at any stage, especially when going onto positive pressure ventilation
 - On supine CXR look for deep sulcus sign or increased radiolucency on one side of the other
 - Add suction only if fails to resolve, or if haemothorax
 - Remove tube when no visible air on imaging and no drainage for 24 hours
- **Open (sucking) pneumothorax:**
 - Tension can develop if air can enter but not exit through the defect
 - Occlusive dressing fixed on 3 sides then intercostal tube
- **Massive haemothorax:**
 - Drain via chest tube and remove when drainage < 100ml/24 hr
 - Less than < 300ml on CT can be managed conservatively as long as it doesn't enlarge

- Massive defined as > 1500 ml \Rightarrow life threatening hypovolaemia and vena caval compression. Needs immediate tube drainage. On-going bleeding of > 200 ml/hr or 600 ml over 6 hours \Rightarrow needs thoracotomy
- Retained haemothorax > 500 ml should be drained within 5 – 7 days. Can try with intrapleural thrombolytic agent with daily repeat. Otherwise Video Assisted Thoracoscopic surgery if able to tolerate single lung ventilation
- If not drained then organises and causes pleural thickening \rightarrow \downarrow lung volume, \downarrow compliance and \uparrow risk of empyema
- Resuscitation thoracotomy: *may* be appropriate in penetrating trauma and PEA. *Must* have appropriate surgical skill
- **Pericardial tamponade:**
 - Suspect if:
 - Gunshot or stab wound. Rare with blunt trauma
 - Hypotension out of proportion to blood loss and distended neck veins
 - More likely is tension pneumothorax and/or cardiogenic shock from severe blunt cardiac injury or inadequate resuscitation
 - Check with subcostal ultrasonography (FAST scan)
 - Needle pericardiocentesis is rarely effective in the acute setting \rightarrow needs thoracotomy

Other Chest Injuries

- Blunt Aortic Injury:
 - Usually the result of an MVA
 - Usually at the junction between the mobile arch and fixed descending aorta, just distal to the L subclavian artery before the first intercostal artery, site of ligamentum arteriosum, with 10 – 20% survival in those making it to hospital
 - Suspect if a severe deceleration injury
 - Are either:
 - Significant: disruption of full thickness of the media. High risk of rupture
 - Minimal: laceration limited to intima and inner media. Intimal flap < 1 cm with minimal periaortic haematoma
 - Imaging: no comparative studies
 - CXR: widened mediastinum (>8 cm at aortic knuckle) sensitive but low PPV. Supine chest accentuates normal mediastinum
 - Multi-slice CT is sufficient to diagnose aortic injury, CT with a normal mediastinum has a very high negative predictive value. If equivocal need angiography prior to surgery. Not sensitive for major branches. Periaortic haematoma is significant. Can be done at short notice and gives other anatomic information, requires immobilisation, transport and contrast
 - TOE: Accurate for aortic injury, and can assess for blunt cardiac injury. Distal aorta, proximal arch and major branches have limited views. Sensitivity and specificity similar to CT. Requires expert use.
 - Aortic angiography: Gold standard for branch vessels but time consuming and requires transport to angiography suite, femoral access and contrast
 - Other lifesaving operations (craniotomy, laparotomy) are more urgent
 - Complications of surgery include spinal cord ischaemia and bleeding from heparinisation
 - Less invasive repair with endoluminal stent can be considered
- Blunt cardiac injury:
 - From compression between spine and sternum, abrupt pressure changes to heart chambers or shear injury
 - Wide spectrum of injury:
 - Minor ECG changes and \uparrow cardiac enzymes – resolve without intervention
 - Complex arrhythmias: can cause heart failure or hypotension
 - Free wall rupture: of anything but the atria is always fatal
 - Heart failure, 2nd to gross myocardial injury, septal rupture, valvular injury (may not manifest for weeks)
 - Echo for patients with hypotension unexplained by other injuries
- Mediastinum:
 - Pneumomediastinum often \rightarrow pneumothorax, but not the reverse
 - Pneumomediastinum \rightarrow vertical translucent streaks, can extend up the neck and cause subcutaneous emphysema
- Tracheobronchial injury:

- Blunt rupture of the trachea, or most commonly right main bronchus
- PC: subcutaneous emphysema and haemoptysis with pneumo thorax and pneumomediastinum, and worsening on ventilation
- Diagnosis: Bronchoscopy
- Treatment: Primary repair
- Diaphragmatic rupture/paresis:
 - Usually results from gross blunt abdominal compression, most commonly lateral. Less from seat belts
 - Left much more common than right as right protected by liver
 - PC: non-specific symptoms – SOB and chest pain, shoulder pain
 - Investigations: Pre-intubation CXR may show elevated or distorted diaphragm, or intrathoracic bowel. CT more accurate, but may require video fluoroscopy
 - Phrenic nerve palsy may not show up till difficulty in weaning with paradoxical abdominal and chest wall movement and ↓vital capacity
- Oesophageal injury:
 - Rare
 - PC: Chest pain, dysphagia, pain on swallowing and subcutaneous emphysema
 - Confirmed by scope or swallow – use gastrografin water soluble contrast to prevent granuloma formation from barium leakage into the mediastinum
 - Treatment: immediate surgical repair. Delayed diagnosis/repair → septic shock
 - Chylothorax due to thoracic duct damage take days to show after trauma
- Lung parenchyma:
 - Pulmonary laceration/haemorrhage: usually homogenous round opacity – decrease in size over months
 - Fat embolism: poorly defined nodular opacities throughout both lungs, resolve within a few days
- Pulmonary injury:
 - CXR: patchy interstitial infiltrates or consolidation not confined to anatomical segments, within a few hours
 - CT more sensitive for contusion, and lung volume affected predicts ARDS
 - Gas exchange deteriorates over 24 – 48 hours
 - If no complications, clinical and radiological recovery over 3 – 5 days
 - Supportive treatment. No steroids. Antibiotics only for superimposed infection
- Clavicle:
 - Fracture: exclude injury to subclavian vessels and brachial plexus
 - Posterior dislocation at the sternoclavicular joint: consider injury to trachea, oesophagus, great vessels or nerves of the superior mediastinum
- Complications of rib fracture are more important than the fracture itself:
 - Fracture of first 3 ribs: high force required, consider major intrathoracic injury including great vessels
 - Fracture of 4 – 9: pulmonary contusion
 - Fracture of ribs 10 - 12: consider diaphragmatic, hepatic, splenic or renal injury
 - Exclude pneumothorax, flail segment, haemothorax and subcutaneous emphysema, intrapulmonary haemorrhage
 - Half of all rib fractures are missed on plain CXR
 - Good analgesia essential to prevent sputum retention
 - Sternal fracture often coexists with thoracolumbar spine fracture. If displaced, suspect blunt cardiac trauma
- Flail Chest:
 - Requires fracture of at least 4 consecutive ribs in two or more places → paradoxical movement
 - This won't be visible once on positive pressure ventilation – look prior to intubation
 - Marker for underlying pulmonary contusion → hypoxia. Contusion will worsen with aggressive fluids
 - Painful → ↓ventilation and ↑atelectasis → hypoxia
 - Deterioration gas exchange or sputum retention → intubate
 - If young and well, can usually be managed with analgesia and NIV or O2
 - Some advocate surgical stabilisation to reduce duration of ventilation – highly controversial
- Extra-pleural haematoma: parietal shadow that doesn't cause blunting of costophrenic angle or shift with gravity. If large then evacuate
- Air Embolism:
 - Following penetrating injury
 - Usually presents with circulatory collapse after starting positive pressure ventilation (pulmonary airspace pressure > pulmonary venous pressure)
 - Also suggested by focal neurology in the absence of head injury

- Try to maintain spontaneous ventilation, with FiO₂ 100. Otherwise low pressures and volumes. Consider single lung ventilation
- Urgent thoracotomy with hilar clamping or lung isolation is usually indicated
- Fat Embolism:
 - Invariably occurs in long bone fractures, including manipulation (eg reaming). Also associated with sickle cell, liposuction
 - Uncommon
 - Clinical syndrome suggested by:
 - Pulmonary: desaturation
 - Neurological: confusion
 - Cutaneous sequelae: eg conjunctival petechiae, petechial rash
 - Treatment is supportive, with early fracture stabilisation. Intramedullary nailing may provoke further embolisation and blood loss, so often externally fixed with nailing later
 - Likely good outcome with good resuscitation

ICU Management of Chest Trauma

- Supportive Care:
 - Rewarm
 - Correct coagulopathy
 - Ongoing resuscitation – restrictive fluid strategy if they've had lung surgery
 - DVT and ulcer prevention, nutrition
- Acute Lung Injury:
 - Common, 2nd to contusion, aspiration, massive transfusion and prolonged shock
 - If persistent lobar collapse then bronchoscopy to exclude particulate obstruction
 - If delayed onset, sepsis more likely
- Ventilation strategies:
 - If ARDS, Lung-protective strategy, except in concurrent head injury when permissive hypercapnia and high PEEP are contraindicated. See Invasive Ventilation in ARDS, page 113
 - Pneumothorax or tracheobronchial injury: low PEEP, low Paw, early spontaneous breathing
 - Flail chest: moderate levels of PEEP
 - Failure to wean: consider fluid overload, diaphragmatic injury, or cardiac dysfunction
- Sputum retention:
 - →progressive pulmonary collapse
 - Especially in smokers
 - Good analgesia without excessive sedation → deep breathing and cough
 - Humidification, tracheal suctioning, regular position changes
- Pneumonia:
 - Sepsis is the main cause of death after major trauma
 - Early onset pneumonia: ?aspiration at the time of injury. Common pathogens are H. Influenzae, Pneumococcus and anaerobes
 - Later onset: G-ive bacilli and staph aureus
 - New infiltrates on CXR may also be caused by pulmonary contusion, pleural fluid, collapse, aspiration, pulmonary oedema

Analgesia

- Facilitates physiotherapy and early mobilisation
- Options:
 - Morphine + paracetamol
 - Thoracic epidural:
 - eg fentanyl 2 µg/ml + bupivacaine 0.125% at 5 – 15 ml/hr
 - Best option for un-intubated patients
 - Can run as an infusion, bolus, or PCA
 - Monitor limits of sensation and motor block
 - Usually remove at 3 days (then what?)
 - Neurological complications:
 - Likely to cause hypotension and bradycardia, which may need fluids +/- noradrenaline (sympathetic outflow to the heart is T3 – 5)
 - Respiratory muscle weakness (helped by adding opiod to spare local anaesthetic)
 - May mask evolving neurological injury
 - Anatomic complications:

- Ensure other injuries found that would otherwise be masked
- Contraindicated if coagulopathic
- Risk of epidural haematoma or abscess
- Risk of dural tap headache
- Drug effects: pruritis, nausea, respiratory depression
- Intercostal nerve block: only if a few lower ribs are fractures. May need to be repeated
- Paravertebral block – rarely used
- NSAIDs if not contraindicated

Spinal Cord Injuries

- See Spine Injury Hot Case, page 382
- 80% are male, usually age 15 – 35
- 2 – 10% with a head injury have a CSI
- 55% are cervical, most at C4 – 6
- 45% are complete, 55% incomplete
- Potential for doing harm through mismanagement. 5% get worse once they get to hospital
- Classification:
 - American Spinal Injury Association (ASIA) has a classification system predicting outcome
 - Cervical – grouped according to the predominant mechanism of injury:
 - Hyperflexion +/- rotation
 - Hyperextension +/- rotation
 - Vertical compression or burst injury
 - Lateral flexion
 - Direct shearing
 - Penetrating
 - Thoracolumbar:
 - Compression fractures
 - Burst fractures
 - Seat belt type injuries
 - Fracture/dislocations
 - Primary injury: → focal compression, laceration, or traction. Trans-section unusual (consider trauma, infarction, transverse myelitis, abscess, tumour)
 - Secondary injury:
 - Local hypo-perfusion and ischaemia, extending over hours in both directions, due to loss of spinal cord autoregulation combined with systemic hypotension from high SCI
 - → Local inflammatory response
 - Petechial haemorrhages in the chord may progress to significant haemorrhage ⇒ poor prognosis
- Terminology:
 - Tetraplegia (preferred to quadriplegia): loss of cervical segment functions
 - Paraplegia: below the cervical chord
 - Neurological level: most caudal segment with *normal* motor and sensory function on both sides
 - Skeletal level: greatest vertebral damage on xray
 - Complete injury: complete absence of motor and sensory function in the *lowest sacral segment*

Spinal Cord Syndromes

- Suspect if:
 - Mechanism of injury
 - Unconscious
 - Focal deficit
 - Spine pain/tenderness
 - Drugs, alcohol and other injuries could be masking spinal injury
- Cervical fractures:
 - C1: Atlas fracture. 5% of cervical fractures. Most common C1 fracture is a burst fracture (Jefferson Fracture): disruption of posterior and anterior rings with lateral displacement of lateral masses, best seen on Open Mouth view.
 - C2 fractures, 18% of cervical spine fractures:
 - Odontoid fractures: 60%. Seen on lateral or open mouth view, need CT to better define. Age < 6 the epiphysis may look like a fracture
 - Hangman's fracture: posterior elements of C2. Caused by extension injury

- C3 – 7:
 - Fracture of C3 is uncommon given its position between the vulnerable axis and the more relatively mobile “fulcrum” at C5/C6 where the greatest extension and flexion of the neck occur
 - Most common level of fracture of the C spine is C5, and most common level of subluxation is C5 on C6
- Thoracic/Lumbar fractures:
 - Axial loading with flexion produces anterior wedge compression fractures. Usually splinted by the rib cage.
 - Burst fractures: cause by vertical-axial loading
 - Chance fractures: transverse fractures through the vertebral body. Caused by flexion about an axis anterior to the vertebral column – eg a lap belt in an MVA. Because of the rib cage, thoracic chance fractures are generally stable. Lumbar chance fractures are associated with hollow viscus injury
- Incomplete syndromes:
 - Central cord syndrome: most common. Hyperextension of the neck, often in the elderly. Also Syringomyelia, tumour. Disproportionate paralysis in the arms compared to the legs. Variable sensory loss, bladder dysfunction
 - Anterior cord syndrome: bilateral paralysis with loss of pain and temperature but retained posterior column sensation
 - Cord hemisection - Brown-Sequard syndrome: damage to one side with ipsilateral motor and proprioceptive and contralateral pain and temperature loss
 - Conus Medullaris syndrome: at T12/L1 → upper and lower motor neuron damage to legs
 - Cauda equine syndrome: injury below L1 → lower motor neuron in legs, bladder and bowel areflexia, saddle anaesthesia and sexual dysfunction

Assessment of Spinal Injury

- Download clerking diagrams from the American Spinal Injury Association
- Motor, spinothalamic and dorsal column sensory function, reflexes
- Signs of spinal shock (think of it as spinal “concussion”):
 - Muscle flaccidity, absent reflexes, vaso-and vasodilatation, loss of bladder function, paralytic ileus
 - A type of neurogenic shock causing loss of somatic and autonomic reflex activity below the injury in the isolated cord segment, lasting 1 – 3 weeks
- Signs of SCI in an unconscious or uncooperative patient:
 - Response to pain above but not below a suspected level
 - Flaccid areflexia in arms or legs
 - Elbow flexion but not extension (⇒ cervical injury)
 - Paradoxical breathing: indrawing of upper chest without obstruction or chest injury
 - Inappropriate vasodilation with hypothermia or in legs but not arms
 - Unexplained bradycardia/hypotension
 - Priapism
 - Loss of anal tone and reflexes

Imaging of Spinal Cord Injuries

- If you see one injury, look for another
- Xrays:
 - 3 view trauma series of cervical spine (lateral, AP and odontoid (open mouth) views) and lateral and AP of thoracolumbar spine
 - Must include C7/T1
 - Don't exclude spinal injury – miss fractures and subluxation
 - Subluxation = greater than 25% loss of alignment, dislocation = greater than 50% loss of alignment
- CT:
 - Indicated if:
 - Inadequate plain xrays
 - High clinical suspicion of injury despite normal plain xrays (persistent neck pain, development of neurological symptoms)
 - Suspicious or abnormal rays
 - Suspect or proven spinal injury
 - First line in severe or multiple trauma or if unconscious
- MRI:
 - Allows visualisation of ligaments, intervertebral discs and spinal cord
 - Helpful for planning surgical management and prognosis

- Urgent if there is an unexplained deficit, or discordance between skeletal and neurological levels
- Spinal cord injury without radiological abnormality (SCIWORA): mainly in kids but now uncommon given MRI scanning. See Specific Injuries in Children, page 329

Clearing the Cervical Spine

- See also Specific Injuries in Children, page 329
- Must be undertaken by an experienced person after suitable imaging
- Principles:
 - 5 – 10% of patients with a severe head injury have an associated unstable cervical fracture. 2% of total trauma patients
 - Clinical clearance is often not possible
 - Maintaining cervical immobility increases risks of complications
 - A conscious patient will protect their own neck
 - 3 and 5 view c-spine xrays (AP, cross table lateral, peg, + right and left obliques) are frequently inadequate, and even when they are adequate and corrected interpreted only detect 75 – 90% of unstable injuries
 - A good 64 slice helical CT with sagittal and coronal reconstructions and experienced interpretation has a false negative rate of < 0.1%. May miss an unstable ligamentous injury without bone fracture. Convenient to do with head or other CT scans
 - MRI will detect spinal cord and soft tissue pathology and epidural haematoma
 - 10% of patients with a C-spine fracture have a second non-contiguous vertebral column fracture so must have the entire spine imaged
 - Requires a clear institutional policy
 - Midline tenderness is relevant to hyperflexion injuries, but less so for eg tackle from the side
- Suggested approach:
 - Detailed history and exam, including speed and mechanism of injury and other injuries
 - 3 view cervical spine xrays (with CT of missed areas), or CT of neck with reconstructions
 - If CT is normal after interpretation by appropriate specialists then “clear”
 - MRI if clinically suspected spinal neurological injury or abnormal CT scan or very high risk for cord injury (high speed, ejection from vehicle). MRI has a material false positive rate for a clinically significant injury
 - Transfer to specialised trauma/spine centre
- Canadian c-spine rule (there are also NICE Guidelines, US Guidelines, and Nexus criteria covering this):
 - In stable, GCS 15 trauma patients:
 - If > 65, paraesthesia in extremities or dangerous mechanism (fall > 1 metre, axial loading, MVA > 100 km/hr, rolled or ejected, bike) ⇒ xray
 - Is it safe to assess movement: simple rear-end MVA, seated, ambulatory, delayed onset of pain, no midline tenderness. If not ⇒ xray
 - Able to rotate neck 45 degrees left and right ⇒ don’t xray
 - If screening xrays are normal, flexion-extension x-ray films of the cervical spine may be obtained in those with neck pain to detect occult instability (APLS guidelines)
 - Reduced GCS:
 - No standardised approach
 - Check trauma series: chest and pelvis. If vertebral fracture/dislocation in lower spine then ↑risk in cervical spine
 - X-rays not sufficient. Generally not done – straight to CT. Never do flexion and extension views if c-spine injury suspected. Can look for soft tissue signs – eg widening of prevertebral soft tissues due to haematoma. Acceptable soft tissue thicknesses are < 1/3 of vertebral body width above the larynx, < width of one vertebral body below the larynx
 - Usual is high resolution 64 slice CT with coronal and sagittal reconstructions, down to at least T1
 - MRI for those with high-velocity mechanism or high injury severity score – rather than flexion/extension imaging to detect unstable ligamentous injuries
- Problems of not clearing the c-spine and leaving in a hard collar:
 - Decubitus ulceration
 - Increased need for sedation
 - Delays in tracheostomy/weaning
 - CVL access problems
 - Enteral feeding intolerance due to supine positioning
 - Pulmonary aspiration due to supine positioning
 - DVT due to prolonged immobility

- Increased staff and equipment for spinal precautions, → increased cross infection risk

General Management of Spinal Injury

- Principles:
 - Prevent secondary injury
 - Promote neurological recovery
- Pre-hospital:
 - All trauma patients have a c-spine injury till proven otherwise
 - ABC: Hypotension may be due to a high c-spine injury. If so, avoid excessive volume expansion otherwise acute pulmonary oedema with insufficient ventilatory drive to compensate. However, *hypotension is due to haemorrhage until proven otherwise*
 - Immobilisation: hard collar, supine, taped, occipital padding and sandbags
 - Prevent hypothermia
 - Initially manual in-line stabilisation then hard collar, packing either side of head with tape across the top and whole body strapped to the back board
- ED:
 - Cervical collar does not provide rigid mobilisation – manual stabilisation necessary with patient transfers. Get them off the back board as soon as possible
 - ABC
 - Opioid analgesia
 - Imaging
 - NG tube to prevent aspiration and distension from associated ileus
 - Urinary catheter: monitor output and prevent over distension
 - Prevent pressure areas. A paralysed patient lying on a back board for 2 hours is at high risk for serious ulcers
 - High dose steroids only if they can be started in the first 8 hours. Methylprednisolone 30 mg/kg bolus followed by 5.4 mg/kg per hour for 23 hours → mild long term improvement in motor and sensory scores (NASCIS trial). Not universally accepted
 - If stable, early transfer to a multi-disciplinary SCI unit
 - Admit ICU for detection and management of respiratory and cardiovascular problems
- Prognosis best judged at 72 hours. Most complete tetraplegics regain one motor level
- On-going management:
 - ↓Sympathetic function and inability to shiver → poikilothermia (loss of temperature control → highly variable temperature). Prevent hypothermia
 - GI problems: Ileus. Early Enteral feeding once resolved. Stress ulcer prophylaxis. Expect and prevent constipation
 - Urinary: catheterise. Expect bacterial colonisation
 - Skin: Pressure sore prevention
 - Metabolic: Hyponatraemia not uncommon. Calcium metabolism may lead to small ↑ in serum Ca. Nitrogen loss from muscle wasting is expected
 - Analgesia from vertebral fractures, ileus and neuropathic pain
 - Psychological: depression common. Difficulty with communication

Specific Spine Injury Management

- Conservative: closed reduction, traction in head tongs or a halo, or halo thoracic brace
- Surgical:
 - Open reduction/internal fixation → early mobilisation and pain control → potentially less muscle wasting and complications
 - No clear evidence in favour of surgical management and little agreement over timing
 - Early decompression (< 24 hours) of incomplete SCI may have benefit

Respiratory Management

- Respiratory complications are the leading early cause of death after SCI
- Tetraplegia:
 - With C5 SCI, 50% will still need short term mechanical ventilation
 - With C3, 50% will need long term ventilation (may benefit from phrenic nerve pacing)
 - Intercostal weakness → paradoxical breathing (chest sucks in with inspiration), abdominal paralysis → inability to cough
 - VC 1 – 1.5 l on admission, significant increase by 3 – 5 weeks after injury. VC depends on posture – is actually best lying down. Intubate if VC falls below 12 – 15 ml/kg

- Paraplegia: paralysis of intercostal and abdominal muscles depending on neurological level
- Humidified O₂
- 2 hourly turn to prevent atelectasis
- Intensive respiratory physio for deep breathing and assisted cough (see Berney et al, Spinal Cord 2011, for a systematic review of case series, no RCTs.). Structured respiratory protocol reduces respiratory complications, mortality, need for tracheostomy and LOS
- Potential complications:
 - Atelectasis
 - Sputum retention
 - Pneumonia
 - Acute respiratory failure
 - Aspiration
 - ARDS
 - PE
- Intubation:
 - Either:
 - Awake fibre-optic nasotracheal intubation. Allows on going neurological assessment but needs cooperative patient. Contraindicated if intubation is urgent, coagulopathy, nasal obstruction or basal skull fracture
 - Orotracheal intubation under GA: required removal of anterior part of the collar and manual in-line stabilisation (MILS) of the head. No specific evidence for this – evidence for C-spine protection is for the whole process of transport and assessment (which shows a significant decrease in 2ndary injury). Risk of worse view
 - Ventilation with larger tidal volumes and I:E ratio of at least 1:2
- Tracheostomy usually necessary:
 - Facilitates comfort, communication and weaning
 - Percutaneous tracheostomy only after internal fixation and if able to extend neck enough, otherwise surgical tracheostomy
- Weaning:
 - No approach shown to be superior
 - Convert to pressure support with flow triggering
 - Incremental reduction in pressure support before conversion to T piece, or T piece trials from the outset (needs more psychological support to prevent anxiety)

Cardiovascular Management in Spinal Injury

- Tetraplegia (and to some extent in paraplegia above T6) → loss of supra-spinal sympathetic control → unopposed vagal activity → bradycardia and systemic vaso- and veno-dilatation:
 - Sensitive to hypotension with postural change, hypovolaemia and IPPV
 - In high SCI, persisting bradycardia and even arrest peaking in first week, eg in context of tracheal suction
- Hypotension after SCI may contribute to secondary chord ischaemia. Consensus guidelines recommend MAP of at least 85 – 90 with vasopressors for 7 days
- DVT common. Pneumatic compression and enoxaparin starting within 72 hours and continuing for 8 – 12 weeks depending on risk
- Autonomic hyperreflexia: Begins ~ 6 months from injury, and is usually only significant above T6. Stimulus below the injury → excessive paroxysmal autonomic activity. Eg bowel or bladder distension → intense vasoconstriction → bradycardia + hypertension which may even → seizures or cerebral haemorrhage. Prevent with removal of stimulus, sitting up, and short acting anti-hypertensives

Abdominal and Pelvic Injury

- Up to 60% of missed diagnoses in preventable trauma deaths
- Issues:
 - Potential for severe haemorrhage
 - Difficult of diagnosing visceral injury
 - Severity of associated injuries (head and chest)
 - Complications, especially sepsis
- Mechanisms:
 - Blunt, mainly road accidents. Compression and torsion injuries. Airbags and seatbelts reduce mortality by limiting head injury, but are associated with more abdominal injury
 - Penetrating injury: mainly stab and gunshot wounds:

- Entry sites don't predict the nature of deeper injury
- Stab wounds are low velocity – injuries along the track only. If haemodynamically stable, investigative algorithms can be safely laparotomy sparing
- Gunshot wounds are generally worse than stab wounds, and generally require laparotomy. High velocity → kinetic transfer of huge amounts of energy → widespread damage

General Management of Abdominal/Pelvic Trauma

- Resuscitation:
 - Resuscitation should not delay surgery for uncontrolled haemorrhage
 - Endpoints for resuscitation are controversial: if rapid surgical haemostasis is achieved, limiting fluid resuscitation may improve outcome
- Assessment:
 - Auscultation for bowel sounds is not useful
 - Check gastric aspirate and urine for blood
 - If conscious, serial assessment can identify those with significant intra-abdominal trauma
- Laparotomy is clinically indicated if:
 - Shock with signs of intra-abdominal haemorrhage (eg peritonism, positive FAST or DPL)
 - Evisceration or peritonism without shock in penetrating trauma.
 - Most gunshot wounds are managed by exploratory laparotomy as the incidence of significant intraperitoneal injury approaches 90%
 - Free air, retroperitoneal air or rupture of the hemidiaphragm after blunt trauma
 - Rupture of visera on CT
- Xrays:
 - CXR essential
 - Abdominal film of no benefit
 - AP pelvis in all blunt trauma, except conscious patients with normal pelvic exam
- Investigations for occult abdominal injury:
 - FAST (focussed assessment with sonography for trauma):
 - Main use is when it is positive in the unstable patient who has failed fluid resuscitation → straight to OT without CT
 - Weaknesses:
 - Operator dependent
 - Specific, but only 85% sensitive – worse than DPL or CT for blunt and penetrating trauma. High false-negative rate may be too high
 - Small but important false-positive rate for intra-abdominal bleeding
 - Cannot diagnose hollow viscus or pancreas injury
 - Not good for bleeding in the pelvis or retroperitoneum
 - Views (screening for free fluid – usually dark and anechoic in appearance):
 - Perihepatic: Morison's (hepatorenal pouch between liver and kidney) – anterior axillary line over the intercostal space between 10th and 11th rib
 - Perisplenic: spleno-renal recess and between spleen and diaphragm – posterior axillary line over the intercostal space between the 10th and 11th rib
 - Pelvic: pouch of Douglas (female) or retrovesical pouch (male) - above pubic symphysis. Place probe longitudinally then rotate transversely
 - Pericardial: sub-xiphoid and parasternal views – showing pericardial fluid
 - Diagnostic peritoneal lavage (DPL):
 - Virtually obsolete given modern imaging, unless no FAST. Potentially of use as part of diagnosis in crumbling post-laparotomy sepsis
 - Diagnosing intra-abdominal bleeding in blunt trauma in shocked patients not going straight to laparotomy or in non-shocked sedated patients
 - Open and closed (percutaneous guide wire) methods both satisfactory
 - Relatively contraindicated if:
 - An indication for laparotomy already exists
 - Pregnancy
 - Significant obesity
 - Previous abdominal surgery
 - Detects intraperitoneal injury with up to 98% sensitivity, but significant false-positive laparotomy rate
 - Hollow visceral injury difficult to detect
 - Drain stomach and bladder, instil 1 litre isotonic saline into peritoneal cavity

- Clinical criteria for diagnostic DPL:
 - > 10 ml frank blood on aspiration, or
 - lavage fluid via chest tube or urinary catheter, or
 - bile or vegetable material in fluid
 - → Urgent laparotomy.
- Otherwise send specimen. If RBC > 100,000 per m3 (lower threshold if penetrating), WBC > 500 per m3, grain stain showing bacteria or vegetable fibres, or ↑amylase then urgent laparotomy
- CT
 - Not indicated in shock, useful in stable patient
 - Favoured over DPL if safe. Is non-invasive, time-consuming and accurate
 - Particular valuable for retroperitoneal injury and pelvic fractures
 - Improving specificity and sensitivity for hollow viscus trauma (although not brilliant)
 - Needs to be performed with IV and oral contrast and interpreted by radiologists experienced in trauma. Value of enteral contrast is controversial. Involves radiation.
- MRI – no advantage over CT in acute trauma
- Urethrography is used for suspected urethral injury
- Treatment:
 - Laparoscopy: useful if haemodynamically stable but may miss organ specific injuries, especially bowel. Best suited for equivocal penetrating wounds
 - Angiography and embolisation: best for dealing with major haemorrhage from spleen, liver, pelvis and retroperitoneal structures
 - Laparotomy:
 - Morbidity of a negative laparotomy insignificant compared to not diagnosing and treating a serious injury
 - Difficult haemostasis can lead to a lethal triad of hypothermia, acidosis and coagulopathy → “damage control” laparotomy: control of haemorrhage and contamination, packing and elective re-exploration and removal of packs in 24 – 48 hours. See Damage Control Resuscitation, page 231
 - May require prosthetic closure to avoid ↑ intra-abdominal pressure
 - Survival is better when the decision to terminate the initial procedure is made earlier

Specific Abdominal Injuries

- Spleen:
 - Most frequently injured in blunt trauma
 - Minor injury may be missed if other severe injuries
 - Lower rib fractures a common association
 - Immediate splenectomy if splenic avulsion, rupture or extensive hilar injury
 - Splenectomy patients must have long term vaccination for encapsulated organisms – polyvalent pneumococcal, haemophilus and meningococcal
 - If no other intra-abdominal injuries, a non-operative approach can give salvage rates of 80%
- Liver:
 - Second most commonly injured in blunt trauma
 - Follow-up scans show resolution, typically over 2 - 3 months
 - Non-operative management has complications of bile leak, haemobilia, necrosis, abscess and delayed haemorrhage, which can be treated with CT guided percutaneous drainage, ERCP and angio-embolisation
 - If laparotomy is required, perihepatic packing gives haemostasis
 - Early complications due to effects of hypoperfusion or massive blood transfusion. Late complications usually septic
- GI Tract:
 - More common following penetrating than blunt trauma
 - Gunshot → need laparotomy. Stab wound consider laparoscopy first
 - For retroperitoneal structures (eg posterior stab) CT with contrast enema may better identify colonic injury
 - FAST or DPL are not accurate in diagnosing isolated bowel trauma
 - CT is a sensitive indicator of free intra-peritoneal air – but duodenal perforation hard to see and may be missed. Have high index of suspicion
 - Uncomplicated injury can often be managed by primary repair and anastomosis rather than colostomy. If significant peritoneal contamination then stoma and delayed repair usual
- Pancreas:

- Blunt injuries require considerable force, expect the spleen, liver and duodenum to also be injured
- ↑amylase doesn't predict pancreatic or hollow viscus injury
- Minor injuries → simple drainage and haemostasis
- Major injuries → partial pancreatectomy
- Double contrast CT may not identify significant pancreatic trauma < 8 hours post injury. Repeat later if pancreatic injury suspected
- Kidney and urinary tract:
 - Gross haematuria requires investigation, CT is best. May need to wait 20 minutes after contrast to see urinary extravasation. Safe to observe microscopic haematuria
 - Many kidney injuries resolve without surgery.
 - Intraoperative iv urography can check for extravasation
 - Bladder rupture associated with pelvic fracture; 95% have macroscopic haematuria. Retrograde cystography is the best investigation – CT has a high false-negative rate
 - Suspect urethral trauma if blood at the urinary meatus, perineal injury or abnormal position (high riding) on prostate exam. Treat with SPC and subsequent definitive repair
- Diaphragm:
 - In < 5% of cases of blunt trauma, 80% are left sided. Suspect in penetrating injury below the 5th rib
 - Difficult to diagnose once on PPV – may not become obvious till weaned
 - CXR is often non-specifically abnormal
 - DPL is insensitive
 - Laparoscopy and thoracoscopy provide good views
 - All defects require surgical repair
- Bony pelvis and perineum
 - Initially the risk is haemorrhage, later it is sepsis. Significant morbidity from nerve, urethral and bony damage
 - Types:
 - AP compression. Can → Open Book fractures. Significant potential space created for haemorrhage
 - Lateral compression: subluxed fractures → less potential for bleeding but more urethral/pelvic organ damage
 - Vertical sheer (eg land on one leg): put short leg in traction then pelvic binder
 - Xray can check for bony injury, but CT is required to identify intra-abdominal injury
 - FAST has a significant false-negative rate with major pelvic fractures. If grossly positive, laparotomy should precede external fixation or angiography. If fast negative or DPL is positive by cell count, then life-threatening intra-abdominal bleeding is less likely, and attention can focus on pelvic haemostasis. Options include:
 - Pelvic binding (to tamponade pelvis – binder or even sheet tied around pelvis at level of the greater trochanter)
 - External fixation of the pelvis can control peri-fracture bleeding
 - Surgical control is required for large vessel bleeding (rarely complete ligation of internal iliac arteries for uncontrolled arterial haemorrhage). General packing (without exploration) for venous haemorrhage
 - Angiography and selective embolisation may be able to achieve control of arterial bleeding where pelvic stabilisation or laparotomy have failed
 - Gross intraperitoneal blood should prompt laparotomy
 - Early fixation permits better respiratory care, pain control and early mobilisation
- Retroperitoneal haematoma:
 - Common following blunt trauma
 - CT the most useful investigation in a stable patient
 - A central haematoma should be explored and controlled because of the risk of pancreatic, duodenal or major vascular injury
 - Lateral or pelvic haematoma should not be explored, unless evidence of major arterial injury, intraperitoneal bladder rupture or colonic injury

Complications of Abdominal Trauma

- Sepsis:
 - Risk factors:
 - Peritoneal contamination
 - External wounds
 - Invasive procedures

- Delayed diagnosis of hollow viscous injuries
- Splenectomy
- Devitalised tissue
- Prophylactic antibiotics for 24 hours for penetrating injuries
- Exclude intra-abdominal infection if unexplained deterioration
- GI failure:
 - Due to:
 - Stress ulceration
 - Delayed emptying
 - Paralytic ileus
 - Enteral nutrition is associated with a lower incidence of sepsis following trauma
- Raised intra-abdominal pressure: see Abdominal Compartment Syndrome¹⁸⁵

Burns

- See Burns Hot Case, page 373
- Phases of burns:
 - “Ebb: phase within 48 hours. Decreased CO, O₂ consumption and metabolic rate, ↑glucose
 - “Flow: phase: Gradual increase in metabolism commences after 1 - 2 days. Hyperdynamic, vasodilated (may need vasopressors), ↑insulin but insulin resistance → ↑glucose
 - After 2 – 5 days → diuretic phase with reducing oedema
- Body temperature on days 1 – 2 may be as high as 40 and persist for several days. Does not necessarily indicate infection
- Avoid suxamethonium for 5 – 150 days post-burn due to risk of rapid and severe hyperkalaemia. May be ↑resistance to non-depolarising muscle relaxants

Assessment of burns patient

- Primary survey, resuscitation. Don't miss other critical injuries eg C-spine
- Secondary survey, looking for:
 - Assessment and management of potential airway burn
 - Extent of body surface burned and depth of burn
 - Other traumatic injury
 - Temperature: Avoid hypothermia
 - Precipitating events: seizures, alcohol/drugs
 - Adequacy of analgesia
 - Collateral history of events and past medical history
- Differential of reduced LOC
 - Traumatic brain injury
 - CO poisoning
 - Hypoxia
 - Alcohol or drugs
 - Other: CVA, seizure, hypoglycaemia
- Early insertion of lines and catheters – swelling may make this difficult after several hours. Avoid putting lines through affected skin
- Disposition:
 - > 20% BSA or airway burn → ICU
 - Transfer to burns centre:
 - > 10% BSA if age < 10 or > 50
 - 20% at any age
 - Special areas
 - Full thickness > 5%

Assessment of the Burn

- % Body Surface Area
 - Lund-Browder Chart
 - Rule of 9s: head and each arm 9%, front of torso, back of torso and each leg 18%
 - Rule of palm (patients palm = 1.5% BSA)
- In kids MUST use a paediatric chart – rule of 9's does not apply – relative surface area of head and limbs changes significantly for different aged children
- Classed as:
 - Superficial: red, no blisters
 - Partial thickness: blistering, skin pink or mottled
 - Full thickness: white or charred, painless, leathery to touch
- Special areas:
 - Face and mouth
 - Hands/fingers: small burns cause significant functional impairment
 - Perineal areas prone to infection
 - Circumferential burns may need escharotomies
- Indicators of significant airway burn:
 - Burns occurring in a closed space

- Cough, stridor, hoarseness of voice
- Burns to face, lips, pharynx, singed hair
- Soot in sputum, nose or mouth
- Hypoxia or dyspnoea
- Carboxyhaemoglobin levels > 2%. Always measure. Normal SpO2 does not exclude carbon monoxide poisoning, as a pulse oximeter measures O2 saturation regardless of haemoglobin concentration (see Pulse Oximetry, page 28)
- Acute confusion/depression of consciousness
- Electrical burns
 - Often not visible on the surface
 - Look for entry and exit wounds
 - Electricity generates heat. Nerves, blood vessels, skin and muscles are damaged most
 - Swelling of damaged tissues, especially muscles, can cause compartment syndrome

Smoke Inhalation

- Injury at 4 levels:
 - Upper airway obstruction from airway oedema
 - Lower airway: tracheobronchitis, retained secretions, bronchospasm, coughing
 - Alveolus: frothy sputum, oedema, raised A-a gradient, shunt
 - Systemic effect:
 - Cyanide toxicity → lactic acidosis, high SvCO2, confusion, hypotension
 - Hypoxia
 - SIRS response

Resuscitation

- Fluid resuscitation:
 - Groins usually spared in a burn and a good clean site for CVL
 - Hypovolaemia occurs later. If initially hypotensive look for another cause
 - Losses increased by uncovered burn (2 ml/kg/hr) and by inhalational injury
 - Modified Parkland formula (aka “consensus formula”): 4 ml fluid * weight * %BSA crystalloid over first 24 hours with ½ over first 8 hours (US), in addition to maintenance. Same in kids.
 - Mount Vernon (albumin based) often used in the UK
 - Clinical endpoints more important than a pre-prescribed formula: urine output of 0.5 – 1 ml/kg/hr a reasonable guide to tissue perfusion, 2 ml/kg/hr in children. Beware myoglobinuria – may lead to ↓urine output requiring frusemide
 - Pre-load measurement (CVP, PAOP) often suggest persistent hypovolaemia despite adequate urine output – interpret with caution
 - Avoid over-resuscitation: may contribute to compartment syndrome of limbs, chest, abdomen, airway swelling, pulmonary oedema
 - Crystalloids the resuscitation fluid of choice, but controversy around colloids and hypertonic saline
 - K and Mg can fluctuate wildly – monitor and replace
- Transfusion:
 - Transfuse to maintain Hb > 100
 - Often debridement → need for transfusion (up to 100ml per 1% BSA grafted)
 - Coagulopathy common: dilutional, SIRS

Burns Management

- Only cool for 10 mins. Never cool during transfer
- Escharotomy. Consider U/S assessment of flows. Expect significant bleeding (cross match before)
- Wound management:
 - Most dressing regimes include topical antibiotics (silver sulfadiazine, silver nitrate) which may reduce bacterial load and local and systemic sepsis
 - Early excision vs topical antimicrobial therapy and skin grafting after spontaneous eschar separation (conservative management). Single centre study of 85 patients > 30% burns showed ↓mortality with early excision (Herndon, Annals of Surgery 1989). Confirmed by meta-analysis of 6 studies. Early excision reduces the hypermetabolic response, possible ↓infection, and improves cosmetic outcome. Facilitated by advances in skin substitutes (eg Biobrane)
 - Graft tracheostomy site early to allow early tracheostomy
- Supportive care:

- There is no role for prophylactic systemic antibiotics. Commonly encountered bacteria are staph aureus, pseudomonas aeruginosa and Acinetobacter – all of which have high rates of resistance
- Analgesia: ketamine useful – anaesthetic and analgesic properties
- Nutrition:
 - Burns reduce the body's ability to metabolise lipids (compared to starvation when lipolysis and ketosis provide energy) → muscle catabolism for fuel → wasting, ↑infection and delays in wound healing, longer respiratory weans
 - Generally small trials
 - Early nutrition improves outcomes. Unclear when to start – generally by day 2
 - Target protein of 1 g/kg + 2 gm per % burn
 - Calories of 20 cal/kg + 50 cal per % burn
 - Could higher proportion of energy as lipid to replace essential fatty acids and reduced burn induced glucose intolerance. However, ↑lipids may → ↑ complications
- Tetanus toxoid
- Heated fluidised bed
- Prevent contractures through careful nursing and physiotherapy
- Eye care if facial burns – eye lids may not approximate correctly
- Oxandrolone (deca-durabalin): testosterone analogue with a low level of virilising androgenic effects → ↑muscle catabolism, less weight loss and better wound healing – trialled in small groups in adults and children
- Propranolol trialled in small studies with apparent effectiveness as an anti-catabolic therapy → ↓infections. Recommended in children, not adults

Toxic Epidermal Necrolysis

- Rapid progression of erythema and extensive epidermal necrolysis (usually > 30%)
- Overlaps with Stevens-Johnson syndrome with high mortality
- Diagnosis:
 - Skin eruption that begins 1 – 3 weeks after a suspicious drug
 - Prodrome of fever and flu-like symptoms 1 -3 days before eruption
 - Poorly defined macules with purpuric centres that coalesce to form blisters then desquamation
 - Symmetrical, primarily over face and trunk, mucosal involvement in 90%
 - Pulmonary complications can occur (excessive secretions, sloughing of bronchial epithelium, BOOP)
- Most cases drug induced (a few are idiosyncratic). Likely offenders are sulphonamide antibiotics, amino-penicillins, quinolones, cephalosporins, carbamazepine, phenobarbital, phenytoin, valproic acid, NSAIDs, allopurinol, corticosteroids
- Treatment:
 - Very controversial
 - Stop offending drugs
 - Treat as for severe burns
 - Emollient
 - NOT steroids: death is usually due to infection, steroids increase that risk

Drowning

- Pathophysiology:
 - Diving reflex → bradycardia and apnoea → hypoxia, acidosis → tachycardia and ↑BP
 - After 20 secs – 5 mins, breathing occurs. Water touches glottis → immediate laryngospasm
 - Shortly afterwards, laryngospasm subsides → aspiration → alveolitis and pulmonary oedema
 - In total: hypoxia → LOC, bradycardia and dysrhythmia (VF rare)
 - Difference between effects of salt and fresh water over-rated
- Assess for concurrent hypothermia, hypovolaemia, injury (especially spinal) and precipitants. Electrolyte abnormalities due to water swallowed are rare
- Dry chest before attaching defibrillator electrodes
- Stomach often full of water ⇒ easy for the patient to aspirate. Suction, secure airway, insert NG
- Respiratory deterioration can be delayed for up to 4 – 6 hours: observation required
- If hypothermic below 30o (VF may be refractory due to temperature) then:
 - Limit defibrillation to single shock, no inotropes or antiarrhythmics
 - Warm as quickly as possible to > 30o before further shocks
 - Dose interval for resuscitation drugs is doubled from 30 – 35o

- Continue resuscitation until core temperature at least 32, or cannot be raised despite active measures
- Rewarming:
 - Active to 34o, passive above that, hypothermia if cardiac arrest
 - External rewarming
 - Core rewarming:
 - Warm IV fluids (39o) and ventilator gases (42o)
 - Gastric or bladder lavage with normal saline at 42o
 - Peritoneal lavage with potassium free dialysate at 42o, 20 ml/kg with a 15 minute cycle
 - Pleural lavage
 - Endovascular warming
 - Extracorporeal blood warming

Poisoning

Basic Management of Poisoning

- In-hospital mortality from overdose is low (< 0.5%)
- In most cases supportive care is all that is necessary
- Few trials – recommendations based on a small literature of case reports
- General principles:
 - Airway management and ventilation
 - Clinical examination: needle marks, self-harm, temperature, pupil size, respiratory and heart rate
 - Investigations
 - Gut Decontamination
 - Enhanced Elimination
 - Supportive Care
 - Specific therapy
- Talk to a toxicologist early

Investigations

- Urinalysis
- Basic biochemistry: significant renal failure will alter management
- ABG:
 - Metabolic and/or respiratory acidosis most common
 - Causes of anion gap acidosis:
 - See also Metabolic Acidosis, page 62
 - Iron, isoniazid, ibuprofen
 - Lithium
 - Carbon monoxide, cyanide, caffeine
 - Respiratory dysfunction, β -blockers, benzyl alcohol
 - Metformin
 - Paraldehyde
 - Ethanol, methanol, ethylene glycol
 - Salicylates
 - Cyanide
- Elevated osmolal gap: ethanol, methanol, ethylene glycol, isopropyl alcohol, acetone
- Drug levels: rarely helpful except in specific cases: paracetamol, salicylates, iron, digoxin, lithium
- CXR: aspiration not uncommon
- ECGs:
 - Bradycardia: β -blockers
 - Broad QRS: type 1 anti-arrhythmics: TCAs, quinine, chloroquine
 - 2nd degree heart block: verapamil, diltiazem
 - Digoxin: any arrhythmia

Decontamination

- Emesis: ineffective and limits use of activated charcoal
- Activated Charcoal:
 - Decreases bioavailability
 - Give to all patients presenting within one hour of serious ingestion, longer if drug slows gastric emptying (eg opioids, TCAs)

- Repeated doses in drugs undergoing entero-enteric and enterohepatic circulation:
 - Carbamazepine
 - Theophylline
 - Digoxin
 - Quinine
 - Phenobarbital
 - Dapsone
 - Sustained release preparations
- Does not improve outcome when given to unselected patients – should not be regarded as routine
- Doesn't work for metals (Fe, lead), methanol, ethylene glycol, strong acids or alkalis and cyanide
- Side effects: vomiting, aspiration, direct administration to lung via misplaced NG tube, impaired absorption of antidotes, corneal abrasions, constipation/bowel obstruction
- 50 gm dose, repeated if appropriate at 4 hourly intervals. Causes vomiting \Rightarrow give antiemetic first
- Given mixed in sorbitol to increase transit time and avoid obstruction
- Gastric lavage:
 - Based on limited data
 - Within one hour of ingestion only (unless anticholinergic which \rightarrow delayed emptying)
 - Tablet has to be able to pass up the lumen of the NG tube
 - Protect airway if any doubt about laryngeal competence. Aspiration more lethal than most overdoses
 - Position head down on left side and pass a large bore tube (36 – 40 Fr) with large side holes into the stomach. Aspirate before lavage. Instil tepid water then remove. Use small aliquots (otherwise may increase gastric emptying). Repeat until clear fluid
 - Contraindicated in corrosives, or in petrol, paraffin or white spirits (cause intense pneumonitis)
 - Follow with charcoal
- Whole bowel lavage:
 - Efficacy only based on case reports
 - With Polyethylene glycol
 - Method of choice for metals (iron, lithium) and slow release preparations
 - 2,000 ml per hour in an adult
- Increase clearance:
 - Urinary alkalisation (previously called forced alkaline diuresis):
 - Eg treatment of choice in severe salicylates, and also methotrexate
 - IV NaHCO_3 infused to maintain a neutral balance and attempt to achieve urine pH of > 7.5
 - Ensure K doesn't fall too quickly
 - Dialysis:
 - Only if severe toxicity in a dialyzable compound and failing to respond to supportive care
 - Best if drug is water soluble, MW < 500 Da, not highly protein bound, low Vd
 - For aspirin, lithium, iron, methanol, ethylene glycol, metformin
 - Continuous haemofiltration, with or without dialysis, at filtration rates of greater than 50 – 100 ml/kg
 - Also help correct fluid and electrolyte abnormalities
 - Haemoperfusion:
 - Blood perfused through a charcoal cartridge rather than a dialysis membrane. Effectively removes non-protein bound molecules of 300-500 D MW (another reference says 100 – 1500)
 - Disadvantages:
 - No data to show superiority
 - Expensive
 - Difficult to source
 - Won't correct acid/base disturbance, electrolytes, fluid overload
 - Leads to \downarrow glucose, \uparrow Ca, thrombocytopenia
 - Effectively removes theophylline, carbamazepine, verapamil, phenobarbitone and paraquat
- Lipid Emulsion:
 - Usually intralipid: long chain fatty acid (as opposed to medium chain) - \uparrow binding capacity
 - Accepted indication in local anaesthetic toxicity
 - In drug overdose, currently only animal models, case reports, small RCTs and registry data
 - Proposed mechanisms include “lipid sink” (?conduit for rapid redistribution), possible sodium channel antagonist, Ca channel effect, and a possible direct inotropic effect (at least in rats!)
 - Suggested as rescue therapy in lipophilic toxins:
 - TCAs: especially amitriptyline

- Ca Channel blockers
- Propranolol (not metoprolol – water soluble)
- Dose 1.5 ml/kg bolus, 15 ml/kg/hr infusion to total dose 12 ml/kg
- Complications: rare pancreatitis, interferes with lab test for up to 24 hours

Corrosive ingestion

- Acute complications:
 - Oral, oesophageal and gastric burns of varying thickness
 - Laryngeal oedema and airway obstruction
 - Oesophageal, gastric perforation
 - Haemorrhage
 - Mediastinitis
- Chronic problems:
 - Laryngopharyngo fibrosis with airway incompetence and chronic aspiration
 - Oesophageal fibrosis, stricture and stenosis
 - Psychosocial problems
 - Carcinoma

Toxindromes

- **CNS depression:**
 - Cholinergic:
 - Signs: confusion, ↓LOC, weakness, salivation, urinary/faecal incontinence, GI cramping, sweating, muscle fasciculations, pulmonary oedema, miosis, hypotension, seizures [ie weeping, sweating, peeing, pooing]
 - Likely agents: organophosphate insecticides. Note these can be absorbed through the skin. Wear protective clothing. Remove patients clothing, wash exposed areas
 - Hypnotic:
 - Signs: coma, CNS depression, nystagmus, hypotension, hypothermia, hyporeflexia
 - Likely agents: BZD, Zopiclone
 - Opioid:
 - Signs: Miosis (contracted pupils), coma, respiratory depression, hypotension, pulmonary oedema
 - Likely agents: heroin, methadone, morphine, codeine, dextropropoxyphene (is also cardiotoxic)
- **Stimulants:**
 - Anticholinergic:
 - Signs: delirium, tachycardia, dry flushed skin, mydriasis (dilated pupils), myoclonus, urinary retention, ↓bowel sounds, (seizures, dysrhythmias) [ie blind, dry, mad and hot]
 - Agents: TCAs, datura, atropine, benztropine, antihistamines
 - Gastric stasis → delayed drug absorption
 - *Serotonin Syndrome:*
 - Excess of synaptic serotonin → hyper-stimulation of 5HT1A receptors, as opposed to neuro-malignant syndrome (which is due to an idiosyncratic reaction to anti-psychotic causing dopamine antagonism and not serotonergic drugs. Treat with supportive care +/- muscle relaxants [diazepam, dantrolene], and ?dopamine agonists [eg bromocriptine])
 - Presentation:
 - Mental status changes, agitation, nausea, myoclonus, hyperreflexia, diaphoresis, tremor, diarrhoea, fever
 - Rarely: rhabdomyolysis, hyperkalaemia, renal failure, DIC, seizures
 - Drug combinations causing it:
 - Inhibition of serotonin reuptake: SSRIs, TCAs, Tramadol, pethidine
 - MAOIs
 - St John's Wort
 - Partial serotonin agonists: LSD, buspirone (anxiolytic)
 - ↑Serotonin release: amphetamines
 - Lithium
 - Serotonin precursors: Tryptophan (antidepressant adjunct)
 - Treatment:
 - Withdrawal of all neuroleptic, dopamine-depleting or dopamine-antagonist medications
 - Renal protection from myoglobin therapy
 - Dialysis doesn't help: drugs too large or protein bound

- Little evidence for drug therapy, although bromocriptine (dopamine agonist), dantrolene, amantadine and levodopa-carbidopa have been used
- Sympathomimetic:
 - Signs: Delusions, paranoia, tachycardia, HTN, fever, diaphoresis, piloerection (erection of hair), mydriasis (dilated pupil)
 - Agents: amphetamines, decongestants, cocaine
- **Discordant:** Anion gap acidosis causing agents, eg ethylene glycol

Cardiotoxic Overdoses

- ECG:
 - Bradycardia and AV node blockade: β and Ca antagonists, digoxin
 - Na channel blockade – slurs the upstroke of QRS \rightarrow wide QRS. If longer than 110 risk of seizures. If longer than 160 then risk of ventricular dysrhythmia
 - K efflux blockers: delayed depolarisation \rightarrow long QRS
- Perfusion (CO/SVR) is the key – not BP. Monitor CO and SCR
- Treatments:
 - Specific antidotes: eg Digibind
 - Na Bicarbonate:
 - For Na channel blockers
 - Sodium load: overcome blockage
 - Changed pH alters ionisation \rightarrow less binding
 - If QRS > 140 ms or unstable or cardiac arrest or eg seizures compounding the acidosis, then 1 – 2 mg/kg boluses (up to every 3 – 5 mins in an arrest), and hyperventilate to pH 7.5 if ventilated
 - High dose insulin (for Ca and β antagonists)
 - Inotrope
 - Enables heart to better use carbohydrates in addition to FFAs as energy
 - Dose: 1 unit/kg + 50 mls 50% glucose stat (aim is to saturate insulin receptors) then infusion at 0.5 units/kg/hr increasing half hourly to 4 – 6 units/kg/hr – or just do 1 unit/kg/hr (100 u per hour ...)
 - Watch glucose and K – although rarely a problem unless the patient is getting better
 - Glucagon not recommended: weak inotrope and very emetic
 - ?Lipid (see Decontamination, page 261).
- Consider lower induction doses for intubation and minimising on going sedation
- Use noradrenaline not adrenaline – the inotrope of choice in low SVR if inotropes are required. Alpha 1 blockade from cardiotoxic overdose (eg quetiapine) leads to unopposed beta1 vasodilation with adrenaline \rightarrow paradoxical drop in BP

Specific Therapy for Poisons

- **Alcohols:**
 - Diagnosis:
 - Ethanol: test ethanol level
 - Methanol (wood alcohol): measure methanol and formate
 - Ethylene glycol (antifreeze – as opposed to polyethylene glycol which is bowel prep): measure ionised Ca and oxalate crystaluria. Interferes with lactate measurement on a blood gas machine, but not in laboratory measurement. A difference between ABG lactates is pathognomonic for ethylene glycol. Glycolate is the metabolite that causes the acidosis, not oxylate
 - Symptoms (incl ocular toxicity and renal failure) and acidosis are due to toxic metabolites via alcohol dehydrogenase (ethanol \rightarrow lactate, methanol \rightarrow formaldehyde, ethylene glycol \rightarrow glycolic acid)
 - Treatment:
 - Gastric lavage (not absorbed by AC), sodium bicarbonate (may need large doses)
 - Ethanol often used but dosing is complex and has side effects
 - Fomepizole: inhibitor of alcohol dehydrogenase (better than ethanol). Expensive but simple. Recommended as first line treatment
 - Haemodialysis
 - Folinic acid enhances the metabolism of formic acid
 - Thiamine: for prevention or treatment of Wernicke-Korsakoff's Syndrome. Cochrane Review (Day, 2013): insufficient evidence to determine dose, frequency, route or duration.
- **Amphetamines**
 - Eg Ecstasy
 - A derivative (NDMA – 3,4 methylenedioxymethamphetamine)

- Rapid rise then depletion of serotonin, release of ADH
- Onset 20 minutes, lasts 4 hours. Persisting abnormalities in the brains of ex-users
- SE: Hyperthermia (→ rhabdomyolysis, AKI, DIC and MODS), seizures, hypertonia, liver impairment, dehydration (or water toxicity from water excess), tachyarrhythmia
- Treatment:
 - Activated charcoal if < 1 hour
 - Benzodiazepines for agitation, and ?central effect on tachycardia, HTN and fever
 - Antihypertensives: α -blockers, labetalol, direct vasodilators
 - Consider hypertonic saline in severe hyponatraemia
 - Fever: cold saline, consider dantrolene of value in controlling body temperature (although ?better to treat central mechanism rather than this symptom?)
- **Aspirin/Salicylates:**
 - Rapidly converted to salicylic acid
 - Activates chemoreceptor trigger zone (→ nausea) and respiratory centre (→ respiratory alkalosis, then superimposed metabolic acidosis 2nd to lactic acid)
 - Presentation: *tinnitus*, *fever* (induced mitochondrial defect), hypoglycaemia, vertigo, nausea, diarrhoea, blurred vision
 - Severe toxicity with serum concentrations > 750 mg/l (5500 μ mol/l)
 - May ↑Hb-O₂ affinity, ↑osmolality, reduce Ca and Mg, and cause rebound alkalosis when acidosis resolves
 - Complications:
 - ↓glucose
 - Pulmonary oedema
 - Cerebral oedema
 - Arrhythmias
 - ↑fever
 - ↓Prothrombin → ↓clotting. Treatment: vitamin K
 - Treatment:
 - Levels don't correlate to toxicity – track acid base status
 - Beware gut bezoars → delayed absorption
 - (?Multidose) Activated charcoal (although aspirin is rapidly absorbed)
 - Supplemental glucose (CNS glucose levels < peripheral)
 - Treatment with bicarbonate only in severe poisoning (despite alkalosis) to leach the weak acid from the CNS and increasing urinary excretion. Renal excretion of salicylates becomes more important when metabolic pathways are saturated. 10 – 20 fold increase in elimination when urine pH ↑5 to 8
 - If ventilated, hyperventilate to prevent worse acidosis
 - Haemodialysis as small Vd. Concentration dependent protein binding → ↑levels free drug
- **β -blockers:**
 - Symptoms: Cardiogenic shock and pulmonary oedema not uncommon
 - See Cardiotoxic Overdoses, page 264
 - Treatment:
 - AC if < 1 hour, and multi dose if sustained release
 - Role of atropine unclear, although commonly used
 - Glucagon: up to 10 mg iv. Evidence only in animal studies. Mix with dextrose – not phenol diluent (cardiac depression in large amounts). Insulin ?better than glucagon
 - Adrenaline or cardiac pacing
- **Benzodiazepines:**
 - AC if < 1 hour. Usually supportive care only.
 - Flumazenil usually only for diagnostic purposes due to brief duration. May ↑seizures if co-ingestion of TCAs
- **Butyrophenones** (including Haloperidol):
 - Symptoms: drowsiness, extra-pyramidal side effects, rarely hypotension, QT prolongation, arrhythmias, seizures
 - AC if < 1 hour. Extrapyramidal symptoms treated with benzotropine. Treat ventricular arrhythmias with cardioversion. Class 1a antiarrhythmics theoretically detrimental
- **Calcium Channel Blockers:**
 - See Cardiotoxic Overdoses, page 264
 - Effects: hypotension and AV block, maybe reflex tachycardia
 - AC if < 1 hour and with sustained release preparations

- Consider iv calcium if hypotensive despite fluids
- Atropine for bradycardia, consider pacing
- In persisting low output states consider phosphodiesterase inhibitors, levosimendan or high dose insulin
- **Carbamazepine:**
 - Maximum serum concentrations may take up to 72 hours. Enterohepatic circulation and metabolised to an active metabolite. Levels do not correlate with severity
 - Effects: nystagmus, ataxia, tremor and seizures → coma, severe tachycardia or bradycardia
 - Gastric lavage if within one hour. Multiple dose AC
 - Haemofiltration
- **Carbon Monoxide:**
 - Mechanisms of toxicity remain unclear. O₂ delivery to the heart and brain is increased
 - No marker reliably detects poisoning
 - Coma or COHb levels > 40% indicated severe poisoning – but can be severe without this. Maybe ST change. Cherry pink skin uncommon. Cyanosis more common
 - Treatment:
 - High flow O₂ (100% if possible) till COHb < 5%. May take 24 hours
 - Hyperbaric O₂ controversial and not recommended on current data – 8 RCTs, generally of poor quality, no statistical reduction in sequelae at 1 month, and significant logistical problems. See Hyperbaric O₂, page 106
- **Chloroquine:** Common overdose in the 3rd world. Diazepam
- **Cocaine:**
 - Stimulant, local anaesthetic, potent vasoconstrictor
 - Blocks reuptake of monoamine neurotransmitters (dopamine, noradrenaline, serotonin)
 - Diagnosis: urinary screen for cocaine metabolites
 - Effects of IV use rarely last > 1 hour
 - Mortality due to respiratory depression, arrhythmias, and seizures, ischaemic or haemorrhagic stroke and SAH. Severe pulmonary disease from chronic inhalation
 - Treatment: AC for oral ingestion. Diazepam infusion to prevent seizures, α -blockers, labetalol or iv nitrates for hypertension. Use β -blockers along with caution due to unopposed α action. Check for other drugs
- **Cyanide:**
 - Severe toxicity is rapidly fatal. Otherwise coma, hypotension, metabolic acidosis
 - Lab features: lactic acidosis and high venous O₂ sats
 - Action: blocks mitochondrial cytochrome oxidase → cytotoxic hypoxia
 - Treatment:
 - Don't contaminate yourself – absorbed orally and through skin. No mouth to mouth
 - Gastric lavage
 - Inhaled amyl nitrate or sodium nitrite: converts haemoglobin to methaemoglobin, which has a higher affinity for cyanide than does cytochrome oxidase. As methaemoglobin does not carry oxygen, too high levels can lead to anoxia. Measure during treatment and target 20 – 30%
 - Chelation: Direct binding of cyanide to EDTA or the vitamin B12 precursor hydroxocobalamin. A huge dose (5 gms) of hydroxocobalamin is required but has minimal toxicity (in contrast to other treatments)
 - Sodium thiosulphate: reacts with cyanide to form the relatively non-toxic thiocyanate, which is excreted in the urine. This action is slow – of little benefit in the acute phase
- **Digoxin:**
 - See also:
 - Digoxin, page 148
 - (Apparent) Volume of Distribution, page 334
 - Cardiac arrhythmia, \uparrow K, \downarrow BP due to blockage of cardiac Na-K-ATPase
 - Cardiac features due to \uparrow automaticity + AV conduction BLOCK: APT with variable block, accelerated junctional rhythms, bidirectional ventricular tachycardia (specific for digoxin), SA node arrest, bradycardia, AV block, VT, VF
 - Interactions: verapamil, diltiazem & amiodarone block p-glycoprotein efflux pump. Erythromycin, omeprazole → \uparrow absorption
 - Toxicity exacerbated by: \downarrow K, \downarrow Mg, \downarrow pH, \uparrow Ca
 - Treatment: Multi-dose AC. Correct K and Mg. Pace bradycardia. Amiodarone for tachyarrhythmias. Avoid DC shock. Digoxin antibodies (Digibind – still needs renal excretion so of questionable value in

renal failure, binds free digoxin, serum level measures bound and free so → ↑levels), magnesium if torsades

- **Gamma-hydroxybutyrate (Fantasy):**
 - Dizziness, blurred vision, hot/cold flushes, sweating, confusion, vomiting, LOC, tremours, , bradycardia, respiratory depression. Usually settles in 2 - 4 hours
 - AC if > 20 mg/kg if < 1 hour. Benzodiazepines for convulsions
- **Iron:**
 - Toxicity levels:
 - < 20 ml/kg elemental iron asymptomatic
 - 20 – 60 GI Symptoms
 - > 60 systemic toxicity
 - > 120 potentially fatal
 - Symptoms: Nausea, diarrhoea, abdo pain, rectal bleeding and haematemesis, tachypnoea (due to acidosis), seizures, cardiovascular collapse (myocardial depression), jaundice (hepatic necrosis)
 - Pathophysiology: corrosive effect on GIT, fluid loss from GIT, disruption of cellular metabolism → gut ischaemia, acidosis, shock, hepatic necrosis, renal failure
 - Do CXR and AXR so see if pills still in the gut.
 - Bloods:
 - ↑serum Fe, hyperglycaemia, coagulopathy (interference with coagulation cascade, hepatic failure), BSL
 - Blood gas: metabolic acidosis due to uncoupling of oxidative phosphorylation
 - Treatment:
 - Desferoxamine, whole bowel irrigation, dialysis if bad (limited efficacy – exchange transfusion with plasmapheresis used), endoscopic removal of tablets, treat coagulopathy, hyperglycaemia
 - Charcoal is ineffective
- **Lithium:** Serum concentrations > 3.5 – 4.0 mmol need dialysis
- **Marijuana/Cannabis**
 - δ-9-tetrahydrocannabinol (THC)
 - Converted in the liver to a psycho-active compound
 - Slow clearance
 - High density of cannabinoid receptors (CB1 and CB2) in the cerebral cortex, basal ganglia and hippocampus
 - Presentation: conjunctival injection and tachycardia
 - Rapid tolerance and ↓pulmonary vital capacity amongst regular users
- **Methaemoglobinaemia:**
 - Altered haemoglobin where Fe²⁺ is oxidised to Fe³⁺, which is unable to bind oxygen. Usual level < 1.5%. Presence results in cyanosis despite a normal PaO₂
 - Testing: ABG to lab. Discrepancy between co-oximetry and pulse-oximetry (see Pulse Oximetry, page 28). A drop of blood on paper is brown and stays brown. Normal venous blood turns brighter red on exposure to O₂
 - Causes:
 - Congenital: cytochrome B5 reductase deficiency, haemoglobin M disease
 - Acquired: exposure to:
 - Benzene derivatives
 - Chloroquine
 - Dapsone
 - Prilocaine: Used in Biers Block. Amide local anaesthetic which specifically causes methaemoglobinaemia. Methylene Blue stored in ED as an antidote
 - Metoclopramide
 - Nitrites (including GTN and nitric oxide)
 - Sulphonamides
 - Management:
 - Confirm diagnosis: co-oximetry +/- specific assays
 - If symptomatic (eg MetHb levels > 20%) then methylene blue (1 – 2 mg/kg over 5 min, repeated as necessary) provides an artificial electron receptor to facilitate reduction of MetHb via the NADPH-dependent pathway. Response can't be followed by co-oximetry as methylene blue is detected as MetHb
 - Ascorbic acid if methylene blue contraindicated (G6PD deficiency)
 - Severe cases: exchange transfusion or hyperbaric O₂
- **Methamphetamine:**

- → ↑release of monoamine neurotransmitters into the synaptic junction
- SE: headache, ↓concentration, ↓appetite, abdo pain, vomiting or diarrhoea, disordered sleep, paranoid or aggressive behaviour, psychosis
- Life threatening: HTN, arrhythmias, CHF, SAH, ischaemic stroke, seizures
- Treatment largely supportive. HTN may respond to nitroprusside or α antagonists
- **Monoamine-oxidase inhibitors:** → accumulation of amine neurotransmitters → neuro-muscular symptoms (muscle spasm, rigidity) and sympathetic overactivity. Treat as for amphetamines and cocaine
- **Non-steroidal anti-inflammatory drugs:**
 - Usually just gastritis. With large ingestions of ibuprofen, seizures and renal failure. Little toxicity if none by 4 hours
 - Treatment: AC if < 1 hour. Benzodiazepines for seizures
- **Organophosphate:**
 - Symptoms: diarrhoea, urination, miosis, bronchospasm, bronchorrhoea, emesis, lacrimation, salivation, fasciculations, tremour, weakness, bradycardia, hypotension, confusion
 - Investigation: Can do cholinesterase mixing studies
 - Atropine: large doses may be required
 - Pralidoxime: to reactivate acetyl choline esterase – only effective before irreversible binding
- **Paracetamol:** NAC. See Paracetamol toxicity, page 179
- **Paraquat:**
 - Corrosive. Toxicity enhanced by oxygen (selectively accumulates in type 2 alveolar cells, reacts with O₂ to form superoxide free radicals)
 - Can test serum levels with plasma paraquat assay. Add sodium dithionite to urine – if it turns blue confirms paraquat. Helpful qualitative screen
 - AC if < 1 hour
 - Efficacy of specific treatment options not established (eg gastric decontamination with Fuller's earth – diatomaceous earth)
 - Monitoring and therapy for ARDS
- **SSRIs:**
 - Symptoms: Drowsiness, tachycardia, mild hypertension. Seizures, coma in 14%
 - AC if < 1 hour
 - Benzodiazepines for agitation or hyperthermic patients. Case reports of cyproheptadine being effective (a first generation antihistamine with antiserotonergic properties)
 - Serotonin syndrome: see Toxidromes, page 263
- **Tricyclic Antidepressants:**
 - Symptoms:
 - Anticholinergic effects: warm dry skin, tachycardia, blurred vision, dilated pupils, urinary retention
 - Severe features: respiratory depression, ↓LOC, arrhythmias (predicted by QRS > 100 ms), seizures (predicted by QRS > 160 ms), and hypotension. Cardiac toxicity mainly due to slowing phase 0 depolarisation
 - Treatment:
 - Multi-dose AC
 - Use NaHCO₃ to ↑arterial pH to > 7.45 → ↓free drug (weak base, then ↑pH will → ↑non-ionised form of drug → ↑distribution away from the heart). ↑Na overcomes Na channel blockade. Use mild hyperventilation and 8.4% sodium bicarbonate in 50 mmol aliquots
 - ?lignocaine for arrhythmias
- **Valproate:**
 - Symptoms: progressive onset lethargy, CNS depression, coma (usually requires > 200 mg/kg), hypotension, diarrhoea, tremour, hypothermia (not nystagmus, dysarthria nor ataxia – as are seen with phenytoin and carbamazepine)
 - Complications: cerebral oedema, encephalopathy (elevated ammonia), hepatotoxicity, electrolyte disorders (↑Na – sodium salt in drug, ↓Ca – Ba binds to anionic VPA metabolites, ↑osmolarity, ↑AG metabolic acidosis)
 - Investigations: valproate level (therapeutic range is 50 – 125), ↑AG, ↑NH₄, transaminitis
 - Treatment:
 - Gastric decontamination with multiple dose AC or whole bowel irrigation (often slow release preparations)
 - Carnitine (50 mg/kg/day PO divided tds) attenuates hepatotoxicity and hyperammonaemia (little used now)
 - Dialysable

Opioid Poisoning

- Types:
 - Derived from poppy: morphine, codeine
 - Semi-synthetic: diacetylmorphine (heroin), oxycodone
 - Synthetic: fentanyl, tramadol, methadone
- Together with endogenous opioids, act on μ , κ , δ receptors to produce analgesia, respiratory depression, sedation, constipation (due to \downarrow gut motility), euphoria, nausea, \downarrow cough reflex (useful as an antitussive)
- Abuse:
 - Genetic risk explains ~ 50% of dependence
 - Mortality 15-fold higher than general population
 - High risk groups:
 - Chronic pain
 - Doctors, nurses, pharmacists with easy access
 - Drug users (also risk of HBV/HCV/HIV)
- Withdrawal:
 - Nausea, diarrhoea, coughing, fever, HTN, diffuse body pain, insomnia, yawning, intense drug craving
 - With shorter half life forms (heroin, morphine) starts 8 – 16 hours after last dose and peaks within 36 – 72 hours (7 – 10 days for methadone). Protracted abstinence phase of mild moodiness and disturbed sleep may persist for > 6 months
 - Treat acutely with graduated reduction (eg methadone), ibuprofen for pain, clonidine (α_2 agonist) to \downarrow sympathetic overactivity
- Maintenance:
 - Methadone or buprenorphine (used in 1/3 of maintenance patients in Australia, safer and more expensive, doesn't prolong QT)
 - Methadone prolongs the QT, is OK in renal impairment
 - Reduces heroin injection, HIV infection, mortality, criminality, but *not* HCV (the longer you're on methadone the higher your HCV incidence, reaching 90 – 95%)
- Overdose:
 - In overdose miosis (pupil contraction) \rightarrow mydriasis (dilation) once brain stem hypoxia develops, bradycardia, hypothermia, coma
 - Treatment: titrate naloxone so as not to provoke a withdrawal state. Repeat 0.4 – 2mg dose every 2 – 3 mins up to 10 mg. Wears off after several hours and may need repeating up to 72 hours with a long acting form such as methadone
- Lemon juice is often used to dissolve heroin for injection \rightarrow risk of candida infection \rightarrow panophthalmitis (must check eyes)

Envenomation

- 24 hour advice on management from the Australian Venom Research Unit: 1 300 760 451 within Australia, from overseas +61 3 8344 7753, www.avru.org

Snake Bites

- Toxins are complex mixtures, usually phospholipases. Critical illness due to:
 - Progressive paralysis due to presynaptic (more difficult to reverse with antivenom, also cause lysis of skeletal and cardiac muscle \rightarrow rhabdomyolysis) and postsynaptic neuromuscular blockers \rightarrow respiratory failure
 - Coagulopathy due to:
 - Pro-coagulation effect by prothrombin activators (factor Xa-like enzymes) \rightarrow consumption of clotting factors (especially fibrinogen and Factors V & VIII) \rightarrow significant haemorrhage. Ie treat with FFP not cryoprecipitate – although early FFP (< 6 – 8 hours after bite) is still consumed
 - Direct anticoagulant effect. Less common
 - Renal failure occurring as a complication of rhabdomyolysis, DIC, haemorrhage, haemolysis or their complications
 - Rapid collapse within minutes is probably due to anaphylaxis
 - Very different from many overseas snakes (eg crotalids and viperids) where massive local reaction and necrosis due to proteolytic enzymes are a major feature
- Symptoms:
 - May vary in the same species due to geographical variation or variable absorption
 - Can wax and wane
 - Transient hypotension soon after envenomation (?due to DIC)

- < 1 hour: headache, nausea, vomiting, regional lymphadenitis
- 1 – 3 hours after bite:
 - Paralysis of cranial nerves (ptosis comes first – do careful exam)
 - Haemorrhage from mucosal surfaces (gums, sputum, urine)
 - ↑HR, ↓BP, ↓Tv
- > 3 hours: paralysis of limb and respiratory muscles, circulatory failure, rhabdomyolysis, renal failure
- Identifying the snake:
 - Venom detection kit:
 - Enzyme immunoassay → indicates type of antivenom
 - Covers main Australian snakes: Tiger, Brown, Black, Death Adder and Taipan
 - Very sensitive – result in 25 minutes
 - Identifying snake by physical characteristics using an identification guide: can be misleading
 - Appearance of the bite not reliable
 - Constellation of symptoms helpful to a limited degree:
 - Paralysis + procoagulopathy: Tiger, Taipan, Brown, Rough-scaled Red bellied
 - Paralysis + procoagulopathy + rhabdomyolysis: Tiger unlikely
 - Paralysis + anticoagulation (consumptive): Black, Copperhead, Death Adder
 - Paralysis + anticoagulation + rhabdomyolysis: Death Adder unlikely
 - Paralysis with neither coagulopathy nor rhabdomyolysis: Death Adder
- Investigations:
 - Bite swab for venom detection
 - Blood for: venom detection, coags, group and hold, CK, FDPs, FBC (platelets), U&E (renal)
 - Urine: venom detection, red blood cells, haemoglobin, myoglobin
- Treatment:
 - Resuscitation: ventilate and restore blood pressure (fluids, vasoactive drugs)
 - Application of pressure-immobilisation first-aid bandage. Crêpe bandage applied from fingers of toes up the limb as far as possible, encompassing the bite. Then *immobilise* with a splint. Probably only effective if applied under 30 minutes. Pressure less than arterial delays movement of venom via lymphatics or small subcutaneous capillary beds. Premature release may result in sudden systemic envenomation. Leave in situ until patient reaches full medical facilities. Keep patient still
 - Administration of antivenom:
 - One ampule in 500 ml saline over 20 mins. Only give one vial. It's about recovery of clotting factors, not continued consumption
 - Anaphylaxis is not rare. Used to premedicate with sc adrenaline (0.25 mg in an adult), antihistamine, steroid – no strong evidence
 - Monovalent (species specific) if species reliably known or identified by venom detection test. A polyvalent (a mixture of all of them) is also available but higher rate of anaphylaxis. Will need a number of vials in severe cases. Must be IV (or IO) – IM useless
 - If critically ill or if species can't be determined, give empirically according to location
 - Titrate antivenom. Can:
 - Give empiric dose – although there is variability, and less certainty about dosing in children
 - Monitor for ↑fibrinogen, ↓coagulopathy, ↓neurotoxicity, plateaux of CK rise, resolution of non-specific symptoms
 - If only mild coagulopathy may be acceptable just to monitor
 - Examine at least hourly to detect slow onset of paralysis, coagulopathy, rhabdomyolysis (correct ↑K, ↓Ca, may need dialysis), renal failure
 - Blood and coagulation factors given without antivenom will worsen coagulopathy. May need coagulation factors +/- platelets. RBC rarely needed
 - If OK watch for 12 hours. Don't discharge at night

Spider Bites

- Anti-venoms available
- Funnel-web spider:
 - Symptoms: nausea, profuse sweating, salivation, abdo pain → muscle fasciculation at the site of the wound → hypertension, tachycardia, vasoconstriction. Usually over several hours – quicker in kids
 - Pathophysiology: one component of the venom stimulates release of ACh at neuromuscular junctions, and the release of catecholamines
- Red-back spider:
 - Symptoms: bite becomes inflamed → severe pain moves up limb → sweating, headache, nausea, abdo pain, fever, hypertension, paraesthesia, rashes

- Australian Paralysis Tick (*Ixodes holocyclus*): injects a toxin that causes flaccid paralysis after some 3 – 5 days of feeding on humans. Resembles GBS.

- See also Pandemic Planning, page 6
- Consider non-drug responses:
 - Source control (eg remove lines)
 - Supportive care, including nutrition
 - Infection control:
 - Isolation precautions
 - Universal precautions
- Causes of failure for sepsis to resolve despite appropriate empirical antibiotics:
 - Wrong antibiotic
 - Delayed antibiotic administration
 - Inadequate source control
 - Inadequate antibiotic levels
 - Inadequate antibiotic penetration to site of infection
 - Antibiotic resistance
 - Super-infection
 - Non-bacterial infection
 - Non-bacterial source of illness
- Risk factors when you don't know the specifics:
 - Extremes of age: < 2 or > 65
 - Chronic infections: Chronic lung disease, sinusitis, otitis media
 - Asplenia (functional and anatomic)
 - Renal insufficiency
 - Immunosuppression
 - Hypo-Ig conditions
 - Transplant
 - Brain infections: CSF leaks/head trauma/Cochlear implants/shunts
 - Alcoholism
 - Diabetes
 - Cachexia/poor nutrition
 - Enteral feeding (↑ gut pathogens), TPN
 - Lines
 - Length of stay
 - Long term care facility
 - Previous antibiotic exposure
 - Prevalence of resistance in other unit patients
- Consequences of resistance when you don't know the specifics:
 - Potential transmission to others
 - ↑ duration of ABs
 - ↑ mortality and LOS
 - ↑ cost
 - Colonisation, with consequence of need for isolation and associated ↑cost

Antibiotic Pharmacology

- Describing an antibiotic:
 - Indications for all: Infection with susceptible organisms
 - Contraindications: Previous adverse reactions
 - Side effects: sensitivity reactions, super-infection (including pseudomembranous colitis), drug interactions

Pharmacokinetics of Antibiotics in Critical Illness

- Pharmacokinetics often only studied in healthy volunteers
- Affects drug absorption, distribution and clearance via changes in fluid compartments, organ function and plasma protein concentrations
- Absorption: unpredictable oral bioavailability due to diarrhoea, ileus, gut oedema and potentially impaired splanchnic blood flow
- Distribution:

- $V_d \uparrow$ by increased body water (dilution)
- \downarrow Protein binding:
 - May \rightarrow shortened $T_{1/2}$ and \uparrow free drug
 - \downarrow Albumin \rightarrow initial \downarrow in bound fraction – but this will then be cleared quicker. Consider continuous infusion
 - Changes in protein binding (eg due to acidosis) will affect highly protein bound ABs: eg flucloxacillin, ceftriaxone, teicoplanin, cephalosporins
- Elimination:
 - Metabolism: slowed by hepatic impairment or \downarrow hepatic blood flow
 - Excretion:
 - Hepatic clearance affected by biliary obstruction, renal clearance by renal impairment and variably restored by dialysis
 - Hyperdynamic circulation (eg \uparrow GFR 2nd to vasopressors)
- \Rightarrow potential for significant \downarrow in AB effectiveness, especially hydrophilic ABs (β -lactams, aminoglycosides) due to $\uparrow V_d$ and \uparrow clearance, and through impaired tissue blood flow

Pharmacodynamics of Antibiotics in Critical Illness

- Effects on organ systems may be therapeutic or toxic
- Complex interplay with pharmacokinetics
- \uparrow Risk of:
 - renal toxicity greater due to impaired renal blood flow eg aminoglycosides, amphotericin
 - cardiovascular toxicity, eg bradycardia with vancomycin bolus
 - cerebral toxicity eg high dose penicillins

Dose alteration in Renal Impairment

- Aminoglycosides: High initial dose. Monitor trough concentrations. Extend interval rather than \downarrow dose
- Fluoroquinolones: Reduce frequency, maintain dose. Monitor QTc
- Beta lactams: \downarrow either dose or frequency
- Carbapenems: \downarrow either dose or frequency
- Glycopeptides (vancomycin and teicoplanin): high initial dosing with monitoring and dose adjustment
- Variety of approaches to dialysis – impacts on kinetics are often unknown:
 - One dose adjustment unlikely to work for all modes of RRT
 - Might be able to extrapolate from drugs we can easily monitor (eg use adjustment for vancomycin to adjust penicillin)

Antibiotic Dosing Regimes

- Concentration dependent: C_{Max}. Peak concentration is what's important. Ideal regime maximises concentration, because the higher the concentration the more extensive is the killing eg, aminoglycosides, daptomycin, metronidazole
- Time Dependent: duration of time above MIC: Penicillins (2 studies show benefit of continuous infusion in sepsis in small studies), carbapenems, linezolid, clindamycin \rightarrow frequent dosing or infusion
- Concentration and time dependent: area under the curve greater than MIC: 24 hour AUC/MIC is a predictor of efficiency. Eg quinolones

Mechanisms of Antibiotic Action

- Cell wall synthesis:
 - Penicillins
 - Cephalosporins
 - Vancomycin
- DNA:
 - DNA Synthesis: Metronidazole
 - DNA Gyrase: Quinolones
 - RNA Polymerase: Rifampicin
- Translation (RNA \rightarrow Protein synthesis):
 - 50S inhibitors:
 - Erythromycin
 - Clindamycin
 - Linezolid
 - 30S inhibitors:
 - Tetracyclines

- Streptomycin
- Tigecycline
- Cytoplasmic membrane/Phospholipid membrane: polymyxins

Drug level monitoring

- Background:
 - MIC increasing over time \Rightarrow less susceptible bacteria \Rightarrow needing \uparrow doses but unclear how much
 - Impact of illness on pharmacokinetics is unclear
- Therapeutic Drug Monitoring:
 - Prevent toxicity
 - Increasingly about ensuring efficiency
 - Although recognition that dosing changes may be required, no studies yet show outcome benefit
 - Eg increasingly used for β -lactams to prevent failure and \uparrow resistance

Preventing Antibiotic Resistance

- Strategies to improve the effective use of antibiotics:
 - Antibiotic evaluation committees
 - Protocols and guidelines to promote consistent and appropriate antimicrobial utilisation
 - Hospital formulary restrictions on broad-spectrum agents
 - Mandatory consultations with infectious diseases specialists
 - Substitution to narrow-spectrum antibiotics
 - Antibiotic cycling
- Infection control measures:
 - Hand-washing compliance (alcohol based gel more effective than soap and water)
 - Barrier precautions: gloves and gowns
 - Isolation
 - Surveillance
 - Monitoring and disseminating the incidence of MDR bacteria
 - Limiting use and duration of invasive devices

Bacterial Infection

Bacterial Overview

- Aerobic G+ive cocci:
 - Catalase +ive \Rightarrow staph (clusters):
 - Coagulase
 - Negative: Epidermidis
 - Positive: Aureus
 - Catalase –ive \rightarrow streptococci (chains):
 - Lancefield A: Pyogenes β haemolytic
 - Lancefield B: agalactiae β haemolytic
 - Lancefield D: now known as enterococci hydrolyses
 - Pneumonia: highly sensitive to optochin, α haemolytic
 - Viridians: mitis and mutans, α haemolytic

G +		Aerobic	1 st , 2 nd line, [add on],	Anaerobic	1 st , 2 nd line, [add on]
Cocci		Staph aureus Staph epidermidis Strep Enterococcus faecalis Enterococcus faecium	F, V [CL] V A V	Peptostreptococcus (gas forming abscess)	P
Rods/Bacilli	Spore forming	Anthrax Cereus	P, CP	Clostridium botulinum Clostridium tetani Clostridium perfringens Clostridium difficile	PG PG, MT PG + CL MT, V (po)
	Non-spore forming	Corynebacterium Lactobacillus Listeria Nocardia Diphtheria	A, V P A, M Co	Actinomyces israeli Propionibacterium	
G -					
Cocci		Neisseria meningitis Neisseria gonorrhoea Moraxella	P, C3 T, C3 AZ	Bacteroides Fusobacterium	T, MT PG
Rods/Bacilli	Enterobacteriaceae	E Coli Enterobacter* Klebsiella Morganella* Proteus mirabilis* Salmonella Serratia* Shigella Burkholderia	C2, G M T, C3 T, M C3, T CP, C3 CP, M CP, Co		
	Misc. Rods (curved shape & motile)	Campylobacter Helicobacter Vibrio cholerae Vibrio vulnificus	CP Clarithromycin		
	Pseudomonas & related	Acinetobacter Burkholderia Pseudomonas aeruginosa Pseudomonas cepacia Stenotrophomonas	M + G, Amikacin or polymyxins for MDR M, C3 + Co T + G, Ceftaz + G CP, Co Co		
Coccobacilli Pleomorphic		Brucella Bartonella Haemophilus Influenzae Legionella Pasteurella	D + G D T, C2 or C3 E, CP PG, D		

See following antibiotic key. * = ESCAPPM

- Intracellular organisms
 - Mycoplasma: Erythromycin, tetracycline
 - Chlamydia: doxycycline + azithromycin
- Rickettsia:
 - Group of small, obligately intracellular G⁻ bacteria, including:
 - Typhus, scrub typhus
 - Spotted fevers:
 - Rocky Mountain
 - Q fever: see Odd Aussi Bugs, page 277
 - doxycycline, chloramphenicol
- Spirochetes:
 - Treponema: penicillin + erythromycin
 - Leptospira: see Odd Aussi Bugs, page 277

Antibiotic key:

		Side Effects and comments
A	Amoxicillin	
P	Penicillin	Great for sensitive streps (pneumonia, pyogenes)
PG	Penicillin G	
F	Flucloxacillin	Beta-lactamase resistant thus improved staphylococcal cover. Cholestatic jaundice
C1	1 st generation cephalosporin	
C2	2 nd generation cephalosporin: cefuroxime	
C3	3 rd generation cephalosporin – cefotaxime, ceftazidime, ceftriaxone	Ceftriaxone: renal excretion, highly protein bound, T _{1/2} 6 – 9 hrs, inhibits cell wall synthesis, doesn't cover pseudomonas, MRSA or G ⁺ D Strep
CP	Ciprofloxacin	Growing cartilage damage (ie not in pregnancy or children), Achilles tendonitis, nephritis, QT prolongation. Rapid plasmid spread of resistance. Haematological/liver enzyme effects
Co	Co-trimoxazole	For G ⁺ cocci and G ⁻ bacilli including adjuvant or sole use for resistant organisms (eg pseudomonas, xanthomonas, pneumocystis). Contraindications: Blood dyscrasias, marked kidney/liver impairment, megaloblastic bone marrow. SE: photosensitivity, GI upset, haematological
T	Tazocin (Piperacillin-tazobactam)	“Augmentin with pseudomonas cover”
CL	Clindamycin	Unique AB. “switches off” strep and staph toxin production. No change in renal or hepatic impairment. Pseudomembranous colitis, leucopenia, thrombocytopenia, neuromuscular blockade
E	Erythromycin	
AZ	Azithromycin	
V	Vancomycin	Nephrotoxicity, ototoxicity, neutropenia, red man syndrome from histamine release. Generally used badly. Needs loading dose 25 – 30 mg/kg. If just started at 1 gm bd will take days to reach steady state
G	Gentamicin (7 mg/kg LBW)	Great for pseudomonas, burkholderia. Renal excretion, T _{1/2} 3 hours. Inhibits protein synthesis. Not good in anaerobic conditions, poor CNS penetration. Nephrotoxic, ototoxic, prolongation of NMBA
M	Meropenem	Covers ESCAPPM and anaerobes. 0.5 – 2 gm TDS. ↓ in renal failure. 2% protein bound. Mainly renal excretion. Inhibits cell wall synthesis. Small seizure risk. Hepatitis, CNS stimulation, salt load. Inactive against enterococcus, MRSA and many pseudomonas. SE: overgrowth, haematological GI and liver effects
D	Doxycycline	
MT	Metronidazole	Leucopenia, altered taste, CNS stimulation

Differentials for common diagnoses

- See also:
 - Management of Sep, page 49
 - Pneumonia, page 117
 - Infective Endocarditis, page 140
 - Intraabdominal Sepsis, page 184
 - Meningitis and Encephalomyelitis, page 218
 - Tetanus, page 221
 - Infection following Bone Marrow Transplant, page 310
 - Toxic Shock Syndrome, page 287
 - Necrotising Fasciitis, page 288
 - Pseudomembranous Colitis, page 289
- Pelvis Inflammatory Disease:
 - Usually polymicrobial including endogenous flora and anaerobes
 - Sexually acquired: chlamydia trachomatis, Neisseria gonorrhoea
 - Non-sexually acquired: mycoplasma hominis, actinomyces if IUCD
- Animal handlers:
 - Coxiella burnetii: Q fever: see Odd Aussi Bugs, page 277
 - Brucella (stock animals and milk → pneumonia)
 - Chlamydia psittaci: especially poultry and birds
 - Francisella tularensis (stock animal carcasses → pneumonia)
 - Pseudomonas mallei (horses → pneumonia)
 - Leptospirosis: see Odd Aussi Bugs, page 277
 - Toxoplasma Gondii (protozoa): cats
 - Hydatid disease: dog faeces
- Encephalitis after fox bite: lyssa virus, rabies virus, rhabdo virus
- Gram negative sepsis in patient returned from PNG in the wet season:
 - Acinetobacter
 - Melioidosis: see Odd Aussi Bugs, page 277
- Gram negative sepsis in patient who has been on meropenem for a week: multi-resistant pseudomonas or Acinetobacter
- Fournier's gangrene:
 - Cellulitis of the scrotum, perineum and anterior abdominal wall
 - Mixed anaerobic organisms spreading along deep external facial planes
 - Treatment: meropenem
- Purpura Fulminans:
 - Cutaneous manifestation of DIC
 - PC: Large echymotic areas and haemorrhagic bullae
 - Differential:
 - Meningococcaemia
 - Post-splenectomy pneumonia
 - DIC
 - Rickettsial infections
 - High dose inotropes
 - Endocarditis
- Bacterial infection in someone already on meropenem and vancomycin:
 - Resistant environmental G-ives: pseudomonas, stenotrophomonas
 - Vancomycin resistant enterococcus (VRE)
 - Atypicals: chlamydia, legionella, mycoplasma

Odd Aussi Bugs

Leptospirosis

- Spirochete
- Common in Northern Queensland (cases from the Yarra River in Melbourne...)
- Transmission: small mammals urine (eg rats). Portal of entry: oral or small cut
- Globally over 1 million cases per annum, especially in infected water in natural disasters
- Can cause inflammatory explosion → liver and renal failure, pulmonary haemorrhage, ARDS, encephalopathic

- Diagnosis:
 - Initially clinical: multi-organ failure after going bush
 - Lab: spirochetes in blood, urine, CSF. Positive IgM. PCR in some centres
- Treatment:
 - Get worse initially with penicillin treatment (inflammatory reaction to spirochete death)
 - Some argue to treat as a vasculitis with methyl prednisolone 1 mg/kg BD. Benefit likely only if given in first 12 hours. ??cyclosporine for lung involvement
 - Early RRT, ?fluid conservative to prevents ARDS

Melioidosis

- Burkholderia pseudomallei
- Common in Northern Queensland. Aka Whitmore's Disease
- Transmission: inhalation, ingestion, cut in skin, especially storm water. Typically wet season, but can be dry season
- Incubation: Can be dormant for years
- Often in immunocompromised people: DM, ETOH, Steroids
- Broad spectrum of illness and focus, include acute pulmonary infection, genitourinary sepsis (including prostate abscess), soft tissue infections, ascending paralysis, septic arthritis
- Diagnosis: readily diagnosed – initially as GNB on culture. Grown on specialised agar (ie tell the lab if suspicious)
- Treatment: high dose meropenem, then orals for 6 months

Q fever

- Coxiella burnetii. Obligate intracellular pathogen
- Uncommon, but found in cattle, sheep, goats and other domestic animals
- Transmission: inhaled spores, rarely tick borne
- Incubation 1 – 3 weeks
- Flu like illness progressing to atypical pneumonia, maybe hepatitis, late endocarditis, myalgia
- Culture negative endocarditis – needs prolonged treatment
- Diagnosis by serology or PCR, culture difficult. Doxycycline, ciprofloxacin effective

Top shelf antibiotics

- G +ives:
 - Teicoplanin:
 - Glycopeptide like vancomycin
 - Good for MRSA, penicillin resistant Strep pneumoniae, clostridium difficile. Van A resistance common in Australia so many VRE are teicoplanin resistant
 - Relatively little toxicity (less than vancomycin): nephrotoxic, ototoxic, "red Man syndrome" for histamine release, thrombocytopenia
 - Linezolid:
 - Cover includes MRSA, MRSE, VRE and intracellular organisms. Good for soft tissue infection (pneumonia and cellulitis). Penetrates well in bone, fat and muscle.
 - Unique mechanism of action so no cross-resistance. G-ive resistance due to efflux pumps. Poor anaerobic cover. 100% bioavailable so oral = IV. No dose reduction in renal or hepatic failure
 - Marrow suppression common → stop treatment. Mitochondrial toxin → peripheral neuropathy, lactic acidosis, ocular toxicity. Serotonin syndrome with serotonergic agents (MOA inhibitor)
 - Tedizolid: new AB not inferior to Linezolid for skin infections (JAMA 2013)
 - Daptomycin:
 - Activity against most G +ives. Equivalent to vancomycin. Probably not useful for VRSA.
 - Inhibited by surfactant ⇒ no use in pneumonia. Myopathy. Generally not your first choice...
 - Quinupristin-dalfopristin: (Streptogramins) active against G+ bacilli (Enterococcus faecium), Neisseria and Moraxella, poor CNS penetration. SE: phlebitis, myalgia, arthralgia
- G –ives:
 - Colistin: Salvage therapy only. Not absorbed orally. Renal and neurotoxicity
 - Amikacin: for multi-resistant pseudomonas, acinetobacter, enterobacter and proteus. Ototoxicity, nephrotoxicity
- Both G+ive and G-ive
 - Moxifloxacin: very broad spectrum: MRSA, streps, many G –ives, anaerobes, leprosy, TB
 - Tigecycline:
 - 30S ribosome inhibitor

- Covers G+ive, G-ive, anaerobic, MRSA and acinetobacter. No activity against pseudomonas or proteus spp
- SE nausea, vomiting, diarrhoea, tooth discolouration in kids, teratogenic, FDA reports ↑ risk of death in HAP or VAP compared to alternative treatments
- Generally not your first choice... FDA issued a black box warning in 2013 of ↑mortality cf other ABs.

G +ive Bacterial troublemakers

- Streptococcus:
 - Resistance: ceftriaxone or high dose penicillin, 2nd line vancomycin + rifampicin (SE: rapid resistance, multiple drug interactions, orange discolouration of secretions, hepatitis, nephritis, thrombocytopenia)
- Pneumococcus:
 - Specific tests: PCR and urinary antigens
 - Risk factors:
 - Age < 2 or age > 65
 - Chronic lung disease
 - Functional or anatomical asplenism
 - Immunosuppression
 - CSF leak
 - Cochlear implants
 - Dexamethasone for Meningitis (see page 220)
 - Vaccination at 5 yearly intervals
- MRSA:
 - Resistant to methicillin ⇒ resistant to all β lactams including cephalosporins
 - Confers resistance to tetracyclines, macrolides, sulfonamides, aminoglycosides
 - NORSA: non-multiply resistant SA. Frequently susceptible to clindamycin, co-trimoxazole, macrolides, gentamicin
 - Mec-A gene on a transposon codes for a penicillin-binding protein mutation
 - cMRSA: mec types IV and V
 - More virulent infections associated with toxic shock and necrotising pneumonia
 - Vancomycin, 2nd line clindamycin/cotrimoxazole
 - Can be sensitive to bactrim, erythromycin
 - Pantan-Valentine Leukocidin is a virulence gene associated with some c-MRSA → necrotising skin infections
 - hMRSA: Mec types I, II, III
 - Vancomycin, 2nd line Teicoplanin (both glycopeptides)
 - Treatment can sometimes include rifampicin, fusidic acid, ciprofloxacin, linezolid
 - No action from meropenem
 - Vancomycin Intermediate Staph Aureus (VISA):
 - MIC required is much higher – 4 – 8 mcg/ml
 - Resistance factors include an unusually thick cell wall, protecting intracellular targets
 - Usually sensitive to linezolid, quinupristin-dalfopristin, daptomycin and tigecycline
 - VRSA:
 - MIC > 16 mcg/ml
 - Teicoplanin (SE: red man syndrome, nephrotoxic, ototoxic) , linezolid
 - Also daptomycin, dalfapristin, co-trimoxazole, chloramphenicol
- VRE:
 - Risks:
 - Previous treatment with antimicrobials (esp vancomycin, broad spectrum, etc.)
 - ↑Length of stay
 - Renal insufficiency
 - Enteral tube feeding
 - Prevalence of VRE colonised patients in the unit
 - Resident of long term care facilities
 - Decreased staff:patient ratios
 - Types:
 - Altered penicillin binding protein, β lactamases, efflux pumps....
 - Usually faecalis, 10 – 20% faecium
 - Van A, B, C (A worst, C indolent)

- Van A: Tigecycline (SE: nausea, vomiting, diarrhoea, tooth discolouration in children). Resistant to vancomycin and teicoplanin
- Van B: Teicoplanin
- Treatment:
 - Normally, enterococci resistant to all cephalosporins and flucloxacillin. Inhibited (not killed) by penicillins and vancomycin → use gentamicin. Carbapenems ineffective (????).
 - 2nd line linezolid, daptomycin, chloramphenicol
 - If colonised, avoid anti-anaerobes, makes spread more likely. Probiotics may have a role
 - Infection control
 - Antibiotic stewardship
- Anaerobes:
 - Above the diaphragm: penicillin
 - Below the diaphragm: metronidazole
 - Or Augmentin (also likely to cover haemophilus)
- Nocardia: G+ive with beaded, branching filaments on modified ZN stain. Can cause CNS infection +/- abscesses especially after organ transplant with immunosuppression

G -ive Bacterial troublemakers

- Inducible β lactamase:
 - Sensitive to cephalosporin in vitro, but rapidly develops in vivo-resistance
 - ESCAPPM G-ive rods: Enterobacter spp, Serratia spp, Citrobacter freundii, Acinetobacter spp, Providencia spp, Proteus vulgaris, (some pseudomonas), Morganella morganii
 - Amp-C gene mediated β -lactam resistance
 - ⇒ Tazocin, carbapenems, tigecycline, C4, quinolone
- ESBL:
 - Arise by mutation in existing β -lactamase gene or plasmid transfer
 - Inducible β -lactam and quinolone resistance
 - E Coli, Klebsiella, Enterobacteriaceae, Pseudomonas, citrobacter, proteus
 - Don't eradicate if colonisation – is likely to come back if ever treated with antibiotics
 - Treat with Meropenem (best carbapenem in head to head trials), aminoglycosides, amikacin, colistin, tigecycline, 4th generation cephalosporins
- Environmental G-ive multi-resistant organisms:
 - Ubiquitous colonizers – if infected then a marker you're sick
 - Clinical scenario for drug resistant strains: infection after a week on meropenem for abdominal sepsis
 - Pseudomonas: Lots of intrinsic resistance.
 - Pseudomonas cover:
 - Tazocin
 - Ceftazidime (3rd gen)
 - Cefepime (4th gen)
 - Imipenem/Meropenem
 - Dual therapy – fluoroquinolone, carbapenem, aminoglycoside, tazocin. If carbapenem resistant then amikacin or colistin. May use antibiotic cycling
 - Acinetobacter Baumannii: In 25% of population as skin flora. Causes wide range of surgical infections + hospital acquired pneumonia, meningitis, UTI. Carbapenem + aminoglycosides (two agents often used), if carbapenem resistant then *amikacin*
 - Stenotrophomonas - treat with co-trimoxazole
- Others:
 - Burkholderia pseudomallei: soil commensal in wet season in northern Australia. Pneumonia and abscesses. Co-trimoxazole plus meropenem or ceftazidime
 - Salmonella typhi: Enteric (Typhoid) fever. Fevers, shock with bradycardia, diarrhoea → constipation, rose spots on trunk, hepatosplenomegaly. Ciprofloxacin, ceftriaxone or azithromycin
 - Legionella: difficult to culture. Urinary antigen test detects L. pneumophila serotypes 1 and 2 only

Mycobacterium

- TB:
 - Including M tuberculosis, M bovis
 - Isoniazid, rifampicin, pyrazinamide +/- ethambutol
- Non-Tb:
 - Kanass, avium
 - Options a mix of: rifampicin, ciprofloxacin, clarithromycin

Protozoa Infection

- Plasmodium/Malaria:
 - Diagnosis:
 - Thick and thin films, 12 hourly for 48 hours (not when fever) give diagnosis and parasite load
 - Antigen testing: for falciparum has same sensitivity and specificity as microscopy
 - Vivax and malariae: dormant hypnozoites in the liver. Chloroquine then primaquine for eradication
 - Falciparum:
 - IV Treatment:
 - Cinchona alkaloids: eg IV quinine or quinidine
 - Artemisinin derivatives: eg IV artesunate, artemether
 - Then to oral artemether + lumefantrine (or add Doxycycline/clindamycin if not-pregnant/pregnant)
 - Used to use exchange blood transfusion
 - Complications:
 - Cerebral involvement +/- seizures
 - Respiratory failure with ARDS
 - Renal failure with haemoglobinuria (Blackwater fever 2nd to haemolysis)
 - Liver failure
 - Haematological: DIC, anaemia 2nd to haemolysis (altered RBCs sequestered by organs),
↓platelets
 - Metabolic: hypoglycaemia, severe acidosis, hyponatraemia
 - Splenic rupture
- Toxoplasma Gondii: Obligatory intracellular protozoa from cats. Causes tissue cysts, typically in retina and brain. Severe in immunocompromise. Treat with pyrimethamine + either sulfadiazine or clindamycin. Add folate to ↓incidence of pyrimethamine-associated myelotoxicity
- Trichomonas vaginalis: vulvovaginitis with a fishy smelling discharge. Treat with metronidazole

Fungal Infection

- ↑Incidence of invasive fungal infections in ICU. Mainly 2nd to immunosuppression
- Antifungal prophylaxis works – but the downsides are resistance, toxicity, cost and selecting for nastier fungi. Meta-analysis of prophylactic fluconazole in immunocompetent high risk surgical patients (Ho et al, Critical Care 2005) showed ↓risks of candidaemia but no change in in-hospital mortality, resistance or side effects. More studies needed to define the role of prophylaxis
- Fungal risk factors:
 - Prolonged antibiotics
 - Immunosuppression – impaired cell mediated
 - Invasive lines/devices/shunts
 - TPN
 - Cancer, especially haematological
 - Pancreatitis
 - Bowel perforation/GI tract surgery

Types of Fungal Infection

- Thousands of fungi – few are capable of causing disease in humans
- Superficial:
 - Candidiasis: oral treatment
 - Ring worm, athlete's foot
 - Risk is as a portal of entry in at-risk patients
- Invasive:
 - Generally, significant fungal infection only after prolonged illness, eg after 3 – 4 weeks of neutropenia following a BMT or lingering abdominal surgical catastrophe
 - Diagnosing invasive disease difficult given colonisation of critically unwell patients common
 - Empiric = Amphotericin B
 - Candida:
 - Ubiquitous environmental saprophyte which a normal immune system is easily able to handle
 - Fluconazole unless glabrata or krusei in which case amphotericin B (voriconazole or caspofungin alternatives)
 - Aspergillus:

- PCR not validated – potential role in BAL but effective use would require standardised Bal sample acquisition and processing – which is problematic
- ABPA
- Invasive: CT may show halo and crescent air signs if neutropenic only. Voriconazole (overtaken itraconazole), 2nd line Caspofungin
- Aspergilloma: surgical resection
- Galactomannan test (an aspergillus antigen) may aid diagnosis. Controversial. Generally used in haematological malignancy as the incidence is high enough to make the pre-test probability high enough to reduce the false positive rate
- Mucor mycosis: surgical source control + liposomal amphotericin. Uncommon in Australasia
- Cryptococcus: encapsulated organism, cause of pneumonia and meningitis, India ink stain and antigen tests, induction amphotericin, maintenance fluconazole
- Pneumocystis jiroveci: cotrimoxazole, 2nd line pentamidine, caspofungin, dapsone. Treat with steroids when initiating treatment in HIV and significant hypoxia
- Management:
 - Slow to grow in lab → delayed diagnosis
 - Pros and cons of both empirical vs diagnose then treat approaches
- If invasive fungal infection consider (→ prolonged treatment):
 - Echo for vegetations
 - CT or abdo US for liver abscess
 - Ophthalmic examination: retinal abscess

Antifungal Drugs

- Issues
 - Some evidence of combination therapy (eg in ascites)
 - Pharmacokinetics in ICU unclear
 - End point of treatment unclear (fever very variable)
- *Triazoles*:
 - Good for yeasts (eg Candida) not moulds (eg aspergillus)
 - Fluconazole:
 - Good bioavailability, renally excreted (dose adjustment with renal impairment)
 - Fluconazole only agent able to achieve good concentration in the urine for UTI infection
 - Mechanism: inhibits fungal enzyme involved in production of cytoplasmic membrane sterol ergosterol. Mainly fungistatic
 - Effective in focal and disseminated sensitive candida infections (not non-albicans infections such as krusei or glabrata) and in cryptococcal infection (as an alternative to amphotericin). Much less activity against other fungal infections (eg aspergillus)
 - May cause hepatotoxicity (monitor LFTs), anaemia, thrombocytopenia, leucopenia, adrenal suppression, SJS, multiple drug interactions (especially CYP2C ⇒ warfarin, cyclosporin, oral hypoglycaemics, phenytoin, midazolam)
 - Some evidence of benefit from empiric therapy in septic shock (especially intra-abdominal focus). Concerns about emergence of non-albicans infection
 - Used prophylactically in HIV with cryptococcal meningitis or recurrent oropharyngeal candidiasis
 - Voriconazole: SE Liver excretion, visual changes. Major variation in inter-patient metabolism. 200 mg bd dose in haematology patient may be too low
- *Polyenes*:
 - Nystatin
 - Amphotericin:
 - Active against cryptococcus
 - Toxicity: liposomal < lipid complex < colloidal suspension < parent drug
 - SE: fevers, chills, myalgia, dysrhythmias, seizures, renal toxicity, peripheral neuropathy, pancytopenia
- *Echinocandins*: Caspofungin (target fungal cell wall). Interactions with inducers, ↓dose in moderate hepatic disease). Otherwise relatively safe. Inferior for CNS penetration

Viral Infection

- HSV: acyclovir, valaciclovir
- Zoster:
 - Risks:
 - Smoker

- Contact with an index case,
- > 100 spots
- Duration of fever
- Chronic lung disease
- 3rd trimester of pregnancy
- Immunosuppression
- Treatment: acyclovir, famciclovir, valaciclovir
- CMV:
 - Diagnosis:
 - Viral cultures: slow and not sensitive ⇒ obsolete
 - Antigenaemia: detection of CMV protein PP65 using monoclonal antibodies
 - PCR: fast and high sensitivity but not standardised
 - Risk factors for infection in immunocompetent individuals:
 - Mechanical ventilation
 - Bacterial pneumonia and sepsis
 - Corticosteroid use: unclear
 - Red cell transfusion: immunomodulatory effect, rather than potential transmission of CMV
 - Burns patients: cell mediated immunity and T-helper 1 cells ↑infection
 - In immunocompromised:
 - → retinitis, interstitial pneumonia, hepatitis, colitis, oesophagitis and encephalitis
 - Prolonged ICU stay/ventilation
 - ↑bacterial/fungal infection
 - Mortality possibly increased
 - Drugs:
 - Ganciclovir/valgancyclovir
 - Foscarnet (Trade name Foscavir), SE: renal impairment, paraesthesia
 - Cidofovir
- HIV: HART
- Hep B & C
- Influenzae A:
 - Oseltamivir: Neuraminidase inhibitor. SE nausea/vomiting, reduces symptoms if taken early.
 - Meta-analysis (Jeffersen, BMJ 2014):
 - Treatment trials: ↓time to alleviation of symptoms (adults by 16 hours)
 - No difference in admission
 - ↑risk of nausea/vomiting
 - Prophylaxis:
 - ↓symptomatic influenza (in 1 study)
 - No effect on transmission
 - More headaches nausea, renal and psych events
 - Amantadine: target M2 ion channel
- Influenzae B: Zanamivir
- SARS: supportive
- H1N1: Oseltamivir

Nosocomial Infection

- Risks:
 - Patient:
 - Severity of illness
 - Underlying disease
 - Nutritional state
 - Immunosuppression
 - Open wounds
 - Invasive devices
 - Multiple procedures
 - Prolonged stay
 - Ventilation
 - Multiple or prolonged antibiotics
 - Blood transfusion
 - Environment:

- Changes in procedures or protocols
- Multiple changes in staff; new staff
- Poor aseptic practice, poor hand washing
- Patient-to-patient: busy, crowded unit, staff shortages
- The organism:
 - Resistance
 - Resilience in terms of survival
 - Formation of slime or ability to adhere
 - Pathogenicity
 - Prevalence
- Common nosocomial organisms:
 - MRSA
 - Coagulase negative staph
 - Enterococcus spp (faecalis, faecium)
 - Pseudomonas aeruginosa
 - Acinetobacter baumannii
 - Stenotrophomonas maltophilia
 - Enterobacter spp
 - Klebsiella spp
 - Escherichia coli
 - Serratia marcescens
 - Proteus spp
 - Candida spp (albicans, glabrata, krusei)

Infection Control

- Respiratory spread:
 - Nurse in a single room, negative pressure with 12 air changes per hour
 - Bacterial filter in ventilator circuit
 - Staff wear N95 or N100 masks
 - Infection warning signs
 - Bronchoscopy:
 - Minimise
 - ↓aerosols, eg from coughing, by paralysing
 - Consider use of powered air purifying respirator if available and staff trained
- Management of resistant organisms:
 - Limit antibiotic exposure: duration and spectrum
 - Antibiotic cycling
 - General infection prevention: lines, catheters
 - Prevention of transmission:
 - Hand hygiene: alcohol based
 - Contact precautions: gowns, gloves
 - Cohorting patients
 - Decolonisation – no effective method
 - Screening
 - Cleaning of patient areas
 - Unit education and audit activities
 - Antibiotic surveillance committee
- Infection control teams:
 - Surveillance and investigation of infection outbreaks
 - Education of staff
 - Review of antibiotic utilisation
 - Review of antibiotic resistance patterns
 - Review of infection control procedures and policies
- Reviewing infection control measures:
 - Monitor infection rates (eg MRSA)
 - Collect data (type of infection, are increases real, change in denominator, patient mix etc.)
 - Examine current policy – when and why was it written. Is it still relevant
 - Get expert help
 - Form a review team

- Review cases, past policy, experience in peer hospitals, literature review, antibiotic usage
- Synthesise this into key findings and recommendations (hand washing, vector control, cleaning, antibiotic usage etc.)
- Consult with staff
- Initiatives to improve hand washing:
 - Education: staff, visitors, needs to be on going
 - Signage: entrance and exit to unit, posters, voice prompts at bedside
 - Good hand washing products available at each bedside
 - Sinks: adequate number and position, automated taps
 - Audit: data collection before and after implementation, microbiology surveillance
 - Feedback to staff
- Recent trials:
 - Chlorhexidine Wash Clothes vs non-antibacterial wash clothes reduced MDR acquisition (5.1 vs 6.6 per 1000 patient days) and ↓hospital acquired blood stream infections in a MRCT, non-blinded cross over trial of 7727 patients, NEJM 2013
 - Large cluster MRCT found universal decolonisation (DB Mupirocin + OD Chlorhexidine wash clothes) of ICU patients was better than MRSA screening and isolation or targeted decolonisation (screened and isolated if positive) for ICU-attributable blood stream infection (Huang, NEJM May 2013). NNT for CLABSI = 54 (6.1 → 3.6 per 1000 days)
 - Cluster MRCT of gloves and gowns for all patients vs standard infection control (Harris, JAMA 2013) – non-statistically significant benefit
 - RCT of 614 patients showed copper alloy surfaces in cubicles → ↓MRSA and VRE infections (Salgado 2013)

Central Line Infections

- See also Central Venous Catheterisation, page 32
- Aka CLAB or CLABSI
- Definitions:
 - CLAB (A = *Associated* – lower threshold than the R = *Related* definition below):
 - Patient has a recognised pathogen cultured from one or more blood cultures and the organism is not related to an infection at another site, *or*
 - Patient has:
 - At least one of the following: fever > 38°C, chills or hypotension, and
 - Signs/symptoms/positive lab results are not related to an infection at another site, and
 - Common skin contaminants are cultured from two or more blood cultures on separate occasions. Eg diphtheroids [*Corynebacterium* spp], *Bacillus* [not *B anthracis*] spp, *Propionibacterium* spp, coag-negative staph, viridians strep, aerococcus spp
 - CRBSI (Cather *Related* Blood Stream Infection): from the Center for Disease Control and Prevention (the complicated version - which is more of a research definition given it's too complicated for surveillance in a clinical setting):
 - **Clinical definition:** Bacteraemia/fungaemia in a patient with an intravascular catheter with at least one positive blood culture obtained from a peripheral vein, clinical manifestations of infections (ie, fever, chills, and/or hypotension), and no apparent source for the BSI except the catheter. One of the following should be present:
 - a positive semi quantitative (>15 CFU/catheter segment) or quantitative (>103 CFU/catheter segment catheter)
 - culture whereby the same organism (species and antibiogram) is isolated from the catheter segment and peripheral blood
 - simultaneous quantitative blood cultures with a >5:1 ratio CVC versus peripheral
 - differential period of CVC culture versus peripheral blood culture positivity of >2 hours.
 - **Surveillance Definition of CRBSI:** Should meet at least one of the following criteria:
 - **Criterion 1:** Patient has a recognized pathogen cultured from one or more blood cultures, and the pathogen cultured from the blood is not related to an infection at another site.
 - **Criterion 2:** Patient has at least one of the following signs or symptoms: fever (>100.4° F [>38° C]), chills, or hypotension, and at least one of the following:
 1. common skin contaminant (eg, diphtheroids, *Bacillus* spp., *Propionibacterium* spp., coagulase-negative staphylococci, or micrococci) cultured from two or more blood cultures drawn on separate occasions
 2. common skin contaminant (eg, diphtheroids, *Bacillus* spp., *Propionibacterium* spp., coagulase-negative staphylococci, or micrococci) cultured from at least one blood culture from a patient with an intravenous line, and the physician institutes appropriate antimicrobial

therapy

3. positive antigen test on blood (eg, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Neisseria meningitidis*, or group B streptococcus)

and signs and symptoms with positive laboratory results are not related to an infection at another site.

- **Criterion 3:** Patient aged <1 year has at least one of the following signs or symptoms: fever (>100.4° F [>38° C]), hypothermia (<98.6° F [<37° C]), apnoea, or bradycardia, and at least one of the following:
 1. common skin contaminant (eg, diphtheroids, *Bacillus* spp., *Propionibacterium* spp., coagulase-negative staphylococci, or micrococci) cultured from two or more blood cultures drawn on separate occasions
 2. common skin contaminant (eg, diphtheroids, *Bacillus* spp., *Propionibacterium* spp., coagulase-negative staphylococci, or micrococci) cultured from at least one blood culture from a patient with an intravenous line, and the physician institutes appropriate antimicrobial therapy
 3. positive antigen test on blood (eg, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Neisseria meningitidis*, or group B streptococcus)**and** signs and symptoms with positive laboratory results are not related to an infection at another site.
- CLAB bundles: Pronovost et al, NEJM 2006. Prospective, observational study of 375,757 patient days in 103 ICUs. Reduced CLABs from 7.7 per 1000 catheter days to 1.4 at 16 - 18 months. More recent studies focus on ways to introduce bundles effectively. Bundles in two parts:
 - Insertion bundles: hat, gloves, gown, mask, scrubs, fully draped, chlorhexidine, dressing while drapes on
 - Maintenance bundles: Daily review for local or systemic infection, on-going need, hand hygiene and catheter hub sterilisation prior to every access
- Antimicrobial impregnated lines offer additional benefit (eg Darouiche et al, NEJM 1999):
 - Cause less bacteraemia than standard polyurethane catheters
 - Options include chlorhexidine and silver sulphadiazine (rare hypersensitivity) or rifampicin and minocycline (risk of resistance)
 - Chlorhexidine and silver sulfadiazine catheters superior to standard lines (eg Veenstra et al, JAMA 281)
 - Antiseptic last longer than antibiotic (2 weeks vs 1 week)
 - More expensive
 - Consider if:
 - CLAB rates high despite good compliance with insertion and maintenance bundles
 - Central lines > 7 days
 - High risk of CLAB (burns, immunocompromised)
 - Cochrane Review 2013:
 - ↓CRBSI 3 → 1%, NNT 50
 - ↓colonisation, ARR 10%, NNT 10
 - No difference in clinically diagnosed sepsis or mortality
 - Better in ICU than longer term use in oncology
- Site:
 - Traditionally, femoral the highest and subclavian the lowest rate of infection
 - Maril et al, CCM 2012, Meta-analysis of 2 RCTs (n = 1006), done before line bundle standards, concludes there is no difference between femoral, IJ or SC lines for CLAB or DVT
 - Timsit et al, Am J or Resp & Crit Care Med 2013, Review of 2 multi-centre studies with 2,527 catheters and found no difference in colonisation on CLAB in femoral and internal jugular lines
- Site sterility and dressing:
 - Alcohol/2% chlorhexidine better than iodine skin prep. Remove hair (clipping better than shaving). *Clean again after insertion*
 - Maximal sterile barrier procedures reduce bacteraemia 6 fold
 - Chlorhexidine body wash reduces CLAB, but place in CLAB bundles unknown
 - Dressings: permeable polyurethane transparent dressings better than impermeable. Replace dressing every 7 days, or if soiled, wet or loose
 - Sutureless securement with PICCS may be associated with less infection and dislodgement – unclear for CVLs
- Other factors:
 - Expertise of operator and ICU nursing levels affect infection rate
 - Keep number of lumens to a minimum

- One lumen should be dedicated to TPN
- Tunnelling may be useful in jugular lines but is not recommended for short term use
- Changing lines:
 - If risk of non-aseptic insertion, then new line at new site within 24 hours
 - Routine changing of lines does not decrease the rate of infection and increases mechanical complications. Not recommended
 - Changing a catheter over a guide-wire when infection is suspected is associated with ↑colonisation but not ↑bloodstream infections (Lane et al, Current Opinions in Crit Care, 2002). Only re-wire if risks of a new site out-weigh the risk of infection in the same site. Send old tip for culture. If positive remove new line
 - If a lumen becomes blocked, line should be removed within 24 hours
 - Pulmonary artery catheter can be replaced with a CVL into the same sheath if the sheath is < 72 hours old and there is no suspicion of CLABSI
- Some evidence in low risk patients (ie if you can afford to wait for the result) for doing a skin swab around the line entry – a negative culture has high negative predictive value

Needlestick protocol

- Immediate first aid: express blood and chlorhexidine
- Assess risk:
 - Hollow needle
 - Presence of gloves
 - Depth of wound
 - Into artery or vein
 - Patient known to be infected with Hep B, C, HIV
- Baseline bloods from:
 - Patient, with consent if possible
 - Doctor
- Report to Occupational health, log incident report
- Post-exposure prophylaxis:
 - Hep B: if patient infected and low immunity in doc → Anti HepB Ig
 - Hep C: none
 - HIV: if patient positive then HARRT within 2 hours
 - Monitor for toxicity
- Provide emotional support.
- Condoms until testing complete
- Follow-up testing: 6 weeks, 6 months
- Review unit guidelines and compliance

Toxic Shock Syndrome

- Many strains produce toxins that cause:
 - Toxic shock (caused by toxic shock syndrome toxin-1 and others [2, 3] which are more common in non-menstrual Toxic Shock)
 - Food poisoning (enterotoxin)
 - Scalded skin syndrome (exfoliative toxin)
- Most toxic shock caused by methicillin sensitive strains, but MRSA rising
- Proportion due to tampon use has declined significantly, but still the most common cause. Next most common cause is post-surgical, cellulitis, sinusitis
- *S. Aureus* exotoxins:
 - Super-antigens
 - Activate large number of T-cells (interact with the invariant region of the class II MHC) – up to 20% of all T-cells activated → massive cytokine production
 - Individuals develop antibodies to TSS1 over their life (⇒ the syndrome more common in the young). Some don't develop the antibody which may explain recurrence
- Presentation:
 - Common symptoms:
 - Hypotension, often unresponsive to large volumes of fluid (which may → tissue ischaemia/oedema)
 - Fever (> 38.9)

- Skin manifestations: macular erythroderma of skin and mucus membranes palms/soles – like sunburn +/- ulceration, bullae or petechiae → desquamation 7 – 14 days later
- Variety of other symptoms:
 - Myalgia
 - Sore throat
 - Vomiting/diarrhoea/abdo pain
 - Confusion 2nd to cerebral ischaemia/oedema
- Diagnosis is clinical on CDC clinical criteria (case definition). Isolation of *S. Aureus* occurs in 80 – 90% (not usually from blood culture) but is not required
- Lab:
 - 25 – 50% immature neutrophils
 - ↓Platelets and Hb, ↑clotting times +/- DIC
 - ↑CK
 - Lab can check for toxins and antibodies to them
- Differential:
 - High index of suspicion in rapid shock in a young person
 - Streptococcal toxic shock: similar, but more severe pain at infection site, may require urgent surgical debridement
 - Rocky Mountain spotted fever: but rash is typically petechial, comes later, and starts in the extremities
 - Meningococcaemia
 - Tropical illnesses: dengue, typhoid
- Management:
 - Supportive
 - Surgical source control if necessary
 - Antibiotics: not clear whether they alter the course of TSS, but eradicate bugs and stop recurrence. Clindamycin suppresses protein synthesis, so suppresses toxin production, whereas cell wall agents such as beta-lactams may increase toxin from lysing bacterial cells. Empirically consider clindamycin + (flucloxacillin +/- vancomycin)
 - Logic but not evidence for the use of IgG (import antibodies to TSS1)

Necrotising Fasciitis

- Type 1: Polymicrobial, especially in diabetes
- Type 2: Monomicrobial:
 - Usually Group A Strep (*Pyogenes*, including in young healthy patients). Can be *S Aureus*
 - Odd cases:
 - Clostridial perfringens myonecrosis: gas gangrene
 - *Vibrio vulnificus*: salt water wound especially if immunocompromised
 - Rhabdomyolysis
 - *Mycobacterium ulcerans*: Some areas in Australia, treat with moxifloxacin, rifampicin + surgery
- Diagnosis:
 - Clinical:
 - Rapidly spreading cutaneous infection with erythema and purplish discolouration, tense oedema, blistering and necrotic tissue (the latter appearing over days), rarely with palpable crepitus
 - Risk factors: immunocompromised, diabetes mellitus, malignancy, alcoholism
 - Evidence of sepsis with shock and MODS
 - LRINEC: Lab risk indicator for necrotising fasciitis score: 6 serologic measures including CRP, WCC, Hb, Na, Cr, glucose – limited value as non-specific
 - CXR/CT/MRI: gas in subcutaneous tissues. MRI may guide extent of debridement
- Differentials:
 - Erysipelas: superficial dermal infection. Usually well-defined margins and due classically to streptococcus
 - Cellulitis: deeper infection extending to subcutaneous tissues. More ill-defined margin and due to a range of organisms
 - Necrotising Fasciitis: Deeper infection still with invasion of the fascial plains and deep tissues.
- Treatment:
 - Urgent surgery with debridement back to bleeding tissue. Easy blunt dissection of adherent fascia – normally resistance. May be thick, watery pus in the subcutaneous space. Expectation of major blood loss and massive transfusion
 - Antibiotics (only get once chance – use broad spectrum):

- Empiric – Meropenem 25mg/kg Q8 hrly + Clindamycin 15mg/kg Q8 hrly +/- Vancomycin for MRSA cover
- Streptococcus pyogenes – Penicillin 45mg/kg Q4 hrly or Cephalothin 50mg/kg Q6 hrly + Clindamycin 15mg/kg Q8 hrly (for “antitoxin” role)
- Clostridial infection – Benzylpenicillin 60mg/kg Q4 hourly or Metronidazole 12.5mg/kg Q8 hrly
- Polymicrobial – Meropenem 25mg/kg Q8 hrly
- Cover water related infections if suggested by history: Ciprofloxacin
- IVIG: improved mortality in Group A streptococcal infection. Neutralisation of streptococcal super-antigens and clostridial toxins
- Hyperbaric O2: observational studies only with conflicting results. Possible reduction in need for debridement. BD or TDS dives of 90 mins to 3 atmospheres. Severe organ failure may limit logistics
- Supportive care
- Later wound management, including reconstruction

Pseudomembranous Colitis

- Caused by C difficile. Not a normal commensal. Asymptomatic carriage in 1 – 3 %
- Infection requires disruption of normal flora (eg antibiotics, esp clindamycin) and an exogenous source
- Risk factors:
 - Broad spectrum antibiotics, in particular clindamycin, quinolones, amoxycillin and cephalosporins
 - Immunosuppressive therapy or cytotoxic chemotherapy
 - Gastric acid suppression – PPIs and H2 antagonists
 - Age > 65
 - Prolonged hospitalisation, nursing home resident
 - Renal impairment
- Diagnosis:
 - Hard to culture
 - Interested in toxin production – especially Toxin B. ELIZAs reasonably sensitive and specific
 - Screening EIA to detect C difficile glutamate dehydrogenase (GDH)
 - PCR-based assays to detect conserved gene targets within the Pathogenicity locus of D. difficile
 - Tissue culture the gold standard
- Severe disease:
 - Associated with:
 - WBC > 15 and < 20% neutrophils
 - 50% rise in Cr
 - fever (> 38.5)
 - ↓albumin < 25
 - ↑lactate
 - Causes colitis, toxic megacolon, perforation, multiorgan failure
- Complications:
 - Related to diarrhoea: hypovolaemia, electrolyte disturbance
 - Intestinal infection: septic shock, perforation, toxic megacolon, bleeding
- Treatment:
 - Treatment with metronidazole or oral vancomycin, pulsed or tapering doses. Some evidence teicoplanin better than vancomycin
 - Small trial evidence for probiotics. Cochrane Review 2013: Moderate quality studies (n = 4212) showed ↓ risk of C Diff (2% vs 5.5%)
 - Significant benefit in small single centre trials for stool “transplantation” (infusion by NJ tube of donated faeces) – mainly for recurrent rather than acute infection
 - Treatment failures due to:
 - Antibiotics don’t eradicate spores → recurrence usually within a week
 - Development of virulence factors (hypertoxin production, hypersporulation, antibiotic resistance)
 - Subtotal colectomy for perforation or toxic megacolon
- Prevention:
 - Antibiotic stewardship
 - Isolation of C diff positive cases
 - Hand washing with soap and water – alcohol hand rub ineffective

- See:
 - Hypercalcaemia, page 75
 - Stem Cell Transplant, page 309
- Managing:
 - The disease
 - Toxicity of agents treating the disease
 - Other comorbidities: often older, post-surgical, etc.
- General caution: given significant changes in treatment regimens over the last 20 years, the introduction of MABs, etc., take care to use up-to-date prognostic information...
- APACHE doesn't model cancer well. Better guided by performance status and number of organ system failures
- Prolonged ICU admission is bad. Early response over first 48 – 72 hours is a key discriminator. Accepting them late is a self-fulfilling prophecy

Malignant Spinal Cord Compression

- Medical emergency
- Rapid treatment is needed to prevent *further* loss of function, not to restore previous function
- Symptoms:
 - Back pain – often worse when lying down, often starting 4 – 6 weeks pre-diagnosis, then
 - Motor weakness, then
 - Sensory changes, then
 - Sphincter dysfunction in half, post void residual supports diagnosis
- Causes:
 - Most is epidural, rather than intradural or leptomeningeal (dural)
 - > 60% by prostate, breast and lung
 - 5 – 10% causes by NHL, multiple myeloma, renal
- Imaging options:
 - MRI preferred. Scan whole spine – one third of MSCC have multiple sites. Gadolinium only particularly helpful with intramedullary and leptomeningeal malignancy
 - CT myelography (intrathecal injection of contrast). Risk of lumbar puncture-induced neurologic decompensation
 - Bone scans
 - Plain films
- Treatment:
 - Goals:
 - Maintain neurological function
 - Control tumour growth
 - Spine stabilisation
 - Pain control
 - Dexamethasone: 16 – 96 mg daily in divided doses. Mitigate vasogenic oedema from compression induced ischaemia. High dose for abnormal neuro exam, moderate dose for all others. Reduce pain and improve symptoms
 - Radiation: prevents further tumour growth and neurological damage in radio-sensitive tumours (lymphoma, myeloma, breast, prostate, small-cell lung, not radiosensitive are melanoma, sarcoma, renal cell carcinoma). Minimal adverse effects
 - Decompressive surgery: surgery + radiotherapy better than radiotherapy alone. Indicated for spinal instability, previous radiation or radio-resistant, paraplegia for < 48 hours, single area of compression

Tumour Lysis Syndrome

- Massive tumour cell break-down 6 – 72 hours after treatment→:
 - Hyperuricaemia (purine nucleic acids → xanthine → uric acid, poor solubility in acidic urine → crystals → obstructive neuropathy)
 - ↑K and ↑PO₄ with acute oligoanuric renal failure
 - CaPO₄ tissue deposition (including in renal tubules → obstructive neuropathy) with hypocalcaemia
 - Metabolic acidosis
- Death due to renal failure, tachyarrhythmias, fluid overload and pulmonary oedema, and uraemia

- Associated with aggressive haematologic malignancies with rapid cell lysis with treatment (especially high grade non-Hodgkin lymphomas and ALL). Can even happen spontaneously
- Prevention:
 - Identify high risk patients: acute leukaemia with high WCC (highly sensitive to chemo), high grade lymphomas, bulky disease, SCLC, renal impairment, nephrotoxic agents, ↑age
 - Actively hydrate +/- diuretics to maintain a high urine output of 1 – 1.5 ml/kg/hr → ↓uric acid precipitation in tubules → prevents AKI
 - Urinary alkalinisation (controversial – not routinely recommended) to reduce uric acid crystallisation in renal tubules (8.4% NaHCO₃ aiming for urinary pH 7.0); consider acetazolamide if difficult to achieve (↓proximal tubular HCO₃ re-absorption). Promotes CaPO₄ deposition
 - Rasburicase (recombinant urate oxidase which converts urate to the more soluble allantoin) or allopurinol (xanthine oxidase inhibitor to reduce uric acid production) for 2 days prior. Rasburicase is the preferred agent if pre-existing hyperuricaemia. Contraindicated in G6PD deficiency
 - Monitor post-chemo: urine output and electrolytes. Rising uric acid → immediate therapeutic intervention
- Management:
 - Liaison with haematologist and/or renal physician
 - Aggressive hydration
 - ↑K:
 - Calcium gluconate/chloride
 - NaHCO₃ and/or actrapid insulin with 50% glucose for intracellular shift
 - Resonium (slow improvement only)/renal replacement therapy for removal from body
 - Avoid K containing fluids
 - ↑PO₄: phosphate binders or RRT. Ensure no PO₄ in fluids
 - ↓Ca: can give Ca – but focus on ↓PO₄
 - RRT for refractory ↑K, ↑PO₄, ↓Ca, fluid overload, symptomatic uraemia or acidosis. CRRT better than IHD due to greater cumulative solute removal and avoidance of solute rebound

Neutropenic Sepsis

- See Infection following Bone Marrow Transplant, 310
- Increasing survival in neutropenic septic shock – especially after conditioning chemotherapy
- However, persisting multi-organ failure is bad
- Some evidence that if you need RRT, early is better than later

Superior Vena Cava Syndrome

- PC: SOB most common, facial swelling, fullness in head, cough, facial plethora, distended neck veins, shoulder pain, hoarse voice (some symptoms may be due to airway or nerve compression/invasion)
- Causes:
 - Malignancy (90%)
 - Thrombosis related 2nd to intravenous lines/catheters
 - Infection: syphilitic aortitis, mediastinitis 2nd to pulmonary TB, histoplasmosis
- Process: mediastinal mass can easily impinge on the SVC. Over 1 - 2 weeks collateral vein dilatation → collateral flow
- Diagnosis:
 - Cytology: sputum, BAL, pleural effusion, palpable nodes
- Treatment:
 - Emergency requiring empiric treatment only if airway obstruction or cerebral oedema – otherwise get tissue and use targeted therapy
 - Elevate head of bed, oxygen
 - Intraluminal stenting can safely precede tissue diagnosis
 - Emergency radio/chemotherapy if malignant tumour underlying – symptoms improve over 1 – 2 weeks (collateral flow provides most of the benefit)
 - Glucocorticoids of unclear benefit, except in lymphoma or thymoma (indicated for the underlying tumour)
 - Diuretics reduce venous return

Malignant pericardial effusion

- Pericardial involvement in up to 34% of cancer patients
- Pericardial fluid:

- has a flat pressure response until it reaches the pericardial reserve volume, then rises sharply due to low compliance of the pericardium \Rightarrow point at which small rise in volume causes big rise in pressure
- Rapid accumulation more significant than absolute volume as pericardium can stretch over time
- Clinical findings:
 - SOB most common symptom
 - Pulsus paradoxus most common sign
 - Beck's triad: hypotension, \uparrow JVP and \downarrow heart sounds with rapid growth leading to tamponade
 - ECG: low amplitude, electrical alternans
- Diagnosis:
 - Echo: size and location of effusion, and haemodynamic consequences (eg RA and RV collapse in diastole)
 - Cardiac catheterisation: elevated and equalised RA, RV and PAOP
- Treatment:
 - If euvoelaemic, fluid may make it worse
 - Pericardiocentesis, under US guidance
 - If reaccumulation: sclerosing therapy, balloon pericardotomy, or surgical window
 -

Haematological investigations

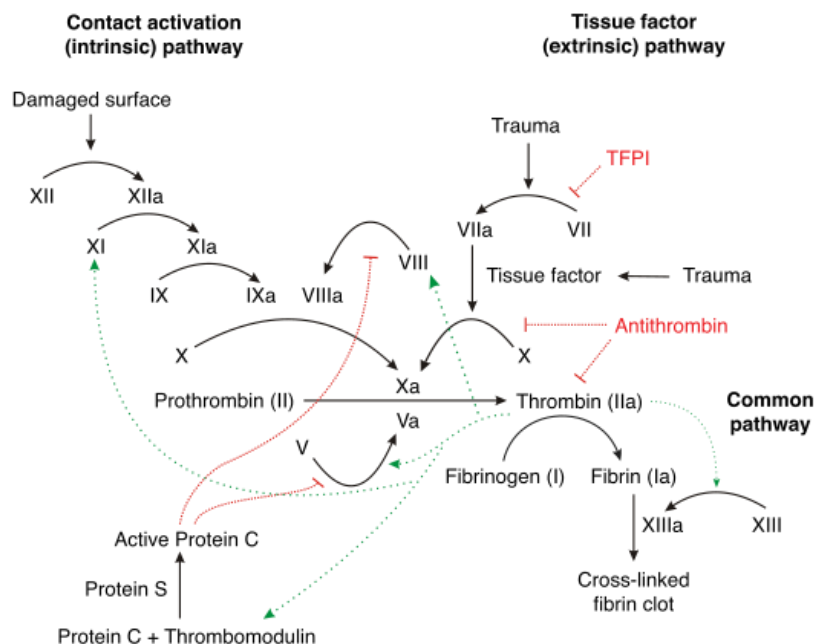
Autoimmune Markers

- ANA: SLE
- Anticardiolipin: APS, SLE, viral illness. ↑significance if lupus anticoagulant and antiphospholipid syndrome present
- Anti-DNA: SLE
- Anti-Smith: SLE
- Anti-Ro and La: SLE, Sjogren's
- Anti-centromere: CREST and Limited cutaneous scleroderma
- Scl-70: Diffuse scleroderma
- Anti-ribonuclear protein: SLE, mixed CTD
- C3 and C4: ↓in SLE, autoimmune hepatitis, ↑ in nephritic syndrome
- C-ANCA: Wegner's granulomatosis > polyarteritis nodosa
- P-ANCA: Polyarteritis nodosa > Wegener's
- Anti-GBM: Goodpasture's
- Anti-smooth muscle: Autoimmune hepatitis
- Anti-mitochondrial: Primary biliary cirrhosis
- Anti-gliadin, anti-endomysial, anti-transglutaminase: Coeliac disease
- Anti-intrinsic factor and parietal cell antibody: pernicious anaemia

Other haematological investigations

- Causes of anaemia: think ↑destruction, ↓production
- Tests not to forget when dealing with a haematological problem:
 - Blood film:
 - For red cell fragments
 - Target cells in haemoglobinopathies, Fe deficiency, spleen removal, liver disease, thalassaemia
 - Plasma cells in: myeloma, B cell lymphoma, plasmacytoma, spherocytosis, zoster infection, TB, leprosy, MGUS, Waldenstrom's
 - Nucleated red blood cells in: hyposplenism, compensatory erythropoiesis, hypoxia, marrow invasion, extramedullary haematopoiesis, other (uraemia, sepsis, liver disease, renal transplant)
 - Haemolysis screen:
 - Reticulocytes
 - Haptoglobin
 - Unconjugated bilirubin
 - Urine: exclude active sediment
 - Differentials: eg sepsis (WBC, urine, blood cultures, LP, etc.)
- Causes of ↑MCV:
 - B12 deficiency
 - Folate deficiency
 - Myelodysplastic syndrome
 - Cytotoxics or immunosuppressants
 - Alcohol and hypothyroidism associated with modest rises
- Leukemoid reaction:
 - Persistent ↑ in neutrophils > 30 – 50,000
 - Different from Leukaemia – circulating neutrophils are usually mature and not clonally derived
 - Other white cell lines normal
- Value of a bone marrow aspirate in pancytopenia:
 - Confirm diagnosis → target therapy
 - Assess marrow cellularity
 - Identify normal or otherwise haematopoietic cells (eg megaloblastic change)
 - Demonstrate infiltration or fibrosis
 - Show macrophages engorged with haematopoietic cells (eg viral haemophagocytic syndrome)
- Urine free haemoglobin implies intravascular haemolysis

Coagulation



- PT = Prothrombin time: extrinsic pathway, INR = normalised ratio of PT
- TCT = Thrombin Clotting Time = common pathway. Conversion of fibrinogen to fibrin. Test clotting time after addition of thrombin to undiluted plasma. Prolonged in ↓fibrinogen, FDPs and heparin
- APPT: Intrinsic pathway. Is unaffected by LMWH so need to monitor factor Xa activity
- Activated Clotting Time = Point of care test which approximates APPT – testing clotting of whole blood
- Echis time: snake venom activates prothrombin without requiring vitamin K ⇒ echis time will be normal in vitamin K deficiency or warfarin (where factors are present but not activated by carboxylation), but prolonged where factor concentrations are reduced (eg liver disease)

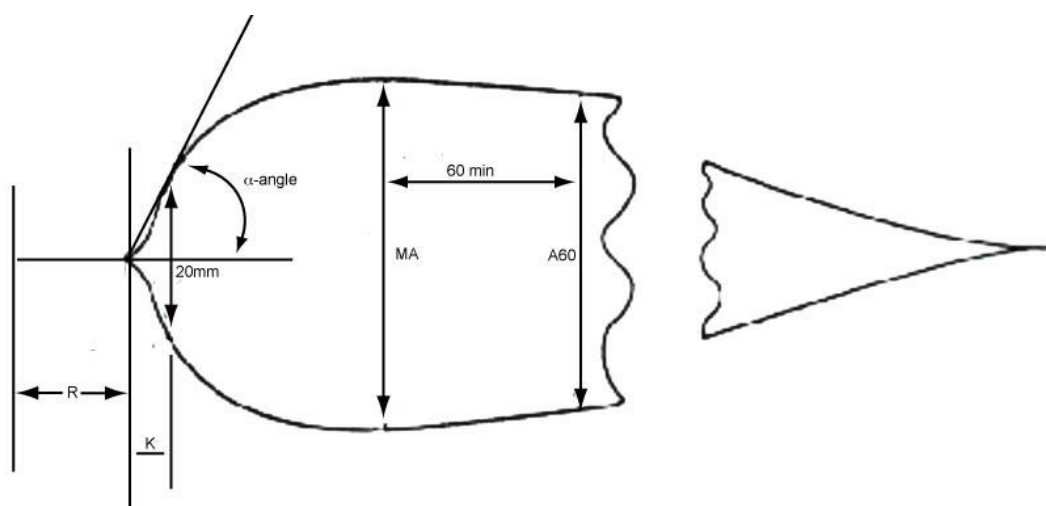
Abnormal Coagulation Tests

- Causes of ↑INR, ↑APPT, ↓Fibrinogen (ie everything wrong):
 - DIC
 - Dilutional coagulopathy
 - Post thrombolysis
 - Snake bite
 - Primary fibrinolysis
- Causes of ↑PT, aPPT N: rare
 - Warfarin
 - Liver disease
- Causes of ↑INR and ↑APPT:
 - TT and fibrinogen level:
 - Normal: Warfarin, liver disease, Vit K deficiency
 - Abnormal: Heparin, Liver disease, DIC. Reptilase time normal in Heparin, abnormal in other causes (dysfibrinogenaemia)
- Causes of ↑APPT and normal PT:
 - Factor 8 or 9 deficiency
 - Factor VIII inhibitor
 - Dilutional coagulopathy
 - Von Willebrand's (also needs ↑bleeding time)
 - Heparins
 - Lupus anticoagulant
 - Tests to differentiate:
 - Thrombin time, factor assay, APL antibodies, reptilase test (measures fibrinogen → fibrin),
 - Mixing test: aPPT corrected by 1:1 mixture with normal pooled plasma:
 - Yes: assay for factors
 - No: test for Lupus (eg dRVVT, anticardiolipin Abs) and other inhibitors
- Causes of normal APPT despite heparin:

- Inadequate heparinisation: too low a dose, drug mixing error
- Antithrombin deficiency
- Increased heparin clearance
- Increased heparin binding proteins
- Procoagulant screen tests for:
 - Antithrombin deficiency: Hereditary or acquired (liver disease, DIC, nephrotic syndrome, vasculitis)
 - ↑factor 2 and 10 activity → ↑clotting
 - Protein C and S deficiency
 - APC resistance: Factor 5 Leiden
 - Lupus anticoagulant and anticardiolipin antibodies
 - Prothrombin gene mutation (G20210A)
 - Fasting homocysteine assay
- Other causes for ↑clotting:
 - Malignancy
 - Oral contraceptive
- Causes of platelet dysfunction:
 - Antiplatelet agents
 - NSAIDs
 - Uraemia
 - β-lactam antibiotics
 - Cardiopulmonary bypass
- Von Willebrand's Disease:
 - → ↑bleeding time and ↓APPT (as vWF acts as a binding protein for FVIII prolonging it's half-life)
 - Diagnosis:
 - History of easy bruising, mucosal bleeding
 - Family history
 - Impaired ristocetin-induced platelet aggregation
 - Plasma vWF levels
 - Factor VIII levels/activity

Thromboelastograph (TEG)

- Potential benefit is that it tests whole blood, rather than just plasma with the interaction with platelets removed (as when testing coags)
- Issues with calibration – often point of care testing equipment languishes in a cupboard somewhere and is not subject to the stringent quality control and calibration requirements of laboratory equipment



		Process	Normal	Blood Component
R	reaction time	Initial fibrin formation rate	6 – 8 mins	Plasma clotting factors
K	clot formation time	Fibrin build-up and cross-linkage	3 – 6 mins	Fibrinogen, platelets
α angle	slope from r to K value	Speed of clot formation	50 – 60°	Decreased by ↓fibrin and platelets

MA	Maximum amplitude	Absolute strength of fibrin clot	50 – 60 mm	Platelet number, function and fibrin interaction
CLI A60	clot lysis index amplitude 60 minutes after MA		>85% MA – 5 mm	

Normal



Anticoagulants/hemophilia



Platelet Blockers



Fibrinolysis



Hypercoagulation



D.I.C

Stage 1



Stage 2



Anticoagulation

- See also DVT Prophylaxis, page 349
- Heparin:
 - Reasons for Heparin resistance:
 - AT3 deficiency
 - ↑Clearance
 - ↑Heparin binding proteins
 - Technical/drug administration problem
 - Side effects of protamine:
 - Anaphylaxis
 - Pulmonary hypertension
 - Hypotension
 - Bleeding
 - Bradycardia
- Direct thrombin inhibitors:
 - Dabigatran:
 - Oral
 - RELY Trial demonstrated non-inferiority in treatment of chronic AF
 - No risk of HITS
 - Renally cleared
 - Escarin clotting time the best test – other clotting studies unreliable
 - Not easily reversed. Try prothrombin X
 - Bivalirudin:
 - Short acting IV infusion
 - Dialysable
 - Monitor with APPT
- Oral Factor 10 a inhibitors:
 - Rivaroxaban
 - Apixiban

Warfarin

- Warfarin reversal (NZBTS guidelines):
 - INR 5.0 – 9.0 and no bleeding: stop warfarin

- INR 5.0 – 9.0 and high risk of bleeding: Vitamin K (1 – 2 mg orally or 0.5 – 1.0 mg iv)
- INR > 9.0 and low risk of bleeding: 2.5 – 5.0 mg oral vitamin K or 1.0 mg iv
- INR > 9.0 and high risk of bleeding: 5 - 10 mg vitamin K iv, Prothrombinex-HT (25 – 50 iu/kg) and FFP (150 – 300 ml)
- ProthrombinX contains factors II, IX and X, but only low levels of factor VII. Use FFP as an adjunctive source of factor VII
- Vitamin K takes ~ 6 – 12 hours for effect, full effect in 24 hours
- If using FFP or ProthrombinX, need vitamin K to sustain its effect
- If surgical bleeding consider tranexamic acid
- Side effects of warfarin:
 - Risk of bleeding (in observational studies) related to age, history of past bleeding, specific comorbid conditions (HTN, renal insufficiency, excessive alcohol intake)
 - Non-bleeding side effects:
 - Alopecia
 - Rarely skin necrosis
 - Teratogenic, especially 6th – 12th week (→ fetal chondrodysplasia punctata), also 2nd and 3rd trimester (optic atrophy and mental retardation). Anticoagulant effect in foetus dangerous at delivery (eg intracerebral bleeds). Safe in breast-feeding
 - Antiphospholipid syndrome: Lupus anticoagulant can → ↑INR – making monitoring problematic

Procoagulants

- Fibrinolysis
 - Fibrinolytics are integral to the maintenance of vascular patency
 - The basis of fibrinolysis is the conversion of plasminogen → plasmin:
 - Catalysed by tissue plasminogen activator and others, expressed in many tissues
 - Inhibited by many inhibitors, including plasminogen activator inhibitor 1
 - Plasmin has impact other than clot lysis. It activates thrombin, cleaves fibrinogen to create fibrin, cleaves receptors on platelets (including glycoprotein 1b and IIb/IIIa), and a broad spectrum of pro-inflammatory actions

DDAVP/Desmopressin

- See also Catecholamine sparing inotropes/vasopressors, page 47
- Vasopressin analogue that induces release of the contents of endothelial cell associated Weibull Palade bodies, including von Willebrand factor
- In doses used in cardiothoracic surgery (ie 0.3 µg/kg) it potentiates primary haemostasis, and may → water retention and vasoconstriction
- Small effect on transfusion rate but associated 2 fold increase in perioperative MI

Tranexamic Acid

- Lysine analogue which is a potent inhibitor of fibrinolysis → stabilises clot
- Cardiac surgery: ↓transfusion rate, re-operation rate but not outcome
- Post-surgical bleeding: Clear evidence of ↓blood transfusion. Less certain evidence of effect on thrombotic events and mortality. (Meta-analysis Ker et al, BMJ 2012)
- CRASH2 Trial, 20,000 patients in 380 hospitals, tranexamic acid (1 gm load, then 1 gm over 8 hrs) vs placebo. Within 8 hours of injury. Showed significant but small ↓mortality (16.0 vs 14.5%, 1.5% ARR) and ↓bleeding but no ↓ in transfusions. Demonstrated safety. Benefit for those only getting it within 3 hours. Fairly soft entry criteria (only 15% had hypotension, mean transfusion only 3 units). Inexpensive
- SE: myopathy, hypotension, intravascular thrombosis, seizures (especially in higher doses than in CRASH-2, possible mechanism is the similarity to GABA)

Recombinant Activated Factor 7a (rFVIIa)

- Promotes clotting, in the presence of other factors
- Given as bolus
- Licensed only for haemophilia A & B with antibody inhibitors to coagulation factors VII or IX. Effective there for surgery and joint bleeding, without thrombotic complications or evidence of systemic activation of coagulation
- Mechanism of action:
 - Vitamin K dependent glycoprotein
 - Dose for effect (90 µg/kg) much greater than what would be needed to saturate the extrinsic (Tissue Factor) pathway

- In sufficient doses, rFVIIa binds to activated platelets in a TF-independent way and promotes factor X activation (→ thrombin generation) → further platelet activation, localised to the site of injury ⇒ relative lack of thrombotic complications
- Half-life is short (2 hours), compared to other factors (next shortest is VIII at 10 – 14 hours)
- Effect modified by:
 - Lack of other coagulation factors, co-factors (eg Ca), and platelet number and function may limit its effect
 - Activity decreases by up to 90% when pH drops from 7.40 to 7.00
 - Activity does not decrease with mild hypothermia (33°C), in marked contrast to other coagulation proteases
- Monitoring: no lab test correlates with clinical efficacy
- Risks: thromboembolic complications range from 1 – 2% to 9% in various studies. Otherwise generally well tolerated
- Indications:
 - Very few high-quality studies to guide use in off licence indications (up to 97% of its use)
 - Logic in Von Willebrand's (and few other options)
 - Possible benefit in coagulopathy of liver disease, but not in liver resection or transplantation or variceal bleeding
 - Used to control microvascular surgical bleeding as a rescue therapy or when the patient declines blood products. Reasonable evidence of reduced transfusion requirements. No difference in mortality or thrombosis. Dose unclear, likely to be at least 50 mcg/kg. One meta-analysis suggests cost-benefit ratio for rFVIIa would be favourable only if each transfused patient was expected to receive 40 units of RBC....
 - Likely to be of greater benefit in blunt trauma (more likely to be coagulopathic) than penetrating trauma (more likely to be damage to large blood vessels)
 - Trauma:
 - Initially South African study in blunt trauma showed benefit, trend to benefit in penetrating trauma
 - 2010 studies showed no mortality benefit
 - Levy 2010 NEJM: ↑ risk of strokes with off label use
- 2011 systematic review suggests:
 - In intracranial haemorrhage, cardiac surgery, body trauma, brain trauma and liver transplantation there is no evidence of mortality benefit
 - In intracranial haemorrhage and cardiac surgery there is evidence of ↑thromboembolism
- Remains a rescue therapy with controversial indication, benefit and dosing despite widespread use. Off label use has clear potential for harm and little evidence of benefit
- A number of RCTs in progress
- Compare to tranexamic acid:
 - No head to head trials
 - More expensive
 - Rescue treatment
 - More procoagulant: more DVT, PE
 - Both equally difficult to monitor

Aprotinin

- Non-specific serine protease inhibitor, inhibiting trypsin, plasmin, kalikrein, contact phase of coagulation. This inhibits fibrinolysis, coagulation and inflammation
- When given before bypass surgery it may prevent clotting activation, factor consumption and platelet dysfunction, preventing blood loss, transfusion, re-operation
- Adverse effects: include fever, anaphylaxis on repeat exposure

Blood Product Replacement

- See:
 - Series on Blood Transfusion, starting Lancet May 25 2013
 - Patient Blood management Guidelines, Module 4 – Critical Care – by national Blood Authority Australia, endorsed by ANZICS and CICM

Principles

- Past guidelines have been product based. Move to clinical guidelines for specific problems – when to give what

- A number of studies have identified blood transfusion as an independent risk factor for morbidity and mortality – presumably due to transfusion-related immunomodulation and storage lesions. Little evidence for the efficacy or appropriateness of many transfusions ⇒ Be cautious
- Issues of stewardship: it's expensive, aging population will ↑ demand and ↓ supply, and many transfusions could be questioned in terms of patient outcomes
- ⇒ Balancing:
 - Anaemia is harmful
 - Questions of whether transfusion is helpful (scant evidence, although obvious in life threatening bleeding)
 - Known harms of transfusion
 - Cost of products:
 - RBC: \$250
 - FFP: \$200
 - Platelets: \$750. Do not refrigerate
 - Cryoprecipitate: \$360

Safety

- Requires:
 - Clearly defined indication and benefits of blood components
 - Accurate patient identification for blood group compatibility
 - Identification and careful management of high-risk patients
 - Appropriate handling and storage
 - Provision of adequate quantity and quality of components
 - Communication of benefits and risks to patients
 - The infusion should not be associated with preventable ill effects
 - Awareness of , early diagnosis and prompt action to adverse events
 - Accurate documentation
 - Input into quality assurance programmes

Headings for Question on Transfusion

- Follow established guidelines (eg NZ Blood Transfusion Service Clinical Guideline)
- Individualised approach
- Reduce blood loss:
 - Source control
 - Phlebotomy
 - Diagnosis and treat pre-existing anaemia
- Consider alternatives:
 - Autologous transfusion/cell saver
 - EPO
 - Iron supplements
- Ethical issues:
 - Approach to someone who declines transfusion
 - Gaining consent
- Clinical management:
 - Determining transfusion threshold: indication, comorbidities, evidence
 - Special precautions: eg indications for irradiated blood
 - Correcting other factors, eg hypothermia and acidosis in massive transfusion
 - Monitoring for side effects: Immune and non-immune (incl coagulopathy)
- System safety: policies around cross-matching and avoiding incorrect transfusion, event reporting systems and audit

Indications for irradiated products in adults:

- Exchange transfusions
- Congenital immune deficiencies
- Lymphoma
- Stem cell or bone marrow transplants
- Aplastic anaemia

Red Blood Cells

Causes of Anaemia in ICU

- Dilutional due to fluid resuscitation
- Blood sampling, filter changes: 100 – 120 mls per day
- Surgical
- Impaired red cell production. Traditionally through due to ↓ EPO production. Now also recognised hepcidin plays a significant role (↓Fe absorption, ↓macrophage release of hepcidin). May be ↑role for giving iron

Red Blood Cell Antigens

- ABO most important
- Rhesus status:
 - After ABO, Rhesus is the most important antigen
 - Presence of D antigen confers Rhesus positivity. No D ⇒ rhesus negative (~ 15% of people)
 - If Rhesus (D) negative, exposure to even a small amount of Rh positive cells → production of anti-D autoantibody
- Other blood groups and potential alloantigens are: Lewis, Kell, Duffy, Kidd....
- Cross-match:
 - Products must be ABO compatible and lack RBC antigens for which the patient has alloantibodies
 - Is essential with: RBCs, granulocyte concentrate
 - Not with: Cryoprecipitate, FFP, IVIG, Platelets and PT concentrate
 - Rh negative patients need Rh – blood to prevent alloimmunization to the D-antigen, although in life threatening situation it may be necessary to transfuse Rh (D) – patients with Rh (D) + RBC or platelets
- O negative transfusions:
 - Issues with Type O transfusions:
 - Complications from any blood transfusion
 - Unclear blood group on subsequent G & H (mixed field group and screen)
 - Limited supply of O negative blood
 - Aren't tested for red cell antibodies → ↑risk of non-ABO alloantibody mediated reaction
 - ↑transfusion related reactions
 - Alloimmunization: delays in future transfusions, transplant problems
 - Can give O positive blood to a rhesus negative person if you're desperate, but Rhesus (D) negative woman of child bearing age should be given Anti-D to attempt to reduce iso-immunisation, which can lead to hydrops fetalis in future pregnancies

Leucodepletion

- Introduced in Australia in 2010, where it costs \$40 m per annum. Now universal
- No phase 3 trial demonstrating a clinically important benefit has been done
- Benefits:
 - ↓Febrile non-haemolytic reactions
 - ↓CMV infection
 - ↓Immunisation to HLA
 - ↑chance of finding an organ transplant match if required
 - ↓in storage lesion effect
 - ↓in transfusion related graft vs host disease
 - ↓mortality in cardiac surgical, orthopaedic and trauma populations (Herbert, JAMA 2003)
 - ↓risk of vCJD transmission (primary reason for its introduction in a number of countries)

Storage of RBCs

- Studies have indicated ↑ complications from blood stored for longer across different ICU clinical subgroups:
 - Age of red blood cells and mortality in the critically ill: Critical Care 2011, Pettila et al (CTG publication). ↑MODS and mortality. Seems to be independent of the number of units transfused
 - Blood stored for > 14 days associated with ↑ surgical morbidity and mortality: Kock, NEJM 2008
 - Current NNT to save one life with fresh blood is 97 on the basis of observational studies. Depends Significantly on background mortality
 - TRANSFUSE study recently funded by NHMRC: ANZIC study of standard vs freshest red blood cell. Pragmatic study – doesn't specify ages of blood – just the usual vs the freshest blood available (average separation of ~ 7 days). Recruiting 5,000 patients. One of 5 studies underway

- Australasian maximum is currently 42 days
- “Storage lesions” begin after 2 – 3 weeks and progress. RBCs undergo structural and functional changes including:
 - Changes in shape:
 - ↓flexibility → ↓microvascular flow (biconcave → spherocytes)
 - ↓ATP → ↓ability to maintain biconcave shape
 - ↑adhesiveness and aggregability → adhere to endothelium in the micro-circulation
 - Changes in storage medium:
 - ↓2,3 DPG → shifts oxyhaemoglobin curve to the left and ↓O₂ delivery. Takes several hours for O₂ carriage and delivery to return to normal
 - ↓concentrations of NO
 - Accumulation of proinflammatory bioactive substances and micro-aggregates
 - Haemolysis – both in stored blood and ↑ rate post-transfusion due to aged cells. It’s suggested free haemoglobin scavenges NO (which is unhelpful) and extra-cellular iron is helpful to bacteria (the body ↓Fe absorption if sick - ?an adaptive response)
- Storage thresholds determined arbitrarily, eg 75% of transfused RBC should survive post-transfusion
- Many storage changes are related to leukocytes and are reduced by pre-storage leucodepletion
- Frozen RBCs are not well investigated. Used in the Netherlands for rare types and remote settings. ↓ in vitro efficiency of 10%. Frozen cells need washing prior to use to remove cryoprecipitate
- Artificial Hb substitutes extensively researched (JAMA 2006 Meta-analysis): ↑risk of MI and mortality. Not there yet....
- Ultra-purified bovine-Hb has been tried....

Fresh Blood Transfusion

- Controversial. Many transfusion specialists would argue there is never an indication for fresh whole blood
- Fresh blood provides immediately functioning oxygen-carrying capacity, volume and haemostatic factors in the on produce
- The number of allogeneic donors to whom a patient is exposed can be reduced
- Problems associated with infusion of massive volumes of stored blood can be minimised
- Risk of viral infection is possibly higher
- Benefit in terms of controlling haemorrhage probably relates to the presence of immediately functioning platelets

Threshold for Red Blood Cells

- See also Massive Bleeding, page 303
- Determined by need to relieve clinical signs and symptoms of impaired O₂ transport
- TRICC, NEJM 1999, Hebert et al, Transfusion Requirements in Critical Care: Multicentre Canadian trial of 838 normovolaemic patients (ie not bleeding) randomised, excluding routine cardiac patients. No change in mortality if transfused at 70 rather than > 100 (p=0.10, liberal group higher), and significantly ↓transfusions. Mortality difference in favour of restrictive in the less sick cohort (APACHE < 20) and age < 55. Prior to universal leucodepletion and includes significant biases. Not powered to look at cardiovascular disease, severe sepsis or acute cerebrovascular disease. More modern issues are the age of blood and the use of erythropoietin
- CRIT study, Crit Care Medicine 2004, Corwin et al, prospective observational study of 4892 patients showed mean pre-transfusion threshold was 8.6 g/dl (ie still high) and the number of units transfused was an independent predictor of *worse* outcome. Same finding as JAMA 2002 Vincent JL. Other studies differ
- Carson et al, NEJM 2011, Liberal vs Restrictive transfusion strategy following hip surgery. 2016 patients age > 50, transfusion thresholds of 100 mg vs < 80 or symptoms of anaemia. No difference in outcomes
- RELIEVE Study: Transfuse at 70 or 90 in patients aged > 55 years and < 4 days ventilation – trend to higher mortality in threshold of 90, Walsh et al, Crit Care Med 2013
- ⇒ restrictive transfusion strategy is the norm. This is a change:
 - from an absolute Hb level to patient assessment
 - from multiple unit transfusions to single unit then reassess
- Holst et al, TRISS Trial Group, multi-centre RCT, n = 1005, NEJM Oct 2014, 9 g vs 7 g in patients with *septic shock*. Transfused one unit at a time. Lower group received median of 1 unit, higher group median of 4 units. 90 day mortality 43 vs 45%
- NBA recommendations:
 - < 70 (raised to 80 in ACS) – transfusion likely to be appropriate but may not be required in all cases
 - 70 - 90 transfusion is not associated with ↓mortality. Transfusion of a single unit followed by reassessment - should be based on the need to relieve signs and symptoms of anaemia
 - > 90 generally unnecessary

- **EPO:**
 - In patients staying longer than 2 days leads to ↓20% RBC transfusion: multi-centre study of 1302 patients, JAMA 2002, Corwin et al. Subsequent study (NEJM 2007) by same authors did not show ↓transfusion, but trend to ↓mortality in trauma patients and ↑thrombotic events
 - Newer agent darbopoietin has ↓ risk of life threatening red cell aplasia, and longer half-life, but no evaluated in ICU
 - Reducing exposure to blood products is attractive, but this is expensive, and concerns about ↑tumour growth in cancer patients (FDA warnings issued)
 - NBA recommendation: should not be routinely used in anaemic ICU patients (eg critical illness)
- **Calcium:** Most patients receiving blood transfusions do not need calcium supplements. Excessive calcium may be harmful

Transfusion of Other Blood Products

- Transfusion of **platelets**
 - Prophylaxis:
 - < 10 without associated risk or < 20 with additional risk factors
 - > 50 in patients undergoing surgery or invasive procedures
 - < 50 in massive haemorrhage and < 100 in diffuse microvascular bleeding
 - Not appropriate if:
 - Thrombocytopenia is due to immune mediated destruction
 - In TTP and HUS
 - In uncomplicated cardiac bypass surgery
- Fresh frozen plasma:
 - Independently associate with adverse events (including ARDS and ALI)
 - Patients with INR < 2 may not benefit from FFP and can generally undergo invasive procedures within the ICU (NBA recommendation)
- Cryoprecipitate: Contains factor VIII, fibrinogen, vWF, factor XIII and fibronectin. Originally used for haemophilia A, now used for hypofibrinogenaemia. Risk of transfusion-related reactions uncertain.

Transfusion Reactions

Immune Mediated Transfusion Reactions

- See NZ Blood Service Transfusion Medicine Handbook 2008
- **Acute Haemolytic Transfusion Reactions:**
 - Due to incompatible RBCs (usually labelling error/systems error)
 - → DIC and acute renal failure
 - Symptoms: agitation, pain at venipuncture site, pain in abdomen, SOB, often within minutes
 - Signs: fever, hypotension, hypertension, general ooze, *haemoglobinuria* (red urine), skin rash
 - Chance of ABO incompatibility if blood given to the wrong person are ~ 1:3. Most severe reaction is from group A red cells given to group O patient
 - May also occur following transfusion of platelets or FFP that have high titres of anti-A or anti-B
- **Delayed Haemolytic Transfusion Reaction:**
 - Occurs > 24 hrs later, appear over days 1 - 14
 - Patient immunised to a red cell antigen by prior transfusion or pregnancy
 - Level of the antibody may be too low to detect in cross-matching
 - PC: fever, ↓Hb, jaundice, maybe haemoglobinuria
- **Non-haemolytic Febrile Transfusion Reaction**
 - Fever or rigors during RBC or platelet transfusion affect 1 – 2 % of recipients
 - Reduced with leucocyte depleted RBCs
 - PC: Shivering within 30 – 60 mins of start of transfusion followed by fever
 - Slow or stopping transfusion and giving paracetamol usually sufficient
 - Caution: may be early signs of haemolytic reaction or contamination
- **Allergic and anaphylactoid reactions:**
 - Due to antibodies and antigens in plasma, or possible due to vasoactive substances in the infusion (→ transient ↓BP)
 - Anaphylactic shock over first 24 hours: most common in patients with IgA deficiency
 - Additives may cause problems: ethylene oxide, formaldehyde, latex...)
- **Transfusion Associated Graft-Versus-Host Disease:**
 - Most commonly in immunocompromised patients
 - Infusion of lymphocytes → reaction against host tissues

- PC: fever, abnormal LFTs, profuse watery diarrhoea, erythematous skin rash and progressive pancytopenia 3 – 30 days after allogenic transfusion
- **Transfusion Related Acute Lung Injury (TRALI):**
 - Definition: Acute respiratory distress and non-cardiogenic pulmonary oedema with 6 hours (usually 1 – 2 hours) after transfusion with plasma-containing blood components, with bilateral infiltrates on CXR, in the absence of other causes of acute lung injury
 - 1 in 5,000
 - Diagnosis is clinical and radiographical. Requires hypoxaemia: $\text{PaO}_2/\text{FiO}_2 < 300$ (regardless of PEEP) or $< 90\%$ on room air
 - ↑risk in those with trauma, burns, critical bleeding, shock, sepsis and cardiopulmonary bypass. These factors ?prime or sequester neutrophils in the lungs
 - Pathophysiology:
 - Donor antibodies against recipient leucocytes (plus other targets). May be other donor biologically active substances (eg cytokines, lipids) implicated
 - Leukoagglutinins and other substances in donor plasma → aggregation and sequestration in microcirculation of the lung which acts as a sieve → endothelial damage → interstitial oedema
 - Donors usually multiparous women. Reactions reduced by using male-only donor FFP
 - Now recognised that there is a broader spectrum of TRALI than purely leukoagglutinin mediated (ie immune and non-immune causes)
 - Management:
 - Treat as per ARDS. Unlike ARDS, usually resolves within 48 hours
 - Stop that donor donating
- **Transfusion Related Immunomodulation:**
 - Allogenic blood transfusion appears to be immunosuppressive (?largely due to donor lymphocytes)
 - Potential for ↑infection and ↑cancer recurrence

Non-Immune Mediated Transfusion Reactions

- **Transfusion associated circulatory overload (TACO):**
 - Volume overload a particular risk with 20% albumin
 - PC: SOB, ↑pulse and ↑BP within 12 hours of completion, with pulmonary oedema on CXR
- **Electrolyte disturbances:** ↓Ca, ↑K, acidosis → alkalosis
- **Bacterial contamination:**
 - Leading cause of transfusion mortality
 - Signs: fever, rigours, hypothermia, ↑pulse, shock, MODS, prominent nausea, vomiting and diarrhoea if not ventilated
 - Most likely in components stored at room temperature (eg platelets) maybe hours later. Sepsis from RBCs is quicker, and 60% mortality. Bugs like pseudomonas can survive the cooling used to “sterilise” products. So empiric treatment should cover that (eg ceftazidime)
 - Common organisms: staph epidermidis, S. aureus, Bacillus cereus, Group B strep (agalactiae), E coli, pseudomonas, other G –ives
 - Much of the problem is endotoxin in the product, not the bug itself
- **Viral infection:**
 - Hep B, C and HIV are now almost completely preventable
 - CMV: swinging fever, atypical mononucleosis and maybe abnormal LFTs 7 – 10 days following transfusion

Massive Bleeding

- See:
 - Damage Control Resuscitation, page 231
 - NZBTS website for Australasian Guidelines
- Definition:
 - Loss > 1 blood volume in 24 hours or > 10 units. Not that helpful as it’s retrospective
 - Loss of 50% blood volume in 1 – 3 hrs
 - Blood loss of at least 150 ml/hr
- Second highest cause of mortality in trauma
- Context:
 - Traditional model: bleeding → acidosis, consumption and hypothermia → vicious cycle
 - Now recognised DIC is a significant contribution: loss of localisation → microvascular damage → depletion of coagulation factors
 - Shock/hypoperfusion is the key underlying problem – fix it!

- In the massively transfused patient, ↓platelets and impaired platelet function are the most consistent significant haematological abnormalities. Factor deficiency is initially confined to factors V and VIII
- Issues:
 - Most important factor is a clearly defined and understood system by all stakeholders
 - Retrospectively acting on coag results is a problem. ?Potential for TEG
 - No RCTs in massive transfusion
- Management:
 - Baseline: FBC, Coags, biochemistry and ABG
 - Optimise: O₂, CO, tissue perfusion, metabolic state
 - Monitor (every 30 – 60 mins): FBC, Coags, Ca⁺, ABG
 - Aim for: temp > 35, pH > 7.2, base excess < -6, lactate < 4, Ca > 1.1, plts > 50, Pt/APPT < 1.5 * normal, INR ≤ 1.5, fibrinogen > 10
 - Control bleeding:
 - Early surgery (vs pre-op stabilisation)
 - Embolisation
 - First 'dose': 4 units rbc, 2 units FFP
 - FFP:RBC:Platelet:
 - Ratio of 1:1:1 is based on components derived from a single whole blood donation. One adult therapeutic dose (ATD) of platelets = 1 pooled unit = 4 – 6 single donor 'units' ⇒ **use ratio of 4:4:1**. Small studies and observational studies only. Large US RCT underway
 - Shaz et al, Transfusion 2010, Increased number of coagulation products in relationship to red blood cell products transfused improves mortality in trauma patients – plus other studies in blunt trauma, military, etc. Stronger evidence for more FFP than there is for more platelets
 - Research is only based on retrospective regression studies showing substantial ↓mortality from more plasma and platelets than previously (eg Holcomb et al, JAMA Surgery, 2013)
 - After each 2nd lot of 4:4:1 check coags, platelets, FBC, ABGs and Ca → additional treatment thresholds:
 - If PR > 1.5 or APTT > 40 consider additional 4 units FFP (15 ml/kg)
 - If fibrinogen < 1 g/L consider additional 3U cryoprecipitate
 - If platelets < 75 * 10⁹ consider one additional ATD of platelets
 - If ionized Ca < 1 mmol/L give 10 mls Calcium
 - Tranexamic acid. Loading dose 1 gm over 10 mins then 1 gm infusion over 8 hours. 1.5% ↓mortality in CRASH2 if given < 3 hours but very few were hypotensive.
 - Factor rVIIa:
 - See Recombinant Activated Factor 7a (rFVIIa), page 297
 - If on-going haemorrhage after 10U RBCs, after discussion with the gatekeeper (on call haematologist), and (ie correct other things first):
 - pH > 7.2
 - Platelets > 50
 - Fibrinogen > 1 g/L
 - Dose 90 mcg/kg rounded to vial
 - Prothrombin X: not licensed in trauma. Potential benefits but risk of clot. Not recommended. Trials in progress
- Special circumstances:
 - Warfarin: add vitamin K, prothrombin X/FFP
 - Obstetrics: early DIC often present, consider cryoprecipitate
 - Head injury: aim for plts > 100, permissive hypotension contra-indicated
- Complications:
 - Those of any transfusion: see Transfusion Reactions, page 302
 - Most recent guidelines: not recommended in trauma except in exceptional circumstances
 - Those of massive transfusion:
 - Over-transfusion: monitor Hb regularly
 - Under-transfusion
 - Volume overload
 - Coagulopathy: thrombocytopenia, factor depletion
 - Oxygen affinity increased
 - Hypocalcaemia 2nd to citrate toxicity. Usually metabolised by the Krebs' cycle in the liver. ↑citrate with transfusion exceeding 500 ml in 5 minutes. Metabolism impaired by hypotension, hypovolaemia, hypothermia and liver disease. A normal, warm, well perfused adult can tolerate a

unit over 5 mins without calcium. A controversial common practice is to give 1.0 gm 10% Ca gluconate following each 5 units of RBC or plasma.

- Acid-base disturbance: lactate, citrate. Initially acidosis. Once these are metabolised to bicarbonate in the liver then *alkalosis*
- Hyperkalaemia. Use younger blood. However, hypokalaemia may develop 24 hours later when RBCs correct from the acidosis that develops during storage (from citrate and lactate).
- Hypothermia. Blood warmed from 4 to 37°C requires 1255 kJ with an O₂ requirement of 62 l. Warm any rapid infusion of > 2 units. Warm patient and other fluids.
- ARDS
- Jaundice: due to haemolysis in storage
- Immune complications

Intravenous Immunoglobulin (IVIG)

- Has been used in most of the immune and inflammatory disorders in which plasma exchange has been used.
- Mechanisms of action include modulation of expression of Fc receptors, interference with activation of the complement system, effects on the activation, differentiation and effector functions of dendritic cells, T & B lymphocytes,.....
- Indications:
 - Treatment or prevention of infection in hypogammaglobulinaemia
 - Adjunct in fulminant sepsis syndrome, especially Strep A toxic shock syndrome
 - Autoimmune disorders (eg ITP, GBS, etc.)

Plasma Exchange

- Process:
 - Separation of plasma from blood cells by centrifugation (plasmapheresis) or membrane filtration (plasma-filter - a dialysis filter with a huge pore size that effectively filters out all plasma)
 - Re-infusion of cells plus autologous plasma or another replacement solution (eg albumin, crystalloid/colloid)
 - Dose: eg 2 exchanges on 3 days per week
- Removes large molecular weight molecules (filters down to 500 kDa):
 - Pathogenic auto-antibodies
 - Immune complexes
 - Cryoglobulins
 - Myeloma light chains
 - Cholesterol-containing lipoproteins/triglycerides
- Most evidence for ICU use is in (autoantibodies or immune complexes):
 - Guillian Barre Syndrome (albumin for 5 treatments then stop)
 - CIDP
 - Goodpastures Syndrome with pulmonary haemorrhage
 - TTP (FFP for on-going daily exchanges)
 - Post-transfusion Purpura
- Potentially Indicated in:
 - Immunoproliferative disorders with monoclonal antibodies:
 - Hyperviscosity Syndromes, eg Waldenstrom's macroglobulinaemia
 - Cryoglobulinaemia
 - Renal failure in multiple myeloma
 - Autoantibodies or immune complexes:
 - Myasthenic Crisis
 - Multiple sclerosis
 - HIV-related neuropathy
 - SLE
 - Pemphigus
 - Paraneoplastic syndromes
 - Rapidly progressive glomerulonephritis
 - Renal transplant rejection
 - Coagulation inhibitors
 - Auto-immune haemolytic anaemia
 - Conditions in which replacement of plasma may be beneficial +/- removal of toxins

- DIC
- MODS
- Overwhelming sepsis syndromes, eg meningococcaemia
- Removal of protein-bound or large molecular weight toxins:
 - Paraquat poisoning
 - Envenomation?
- Complications:
 - Hypotension due to excess fluid removal +/- inadequate volume replacement
 - Anaphylactic/transfusion reactions to fresh frozen plasma replacement solution, including paraesthesia, muscle cramps, allergic reactions
 - Citrate-induced hypocalcaemia
 - Coagulation abnormalities due to removal of clotting factors no replace when albumin replacement used
 - Removal of useful immunoglobulins and complement → theoretical immunodeficient state
 - Drug removal: especially drugs with high protein-binding and low Vd (eg cyclophosphamide and azathioprine)
 - Hypothermia

Haematological Pathology

Anaemia

- Common in ICU patients. Up to 99% become anaemic by the third day of their ICU stay
- Test reticulocytes: if index (standardised count) < 2.5% (or perhaps more practically < 1%) then:
 - Test red cell morphology:
 - Normocytic ⇒ hypoproliferative:
 - Marrow damage
 - Fe deficiency
 - ↓Stimulation: inflammation, renal disease
 - Micro or macrocytic ⇒ maturation disorder:
 - Fe deficiency
 - Thalassemia
 - Sideroblastic anaemia
 - Folate deficiency
 - B12 deficiency
 - Drug toxicity
 - Index > 2.5 ⇒ haemolysis/haemorrhage
- Sickle Cell Crisis:
 - PC: severe pain
 - Investigation: sickle cells on blood film, likely anaemia
 - Management:
 - Supportive care, including O2
 - Analgesia
 - Exclude possible precipitants
- G6PD deficiency:
 - → Heinz bodies (which indicate oxidative stress) and haemolysis (high reticulocyte count, high MCV, damaged red cells usually sequestered in the spleen rather than intravascular haemolysis) when precipitated by drugs such as primaquine, dapsone, methylene blue, broad beans (favism), infections, diabetic ketoacidosis
 - X-linked recessive hereditary disease → low levels of glucose-6-phosphate dehydrogenase, especially important in red cell metabolism for facilitating NADP → NADPH which mops up free radicals which otherwise cause oxidative stress
 - Mainly males who are symptomatic

Antiphospholipid Syndrome

- Coagulopathy
- Livedo Reticularis
- Obstetric complications
- Thrombocytopenia/Thrombosis

Thrombocytopenia

- Differential:
 - Artefact: clumping in collection tubes, dilution
 - Decreased production:
 - Marrow failure
 - Drugs: eg quinine, linezolid
 - Marrow infiltration (eg neoplastic)
 - Nutritional
 - Toxins
 - Non-immune mediated destruction/sequestration:
 - Sepsis
 - Splenomegaly
 - Drug-induced: NSAIDs, anti-epileptics
 - Immunological mediated destruction:
 - Heparin-induced thrombocytopenia (See page Heparin Induced Thrombocytopenia, page 308)
 - Thrombotic thrombocytopenia purpura (TTP):
 - Microangiopathic haemolytic anaemia, renal failure, fever, ↓↓ platelets, headache/seizures/fluctuating focal deficits (FAT RN: fever, anaemia, thrombocytopenia, renal failure, neurology)
 - Acquired antibody to ADAMTS13 which cleaves ultra-large vWF multimers → pathogenic platelet activation and aggregation → endothelial damage → microangiopathic haemolysis
 - Seen with certain infections, drugs (eg clopidogrel), pregnancy, SLE and graft vs host disease
 - Labs show ↓platelets, ↓Hb, ↑reticulocytes, ↓haptoglobin, ↑LDH, ↑unconjugated bilirubin, ↑Cr
 - Plasma exchange shows benefit in meta-analysis of 7 RCTs +/- immunosuppression. Daily plasma exchanges of 1.5 plasma volumes with FFP until remission (platelet count > 150). Some use cryodepleted FFP (less vWF and enough ADAMTS13) but no demonstrated advantage
 - Haemolytic Uraemic Syndrome: presentation as for TTP but *no neurology symptoms in HUS*. Recent E Coli infection O157:H17 → toxic damage to endothelium. ?Part of the same spectrum as TTP
 - ITP: chronic problem, less of an issue for ICU. Exclude HIV, Hep C, SLE, protein electrophoresis and do Combes test to exclude autoimmune haemolytic anaemia with ITP
 - Pregnancy related (HELLP): ↑uric acid, ↑urea/creatinine, proteinuria, microangiopathic haemolytic anaemia, ↑LFT, ↓platelets, normal coags
 - Consumptive:
 - DIC: Consumptive coagulopathy, micro-thrombi → ischaemia. PC: On-going bleeding, haemorrhage, bruising, epistaxis, bleeding round lines, ischaemic digits
 - Massive blood loss
 - Reduced platelet function in uraemia, post-cardiopulmonary bypass, antiplatelet drugs, beta-lactam antibiotics, corticosteroids, vasculitis, vitamin C deficiency, paraproteinaemias

Disseminated Intravascular Coagulation

- Aka consumption coagulopathy
- Acute (tends to lead to bleeding):
 - Triggered by exposure to large amounts of tissue factor
 - Leads to:
 - Wide intravascular fibrin deposition and platelet activation
 - Microangiopathic haemolytic anaemia
 - Haemorrhage: petechiae, wound oozing, GI or pulmonary haemorrhage
 - End organ damage, especially renal, liver
 - Raised unconjugated or conjugated ↑ bilirubin
 - Causes:
 - Haemorrhage → ↓coagulation factors
 - Infection: G-ive, anaerobes, viral (HIV, CMV)
 - Multi-trauma, burns
 - Toxin/snake bites
 - Transfusion reaction
 - Liver failure

- Extracorporeal circuit
- Heat stroke
- Malignancy, especially APML
- Obstetric causes:
 - Eclampsia
 - Amniotic fluid embolism
- Chronic: on-going release of tissue factor (eg solid tumours) → up-regulation of clotting factors → more thrombosis (a controversial indication for heparin). May also have arterial thrombosis (→digital ischaemia, renal infarction, stroke...)
- Laboratory tests:
 - Platelets < 100
 - Blood film consistent with intra-vascular haemolysis
 - Elevated D-dimer reflecting degradation of cross-linked fibrin (not specific)
 - Elevated INR (factors VII, X and V and prothrombin are the most frequently decreased), APPT is less sensitive to deficiencies of the components of the common pathway
 - Low fibrinogen (note should normally be raised in pregnancy, so normal may be low)
 - Other tests: specific assays for coagulation factors, prolonged thrombin time, ↓antithrombin, protein C and S
- Differential:
 - Severe liver disease: → ↓coagulation products and thrombocytopenia 2nd to hypersplenism
 - TTP-HUS – usually have ↓platelets and HAMA but normal levels of coagulation factors and little if any rise in INR/APPT. Important to differentiate – TTP is treated with plasma exchange
 - HITS
- Treatment:
 - Correct underlying cause
 - Product replacement if high risk for bleeding, and/or heparin (controversial). No controlled studies showing benefit

Heparin Induced Thrombocytopenia

- 5 – 10 days into exposure, unusual for platelets to drop below 20, marked ↑ risk of thrombosis
- Type 1: Non-immune mediated more common, earlier onset, not associated with thrombosis, caused by a direct heparin reaction with the platelet membrane → platelet aggregation and a small drop in platelets
- Type 2:
 - Due to an antibody to Heparin-PF4 (on platelet) complex → activates platelets. Only a fraction with the antibody develop thrombocytopenia (ie test not specific)
 - 10 times more common with heparin than LMWH
 - Pre-test probability assessed from 4 T's:
 - Thrombocytopenia > 50% drop in platelet count
 - Timing: 5 – 10 days from starting heparin
 - Thrombosis: new thrombosis or skin necrosis
 - No other cause
- Clinical diagnosis (test takes too long and isn't specific enough):
 - Repeat test ?lab error
 - Consider differentials of ↓platelets: sepsis, other drugs (eg vancomycin, ranitidine, trimethoprim)
 - Investigations: blood cultures/septic screen, ELISA for heparin-PF4 antibodies, serotonin release assay if ELISA is positive
 - Clinical examination and imaging to assess for burden of thromboembolic disease
- Management:
 - Stop heparin
 - Switch to: Fondaparinux, Direct thrombin inhibitors (eg bivalirudin, lepirudin, and argatroban) and danaparoid (heparinoid) have all been used. No head to head trials between classes.
 - Bivalirudin: short half-life, quick onset, doesn't bind to anything other than thrombin ⇒ good pharmacokinetics
 - For anticoagulation while on CRRT, see Anticoagulation, page 197

Thrombocytosis

- Differential:
 - Primary: essential, thrombocytopenia, myeloproliferative diseases
 - Reactive: inflammatory disease (eg RA), bleeding, post-splenectomy

Stem Cell Transplant

- See Transplant Hot Case, page 373
- Most transplants are now of GCSF stimulated peripheral blood stem cells – shorter period of profound neutropenia than BMT
- 3 basic groups presenting to ICU:
 - Acute leukaemia with complications of chemotherapy (ie not a transplant)
 - Allogenic transplants
 - Autologous transplants – predictable recovery at day 14 to a more normal immune system than allogenic transplants
- If a neutropenic person has a fever, they have an infection, and MUST be treated. Even if they look well...

Predictors of Mortality

- Overall mortality = disease risk + transplant risk. The major risk is relapse of the underlying malignancy. Prognosis of haematology malignancy varies dramatically on the underlying malignancy
- 20% of allogenic transplants die from transplant complications – GVHD the biggest. Worse prognosis if previous lung dysfunction/pathology
- ICU intubation post BMT carries a 42%, 64%, 69% and 76% ICU, hospital 6 and 12 month mortality – an improvement over the last decade (Agarwal IMJ 2012)
- Dying in ICU independently associated with:
 - Fungal infection
 - Early onset of organ failure
 - GVHD is protective

Conditioning regime

- Aim: kill tumour and suppress immune system to permit engraftment
- Usually high dose cyclophosphamide + total body irradiation
- Early complications:
 - From 2 days after chemo (7 days before transplant) to ~ day 30 post-transplant
 - Oral/gut mucositis: universal with myeloablative conditioning, resolves with engraftment
 - Hair loss
 - Profound neutropenia/bone marrow failure
 - Cardiomyopathy: especially if prior EF < 40%, ↓ with reduced intensity transplants, monitor proBNP
 - Renal impairment 2nd to nephrotoxic drugs: cyclosporin, gentamicin, vancomycin
 - Haemorrhagic cystitis. Prevent with hyperhydration and mesna (binds acrolein)
 - Pulmonary: diffuse alveolar haemorrhage (due to damage to endothelial lining, treat with methylprednisolone +/- factor VIIa, mortality 75%), idiopathic pneumonia syndrome (TNFα blockers effective, 75% mortality)
 - Veno-occlusive disease of the liver: aka Sinusoidal Obstruction Syndrome (SOS). In 10% peaking at 16 days (2nd to endothelial injury from conditioning regime, compounded by pre-existing liver disease). Can occur later. PC: oedema/ascites, enlarged tender liver, ↑bilirubin (200 – 300). Diagnosis: Ultrasound. Biopsy gold standard but 5% mortality from trans-jugular biopsy. Treatment: TIPS, diuretics. No benefit from thrombolytic or antithrombotic agents in trials. Restrict salt/water intake, diuretics but maintain intra-vascular volume, Defibronate (response in 36 – 50%)
- Late complications: Cataracts, obstructive/restrictive lung disease, osteoporosis, gonadal failure, thyroid dysfunction, aseptic necrosis of the femoral head (main risk is steroid use), 2nd malignancies (Acute leukaemia, MDS, Post-transplant lymphomas, solid tumours)

Engraftment Syndrome

- Approximately 10% of SCTs
- Develops within 72 hours of the start of neutrophil recovery, high fevers (without infection), *skin rash* affecting > 25% of the body, lung infiltrates, liver, kidney or CNS dysfunction
- Probably 2ndary to massive release of pro-inflammatory cytokines
- More common in autologous SCT (possibly because it's difficult to distinguish from GVHD in allograft patients).
- Usually very sensitive to a short course of methylprednisolone with rapid taper – may see an improvement over 12 hours

Graft Versus Host Disease

- Inversely proportional to relapse

- Delays immune reconstitution – despite the graft apparently being “up and running” – significant immune dysregulation will exist
- Acute (first 3 months but can be later):
 - Skin, gut, liver (rash, green and watery diarrhoea, ↑cholestatic LFTs + bilirubin)
 - In 75% of patients, 10 – 15% Grade III-IV
 - Mimics other problems – may need biopsy to confirm
 - Prevention: immunosuppression early after transplant (methotrexate and either cyclosporine or tacrolimus, plus prednisone)
 - Treatment: steroids, anti-thymocyte globulin, anti-T monoclonal antibodies
- Chronic (later than 6 months) in 50%:
 - Like autoimmune disease: malar rash, sicca symptoms, arthritis, BOOP, bile duct degeneration
 - Usually resolves over several years
 - Treatment: single agent prednisone or cyclosporin

Graft Failure

- Approximately 5%
- No engraftment by “day 42” (worry from day 25)
- Associated with CMV, herpes virus 6, or rejection by immunocompetent host cells
- 2nd transplant or palliate

Infection following Bone Marrow Transplant

- Old immune system is destroyed, new immune system introduced, with stepwise maturation (called immune reconstitution). GVHD delays immune reconstitution
- Typical post-transplant drug chart: cyclosporin, acyclovir, fluconazole, Intragam, Ganciclovir, cotrimoxazole (very effective for PCP prophylaxis – if they’ve been taking it it’s most unlikely they’ve got PCP)
- Prophylaxis usual with neutrophils < 500: ABs and antifungals. Acyclovir if HSV seropositive
- Phases of infection:
 - Pre-engraftment (aplastic phase):
 - Aplastic Phase: (1 – 4 weeks): G+ive and G –ive bacteria, viruses (including HSV, respiratory), fungi (aspergillus, candida)
 - Often gut and mucosal related as chemo has damaged this → portal of entry
 - Neutropenic sepsis treatment: generally Tazocin 4.5 gm TDS + gentamicin
 - Post-engraftment till ~ 12 weeks:
 - Basic innate immunity back on-line – but can’t cope with encapsulated bacteria or sophisticated viruses. T & B cell numbers low + immunosuppressive medication
 - Deficiency of cell-mediated immune deficiency till granulocytes, monocytes, macrophages and NK cells reconstitute
 - CMV (ganciclovir prophylaxis – see below), BK virus, toxoplasma Gondii
 - Last risk period (12 – 52 weeks):
 - T and B lymphocytes remain severely reduced for months to years → immunoglobulin deficiency
 - VZV, encapsulated bacteria (due to ↓IgG resulting in a situation like asplenic. Strep pneumoniae - vaccinate, haemophilus, Neisseria meningitidis)
 - Late haemorrhage cystitis (compared to early 2nd to cyclosporin) may be due to viral reactivation (BK, JC, occasionally adenovirus, rarely CMV). ↑incidence of late CMV disease, especially in reduced intensity transplantation
- At any stage: PJP (cotrimoxazole prophylaxis common), adenovirus, HHV-6, EBV, nocardia, legionella, mycobacterium spp, listeria
- Cell mediated immune compromise lingers – takes up to ~ 1 year for B cells and ~ 2 years for T cells. Significant GVHD will delay this process
- CMV:
 - Prior to ganciclovir CMV mortality was ~ 25%
 - Target organs:
 - Early: lungs, GIT tract, liver
 - Late: retinitis
 - Prevention: all blood products now leucodepleted (don’t need to ask for this). If profoundly neutropenic then foscarnet (but renal toxicity and electrolyte disturbances)
 - Weekly PCR is sensitive at detecting very early reactivation, allowing pre-emptive treatment
 - Prophylaxis in high risk patients with ganciclovir (mismatched transplants, high doses of steroids, GVHD – due to its treatment with ↑immunosuppression. SE myelosuppression)

- Invasive fungal infections:
 - At highest risk in GVHD and early in leukaemia treatment. Correlates with duration of neutropenia
 - Yeasts eg candida invading through the GI tract (mucositis a major risk) → hepatosplenic candidiasis
 - Moulds eg aspergillus invading through lungs → haematogenous spread eg to CNS. Nodules with halo or air crescent on lung CT. NOT covered by fluconazole
 - Difficult to diagnose:
 - Histology or culture definitive from a sterile site
 - Often “probably” infection based on radiology and labs. Galactomannan (false test with tazocin), CXR or HRCT Chest supportive.
 - Cryptococcal antigen is a definitive diagnosis

Pulmonary Syndromes Post Allograft

- Diagnostically difficult. All present with breathlessness, tachypnoea, dry cough and fever. All look like infection. Most will have had a bacteraemia at some stage
- Diffuse Alveolar Haemorrhage (see page 109). Usually in the first 30 days. Focal or diffuse change. Haemoptysis is rare. Bloodier and bloodier aspirates as you wash with BAL may be a clue. Treatment: high dose steroids (low level evidence). 75% mortality
- Engraftment Syndrome (see page 309)
- Idiopathic pneumonitis:
 - ?2nd to conditioning toxicity and inflammatory cytokines around engraftment. But no rash and less fluid retention (measure weight)
 - Mortality ~ 90%
 - Steroids generally not effective. TNF α blockers can have dramatic effects – but high risk of infection later (eg S Aureus) so overall impact on mortality unclear

Immunosuppression

- See also RACP Notes, Kidney Transplants, pg 120
- Aim: protect transplant but still permit immune function to prevent infection
- Macrophages present antigen on MHC2 receptor to T cell receptor
- Pharmacological options:
 - Stop T cell activation. Calcineurin inhibitors cyclosporine and tacrolimus:
 - Introduction lead to significant ↑length of survival after transplant
 - Both have narrow therapeutic ranges
 - Lots of interactions given CYP metabolism (eg with azoles)
 - Toxicity including nephrotoxicity (arteriolar vasoconstriction, thrombotic microangiopathy, chronic fibrosis)
 - Block DNA replication of cytokines in activated cells: Purine synthesis inhibitors
 - Stop clonal expansion of activated cells
 - Azathioprine: GI side effects
 - Mycophenolate: expensive
 - No evidence of benefit of one over the other
 - Monitor – want lymphocytes < 1 but normal total WBC
 - Steroids:
 - Down regulate expression of self-molecules on graft → ↓cytokines
 - For solid organs reduce over time but usually lifelong low dose
 - MABs:
 - Basiliximab – IL2 antagonists, induction immunosuppression. Kind on kidneys
 - Rituximab – for antibody mediated rejection

- See also Electrolytes, page 70

Myasthenia Gravis

- Key questions on history:
 - Usual medications (including steroids)
 - Had a thymectomy (a treatment option if not done previously)
 - Previous complications
- Anaesthetic issues:
 - Consider an epidural (avoid analgesia causing respiratory depression)
 - Keep intubated. May be breathing OK but may have little respiratory reserve
- Options in ICU to improve strength:
 - Neostigmine infusion
 - Plasmaphoresis
 - Early Nutrition (but limit CHO)
 - Tensilon test: give edrophonium – can determine whether weakness is due to under or over treatment with ACh inhibitors. If weakness worsens, then it's due to over treatment and edrophonium will wear off soon
- Drugs exacerbating MG:
 - Aminoglycosides
 - Mg
 - Iodinated contrast
 - NM blockers
 - Opioids
 - CV drugs: β -blockers, Ca channel blockers

Phaeochromocytoma

- Tests:
 - HMMA in 24 hr urine as screening test
 - Plasma metanephrines
 - CT with contrast
 - MRI T2 most sensitive
 - PET
- Treatment:
 - SNP/GTN for hypertensive crisis
 - Start alpha blockade with IV phentolamine if needed, then oral phenoxybenzamine
 - Once established, add β -blocker
 - Ca channel blocker for AF rate control
 - Some recommend Mg infusion
 - Screen for myocardial damage: ECG, echo

Adrenal Insufficiency

- Causes:
 - Primary (diseases of the adrenal gland):
 - Autoimmune
 - Haemorrhage (eg sepsis, anticoagulants)
 - Emboli
 - Sepsis
 - Adrenal vein thrombosis
 - Secondary (pituitary destruction):
 - Tumour, cellular inflammation
 - Infection
 - Head trauma
 - Infarction
 - Tertiary:
 - Abrupt cessation of high dose steroids

- Hypothalamic damage (tumour, infiltration, radiation)
- Consequences:
 - Shock
 - Abdo tenderness, myalgias, nausea, volume depletion, fever, confusion
 - Physiological changes: ↓Na, ↑K, normal anion gap metabolic acidosis, ↓glucose (due to ↓gluconeogenesis), ↑Ca
- Management:
 - Hydrocortisone 100 mg or dexamethasone 4 mg (interferes least with cortisol assay)
 - Rehydration and electrolyte management
 - Treatment of underlying causes, including sepsis
- Diagnosis and treatment of stress induced functional adrenal insufficiency is controversial: see Corticosteroids in Septic Shock, page 54

Thyroid

Sick Euthyroid/Non-thyroidal Illness Syndrome (NTIS)

- Low serum total T3 – down to 40% of normal. Caused by a reduced peripheral conversion of T4 to T3 secondary to inhibition of type 1 5'-deiodinase
- Free T3 is also reduced – but less so
- Reverse T3 (rT3) is increased
- Serum T4 and TSH may transiently rise then return to normal
- Amiodarone, propranolol and glucocorticoids all inhibit peripheral conversion of T4 to T3

Thyrotoxic Crisis

- 3 pronged approach....
- Halt synthesis:
 - Thionamides: propylthiouracil
 - Imidazoles: Carbimazole
 - Both block the formation of T4 and T3
- Prevent release of stored hormone: Separate treatment to inhibit proteolysis of colloid and continuing release of T3 and T4. Inorganic iodine therapy (Lugol solution or potassium iodide). Only used 30 – 60 mins after thionamides as hormone synthesis may be stimulated
- Blockade of peripheral effects (including blocking conversion of T4 to T3 as well as control of adrenergic symptoms): β-blockade, eg propranolol (also decreases T4 to T3 conversion). Glucocorticoids also block conversion of T4 to T3

Diabetes

Stress-Induced Hyperglycaemia (SIH)

- Transient hyperglycaemia during acute illness returning to normal after discharge, with no evidence of prior diabetes
- Different process and different outcomes from diabetic hyperglycaemia
- Due to:
 - Complex interplay of counter-regulatory hormones: catecholamines, GH, cortisol, cytokines
 - Insulin resistance 2ndary to SIRS
 - Underlying illness
 - Treatments: TPN, enteral feed, steroids, vasopressors, adrenaline
- Main contributor appears to be high hepatic gluconeogenesis driven by glucagon, adrenaline and cortisol
- Clinical implications: Some studies: ↑mortality, adverse effects and organ failure compared to those with diabetes. Unknown whether SIH is the cause or just a marker for badness.
- Treatment:
 - Can't be distinguished from hyperglycaemia due to other causes
 - Generally not predictable or preventable
 - Insulin therapy

Intensive Insulin Control

- Background:
 - Increased mortality has been found in patients with ↑glucose in TBI, sepsis, haematological malignancy, CHF or shock post AMI (is this a cause or marker of severity?)

- Glucose is controlled to prevent:
 - Hypoglycaemia → arrhythmias, cardiac events, neurological deficits
 - Hyperglycaemia (2nd to ↑cortisol, adrenaline, noradrenaline, glucagon, immobilisation) → can impair immune response, ↑endothelial apoptosis and mitochondrial dysfunction
- Traditional goals were 10 – 15 mmol/L, but no prospective trials till the last 15 years. Main intention was to prevent osmotic diuresis and hypovolaemia
- Much of the focus has been in two main groups: MI in diabetics and in the surgical ICU
- DIGAMI study (Malmberg, JACC 1995) showed an insulin infusion then bolus regime targeting BSL < 9.1 (vs control) → ↓one year mortality in diabetic patients with AMI
- NEJM 2001, Van den Berge: single centre surgical ICU in Belgium, with many cardiac patients. Compared targets of 4.4 – 6.1 with 10 – 11.1 in 1548 ventilated patients. Unblinded. Very high glucose loads. Stopped early for benefit. Intensive insulin control → ↓ICU mortality from 8 to 4.6% (pretty implausible for a single intervention...), ↓infections, ↓dialysis, ↓transfusions. Of note patients with diabetes didn't benefit from tight control. High baseline mortality due to ?overfeeding in the first 24 hours. Incorporated into surviving sepsis guidelines
- Subsequent confirmatory trials not so convincing:
 - NEJM 2006: Van den Berge, 1200 medical ICU patients → ↓LOS but not change in mortality
 - Also VISEP and Glucontrol Studies (both European) multicentre RCTs stopped early due to harm from tight control (which → ↑ rate of severe hypoglycaemia)
 - Subsequent meta-analysis showed no benefit
 - Not adopted in Australia and NZ: high baseline mortality in Van den Berge's study. Unusual nutrition regime in the trials (more TPN, more calories ⇒ so needed more insulin)
- NEJM 2009: NICE-SUGAR trial and associated editorial (Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation), 6104 patients, multi-centre, unblinded, enrolled if expected ICU stay > 3 days, comparing target of 4.5 – 6 with 8 – 10. Tight glucose had higher mortality (27.5% vs 24.0%, NNH 38) and more episodes of severe hypoglycaemia (6.5% vs 0.5%, but lower rates of hypoglycaemia than previous trials). Did not differ between surgical and medical patients. No difference in LOS or days off ventilation
- MRCT in 2,684 French patients of tight computerised glucose control (4.4 – 6.1 mmol/L) with < 10 mmol/L. No difference in 90 day mortality. Severe hypos 13.2 % vs 6.4% (Kalfon, ICM 2014)
- Van den Bergh 2012: 4 year follow-up of children. Showed no correlation between hypos and neuro cognitive development and higher IQ for tight glucose control
- Summary:
 - One single centre trial showed benefit from tight insulin control in a broad cohort of surgical ICU patients, this has not been confirmed in 3 subsequent multi-centre RCTs
 - Both the incidence of hypoglycaemia and ↑blood glucose variability are associated with mortality
 - Optimal glucose targets remain unclear – despite extensive evidence. Preventing even mild hypoglycaemia should be a prominent goal
 - Point of care systems have a threshold for measurement error of 20% (too much for tight control) and don't account for haematocrit, tissue oedema in finger pricks, or ↓sats – all of which may compound error in critical illness
 - The place of continuous glucose control is unclear (a number of monitors in the pipeline)– potential to enable tighter control without hypoglycaemia
 - Patients with pre-existing diabetes may benefit from a higher target as they have a lower association between hyperglycaemia and mortality

Hypoglycaemia

- Causes:
 - Drugs: insulin, oral hypoglycaemics, quinine, β-blockers
 - Addison's
 - Liver disease
 - Infection + malaria
 - Starvation
 - Alcohol
 - Hypothyroidism
 - Insulin secreting tumours
- 50 mls of 50% glucose. Glucagon an out of hospital alternative, but is slower

Diabetic Ketoacidosis

- Disposition: to ICU if

- Cardiovascular instability
- Inability to protect the airway
- Altered sensoria
- Acute abdominal signs suggestive of acute gastric dilatation
- Resuscitation:
 - IV fluids: 500 – 1000 ml stat then reassess
 - ABG to guide fluid therapy
 - Maintenance fluids: N saline till BSL < 15 then 5% dextrose (with sodium targeting 140 – 150)
- Monitoring/investigations:
 - Bloods
 - Urine
 - Blood gas: raised AG acidosis
 - Ketones in blood and urine
 - NB: Ketones interfere with the Cr assay
- Insulin:
 - Infusion 0.01 – 0.1 units/kg/hr
 - Titrate to decrease BSL 1 – 2 mmol/hr
 - Continue till metabolic disturbance is corrected (acidaemia and ketosis) rather than correction of BSL). Dextrose infusion if BSL drops below the normal range
- Electrolytes:
 - K replacement when K < 5 mmol/l as insulin and improved pH will lead to a precipitous fall → arrhythmias
 - Na: need to correct for high glucose (add 1 Na for every 3 glucose). Enables you to predict where Na is likely to go when glucose is corrected. Use measured Na to calculate anion gap. The measured value is actually what is there. See Hyponatraemia, page 70
 - PO₄ and Mg are likely to need replacement
 - HCO₃ – almost no indications. See Bicarbonate for Treatment of a Metabolic Acidosis, page 66
- Identify and treat precipitant:
 - Non-compliance/psychosocial issues
 - Infections
 - Ischaemia: AMI, PVD, mesenteric
 - Pregnancy
- Major acute complications:
 - Cerebral oedema:
 - Attempt to avoid by slow normalisation of osmolarity and hydration over 36 – 48 hours – especially in de-novo ketoacidosis
 - Monitor for headache, recurrence of vomiting, GCS, inappropriate bradycardia and hypotension
 - Treat with mannitol or hypertonic saline
 - Cardiac dysrhythmias: usually secondary to K disturbance
 - Pulmonary oedema: limited by appropriate fluid replacement
 - Acute renal failure: uncommon because of high osmotic urine flow

HONK

- = Hyperosmotic non-ketotic state
- = hyperosmolar hyperglycaemia syndrome (HHS)
- Dominant feature is hyperosmolarity (>320 mosmol/kg). May present with obtundation or focal neurology
- Differences compared with DKA:
 - Higher glucose
 - Acidosis less severe
 - No anion gap acidosis (although HHS may → lactic acidosis)
 - Ketones high in DKA, low or absent in HHS (sufficient basal insulin to prevent ketogenesis)
 - Dehydration usually worse than DKA due to longer onset
- Causes:
 - Typically the elderly with NIDDM
 - Without diabetes in severe burns, TPN, dialysis
 - Risk increased with diuretics, steroids, β-blockers, phenytoin
 - Lithium can cause a DI induced HHS
- Complications:
 - Cerebral oedema
 - Vascular thrombosis

- Electrolyte derangements: ↓K, ↑Na
- Intercurrent events: sepsis, aspiration, MI
- Hypotension due to volume depletion
- Death
- Management:
 - Aim to correct hyperosmolality at < 3 mosmol/hr
 - Calculate corrected Na (see Diabetic Ketoacidosis, page 314)
 - Water deficit = $(0.6 * \text{premorbid weight}) * (1 - 140/\text{Corrected Na})$
 - Give 50% over first 24 hours as $\frac{1}{2}$ **N saline**. Avoid Na drop by > 10 mmol/L/day. If sodium low use 0.9% saline
 - Start D5W 1ml/kg/hr
 - Start insulin 0.05 - 0.1u/kg/hr, aiming for steady slow reduction in blood sugar levels (eg 5 mmol/hr)
 - Once glucose < 15 start D5W 1-2 ml/kg/hr and give remainder of fluids as N Saline by the end of day 2
 - Aggressively treat low K, Mg, Ca, Phos (if < 0.3). 20 – 30 mmol K⁺ in each litre of fluid, aiming for K 4 – 5 mmol/L
 - Treat underlying disorder: sepsis, MI, other
 - Thromboprophylaxis

- See also:
 - Trauma in Pregnancy, page 233
 - Brain Death in Pregnancy, page 362
- Generally a lack of randomised trials for the treatment of obstetric emergencies
- Scoring systems generally work when the primary problem is medical, but generally over-estimate mortality of obstetric problems (mainly because of abnormal physiological variables that are normal in pregnancy)
- General Considerations in an Obstetric Emergency
 - Involve Obstetrics
 - Potential conflict between the well-being of the baby and mother
 - Need for regular fetal monitoring
 - ↑patient and family anxiety
- Failure to recognise the severity of illness on the ward or manage it appropriately until ICU transfer features commonly in the UK Maternal Death reports
- In general, what is good for the mother is good for the baby (including xrays!)

Normal Values in Late Pregnancy

- Persist to up to 6 weeks post-partum
- Respiratory:
 - Fully compensated respiratory alkalosis:

pH	7.4 – 7.45
PaO ₂	~ 105
PaCO ₂	< 30 (ie a “normal” CO ₂ in a pregnant mother is abnormally high)
HCO ₃	18 - 20
 - Upper respiratory tract oedema and capillary engorgement (→ difficult intubation, further risk from delayed gastric emptying)
 - ↑ minute volume, TV (+40%), RR (+10%) [makes ↓TV management of ARDS problematic]
 - ↑VO₂ by 20% (hypoxia and hypercarbia develop rapidly with airway obstruction, apnoea, etc.)
 - ↓FRC, RV, TLC
 - Susceptible to atelectasis
- Haematological:
 - ↑blood, plasma and red cell volume, from 6 weeks, maximal at 28 – 32 weeks (tolerate blood loss better)
 - ↓Hb due to relative haemodilution
 - ↓Albumin concentration by 5 g/l (→ a contributor to ↑risk of pulmonary oedema 2nd to ↓oncotic pressure)
 - Hypercoagulable
- Cardiovascular:
 - ↑cardiac output, 33% by 10 weeks, to 40 – 50% by 28 to 32 weeks
 - ↑Pulse by 15%, ↑SV by 30%
 - ↓SBP by 5, ↓MAP by 5, ↓DBP by 10 due to low SVR
 - Cardiac hypertrophy with ↑wall thickness and chamber volume
 - Left axis deviation, horizontal heart
 - Aortocaval syndrome: supine hypotension

Haemorrhagic Complications of Delivery

- Blood loss often under-estimated. Haemodilution from too much crystalloid worsens haemorrhage
- Accounts for 25% of maternal deaths (higher proportion in the 3rd world)
- Causes:
 - Pre-delivery:
 - Praevia – placenta implants in advance of the presenting part of the fetus → painless bleeding during the 2nd or 3rd trimester
 - Abruptio – normal placement but early separation. High perinatal mortality
 - Post-delivery:
 - Placenta accreta: needs good planning

- Uterine atony
- Lacerations
- DIC (partly because tissue thromboplastin is released during abruption)
- Treatment:
 - Pharmacological:
 - Oxytocics +/- misoprostol
 - Tranexamic acid
 - Blood products including FFP and cryoprecipitate using massive transfusion protocol
 - rVIIa has been used but place unclear
 - Mechanical:
 - Bimanual compression of the uterus
 - Tamponade with gauze packs or intra-uterine balloon tamponade
 - Surgical:
 - Deliver placenta
 - Stitch tears
 - Uterine artery embolisation/hysterectomy. Case series supporting benefit of angiographic arterial embolisation for severe postpartum haemorrhage, is fertility sparing. Has been used pre-emptively in women with very high risk (eg placenta accreta)
- Causes of coagulopathy post-partum:
 - DIC
 - Amniotic fluid embolism
 - Sepsis
 - Intra-uterine fetal death
 - Mismatched/massive transfusion

Hypertensive Complications of Pregnancy

- Overlap between pre-existing hypertension, pre-eclampsia, and non-proteinuric gestational hypertension
- Other differentials:
 - HUS/TTP causing haemolysis. (See Thrombocytopenia, page 307). Treatment of HUS/TTP:
 - Deliver baby
 - ?FFP for treatment of haemolysis
 - Plasma exchange
 - Corticosteroids
 - ?Rituximab
 - Cocaine toxicity: chest pain, CV compromise, placental abruption, cerebral haemorrhage, seizure
- Nifedipine, labetalol, prazosin, alpha-methyldopa and hydralazine all proven to ↓ BP in pregnancy

Eclampsia

- Cause unclear: inadequate endovascular invasion of fetal trophoblast → fetal hypoxia → diffuse inflammatory response with endothelial dysfunction → vasoconstriction, fluid extravasation, ↓organ perfusion
- Investigations include urinalysis and renal ultrasound
- Pre-eclampsia:
 - New onset of hypertension (SBP > 140, severe > 160 or DBP > 90, severe > 110) or and proteinuria (> 300 mg protein in a 24 hour collection) after 20 weeks
 - Oedema and hyperreflexia typically also occur
 - Mg prophylaxis is controversial, as most with pre-eclampsia do not progress to eclampsia. MAGPIE study, Lancet 2002, Altman et al, Magnesium sulphate (4 g loading dose then 1 g/hr iv) in 10,141 women with pre-eclampsia → significant reduction in eclampsia, non-significant ↓maternal mortality, no change in infant mortality, few side effects – most common was maternal flushing
 - Resolves over days following delivery. If it persists it's at least compounded by another hypertensive disorder
- Magnesium in severe pre-eclampsia:
 - IV: Loading dose 4 – 6 g over 20 mins, maintenance infusion 1 - 2 g/h (MAGPIE Trial, 10,000 patients, 2001). Most benefit was in income poor countries. The downside is the patient is in ICU separated from baby for modest overall benefit
 - Alternative: Intramuscular: 4 g every 4 h
 - Renal excretion, half-life 4 hours with normal renal function
 - Target serum 2 – 3.5 mmol/l

- Toxicity: muscle weakness, respiratory paralysis at > 7.5 mmol/l, \uparrow conduction time (\rightarrow heart block), arrest > 12.5 . Toxicity unlikely if deep tendon reflexes are present
- Differential of a seizure in late pregnancy:
 - Eclampsia
 - Epilepsy
 - Intra-cerebral event: haemorrhage, infection, space occupying lesion
 - Metabolic: hypoglycaemia, hyponatraemia, hepatic encephalopathy
 - Hypertensive encephalopathy
 - Cerebral vasculitis
 - Drugs: amphetamines, cocaine
 - Reversible Posterior Leukoencephalopathy Syndrome: see Other Pregnancy specific conditions, page 321
- Seizure management due to eclampsia:
 - Priorities: airway, oxygenation, termination and prevention of seizures
 - 30% of seizures are post-partum (eg at home 2 days later)
 - Patent airway
 - O₂ via rebreather
 - Left lateral tilt
 - Terminate seizure:
 - MgSO₄ bolus or (Mg 4 g IV over 20 mins) followed by infusion. Shown to be more effective than phenytoin or diazepam in treating recurrent seizures
 - Add diazepam (5 – 10 mg) if recurrent seizures despite MgSO₄
 - Manage hypertension:
 - Labetalol:
 - Bolus 20 – 40 mg IV every 10 – 15 mins to a maximum of 220mg
 - Infusion ix 100 mg in 20 mg (5 mg/ml). Load 10 – 20 mg (2 – 4 ml) over 2 mins, maintenance 20 – 160 mg/hr
 - Nifedipine: 10 mg orally repeated after 30 mins as required
 - Hydralazine: bolus 5 mg IV followed by 5 – 10 mg every 20 min to maximum of 40 mg, action over 10 – 20 minutes and duration of 6 - 8 hours. Third line – problem of tachycardia and not a brilliant antihypertensive
 - Increasing trend to use of other mainstream agents in late pregnancy
 - Brief period of resuscitation then plan for urgent delivery
- Other management:
 - Prophylactic betamethasone or dexamethasone if < 34 weeks and delivery anticipated
 - SNP (initial dose 0.25 μ g/min maximum dose 5 μ g/min for max 4 hours)/GTN (initially dose 5 μ g/min, max 100 μ g/min) if intravenous agent required for hypertensive crisis
 - Oral antihypertensives: hydralazine, β -blockers
 - Should also give fluids as likely to be intravascularly dry – but risk of pulmonary oedema (leaky capillaries + \downarrow albumin, greatest risk is post-delivery)
 - Post-partum: continue anticonvulsants until fall in BP and diuresis

Liver Dysfunction In Pregnancy

- See also Acute Liver Failure, page 173
- Generally 3rd trimester
- ALP normally rises 2 – 4 fold (produced in placenta)
- Acute Fatty Liver Of Pregnancy (AFLP):
 - Rare. Potentially lethal
 - Vomiting, abdo pain, \uparrow bilirubin, \downarrow glucose, DIC (check for haemolysis – reticulocyte count, haptoglobins, bilirubin)
 - Correct DIC
 - Supportive therapy
 - Monitoring and treatment of complications eg pancreatitis
 - Consider liver transplantation if irreversible liver failure despite delivery and aggressive supportive care
- HELLP Syndrome:
 - **H**aemolysis, **e**levated liver enzymes and **l**ow **p**latelets (which may worsen for 24 – 48 hours post-delivery). Haemolysis may not be evident initially. Rate of fall of Hb is important
 - High risk form of pre-eclampsia with more pronounced hepatic rather than cerebral or renal involvement

- Presentation: acute RUQ or epigastric pain, nausea, headache. Requires careful history to distinguish from reflux which is common
- Differentiate from TTP/HUS by prolonged thrombin time in HELLP.
- Treat with delivery and plasma exchange with FFP (described in delayed recovery of HELLP after delivery)
- High dose steroids: helps normalise platelets numbers and liver function, no difference in serious morbidity found. Controversial
- Supportive care following in HDU, monitoring for complications:
 - Hepatic haemorrhage/rupture – may be managed conservatively
 - Progressive renal failure
 - Pulmonary oedema
- Pre-eclampsia with hepatic involvement
- Possible, but generally not causing severe hepatic failure:
 - Intra-hepatic cholestasis of pregnancy. Presents with pruritus with rash and nausea from week 37
 - Viral hepatitis: commonest cause of jaundice in pregnancy. May occur at any time. Expect ALT and AST to be > 500 – 1000.
 - DIC is rare
- Investigations:
 - Full liver function tests
 - Micro: blood culture, urine, vaginal swab for MC&S
 - Urine: protein, WBC, RBC, casts
 - Haemolysis screen:
 - Peripheral blood film smear: evidence of haemolysis (micro-angiopathic haemolytic anaemia)
 - Reticulocytes, haptoglobins, conjugated/unconjugated bilirubin

Respiratory Problems in Pregnancy/Labour

- Differential of sudden respiratory distress:
 - PE. Leading cause of maternal mortality. Thrombolysis previously considered contraindicated and would not be able to be trialled, but case reports suggest a 1% maternal mortality and 6% fetal mortality (lower than surgical embolectomy)
 - Pneumothorax
 - Amniotic fluid embolism:
 - Rare, unpredictable, unpreventable
 - Uncertain pathophysiology: amniotic fluid enters maternal circulation through endocervical or uterine lacerations or site of placental separation. More in keeping with anaphylaxis than obstruction
 - Leads to severe hypoxia and pulmonary hypertension 2nd to pulmonary vasoconstriction → L ventricular failure. DIC common (key to differentiating from other causes of respiratory distress)
 - 25 – 50% with suspected or proven cases die in the first hour. Overall maternal mortality of up to over 80% (with neurological sequelae common if they survive), and neonatal mortality of 40% with neurological problems in many surviving neonates
 - Treatment: supportive + urgent delivery (presumed to prevent further embolism)
 - Air embolism
 - Pulmonary oedema 2nd to:
 - Pre-eclampsia
 - Tocolytics (rapid improvement with O₂ and diuretics)
 - Acid Aspiration: Mendelson's Syndrome. Due to ↓gastric emptying, ↑acidity and ↑abdominal pressure. Initially hypoxaemia and bronchospasm → pneumonitis and pulmonary oedema over hours. BAL and steroids not helpful. Antibiotics only for proven infection
 - Anaphylaxis
 - Uterine rupture/haemorrhage
 - Transfusion related complications (TACO, TRALI)
 - Cardiac causes: see Heart Disease in Pregnancy, page 321
- Asthma in pregnancy:
 - Can be worsened due to pulmonary congestion, reflux, ↓FRC
 - ↓reserve → rapid decompensation
 - Different blood gas values
 - Medications:
 - Steroids: potential congenital deformities from first trimester use (eg cleft lip) – little evidence of this

- β -agonists \rightarrow delay labour, risk of tocolytic pulmonary oedema
- Hypercapnia \rightarrow \downarrow utero-placental blood flow, and right shift of fetal oxy-Hb dissociation curve \rightarrow impairs fetal oxygenation
- Position of patient: risk of aortocaval compression
- \uparrow Risk of aspiration with NIV
- If ventilated:
 - Risk of difficult airway
 - High pressures due to intra-abdominal pressure
 - Benzodiazepines \rightarrow floppy baby
 - Opiates \rightarrow respiratory depression in baby

Other Pregnancy specific conditions

- Endocrine: Sheehan's syndrome/pituitary apoplexy. 2nd to growth of pituitary gland without \uparrow blood supply \rightarrow more susceptible to shock states. Only affects anterior pituitary – posterior pituitary has separate arterial supply
- Neurological:
 - Posterior Reversible Encephalopathy Syndrome (PRES). Headache, confusion, seizures and visual loss. Patchy brain oedema in hypertensive crisis with characteristic leucoencephalopathy on MRI. Not specific to pregnancy – also 2nd to other hypertensive crises and some drugs eg tacrolimus and cyclosporin
 - Hypertensive encephalopathy
 - Cerebral venous thrombosis
- Other risks of pregnancy complicate management:
 - Diabetes
 - \uparrow DVT risk. No adequate evidence for a definite recommendation

Sepsis in Pregnancy

- Difficult to diagnose sepsis in labour because:
 - SIRS criteria may be due to labour (\uparrow WBC, \uparrow temperature, \uparrow pulse, \uparrow RR)
 - Investigations are problematic: CXR relatively contraindicated, bacteruria often present
 - Staff may not be experienced in spotting sepsis
 - Symptoms of sepsis may be mistaken for labour: hyperventilation, agitation, sweating, pain
- Uterine blood flow 800 ml/min at term. Low resistance circulation \Rightarrow pressure dependent circulation without autoregulation. Susceptible to shock states
- Causes of sepsis in pregnancy/labour:
 - Pyelonephritis
 - Chorioamnionitis
 - Septic abortion: miscarriage 2nd to uterine infection
- Septic complications post delivery
 - Sepsis + DIC \rightarrow blood picture that looks like primary liver failure
 - Retained products/sepsis
 - Post-partum endomyometritis – especially following emergency Caesar after prolonged ROM, usually polymicrobial
 - Episiotomy infections
 - Septic thrombophlebitis
 - Aspiration pneumonia
 - Necrotising fasciitis
- Frequent pathogens include E Coli, Klebsiella, group B strep, often polymicrobial. G –ive more common than G +ive.
- Contraindicated antibiotics include tetracyclines (eg doxycycline), chloramphenicol, aminoglycosides, metronidazole, trimethoprim

Heart Disease in Pregnancy

- Pulmonary hypertension of any cause is a contra-indication to pregnancy. High mortality (30 – 50%), susceptible to pre-eclampsia, post-partum haemorrhage, pre-term delivery and fetal growth retardation
- Valvular disease. MS most likely to cause death. AS variable. MR and AR generally well tolerated
- SVT: treat as non-pregnant. Adenosine acceptable risk. DC cardioversion well tolerated
- Heart failure specific to pregnancy
 - Cardiomyopathy: uncommon myocarditis. Causes 25% of cardiac deaths in pregnancy. May recover. May progress to dilated cardiomyopathy. Differential of breathlessness in last trimester. Highest risk

is during auto-transfusion following delivery (uterine contraction → sudden ↑ intravascular volume → overload)

- 2nd to pre-eclampsia, tocolytic pulmonary oedema, pulmonary embolism or amniotic fluid embolism
- CPR in pregnancy. Major differences to algorithm:
 - CPR in left lateral position (27 degree tilt, if desperate position against your thighs)
 - Consider emergency/perimortem C-section if no immediate response to advanced life support and fetus > 20 weeks (no aortocaval compression prior to this). Start within 4 minutes of arrest and deliver by 5
 - No evidence but postulated that intubation is of more benefit than in normal CPR (more rapid hypoxia, abdominal compression of chest, etc.)
 - Hand slightly higher on the sternum for chest compressions
 - Additional personnel/equipment for emergency C-section and neonatal resuscitation
 - Remove uterine monitors before defibrillation
 - Differences in causes: Mg or local anaesthetic toxicity, amniotic fluid embolism

- Formulas
 - Weight = (Age + 4) * 2. Alternative (APLS):
 - 0 – 12 months: Weight (kg) = (0.5 * age in months) + 4
 - 1 – 5 years: Weight (kg) = (2 * age in years) + 8
 - 6 – 12 years: Weight (kg) = (3 * age in years) + 7
 - Cardiovascular:
 - Blood volume: 80 ml/kg
 - Systolic BP: 80 + (age * 2)
 - Poorly compliant LV \Rightarrow can only increase cardiac output via rate not stroke volume \Rightarrow impressive tachycardia with shock. Don't ignore a tachycardia
 - Urine output: 1 – 2 ml/kg

Paediatric Arrest

- From APLS
- Emergency calculations:
 - Weight: (Age + 4) * 2
 - Energy: 4 J/kg
 - Tube: age/4 + 4
 - Fluid: 20 ml/kg
 - Adrenaline 0.1 mg/kg of 1: 10,000
 - Glucose: 2 ml/kg of 10% glucose
- Arrest:
 - > 50% arrests are respiratory
 - DRS: Dangers, responsive, send for help
 - A: Open airway
 - B: Normal breathing?: 2 slow breaths
 - C:
 - Check pulse (brachial, femoral, carotid in older child): no more than 10 secs
 - Start CPR 100 bpm with compression to ventilation ratio of 30:2 (one rescuer) or 15:2 (two rescuers). Guidance for lay rescuers is 30:2 (to make it standard across all ages). Single handed experienced rescuers can also do 30:2 if swapping from one to the other is too hard
 - D: Attach defibrillator
 - Asystole is the most common rhythm due to hypoxia, VF or VT think poisoning or cardiomyopathy
 - Non-shockable: (PEA/asystole) adrenaline 10 mcg/kg (immediately then every 2nd loop), CPR for 2 mins
 - Shockable: (VF/pulseless VT): shock 4 J/Kg, Adrenaline 10 mcg/kg after 2nd shock then every 2nd loop, CPR for 2 mins
 - During CPR:
 - Airway adjuncts: LMA, ETT
 - O₂
 - Waveform capnography
 - IV/IO access
 - Plan actions before interrupting compressions
 - Consider and correct:
 - Hypoxia
 - Hypovolaemia
 - Hyper/hypokalaemia/metabolic disorders
 - Hypo/hyperthermia
 - Tension pneumothorax
 - Tamponade
 - Toxins
 - Thrombosis (pulmonary/coronary)
 - Access: Intraosseous needle:
 - Recommended in cardiac arrest. Indicated in other critically unwell children if IV access taking longer than 1.5 minutes

- Risks of cellulitis, osteomyelitis, compartment syndrome from fluid extravasation, bone marrow embolism, fracture
- Reduce risks with training, sterile technique, limb observation
- Drugs:
 - Never use atropine in an arrest: Its only use is to combat excessive vagal tone causing bradycardia in a child with a perfusing rhythm
 - Amiodarone, 5 mg/kg in 5% glucose IV or IO over 3 mins after 3rd shock in VT. Repeat if needed. Not if due to an overdose of antiarrhythmics, less effective in hypothermia. For VT with pulse, infuse over 30 mins
 - Lignocaine 1 mg/kg IV or IO if no amiodarone
 - Mg if torsade
- Post resuscitation care:
 - Re-evaluate ABCDE
 - 12 lead ECG
 - Treat precipitating causes
 - Re-evaluate oxygenation and ventilation
 - Hypoglycaemia common in serious illness and associated with poor outcomes. Check regularly and target normal glucose
 - Temperature control (cool): evidence in adults and neonates. No direct evidence in children
- Recommended stopping at 20 mins unless hypothermic or poisoning
- Parental presence recommended if there are staff to support them
- Choking:
 - Effective cough: encourage coughing
 - Ineffective cough and conscious: 5 back blows, 5 chest thrusts, assess and repeat
 - Unconscious: open airway, 2 rescue breaths, CPR 15:2, check for FB
- Drowning:
 - Issues: hypoxia and hypothermia
 - Airway: C-spine precautions and risk of aspiration
 - Breathing: consider gastric aspiration
 - Only one defibrillation till > 30o
 - No medications till over 30o

Assessment and Management of a Child

General

- Assessment:
 - Birth, APGAR, immunisations, family history
 - Speed of onset
 - Symptoms: respiratory, colour change, tone, feeding, mental state
- Signs:
 - Mental state: AVPU
 - Respiratory rate and pattern:
 - Intercostal recession, grunting, flaring, head bobbing
 - Signs of respiratory distress may not be present in chronic respiratory disease
 - Fatigue and cyanosis are pre-terminal signs
 - Cerebral depression (raised ICP, poisoning, encephalopathy) or neuromuscular disease→ respiratory insufficiency without increased work of breathing
 - CVS: bounding pulses (\uparrow CO, \uparrow CO₂), slow capillary refill, blood pressure
 - Temperature
- Common adult/mixed ICU admissions: Bronchiolitis, seizures, asthma, croup, head trauma, pneumonia, DKA and septic shock
- Normal values:

Age	Respiratory Rate	Heart Rate	Blood Pressure
neonate	30 – 50	100 – 160	60 – 80
< 1	30 – 40	100 – 160	80 – 90
1 – 2	25 – 35	100 – 150	85 – 90
2 – 5	25 – 30	95 – 140	90 – 95
5 – 12	20 – 25	80 – 120	100 – 105
> 12	15 – 20	60 – 100	110 – 120

Weight	Water ml/kg/day	Sodium mmol/kg/day	Potassium mmol/kg/day	Energy kcal/day	Protein g/day
First 10 kg	100	2 – 4	1.5 – 2.5	110	3
Second 10 Kg	50	1 – 2	0.5 – 1.5	75	1.5
Subsequent	20	0.5 – 1	0.2 – 0.7	30	0.75

- Assessing degree of dehydration:

	Mild	Moderate	Severe
Weight Loss	< 5%	6 – 9%	> 10%
Consciousness	Alert	Restless, unsettled	↓LOC
Respiratory	Normal	Rapid	Rapid and shallow
BP	Normal	Normal	↓
Pulse	↑	↑↑	↑↑ and weak
Cap refill	Normal	Delayed	Mottled

- Also consider thirst, sunken eyes, skin turgor, mucous membranes, urine output
- Differential of ↓LOC:
 - Hypoxic brain injury after respiratory or circulatory failure
 - Seizures
 - Head trauma
 - Infections: meningitis, encephalitis, cerebral and extracerebral abscesses, malaria
 - Intoxication
 - Metabolic: renal, hepatic, ↑ or ↓ Na, glucose, temperature, ↑CO₂
 - CVA/tumour
 - Hydrocephalus, including blocked shunts

Airway Management in Children

- Nasopharyngeal tube in a child: size from tip of nose to tragus of ear, or diameter of little finger
- Needle cricothyroidotomy preferred < 12 (shorter neck), surgical > 12
- Differences in infant airway:
 - Absolute size small, and small relative to large tongue, tonsils, small mandible → need shorter narrower, straighter blade
 - Large head: neck already flexed so don't need pillow or as much head extension
 - Epiglottis is long and stiff: use straight blade posterior to epiglottis
 - Larynx is high and anterior. Narrowest point is usually the laryngeal outlet/cricoid cartilage ⇒ used uncuffed tubes, concern about laryngeal stenosis
- Differential of stridor in a child:
 - Very common: viral croup (Laryngotracheobronchitis). Parainfluenzae most common
 - Common: recurrent croup (sudden onset, recurrent, history of atopy)
 - Uncommon: laryngeal foreign body
 - Rare: epiglottitis, bacterial tracheitis (staph aureus, strep or HIB), trauma, retropharyngeal abscess, inhalation of hot gases, infectious mononucleosis, Angioneurotic oedema, diphtheria
 - Lateral xray of neck of little/no value. May not be safe for transfer
- Airway management in epiglottitis:
 - Optimise medical management:
 - High flow oxygen
 - IV steroids: Dexamethasone: use high doses, eg 0.6 mg/kg
 - Repeated adrenaline nebs
 - If there is time, get most experienced paediatric airway management team and do it in theatre
 - Preparation of intubation:
 - Equipment: two laryngoscopes with range of blades, suction
 - Range of ET sizes
 - Small diameter bougie
 - Suction
 - Equipment for needle cricothyroidotomy
 - Two approaches (mention difficult airway guidelines):
 - Gas induction with maintenance of spontaneous ventilation until adequate depth to allow intubation

- IV induction + paralysis: risk of being unable to ventilate

Ventilation in Children

- Intubation:
 - Indications: obtundation, hypoxia, hypotension (need for inotropes), large volume resuscitation, worsening acidosis
 - Child FRC is small, so bag with 100% O₂ a little longer. May inflate stomach, consider NG decompression
 - Up to two years tongue is bigger and epiglottis floppier – need a straight blade posterior to the epiglottis
 - Cricoid pressure more likely to impair view and cause trauma than in adults
 - ET tubes:
 - Internal diameter: Age/4 + 4 mm (neonate 3.5)
 - Inserted orally to age/2 + 12 cm (15 cm for nasal tube)
 - Ideally should be a small leak as the narrowest part of the upper airway is at the cricoid cartilage and is prone to subglottic swelling and post-extubation obstruction. Cuffed tubes not usually used till > 8 years
 - Cuffed tubes: high volume, low pressure cuffs → significant ↓ in laryngeal and tracheal mucosal injury
 - Surgical airway: needle cricothyroidotomy preferred to surgical cricothyroidotomy < 12 years
 - Drugs:
 - Give fentanyl 2 mg/kg, ketamine 1-2 mg/kg (cardiovascularly kinder, not if ↑ICP)/atracurium 0.3 – 0.6 mg/kg+ ?atropine 20 mg/kg before intubation (airway manipulation results in vagal induced bradycardia)
 - Ketamine 1 – 2 mg/kg: potent analgesia, dissociative anaesthesia, less hypotensive. May ↑ICP – use with caution in head trauma
 - Propofol: 5 mg/kg, 1 – 2 mg/kg may be enough in a sick kid. More hypotension than ketamine
 - Titrate thiopentone: 5 mg/kg, 1 – 2 mg may be sufficient if sick. Smooth onset but may → marked hypotension
 - Beware negative inotropy from midazolam. Lower doses may be needed in a sick child
 - Use muscle relaxant. Some would argue you can sedate, look and paralyse if necessary. The risk is poorer view and aspiration. Make your first view the best
 - Capnography
 - CXR: tube position must be just right
- Ventilation settings:
 - IT 1 sec, PEEP 5 – 10, PIP < 30, rate < 30
 - Permissive hypercarbia
 - Early use of HFOV, iNO

Resuscitation and Shock in Children

- SV is fixed, ↑HR to maintain output
- Shock is myocardial, not vasodilatory
- BP stable till 25% loss
- Signs of shock in children:
 - Hypotension (SBP < 65 children, < 55 infants)
 - Hypoxia and altered mental state
 - Perfusion abnormalities and lactic acidosis
 - Bradycardia nearly always hypoxia. Can also be vagal stimulation or ↑ICP
- Access:
 - 2 large bore cannula, including EJV
 - UVC/UAC
 - Central line: femoral first (hypoxic and coagulopathic), IJV
 - If arrest situation then no access after 90 secs then IO. Minimal complications
- Fluids:
 - Resuscitation: 10 ml/kg 0.9% saline bolus. Repeat. May need > 100 ml/kg. If:
 - > 30 consider colloid ?inotropes. Femoral multi-lumen CVL (IJV if sufficient experience)
 - > 40 blood/platelets/FFP
 - Deficit: % dehydration * weight * 10 given over 24 hours
 - Maintenance:
 - 4 ml/kg/hr for 1st 10 kg, 2 for next 10, then 1 for each 10 after that

- isotonic fluids, 80% if intubated
- Neonates: 10% dextrose + electrolytes
- Feed within 24 hours
- Alkalisating agents:
 - Use of routine bicarbonate after arrest has not been shown to be of benefit
 - Arterial pH does not correlate well with tissue pH – use central venous pH
 - Specifically recommended for hyperkalaemia and TCA overdose
 - Dose is 1mmol/kg (1 ml/kg of an 8.4% solution). Will precipitate with calcium. Inactivates adrenaline and dopamine so flush lines before and after
- Inotropes:
 - See Inotropic/Vasopressor Support, page 44
 - Dopamine generally used in preference to dobutamine in circulatory shock following resuscitation (APLS guidelines – but controversial). 15 mg/kg in 50 ml of 5% dextrose or normal saline gives 5 mcg/kg/min if run at 1 ml/hr. Normal dose is 5 – 20 mcg/kg/min \Rightarrow 1 – 4 ml/hr. May produce tachycardia, vasoconstriction and ventricular ectopy. Inactivated by alkaline solutions – don't run with bicarbonate
 - Adrenaline: may be preferable to dopamine if severe hypotensive shock and in very young infants. Titrate from 0.05 mcg/kg/min to 1 mcg/kg/min. 0.3 mg/kg in 50 ml of 5% dextrose or normal saline at 1 ml/hr gives 0.1 mcg/kg/min, so run at 0.5 – 20 ml/hr
 - Calcium: inotrope, low in sepsis
- Monitoring cardiac output:
 - Clinical: HR, BP, temp, CVP, UO, GCS
 - Lactate a good monitor. If > 10 think cardiac lesion
 - PICCO
 - Warning signs:
 - Persistent or rising tachycardia, acidosis, lactate
 - Hypotension, poor perfusion, spreading rash
 - Could it be cardiac?
- SVT:
 - Resuscitate first, if shocked then shock
 - Cold ice on face for 20 secs, adenosine then amiodarone
- CPR:
 - 2 rescue breaths
 - Compression ratio:
 - 100 per minute/single rescuer
 - 2 rescuers: 15:2
 - Neonate (till they leave delivery suite): 3:1 on room air

Could it be cardiac?

- Presents at any age
- History:
 - Cyanosis not correcting with O₂
 - Sweating
 - Poor feeding
 - Sudden change (?duct dependent \Rightarrow give PGE₁, side effect apnoea), triggered by sepsis?
- Examination findings:
 - Tachycardia out of proportion to respiratory difficulty
 - \uparrow JVP
 - Gallop rhythm/murmur
 - Enlarged liver
 - Absent femoral pulses
- Presentations:
 - Shock: CoA, ASD, HLH, arrhythmia
 - Cyanosis: TGA, PS
 - Failure: VSD, ASD, truncus, PDA, cardiac dysfunction
 - Arrhythmia: SVT. HR > 200 – resuscitate first. DC shock 0.5 – 1.0 (2 – 4 KJ/kg for VT/VF)
- Management: Incl 4 limb BP, ECG and Echo

Neonatal Resuscitation

- Warm child

- Room air only unless the baby declares a need for oxygen. O₂ should rise from 60 to 90 over first 10 mins
- Chest compressions 3:1 @ 120

Circulatory Changes at Birth

- Closure of umbilical vessels → ↑SVR and ↑BP
- Respiratory centre activated → expansion of lungs → ↓pulmonary vascular resistance and ↑flow → ↑LA pressure
- → Reversed pressure over intra-atrial septum closing the valve over the foramen ovale
- Fall in pulmonary artery pressure and ↑ aortic pressure → flow reversal through the ductus arteriosus
- Constriction of the ductus seems to be mediated by increased O₂ tension and/or bradykinin released by newly oxygenated lungs
- Before birth, RV is thicker than the LV > Reverses by one month old
- Persisting foetal pattern circulation is essentially due to persistent hypoxia and elevated PVR, which may be due to:
 - Low lung tidal volume: hyaline membrane disease, perinatal asphyxia
 - Pulmonary hypoplasia
 - Meconium aspiration
 - Chronic placental insufficiency
 - Sepsis (eg Gp B Strep)

Shocked Neonate

- Be slow to intubate
- Differential:
 - Infection: sepsis, GBS, Herpes (acyclovir)
 - Respiratory: infection, congenital illnesses (eg diaphragmatic hernia), persistent pulmonary HTN of the neonate
 - Cardiac lesions: Duct dependent: Extra-pulmonary shunt → no improvement with O₂. Use prostaglandin 10 – 20 mg/kg/min to keep duct open (more to open it). Side effect apnoea
 - Malrotation
 - Metabolic Disorders

D and Drugs

- Always check glucose. If shocked often high then plummet. Don't give insulin
- Sedation/Analgesia:
 - Morphine (0.1 – 0.2 mg/kg), chloral, clonidine (0.5 – 1.0 mg/kg), diazepam, avoid propofol
 - Nitrous oxide: O₂ and nitrous separate in a cylinder that has been standing for a long time. Shake first. Contraindicated in gaseous spaces – pneumothorax, inner ear problem
- Empirical antibiotics:
 - < 3/12: cefotaxime/amoxycillin
 - > 3/12: cefotaxime/gentamicin
- Hydrocortisone 2 mg/kg if: shock, purpura fulminans, adrenal insufficiency
- If ↑K then CaCl 0.5 ml/kg of 10%CaCO₃
- Adenosine: 100mcg/kg then 200 then 300

Paediatric Trauma

- See Trauma, page 228
- Overall incidence of c-spine injury is lower than adults
- Mechanism of injury: falls and assaults more likely
- Patterns of injury: more likely blunt trauma with multiorgan injury and head injury common
- Physiological and anatomic differences to adults:
 - Different airway anatomy: See Airway Management in Children, page 325
 - Large body surface area/volume ratio: easier heat loss
 - Different normal values
 - More cardiovascular reserve
 - Immature skeleton: More flexible bones (eg lung contusion without rib fracture)
 - Blood: small volume ⇒ blood loss may be life threatening
 - Drugs and equipment according to size

Structured Assessment Compared to Adult

- Outline of assessment the same (ABCDE) but:

- History harder
- Exam: needs modification for age (eg AVPU),
- Investigations: may need to be modified for an uncooperative child (eg GA for CT)
- Primary survey and resuscitation:
 - Airway with c-spine: uncuffed tube, according to age
 - Breathing with ventilatory support
 - Circulation with haemorrhage control:
 - Access difficult
 - Less tolerance for hypotension in a child: hypotension = peri-arrest
 - Specific fluid bolus and maintenance regimes according to weight: 2 fluid boluses max then blood
 - Disability: with prevention of secondary insult
 - Exposure with temperature control
- Secondary survey and emergency treatment of injuries
- Continuing stabilisation

Specific Injuries in Children

- Head/spine:
 - See also Clearing the Cervical Spine, page 251
 - Large head on a small body, weak neck muscles and likely to be thrown \Rightarrow closed head injury with shearing; cervical injury rare
 - Ligament flexibility and heavier head: spine injuries above C4 more likely and consider high SCIWORA (spinal cord injury without radiological abnormality)
 - Thoraco-lumbar injury very rare. If present often involves multiple levels
 - Cervical spine protection:
 - Collars don't fit, compromise respiration, large occiput causes head flexion \Rightarrow in line stabilisation requires body elevation. Use sandbags/tape/collar
 - Need lateral C spine and AP XR (odontoid only in kids > 5) and CT C1-7. There are numerous cervical physal lines which can be confused with fractures. 9% of normal kids have pseudo-subluxation of C2 on C3 or C3 on C4
 - Atlantoaxial rotary subluxation is the most common injury to the cervical spine, presenting with torticollis following trauma. Upper segments of the C-spine have greatest mobility \Rightarrow more commonly injured
 - Cervical spine clearance:
 - Inspect, palpate and do neuro exam
 - If OK, and no sedating drugs, and active movement of neck without pain then clinically clear and doesn't need imaging
 - If not OK, then plain xray (usually cross-table lateral), CT and specialist review
- Chest: Compliant chest \Rightarrow may be lung contusion without fracture
- Abdomen:
 - Abdominal injuries:
 - Less rib protection
 - Thinner abdominal wall
 - More horizontal diaphragm
 - Suprapubic bladder
 - Liver, spleen and bladder are exposed \rightarrow laceration or transection
 - Only do a rectal exam at most one – surgeon should do it – they're the one that needs to know
 - Laparotomy for shock, perforation or penetrating injury
 - No indication for diagnostic lavage
 - FAST Scan:
 - Lesser place in children
 - Want to be conservative if you can. Won't take child to OT solely on the basis of +ive fast scan. Need failed resuscitation
 - If FAST negative, and failed resuscitation, will still take to OT
- Limbs: Incomplete ossification \Rightarrow fractures, blood loss
- Psychological issues: parents, consent, potential for abuse
- Non-accidental injury with head trauma:
 - Recognition: discrepancy between description and severity, delayed presentation, changing history, doctor shopping
 - Similar management to adults: management of ICP/CPP with attention to coagulation and metabolic conditions. May consider therapeutic hypothermia

- Check for retinal haemorrhages and other injuries (eg bone fractures)
- Consider safety of child and any siblings

Common Medical Conditions

- Critically unwell child:
 - SEPSIS
 - Trauma, including falls, poisoning
 - Respiratory failure
 - Cardiac disease (congenital conditions can present at any stage)
- Tachycardia:
 - Low output state
 - Fever
 - Pain
 - Seizures while sedated
 - Drugs
 - Also:
 - Poisoning
 - Metabolic disturbance
 - Primary Tachyarrhythmias more uncommon, usually regular:
 - Re-entrant pathway (common). Rate 220 – 300. Negative P waves in II, III and aVF. If SVT titrate IV/IO adenosine 100 mcg/kg max 500 mcg/kg
 - After cardiac surgery
 - Cardiomyopathy
 - Long QT syndrome
- Bradycardia – usually irregular:
 - Pre-terminal hypoxia or shock
 - ↑ICP
 - After conduction pathway damage in cardiac surgery
 - Congenital heart block (rare)
 - Long QT
- Asthma: consider
 - High risk: those with food allergies and teenagers not taking preventers
 - IV hydrocortisone: if sick then gastric stasis and won't absorb prednisone
 - Salbutamol bolus 5 mcg/kg. If persistent ↑RR then ?acidotic from salbutamol. Stop and see how they go. Infusion 1 – 5 mcg/kg/min
 - Aminophylline bolus (10 mg/kg over 1 hour)/infusion
 - Magnesium: 50 mg/kg (0.1 mL/kg of 50%) over 20 mins
 - CPAP/intubation rare
- Bronchiolitis (differential heart failure):
 - Cause by respiratory syncytial virus
 - ↑Risk in premature, age < 6 weeks, chronic respiratory or cardiac disease or immunosuppression
 - Exam: ↑RR, recession, cough, hyperinflation with depressed liver, tachycardia, fine end-inspiratory crackles, high pitched wheeze (expiratory > inspiratory), cyanosis, irregular breathing, recurrent apnoea
 - Supportive treatment: O2 + NIV (bubble CPAP, HFNP - at 2 litre/kg increasing to 3 if failing - or face mask BIPAP), suction nasal passages. Consider humidification, prone positioning. Fluids via NG or IV (at 2/3rds normal rate)
 - Intubate if recurrent apnoea, exhaustion, or severe hypercapnia and hypoxia despite high O2.
 - No drugs (salbutamol, steroids, nebulised adrenaline, heliox) have shown benefit, but in severe cases may temporise respiratory failure
 - Ribavirin in extreme cases or immunosuppressed
 - Aminophylline or caffeine may be helpful in reducing apnoeas if premature
- Croup: barking cough, stridor, fever. Treatment: oral dexamethasone (0.15 mg/kg PO), prednisone 1 mg/kg an OK alternative. Nebulised adrenaline 0.5 ml/kg of 1:1000 up to a maximum of 5 mL) – buys time but does not reduce intubation rates. 5% of hospitalised croup patients require intubation, and for an average of 3 days
- Diabetic Ketoacidosis (different from adults) – see national guideline on www.starship.org.nz:
 - 10 – 20 ml/kg fluid max
 - Fluid resuscitate over 24 – 48 hours otherwise cerebral oedema. See Diabetic Ketoacidosis, page 314

- Poor perfusion/shut down is pre-dominantly due to acidosis not hypovolaemia
- Do all you can to avoid intubation. Avoid sux. If you ventilate you need to match PCO₂ to what's predicted from HCO₃
- Pertussis:
 - Bordetella pertussis
 - Worst in those under 2 months (prior to vaccination) → cough paroxysms with apnoea and bradycardia
 - Rarely pertussis toxemia: pertussis toxin → toxin mediated cardiovascular compromise with high mortality
- Sepsis:
 - Kids are usually shut down rather than vasodilated
 - Meningococcal and pneumococcal diseases still occur despite vaccination
 - Should consider intubation after 40 – 60 ml/kg boluses
 - Intubate with ketamine, atropine premed, with dopamine or noradrenaline running
 - Antibiotics: cefotaxime (50 mg/kg max 2 g) and vancomycin (15 mg/kg max 500mg over 1 hour), consider clindamycin if toxic shock
 - Steroid replacement has no evidence, but if inotrope resistance draw a free cortisol and give stress dose hydrocortisone
 - Electrolyte correction:
 - Glucose: if < 3 mmol/L: 2 ml/kg 10% glucose followed by maintenance glucose
 - Potassium < 3.5 mmol/L: 0.25 mmol/kg KCL over 30 mins with ECG monitoring
 - Calcium ionised < 1 mmol/L: 0.3 ml/kg 10% Ca gluconate over 30 min (max 20 ml)
 - Magnesium < 0.75 mmol/L: 0.2 ml/kg 50% MgSO₄ over 30 min (max 10 mL)
- Seizures:
 - Always check glucose
 - Febrile seizures are common. Associated with temperature > 38o, age < 6, no CNS infection, no history of previous afebrile seizures, generalised rather than focal, generally short (< 15mins), single rather than multiple
 - Antibiotics: cefotaxime/vancomycin (for resistant pneumococcal meningitis). Acyclovir if focal
 - CT if prolonged or focal
 - Intubate if airway concerns or fitting more than 60 mins
 - Drugs:
 - Midazolam: 0.15 mg/kg iv, 0.3 mg/kg im, 0.5 mg/kg buccal. Rapid onset, alternatives to IV administration, causes sedation and respiratory depression
 - Diazepam: 0.3 mg/kg iv, 0.7 mg/kg pr
 - Phenytoin 20 mg/kg. Prevents recurrence, slow onset (up to 30 mins), ↓BP, ataxia, nystagmus, blurred vision...
 - Sodium Valproate 20 – 40 mg/kg followed by infusion of 1 – 5 mg/kg/hr. Effective in refractory seizures, less sedating than barbiturates, contra-indicated in liver impairment
 - Levetiracetam 5 – 30 mg/kg bolus dose, 25 – 50 mg/kg maintenance in two daily divided doses. Good safety profile. Limited published data in paediatric age group
 - Phenobarbitone: 10 - 20 mg/kg, up to 40 mg/kg as required. More effective than phenytoin. Severe respiratory depression
 - Thiopentone 2 -3 mg/kg IV, repeat as needed. Most potent anti-epileptic. Requires intubate. Hypotension
 - Consider paraldehyde: 0.3 ml/kg pr, max 10 ml
- Brain death testing: see Brain Death in Children, page 361
- Transport: Resuscitate on the ground then hands off. Stability before speed. See MET/Rapid Response Teams, page 4

Short Answer Question

- Class
- Pharmaceutics, including formulation and administration
- Kinetics: bioavailability, protein binding, distribution, elimination half-life, metabolism, excretion, effect of various disease states
- Dynamics: dose, mechanism of action, effect of various disease states, adverse effects and interactions

Effect of critical illness on Pharmacology

- Enteral drug absorption:
 - Gastric emptying/motility affected by drugs (opioids, anticholinergics, antacids, inotropes)
 - Changes in pH
 - GI mucosal absorption altered by oedema, disordered motility, disordered mucosal blood flow
- Drug clearance:
 - Reduced liver clearance due to:
 - Lower hepatic blood flow
 - ↓hepatocellular enzyme activity
 - Lower bile flow
 - Administration of other drugs competing for enzymes
 - ↑liver clearance of some drugs due to enzyme induction
 - Renal clearance reduced due to:
 - Reduced perfusion
 - 2nd to ischaemic injury, drug toxicity or immunological injury. ↓GRF → longer half-life of renally cleared drugs
 - Renal clearance increased due to:
 - ↑cardiac output in early sepsis
 - Burns, diuretics and hypertonic saline → ↑GFR
 - Protein binding changes:
 - ↓Albumin → ↑free drug
 - Some proteins (eg alpha 1-acid glycoprotein which binds morphine) are ↑ in critical illness
 - Changes in protein binding also due to ↑endogenous binding inhibitors, qualitative changes on binding sites, competition for binding by other substances
 - pH changes

Effect of Age on Pharmacokinetics

- Age is an independent risk factor for adverse drug reactions
- Poly-pharmacy is common
- Age related physiological changes affect:
 - Absorption
 - Distribution: reduced protein binding due to malnourishment
 - Metabolism
 - Elimination: eg ↓GFR → accumulation
- Cognitive impairment → overdose, non-adherence, failure to disclose full list

Effect of Obesity on Pharmacokinetics

- Ideal body weight approximately (kg):
 - Males = height (cm) – 100
 - Females = height (cm) – 110
 - Lean body weight = ideal body weight + (ABW – IBW) * 0.4
- Distribution:
 - Markedly affected by ratio of adipose tissue to lean body mass
 - Lipid soluble drugs usually dosed on ABW, water soluble drugs dosed on ideal or lean body weight
 - ↑volume of distribution for lipid soluble drugs
 - Accumulation of lipophilic drugs in fat stores
 - Vd of hydrophilic drugs less affected, but blood, ECF, body organ and connective tissue volume are also increase
 - ↓C_{max} and ↑T_{1/2}

- Metabolism: Variable effects. More likely to be affected by critical illness with drug interactions, ↓hepatic blood flow, altered protein binding
- Excretion:
 - Obese patients with normal renal function have ↑GFR → ↑clearance of renally excreted drugs. Comorbid disease (eg diabetes) may alter this
 - Calculated and measured creatinine clearance correlate poorly in obesity and in the critically ill. Doubly uncertain if both. May need to measure serum levels in drugs with low therapeutic index
- Specific drugs:
 - Propofol: may need higher doses
 - Fentanyl: lipophilic. Clearance no linearly correlated with TBW above 70 kg. Use of a corrected dosing weight (body mass into which the drug distributes) has been validated
 - Benzodiazepines are lipophilic and highly protein bound. For single doses all should be dosed on TBW.
 - Neuromuscular blocking agents: are polar and hydrophilic. Dose rocuronium on IBW. Dose atracurium on TBW due to clinically observed hyposensitivity in obese patients
 - Antibiotics: paucity of data

Withdrawal States in ICU

- Potential candidate drugs:
 - Alcohol
 - Tobacco
 - Opioids
 - Benzodiazepines
 - Caffeine
 - Other street drugs, eg cocaine
- Principles of management:
 - Prevention: Avoid prolonged high dose narcotics, benzodiazepines
 - Detection/diagnosis: low threshold for signs (eg tachycardia, fever)
 - Treatment:
 - Sedation to control systemic effects
 - Replacement/substitution: eg nicotine patch
 - Specific therapies: eg seizure prevention
 - Support: airway, respiration, fluid replacement
 - Reassurance/orientation: reality orientation, clock, presence of a relative

Absorption

Bioavailability

- The fraction of the drug available to the systemic circulation after oral, sc, im, pr or sl administration, F mg.h/L
- Absolute oral bioavailability, $F = AUC_{oral}/AUC_{IV}$ (Curve of plasma concentration vs time)
- Oral bioavailability is affected by:
 - Food: can ↓absorption (↓bioavailability, eg rifampicin, glipizide) and ↓first pass effect (↑bioavailability) – but general affect is just a delay
 - Binding with aluminium-containing antacids or bile acid sequestrants
 - ↑gastric pH (eg with PPIs) → ↓solubility and hence absorption of weak bases (eg ketoconazole)
 - Drug solubility: Lipid-soluble → ↑absorption (+ distributes more widely)
 - First pass metabolism: is often significantly reduced in liver disease
- Relative bioavailability = the oral bioavailability of a test formulation (eg a generic) vs a reference formulation (eg the brand name drug)

First Pass Effect

- Extent to which a drug is removed by the liver of the gut prior to reaching the systemic circulation
- Due to biliary excretion and liver (and some gut enterocyte) metabolism
- Important in drugs with high hepatic extraction ratio
- ↓ with any form of hepatic obstruction (eg portal thrombosis), due to shunting via other routes (eg in advanced liver disease)
- Examples:
 - GTN can't be administered orally because of complete first pass metabolism
 - Verapamil: high pre-systemic metabolism. Iv dose is 1 – 5 mg, oral dose is 40 – 120 mg

- Morphine: equivalent IV dose is about a third of oral due to first pass effect
- Low dose aspirin: platelets affected in the portal vein, but systemic sparing because of first pass deacetylation in the liver

(Apparent) Volume of Distribution

- Distribution:
 - = volume into which the drug appears to be uniformly distributed with a concentration equal to that of plasma
 - $V_d (L) = \text{Amount of drug in the body (Ab, mg)} / \text{its plasma concentration (Cp, mg/L)}$
 - Depends on drug solubility: lipid soluble $\rightarrow \uparrow V_d$
 - Determines loading dose:
 - **Loading dose (mg) = $V_d \times \text{desired } C_p$**
 - Allows C_p to quickly reach therapeutic levels and allows for immediate establishment of C_{pss} (steady state plasma concentration)
 - Rate of distribution: the rate at which a drug distributes is dependent on perfusion, lipid solubility, passive > active uptake. Can lead to a different therapeutic effect of the plasma concentration
 - Examples:
 - Digoxin: plasma level falls quickly after iv administration but takes hours to reach sufficient concentration at site of action. After 6 – 8 hours (when distribution is nearly complete) plasma concentration reflects therapeutic effect – that is the time to measure plasma levels. $V_d = 500$ litres
 - Gentamicin has an apparent V_d of extracellular H₂O (~ 15 litres)
 - Midazolam: Rapid uptake by the brain during distribution \rightarrow quick sedation, with subsequent redistribution – so subsequently will have +ive blood concentration but no effect
 - Adenosine: very rapid elimination by uptake into erythrocytes and endothelial cells. Have to give it rapidly to have any left by the time it reaches the AV node
 - Fluoxetine: $V_d = 3500$ litres
 - Warfarin: $V_d = 8$ litres
- Protein Binding:
 - Drug response related to free rather than total circulating drug concentration
 - Only free drug is active
 - Only free drug is metabolised and/or renally excreted
 - Measured drug levels include both bound and unbound portions
 - Only of relevance for highly bound drugs (> 90%). Small changes in binding or a large change in plasma protein levels (uncommon) can make a big difference. Eg hypoalbuminaemia, liver disease, renal disease affecting drug binding, especially of acidic and neutral drugs like phenytoin. Displacement of drugs from plasma proteins is not usually clinically significant as the \uparrow free drug is rapidly cleared
 - Examples of highly protein bound drugs: propranolol, phenytoin, amiodarone
 - Binding of drugs in tissues is quantitatively more important in terms of drug distribution than binding to plasma proteins
 - Volume of distribution of drugs extensively bound to plasma proteins but not to tissue components approaches plasma volume (eg warfarin)
 - Drugs highly bound to tissues (eg digoxin and TCAs) have a volume of distribution of hundreds of litres. Not removed in overdose by haemodialysis
 - Drug interactions based on displacement from plasma binding sites alone are transient and not clinically significant
- Hysteresis Index:
 - Anticlockwise/Reverse: delayed distribution eg digoxin
 - Clockwise: rapid tolerance (tachyphylaxis) eg adrenaline

Elimination

- Clearance:
 - = Elimination
 - = Metabolism (mainly liver) + Excretion (mainly kidney)
 - Viewed as: concentration at the beginning and end of a period of time is unchanged, and a specific volume of the body has been cleared, ie measured in volume/time
 - Volume of plasma cleared of drug per unit time
 - May related to a single organ or the whole body
 - Can't be greater than the blood flow to the eliminating organ

- **Cl (L/min) = Vd * K** (elimination constant) = **Vd * 0.693/T_{1/2}** [NB K is the proportion of drug eliminated per unit of time, 0.693 = log of 2]
- Determines *maintenance dose*: **Maintenance Dose = clearance * desired concentration** [ie for a given maintenance dose rate, clearance is the sole determinant of C_{ss}]
- Elimination **rate** (mg/hr, ie weight of drug per unit time) = Clearance (L/hour) * plasma drug concentration (mg/L) [NB elimination rate is very different at different concentrations]
- Initial rapid drop in drug concentration is not elimination but distribution into and out of peripheral tissues (also a first order process)
- Renal Excretion:
 - Fraction excreted unchanged (f_u):
 - = 1: totally renally excreted, eg digoxin
 - = 0: no renal excretion, eg phenytoin
 - Renal excretion is proportional to CrCl
 - Active and passive excretion
 - Highly susceptible to disease states
 - Examples:
 - Salicylate → ↓ renal clearance of methotrexate
 - Probenecid → ↓ renal clearance of penicillin (used for therapeutic effect)
 - Triple whammy: NSAIDs, diuretics and ACEI → renal failure (fatality rate of renal failure is 10%)
- Capacity limited metabolism/elimination:
 - First-order metabolism (= linear kinetics [except the graph is exponential not linear!]): Same proportion of the drug is eliminated per unit time. Rate of the process depends on the amount of drug present. Applies to most drugs
 - Zero-order metabolism (=Michaelis-Menten Kinetics):
 - Elimination becomes *saturated* at high doses, so elimination then happens at a fixed *amount* per unit time → plasma concentrations change disproportionately more than alteration in the dosing rate
 - Risk of toxicity or poor efficacy
 - Dose changes should be small and monitored carefully
 - Eg phenytoin, theophylline, alcohol, aspirin, perhexiline (CYP2D6 poor metabolisers)
 - Any drug at some dose will exceed the metabolic capacity, but this is unusual at the therapeutic dose
- **Half Life (T_{1/2}):**
 - The time taken for the plasma concentration to decrease by 50% – an exponential process. A constant proportion of the drug is eliminated per unit time
 - Is constant for drugs that follow first-order elimination kinetics
 - Composite of clearance and volume of distribution. Cl and Vd are independent variables, T_{1/2} is dependent on them. **T_{1/2} = 0.693 Vd / Cl**
 - Determines:
 - Duration of action of a single dose
 - The time to reach steady state with continuous dosing
 - Time course of elimination
 - Time course of accumulation
 - Choice of dose interval to avoid a large fluctuation in C_p
- Steady-State: drug administered per unit time = drug eliminated per unit time
 - C_{ss}: steady-state plasma concentration, is most determined by Vd
 - Magnitude of steady state is determined by clearance and dose alone:
 - C_{ss} = F (bioavailability, mg.h/L) * D (dose) / Cl * T (dose interval)
 - As Cl = (Vd * 0.693)/T_{1/2}, then
 - C_{ss} = (F * D * T_{1/2}) / (0.693 * Vd * T)
 - Is proportional to dose and inversely proportional to interval
 - C_{ss} is reached in 4 to 5 half-lives then stays constant
 - C_{ss} is proportionately and predictably changed by changing dose and/or dosing interval
- Dosing regimens:
 - For drugs with T_{1/2} 8 – 24 hours, dosing interval = T_{1/2}
 - For drugs with a short T_{1/2} (and low therapeutic index), use slow release preparations
 - For drugs with a T_{1/2} > 24 hours, use once daily dosing
 - If dosing interval is equal to drug's half-life, fluctuation is about twofold, which is usually acceptable
 - If drug is eliminated rapidly, it can still be given infrequently if it has a wide TI. Eg captopril has a half-life of 2 hours, but can be given 12 hourly because it is safe to keep the plasma concentration well about the threshold for pharmacologic effect

Liver Metabolism

- Metabolism occurs mostly in the liver (other sites: kidney's, lungs, adrenals), mostly leading to inactivation of the drug, and increasing water solubility (→ renal excretion). Two phases:
 - Phase 1: oxidation, reduction, hydrolysis (eg via Cytochrome P450 [CYP] monooxygenase superfamily) – see below
 - Phase 2: conjugation via enzymes including: glucuronyl-, acetyl-, sulfo- and methyltransferases
- Active drug metabolites:
 - Prodrugs: require metabolism to generate active metabolites: eg many ACEIs, losartan, irinotecan, codeine (active metabolite morphine)
 - N-acetyl-procainamide (NAPA) is a major metabolite of procainamide, and accumulation → QT prolongation and torsades

Phase 1 Metabolism

- See NEJM 26 May 2005
- Phase 1/CYP Mono-oxygenase variants:
 - Mixed function oxidases in the liver, also present in enterocytes of the intestinal epithelium
 - P450 refers to a characteristic absorption peak at 450 nm when they bind in their reduced form to carbon monoxide
 - 13 CYP families – some involved in steroid and bile acid biosynthetic pathways, 4 families involved in xenobiotic metabolism. CYPs relevant to xenobiotic metabolism:

P450	No of subfamilies	No of forms
CYP1	1	2
CYP2	8	57
CYP3	2	10

- Causes of variation in metabolism:
 - Genetic variation in enzymes and their regulation:
 - Single nucleotide polymorphisms (SNP)
 - Insertion or deletion of one or more nucleotides – either exons (coding regions) or introns (non-coding regions)
 - Genetic variation leads to:
 - Poor metabolisers (PM): usually two loss of function alleles
 - Extensive metabolisers (EM), and
 - Ultra-rapid metabolisers (UM)
 - Inducers of CYP:
 - Lowers plasma levels over 2 – 3 weeks as gene expression of the eliminating enzyme increases
 - Toxicity can occur if inducing agent is stopped
 - Inhibitors of CYP:
 - Have rapid effect
 - Inhibition *will not affect PMs*, but will convert genotypic EMs to phenotypic PMs
 - Fluoxetine's inhibition with CYP2D6 takes weeks due to long half-life and slow generation of a CYP2D6-inhibiting metabolite
 - Inhibition can also occur competitively when two drugs metabolised by the same enzyme are given together
 - Some drugs have a non-specific effect on many enzymes:
 - Cimetidine (H2 receptor antagonist for peptic ulcer disease) and ketoconazole are inhibitors → ↑levels of many drugs
 - Phenobarbitone and rifampicin are inducers
- Specific enzyme families:
 - CYP3A refers to both of:
 - CYP3A4: the most abundant hepatic and intestinal CYP and metabolises over half of all drugs. Activity varies by up to an order of magnitude between individuals but reasons not well understood
 - CYP3A5: closely related, shares substrates, and displays loss of function variants, especially in African populations
 - Note: cyclosporin is a substrate, azoles can augment its effect in transplants via inhibition
 - CYP2D6:
 - Second to CYP3A in the number of common drugs it metabolises
 - UMs:
 - Have multiple functional copies
 - May need high doses of TCAs for clinical effect, may be euphoric or nauseous after codeine due to rapid production of morphine

- SSRIs to treat tamoxifen related hot flushes → inhibition of CYP2D6 → Tamoxifen toxicity
- CYP2C9: Loss of function variants → ↓warfarin doses, and if homozygous then ↑ bleeding risk.
- CYP2C19: PM in 20% Asians, 3-5% Europeans. *Omeprazole* is a substrate: Ulcer cure rates with “standard doses” 29% in EM, 100% in PM. Clopidogrel is also a substrate, and is metabolised to the active drug by 2C19. Two PM alleles associated with poorer outcomes after PCI. Omeprazole and clopidogrel compete in PMs
- CYP1A2: metabolises caffeine, TCAs, antipsychotics, theophylline, propranolol, verapamil
- CYP2E1: metabolises ethanol.
- For a more exhaustive list, see <http://medicine.iupui.edu/flockhart/table.htm> (a good table)

	Substrate	Inhibitor	Inducers
CYP3A4/5 No PM's identified Chromosome 7	CCB: diltiazem, felodipine, nifedipine, verapamil Antiarrhythmics: lidocaine, quinidine Carbamazepine (??) Statins: Simvastatin (?), atorvastatin (not pravastatin) Macrolides: clarithromycin, erythromycin Cyclosporin, tacrolimus NRTI and PIs Midazolam Losartan Sildenafil Warfarin (r-enantiomer – less clinical relevance) Oestrogen Methylprednisone Cisapride was withdrawn because of Torsade with concurrent inhibitors	CCB: Verapamil, Diltiazem (NB also substrates) Amiodarone Azoles: Ketoconazole & Itraconazole Macrolides: Erythromycin, clarithromycin NB also substrates (not azithromycin) Ritonavir Large quantities of grapefruit juice Fluoxetine (small effect, nil from paroxetine)	Rifampicin Anticonvulsants: Carbamazepine, Phenytoin ART: Efavirenz, nevirapine St John's Wort Chronic alcohol Dexamethasone Activate PXR (nuclear receptor) which binds to the CYP3A4 promoter
CYP2D6* PM in 7% Europeans & Africans 1% UM	Betablockers: Metoprolol, carvedilol, propranolol, timolol (→ systemic β blockade if inhibited) <i>Codeine</i> Flecainide (also renally excreted, so little impact) TCAs: Nortriptyline, amitriptyline (in part) Fluoxetine, paroxetine Simvastatin (note also 3A4) Haloperidol Venlafazine <i>Tamoxifen</i> (transformed to active metabolite)	Quinidine (even a ultra-low doses) TCAs: Clomipramine Fluoxetine, (larger effect, but ?clinical significance), trace from paroxetine, (NB also substrates) Neuroleptics: chlorpromazine & haloperidol	
CYP2C9* 1 – 3% PM Little expression at birth Chromosome 10	<i>Warfarin</i> (S-enantiomer – which has the greatest anticoagulant effect – PM's require only ~ 1mg/d) Phenytoin Glipizide Losartan (transformed to active metabolite)	Amiodarone Fluconazole, miconazole Celecoxib Cimetidine and omeprazole impair R-enantiomer of warfarin → less effect	5' regulatory region has an PXR-RXR element, so CYP3A inducers also induce CYP2C9 (→ warfarin effect)

* = Clinical significant genetic variants described

Phase 2 Metabolism

- Phase 2/Transferase Variants:

- Acetylation: N-acetyl transferase. Matures in infancy. Polymorphisms define slow and rapid acetylators (NAT1 expressed in virtually all individuals, NAT2 only in rapid acetylators, products of different genes). Caucasians 50% slow, 50% fast. Slow acetylators have higher risk of:
 - Drug lupus with procainamide and **hydralazine**
 - Hepatitis with **isoniazid** (peripheral neuropathy if rapid)
- Aldehyde Dehydrogenase: deficient in 50% Mongoloids \Rightarrow unable to metabolise acetaldehyde from alcohol \rightarrow disulfiram reaction (flushing)
- TMPT – metabolises azathioprine
- P-glycoprotein:
 - Most widely studied membrane drug-transport protein – an efflux pump
 - Product of the MDR1 gene
 - Expressed:
 - On apical aspect of the enterocyte (pumps back into the gut lumen)
 - On the canalicular aspect of the hepatocyte
 - In the kidney: is responsible for active excretion of some drugs in the kidney. *Major mediator of digoxin clearance* (excreted unchanged)
 - On the blood-brain barrier. Limited drug penetration of the blood-brain-barrier often due to a robust P-glycoprotein efflux process (?reason for poor CNS penetration of HIV protease inhibitors)
 - Also present in tumour cells
 - Can be affected by drug interactions or genetically determined variability in gene transcription
 - *Quinidine, amiodarone, verapamil, cyclosporin, erythromycin and ketoconazole* inhibit MDR-1, affecting digoxin, cyclosporin, flouroquinolones, HIV protease inhibitors, lignocaine and ranitidine and many CYP3A substrates

- Conflicting evidence. See Review article “The Truth about ICU nutrition”, ICM 2014
- Lots of guidelines
- Generally accepted that it’s better to provide nutrition than not to. Small study evidence in TPN in severe head injuries and severe pancreatitis showing ↓mortality if adequate nutrition vs none
- Key questions:
 - How long is it safe to leave a patient without feeding
 - If they’re not going to feed prior to then, can you start now? 1997 guideline suggested starting nutrition on anyone unlikely to regain oral intake in 7 – 10 days, on the basis that nitrogen loss of 20 – 40 g/day gets dangerous at 14 days. A meta-analysis for early (first 48 hours) to late feeding showed ↓infectious complications...
- ACCEPT Trial – cluster randomised trial of an evidence-based feeding guidelines on mortality of critically ill adults showing non-statistical reduction in mortality
 - JAMA Dec 2008, Doig et al, CTG Publication, 1118 patients in 27 hospitals
 - Protocol was: Can EN be started within 24 hours:
 - No, due to gut conditions: being TPN and reassess every 12 hours for EN eligibility
 - Yes: Gastric challenge with full strength concentration +/- prokinetic. Goal of at least 80% requirements at 72 hours. Is it working:
 - No: Use prokinetic or post-pyloric tube
 - Yes: increase to 100% requirements
 - Guideline ICUs commenced earlier, but feed per patient per day, and LOS was not different
- Canadian Clinical practice guidelines, 2003, updated in 2007 and 2009, at www.criticalcarenutrition.com:
 - TBI: start at a target rate, accept high residuals (ie benefits of pushing nutrition)
 - ARDS: enteral formula with fish oils, borage oils and antioxidants
 - Burns and trauma: glutamine recommended
- Take home messages:
 - Try early enteral feeding
 - Supplementary (or “top-up”) parental nutrition is not currently supported by evidence
 - Ideal caloric goals are unclear – but may not matter in the first week. There is no rush if you can’t feed enterically
 - Feeding is complex, it is a potent therapy with potential for benefit and harm, and evidence is thin

Nutritional Assessment

- Nutritional assessment:
 - Is difficult in ICU
 - Lab measurements non-specific in the critically ill
 - Greater emphasis on pre-op nutritional assessment
- History:
 - Indicators of malnutrition:
 - Involuntary weight loss
 - Impaired swallow
 - Changes in appetite or bowel habit
 - Chronic alcohol
 - Metabolic comorbidities: thyroid disease, diabetes, liver and renal disease
 - Food intolerances (eg Coeliac)
 - Nutritional preferences: eg vegan
- Exam:
 - Weight, height, BMI
 - Muscle wasting
 - Anthropometric measurements, eg skin fold thickness, mid-arm muscle circumference
 - Specific micro-nutrient deficiency: eg glossitis, angular stomatitis, anaemia, bleeding gums, skin/nail/hair condition
- Investigations:
 - Serum albumin (better indicator of chronic nutritional status) and pre-albumin levels (better indicator of changes in current nutritional status)
 - Transferrin and coagulation factors: reflect liver synthetic function rather than nutrition per se
 - Fat-soluble vitamin levels: A, D, E

- Water soluble vitamin levels: ↓Thiamine common in alcoholic liver disease. Check this and other treatable vitamin levels (zinc, selenium, B12, folate)
- Direct and indirect calorimetry (see below) to measure energy expenditure (metabolic cart, VO₂, VCO₂)
- Nitrogen balance: calculations inaccurate in liver and renal failure

Physiology of Nutrition

- Metabolic response to stress is highly preserved across species. Largely expressed as insulin resistance (an adaptive mechanism) → ↑ endogenous glucose production for at least 3 days after injury. Caloric debt is therefore [energy expenditure – (exogenous + *endogenous* calories)]

Cachexia

- Weight loss and skeletal muscle wasting due to illness where the body does not reduce catabolism (unlike the adaptive reduction in protein metabolism that occurs in starvation)
- Mechanisms not clearly understood
- Predisposing factors:
 - Pre-existing malnutrition/malabsorption
 - Hormonal:
 - Cytokine-induced up-regulation of muscle protein degradation
 - Neuro-endocrine: stimulation of hypothalamic-pituitary-adrenal axis
 - Reduced circulating anabolic hormones
 - Immobility and prolonged length of stay
 - Corticosteroid therapy
 - Malignancy
 - Chronic inflammatory states: infection/connective tissue disease
- Consequences:
 - ↑mortality
 - ↑ventilator-days, ↑LOS
 - ↑risk of nosocomial infection
 - Poor wound healing
 - Malnutrition and nutritional deficiency syndromes

Starvation

- State of adaptive hypometabolism using fat as the primary fuel and sparing protein.
- Lipolysis and ketosis increase, marginal increase in catabolism, glycogenolysis and gluconeogenesis
- Fall in insulin → ↓mobilisation of protein, glucose and lipids
- After 24 – 48 hours gluconeogenesis increases and supplies glucose dependent tissues (brain, immune system, renal medulla). Sourced from peripherally released amino acids and glycerol (from lipolysis)
- After 48 hours, ketosis occurs using FFA for energy (↓demand for amino acids → preserves muscle)
- Initially stable albumin. Low urine urea

Stress

- ↑Stress mediators such as cortisol, catecholamines, GH, glucagon and cytokines
- ↑Catabolism, glycogenolysis, gluconeogenesis
- ↑Lipolysis with no increase in ketosis
- Albumin levels drop precipitously
- Urine urea increases

Refeeding syndrome

- Aka Nutritional Recovery Syndrome
- Rare: ~ 2% in individuals with risk factors. Predicted by poor intake > 10 days, weight loss > 15% prior to presentation and low Mg
- Can occur after a prolonged fast even if not low BMI
- Can occur with enteral or parenteral nutrition
- Marked ↓PO₄ and also ↓K and ↓Mg on commencing feeding after starvation
- Feed → ↑insulin → intracellular shift of these electrolytes → depletion of ATP and 2,3-DPG → failure of energy metabolism → ↑glucose and:
 - Respiratory failure and muscle *weakness* (compounded by ↑RQ → ↑CO₂ → ↑work of breathing)
 - Cardiac failure: cardiomyopathy, hypotension, *arrhythmias*
 - Neurological: altered mental state, paraesthesia and seizures

- Renal: acute tubular necrosis
- Skeletal: rhabdomyolysis, weakness
- Endocrine: insulin resistance, osteomalacia
- Haematological: white cell dysfunction, thrombocytopenia, ↓platelet function, haemolysis
- Immune dysfunction
- *Thiamine deficiency*. Red-cell transketolase is reduced in thiamine deficiency
- Multifactorial fluid overload
- Prevention:
 - Gradual introduction of nutrients (eg limit to 20 kcal/kg for the first day). Fat infusion not exceeding 2 – 2.5 g/kg/day initially
 - Anticipate and replace electrolytes. Replace phosphate < 0.5 mmol/L. No evidence. 50 mmolPO₄ over 24 hours suggested
 - Replace thiamine (Vit B1)
 - Some suggest low carbohydrate high protein initial regime, with caloric intake increasing over a week

Complications of over-feeding:

- Hepatic steatosis
- Hyperglycaemia
- Hyperlipidaemia
- Hypercarbia
- Hyperosmolarity and hypertonic dehydration (in patients fed excess nitrogen who have impaired urine concentrating ability)
- Azotemia (due to excess nitrogen intake)

Nutritional Requirements

Energy

- Estimated requirements have drifted down – some nitrogen loss is inevitable and caloric requirements previously probably over-estimated
- Assessed by:
 - Basal Metabolic Rate (BMR):
 - Lots of equations, including the Harris-Benedict equation (> 80+ years old), adjustments for stress, diagnosis, etc.
 - Weir equation: $3.9 \times \text{VO}_2 \text{ ml/min} + 1.1 \times \text{VOC}_2 \text{ ml/min} - 2.2 \text{ urinary nitrogen g/day}$ (in practice urinary nitrogen is not measured as its contribution to energy expenditure is limited)
 - Indirect calorimetry:
 - Gold standard measurement of resting energy expenditure (REE)
 - Inputs are inspired and expired O₂ and CO₂ and minute ventilation, using the Weir equation
 - Tricky, and no standard to related this to caloric intake. Very sensitive to errors in measurement of gas volume and concentration. Sensors less accurate at FiO₂ > 0.6. Can't have circuit leak or draining pneumothorax
 - Hasn't been shown that use improves outcomes
 - Gives resting energy expenditure
 - Direct calorimetry: put patient in sealed chamber and measure heat production
 - Fick Principle: calculating cardiac output, PaO₂ and ScvO₂ from a PAC. Excludes O₂ consumed by lung
- Aim is to titrate caloric intake to REE
- RQ (respiratory quotient):
 - = $\text{VCO}_2 / \text{VO}_2$ (CO₂ production and oxygen consumption)
 - VO₂ measured from (arterial – venous O₂) * CO does not measure lung oxygen consumption
 - If high, then ?excess carbohydrate load/Over-feeding: Excess calories are converted to fat – a process with a RQ of 9 owing to excess CO₂ production. Reduce caloric intake and consider changing to a high fat intake
 - Some use serial measurements of respiratory quotient to tailor feeding regimes. Lots of confounders. Neither sensitive or specific:
 - A RQ < 0.85 may indicate underfeeding
 - A RQ > 1 overfeeding
 - RQ for fat is 0.7, protein 0.8 and carbohydrate 1.0
 - If failing to wean may need less carbohydrate given greater CO₂ production
- General consensus 25 kCal/kg/day:

- Based on 2000 kCal a day in a healthy 80 Kg man
- Some evidence that less may be better in enteral feeding. Arabi 2011 in Saudi Arabia: target of 60% better than 100% for mortality (?U shaped curve)
- Eden Study (JAMA 2012, ARDSNET group) in RCT of 1,000 ARDS patients, randomised to full feeding or tropic feeding over the first 6 days (~ 20% requirements), achieved good separation between 2 arms (400 vs 1400 calorie delivery), no difference in ventilator free days, LOS, mortality. Suggests it doesn't matter how much we give in the first week (and suggests TPN top up isn't required). Study excluded malnourished and obese patients
- CTG study planned on 60 vs 100% feeding
- Most just give 25 kcal/kg/day per day...
- Some patient groups you'd be worried about sub-optimal calorie delivery:
 - Trauma
 - Burns
 - Don't know how to feed obese patients – conflicting data

Protein

- Urinary nitrogen measurement too variable to guide requirements
- Generally given 0.15 – 0.2 g/kg nitrogen (1 – 1.25 g/kg protein) per day
- Highly catabolic (eg burns) up to 2 g/day protein

Enteral Nutrition

- Advantages of enteral route:
 - Cheaper
 - Simpler
 - Fewer infective complications
 - No risks of central line associated sepsis
 - Lipid containing TPN is immunosuppressive. Benefit shown from lipid-free TPN over lipid-containing TPN
 - Enteral feeding may protect against infective complications by maintaining gut integrity (but effect may be stronger in animal models [rats] than people). Not clear that increased gut permeability necessarily leads to bacterial translocation. Positive studies in gut trauma and pancreatitis (and other conflicting ones – generally they're all old)
- Disadvantages:
 - Tube complications:
 - Misplacement: pneumothorax, pulmonary infusion, sinusitis
 - Trauma: pressure areas on nose/lip, trauma to nasopharynx, oesophagus, stomach. → perforation, haemorrhage.
 - Feed complications:
 - Difficult to achieve nutritional targets
 - Independent risk factor for VAP
 - ↑Diarrhoea – although usually multifactorial (antibiotics, C difficile, faecal impaction, malabsorption, prokinetic agents, magnesium, sorbitol containing medications [liquid paracetamol]...). No evidence that changes in composition (eg adding fibre, probiotics) changes incidence. One small study of fibre showed no difference, one in pancreatitis showed ↑risk of bowel ischaemia with probiotics
 - Hyperglycaemia
 - Electrolyte abnormalities
- Options for route of enteral feed:
 - Nasal tubes preferred to oral, except for base of skull fractures
 - Large bore to start with when residual volumes need to be checked. Reduce to small bore when feed established. Coke, fruit juice or pancreatic enzymes instilled for an hour to unblock
 - Naso-jejunal tube:
 - If impaired gastric emptying is refractory to pro-kinetics
 - Needs endoscopic or fluoroscopic guidance for reliable placement. Spontaneously migrating tubes available
 - Conflicting studies on whether they reduce VAP (Meta-analysis by Jiyong, Clinical Nutrition 2013, says it does)
 - Small bowels seems to resume function earlier than stomach
 - ENTERIC Study (CCM 2012) – Multicentre ANZICS RCT no difference in quantity of nutrition delivered between a spontaneously migrating nasojejun tube compared to NG tube in ICU patients with elevated gastric residual volumes

- PEG: better tolerated and less likely to be misplaced than naso-gastric. Can assess and retrieve gastric contents if large bore and in stomach, avoids interfering with gastro-oesophageal sphincter. More complex and expensive to insert, percutaneous wound, risk of trauma or displacement. Generally reserved for long term feeding – high 30 day mortality in the acutely ill
- Percutaneous feeding jejunostomy: better tolerated and less likely to be displaced. Allows for earlier feeding (avoids gastric distension and gastroparesis), theoretically better for pancreatitis. Requires endoscopy and/or surgery to insert, small bore → less tolerant of bolus or high volume infusions, potential for blockage (eg with enteral drugs)
- When to start:
 - There is physiological evidence of gut mucosal impairment with fasting. Leads to subsequent ↓absorption when feeding commences
 - Trend is to earlier nutrition but evidence is scant
 - Eden Trial (Rice et al, JAMA 2012): RCT of 1,000 relatively young, well-nourished patients within 48 hours of diagnosis of ALI, randomised to 6 days of trophic or full feeding. No difference in mortality or physical function at 1 year. Both groups of survivors had substantial physical, psychological and cognitive impairment
 - Doig (2009), meta-analysis of 6 RCTs total 239 patients: improved mortality and ↓pneumonia if enteral nutrition started in 48 hours. Meta-analysis of 13 trials (n = 1,173) shows benefit of EN within 24 hours of intestinal surgery vs later. (Lewis, J Gastrointestinal Surgery Mar 2009)
 - Evidence that small intestinal mucosa is affected by fasting
- Titration:
 - Risk of high residuals is aspiration. Some studies have found an association between VAP and high residual volumes, others not (eg Reigner JAMA 2013, MRCT in 452 patients. No difference in VAP between usual practice and not monitoring residuals
 - Wide variation in what gastric residual volume is too much. REGAIN Study (2010) randomised GRV of 200 vs 500 showed no difference in safety. However, large GRV suggests slow gastric emptying.
 - Post-pyloric tubes do not seem to increase amount of feed in RCTs – although often used in persisting high residual volumes
 - Not proven that slow titration avoids diarrhoea or high gastric residuals
 - No evidence that concentrated feeds reduces residuals
 - Small study evidence that running feeds right till they leave for OT is not harmful and ↑ caloric intake
- Composition:
 - Polymeric feeds: intact proteins (from whey, meat, soy and caseinates) and complex carbohydrates. Need pancreatic enzymes to digest
 - Elemental feeds: not of benefit routinely. May help with impaired small bowel absorption. Generally only in bad pancreatitis with lots of diarrhoea to try and improve absorption
 - Lipids usually from long chain triglycerides from vegetable oils, some contain more easily absorbed triglycerides
- Anastomosis:
 - Weak evidence supports early gastric or oral feeding is safe
 - Animal studies show that histologically anastomosis heal better with earlier feeding
- When to switch to parenteral: Recommended if failing enteral feeding despite a rigorous feeding protocol for 5 days. Little robust evidence to guide us
- Gastric Residuals:
 - REGANE Trial, Mortejo, ICM 2010, n = 329, residual volumes of 500 ml were safe
 - NUTRIREA 1, Reigner, JAMA 2013, n = 449, NOT measuring gastric volumes did not ↑risk of aspiration or complications
 - These trials showed that allowing large residuals → ↑feed but no effect on clinical outcomes

Prokinetics

- Principle: a major limitation of early enteral feeding is slow gastric emptying, leading to ↑gastric residuals, reflux and aspiration
- Intolerance may be suggested by diarrhoea, abdominal distension, nausea and vomiting despite low gastric volumes. Absence of bowel sounds is common in ventilated patients, not specific for ileus
- Most studies have demonstrated improved gastric emptying with cisapride (10 mg QID), erythromycin (250 mg BD) and metoclopramide (10 mg TDS)
- If 2 successive residuals > 250 ml, metoclopramide 10 mg TDS or erythromycin 250 mg bd iv seems to improve tolerance, but no discernible effect on mortality or morbidity. Tolerance develops (especially to erythromycin)
- Australian study shows erythromycin + metoclopramide > erythromycin > metoclopramide
- Erythromycin is a motilin agonist – new non-antibiotic motilin agonists in the pipeline

- However:
 - No double blind studies
 - Only small studies
 - No studies have shown any improvement in clinical outcome (ie mortality, infection incidence)
 - Most studies haven't reported APACHE scores
 - Use of other drugs influencing gastric motility (eg opioids) unequal or not reported
- Side effects:
 - Cisapride: not commonly available. Cardiac arrhythmias
 - Erythromycin: nausea, vomiting, diarrhoea, arrhythmia (dose dependent and unlikely at 100 – 200 mg BD), risk of resistance
 - Metoclopramide: confusion, agitation, somnolence, dystonic reactions
- Enteral naloxone also proposed: need 8 mg – huge dose \Rightarrow expensive
- Bottom line: prokinetics seem to have a beneficial effect on gastrointestinal motility in critically ill patients. Concerns about safety and the lack of outcome data preclude strong recommendations

High Ileostomy Losses

- Exclude:
 - C difficile
 - Intra-abdominal sepsis
 - Sudden cessation of opioids
- Try:
 - Antimotility drugs (loperamide, codeine)
 - Anti-secretory drugs (octreotide)
 - H2 antagonists, PPIs, occasional steroids

Parenteral Nutrition

- Background:
 - 10 – 20 years ago TPN reduced in popularity due to concerns about high infection rates, liver function abnormalities, high blood sugars in an age of tight glucose control, and the growing physiological evidence to maintain enteral nutrition.
 - Now better feeds – more modern lipids (used to be soya based, now also fish and olive oils with medium chain fatty acids), better concentrations of glucose and protein
 - Trials generally exclude patients who are malnourished at the start (a reasonable proportion of ICU patients)
 - European guidelines have favoured earlier PN compared with American and Canadian Trials
- Standard feed: 1ml/kg/hr of iso-caloric feed in a double or triple phase bag. Aiming for 25 cal/kg lean body weight/day. Can calculate actual requirements with indirect calorimetry – but not many can do this.
- NEJM 2011, Caesar et al: Belgium study of early vs late TPN (EPaNIC trial):
 - 4640 patients, including high proportion of cardiac electives (with tight glycaemic control in both arms)
 - All had “insufficient” enteral nutrition +/- early PTN
 - All given sufficient dextrose to meet caloric requirements till day 3 or 8. We would not usually feed these patients at all
 - Endpoint was ICU LOS
 - Early TPN worse: \uparrow LOS and \uparrow mortality
 - Conclusion: if you give lots of TPN then you need insulin!
- Doig et al (JAMA 2013, ANZICS CTG Trial), Early Parenteral Nutrition Trial, MRCT of 1372 patients with relative contraindications to early EN, randomised to immediate PN or pragmatic stand of care (mean 2.8 days to EN or PN). No difference in 60 day mortality. Small (?clinically meaningful) improvement in muscle mass and ventilator free days. Is the real problem our aversion to early EN?
- CALORIES Trial:
 - Harvey et al, NEJM Oct 2014
 - Sought to answer the question as to whether risks of TPN outweighed benefits in terms of supposed superior achievement of caloric targets over often-interrupted NG feeding
 - RCT in 33 English ICUs, n = 2400, assigned to either NG or TPN within 36 hours of admission for 5 days. In TPN there was less hypoglycaemia (3.7 vs 6.2%) and vomiting (8.4 vs 16 %), no difference in number of infections or 90 day mortality (37.3 vs 39.1%)
- Top-up TPN:

- Some resurgence in “top-up” TPN but small studies nor meta-analysis do not yet show mortality benefit. Larger trials awaited. The rationale is that patients often have inadequate or frequently interrupted enteral feeding
- Lancet 2013, n = 305. Supplemental PN on days 3 – 8 not meeting EN targets (<60% target determined by indirect calorimetry). EN got 73% target, PN 103%. → ↓ antibiotic days but same infection rate in first 28 day (ie not worse but not better!). SPN (Supplementary Parenteral Nutrition) Trial, Heidegger
- Elke et al (2013), secondary analysis of VISEP study (Insulin Control in Severe Sepsis in patients > 7 days in ICU), comparing EN, PN and EN + PN. More calories delivered in the EN + PN route but higher mortality and secondary infection
- Monitoring with TPN:
 - 4 hourly glucose when commencing
 - Daily urea, electrolytes and creatinine
 - Weekly FBC, coags, LFTs, Mg, Ca, PO4, weight
 - Best assessment is indirect calorimetry – but generally impractical
- Composition:
 - Energy:
 - Provided by CHO and lipid – optimal balance unknown. Can provide all energy from glucose and just infuse essential lipids (linoleic and linolenic acids) once or twice a week
 - Some concerns about immunosuppression from lipids (↓neutrophil function, etc.)
 - Lipids mainly from soybean oil emulsified with glycerol and egg phosphates
 - Care not to exceed bodies capacity to metabolise glucose (4 mg/kg/min in the septic patient) otherwise hypoglycaemia, lipogenesis and ↑CO₂ production. May need exogenous insulin
 - Nitrogen: L-amino acids. Glutamine, tyrosine and cysteine often absent due to instability
- Complications:
 - Line issues:
 - See Central Line Infections, page 285
 - One lumen should be dedicated to TPN
 - Misplacement
 - Bleeding
 - Air embolus
 - Nutrition related:
 - Electrolyte abnormalities: especially ↓PO₄, ↓K and ↓Mg in the first 24 – 48 hours
 - Hyperchloraemia from amino acid solutions with high Cl content. Can replace some of this with acetate
 - Rebound hypoglycaemia when TPN is stopped suddenly. Wean over 12 hours
 - Metabolic acidosis
 - Liver dysfunction: hepatic steatosis, intrahepatic cholestasis and biliary sludging from gallbladder inactivity
 - Deficiencies of trace elements and vitamins (especially thiamine, folic acid and vitamin K)

Nutrition and Specific Diseases

- See also Obesity, page 348
- Renal failure:
 - Normal nutritional support is appropriate in acute renal failure
 - Specialised lipid or amino acid formulation in TPN not supported by evidence
 - Low potassium, low protein EN feeds advocated for renal failure, aiming to ↓dialysis requirements. Suggestion in the literature that higher protein (1.5 – 2 gm/kg/day) is actually better in renal failure, even if you have to wear an increase in dialysis requirements
- Respiratory failure: High fat feeds (and low CHO) have been proposed. But high fat content slows gastric emptying. No firm evidence.
- Liver disease:
 - No change in energy requirements in chronic liver disease
 - ↑Lipolysis so limit lipid to avoid hypertriglyceridemia
 - May need protein restriction in hepatic encephalopathy – start at 0.5 g/kg/day and titrate up slowly. Use of branched-chain amino acids (BCAA – possibly more encephalopathy friendly) may permit higher protein levels
 - Fat soluble vitamins and thiamine deficiencies common
- Acute pancreatitis: See Nutritional Support, page 172
- Burns: Burns Management, page 259

Adjunctive Nutrition

- Possibility of modulating immune or metabolic responses
- No benefit yet shown in unselected critically ill patients
- Studies complicated by studies of multiple compounds simultaneously at different doses in heterogeneous populations with a variety of outcomes with retrospective subgroup analysis used to demonstrate benefit, multiple meta-analysis attempting to aggregate heterogeneous studies
- Given the increased cost, lack of consistent benefit, and the potential for harm, the overall role in the critically ill is still to be established
- Micronutrients:
 - ↑requirements of vitamins A, E, K, thiamine (B1), B3, B6, vitamin C, folic acid...
 - Dialysis can cause loss of water-soluble vitamins and trace elements
 - Anti-oxidant vitamins: Vitamins A, C, E – not supported. Only study showing a benefit had high mortality in the control group....
 - Commercial preparations contain standard amounts of micronutrients
- Omega-3-fatty acids. No statistically mortality difference in meta-analysis of 8 small RCTs
- Vitamin D: Low levels of Vitamin D have increased mortality/morbidity in ICUs. Amrein et al, JAMA Oct 2014, single centre RCT, n = 492, supplementing ICU patients deficient in Vitamin D. No difference in hospital LOS or 6 month mortality. Lower hospital mortality in sub group with severe deficiency.
- Probiotics:
 - Reduced antibiotic associated C Diff diarrhoea (Hickson et al, BMJ 2007) with lactobacillus – no critically ill patients
 - Suggestion that they reduce the carriage of VRE
 - ↓nosocomial infections in trauma in RCT of small heterogeneous studies
 - Optimal preparations, appropriate bacterial species, and safety in immunocompromise still be determined
- Glutamine:
 - Nucleotide precursor, regulates gene expression, released from muscle in catabolic states, ?vulnerable to depletion
 - Contradictory studies, largest is negative (SIGNIT Trial) – but perhaps a signal there.... Meta-analysis of 40 trials (Booholder, Clinical Nutrition 2013) showed no change in mortality, but ↓infections and ↓LOS (heavily influenced by one large trial)
 - Heyland et al (NEJM 2013), MRCT in 1223 ventilated patients, ↑hospital & 6 month mortality with glutamine. No difference with antioxidants
 - Dipeptide form more stable in TPN
 - Study in burns (Crit Car Med 2003, Garrel et al) in 45 patients showed ↓mortality in burns
 - Study nearing completion of giving Glutamine BD as a drug.
- Selenium:
 - Crucial to regulation of glutathione peroxidase (most important plasma redox factor metabolising H₂O₂) → major scavenging system for oxygen free radicals
 - Oxidative stress: ↑O₂ free radicals and/or ↓scavenging, including in respiratory chain → cascade of damage → multi organ dysfunction, red cell lysis....
 - Trace element required in minute quantities. Naturally occurring in cereals grown in selenium rich soils
 - Small observational studies show that ↑APACHE score correlated to ↓selenium (?changed binding ?so what)
 - Intention to treat analysis of large randomised trial did not reach statistical significance
 - Meta-analysis of small trials suggests benefit (Huang et al, Alhazzani et al 2013)
 - Studies generally test a cocktail of anti-oxidants – beware of meta-analyses)
 - Watch this space... Large RCTs in progress (esp Canadian Clinical Trials Group)
- Arginine and immuno-nutrition:
 - Precursor to nitric oxide, nucleotides....
 - Meta-analysis suggest reductions in hospital stay and infections but not mortality, subgroup analysis of septic patients showed ↑mortality and subsequent trial in septic patients terminated for safety reasons

- See also:
 - Sedation in Ventilated Patients, page 88
 - Intensive Insulin Control, page 313

Multi-Disciplinary Team

- Effective interdisciplinary teamwork is based on:
 - Clear individual roles
 - Members who share knowledge, skills, best practice and learning
 - Systems that enable shared clinical governance, individual and team accountability, risk analysis and management
- Role of intensivist (Oh p 499): seeing the big picture, meticulous bedside care, negotiating and maintaining consensus, good communication and teamwork between various clinicians and the family

Nursing

- Nursing is a vehicle for enabling adaptive adjustments to any dysfunction
- Inadequate nurse staffing is linked to increase in adverse events, patient morbidity and mortality
- Potential roles:
 - Developing role in decision making, sophisticated monitoring and invasive procedures
 - Critical care outreach teams: caring for at-risk and deteriorating patients, and care of post-ICU patients
 - ICU management
 - Stress management and motivation
 - Nurse Education
 - Research

Physiotherapy

- Critical illness is a pro-inflammatory catabolic state. Exacerbated by bed rest. Postulated that early exercise decreases the inflammatory load.
- Weakness is correlated to ICU LOS and duration of ventilation

Optimisation of Pulmonary function

- Evidence is scant
- Aims:
 - Improve VQ mismatch
 - Increase lung volume by recruit collapsed lung
 - Reduce work of breathing
 - Remove pulmonary secretions
- Suction:
 - Of naso-pharynx and ET tube
 - Clear secretions from central airways where cough is impaired and may stimulate cough.
 - Disadvantages: invasive, contraindicated if unexplained haemoptysis, severe coagulopathies, severe bronchospasm, stridor, base-of-skull fracture, haemodynamic compromise. Tracheal stimulation may → sympathetic stimulation may → arrhythmias
- Manual Hyperventilation: self-inflating circuit delivers 150% Vt to recruit atelectatic lung. May mobilise secretions (by ↑expiratory flow rate or stimulating cough). However, ventilator hyperinflation as effective
- Recruitment procedures: different approaches – transiently improve oxygenation, no proven outcome benefit
- Manual Techniques:
 - Chest shaking and vibrations: during expiration to aid clearance. ↑sputum production if head down tilt over flat side-lying
 - Chest wall compression: expiratory “huff”
 - Chest clapping/percussion: mobilise secretions (little evidence)
 - Positioning: drainage of secretions via gravity-assisted positioning for specific bronchopulmonary segment (in conjunction with other techniques), reduction of work of breathing (optimise length-tension relationship of the diaphragm, promote relaxation of the shoulder girdle, eg high side-lying in NIV, discourage use of accessory muscles), optimise VQ (improve ventilation of dependent, better

perfused areas of lung – eg prone positioning in ARDS improved oxygenation but outcomes controversial)

- Active Cycle of Breathing Technique (ACBT): needs alert patient – 4 breaths aimed at breathing control, 4 aimed at lower thoracic expansion, huff
- Mechanical adjuncts:
 - Intermittent Positive-pressure breathing: augmenting V_t in self-ventilating patients throughout inspiration with passive expiration. Increases V_t (not FRC) → helps with secretions
 - Continuous positive airways pressure: increase FRC via recruitment of atelectatic lung (doesn't augment V_t)
 - NIV: ↑ V_t and FRC
- Assistance with weaning
- Risks:
 - Deterioration in gas exchange
 - CVS instability
 - Barotrauma
 - Rise in ICP
 - Increased patient pain, stress and anxiety

Early rehabilitation/mobilisation

- See Kayambu et al, CCM 2013, for systematic review. Positive benefits found in trials of moderate methodological quality for improvement in peripheral and respiratory muscle strength. QoL, physical function, ventilator free days, ↓hospital and ICU LOS, not mortality
- Deconditioning:
 - Affects cardiovascular (↓SV, ↑heart rate, ↓CO, orthostatic intolerance), respiratory (compliance, respiratory muscle function, diaphragmatic dysfunction) and neuro-muscular-skeletal system (muscle atrophy, ↓muscle endurance, muscle shortening, ↓bone density, critical illness neuropathy/myopathy is frequent in LOS > 1 week especially in sepsis, SIRS and severe MOF)
 - Orthostatic tolerance, bone mass and muscle endurance are slowest to recover
 - Compounds age, premorbid condition, nature of illness/injury
 - Leads to poorer outcomes, ↑LOS, ↓functional independence → ↑depression and ↓self-efficacy
- Non-linear pattern of exercise progression incorporating functional activity, assisted, active and resisted exercise, pain control and education
- May require eg ↑O₂ - ↑activity coincides with weaning – both of which challenge physiological reserves

Other Roles of Physiotherapy

- Advice on positioning to protect nerve/soft tissue/joint damage
- Muscle tone maintenance particularly in the neurological patient
- Voluntary movement to promote functional independence and improve exercise tolerance, maintaining joint function
- Assistance/advice with collars, braces, slings, TENS
- Advice/education for family members and carers

Obesity

- See also:
 - Trauma in Obesity, page 234
 - Effect of Obesity on Pharmacokinetics, page 332
 - Obesity Hot Case, page 374
- Definition:
 - BMI > 30
 - BMI > 40 or > 35 with comorbidity ⇒ severe, extreme or morbid obesity
 - BMI > 55 – super-morbidly obese
- Outcomes for the obese:
 - Conflicting evidence between obesity and outcome
 - Obesity paradox – in some groups of ICU patients, obesity seems protective
 - ↑mortality, greater duration of mechanical ventilation and ↑LOS - ?overall effect modest
 - In trauma, mortality increases after 4 days compared to non-obese
 - In cardiac patients, outcomes appear to be unaffected by obesity, except in extreme obesity
- Cardiovascular effects:
 - Blood volume and CO increase linearly with BMI. ↑DO₂ and ↑CO₂ production. Heart rate unaffected. Cardiac index unaffected

- Ventricular enlargement and wall thickness correlates to degree of obesity, decrement in cardiac performance relates to duration. 10 times the risk of HTN
- Higher resting cardiac filling pressures, increasing when supine (may → pulmonary oedema)
- Non-invasive BP may underestimate actual BP ⇒ invasive monitoring more common
- Pulmonary function:
 - ↑elasticity, mainly due to ↓chest wall compliance, also ↓lung compliance
 - May ↑respiratory resistance due to early airway closure
 - Higher work of breathing → higher resting O₂ consumption
 - ↓Functional residual capacity, total lung capacity and vital capacity unchanged, likely ↓FEV₁
 - Hypoxaemia corresponds to ↓FRC 2nd to airway closure and atelectasis. Worse under anaesthesia and when supine
 - Calculate tidal volume on ideal rather than actual body weight, prophylactic PEEP up to 10 cm and reverse Trendelenburg position
 - Higher risk for OSA: see Obstructive Sleep Apnoea, page 105
 - Obesity Hypoventilation Syndrome: Reduced ventilatory response to ↑CO₂
 - Akinnuse et al, Crit Care Med 2008, Meta-analysis of 14 studies of 15,347 patients comparing obese and non-obese. Obesity is not associated with ↑mortality but is associated with prolonged ventilation and ICU LOS
- Other:
 - More difficult airway
 - Fatty liver. Reverses with weight loss but progresses to steatohepatitis and cirrhosis if untreated
 - Increase insulin resistance
 - High aspiration risk given gastro-oesophageal reflux and ↑intra-abdominal pressure
 - Increase risk of pressure areas
 - Implications of stigma
- Nutrition:
 - Characterised by a number of metabolic derangements:
 - Insulin resistance
 - Hyperlipidaemia
 - Pro-inflammatory state
 - ↑resting energy expenditure, with central adipose tissue being more metabolically active than peripheral adipose tissue. Whether to use actual or ideal body weight in estimating equations is contentious
 - Small studies of hypocaloric feeding showed little benefit – none has shown a worse outcome. Treat as normal
 - Some argue for a high protein, low carbohydrate feed. Most studies using this method give:
 - 11 – 14 kcal/kg/actual body weight per day or 22 – 25 kcal/kg IBW per day, equating to about 60 – 70% of calorie requirement determined by indirect calorimetry
 - Meet protein requirements to maximise protein synthesis and preserve lean body mass (2.0 – 2.5 kg/kg IBW/day)
- Central venous access:
 - Normal anatomic landmarks obscured
 - In adults, use of US for IJ and femoral veins unequivocally decreases the risk of failed placement, and gives faster placement
- DVT prophylaxis:
 - Obesity is an independent risk factor of DVT
 - Most studies in bariatric surgery
 - Small trials suggest that weight based prophylaxis is better than fixed dose 40 mg for BMI > 30 (eg 40 mg bd better than 30 bd with no difference in bleeding). Not yet incorporated into major guidelines

DVT Prophylaxis

- See also:
 - Anticoagulation, page 296
 - Obesity, page 348
- PE most common cause of preventable hospital death
- Risk factors:
 - Environmental: surgery, trauma, cancer, immobility, recent sepsis... (applies to most ICU patients)
 - Haematological: Protein C or S deficiency, AT3 deficiency, Factor V Leiden, Lupus anticoagulant
- Investigations for DVT:

- Compression ultrasonography: sensitivity 97% and specificity 94%, non-invasive
- D-dimmer: negative test has predictive value of 100%. Positive test has sensitivity of 100% and specificity of 60%
- MRI has good specificity and sensitivity (and safe in pregnancy)
- Renal failure: Paucity of data on dosing as most trials exclude CrCl < 30. Anti-Xa monitoring is not recommended to assess efficacy due to unreliability with low doses in renal failure
- Drugs:
 - No studies compare TDS heparin with LMWH, but BD not inferior to TDS
 - Fondaparinux: synthetic LMWH. Meta-analysis of 4 RCTS in orthopaedic patients: Fondaparinux superior to enoxaparin for DVT, with no difference in complications. OK in HITS
 - PROTECT Study in a multicentre RCT of 3764 critically ill patients of dalteparin (5000 IU sc OD) vs UF heparin (5000 IU sc BD) for proximal vein thrombosis: dalteparin not superior (approx. 5% in each), but proportion of patients with PE and incidence of HITS lower in the dalteparin group (not statistically significant)
- Mechanical methods:
 - Intermittent pneumatic compression (IPC) alone effective in surgical patients in meta-analysis, not in PVD. Hypothetical risk if starting after ~ 3 days unprotected immobility. CLOTS Trial, Lancet 2013, IPC, MRCT in 2876 immobile stroke patients. DVT in 8.5 vs 12.1%, trend to ↓ mortality (11 vs 13%, $p = 0.057$), ↑ leg skin breaks (3% vs 1%)
 - IVC filter

Pressure Area

- Risk factors for pressure area:
 - Local factors:
 - Duration of surgery
 - Faecal/urinary incontinence
 - Moisture
 - Impaired circulation, vasopressors
 - Neurological impairment: paralysis, ↓ sensation
 - Systemic factors:
 - Low albumin
 - Obesity
 - Diabetes
 - Too unstable to turn
 - Decreased mobility
 - High Apache 2 score
- Assessment:
 - Severity of ulcer: size and depth. Serial photos may help management
 - Signs of infection: local and systematic
- Management:
 - Dressings: occlusive or semipermeable dressing that will maintain a moist wound environment
 - Treat infection
 - Surgery: options from debridement through to grafting
 - Pressure relief:
 - Positioning and regular turns
 - Pressure relief devices: mattresses, gel pads, sheep skins
 - Avoid friction
 - Manage urinary/faecal incontinence
 - Wound specialist involvement
 - Supportive care
 - Early mobilisation
 - Adequate analgesia
 - Nutrition
- Collect information for audit and review unit protocols

Swallow Assessment

- Usual phases of swallowing:
 - Oral preparatory: mastication and creation of a bolus

- Oral transit: delivering the bolus to the back of the tongue, soft palate rises
- Pharyngeal: most complex phase. Pharyngeal constriction to create a pressure gradient, breath holding, elevation of arytenoids, cord adduction and epiglottic inversion
- Oesophageal phase: Peristaltic waves carry bolus with relaxation of oesophageal sphincters
- Causes of poor swallow:
 - Neurological (stroke, head injury, GBS)
 - Drug induced: anticholinergic, neuroleptic
 - Mechanical: trauma
 - Tracheostomy
 - Pre-existing problems: diverticular, pouch, CREST
 - Infection
 - Myopathy
- Assessment of swallow:
 - General: are they well enough to co-ordinate swallowing
 - History: hoarseness, weak cough, slurred speech
 - Clinical assessment:
 - Cranial nerves, oral cavity, dentition, dry mouth
 - Motor movements of mouth: strength, symmetry, speed, accuracy
 - Strength of cough and timing and fullness of laryngeal excursion
 - Test of swallowing – varying consistencies of food mixed with dye. Suction tracheostomy after each. False negatives are common \Rightarrow persisting vigilance required
- Investigations:
 - Nasopharyngeal laryngoscopy: visual inspection
 - Video fluoroscopy: assesses aspiration, pooling of secretions and muscle movements
 - Barium swallow: identifies anatomical abnormalities, diverticula, tumours
 - Upper GI endoscopy

Stress Ulcer Prophylaxis

- Presentation of Stress Ulcers:
 - Associated with shock, sepsis, burns, multiple trauma, head injuries, spinal injuries and respiratory, renal and hepatic failure, steroids
 - Major risk factors (1994 study of 2,000 patients):
 - Ventilation > 48 hours
 - Coagulopathy (INR > 1.5, plts < 50)
 - Risk if one or both ~ 3%, if neither then 0.1% risk
 - Usually in gastric fundus
 - Mechanism unclear: likely related to hypoxia and hypoperfusion
 - Stress ulcers rare: 1 – 2 % of ventilated patients. Incidence declining due to better:
 - Management of hypotension and hypoxaemia (eg better resuscitation)
 - Prophylaxis
 - Perforation rare (< 0.5 % of surgical ICU patients)
- Prophylaxis:
 - Aiming for gastric alkalisation with pH > 3.5
 - Incidence of ulceration lower but no improvement in survival shown
 - Concerns about gastric bacterial overgrowth and associated nosocomial pneumonia not substantiated by existing data
- Little consensus on choice of prophylactic agent:
 - Antacids: Now less common. Gastric pH monitoring is necessary. May \rightarrow excessive intake of Mg, Al, Ca, or Na. Bowel stasis and diarrhoea can occur
 - Sucralfate: An aluminium salt which \rightarrow \uparrow mucus secretion, \uparrow mucous blood flow and \uparrow local prostaglandin production \rightarrow better healing. Doesn't alter gastric pH \rightarrow G-ive colonisation unlikely
 - H2 receptor antagonists:
 - Compete for histamine receptor on the parietal cell. Tachyphylaxis after day 1. Some data suggests little benefit
 - \downarrow GI bleed if not feed
 - No benefit of H2 blockers if enterally feed. \uparrow risk of mortality if enterally feed
 - Hospital acquired pneumonia: no \uparrow risk of H2 blockers if not enterally feed, \uparrow risk if enterally feed
 - See Marik, CCM 2010, Chanpura CCM 2012

- Protein Pump Inhibitors:
 - 2 non-randomised studies have shown IV omeprazole protects critically ill patients. No prospective trials to indicate who are the high risk patients
 - PPI vs H2 blockers (Meta-analysis 2012 and Crit Care Med 2013, 1720 patients):
 - Variety of studies with different criteria
 - PPIs better, no difference between them in VAP and mortality
 - Studies may be out of date due to trend to early EN
 - Limitations of PPI:
 - Pneumonia: controversial – only in meta-analysis – not in any individual RCT
 - ↑Enteric infection, including C Difficile: from observational correlation only
 - ↑Fractures
 - Rare interstitial nephritis
- Assumed to be of benefit:
 - Adequate resuscitation
 - Correction of coagulopathy
 - Avoiding precipitants (eg NSAIDs)
 - Early enteral feeding. Enteral feeding → OR of an ulcer of 0.3 ⇒ really not indicated at all if feed – although the recommendation is still for PPI if high risk

Delirium and Pain

- See
 - NEJM review article, Reade et al, 2014
 - Clinical Practice Guidelines for the Management of Pain, Agitation and Delirium in Adult Patients in the ICU, Barr et al, CCM 2013 (extensive evidence based guideline)
 - Reston et al, In-facility delirium Prevention Programs as a patient safety strategy, Annals of Medicine, 2013
- Several quality improvement bundles have been developed, emphasising improved communication, standardised care, early mobilisation

Pain

- Pain is commonly and often poorly treated. It is the most common memory people have of their ICU stay
- Consequences of untreated pain:
 - Short term: ↑energy expenditure, immunomodulation
 - Long term: ↑PTSD
- Procedural pain is common. The three most painful procedures are chest tube removal, wound drain removal, arterial line insertion (Puntillo, Am J Resp Crit Care Med 2013)
- Validated pain monitoring scales (useful as HTN and tachycardia correlate poorly with pain):
 - Behavioural Pain Scale
 - Critical Care Pain Observation Tool (CPOT)
 - Vitals observation alone is likely to be poorly sensitive and specific, but is a useful queue to further assessment
- Treatment:
 - IV Opioids are first line in non-neuropathic pain
 - All IV opioids, when effectively titrated, are equivalent (weak evidence)
 - Non IV opioids can be considered to reduce opioids (weak evidence, weak recommendation)
 - Either enterally gabapentin or carbamazepine (in addition to IV opioids) for neuropathic pain (strong evidence)
 - Thoracic epidural for AAA, no evidence about lumbar for AAA or thoracic for intrathoracic AA
 - Thoracic epidural for patients with traumatic rib fractures (Grade 2B)

Delirium

- Disturbance of consciousness with inattention accompanied by a change in cognition or perceptual disturbance that develops over a short period and fluctuates over time (DSM 4). Occurs as a result of a general medical condition and is not better accounted for by a pre-existing dementia. Inattention is one of its hallmarks
- Classified as hypoactive, agitated or mixed
- Diagnosis in the critically ill patient:
 - Subjective: Not diagnosed by ICU staff in nearly ¾ of patients with delirium
 - Objective:
 - ICDSC: Intensive Care Delirium Screening Checklist

- CAM-ICU: Confusion Assessment Method for ICU – four areas assessed on history or simple tests. You have to be squeaky clean not to have delirium:
 - Acute onset or fluctuation
 - Inattention
 - Altered level of consciousness (using a Richmond agitation score of ≤ 0)
 - Disorganised thinking
- Measures of brain function (eg BIS) are not recommended in un-paralysed patients, and they are inadequate substitutes for subjective sedation scoring systems (moderate evidence)
- Routine monitoring is recommended and feasible
- Prevalence: reported as being > 80% of ICU patients
- Risk factors for delirium:
 - Age
 - *Previous cognitive impairment*
 - *Illness severity*
 - *Alcohol & nicotine*
 - Fever
 - Metabolic disturbance
 - Sleep disturbance
 - Drugs: opioids (conflicting evidence), benzodiazepines. Insufficient data on propofol
- Impacts:
 - Longer LOS
 - ↑Mortality
 - ↑Community care/nursing home placement
 - Long-term cognitive dysfunction
- Prevention/treatment:
 - Early recognition
 - Stabilise/ensure safety of patient (including ABC)
 - Identify precipitants: metabolic, hypoxia, infective, drugs, drug withdrawal, alcohol, cerebral event, etc. and treat
 - Lighter sedation (increased arousal is not associated with ↑myocardial ischaemia)
 - Non-pharmacological:
 - Mobilisation (Grade 1B recommendation)
 - Sleep hygiene: control light and noise, cluster patient care activities, decreasing stimuli at night (weak evidence, strong recommendation)
 - Early de-escalation of monitoring
 - Orientation, including with family
 - Hearing aids, glasses and dentures
 - Treat pain, constipation and urinary retention
 - Evidence outside of ICU suggests a number of measures may prevent delirium
 - Pharmacological management:
 - “Analgesia-first” sedation. Treat pain *then* sedate
 - Beware polypharmacy
 - No compelling evidence demonstrates the effectiveness of a pharmacologic prevention protocol
 - Avoid precipitating drugs: benzodiazepines, opioids, anticholinergics (eg TCAs, atropine, antihistamines). Non-BZD (propofol, dexmedetomidine) are preferred over BZDs (moderate evidence, weak recommendation)
 - Thiamine if indicated
 - For hyperactive delirium, use of haloperidol or possibly atypical antipsychotics eg olanzapine or quetiapine (except if long QTc). Weak evidence in studies that didn’t differentiate between hypo and hyperactive delirium. There are no FDA drugs approved for the treatment of delirium)
 - $\alpha 2$ agonists, eg clonidine
- Implementation of a bundle of interventions to reduce night-time disturbance (sound, light, ↓awakenings for cares) in a before/after study, n = 338, delirium 33% → 14%, Patel Anaesthesia 2014
- RCT in 373 ventilated patients of patient initiated music vs noise cancelling headphone vs none showed the music group had less sedation and less anxiety (Chlan, JAMA 2013)
- Do windows or natural views affect patients, retrospective study of 6,000 patients, no difference in mortality or delirium. Didn’t measure effect on families or staff. CCM 2013, Conn et al.

Sleep

- Reason for sleep still unclear – but lots goes wrong without it
- Poor sleep and short sleep (< 6 hours) in the general population → ↑IHD and cancer in addition to ↓ wellbeing
- Sleep deprivation in ICU:
 - Short and fragmented (often only minutes at a time)
 - Difficult to isolate impact from underlying illness. No clear cut evidence of causal impact on delirium
- Impacts on sleep:
 - Illness and inflammatory mediators
 - Modes of ventilation
 - Environment: noise (living next to a busy road → poorer health after controlling for other variables)
 - Delirium → sleep/wake disturbance (direction of causality unclear)
 - ICU patients rarely reach level 3 or 4 or REM sleep (in OSA patients this correlates with unrestorative sleep)
- Measurement:
 - Polysomnography the gold standard (measure EEG and eye movement)
 - Richard Campbell's Sleep Questionnaire (validated analogue scales)
- Improving sleep:
 - Quieter environment
 - Clustering sick and well patients
 - Treating pain/anxiety
 - Earplugs: Small single centre RCT showing benefit (Crit Care May 2012)
 - Drugs:
 - ??low dose propofol at night
 - Consider low dose antipsychotics
 - No strong evidence for melatonin

Other

- Thirst: single blinded RCT in 3 centres of a thirst bundle (oral swab wipes, sterile ice-cold water sprays and a lip moisturizer) vs standard care materially reduced thirst intensity and/or thirst distress, halving incidence of dry mouth on day 1. (Puntillo, ICM 2014)

Age Related Factors

- Cardiovascular:
 - High incidence of coronary artery disease
 - Less responsive to sympathetic stimulation
 - Greater diastolic dysfunction
 - Already on cardiac drugs → interactions and side effects
- Respiratory:
 - ↓ventilatory response to hypoxia and hypercapnea
 - ↓chest wall compliance, muscle strength and ↑closing volumes
- Renal:
 - ↓in renal function
 - ↓muscle mass ⇒ creatinine understates renal impairment
- CNS: high incidence of delirium, age related loss of cerebral volume
- Musculoskeletal:
 - ↑risk of pressure sores
 - Arthritis/pre-existing poor conditioning → pain and difficulty mobilising
- Pharmacology:
 - Altered pharmacokinetics
 - ↓renal and hepatic clearance
 - ⇒ need dose adjustments, ↓↑sensitivity to sedation and analgesics
- Greater operative and ICU related morbidity and mortality well documented

Problems after ICU

- Risk assessment for problems on transfer to ward. See Hosen et al, Crit Care 2013, for review of 8 risk assessment tools. May help target transitional interventions (eg MET team, outreach nurse, etc.)

- Increasing interest in morbidity as well as mortality post ICU: There is more to life than measuring death (Kings Fund 1989)
- Rehab following ICU can fall in the cracks: multi organ failure gets carved up between various outpatient departments and GPs
- 1 year follow-up of 115 of 1,000 patients in Eden trial (nutrition in ALI), survivors (both arms pooled) had impairment in 6 minute walk (66% predicted) and cognitive impairment in 25% at 12 months
- Assessing morbidity:
 - Objective:
 - QALY (Quality of life tool)
 - Glasgow Outcome Scale
 - Subjective:
 - HAD (Hospital Anxiety and Depression)
 - PQOL (Perceived Quality of Life)
 - EuroQol (European tool)
 - SF36 (36-item short-form survey)

System Specific Long Term Problems

- Airway: See Complications of Tracheostomy, page 97
- Limited motility:
 - Poor muscle tone or wasting, joint pain or stiffness, critical illness neuropathy/myopathy. Muscle relaxants implicated but not shown to be statistically significant in terms of weaning time or LOS
 - Prospective follow-up of 220 survivors of ALI after 2 years (CCM April 2014):
 - Muscle weakness in 1/3 at 12 months
 - Correlating to duration of bed rest. Steroids/NMBA not associated with muscle strength
- Skin: hair loss, nail ridging, itching, pressure sores, scarring for ET tube tap
- Eyes: Ocular trauma, visual acuity reduced following prolonged hypotension
- Infection: colonisation with MDR organisms
- Sexual dysfunction: untreated given embarrassment of reporting it. Exclude drugs (L-Dopa, H2 blockers), surgery (AAA repair), trauma/radiotherapy to pelvis, diabetes
- Loss of appetite
- Poor sleep, nightmares
- Poorly fitting clothes
- Unnecessary medications started acutely but not stopped (amiodarone, omeprazole)
- Psychological problems:
 - Memory impairment – don't have a structured memory of ICU stay, However false memories or delusions can have a negative impact on psychological recovery and factual memories may reduce anxiety
 - Cognitive Impairment: Pandharipande, NEJM 2013, prospective study of 821 medical and surgical ICU patients (with either respiratory failure or shock). At 12 months 34% has scores similar to moderate TBI and 24% similar to mild Alzheimer's
 - PTSD: in about 15 - 27.5% in ARDS, nightmares
 - Depression: Jackson, Lancet Respiratory Medicine 2014, follow up of 821 patients with respiratory failure or shock in the BRAIN-ICU study. Depression present in 29% at 12 months (in 382 followed up) in those without a history of depression
 - Chronic Fatigue Syndrome: presence of fatigue at 6 months impairing daily living without other medical cause. Graded exercise programme helps, fluoxetine doesn't
 - Griffiths et al, BMJ 2013, n = 293, 12 months after discharge, 73% had moderate or severe pain, 44% had significant anxiety or depression, 28% had ↓learning ability and 32% had a family member with ↓learning ability
- Factors during ICU stay:
 - Continuous sedation → ↑ LOS. Use daily interruption
 - Etomidate causes excess mortality in trauma patients
 - Small association of midazolam with discharge on oral benzodiazepines
 - Natural day light helps establish circadian rhythms

- See
 - College Policy IC-14 on Withholding and Withdrawing Treatment (very brief)
 - ANZICS policy on Organ Donation (very thorough)

Withdrawing or Withholding Treatment

- See also Ethics in Intensive Care, page 12
- See College Policy IC-14 on Withholding and Withdrawing Treatment
- We can't cure everything. We have medicalised death and often do too much to prevent it.
- Deciding for others should be a last resort. Three different approaches:
 - Substituted judgement:
 - A person with knowledge of the patient's values or wishes makes a decision which they believe the patient themselves would make
 - This person is called a surrogate. If court appointed they are called a guardian (protect a person's autonomy by taking it from them!)
 - Best interest standard:
 - When a person makes a decision about a patient they consider to be in the patient's best interests
 - Studies have shown medical staff and surrogates have different approaches
 - Supported decision making – assisting a person with reduced decision making capacity to make decisions
- Capacity:
 - Presumption is that a person has "capacity". You've got to prove they don't
 - Dementia doesn't preclude capacity
 - Person must understand the nature and effect of the decision to be made, and be able to communicate this
- Withholding vs withdrawing treatment:
 - The consensus view is that they are ethically equivalent (I disagree!)
 - However, we prefer with-holding treatment because we feel less morally responsible
 - The ability to withdraw treatments enables us to give trials of therapy
 - Particular issues:
 - A pacemaker – is it like a ventilator or a transplanted kidney?
 - Are tube feeding and oral feeding ethically equivalent?
- Particular issues in ICU:
 - See Campbell, et al, Am J Resp Crit Care Med, 2012
 - Are there patients dying in the ICU who would not have chosen this? Rather than focusing on predicting outcomes (which we're bad at), should we focus on the intensity of care the patient would want (ie are we achieving the patient's goals)?
 - Are there patients for whom earlier palliative treatment would have reduced costs without affecting treatment? But will shortening stays in ICU actually reduce costs, since many costs are fixed?
 - Those patients for whom family want everything done despite trivial chance of survival are a small group, and should not be our primary focus
 - Evidence suggests the quality of communication about end of life remains poor. Evidence from cancer and elderly patients suggests good communication reduces ICU admission and improves quality
- Surveys of community concerns about terminal illness rank as follows:
 - Loss of mental faculties
 - Loss of control
 - Loss of independence
 - Last... Dying
- A just health care system offers people what they are entitled to (they can choose to accept it or not) and does not offer what they are not entitled to (which includes futile or non-beneficial care)

Advanced Care Planning

- US data: 29% of Medicare deaths have an ICU admission in the last month of life (JAMA 2013)
- Process should be values → goals → specific treatments. Encourage people to think about values before talking about ACP. See Personal Values Profile, Barwon health, Attitudes to medical treatment
- Outline of an "end of life" discussion in a terminal-illness-but-not-dying patient:

- Establish current status of illness. “Just so we’re on the same page, tell me what’s been said so far...”
- Invite a conversation. “Can we talk about what the future might bring...?” Discuss the unpredictable natural history. Describe the rationale for discussing future decisions now
- Identify patient perceptions and questions about the future:
 - Don’t ask what people “want”, instead ask “what are you thinking”
 - Ask “what questions do you have”, not “do you have any questions”. People don’t ask the most important question first
 - “Who are you going to talk to when you go home – tell me what they say?”
- Explicitly acknowledge the patient’s emotions
 - Hopes: “If time was limited, what would be most important to you... what would that look like”.
 - Use “wish” statements – eg “I wish this was different”. Aligns the doctor with the family. Don’t say “I’m sorry” – the socially acceptable response is to say “That’s OK” when it’s not. Say “I wish it hadn’t gone this way”
- Summarise. Start with what you can achieve. “Because you care about... we’ll try..... and we won’t...”
- “Mitigating regret” as a guiding principle for doctors
- Advance directives:
 - Prior declaration (written or verbal) or patient’s wishes in certain situations
 - Issues with advance directions:
 - How current they are
 - How specific to the current problem – real life is usually much more complex than planned
 - Under what circumstances and with what knowledge did the person sign the form
 - If the person has appointed an Enduring Power of Attorney they have the same legal standing as the patient themselves – ignoring the EPOA is the same as disregarding a patient’s wishes
 - Patient preferences in advance directives in the US: Comfort care 94%, aggressive care 3%
- Consent:
 - Simple consent: “I’m going to do this... is that OK”
 - Informed consent: must include alternatives and their consequences
- Random references:
 - On line ACP material, Alberta Canada – “Conversations Matter”
 - Advance Care Plan and Acute Resuscitation Plan on Queensland Health Government website
 - Grades of care plan: Royal Hobart, Dr Robyn Thomas
 - www.oncotalk.info

Communication Skills

- Osler: it is much more important to know what sort of a patient has a disease, than what sort of a disease a patient has
- Can you teach communications skills:
 - Back, Arch Int Med 2007: 167; 453
 - Fallowfield, Lancet 2002: 359;650
- Conflict:
 - Common response: avoidance of convincing
 - Signs of conflict: body language, sarcasm, talking in circles, getting no where
 - Internal negative feelings/judgements and resulting feelings
 - Process
 - Ask: why is this otherwise well-meaning person reacting in this challenging way?
 - Get the facts:
 - What is their story
 - What do they think is true
 - Listening is a bad way to retain information – learn their story and aim to tell their story as well as they can
 - Feelings: we have not learned to respond to feelings. It is essential to respond to emotions. You *can’t* think in the face of strong reactions.
 - Name
 - Understand
 - Respect
 - Support
 - Explore

- Identity conversation: We have views about what our job is, and what a good/bad one is. Am I making assumptions about the other person's intentions
- Miracles:
 - "I see how important a miracle is to you. I would like that too". Join them in hoping for a miracle – attend to their experience. AND ask what else you are hoping for
 - Removal of futile treatment is good medical practice

Palliative Care

- PEACE tool considers
 - Physical symptoms - pain, nausea, other
 - Emotional and cognitive symptoms - anxiety, fear, denial
 - Autonomy - a sense of control and participation in decision making
 - Closure of life affairs - spend time with family and other matters
 - Economic - assistance, arrangements, insurance - and existential issues (spiritual / religious)
- Twelve Principles of a good death (Smith et al, BMJ Jan 2000)
 - To know when death is coming, and to understand what can be expected
 - To be able to retain control of what happens
 - To be afforded dignity and privacy
 - To have control over pain relief and other symptom control
 - To have choice and control over where death occurs (at home or elsewhere)
 - To have access to information and expertise of whatever kind is necessary
 - To have access to any spiritual or emotional support required
 - To have access to hospice care in any location, not only in hospital
 - To have control over who is present and who shares the end
 - To be able to issue advance directives which ensure wishes are respected
 - To have time to say goodbye, and control over other aspects of timing
 - To be able to leave when it is time to go, and not to have life prolonged pointlessly
- Models of palliative care in ICU:
 - Consultative model: liaison with palliative care specialists – evidence suggests it improves quality and reduces cost
 - Integrative model: intensivists are trained in palliative care – mixed evidence
 - Mixed model: both approaches – no evidence

Brain Death

- Brain Death= irreversible loss of brain function, including loss of brainstem function
- Occurs when ICP is equal to or greater than systemic arterial pressure, causing loss of cerebral circulation (either ICP rises or systemic pressure falls). Causes are:
 - Traumatic brain injury (50%)
 - Subarachnoid haemorrhage (30%)
 - Severe hypoxic-ischaemic injury (20%)
- Brainstem reflexes are lost sequentially from top to bottom – apnoea is late due to failure of the medulla oblongata
- Neurons of the brainstem are the most resistant to anoxia, so patients may retain the ability to breathe but survive with irreversible and severe cortical damage (ie persistent vegetative state, awake but not aware). Not recognised as death in any jurisdiction, withdrawal of support may require legal authority
- Different jurisdictions:
 - UK: common law definition "irreversible loss of the capacity for consciousness combined with the irreversible loss of the capacity to breathe" (ie brain-stem based)
 - Australia: "irreversible loss of all brain function" (or irreversible cessation of circulation of blood in the body of the person). If pathology known to only affect the brain stem and known blood flow to the supratentorial part of the brain is not sufficient for brain death
 - New Zealand: Human Tissue Act 2008: "satisfied... that the individual concerned is dead" without statutory definition. We follow Australia and require whole brain death.
 - US: Uniform Determination of Death Act states brain death as death of the whole brain
- Dying is a process not an event. The determination of death indicates an irrevocable point in the dying process – not that the process has ended. Death of "a person" – not their organs

Changes During Brain Death

- Aim of care after brain death is to maintain organ perfusion and prevent physiological derangement

- Cardiovascular:
 - Brain herniation → intense sympathetic surge with HTN, tachycardia and/or arrhythmias ('autonomic storm'). Can result in cardiac ischaemia. Treat HTN only if necessary with short acting agents (esmolol, sodium nitroprusside)
 - Following this, loss of sympathetic outflow → vasodilation and hypotension, exacerbated by DI. Treat hypotension with inotropic support, nor-adrenaline the most commonly used. If persistent hypotension consider steroids
 - Treat arrhythmias by maintaining normal electrolytes, BP, volume and temperature. Amiodarone and cardioversion as usual. CPR may recover function in arrest. Bradycardia may be resistant to atropine but not to adrenaline, isoprenaline or pacing
 - Lungs are better with a minimally positive fluid balance
- Diabetes Insipidus:
 - In 80 - 90 % of brain-dead donors due to deficiency of ADH → polyuria, hypernatraemia and hypovolaemia, ↑ plasma osmolarity, ↓ urine Na
 - Treat on suspicion, don't wait for test results otherwise instability
 - Give DDAVP (desmopressin, 1-desamino-8-D-arginine vasopressin) IV bolus 2 – 4 µg every 2 to 6 hours or vasopressin (arginine vasopressin [AVP]) IV infusion 0.5 – 2.0 U/h, targeting a urine output of 30 – 200 ml/h
 - Beware a rapid fall in Na
 - Replace large urinary volume loss with low sodium fluids (eg D5W)
- Hypothermia due to ↓ metabolism, inability to conserve heat, and loss of hypothalamic thermoregulation. Easier to prevent than correct
- Anterior pituitary function is probably sufficiently preserved to maintain thyroid and cortisol levels. Can treat with products – but best to expedite organ removal
- Coagulopathy: ?2ndary to substances released from the necrotic brain, dilution and hypothermia
- Cytokine profiles become proinflammatory (eg ↑IL-6)
- Continuing NG feed to the time of donation may be beneficial

Diagnosis of Brain Death

- As per ANZICS Statement on Death and Donation Edition 3.2
- See Brain Death Hot Case, page 381
- Preconditions:
 - Patient should be in apnoeic coma
 - Underlying condition must be established
 - Condition must be due to structural brain damage and consistent with brain stem death
- Prior to the first set of testing there must be 4 hours of careful nursing observation recording:
 - unresponsive coma (GCS 3)
 - with no pupil response
 - absence cough reflex
 - and no spontaneous breathing
- Longer if:
 - 24 hours needed after restoration of spontaneous circulation in cardiorespiratory arrest/hypoxic encephalopathy (can image for absent blood flow earlier than this)
 - Do not test after therapeutic hypothermia until 24 hours after rewarming complete. Can image earlier
 - Barbiturates (including thiopentone) may take days to metabolise. If given, blood levels should be measured or brain death determined by imaging

Exclusions for Clinical Brain Death Testing

- Reversible causes of coma must be excluded
- Exclude effect of drugs:
 - Alcohol/drug overdose
 - Effects of therapeutic drugs: narcotics and hypnotics. In the absence of organ dysfunction, 3 – 4 times the half-life is recommended. Plasma concentration does not always correlated with therapeutic effect in critically ill brain-injured patients. Antagonists may be useful. Barbiturates problematic due to long and unpredictable action. Recommended to wait 2 – 5 days – but that's a long time to wait... High dose barbiturates mimicking brain death is very rare (more likely with hypothermia).
 - No effective of neuromuscular blocking agents (check peripheral nerve stimulation or deep tendon reflexes unless it is know for certain that these have not been given)
- Hypothermia: core temperature should be > 35o
- Hypotension: SBP should be > 90, MAP > 60

- No high spinal lesion or severe respiratory failure: may interfere with apnoea test
- Absence of severe metabolic and endocrine disturbances:
 - Correct Na < 115 or > 160 before testing. DI as a sequelae of brain death may be acceptable as opposed to abnormal Na which is the precipitant
 - Blood glucose between 2 and 20 mmol/L
 - K > 2 to avoid any effect on neuromuscular function
 - Check Mg and PO₄ and replace
 - Exclude severe renal or hepatic dysfunction
 - Coexistent endocrine disorders excluded or treated
- Ability to perform clinical examination of cranial nerves: Must be able to examine one ear and one eye (ANZICS statement)
- Neurological conditions mimicking brain death:
 - See Coma like syndromes, page 203
 - Locked-in syndrome
 - Guillian-Barre: may involve cranial nerves and cause respiratory paralysis, but pupil dilation is rare
 - Brainstem encephalitis: brainstem reflexes may be absent, but patient is usually drowsy rather than comatose
- Seizures are incompatible with brain death

Clinical testing for Brain Death

- Two senior doctors confirm brain death independently – not simultaneously
- No reported instance of the 2nd set being of brain death being reported on the first and not second set, so no reason to wait (even though 4 hours was recommended in the past). So can be done consecutively
- Time of death is the second set of tests
- Absence of responsiveness:
 - Apply stimuli in the cranial nerve distribution, trunk and all 4 limbs (eg bilateral supra-orbital nerve, sternal rub, and deep nail bed pressure).
 - Any response within the cranial nerve distribution, or in the limbs in response to cranial nerve stimulation, precludes brain death
 - Spinal reflexes may be present in patients with brain death: extension-pronation movements of the upper limbs (including in response to pain in that limb), undulating toe reflex, Lazarus sign (bilateral arm flexion, flexion of trunk, hips and knees, spinal reflex in response to acidosis occurring with hypercapnea), deep tendon reflexes, plantar responses, respiratory like movements without significant tidal volume, head turning
- Absence of brain stem reflexes:
 - Both pupils unresponsive to bright light. Pupil size ≥ 4 mm. Note anticholinergic drugs such as atropine can cause dilation. Cataract or sclera surgery is not a contraindication. Tests optic (II) and oculomotor (III) nerves
 - Corneal reflexes (blinking, withdrawal) are absent during touch with soft cotton wool or gauze over the cornea (not sclera). Tests trigeminal sensory (V) and facial (VII) nerves
 - Painful stimuli in 3 areas of trigeminal nerve distribution do not elicit a motor response in cranial or somatic distributions (eg supraorbital pressure, jaw thrust). Tests trigeminal (V) and facial (VII) nerves.
 - No gag reflex with stimulation to both sides of the posterior pharyngeal wall.
 - No cough reflex in response to tracheal stimulation with suction catheter – tests glossopharyngeal (IX) and vagus (X) nerves. Efferent limbs are the Phrenic nerve so can't be assess in patients with high cervical injury
 - Absent oculovestibular reflex. Check clear access to each tympanic membrane. 50 ml ice cold water injected in each ear with head flexed at 30° (so horizontal semi-circular canal is in the horizontal position). Hold eyelids open and observe for eye movement for 60 seconds. No tonic deviation of eyes towards the side being tested. Tests oculomotor (III), abducens (VI) and Vestibulochoclear (VIII) nerves. A rupture eardrum does not preclude the test. Base of skull fractures may obliterate the response on the side of the fracture. Confirmation of the absence of occulocephalic reflex ("dolls eye") tests this same pathway but is a sub-maximal stimulus.
- Apnoea test:
 - ONLY if ALL above reflexes are absent otherwise risk of further damage from hypoxia
 - Absence of spontaneous respiration despite a PCO₂ above the threshold for stimulation of respiration. PaCO₂ usually rises by ~ 3 mmHg (0.4 KPa) for every minute of apnoea. The ventilatory centre is maximally stimulated by a PaCO₂ of ~ 60 mmHg
 - Pre-oxygenate at 100% for 5 minutes. Get baseline ABG. Maintain oxygenation with suction catheter insufflating O₂ at 2 l/min into trachea (don't wedge otherwise barotrauma) and disconnect ventilator

for 5 mins. May need recruitment or a T-piece/CPAP if maintenance of O₂ is difficult (turn off back up apnoea ventilation). Check ABG again to demonstrate rise in PaCO₂ > 60 and pH < 7.3. If not there yet, wait another 5 minutes. If pre-existing hypercapnea wait for a rise of > 20 mmHg and a pH < 7.3

- Ventilator may be triggered by:
 - Cardiac oscillations
 - High sensitivity settings
 - Circuit leak
 - Water condensation in the tube
 - In which case connect the patient to a T-piece circuit with capnograph and look for spontaneous breathing movements and CO₂ waveform
- An increase in pulse is due to ↑CO₂ → ↓pH → ↑adrenaline and does not exclude brain death

Diagnostic tests

- Not required in UK, Australia or NZ (clinical tests are gold standard). Required by law in some European countries where diagnosis is on the basis of whole brain death; optional in the US
- Are surrogate markers for cortical function. If a prior study has demonstrated parenchymal flow, another is needed before brain death can be determined
- Intention of tests: demonstrating absence of intracranial blood flow
- Systolic pressure should be > 90 mmHg, MAP > 60 mmHg
- *Indications:*
 - No clear cause for coma
 - Possible drug or metabolic effect that can't be excluded
 - Cranial nerves cannot be adequately tested (periorbital oedema, eye injuries, bilaterally ruptured tympanum)
 - Apnoea testing cannot be performed:
 - Cervical cord injury is present or suspected
 - Instability precludes apnoea testing (eg severe respiratory failure)
- Transcranial Doppler may be used as a screening test to guide the timing of a definitive contrast study
- ANZICS recommends *four vessel angiography, nuclear image scan, or in some circumstances CT angiography* (although less experience with this technique)
- Assessment of blood flow in larger cerebral arteries:
 - *Four vessel angiography:* confirms no filling of intracerebral vessels. Invasive and time-consuming, but is the gold standard in some jurisdictions. Positive result is no blood flow above the carotid siphon in the anterior circulation and no blood flow above the foramen magnum in the posterior circulation. Some contrast in the circle of Willis may still be compatible with the absence of intra-parenchymal flow
 - MR or CT angiography (absent intra-cranial flow but present extra-cranial flow). Some concerns that studies not constructed to ensure 100% specificity. Some MRI techniques have reduced sensitivity to slow flow.
 - Transcranial Doppler ultrasonography. 91 – 99% sensitivity with 100% specificity in skilled hands. Significant operator dependence and not possible in all patients. May be used as a screening test to optimise the timing of a contrast study (it's a hassle if the study is done before flow has completely stopped). Not approved by ANZICS for demonstrating absence of brain perfusion
- Assessment of brain tissue perfusion: Contrast enhanced CT cerebral perfusion, PET or *nuclear image scan with TC-99m HMPAO* (other Tc-99m agents don't cross the BBB or remain long enough for a gamma camera to capture them)
- Assessment of neurophysiological function:
 - Useful as confirmatory testing in jurisdictions where this is required, not sufficient on their own when preconditions for clinical testing are not met.
 - EEG: widely used where loss of whole brain function must be shown. Looking for absence of cortical electrical activity over 16 or 18 channels over 30 minutes using high sensitivity. Artefacts common. Can confirm cortical death, but not brainstem death.
 - Somatosensory evoked potentials (SSEPs) and brainstem auditory evoked potentials (BAEPs): non-invasive, relatively unaffected by sedatives, increasingly used as confirmatory test

Brain Death in Children

- Confirmatory tests (eg EEG or cerebral angiography) are more common
- Higher PaCO₂ target used during apnoea testing
- Open cranial sutures complicate the picture
- Different age issues:

- Less than 37 weeks gestation: apnoea and coma are common, and the development of brainstem reflexes is uncertain. The concept of brain death is probably inappropriate – withdrawal of support should be based on futility
- 37 weeks to 1 month: hypoxic-ischaemic encephalopathy a common cause. Multisystem dysfunction is commonly associated, so withdrawal on the basis of futility is usual. If brain death testing, 24 – 48 hours before and between tests
- Children older than 1 month (ANZICS recommendation): use adult criteria
- Absence of cerebral blood flow confirms brain death, but some flow in brain dead infants widely reported.
- DCD is not currently a paediatric option

Brain Death in Pregnancy

- Options: withdraw treatment +/- organ donation vs support of mother with hope of delivering baby
- For fetus:
 - Consider screening for fetal abnormalities
 - Assess risk by gestation: high risk < 24 weeks
 - Regular obstetric support with daily fetal ultrasound check, serial US to assess for growth
 - Glucocorticoids after 24 weeks for fetal lung maturation
 - Tocolytics may be required to prevent contractions
 - Deliver at 26 – 28 weeks, longer if possible
- See Majid et al, One life ends, another begins: Management of brain-dead pregnant mother – A systemic review, BMC Med

Organ Donation

- See ANZICS Statement on Death and Organ Donation, Edition 3.1, 2010

Principles of Organ Donation

- Donation is an altruistic, non-commercial act. No one should profit from donation, and the family of the donor should not incur any cost. Donors should not exclude recipients as this is counter to the altruistic spirit of donation. Positively directed donation might be reasonable under uncommon circumstances (is it consistent with the deceased's wishes and is it medically appropriate – not dissimilar to directed donation from a living donor). Tricky.
- Donated tissues are allocated to the most suitable recipients
- The anonymity of the donor, donor's family and recipient must be safeguarded
- ANZICS Recommendations:
 - All hospitals should have someone (in NZ referred to as “the person lawfully in possession of the body”, separate from those determining brain death and removing tissues, who ensures documentation has been done correctly
 - If someone is known to have wanted to donate, the family should be contacted. Donation should not proceed if the family disagrees. NZ does not have a hierarchy of next of kin, but allows for overriding objection by a close available relative. Consensus does not necessarily require unanimity, but is agreement as defined by the family
 - NZ legislation contains no provision for donation where the patient's wishes are unknown and no family exists
 - Determination of brain death should be carried out by two medical practitioners (regardless of donation), at least one should be a specialist, and neither should be the person authorising removal of tissues nor the person removing tissues. In NZ, the number or qualifications of doctors determining brain death are not specified

Developments in Organ Donation Organisation

- Developing national organisation and standards for donation and recipient waiting lists
- Public awareness campaigns
- Use of “paired donation” – living donors wanting to donate to a relative but not compatible, being paired with some else who is and doing a swap
- Improving the “conversion rate”: potential donors who become actual donors. US average is 60%, best hospitals achieve 75%
- Policy changes that may increase donation:
 - Presumed consent (Opt out): generally thought wouldn't change the rate of donation
 - Required request: but we are already pretty good at asking
 - Improving consent rates....

- Spain has the highest rate of organ donation (double the European average) due to an integrated approach of legal opt-out system, education, public relations, hospital reimbursement and quality improvement, acceptance of older organs (average age of donation ~ 54, 45% older than 60). May also be facilitated by low rates of withdrawal of treatment. See Lancet Viewpoint, Sept 25 2010

Process (ANZICS statement)

- Tissues that can be donated: most patients can donate corneas, sclera, heart valves, bone and skin
- Intensivist should discuss donor suitability with the donor coordinator before discussion with the family
- Discussion with family usually after death has been determined – but may be earlier if not to the detriment of the patient or the family
- Donor registries: A record of objection excludes donation. The Human Tissue Act 2008 phased out the choice previously recorded with the drivers licence
- Discussion with family should cover:
 - Intensivists role is to provide information and support, not to persuade
 - Donation is an option not an obligation
 - They can change their decision prior to organ removal
 - The donation can only take place after death
 - How death will be determined
 - The specific organs to be donated (note: whole eye is usually taken for corneas), appearance after organ removal
 - Usually a delay of 6 – 12 hours before retrieval happens
 - Some retrieved organs may not end up being used
 - Donated organs are not used for research
 - Will usually want to do a most morTEM to exclude occult malignancy that may harm the recipient
 - Acting in the patient's interests is always the priority
- The family of a potential donor should be given the opportunity to meet with the donor coordinator (in person or by phone) to meet the family's needs for information, care and support
- If official identification is required by the coroner, this should happen before donation
- Families are contacted by phone 1 – 2 days after donation and provided with general non-identifying information about the recipients
- The need for support for hospital staff (peer support, debriefing, professional counselling) should be considered

Talking with Families

- Consider setting – quiet room
- Give truthful information in simple terms in small amounts
- Ask the family what their understanding is “can you tell me what it is that you understand about brain death and why it has occurred?”
- Show scans
- Allow relatives time to react without judgement, try not to control behaviour
- Provide opportunity for the family to observe clinical brain death tests
- Give time before moving onto donation. Create a sense of separation:
 - A separate meeting may be best. “This has been difficult news. I’d like to take a break for 20 mins...”
 - If family ask “what next” – clarify what’s on their minds – they may not be asking about the immediate process
- “There is an opportunity to make a decision about organ donation. I’ll give you some information. I want you to ask me any questions you have. Then you can have some time to think about our discussion”....
- “After the ventilator is removed X’s heart will stop after several minutes. His/her body will then take on the more familiar appearance of someone who had died”
- Offer the family locks of hair and handprints
- Language:
 - Limiting or withdrawing *treatment*, not withdrawing *care*
 - Don’t use the word “futile” – they are subjective, can’t be defined prospectively, and may be interpreted as saying the patient is worthless
 - End-of-life care, or comfort care, not “terminal care”
 - Refer to the patient by name
 - Organ removal or retrieval better than procurement or harvest
 - Mechanical ventilation not “life support” (we’re saying they’re already dead)
 - Family focused terms (“discussing organ donation”, “offering the option of donation”, “family agreement to donation”, “declining organ donation”) rather than “organ-focused” (“seeking consent”, “requesting organs”, “asking for organs”)

Medical Issues in Organ Donation

- Medical Suitability:
 - Absolute contraindications:
 - HIV or CJD
 - Metastatic or non-curable malignant disease
 - A history of malignancy that poses a high risk for transmission regardless of disease-free period (eg melanoma, choriocarcinoma)
 - Potential donors include:
 - Those with distant malignancy (eg childhood leukaemia and lymphoma)
 - Infection with Hep B or C – donation agency will consider risks and benefits
 - Acute renal function if previously normal
 - The elderly (can donate kidney's and livers even into 80s)
 - HTN and diabetes do not preclude donation
 - Investigations required:
 - Blood group, ABG, CXR, ECG, urea, Cr, electrolytes, glucose, bilirubin, transaminases, ALP, GGT, Clotting, Hb, WBC, microbiology
 - Donation agency will take blood for serologic testing and tissue typing, and only after the family has agreed to donation
- Little RCT evidence to guide the physiological management of a brain dead donor. All well conducted trials are negative
- Duration of retrieval operation:
 - Only NMBA used for anaesthetic, to stop spinal reflexes causing distress to staff (see Editorial, Anaesthesia, 2000, 55: p 105 for an opposing view)
 - Multi-organ retrieval: 3 – 7 hours
 - Kidneys only: 3 hours
 - Acceptable total ischaemic times (cross-clamp at removal to revascularisation) are:
 - Heart: 4 – 6 hours
 - Lungs: 6 hours
 - Liver: 12 hours
 - Pancreas: 12 hours
 - Kidneys: 24 hours
- Allocation:
 - Kidneys allocated primarily on the degree of matching of HLA A, B and DR loci, secondarily on waiting time
 - Heart, lungs and liver allocated primarily on ABO blood group, size comparability and urgency. Donor lymphocytes and HLA typing also done
 - Lungs:
 - Lungs for people with a smoking history are associated with worse outcomes, but the recipient has a better chance of survival if they are accepted over waiting for a lung from someone with a negative smoking history. (Bonser et al Lancet 2012)
 - Risk factors affecting survival of lung recipients are:
 - Recipients age
 - Donor-related CMV matching
 - Donor-recipient height difference
 - Donor's sex
 - Total ischaemic time
 - Donation to recipients who are ventilated at the time (eg as bridge to transplant) is controversial. Have better survival if transplanted than not, but poorer outcomes compared with recipients who are not ventilated

Donation after Cardiac Death

- = organ retrieval after cessation of circulation following withdrawal of treatment. Typically severely brain injured but not brain dead patients. In Australia and NZ, only suitable patients are:
 - withdrawal of treatment in ICU
 - Cardiac arrest following formal determination of brain death but before planned organ retrieval
- Priority must be patient's best interests and the quality of end-of-life care, not donation
- Outcomes:
 - For kidneys, pancreas and lung are similar to brain death, except for more delayed graft function in kidneys. Outcomes may even be better – organs not affected by the catecholamine storm of coning in brain death which → inflammatory reaction

- Liver graft survival is lower
- Warm ischaemia time – time from treatment withdrawal (especially SBP < 60) to the start of cold perfusion. Should not exceed 30 mins for liver (→ ↑biliary stricture), 60 mins for kidney and pancreas and 90 mins for lung
- No predictive tool for death within 60 – 90 mins has been adequately validated. Most relevant is whether the patient will breath when extubated. Check with a trial of spontaneous ventilation.
- Specific issues for DCD:
 - Must seek permission from the coroner
 - Members of the retrieval team must not be present at the withdrawal of treatment or participate in the determination of death. It must be clear that withdrawal of treatment is unrelated to donation decision
 - The family will have very little time with the patient once death has been declared
 - Consenting to donation will result in significant delay in the time to when treatment can be withdrawn
 - Requires detailed local planning
- Locations for treatment withdrawal:
 - ICU: if death doesn't occur within the desired time, doesn't have to be moved
 - Near theatre: still requires transfer after death
 - In theatre: may limit time with family
- Interventions to maintain organ viability are acceptable if:
 - There is evidence the individual wanted to be a donor
 - The patient/family have sufficient information, time and given consent
 - Interventions do not contribute to patient's death
 - Appropriate measures are taken to prevent pain or discomfort
 - Such interventions include heparin, femoral cannulation to infuse preservation fluid and bronchoscopy
- Determination of death when:
 - Immobility
 - Apnoea
 - Absent skin perfusion
 - Absence of circulation for two minutes by feeling the pulse, or preferably by monitoring intra-arterial pressure
 - Not ECG monitoring – electrical activity may persist for many minutes

Short Answer Outlines

- See literature reviews:
 - ICM Literature Hit Parade: www.dicm.co.uk/papers.htm
 - Gordon Doig's website: www.evidencebased.net

General

- Use bullet points
- Operator (circle these):
 - List
 - Define: include normal limits, units of measure
 - "Describe" \Rightarrow stepwise, protocol driven detail without interpretation
 - "Discuss" \Rightarrow what are the pros and cons, consider all angles, give value of arguments. Don't describe
 - Outline: emphasise global structure, avoid detail
 - Management: specific and general/supportive
- Limits (underline these):
 - In the adult trauma patient
 - In neuro intensive care (ie include SAH, meningitis)
 - In the first 24 hours: includes diagnosis, immediate treatment, monitoring, disposition, ongoing management, discharge planning, family involvement
- Consider the "features" of: go broad – history, exam, investigations, complications, etc.

Management Question

- Situation: Definition/assessment/risks/contributors/variation from normal/balancing X&Y
- Assess and treat immediate life-threatening conditions (contextualised resuscitation)
 - A: remember capnography
 - B: Sats, auscultate for pneumothorax, order CXR
 - C: check art line working, check for malignant rhythm
- Focused history and exam looking for X, Y and Z
- Simultaneous assessment and treatment of (guided by cause, tailored to individual patient, while pursuing definitive cause):

	DDx (by organ system)	Hx/Exam/Ix	Mx	Prognosis
1				
2				
3				

- Monitoring
- Disposition: ICU, HDU, transfer to a tertiary level centre
- Prevention of complications
- Supportive care: FASTHUG
- MDT
- Family, offer support person, etc.
- Quality Improvement: Audit, M&M, education, unit issues, prevention
- One liners:
 - "Controversial"
 - "Dogma currently being challenged by...."
 - Refer to guidelines
 - APLS
 - Resuscitation Council
 - Surviving Sepsis
 - Brain Trauma Foundation
 - International Liaison Committee on Resuscitation
 - CONSORT Statement: how to assess the internal validity of a paper
 - UK Difficult Airway Society Guidelines

Procedure

- Indications/Aim
- Contraindications (risk/benefit): including anticoagulation/platelets

- Preparation:
 - Prepare patient:
 - Consent
 - History and examination of patient
 - Place
 - Positioning and landmarks
 - Prepare Staff:
 - Assign roles, explain procedure and bail-out plans
 - Minimise other disturbances
 - Prepare Equipment:
 - Asepsis
 - Drugs
- Process: include monitoring
- Post procedure checks (eg CXR)
- Good outcomes
- Complications/challenges
- Quality Assurance

Critically Evaluate

- Definition
- Rational/importance/potential indications
- Advantages
- Disadvantages
- Evidence
- My Practice
- Nice conclusion: X seems to have a beneficial effect on [surrogate end point] in critically ill patients. Concerns about safety and the lack of patient centred outcome data preclude strong recommendations

Compare and Contrast

- A: Availability and cost
- E: Evidence
- I: Information provided
- O: Oh dear – side effects and complications
- U: User and technical factors

General

- Maintain eye contact
- Speak normally – not fast or quiet
- Structure:
 - History
 - Exam,
 - Investigations:
 - Bedside: ABG, ECG
 - Lab: bloods including coags, micro
 - Imaging
 - Other: eg cardiac or EEG
 - Specific and general management
 - Treatment: what, how much, targets, monitoring, complications

Discuss a vignette

- Motherhood statement: a brief, concise summary, eg “this patient has septic shock without a clear focus. I would...”
- Answer the question
- Start broad and be directed

Communication Viva

- With thanks to the Social Worker from the Princess Alexander in Brisbane
- Outline:
 - Introductions:
 - What would you like me to call you...?
 - Who else is with you/Can I call someone in...?
 - Determine the reason for the meeting
 - Get their understanding of the situation. However, if catastrophic news, get to it quickly
 - Tell the story so far from your perspective
 - Offer/find a resolution, arrange another meeting. Resolution may not be reached in 10 mins
- If the family member asks “How could this have happened”, they’re not asking for a pathology lecture. They’re asking how life could be so cruel. Reply “It’s tragic isn’t it”
- Finishing up:
 - Arrange support: patient advocate, friend, chaplain
 - Arrange to meet again
- Principles:
 - Listen
 - Show empathy
 - Communicate in lay terms
 - Allow relatives to speak freely and without interruption
- Purpose of communication with family:
 - Maintain trust
 - Reduce uncertainty
 - Prevent inappropriate hope
 - To allow appropriate adjustment
 - To make informed decisions

Complaints

- Use open disclosure – be clear about what has happened and that it was an error
- If an error has been made express regret
- Listen to concerns – give permission to have them discussed

Breaking Bad News

- Why is it hard for us:
 - Feeling incompetent

- Wanting to shield the family from distress
- Feeling awkward about showing sympathy in a professional capacity
- Being powerless
- Being reminded of human vulnerability
- Can touch past issues for you (ie be close to home)
- Preparation:
 - Have the correct person and correct relationship
 - Know all the facts
 - Who should be there
 - Be aware of cultural differences
 - Set time aside
 - Avoid interruptions
 - Quiet, private room
 - Comfortable chairs, tissues
 - Recognise impact of critical illness on the psychology of family members (eg guilt)
- Content:
 - Give a warning shot: "I'm afraid it looks serious..."
 - Be honest, not blunt
- Considerations:
 - Be comfortable with silence
 - Use short sentences, take a break
 - Check understanding
 - Allow ventilation of feelings
 - Don't pretend to know how a person feels
 - Avoid platitudes
 - Be guided by what they want to know:
 - Allow denial: it's a coping mechanism

- Initial:
 - Construct a differential for the question in your mind before beginning
 - Sterigel hands, glove and gown
 - Introduce yourself
 - Environmental scan:
 - Infection control measures
 - Specialist waste (eg cytotoxics)
 - Signs of a lengthy stay, weaning or activity plans on the wall
 - Smells
 - Special bed
 - Round the head:
 - **Pumps, medications, blood products:**
 - Heparin: think VTE or acute coronary syndrome
 - Vasopressin, noradrenaline: distributive shock
 - Nimodipine: subarachnoid haemorrhage
 - Ratio of vasopressors to inotropes suggests balance of haemodynamic disturbance
 - **Feed: ask about tolerance, bowel motions**
 - Start on your right:
 - Ventilator settings:
 - Mode – often unit specific
 - Fraction inspired O₂: if SpO₂ < 95% and FiO₂ > 0.3 then “there is a significant Aa gradient”
 - Ventilatory strategy: Protective lung (↓tidal volumes, ↑PEEP)/Open Lung or obstruction strategy (↓rate, ↓PEEP, ↑inspiratory flow rates)
 - If appropriate ask to assess: AutoPEEP with expiratory pause or plateau pressure with inspiratory pause
 - Estimate dynamic lung compliance: tidal volume/driving pressure (plateau pressure – PEEP)
 - “What’s the quantity and character of the sputum”
 - Monitor and *temperature*
 - If head injury: ICP, CPP and EtCO₂
 - **Look at the floor:**
 - Chest drains (swinging, draining, bubbling)
 - Surgical drains: location, nature, content
 - Urethral or suprapubic catheters, colour and amount of urine
 - Sequential compression limb devices
 - Other machines: PICCO, CRRT, pacing – check or ask for settings
 - If not awake and no sedation: Has he received recent sedatives or NMBAs
- Think: What is my “end of the bed-o-gram”
- Drive the exam: “Given Y and Z I’m going to first examine his X system”
- Examination:
 - Take down bed rail and **expose** (full but dignified)
 - Ask to reposition them for appropriate exams – you’ll generally be told no but given the findings
 - General appearance:
 - Obesity, cushingoid, malnutrition, hyper-expanded chest, prone positioning
 - Skin: steroid purpura and thinning, rashes, burns
 - Alopecia
 - Head to toe: pallor, bruising, scars, all lines (I notice this is red, how long has it been in?), check all dressings – ask what’s underneath
 - If brain death, then commence with brain stem reflexes
 - If multisystem, start with GCS, then:
 - Hands: nails, tar staining, interosseus wasting, infective endocarditis
 - Arms, head, neck
 - Eyes: pupils, jaundice
 - Mouth: ulcers, pressure sores, signs of difficult airway
 - Chest, including:
 - Trachea, previous tracheostomy, tracheal tug, reduced crico-sternal distance (hyperinflation), old drain sites
 - Cardiac: apex

- Abdomen, groins, lower limb, then ask to examine back
- Ask to look at the back (and in particular what you'd be looking for – scars, rashes, pressure sores, LP dressings...)
- Presentation:
 - Opening Statement
 - Answer the question
 - Identify problems
 - Investigations
 - Plan of management
 - Future/family
- Random on-liners”
 - “I believe there are several potential causes... or multifactorial. I would establish the diagnosis by....
 - Tell them how you are going to sort their patient out today
 - “This is an emergency. I would call for help and simultaneously conduct an assessment of the patient while I commenced resuscitation and treatment, paying particular attention to the airway, ventilation and circulation...”
- Other random tips:
 - Answer the question. Be structured
 - If you make a mistake, dig yourself out of the whole by saying “On reflection, my preferred course of action would be...” or “Hang on – that’s not right!”
 - Don’t ever confabulate. If you didn’t do it, don’t say so. Ever.
 - Be seen to be thorough. Don’t say “I’m not going to take the TEDs off”. Sounds lazy. Say “I normally take the TEDS off – are you happy for me to proceed”
 - Think. Make deductions. Do you know what you’re seeing
- Examiners want to see:
 - Rapid assessment
 - Prioritisation
 - Effective communication
 - Confidence
 - Common sense
 - Humility

Multi-System Hot Cases

Structured approach to a clinical emergency

- From APLS:
 - Prepare for the patients arrival
 - Immediate management:
 - If not responsive/breathing/pulse then cardiac arrest management
 - Primary assessment (ABCD) looking for life threatening issues
 - Resuscitation
 - Focused:
 - Secondary assessment/survey looking for key features
 - Emergency management
 - Detailed review:
 - Reassess focusing on system control
 - Continuing stabilisation
 - Handover to continuing care

Why is this patient febrile

- Differential:
 - Infectious cause:
 - Head: Meningitis, sinusitis, otitis media
 - Chest:
 - Upper/lower URTI/VAP
 - Endocarditis
 - Abdomen:
 - UTI

- Intra-abdominal collections
 - acalculous cholecystitis
 - C difficile
- Musculo-skeletal: cellulitis, septic joint, burns, wound infection
- Non-infectious causes:
 - Pancreatitis
 - Head injury/SAH
 - Drug or toxin effect
 - Drug or ETOH withdrawal
 - DVT
 - Fluid connective tissue disease (eg RA, SLE)
 - Blood transfusion
 - Large resolving haematoma
- Hyperthermic emergency:
 - Hyperthyroidism
 - Neuroleptic malignant syndrome
 - Malignant hyperpyrexia
 - Heat Stroke
- Examination:
 - Could fever be masked: eg age, steroids, immunosuppression, dialysis
 - Lymph nodes for haematological malignancy
- Questions:
 - Has a female patient had a PV examine to check for retained tampon
 - How long have the lines been in
 - Medications: is the patient had a recent anaesthetic (malignant hyperthermia), on neuroleptic medications, or receiving antibiotics (eg penicillin drug fever)

Multi-organ failure Host Case

- Key thoughts:
 - Which organs have failed – what is the trend for each organ
 - Is the initial illness responding to treatment
 - Is the diagnosis correct
 - Is there an occult process (sepsis, ischaemic bowel) driving the failure
 - Is it possible and appropriate to give further support to any organ
- Statements: “This patient with multi-organ failure is unlikely to survive. He continues to deteriorate despite maximal therapy. I would like to meet with the family to discuss shifting our goal to comfort care”.

Trauma Hot Case

- Examination:
 - ABC
 - Careful inspection of chest for symmetrical movement
 - Check GCS and movement of all limbs
 - Heat to toe:
 - Head: scalp wounds, mastoid bruising, haemotympanum, CSF from nose, facial bone fractures. If concerned auscultate eyes
 - Neck: auscultate for carotid bruit from traumatic dissection
 - Chest: subcutaneous emphysema. If clavicle injury, check shoulder and scapula carefully
 - Pelvis: palpate for stability but don't spring. Scrotal bruising → urethral injury
 - Ask to do PR. If spinal injury ask if you can look for a bulbo-cavernosus reflex
 - Log roll to check back
 - Legs: palpate for compartment syndrome
 - Adequacy of IV access
- Questions:
 - What was the speed and mechanism of injury, was the patient restrained, what was the penetrating instrument
 - What was the GCS at the scene
 - Has the spine been clear, thoraco-lumbar views?
 - Are tracheal secretions/intercostal drain outputs/NG aspirates blood stained
 - Is tetanus status up to date
 - Have compound fractures been scrubbed

- What further surgery is planned, when

Burns Hot Case

- See Burns, page 258
- Three phases:
 - Resuscitation (0 – 36 hours): managing airway burns, fluid resuscitation (via Parkland formula), consumptive coagulopathy, compartment syndromes, management of other traumatic injuries
 - Post-resuscitation phase (day 2 – 6): Operative phase and ongoing fluid and blood product replacement, high nutritional requirements
 - Inflammatory/infective phase (day 7 to complete wound closure): problem of differentiating SIRS from sepsis
- Exam:
 - ↑ambient temperature
 - Isolation precautions
 - Pulse of 110 – 120 for up to 6 months
 - Odour of vinegar ⇒ ?pseudomonas
 - Look for signs of inhalation: black sputum, burns to face, singed facial hair, stridor, hoarse voice (→ “Can I see results of bronchoscopy”)
 - Possibility of a tracheostomy – neck burns?
 - Examine limbs *and digits* for compartment syndrome
- Issues:
 - Analgesia: usually opioid +/- ketamine for dressing changes
 - Feeding
 - Fluids: free water loss through evaporation alone = $(25 + \%TBSA) * BSA$ (use 2 m²). For 50% burn ⇒ 150 ml/hour in addition
 - Antibiotics: prophylactic for theatre
 - Swabs don’t tell about infection – need biopsies
 - Current surgical plan

Transplant Hot Case

- See:
 - Heart-Lung Transplant Patient Representing to ICU, page 156
 - Liver Transplant, page 179
 - Stem Cell Transplant, page 309
- Issues in ICU:
 - Post-operative management: liver, heart, lung
 - Post-operative renal or pancreatic with haemodynamic instability (eg needing CRRT)
 - Late complications: sepsis
 - Bone marrow transplant (haematological malignancy) with sepsis – eg respiratory failure or shock
- Think of:
 - Surgical issues:
 - Anatomic issues: anastomosis leak or thrombosis
 - Preservation injury with poor graft function
 - Haemodynamic stabilisation: optimise tissue perfusion. Avoid overload
 - Infection: early bacterial, delayed opportunistic. Start prophylaxis
 - Immunosuppression:
 - Rejection:
 - Hyperacute: < 12 hours, alloantibody related
 - Acute: usually < 1 month, T-cell related
 - Chronic: vasculitis → vanishing bile duct syndrome, accelerated IHC, BOOP etc.
 - Graft vs Host disease: Acute (< 3 months) and chronic: rash, GI symptoms and ↑LFTs. May need biopsy. Prevent with immunosuppressives following transplant. Treat with steroids and anti-T cell antibodies
 - Other complications of bone marrow transplant:
 - Bad mucositis (usually from cyclophosphamide conditioning regime)
 - Veno-occlusive disease of the liver: in 10%, peak at 16 days, 30% mortality
 - Drug side effects: eg cyclosporin → renal toxicity, HTN, rarely HUS, anthracyclines and cardiomyopathy
 - Specific disorders:
 - Respiratory failure with pulmonary infiltrates:

- In APML (AML-M3 under FAB system), can present with DIC and pancytopenia. Treated with All-trans-retinoic acid (ATRA) → myelocyte differentiation → Retinoic Acid syndrome in >25 days (ARDS like), treat with steroids then restart ATRA
 - Toxicity: bleomycin and amiodarone
- Acute abdomen:
 - Neutropenic enterocolitis (“typhilitis”)
 - Infective diarrhoea: C difficile, CMV
 - Immunological: mucositis from chemotherapy
 - Intestinal GVHS
 - malignant obstruction and ileus
- Exam:
 - Is the patient in a negative or positive pressure room
 - RIJ spared in cardiac transplant so it’s available for future endocardial biopsies
 - Fever/tachycardia/hypotension can be infection (including opportunistic), rejection, drug reaction, dry due to diarrhoea or bleeding from coagulopathy
 - Ventilation: Possible lung protective strategy. Low FiO2 despite hypoxia may be trying to avoid O2 toxicity with bleomycin
 - Infusions:
 - Mesna ⇒ cystitis 2nd to cyclophosphamide
 - Rasburicase and/or HCO3 ⇒ tumour lysis syndrome
 - Chemotherapy issues: alopecia, long term catheters, steroids (Cushingoid, myopathy)
 - Radiotherapy issues: ink/tattoo markings, skin irradiation
 - Look for:
 - Signs of underlying disease necessitating transplant
 - Rashes: drugs or GVHD
- Questions:
 - Assessment of new organ viability
 - Liver: US (Portal vein and hepatic artery, new haematomas), LFTs, glucose, coags
 - Lung: bronchoscopy
 - Heart: Echo
 - Kidney: ultrasound for renal blood and urine flow
 - Have any graft tissue biopsies been done

Obesity Hot Case

- See Obesity, page 348
- Issues:
 - Underlying problem
 - Complications caused by obesity:
 - Diabetes
 - Difficult access
 - OSA (mechanical problem during sleep → daytime somnolence) vs Obesity Hypoventilation (metabolic disorder, ↓alveolar ventilation, ↑awake CO2 and ↓O2)
 - ↑risks of:
 - Pressure areas
 - VTE
 - Sepsis
 - Mortality (compared to other patients > 4 days)
 - Weaning difficulty + difficulty reintubation → surgical tracheostomy (can’t do percutaneous due to loss of landmarks)
- Exam:
 - Exam from both sides
 - Is non-invasive BP accurate
 - Tidal volumes should be set on ideal bodyweight
 - Baseline PEEP at 10
 - Note special equipment: hoists, chairs, mattresses, CPAP devices
 - Assess:
 - Airway
 - Signs of heart failure
 - Evidence of a DVT
 - Repeated attempts at IV access

- Skin-folds for intertrigo
- Discussion:
 - Obesity bias, maintaining dignity
 - Difficulty of drug dosing: varies between lipid and water soluble
 - Difficulty of imaging
 - Difficulty of assessing intra-abdominal pathology
 - Difficult of manual handling and mobility
 - Obesity paradox:
 - ↑Risk for cardiovascular/PVD
 - But when decompensation occurs have a survival benefit (?younger patients, ?closer watch)

Long Stay Patients

- Potential causes:
 - Failure to wean +/- weakness
 - Sepsis
 - Persisting multi-organ failure
 - Pancreatitis
- Exam:
 - Look for weaning plan, daily plan, rehab plan
 - How much ventilation support are they needing? If a lot, why?
 - Complication prevention: DVT, mattress, splints, mouth care
 - Signs of degree of engagement: wearing clothes, glasses, dentures, etc.
 - Depressed: flat affect, no eye contact
- Questions:
 - What needs to happen for them to be discharged
 - Constipated?
 - Nutrition?
 - Psychoactive medications?

How would you talk to families

- “Based on the following observations I feel that the prognosis for a meaningful recovery is...”
- “I would meet in a private room...take nurse or social worker... check families understanding...explain... invite questions”
- “Has Fred ever discussed what he would want in this situation”
- “Would meet family again soon.... My experience is it takes time for families to come to terms with this”

Respiratory Hot Cases

- Airway question: “Assess the airway for patency and adequacy, and manage with simple measures progressing to intubation as necessary”

Differential of Respiratory Failure/Failure to Wean

- See Weaning, page 95
- Failure to wean: Has the original problem been fixed yet?
- Parenchymal problems:
 - Pneumonia: primary, hospital acquired, bacterial, viral, fungal, immunosuppressed
 - Contusion
 - Collapse/sputum
 - Non-cardiogenic pulmonary oedema (what is the trend in fluid balance and albumin)
 - ARDS
- Ventilatory problems: Can patient cough/clear secretions – try it.
 - Sternotomy (wired?)
 - Neurological injury (?phrenic nerve), brain injury. Test strength: lift head off bed, lift arms, for how long
 - Weakness: Prolonged illness, ICU, GBS, NMBA
 - Over sedation, insufficient analgesia
 - Overfeed/malnourished
- Cardiovascular problems:
 - LVF
 - Anaemia

- PE
- Foreign body (especially if unilateral signs)
- Contributed to by chronic disease: smoking

Can you Extubate this Patient?

- See Weaning, page 95
- Has this initial insult resolved
- Procedures planned in the next 24 hours
- Have they already been re-intubated, if so why
- Could they be re-intubated:
 - Difficult airway: Mallampatti score and Cormack and Lehane grade
 - Skill mix on the floor and current workload
 - Are they being feed/are they fasted
- Check:
 - Airway patency:
 - Protection of airway: cough, gag, able to clear secretions
 - Leak test (cuff down and listen for leak) then occlusion test (can they breath around tube). Reinflate cuff.
 - Adequacy of oxygenation: usually $\text{FiO}_2 < 0.4$ and PEEP 5 (ie adequate gas exchange/ Low A-a gradient)
 - Adequacy of ventilation:
 - Able to clear secretions to the mouth
 - Minimal respiratory support, eg pressure support ≤ 10
 - Vital capacity ($> 8 - 12 \text{ ml/kg}$) measured with 0 PS – measure it at the bedside – ask the person to take a big breath... what the ventilator. That's what you'd do on a ward round...
 - Minute ventilation $< 10 \text{ l/min}$
 - Able to \uparrow work of breathing to cope with the \uparrow dead space of normal airway
 - Could also use rapid shallow breathing index (f/V_t), negative inspiratory force ($< -20 \text{ cm}$), respiratory rate
 - Stable haemodynamics & rhythm
 - Neurological:
 - GCS: obeys commands
 - No bulbar dysfunction: difficult to assess with tracheostomy in
 - Strength
 - Not weak: able to raise arms, head
 - Metabolic/biochemical parameters normal
- Comment: I do not consider this person safe to extubate. I would consider percutaneous tracheostomy /or repeat my assessment daily until...
- Predictors of successful extubation: ABG near pre-morbid values, $\text{RR} < 25$, airway occlusion pressure > 6 , tidal volume $> 5 \text{ ml/kg}$, minute ventilation < 10 , vital capacity $> 10 - 15 \text{ ml/kg}$, $\text{FRC} > 50\%$, rapid shallow breathing index (RR/TV) < 100

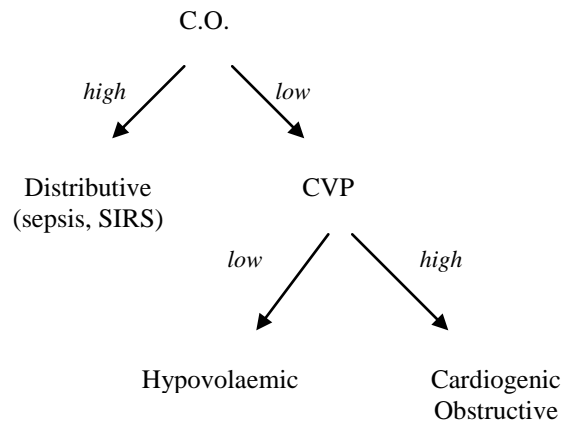
COPD

- Questions:
 - Can I review the patients pre-morbid lung function tests and arterial blood gases on room air
 - I would like to know the patient's functional status prior to this illness
 - How often is this patient receiving physiotherapy

Shock and Cardiac

Differential of Shock Hot Case

- See Clinical classification of Shock, page 38
- Clinical signs of shock:
 - Skin: mottled/clammy
 - Oliguria: an early sign of hypoperfusion – but be careful – renal perfusion and urine output are poorly correlated
 - Mutation



- Hypovolaemia:
 - Exam findings: cool peripheries, ↓cap refill, ↓JVP, wide pulse pressure, swing on art line, fluid balance, blood loss, drain output, occult blood loss (chest, abdomen, pelvic or limb trauma) , positive response to straight leg raise
 - Differential:
 - Under filled
 - 3rd spacing
 - Ascites
 - Occult bleeding
 - GI/burns losses
- Due to ↓CO:
 - Cardiogenic:
 - Exam: narrow pulse pressure, evidence of heart failure: ↑JVP, fine inspiratory crackles, SvO₂
 - Differential: Cardiomyopathy, valve involvement, arrhythmia
 - Obstructive:
 - Differential: Pneumothorax, PE, tamponade from effusion, high PEEP or autoPEEP
 - Exam:
 - Tension: has an intercostal drain become blocked, surgical emphysema, tracheal deviation, ↓breath sounds with hyper-resonance
 - Tamponade: pulsus paradoxus, ↑JVP on inspiration (Kussmaul's sign), muffled heart sounds, L and R ventricular and atrial diastolic pressures tend towards each other (driven by tamponade pressure)
- Distributive shock:
 - Exam: Febrile, warm peripheries, oedema, obvious source of infection, neurologic injury
 - Differential:
 - SIRS, pancreatitis
 - ↓cortisone
 - Infection:
 - Poor source control
 - Inappropriate AB/resistance
 - New septic source: VAP, UTI, CLAB, endocarditis, cholecystitis
 - Neurogenic: spinal cord injury/epidural
- Histotoxic
- Drug reaction:
 - Anti-hypertensives
 - Anaphylaxis
- Endocrine: ↓steroids, thyroid
- Electrolytes: ↓PO₄, ↓Ca
- Technical:
 - Measurement error: wrong cuff size, art line not zeroed, transducer wrong height, over damped
 - Radial/central discrepancy: severe vasoconstriction, upper limb vascular disease, dissection
- Questions:

- CXR, ECG and echo, troponin. Does echo show signs of hypovolaemia: ↓LVEDV, ↓LVESV, ↓IVC diameter with pulse variation
- Renal function, fluid balance
- Response to fluid bolus
- Lactate
- Transfusion requirement

Post Cardiac Patient Hot Case

- See Intensive Care after Cardiac Surgery, page 151
- If young, consider atypical causes: infective endocarditis, congenital heart disease
- Examination:
 - End of bed: Marfanoid features
 - Monitoring:
 - Check ECG and pacing
 - Check art line trace: slow upstroke suggests poor CO, low diastolic with reduced SVR
 - Check CVP trace: note value and character – giant C and V waves with tricuspid regurgitation
 - Arms:
 - Infective endocarditis: clubbing, splinters, IV track marks
 - Pulse character: plateau or collapsing
 - Head:
 - Hypercholesterolaemia: Xanthelasma, tendon xanthomata
 - Neck: Check JVP at 45 ° or CVP waveform
 - Chest:
 - Palpate sternotomy for stability, signs of infection
 - Position of apex beat, thrills, heaves, P2
 - Put balloon pump on hold (or 1:2) for auscultation while palpating carotid pulse
 - Dull unilateral base: consider phrenic nerve palsy as complication of surgery
 - Increased FiO₂/PEEP: consider:
 - Cardiogenic pulmonary oedema
 - Atelectasis
 - ARDS
 - Nosocomial pneumonia
 - Increased A-a gradient with normal compliance: PE
 - Clarify position of drains
 - Distended abdomen: ischaemia from dissection or mesenteric embolism, pump pancreatitis
 - Peripheries:
 - Shut down or vasodilated
 - Graft sites
 - Peripheral oedema: ?chronic CHF
 - Femoral artery puncture sites: recent angiography, balloon pump or bypass catheter
 - Neurological status: low GCS and localising signs suggest CVA
 - Urine output: ?low cardiac output state, ?compromised renal perfusion
 - Aortic Balloon Pump: always check
 - Correctly zeroed before balloon insertion
 - Check helium tank not empty
 - Put on 1:2 and check timing
 - Check perfusion in both legs
 - Palpate distal pulses, check with ultrasound
 - Inspect insertion site
 - Check L radial pulse
 - Check placement on CXR (should be just above the L main bronchus)
 - Check platelets
 - Questions:
 - Drain losses: ask about exposure to anticoagulants, antiplatelet agents, pro-coagulant disorders (eg uraemia)
 - What were the details of the surgery, duration of cardiac bypass and cross-clamping
 - Review ECG and echo

ECMO Hot Case

- See Extracorporeal Membrane Oxygenation, page 162

- Types:
 - VV ECMO: potentially reversible respiratory failure: pneumonia, H1N1 or other viral pneumonitis, pulmonary vasculitides
 - VA ECMO:
 - Respiratory failure + severe haemodynamic instability
 - Refractory heart failure, as a bridge to VAD or transplant
- Common complications:
 - Bleeding: including intracerebral (IV heparin is the norm)
 - Thrombosis: intracerebral or in the circuit
 - Sepsis, including insertion site
- Exam:
 - If on VA-ECMO, look for indication of pulsatility on arterial pressure trace
 - High dose analgesia, sedatives – absorbed by the circuit and membrane oxygenator
 - Fever will be masked by the cooling of the circuit
 - Ventilator: will usually be on “rest” ventilation: low frequency, very low volume + PEEP to prevent atelectasis. If high FiO₂, then ECMO not working well enough
 - Look at all line sites for infection (may be reluctant to change in anticoagulated)
- Questions:
 - What amount of cardiac output is being delivered by the machine
 - How long has the patient been on ECMO? If longer than several days, has the patient had an assessment of their function independent of support?
 - Review the plasma free haemoglobin and serial coagulation results
 - Review the ABG pre and post oxygenator
 - Review CXR. Getting a CT is complex...

Abdominal Hot Cases

Causes of Reduced Urine Output Hot Case

- See Acute Kidney Insufficiency, page 187
- Differential:
 - Pre-renal ⇒ why is this patient shocked
 - Renal:
 - Chronic renal failure
 - Acute renal failure: shock (→ ATN), rhabdomyolysis, hepatorenal failure, drugs, contrast (is there NAC or sodium bicarbonate running), glomerulonephritis (rashes?), *abdominal compartment*
 - Post-renal: catheter blocked, pelvic surgery
- Exam:
 - Look for new and old vascular access sites: fistula, Tenckhoff catheter
 - Perfusion of peripheries
 - Abdo: scars, palpable polycystic kidneys
 - Signs of chronic liver disease
 - Low aortic balloon pump
 - Compartment syndromes: limbs, buttocks, abdomen
- Questions:
 - Urine output, has catheter been flushed
 - Dialysis machine: mode, rate of fluid removal, what filter life spans have been achieved, lactate of bicarbonate buffer
- Investigations:
 - Urine dipstick
 - Paired urine and serum electrolytes to help distinguish pre-renal and renal
 - Pregnancy test (pre-eclampsia)

Abdominal Catastrophe Hot Case

- See Abdominal Surgical Catastrophes, page 182
- Infusions:
 - Omeprazole: ? ulcer
 - Octreotide/Terlipressin: ?varices
 - Terlipressin: ?hepatorenal syndrome
- Differential of abdominal badness:

- Persistent sepsis
- Acute necrotising pancreatitis
- Peritonitis from perforated viscus: duodenal ulcer, appendix, diverticulum, obstruction, cancer, surgical anastomosis
- Massive blood loss:
 - Upper GI: ulcer, varices, angiodysplasia, tumour
 - Lower
- Abdominal Trauma:
 - Blunt: spleen, liver injury
 - Penetrating: perforated viscus
- Considerations:
 - What is the original cause
 - Is the patient being feed?
 - Could abdominal compartment syndrome be complicating things (?bladder pressure monitor, > 25 cm H2O significant)
 - What are the risks for fungal infection? ?place of empiric fluconazole treatment
 - What's required now
- Exam:
 - Signs of resistant bugs: infection control precautions, AB infusions
 - Octreotide for variceal bleeding
 - Omeprazole for peptic ulcers (?Minnesota tube), varices
 - Terlipressin for hepatorenal syndrome
 - ↑FiO2/PEEP: abdominal excursion, ARDS, nosocomial pneumonia, chest injuries in a trauma patient
 - Jaundice: massive haematoma resorption (ie unconjugated), biliary obstruction, acute on chronic liver disease
 - Signs of liver disease: clubbing, nail changes (leuconychia – white transverse opaque bands in hypoalbuminaemia. White/brown bands also in renal failure), palmer erythema, malnutrition, Dupuytren's, flap, bruising, itching, spiders, hair loss, gynaecomastia, parotidomegaly, fetor, encephalopathy
 - Cullen's sign (periumbilical bruising), Grey-Turner's sign (flank bruising) → haemorrhagic pancreatitis
 - Rectal tube: ?melaena
 - Check lower limb perfusion and neurology, and compartments
- Questions:
 - Amylase, lipase
 - Results of fluid drain cultures

AAA Repair Hot Case

- See Abdominal Aortic Aneurysm, page 183
- Considerations:
 - Acute or elective
 - If supra-renal, what was the supra-renal clamp time
 - Lower limb ischaemia
 - Secondary shock and it's sequelae
- Exam:
 - BP – avoid hypertension in early post-op period

Neurology Hot Cases

- Always work out and state the GCS of the patient

4 Different Neuro Exams

- Paralysed and sedated: pupils only
- Unconscious examination (ie not able to obey commands):
 - GCS or responsiveness
 - CN: pupils, oculoccephalic reflexes, cornea, cough, gag
 - Limbs (posture, tone, reflexes, movement to pain)
- Quick examination where neuro not the focus:
 - GCS or responsiveness
 - Pupils

- Movement of limbs
- Reflexes
- Conscious examination: everything
 - GCS
 - CNS
 - PNS

Neurological Impairment Hot Case

- Quick review:
 - GCS – motor response most predictive. Ask if they speak English. Test pain in all limbs, both supraorbital ridges. Don't do sternal rub – it's not particularly elegant – are they localising or flexing, etc...
 - Pupillary reaction
 - Presence of spontaneous breathing
 - Localising signs suggests primary CNS cause
 - Meningism
 - Urine output
- Check femoral sites for ?cerebral angiogram
- Questions:
 - If post arrest
 - heart investigations: ECG, Echo, coronary angiogram
 - "Could I clarify the history to aid prognostication: Time to CPR, time to ROSC, rhythm, number of shocks
 - If subarachnoid haemorrhage:
 - When were last sedatives given
 - Can I see the head CT and results of cerebral angiography
 - Has CSF been sent for culture

Why is this patient not waking up

- See The Unconscious Patient, page 202
- Differential:
 - Primary focal neurological cause:
 - CVA
 - Cerebral haemorrhage +/- hydrocephalus or vasospasm
 - Meningitis, encephalitis
 - Cerebral abscess
 - Global encephalopathic process:
 - Sepsis
 - Uraemia
 - Liver failure
 - Drugs/toxic, including sedation/paralysis
 - ICU encephalopathy
- Exam:
 - Carefully assess GCS. Is the patient unable to move (locked in, NMBA, response to train of four)
 - If not sedated, focus on brain stem reflexes
 - Craniotomy wounds
 - Check for neck stiffness
 - Agitation: consider hypoxia, hypotension, withdrawal, blocked catheter
 - Peripheral neurological exam:
 - Muscle wasting
 - Reflexes – if depressed more lower than upper, and proximal then ?critical illness polyneuropathy
 - Signs of liver disease
- Questions:
 - "Has he had a CT scan"

Brain Death Hot Case

- See Diagnosis of Brain Death, page 359
- Exam:
 - ↑ICP – duration – calibration drift after 5 – 7 days
 - ↑BP, ↓HR

- No spontaneous breaths
- Check for ↑urine output
- Ask for equipment: torch, cotton bud, tongue depressor, otoscope, ice cold water and syringe, kidney dish or towel to catch the water, end-tidal CO₂ monitor, O₂ catheter and laryngoscope (to test gag with direct vision)
- Check train of four
- Questions:
 - Check temperature
 - No sedation, no NMBA (might have been given for cooling)
 - Has an irreversible cause been established (ECG, echo or coronary angiogram)
 - How long has the patient been in this state
 - Metabolic and endocrine state normal
 - Possibility of poison/toxin
 - What neuro imaging has been done (CT, 4 vessel angiogram)

Weakness Hot Case

- See Neuromuscular disorders, page 222
- Differential:
 - Primary neuromuscular conditions:
 - CVA
 - GBS
 - MG
 - Old polio
 - Infection: tetanus, botulism
 - Systemic:
 - CTD
 - Infection
 - Critical illness polyneuropathy
 - Generalised weakness
- Differentiating:
 - Myopathy: weakness is a late sign, usually proximal, reflexes preserved till late, normal sensory exam, may be muscular tenderness
 - Neuropathy: wasting earlier, fasciculation, often distal, ↓reflexes, maybe abnormal sensory exam
- Exam:
 - Immunoglobulin given for GBS, MG and Vasculitis
 - Examine CN carefully, especially gag, cough and swallow
 - May have higher PEEP given risk of collapse if weak
 - What is unassisted vital capacity
 - Assess nutritional status
- Questions:
 - How long has the patient been in ICU
 - What was the reason for his original admission
 - Investigations: nerve conduction studies, muscle biopsy, CK and trend

Horner's Syndrome

- Sympathetic paralysis: ptosis (dropping eye lid), miosis (contraction of the pupil), ipsilateral loss of sweating (anhidrosis)
- Sites of lesions:
 - Hemispheric lesion: massive hemispheric CVA, thalamic CVA
 - Brainstem lesion: infarct, MS, cancer
 - Central cord lesion: Syringomyelia, glioma, traumatic
 - T1 root lesion: Pancoast tumour, brachial plexus evulsion, aortic/subclavian aneurysm
 - Sympathetic chain: laryngeal, pharyngeal, thyroid or parathyroid surgery, carotid artery lesion, malignancy at base of skull

Spine Injury Hot Case

- See Spinal Cord Injuries, page 249
- Think:
 - Has the spine been stabilised yet?
 - What phase of injury:

- Acute → cardiovascular problems, ileus
- Sub-acute → recurrent atelectasis and segmental collapse
- Chronic → pain, psychological issues, urosepsis
- Exam:
 - Device to assist speech: Passy-Muir valves
 - Spinal immobilisation devices
 - Splints to prevent contractures
 - Naso-jejunal feeding tubes: feed intolerance is a common early problem
 - Motor exam:
 - Check myotomes
 - Flaccid weakness initially → hyper-reflexia and clonus with time
 - As limb reflexes return so does chest wall tone → ventilatory weaning (+ painful muscle spasms)
 - Anal tone and bulbo-cavernosus reflex (pull on urinary catheter – if present ⇒ spinal shock is over. If persistent sensorimotor deficit then established complete spinal cord injury)
 - Sensory exam:
 - Check dermatomes – dorsal columns and spinothalamic tracts
 - Level is the last spinal segment intact on each side
 - Check pressure sores
- Questions:
 - From examination I've localised the trauma to.... Can I please see imaging of this area

Head Trauma Hot Case

- See Traumatic Brain Injury, page 235
- Consider:
 - Impact of other injuries (fat embolism) → secondary brain insult
 - What phase of the injury – acute, later with persistent ↑ICP
- Exam:
 - Check temperature and CO₂
 - Thiopentone if refractory raised ICP
 - Stigmata of basal skull fracture: Haemotympanum, CSF otorrhoea/rhinorrhoea, Battle's sign, racoon eyes
 - Pupils: check consensual reflex. If unilaterally dilated, check traumatic mydriasis
 - Fundoscopy for retinal haemorrhages, papilloedema
 - Check nothing compressing neck veins
 - High FiO₂/PEEP – consider chest injuries, aspiration, nosocomial pneumonia
 - Urine output: if ↑ consider DI or osmotherapy
- Questions:
 - See CT
 - Could I review the full history to clarify the nature of primary and secondary brain insults
- Comment: "This young man with signs of head trauma is experiencing refractory raised ICP despite multiple therapies, including heavy sedation, tight CO₂ control, osmotherapy, CSF drainage and induced hypothermia with paralysis. I suspect he has a severe traumatic brain injury"

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