Clinical pharmacy for paediatric critical care

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Revised October 2011
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Clinical pharmacy for paediatric critical care

2009

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Abbreviations

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Case Studies
Disclaimer
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This website is intended as an education package in order to provide some basic principles, advice and support for clinical pharmacists new to paediatric critical care. Patient care should be adjusted on an individual patient basis based on clinical data available and on local and national guidelines in the light of available evidence.

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>5HT₃</td>
<td>5 Hydroxytryptamine (serotonin)</td>
</tr>
<tr>
<td>ACCM</td>
<td>American College of Critical Care Medicine</td>
</tr>
<tr>
<td>ACE</td>
<td>Angiotensin converting enzyme</td>
</tr>
<tr>
<td>Ach</td>
<td>Acetylcholine</td>
</tr>
<tr>
<td>ACT</td>
<td>Activated clotting time</td>
</tr>
<tr>
<td>ACTH</td>
<td>Adrenocorticotrophin hormone</td>
</tr>
<tr>
<td>ADH</td>
<td>Antidiuretic hormone</td>
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<tr>
<td>ADP</td>
<td>Adenosine diphosphate</td>
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<td>AKI</td>
<td>Acute kidney injury</td>
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<tr>
<td>ALF</td>
<td>Acute liver failure</td>
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<tr>
<td>ALI</td>
<td>Acute lung injury</td>
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<tr>
<td>ALP</td>
<td>Alkaline phosphatase</td>
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<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
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<tr>
<td>ANC</td>
<td>Absolute neutrophil count</td>
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<tr>
<td>ANP</td>
<td>Atrial natriuretic peptide</td>
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<tr>
<td>AO</td>
<td>Aorta</td>
</tr>
<tr>
<td>APAH</td>
<td>Associated pulmonary arterial hypertension</td>
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<tr>
<td>APC</td>
<td>Activated protein C</td>
</tr>
<tr>
<td>aPPT</td>
<td>Activated partial thromboplastin time</td>
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<tr>
<td>APTT</td>
<td>Activated prothrombin time</td>
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<td>ARDS</td>
<td>Acute respiratory distress syndrome</td>
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<td>Acute renal failure</td>
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<td>ASD</td>
<td>Atrial septal defect</td>
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<tr>
<td>AST</td>
<td>Aspartate aminotransaminase</td>
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<td>AT</td>
<td>Antithrombin</td>
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<tr>
<td>ATN</td>
<td>Acute tubular necrosis</td>
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<td>Adenosine triphosphate</td>
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<td>Atrioventricular re-entry tachycardia</td>
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<td>BAL</td>
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<tr>
<td>BBB</td>
<td>Blood brain barrier</td>
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<tr>
<td>BE</td>
<td>Base excess</td>
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<tr>
<td>BiPAP</td>
<td>Biphasic positive airway pressure</td>
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<tr>
<td>BIS</td>
<td>Bispectral index monitoring</td>
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<tr>
<td>BMR</td>
<td>Basal metabolic rate</td>
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<tr>
<td>BNF-C</td>
<td>British National Formulary for Children</td>
</tr>
<tr>
<td>bpm</td>
<td>Beats per minute</td>
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<tr>
<td>BSEP</td>
<td>Brain stem evoked potentials</td>
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<tr>
<td>BSI</td>
<td>Blood stream infection</td>
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<tr>
<td>cAMP</td>
<td>Cyclic adenosine monophosphate</td>
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<tr>
<td>CAP</td>
<td>Community acquired pneumonia</td>
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</table>
CATS  Children's Acute Transport Service
CAVH  Continuous arteriovenous haemofiltration
CBD  Common bile duct
cGMP  Cyclic guanosine monophosphate
CHB  Complete heart block
CI  Cardiac Index
CMV  Controlled mode mechanical ventilation
CMV  Cytomegalovirus
CNS  Central nervous system
CO  Cardiac output
COPD  Chronic obstructive pulmonary disease
CPAP  Continuous positive airway pressure
CPB  Cardiopulmonary bypass
CPP  Cerebral perfusion pressure
CPS  Carbamylphosphate synthase
CRH  Corticotrophin releasing hormone
CRP  C-reactive protein
CSF  Cerebrospinal fluid
CSM  Committee of Safety of Medicines
CSW  Cerebral salt wasting
CT  Computerised tomography
CTZ  Chemoreceptor trigger zone
CVC  Central venous catheter
CVP  Central venous pressure
CVVH  Continuous venovenous haemofiltration
CVVHD  Continuous venovenous haemodiafiltration
D₂  Dopamine
DI  Diabetes insipidus
DIC  Disseminated intravascular coagulation
DKA  Diabetic ketoacidosis
DM  Diabetes mellitus
DOPA  dihydroxyphenylalanine
DORV  Double outlet right ventricle
EAR  Estimated average requirements
EBV  Epstein Barr virus
ECG  Electrocardiogram
ECL  Enterochromaffin-like cells
ECMO  Extracorporeal membrane oxygenation
EEG  Electroencephalogram
EFAD  Essential Fatty Acid Deficiency
ELC  Enterochromaffin-like
EN  Enteral nutrition
ESBL  Extended spectrum beta lactamase
ESR  Erythrocyte sedimentation rate
ESRF  End stage renal failure
ET  Endotracheal
ETT  Endotracheal tube
EVD  Extra-ventricular drain
FF  Filtration fraction
FFA  Free fatty acids
FFP  Fresh frozen plasma
F₁O₂  Fraction of inspired oxygen
Fr  French
FSH  Follicle stimulating hormone
GABA  Gamma aminobutyric acid
gal-1-put  Galactose-1-phosphateuridylyl transferase
GCS  Glasgow coma score
GFR  Glomerular filtration rate
GGT  Gamma glutamyl transferase
GH  Growth hormone
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full Form</th>
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<td>GHIH</td>
<td>Growth hormone inhibiting hormone</td>
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<td>GI</td>
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<td>GnRH</td>
<td>Gonadotrophin releasing hormone</td>
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<td>GORD</td>
<td>Gastro-oesophageal reflux disease</td>
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<td>Glyceryl trinitrate</td>
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<td>h</td>
<td>Hour</td>
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<td>Histamine₂</td>
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<tr>
<td>HB</td>
<td>Heart block</td>
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<td>HCl</td>
<td>Hydrochloric acid</td>
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<td>HD</td>
<td>Haemodialysis</td>
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<td>HFOV</td>
<td>High frequency oscillatory ventilation</td>
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<td>Heparin induced thrombocytopenia syndrome</td>
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<td>Hypoplastic left heart syndrome</td>
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<td>HOCM</td>
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<td>HPA</td>
<td>Health protection agency</td>
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<td>Home parenteral nutrition</td>
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<td>H₂RA</td>
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<td>Herpes simplex encephalitis</td>
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<td>Herpes simplex virus</td>
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<td>Interleukin</td>
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<td>Intramuscular</td>
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<td>International normalised ratio</td>
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<td>Intraosseous</td>
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<td>JET</td>
<td>Junctional ectopic tachycardia</td>
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<tr>
<td>kg</td>
<td>Kilogram</td>
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<tr>
<td>LA</td>
<td>Left atrium</td>
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<tr>
<td>LBB</td>
<td>Left bundle branch</td>
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<td>LCOS</td>
<td>Low cardiac output state</td>
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<td>LCPUFA</td>
<td>Long chain polyunsaturated fatty acids</td>
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<td>Long chain triglycerides</td>
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<td>LFT</td>
<td>Liver function tests</td>
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<td>LMWH</td>
<td>Low molecular weight heparin</td>
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<td>LP</td>
<td>Lumbar puncture</td>
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<td>LV</td>
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<td>MAP</td>
<td>Mean arterial pressure</td>
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<tr>
<td>MARS</td>
<td>Molecular absorbent recirculation system</td>
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<td>MCT</td>
<td>Medium chian triglycerides</td>
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<tr>
<td>MD</td>
<td>Meningococcal disease</td>
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<td>MDRB</td>
<td>Multi drug resistant bacteria</td>
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<tr>
<td>mg</td>
<td>Milligram</td>
</tr>
<tr>
<td>min</td>
<td>Minute</td>
</tr>
<tr>
<td>ml</td>
<td>Millilitre</td>
</tr>
<tr>
<td>mm</td>
<td>Millimetre</td>
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<tr>
<td>MMC</td>
<td>Migratory motor complexes</td>
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<td>MODS</td>
<td>Multi organ dysfunction syndrome</td>
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<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>MSAFP</td>
<td>Maternal serum alpha-fetoprotein</td>
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<tr>
<td>NAGS</td>
<td>N-acetylglutamate synthetase</td>
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<td>NAI</td>
<td>Non-accidental injury</td>
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<tr>
<td>ND</td>
<td>Nasoduodenal</td>
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<td>NEC</td>
<td>Necrotising enterocolitis</td>
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<td>NG</td>
<td>Nasogastric</td>
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<tr>
<td>Acronym</td>
<td>Term</td>
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<tr>
<td>NJ</td>
<td>Nasojejunal</td>
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<td>NMBA</td>
<td>Neuromuscular blocking agent</td>
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<tr>
<td>NMDA</td>
<td>N-Methyl-d-aspartate</td>
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<tr>
<td>NO</td>
<td>Nitric oxide</td>
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<tr>
<td>NPT2a</td>
<td>2a sodium dependent phosphate transporter</td>
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<tr>
<td>NSAIDs</td>
<td>Non steroidal antiinflammatory drugs</td>
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<tr>
<td>OD</td>
<td>Overdose</td>
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<td>OLT</td>
<td>Orthotopic liver transplant</td>
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<td>OTC</td>
<td>Ornithine transcarbamylase</td>
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<tr>
<td>PA</td>
<td>Pulmonary artery</td>
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<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
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<tr>
<td>PD</td>
<td>Peritoneal dialysis</td>
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<td>PDA</td>
<td>Patent ductus arteriosus</td>
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<td>PDE</td>
<td>Phosphodiesterase</td>
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<td>PEG</td>
<td>Percutaneous endoscopic gastrostomy</td>
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<td>PF</td>
<td>Purkinje fibres</td>
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<td>PH</td>
<td>Pulmonary hypertension</td>
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<td>PICC</td>
<td>Peripherally inserted central catheter</td>
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<td>PICS</td>
<td>Paediatric Intensive Care Society</td>
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<td>PICU</td>
<td>Paediatric intensive care unit</td>
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<td>PIH</td>
<td>Prolactin inhibiting hormone</td>
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<td>PKD</td>
<td>Polycystic kidney disease</td>
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<td>PN</td>
<td>Parenteral nutrition</td>
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<td>PONV</td>
<td>Post operative nausea and vomiting</td>
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<td>PPI</td>
<td>Proton pump inhibitor</td>
</tr>
<tr>
<td>PR</td>
<td>Rectal</td>
</tr>
<tr>
<td>PRBC</td>
<td>Packed red blood cells</td>
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<td>PRH</td>
<td>Prolactin releasing hormone</td>
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<td>Parathyroid hormone</td>
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<td>PVC</td>
<td>Polyvinylchloride</td>
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<td>Pulmonary vascular resistance</td>
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<td>RA</td>
<td>Right atrium</td>
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<td>RAAS</td>
<td>Renin-angiotensin-aldosterone axis</td>
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<td>Right bundle branch</td>
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<td>REE</td>
<td>Resting energy expenditure</td>
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<td>RQ</td>
<td>Respiratory quotient</td>
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<td>Renal replacement therapy</td>
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<td>Respiratory syncitial virus</td>
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<td>RTA</td>
<td>Renal tubular acidosis</td>
</tr>
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<td>RV</td>
<td>Right ventricle</td>
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<td>Surface area</td>
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<td>Sino-atrial</td>
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<td>SBR</td>
<td>Serum bilirubin</td>
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<td>Short chain fatty acids</td>
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<td>Status epilepticus</td>
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<td>SGA</td>
<td>Small for gestational age</td>
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<td>SIADH</td>
<td>Syndrome of Inappropriate ADH secretion</td>
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<tr>
<td>SIMV</td>
<td>Synchronised intermittent mandatory ventilation</td>
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<td>SIRS</td>
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<td>Systemic lupus erythematosis</td>
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<tr>
<td>SNP</td>
<td>Sodium nitroprusside</td>
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<tr>
<td>SRBA</td>
<td>Selective Relaxant Binding Agent</td>
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<td>SSEP</td>
<td>Somatosensory evoked potentials</td>
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<td>SVC</td>
<td>Superior vena cava</td>
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<td>SVT</td>
<td>Supraventricular tachycardia</td>
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<tr>
<td>T3</td>
<td>Tri-iodothyronine</td>
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<td>TAPVD</td>
<td>Total anomalous pulmonary venous drainage</td>
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<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TBM</td>
<td>Tuberculosis meningitis</td>
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<td>TEN</td>
<td>Transpyloric enteral nutrition</td>
</tr>
<tr>
<td>Acronym</td>
<td>Definition</td>
</tr>
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<tr>
<td>TGA</td>
<td>Transposition of the great arteries</td>
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<td>TIVAD</td>
<td>Total implanted venous access device</td>
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<td>Tumour necrosis factor</td>
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<td>TOF</td>
<td>Tetralogy of fallots</td>
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<td>TPN</td>
<td>Total parenteral nutrition</td>
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<tr>
<td>TRH</td>
<td>Thyrotropin releasing hormone</td>
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<tr>
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<td>Thyroid stimulating hormone</td>
</tr>
<tr>
<td>U + E</td>
<td>Urea and electrolytes</td>
</tr>
<tr>
<td>UFR</td>
<td>Ultrafiltration rate</td>
</tr>
<tr>
<td>UTI</td>
<td>Urinary tract Infections</td>
</tr>
<tr>
<td>VAD</td>
<td>Ventricular assist device</td>
</tr>
<tr>
<td>VAP</td>
<td>Ventilator associated pneumonia</td>
</tr>
<tr>
<td>VC</td>
<td>Vomiting centre</td>
</tr>
<tr>
<td>VCO₂</td>
<td>Volume of consumed carbon dioxide</td>
</tr>
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<td>Vd</td>
<td>Volume of distribution</td>
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<td>VEP</td>
<td>Visual evoked potentials</td>
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<tr>
<td>VO₂</td>
<td>Volume of consumed oxygen</td>
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<td>VRE</td>
<td>Vancomycin resistant enterococci</td>
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<td>Ventricular septal defect</td>
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<td>Ventricular tachycardia</td>
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<td>VTE</td>
<td>Venous thromboembolism</td>
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<td>vWF</td>
<td>Von Willebrand factor</td>
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<td>VZV</td>
<td>Varicella zoster virus</td>
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<td>WCC</td>
<td>White cell count</td>
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<td>WPW</td>
<td>Wolff-Parkinson-White syndrome</td>
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</table>
1. Introduction
   1.1 The service
   1.2 Definitions

2. Admission to Paediatric Intensive Care
   2.1 Inflammatory response
   2.2 Fluid management
   2.3 Respiratory support
   2.4 Blood gases
   2.5 Circulatory support
   2.6 Sedation and Analgesia
   2.7 Paralysing agents

3. Drug Administration in PICU
   3.1 Drug handling in critical care
   3.2 Intravenous administration
      3.2.1 Calculations

Further Reading
References
Answers to calculations
Objectives

- To understand the role of paediatric intensive care within the United Kingdom
- To be able to understand and use a “body system” approach to analysing pharmaceutical care needs of critically ill infants and children
- To understand the principles, characteristics and clinical use of intravenous fluids
- To understand the differences between crystalloids and colloids
- To understand the basics of mechanical ventilation
- To understand the mechanism of action/characteristics of inotropes and how to use them to manipulate the cardiovascular system
- To understand the principles of sedation management in critically ill infants and children
- To understand the principles of neuromuscular blockade management in critically ill infants and children
- To be able to describe the altered pharmacokinetics in critically ill infants and children and the principles of therapeutic monitoring
- To be able to demonstrate a high level of understanding of appropriate use of intravenous drugs (bolus to continuous infusion as well as half lives and administration details)
- To be able to solve problems of intravenous drug compatibility issues
1. Introduction

1.1 The service

“……. a service for children (0-18) with potentially recoverable diseases that can benefit from more detailed observation, treatment and technological support than the available in standard wards” (PICS 2001)

The definition of Paediatric Intensive Care service was defined in the standards set by the Paediatric Intensive Care Society in 2001 and sums up the essentials of practice in this area of paediatrics. The emphasis is placed on the provision of a detailed package of treatment and support in order to facilitate the patient’s recovery. There are many variations within PICU’s across the UK because of specialities and demographics and, although the basic definitions and practices will be universal, individual pharmacists must ensure that they are aware of the practices in their unit.

In the UK the majority of cases seen in PICU are unplanned emergencies (70%) occurring at all times of the day and night and to some extent the causes of admission reflect the different patterns of mortality in childhood. Typically just less than 40% of admissions occur in the context of congenital heart disease and roughly 20% occur in the context of respiratory disease although seasonal and geographical variations do apply. Major trauma accounts for about 15% and neurological problems (other than trauma) make up less than 10%. The composition of the remainder is more varied, depending upon the allocation of neonatal surgical patients and other services. The main seasonal variation is respiratory disease, which is more common in the winter months both as a primary cause of admission and as a complication of admissions for other reasons. This leads to a seasonal increase in bed occupancy during the winter months. It should be emphasised that many children who require prolonged intensive care for respiratory diseases have a predisposing history, for example chronic respiratory disease, a history of prematurity, bronchopulmonary dysplasia, asthma or a background of congenital heart disease.

Despite the fact that the majority of admissions are unplanned emergencies the median length of stay can be as low as 24 hours. In contrast to adults requiring intensive care, crude mortality rates are low (6-8%) and the quality of survival is normally high (Paediatric Intensive Care Society, National Standards Document 2001).

Further information regarding the standards and service provision by paediatric intensive care units can be found on the website for the Paediatric Intensive Care Society at http://www.ukpics.org.uk/
1.2 Definitions

On or before admission to PICU the patient will have been assessed according to the level of dependency required. This is an ongoing assessment and patients will move through different levels as their condition changes. This level of dependency is an indication of the severity of illness of the patient according to the number and nature of the interventions required.

Levels of Care

- **Level 1 high dependency care** - for children needing close monitoring and observation, but not requiring ventilatory support.
  *Nurse to patient ratio 0.5:1*

- **Level 2 intensive care** - for children requiring continuous nursing supervision while ventilated. Two or more organ systems may need support.
  *Nurse to patient ratio 1:1*

- **Level 3 intensive care** - for children needing intensive supervision at all times, and requiring complex nursing and therapeutic procedures. This category would include ventilated patients with multiple organ failure.
  *Nurse to patient ratio 1.5:1*

- **Level 4 intensive care** – for children requiring the most intensive interventions such as ECMO.
  *Nurse to patient ratio 2:1*

Multidisciplinary approach

Paediatric critical care is undertaken by a multi-disciplinary team consisting of
- Medical staff
- Nursing staff
- Dieticians
- Physiotherapists
- Clinical psychologists
- Technical staff
- Pharmacists
- Administrative support staff

Many units also provide a retrieval service for patients in district general hospitals who may need urgent admission to a regional PICU. The organisation of this service varies according to the geographical area, for example in large cities there may be one service supporting several units.
2. Admission to PICU

Once the patient has been accepted for treatment by the intensivist, whether in the PICU or the referral centre, the initial treatment involves the stabilisation of the patient until diagnosis and more specific treatment is started. This initial treatment may include institution of ventilatory and circulatory support in order to reduce the risk of multi-organ failure. (Figure 1.1)

2.1 The Inflammatory response

The patient can mount an inflammatory response to many different stimuli including infection and trauma and these will be covered in detail in the clinical chapters but it is important to understand the terminology and the basic response of the body to such stimuli and the interventions which can be initiated in the early stages of a PIC admission in order to stabilise the patient.

When looking at the adult population, following a clinical insult the body may mount a major inflammatory response which is referred to as “Systemic Inflammatory Response Syndrome” or SIRS and this will be defined in these adults as a response fulfilling at least two of the following conditions:

- Temperature > 38°C or < 36°C
- Heart rate > 90 beats per minute
- Respiratory rate > 20 breaths per minute or PaCO₂ <32 mmHg
- White cell count (WCC) > 12,000/mm³ or < 4000/cu mm³ or >10% immature neutrophils (left shift)

These criteria must be age adjusted so that the figures will be changed to a response more than two standard deviations from normal values.

Any patient presenting with these symptoms will require adequate fluid resuscitation to ensure tissue perfusion as acute circulatory failure results in generalised cellular hypoxia. If abnormalities of tissue perfusion are allowed to persist the function of vital organs will be impaired. Perfusion abnormalities such as a lactic acidosis, oliguria or an acute alteration in mental state may be seen if hypotension persists despite adequate fluid resuscitation.
Pathway for multi-organ failure.

**Figure 1.1**
2.2 Fluid Management

Which Fluid?
Fluids used for IV replacement can be divided broadly into crystalloids which pass readily through semi-permeable membranes and colloids which do not and remain in the intravascular space.

In order to understand the movement of water into and out of cells it is important to understand the terminology used.

Osmolarity: - Number of osmoles of solute/L of solution

Tonicity: - Total concentrations of solutes that exert an osmotic force across a membrane in vivo.

The distinction between the two can be shown with reference to some of the most commonly used intravenous fluids:

Glucose 5% solution is iso-osmolar compared to plasma but is rapidly metabolised in blood to water so, in vivo, tonicity is equivalent to electrolyte free water. One litre of 5% glucose results in the expansion of the intracellular and extracellular fluid space by one litre (2/3 in the intracellular space).

Sodium chloride 0.9% (+ Glucose 5% or 10%) is isotonic compared with plasma and so is distributed throughout the extracellular space with approximately 20% of it remaining in the intravascular space.

Hartmann’s solution is an isotonic solution with an electrolyte profile similar to that of extracellular fluid throughout which is distributed. It contains calcium so blood administered subsequently may clot if given through the same administration set.

Synthetic colloids & Plasma substitutes can be used to maintain or replace plasma volume since crystalloids are rapidly lost from plasma. The persistence of a colloid effect is dependent on molecular size.

Gelatins: The gelatins have a plasma half life of 4 hours (h). Bleeding due to a dilution of clotting factors may be a risk following administration of large volume of gelatins. Haemaccel contains calcium and may cause agglutination of transfused blood.

Starches: Starches have a plasma half-life of about 24 hours and thus remain in the body for prolonged periods. In patients with capillary leak there is considerable leak of albumin & lower molecular weight colloids to the interstitial space. Starches consist of molecules with a higher molecular weight and can be used to expand the blood volume.

Albumin: Albumin (HAS) has a plasma half life of 5-10 days and is used to treat hypovolaemia. It effectively replaces volume and supports colloid oncotic pressure. There is no evidence that albumin is better than synthetic alternatives for volume replacement in terms of outcome, length of stay or need for blood products.
**How much fluid should be used?**

**Resuscitation**
The first priority is to correct hypovolaemia and thus perfusion of the child.

**Fluid boluses of 10 – 20 ml/kg of sodium chloride 0.9% should be given.**
The child should be reviewed after the initial fluid bolus has been given to assess the need for further fluid boluses. Children who require more than 40ml/kg of fluid boluses should be discussed with the paediatric ICU as further fluid may lead to pulmonary oedema and the need for intubation and ventilation.

The volume of fluid given as resuscitation fluid will vary according to the severity of illness of each child and should not be included in subsequent calculations of maintenance and deficit.

Once the child has been fully fluid resuscitated an assessment can be made of further fluid requirements.

**Deficit Fluid**
A child’s water deficit, in ml, can be calculated after the degree of dehydration has been expressed as a percentage of the body weight (e.g. a 10 kg child whom is 7% dehydrated has a water deficit of 700 ml).

\[
\text{Total deficit volume to be replaced (ml)} = \text{Weight} \times \% \text{ dehydration} \times 10
\]

The best estimate of dehydration (water deficit) is the difference between the child’s immediate pre morbid weight and the current weight. However it is a widely accepted fact that the calculation of water deficit based on clinical signs is usually inaccurate.

The use of clinical signs is therefore the best available method as the pre morbid weight is most often not available.

The most common clinical signs used in estimation of water deficit are:

- Cool pale peripheries with prolonged capillary refill time.
- Decreased skin turgor (beware hypernatraemic dehydration)
- Dry mucosal membranes
- Sunken eyes
- Sunken fontanelle
- Irritability and lethargy
- Deep (Kushmauls) breathing
- Increased thirst

Depending of the degree of and number of these signs present the child can be placed in one of three categories:

- Mild or no dehydration (< 5% dehydrated) - No clinical signs
- Moderate dehydration (5 – 10 % dehydrated) - Some clinical signs
- Severe dehydration (≥ 10% dehydrated) - Multiple clinical signs
  
  +/- acidosis and hypotension

Any fluid deficit is replaced over a time period that varies depending on the underlying condition of the patient.
Replacement should be rapid (24 hours) in most cases of gastroenteritis, but slower in diabetic ketoacidosis, meningitis and hypernatraemia (48 hours). In hypernatraemia the serum sodium should not be allowed to fall by more than 0.5 mmol/litre/hour.

**Maintenance fluid**

Maintenance fluid is the volume of daily fluid intake which will replace all insensible losses (through respiration, skin and stool) and allow excretion of the daily production of excess solute load (urea, creatinine, electrolytes etc) in a volume of urine that is of an osmolarity similar to plasma. The maintenance fluid requirement of a child decreases proportionately with increasing age and weight. There are two recognised methods that use a patient’s weight to estimate their normal maintenance fluid requirements. They are the “100, 50 20” and “4, 2, 1” rules as demonstrated below. (Table 1.1)

<table>
<thead>
<tr>
<th>Patients weight</th>
<th>ml/day</th>
<th>ml/hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 to 10 kg</td>
<td>100 x weight</td>
<td>4 x weight</td>
</tr>
<tr>
<td>10 – 20 kg</td>
<td>1000 + 50(wt -10)</td>
<td>40 + 2(wt-10)</td>
</tr>
<tr>
<td>&gt;20 kg</td>
<td>1500 + 20(wt – 20)</td>
<td>60 + 1(wt-20)</td>
</tr>
</tbody>
</table>

Table 1.1 Fluid requirements

100mls/hour (2500mls/day) is the normal maximum amount

Although these calculations can be used, the individual requirements vary depending on the disease process and this has to be taken into account when calculating the individual’s maintenance fluids.

**Acute Respiratory illnesses such as pneumonia, bronchiolitis or asthma** Due to inappropriate ADH secretion (SIADH) patients may have increased fluid retention and therefore their maintenance fluid requirement is approximately 80% of that of a well child.

**Meningitis** The prescribed maintenance fluids in children with meningitis should be 60% the of the maintenance fluids of a well child. This is due to SIADH as well as the importance of preventing hyponatraemia and the resulting cerebral oedema.

Apart from the disease process there are other factors that should be taken into account such as, inactivity of patient lying in bed (less 25%), mechanical ventilation with humidified gases (less 25%) and patients with significant pyrexia ( add 10 to 20%).
An important aspect of treatment of a patient in PICU is the careful monitoring of fluid balance and the use of diuretics and fluid boluses to ensure the patient maintains good tissue perfusion while avoiding oedema.

During resuscitation of the patient it is important that the signs of tissue hypoxia are monitored and treatment is escalated as required. The patient may require respiratory and cardiovascular support which will require the intubation and ventilation of the patient and the commencement of inotropes.

Organ failure may be indicated by:
- Increased respiratory rate
- Peripheries: warm & vasodilated or cold & vasoconstricted
- Poor urine output
- Reduced conscious level
- Metabolic acidosis
- Poor oxygenation

Metabolic acidosis will be seen on “blood gases” with a reduced arterial pH and a raised blood lactate. The anaerobic production of lactate may occur secondary to global hypoxia, such as septic shock or cardio-respiratory failure, or may be the result of focal hypoxia from a localised injury such as an infarcted bowel. Metabolic causes of the increase in lactic acid will be discussed in the clinical section.

2.3 Respiratory support

Respiratory support is one of the main reasons for admission to PICU and this can take the form of invasive or non-invasive ventilation and within each of these there are various levels of support.

Oxygen therapy is started when saturations (SaO₂) reach less than 95% in a normally healthy child. Care should be taken if the child has an underlying cardiac anomaly as the saturations may normally be much lower and in some conditions oxygen therapy can cause the patient to deteriorate further. Oxygen therapy can be given via a facial mask or nasal cannulae and the flow rate will vary according to the mode of delivery and the percentage of oxygen required.

Ventilatory support can vary depending on the requirements of the child but whichever method is used it needs to reflect the respiratory cycle which consists of inspiration and expiration and the relative movement of gas during the two phases. Inspiratory flow occurs as a result of a pressure gradient between the airway and the lung and, after a plateau phase, expiration is usually passive. The choice of ventilator and the mode of ventilation are based on various criteria including age, diagnosis, and cardiovascular and haemodynamic status.

Invasive ventilation is based on the principle of intermittent positive pressure ventilation where the lungs are inflated by applying a positive pressure to the airways. They can be classified according to the criteria for terminating the active inspiratory phase and initiating passive expiration. These criteria include preset pressures, preset volume or a preset inspiratory time. The requirements for differing modes are dependent on the compliance of the chest and lungs as well as the airway resistance.
Controlled Mode Mechanical ventilation (CMV) delivers a mechanical breath irrespective of spontaneous effort. This can be volume or pressure regulated and, in this mode, the patient’s spontaneous breathing may interfere with the delivery of the mandatory breaths by the ventilator. In these cases the use of sedation, with or without a paralysing agent, may be required to prevent the patient “fighting” the ventilator.

Synchronised Intermittent Mandatory Ventilation (SIMV) allows both mandatory and spontaneous breathing which has the advantage of improving patient synchronisation and allows the continuing use of the respiratory muscles.

There are many variations of the basic ventilators and each unit will have their own preferred makes and modes of ventilator depending on the requirements of their patients.

High Frequency Oscillatory Ventilation (HFOV) is a strategy used to protect the lungs from over-distension by delivering very small tidal volumes at high frequency and preserving end-expiratory lung volume.

Extracorporeal Membrane oxygenation (ECMO) is a specialist method of providing oxygenation for patients in acute respiratory failure and will be discussed further in the cardiology section.

Non-invasive forms of ventilation without the use of an endotracheal tube can be used in some patients to prevent further deterioration and the need for intubation or to allow weaning of ventilatory support. Biphasic Positive Airway Pressure (BiPAP) is a form of pressure support ventilation. The inspiratory and expiratory pressures can be adjusted independently to provide Continuous Positive Airway Pressure (CPAP)

Adequate humidification is required for all forms of ventilation to ensure that secretions do not become dry and viscous which will make them more difficult to remove. Further damage to the mucosa and a reduction of the ciliary motility can increase the risk of infections.

Patients who are being ventilated will normally require sedation and analgesia to allow them to tolerate the presence of an endotracheal tube (ETT) and to relieve anxiety and distress. Muscle paralysis may also be required to allow synchronisation with the ventilator. The drugs and their side effects will be discussed later in this section.

Before the patient’s endotracheal tube is removed the patient may be given dexamethasone to reduce inflammation of the trachea, particularly if the child is known to have had a difficult intubation.
2.4 Blood gases
Further detail on acid base balance can be found in section 6 on respiratory medicine.

It is important to monitor the patient’s respiratory status carefully as the artificial respiration from mechanical ventilation overrides the body’s normal methods of maintaining homeostasis. The understanding of acid-base balance and knowledge of normal values is essential in the interpretation of the blood gases used to monitor respiration. (Table 1.2)

![Table 1.2 Normal values]

<table>
<thead>
<tr>
<th>Acid-base abnormality</th>
<th>Primary disturbance</th>
<th>Effect on pH</th>
<th>Effect on P02</th>
<th>Base excess</th>
<th>Compensatory response</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory acidosis</td>
<td>↑ Pco2</td>
<td>↓</td>
<td></td>
<td>↑ HCO3-</td>
<td>Compromise in ventilation/perfusion/diffusion</td>
<td></td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>↓ HCO3-</td>
<td>↓</td>
<td>N or ↑-ve</td>
<td>↓ Pco2</td>
<td>Loss of HCO3- or increase in metabolic acids</td>
<td></td>
</tr>
<tr>
<td>Respiratory alkalosis</td>
<td>↓ Pco2</td>
<td>↑</td>
<td>N or ↑</td>
<td>↓ HCO3-</td>
<td>Alveolar hyperventilation or hypocapnia</td>
<td></td>
</tr>
<tr>
<td>Metabolic alkalosis</td>
<td>↑ HCO3-</td>
<td>↑</td>
<td>N or ↑+ve</td>
<td>↑ Pco2</td>
<td>Loss of H+ or gain in HCO3</td>
<td></td>
</tr>
</tbody>
</table>

Table 1.3 Causes of abnormal values
Although the changes in blood gases may be the result of changes in ventilation there are many other reasons for a change in pH and these are listed below.

**Respiratory acidosis**
Any cause of hypoventilation:-
- Obstructive airway disease e.g. asthma
- CNS depression e.g. head injury
- Neuromuscular disease
- Artificial ventilation

**Metabolic acidosis**
*With normal anion gap*
- Intestinal loss e.g. diarrhoea
- Renal losses e.g. renal tubular acidosis
*With increased anion gap*
- Overproduction of organic acid - diabetic ketoacidosis, lactic acid
- Decreased ability to conserve $\text{HCO}_3^-$ – e.g. renal failure
- Poisoning e.g. salicylate, methanol

**Respiratory alkalosis**
Any cause of hyperventilation:-
- Psychogenic e.g. hysteria, pain
- Central e.g. raised intracranial pressure
- Pulmonary e.g. hypoxia, pulmonary oedema,
- Metabolic e.g. fever, acute liver failure
- Drugs e.g. acute salicylate poisoning
- Artificial ventilation

**Metabolic alkalosis**
- Excess acid loss e.g. persistent vomiting as in pyloric stenosis
- Diuretic therapy
- Excess intake of alkali

During normal self ventilation metabolic disturbances are compensated acutely by changes in ventilation and chronically by appropriate renal responses. Respiratory disturbances are compensated by renal tubular secretion of hydrogen. However during mechanical ventilation patients lose this ability to compensate.

The following markers are also indicators of the acid-base status of the patient.

**Anion Gap**
The anion gap is a useful marker for indicating the cause of a metabolic acidosis.
Anion gap = (sodium + potassium) – (bicarbonate + chloride) with a normal range of 5-12mmol/L. A patient with a metabolic acidosis and a normal anion gap will have lost base, e.g. with diarrhoea, whereas a patient with a metabolic acidosis who has an increased anion gap will have gained acid, e.g., in ketoacidosis.
Electrolyte changes
In an acidotic patient a rise in H⁺ across the cell membrane causes an efflux of K⁺ which preserves the cell membrane but results in hyperkalaemia. In alkalosis there is an influx of potassium into the cell causing hypokalaemia and there is also an increase in the ratio of bound to unbound calcium.

Base Excess
The base excess equates to the approximate amount of acid (or base for a base deficit) which would be required to titrate 1 litre of blood to a pH of 7.4. Negative values indicate a metabolic acidosis and positive values indicate metabolic alkalosis.

Lactate
Lactic acidosis may result from tissue hypoxia but in critically ill children a rise in blood lactate may occur for reasons other than inadequate oxygen delivery, for example, in sepsis muscles may generate lactate under aerobic conditions.

2.5 Circulatory support
The most important measure of circulation is the measurement of blood pressure but because of the wide range of normal values in the paediatric population it is important to know the correct values for individual patients, based on age, gender and height appropriate norms. Patients with a low cardiac output can sometimes maintain a reasonable blood pressure by vasoconstriction, while vasodilated patients may be hypotensive despite a high cardiac output. Percutaneous placement of an IV arterial cannula allows continuous monitoring of blood pressure and repeated sampling of blood for gas and acid-base analysis. Central venous pressures are monitored within a large intrathoracic vein and are a simple method of assessing circulating volume and myocardial function. Pulmonary artery catheterisation with a balloon flotation catheter allows measurement of the filling pressure of the left ventricle (pulmonary artery occlusion pressure).

In order to appreciate the management of cardiac instability in infants and children it is important to understand the basics of cardiac function.

Definitions

Cardiac output (CO) is the volume of blood that exits the left ventricle in a minute and is equivalent to the stroke volume x heart rate.
Cardiac Index (CI) is cardiac output related to surface area (SA)  CI = CO/SA
Preload is the amount of myocardial stretch present before contraction and is related to the volume of blood in the ventricles prior to contraction.
Afterload is the force opposing ventricular ejection and the major component is the systemic vascular resistance.
Contractility is the force generated by the myocardium and is independent of preload and afterload. Drugs which affect the contractility of the heart are known as inotropes. The essential mechanism of all drugs which increase the contractility of the heart is the movement of calcium ions into the cells. This occurs because of stimulation of adrenergic receptors which cause the conversion of adenosine triphosphate (ATP) to
cyclic adenosine monophosphate (cAMP). The most important class of inotropes are the adrenergic receptor agonists including adrenaline (epinephrine), noradrenaline (norepinephrine), dopamine and dobutamine. (Figure 1.2)

![Diagram of inotropic factors (preload, contractility, afterload, heart rate, stroke volume, cardiac output, systemic vascular resistance, blood pressure)]

**Figure 1.2**

Inotropes affect the contractile state of the cardiac muscle and the myocardium. Positive inotropes enhance contractility and negative inotropes reduce it but the term inotrope is usually applied to those drugs which increase the contractility of the heart.

The ideal inotrope
- Does not
  - Increase myocardial oxygen demand
  - Change heart rate
  - Cause vasoconstriction
- Is predictable and easily titratable
- Redistributes blood flow to vital organs
- Does not produce tolerance
- Is easy to administer and compatible with other infusions

Inevitably this type of drug does not exist and therefore it is important to understand the properties of the available inotropes in order to produce the effect that is required. The majority of inotropes work on receptors in the adrenergic nervous system and these are affected by both endogenous and exogenous transmitters. The adrenergic nervous system innervates the gut, heart, lungs and blood vessels and the transmitters include noradrenaline, adrenaline and dopamine. Chemically these are formed in the body from tyrosine which is an amino acid precursor obtained from the diet. The tyrosine is hydroxylated to dihydroxyphenyalanine (DOPA) and then to dopamine, noradrenaline and adrenaline. Adrenaline is both a CNS transmitter and is also secreted from the adrenal glands. There are several types of receptors and the understanding of the variety of receptors is expanding but the important receptors to understand for circulatory support are tabled below. (Table 1.3)
Alpha1 | Myocardium, peripheral vessels (vasoconstriction)  
---|---  
Alpha2 | Central, presynaptic (vasodilatation)  
Betalpha1 | Myocardium (inc contractility and heart rate)  
Beta2 | Bronchi, peripheral vessels (bronchodilatation and vasodilatation)  
Beta3 | Adipose tissue

Table 1.3 Location of Adrenergic receptors

The action of the adrenergic drugs is to allow the intracellular flow of Ca\(^{2+}\) which results in elevated intracellular Ca\(^{2+}\) concentrations and an increase in the strength of cardiac contractility. All of the adrenergic inotropes have a short half-life, measured in seconds and therefore have to be given by continuous infusion. The main adrenergic inotropes used in PICU are adrenaline, noradrenaline, dopamine and dobutamine. Isoprenaline also has a role in the treatment of bradycardia.

The choice of inotrope is a clinical decision based on an understanding of the effect produced by the stimulation of the various receptors. (Tables 1.4 and 1.5)

<table>
<thead>
<tr>
<th></th>
<th>α(_1)</th>
<th>β(_1)</th>
<th>β(_2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenaline</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>+</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Dopamine</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Isoprenaline</td>
<td>0</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>+++</td>
<td>+++</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 1.4 Adrenoreceptors

Dopamine will also stimulate dopaminergic receptors which will cause some vasodilatation in the renal and splanchnic vessels.

Inotropes such as dopamine, dobutamine and adrenaline also act as positive chronotropes. Chronotropic drugs can increase the heart rate, a positive chronotrope or decrease it, a negative chronotrope. Beta-blockers and digoxin are examples of negative chronotropes.

The short half life of inotropes has implications for the management of a patient on PICU. Any unstable patient who is treated with inotropes will be dependent on a continuous supply of the selected drug and this will include during the change over of
pumps when new syringes are connected. Continuous infusions will be discussed further later in the section.

**Phosphodiesterase inhibitors** are another group of drugs used in paediatric critical care for their inotropic properties and they differ from the adrenergic stimulants in their mode of action. Phosphodiesterases (PDEs) are a group of enzymes which inactivate cGMP (cyclic guanosine monophosphate) and cAMP (cyclic adenosine monophosphate). Although there are over 11 families described, the functionally relevant isozymes are PDE 1,2,3,4, and 5. The phosphodiesterase inhibitors which are used as pharmacological agents include aminophylline, sildenafil and milrinone. Milrinone is one of the group of inodilators which increase the cAMP levels by inhibiting the PDE-3 resulting in a more prolonged influx of Ca\(^{2+}\) into the myocardial cells causing an increase in contractility. Their action on cAMP breakdown in arterial and venous smooth muscle results in a marked vasodilatation. One advantage of phosphodiesterase inhibitors is that, as they use a different pathway to increase the calcium influx, they continue to act when the adrenergic inotropes become less effective due to tachyphylaxis.

The major trial of phosphodiesterase inhibitors in children was the “Prophylactic Intravenous Use of Milrinone after cardiac operation in pediatrics” the PRIMACORP study published in 2002.[1] However milrinone is not licensed for use in paediatrics and following this study the MHRA concluded that

“The kinetics of milrinone are not established in children and infants and literature data suggest that the kinetics may be substantially different in these groups………

When used as a prophylactic in children undergoing cardiac surgery, the proportion of patients who benefit in terms of prevention of low cardiac output state (LCOS) is small. Such benefit is limited to the high dose used and it is not associated with clinical usefulness in terms of outcome. The risk-benefit assessment is therefore considered not to be in favour of the licensing of the product, when used as a prophylactic in children undergoing cardiac surgery.” Milrinone Paediatric Working Group. Despite the unlicensed status, milrinone is frequently used in many PICUs.

A new agent which has been licensed in several countries is Levosimendan which acts by increasing the sensitivity of cardiac muscle to calcium thereby increasing contractility. It has a novel mechanism so may work when other inotropes fail and it does not increase oxygen uptake by the heart. It is administered by IV infusion over 24 hours and is metabolised to form active metabolites with half life of several days. It is unlicensed in UK and therefore is imported when required. The experience of its use is variable but there have been several clinical trials. The LIDO (2002) [2] and CASINO (2004)[3] trials showed a mortality benefit with levosimendan but a large trial published in 2007 (SURVIVE)[4] showed no statistical differences between treatment groups (dobutamine 5-40mcg/kg/min) vs levosimendan) over a series of secondary endpoints and the primary outcome of all-cause mortality at 180 days. Following this a planned phase 3 study in the US was not undertaken by the drug company and it is not being taken forward to further licensing. However in September 2008 a case series of seven infants was published in The European Journal of Paediatrics. This concluded that “levosimendan is a new rescue drug which has beneficial effects even in paediatric cardiac surgery”. The role of this drug in paediatric critical care has still to be fully established.
| Adrenaline | • Endogenous  
|           | • Mixed $\beta_1$ and $\beta_2$ stimulation with some $\alpha_1$ effects at high dose  
|           | • Effects dose related  
|           | • $<0.01$mcg/kg/min decreases BP  
|           | • $0.04-0.1$mcg/kg/min increase in HR + contractility  
|           | • $>0.1$mcg/kg/min increase in BP and peripheral resistance  |
| Noradrenaline | • Endogenous  
|              | • Strong $\beta_1$ and $\beta_2$ activity  
|              | • Administration leads to a rise in contractility and a substantial increase in systemic vascular resistance.  
|              | • May cause reflex reduction in heart rate as BP increases (baroreceptor mediated)  |
| Dopamine | • Stimulates DA$_1$ and DA$_2$ to cause peripheral dilatation  
|          | • Stimulates $\beta_1$ to increase myocardial contraction and increase cardiac output (doses 5-10mcg/kg/min)  
|          | • Stimulates $\alpha_1$ to increase arteriolar and venous constriction and afterload (doses $>10$mcg/kg.min)  
|          | • Endogenous –pre-cursor of noradrenaline  |
| Dobutamine | • Synthetic agent  
|            | • Pre-dominantly $\beta_1$ effects and weak $\beta_2$ and $\alpha$ effects.  
|            | • At lower doses myocardial contraction is improved without a significant increase in heart rate or systemic vascular resistance so improving cardiac output  |
| Isoprenaline | • Synthetic  
|              | • Stimulates $\beta_2$ and $\beta_2$ receptors improving contractility and cardiac output and causing vasodilatation and a marked increase in heart rate  
|              | • Mainly used in treatment of bradycardia.  |

**Table 1.5 Comparison of Adrenergic receptor stimulants**
2.6 Sedation and Analgesia

In the PICU sedatives are frequently administered to reduce anxiety and distress in the child, facilitate diagnostic and therapeutic procedures, assist mechanical ventilation, avoid inadvertent self-extubation, reduce metabolic rate and oxygen demand, and enhance analgesia and less disrupted sleep. Failure to meet these end points may have deleterious effects on the critically ill child.

Inadequately treated pain results in physiological responses that are associated with poor outcomes. These include hypercoagulability, immunosuppression, and persistent catabolism. Pain increases levels of sympathetic nervous system activity and catecholamine release, which places additional demands on the cardiovascular system of the critically ill child. The hypermetabolic state following an injury is exacerbated by pain, and this can lead to diminished immune function and impaired wound healing. As prolonged periods of pain can result in the development of severe anxiety, achieving adequate analgesia is of prime importance when managing these patients. Once a pain free state is achieved, anxiolysis, hypnosis and amnesia become the primary goals of sedative therapy. Many sedative agents have good analgesic properties but it is important to supplement when necessary with standard analgesia such as paracetamol and NSAID’s if indicated.

The ideal level of sedation varies from child to child and for the different clinical situations encountered, however most intensivists seek to maintain a mechanically ventilated child during the acute phase of the illness in a sleepy but rouseable state. Deeper sedation is usually reserved for selected patients such as those receiving muscle relaxants or those with inadequate tissue oxygen delivery.

**Sedative agents commonly used in PICU**

Ideally the choice of sedative should be based on the pharmacokinetic and pharmacodynamic characteristics that allow safe, efficacious and titratable use as well as being affordable. (Table 1.6)

In recent years a better understanding of the benefits offered by a combination of drugs, acting at different effector sites, has improved the quality of analgesia or sedation provided when compared to drugs acting alone. The combined action of the different drugs often allows a reduction in the doses used of each individual drug, thereby minimising side effects while maintaining adequate analgesia/sedation. This concept of co-analgesia has become routine practice in PICU [5].
### Table 1.6 Comparison of sedative agents

<table>
<thead>
<tr>
<th></th>
<th>Morphine</th>
<th>Fentanyl</th>
<th>Midazolam</th>
<th>Lorazepam</th>
<th>Clonidine</th>
<th>Chloral Hydrate / Triclofos</th>
<th>Ketamine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Action</strong></td>
<td>Analgesic, Sedative</td>
<td>Analgesic, sedative</td>
<td>Hypnotic, anxiolytic,</td>
<td>Hypnotic, anxiolytic</td>
<td>Analgesic, Sedative</td>
<td>Analgesic, sedative and</td>
<td>Analgesic, sedative</td>
</tr>
<tr>
<td></td>
<td>Opioid Receptors</td>
<td>Opioid Receptors</td>
<td>amnesic, muscle relaxant &amp; anticonvulsant</td>
<td>amnesic &amp; anticonvulsant</td>
<td>α2-adrenoreceptors</td>
<td>and dissociative anaesthetic.</td>
<td>and dissociative</td>
</tr>
<tr>
<td><strong>Pharmacokinetics</strong></td>
<td>t₁/₂=1.5-4.5 hrs (longer in neonates). Hepatic metabolism (active metabolites). Renal excretion.</td>
<td>t₁/₂=3-4 hrs (longer in neonates). Hepatic metabolism (inactive metabolites). Renal excretion.</td>
<td>t₁/₂=3-4.5hrs, short acting. t₁/₂ prolonged in neonates &amp; liver impairment. Hepatic metabolism (active metabolites). Renal excretion.</td>
<td>t₁/₂=10-20 hrs. Increased to 30 hours in neonates. Hepatic metabolism (inactive metabolite). Renal excretion.</td>
<td>t₁/₂=8-12hrs. Hepatic metabolism (inactive metabolites). Renal excretion.</td>
<td>t₁/₂=6-8hrs (in babies t₁/₂ is 3 times longer, it can lead to accumulation and toxicity). Hepatic metabolism to active molecule: trichloroethanol.</td>
<td>t₁/₂=1-2 hrs Hepatic metabolism Renal excretion</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>IV bolus or infusion, Oral</td>
<td>IV bolus or infusion</td>
<td>IV bolus or infusion, Oral</td>
<td>IV bolus</td>
<td>IV infusion, Oral</td>
<td>Oral, rectal</td>
<td>IV bolus or infusion</td>
</tr>
<tr>
<td><strong>Side Effects</strong></td>
<td>-Respiratory depression (neonates &amp; infants susceptibility). -Hypotension &amp; tachycardia. -↓gastric emptying, constipation, pruritus. -Tolerance, dependence, withdrawal if discontinued abruptly.</td>
<td>Respiratory/circulatory depression. ↓gastric emptying, constipation. Tolerance, dependence, withdrawal if discontinued abruptly.</td>
<td>Respiratory/circulatory depression.</td>
<td>Respiratory/circulatory depression. As midazolam but less marked. Less hepatic metabolism than midazolam (safer in liver disease)</td>
<td>-Hypotension. -Bradycardia. -Rebound hypertension if stopped abruptly. -Dry mouth.</td>
<td>Respiratory/circulatory depression. -Hepatotoxicity. -Gastric irritation (corrosive to skin and mucous membranes, triclofos more palatable &amp; causes less GI irritation). -Tolerance &amp; dependence with prolonged used.</td>
<td>-Hallucinations. -Tachycardia. -Cardiac tachyarrythmias. -Hypertension. -Increased secretions. -Respiratory depression -apnoea if rapidIVadm</td>
</tr>
<tr>
<td><strong>Cautions</strong></td>
<td>Lower doses in neonates &amp; hepatic/renal failure</td>
<td>Raisedintracranial pressure, head injury, renal impairment, liver disease &amp; myasthenia gravis.High doses are associated with chest wall rigidity.</td>
<td>High risk for drug withdrawal if used &gt;48h.</td>
<td>Patients with muscle weakness, impaired liver or kidney function. High doses or parenteral administration may cause hypotension.</td>
<td>Hypotension &amp; sepsis</td>
<td>Hypotension &amp; sepsis</td>
<td>Use together with benzodiazepine to prevent agitation.</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>Potent analgesic</td>
<td>Potent analgesic</td>
<td>Rapid effect with infusion.</td>
<td>Less side effects compared to midazolam.</td>
<td>Analgesic &amp; sedative. ↓morphine requirements ↓Drug withdrawal. It does not cause respiratory depression.</td>
<td>Strong sedative.</td>
<td>Boncholoditatory, minimal respiratory depression.</td>
</tr>
</tbody>
</table>

2.7 Paralysing agents

Paralysing agents or neuromuscular blocking agents are important for both short term paralysis to allow intubation and for longer term paralysis in a variety of strategies in ventilation and during neuro-protective measures. There are several groups of agents and it is important to understand the various mechanisms and the side effect profile of each drug in order to select the correct one for the patient. More detail on mechanism of actions is included in section 8 on the central nervous system.

Competitive antagonists (non-depolarizing)
Pancuronium, vecuronium, rocuronium and atracurium.

Depolarizing blockers
Suxamethonium.

Competitive antagonists compete with acetylcholine at the neuro-muscular receptors but do not initiate ion channel opening. By reducing the endplate depolarisations produced by acetylcholine to a size that is below the threshold for muscle action potential they cause a flaccid potential. They have a slower onset than depolarizing blockers but have a longer duration of action. It is possible to reverse the effect by administration of an anticholinesterase such as neostigmine. The reversing agent acts quickly and can last for about 20-30 minutes but then may need repeating. Because of this they are not used for reversal in patients in intensive care but can be useful to check that the block is reversible and not a critical care myopathy.

The choice of blocking agent will depend on the side effect profile and the duration of action required. They are used to facilitate ventilation in patients who fail to respond to sedation alone. It is important to ensure adequate sedation and analgesia before starting a paralysing agent. They also have a role in controlling intracranial pressure in patients requiring neuro-protective measures. The major side effects include histamine release, vagal blockade, and sympathomimetic actions.

Vecuronium has a rapid onset (1-2 minutes) and the blockade from a single dose will last between 20-50 minutes. It is often delivered by infusion particularly in patients with cardiac instability as it has less cardiovascular effects than pancuronium. It is important to titrate the infusion to achieve adequate paralysis without accumulation of the drug which may prevent the patient being extubated appropriately. Vecuronium will accumulate particularly in patient with renal or hepatic impairment and its action is potentiated by an acidosis and also by interactions with drugs such as gentamicin, clindamycin and some diuretics. Higher doses may be required in alkalosis and in patients on phenytoin. Some units have planned breaks from vecuronium paralysis and stop the drug until the patient moves and then assess them before re-paralysing, this is often known as a “vec holiday”. A myopathy may occur following prolonged use of muscle relaxants in conjunction with high dose steroids, although this is rare.

Rocuronium has a similar profile to vecuronium with an intermediate duration of action, around 30 minutes and a rapid onset (1-2 minutes) and has no cardiovascular effects.

Atracurium is a mixture of 10 isomers and has an intermediate onset (2-4 minutes) and an intermediate duration (8-50 minutes). Again atracurium has few cardiovascular effects but it causes some histamine release which may lead to flushing and hypotension. The advantage of atracurium is that it undergoes non-enzymatic
metabolism which is independent of liver and kidney function “Hofmann elimination”. This metabolism occurs at physiological pH and temperature and produces laudanosine which has no NMB effect. Atracurium is also hydrolysed by non-specific plasma esterases and excretion is via the urine and bile. Care must be taken when using atracurium in neonates. Lower doses are necessary due to this group of children being more sensitive to its effects.

**Cisatracurium** is a single isomer of atracurium and is more potent and has a slightly longer duration of action. Because of a lack of histamine release it shows more cardiovascular stability than atracurium. In children 1 month to 12 years cisatracurium can have a shorter duration of action and faster spontaneous recovery.

**Pancuronium** has a rapid onset (1-2 minutes) and a long duration of action (>50 minutes) and can be given as bolus injections in intensive care. Because of its sympathomimetic effect, pancuronium has a tendency to increase arterial pressure and its vagolytic activity can cause tachycardia. It has no histamine releasing activity and its half life is increased in neonates.

**Depolarizing blockers**

**Suxamethonium** acts by mimicking acetylcholine at the neuromuscular junction and has an ultra-rapid onset (<1 minute) and an ultra-short duration of action (<8 minutes) making it a useful drug for intubation. Neonates and young children appear to be less sensitive to suxamethonium and may require higher doses. Suxamethonium is hydrolysed rapidly by plasma pseudocholinesterases. Some people inherit an atypical form of the enzyme and the neuromuscular blockade may last for several hours in such individuals. Suxamethonium acts by depolarising the endplate and it should be given after anaesthetic induction as the patient can get asynchronous twitches and subsequent muscle pain. Pre-medication with atropine reduces the bradycardia which can be seen with repeated doses and will also reduce the excessive salivation that may occur. Depolarizing agents cannot be reversed with neostigmine. Suxamethonium is contra-indicated in patients with severe burns or trauma as there is a potential increase in potassium due to the initial muscle stimulation which will be worse in damaged muscle. It is also contra-indicated in patients with Duchenne muscular dystrophy, or a family history of congenital myotonic disease, low plasma cholinesterase activity or malignant hyperthermia. Children with myasthenia gravis are resistant to suxamethonium.

**Malignant hyperthermia (hyperpyrexia)** is a rare but potentially lethal complication of anaesthesia characterised by a rapid rise in temperature, tachycardia, acidosis and increased muscle rigidity. The volatile anaesthetics appear to be the most potent triggers but suxamethonium has also been implicated. The treatment is by rapid intravenous injection of dantrolene sodium starting at a dose of 1mg/kg and repeated as required to a maximum of 10mg/kg. Dantrolene acts on the skeletal muscle by interfering with calcium efflux and stopping the contractile process.

**Selective Relaxant Binding Agent (SRBA)**

Sugammadex is a new agent that is being used in selected patients in the adult and paediatric population. It was originally developed to completely reverse
neuromuscular blockade of the rocuronium molecule but it also binds sufficiently to vecuronium to antagonise its neuromuscular blockade. It is a modified γ-cyclodextrin, a selective relaxant binding agent. There is currently limited data for its use in children and is only recommended for routine reversal of moderate rocuronium induced blockade in children and adolescents. The benefit of sugammadex is that it can rapidly reverse any depth of neuromuscular blockade induced by rocuronium or vecuronium. This agent has great potential, but more data will be needed for our paediatric population.


3.1 Drug handling in critically ill children

In order to be able to understand the effects of the drugs that are used to stabilise and treat a critically ill child it is important to have a good background knowledge of the variety of changes that might affect drug handling in children in the intensive care setting as well as the normal variations due to development through infancy, childhood and into adolescence.

Absorption depends on the route of administration and often the intravenous route is preferred if there are concerns regarding the patient’s ability to fully absorb the drugs required. Oral absorption will be affected by the formulation of the drug and its stability to acid and enzymes but also the co-administration of drugs such as opioids can reduce absorption by reducing gut motility. The gut oedema which can result from chronic renal failure and the poor gut perfusion in patients with some congenital cardiac defects can also reduce drug absorption. The use of naso-gastric (NG) tubes and naso-jejunal (NJ) tubes can also affect the absorption of drugs particularly in relation to feeds. There are several reference sources that discuss the options for individual drugs given via NG and NJ tubes including “Drug Administration via Enteral Feeding Tubes” edited by Rebecca White and published by the Pharmaceutical Press.

Rectal (PR) administration can be useful if the oral route cannot be used and chloral hydrate and paracetamol administered rectally are mainstays of sedation and analgesia in many units. Intramuscular (IM) injection gives slow and erratic absorption in all children because of the poor blood supply to the muscle and a small muscle mass.

In an emergency situation, intraosseous (IO) access allows access to the vascular network in the long bones and drugs or fluid can be administered through an IO needle usually placed in the tibia. The absorption is comparable to drugs given via the intravenous and the same doses may be used.

Endotracheal (ET) access can be used for administration of some resuscitation drugs although it is less reliable and doses need to be increased to 2 or 2.5 times the intravenous dose. The dose should also be diluted with water or sodium chloride 0.9%. The drugs which can be given via the ET are adrenaline, atropine, naloxone, vasopressin and lidocaine.

Distribution of drugs in children differs from in adults because of the body composition and this therefore, changes throughout childhood as well as in those patients who are critically ill. At birth the proportion of water is approximately 75-85% of body weight and this will not drop to adult levels until 12 years of age. The
volume of distribution of water soluble drugs will therefore be proportionally greater in neonates and higher doses are required on a mg/kg basis to achieve therapeutic concentrations. Critical illness can cause muscle mass depletion which will increase the proportion of the body mass as water and again increasing the volume of distribution of water soluble drugs. Other causes of a change in the volume of distribution and the need for increased doses in critically ill patients include ascites, congestive heart failure, fluid overload, and low albumin. Dehydration can cause a reduction in the volume of distribution and require a dose reduction. Patients with severe burns can cause particular problems with fluid management and drug levels should be monitored if possible.

**Drug metabolism** is dependent on the maturity of the enzyme systems in the liver which is important in drug handling in neonates. The importance of liver damage will be covered in detail in the clinical section on hepatology but it is important also to realise that a reduction in liver blood flow can also affect the extent that a drug is metabolised. Acute respiratory distress, acute cardiovascular disease and low cardiac output states can reduce liver blood flow and increase the amount of drug reaching the systemic circulation. For example, morphine has a high extraction ratio and the rate of metabolism depends on liver blood flow, however morphine relies on active metabolites e.g. morphine-6-glucuronide for some of its effect and the reduction in liver blood flow can cause a reduced clinical effect. In other cases the reduction in metabolism can lead to toxicity. Drug interactions are also important and several commonly used combinations in critical care may interact to alter the metabolism of one of the drugs e.g. erythromycin can inhibit the metabolism of midazolam causing prolonged sedation.

**Elimination** and drug handling in renal disease and with renal replacement therapies will be covered in detail section on genito-urinary section, but it is important to correct dosing regimes for neonatal immaturity as well as for renal failure.

### 3.2 Intravenous Administration

As discussed above the main method of administration of drugs on PICU are by means of an intravenous infusion or bolus and it is important to understand the problems relating to administration via this route and also the options available.

**Infusion pumps** including volumetric and syringe pumps are the most common forms of device for delivering intravenous drugs to critically ill patients. There are many different types of pumps with varying degrees of sophistication. The pharmacist must be aware of the limitations of the pumps used on their unit in order to ensure safe practice. Volumetric pumps are useful for medium or high flow rates and large volume infusions and can be used for rates down to 5ml/hr – although they can be set lower they are less accurate and caution should be taken in using them at lower rates.

**Syringe pumps** are preferred for lower volume and low flow rate infusions. At low flow rates it can take some time for the drug to reach the patient and caution must be taken when changing syringes of drugs with a short half life to ensure continuous administration of the drug. Monitoring, safety features and displays of the various models can vary greatly and education of nursing and medical staff in the safe use of them is important.
The Medical Devices Agency has an infusion systems bulletin which contains information regarding the purchase, management and use of infusions systems and the training of users.  
http://www.mhra.gov.uk/Publications/Safetyguidance/DeviceBulletins/CON007321

**Venous Access**

In order to administer the intravenous drugs venous access must be obtained. There are various types of IV access and options for location of their position. The decision will depend on the number of drugs to be administered and the length of time that it is anticipated that these drugs will be required.

*Peripheral Venous Access* is a short catheter inserted into a small peripheral vein. Medications can be irritant as veins are small with low blood flow and peripheral access does not give long term access and is not often used as the only access for patients required intensive care. Peripheral administration of inotropes should only be done in an emergency or prior to getting central access.

*Central Venous Catheters* (CVC) are placed into a large vessel, such as the internal jugular, subclavian or femoral with a fast blood flow which allows mixing of the drug and a reduction in risk of irritation. The CVC can have several lumens and in paediatric critical care triple lumens are most commonly inserted to allow several drugs to be administered at the same time. There are several different types of CVC including heparin coated and silver or antibiotic coated lines which aim to reduce the risk of infection and blockage and increase the time that the line can be used. Lines and the site of insertion should be monitored for signs of infection, including erythema and tenderness as well as for bacteraemia. The common organisms found in CVC infections are *Staphylococcus Aureus* or Coagulase negative *Staphylococcus epidermididis*. Further information regarding catheter related sepsis is included in the sections on infections. (Section 2.1)

*Periphrelly inserted central catheter* (PICC) is centrally placed so that the tip is in the superior vena cava (SVC) but is inserted at a peripheral site and threaded through the vessels. Its position should be checked by X-ray before it is used to ensure that it is in a sufficiently large vessel to be used as a central line.

*Tunnelled central lines e.g. Hickman® or Groshong®* are placed in the SVC but tunnelled in to the chest wall with a Dacron® cuff to seal the line and prevent infection from the skin.

*Implanted port e.g. Portacath®* contains a small titanium reservoir with a rubber “stopper” attached to the catheter and implanted under the skin. The port is made to withstand up to 2000 needle entries but frequent puncturing of the skin can cause irritation and therefore ports are often used for intermittent access.

Procedures for accessing, flushing and locking lines should be part of the regular training for anyone who handles lines. Units may differ regarding these procedures.
and pharmacists must ensure that the correct preparations are available for the safe handling of all venous catheters.

Compatibility data

Information on compatibilities of drugs delivered into the same lumen of a venous catheter is available from various sources and the most comprehensive guide available is the “Handbook of Injectable Drugs” edited by Trissel. This contains detailed monographs of drugs tested at various concentrations and in various fluids. Most PICU’s will routinely run several drugs through Y-site connectors into a single lumen and it is important, not only to be sure that the drugs are chemically compatible, but also that they is no risk of interrupted delivery or accidental bolusing of drugs because of other drugs run concurrently, e.g. most units will try to keep only inotropes running through one lumen as this avoids the risk of inadvertently bolusing inotropes when increasing sedation etc.

Infusions

There are two main ways of calculating the concentration of drug to be put in to a syringe for a continuous infusion, standard solutions and “the rule of six”.

Standard infusions can be prepared, often in dose banded concentrations, either commercially or in a Central Intravenous Additive Service (CIVAS). When used with “smart” pumps or computerised systems information regarding doses can be readily available. The advantage of these fixed concentration solutions is that the risk of errors in calculation and preparation can be reduced but this disadvantage is that the dose being administered needs to be calculated individually for each patient unless “smart” pumps are available. There are some drugs which are only available as fixed concentrations e.g. fentanyl.

3.2.1 Calculations

1) Patient weighs 3.6 kg and is prescribed dopamine infusion at a rate of 5-10 microgram/kg/min. The concentration of the available solution is 50 mg in 50 mls. What range can the infusion be run at in mls/hr?

2) Patient weighs 7.2 kg and is prescribed morphine at a dose of 10-20 microgram/kg/hr

The concentration of the available solution is 10 mg in 50 mls. What range can the infusion be run at in mls/hr?

“Rule of Six” requires solutions to be made to a concentration based on the weight of the child and allows the rate of administration to be standardised for all patients regardless of size. The disadvantage is that the infusions have to be made for each individual and cannot be prepared and held as stock and there are risks related to the calculation and preparation of the infusions. Electronic dose calculators are used in several hospitals to reduce the risk of error. The advantage of these solutions is that
the medical and nursing staff have an immediate assessment of the dose requirements of the child without the need for calculations or “smart” pumps.

The “rule of six” is based on the formula
6mg/kg of drug in 100mls gives 1ml/hr equivalent to 1microgram/kg/min
Most units in the UK use “rule of three” as they use 50mls syringes.

Calculations.

3) Patient weighs 3.6 kg and is prescribed dopamine infusion at a rate of 5-10 microgram/kg/min.
How much should be added to 50 mls so that 1 ml/hr = 5 microgram/kg/min?

4) Patient weighs 7.2 kg and is prescribed morphine 7.2 mg in 50 mls of Glucose 5%. How much morphine in micrograms/kg /hour will the patient receive if the infusion is running at 1.5mls/hour?

Answers at the end of section

Task 1.1

Propofol is a common agent that was used very often in PICU for sedation:
Why is it not used very often nowadays?
What are the main indications of use?
What is the maximum recommended dose?
How does it work?
Any contraindications?

Task 1.2

Try to find a patient in PICU that has been on long term sedatives and design a weaning off protocol to come off safely from the agents.

What are the main symptoms of withdrawal?

Further Reading


Williams NT, Medication Administration through Enteral Feeding Tubes. American Journal of Health System Pharmacy 2008; 65(24): 2347-2357

Websites

Paediatric Intensive Care Society    http://www.ukpics.org.uk/

Medical Devices Agency
http://www.mhra.gov.uk/Publications/Safetyguidance/DeviceBulletins/CON007321

References


2. Follath F et al, Efficacy and Safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study); a randomised double-blind trial. Lancet 2002, 306: 196-202

3. Zairis MN, Apostolatus C, Anastasiadis P et al. The Effect of a Calcium Sensitizer or an inotrope or None in Chronic Low Output Decompensated Heart Failure; Results from the Calcium Sensitizer or inotrope or none in Low Output Heart Failure Study (CASINO). Program and abstracts from the American College of Cardiology Annual Scientific Sessions 2004 March 7-10, 2004 New Orleans Louisiana Abstract 835-6


Answers to calculations;

1) Patient weighs 3.6 kg and is prescribed dopamine infusion at a rate of 5-10 microgram/kg/min. The concentration of the available solution is 50 mg in 50 mls. What range can the infusion be run at in mls/hr?

Dose required per hour = 5 to 10 micrograms/kg/min
= 5 x 3.6 x 60 to 10 x 3.6 x 60
= 1080 microgram/h to 2160 microgram/hr

Solution contains 1000 microgram/ml
Rate should be 1.08 to 2.16 mls/hr. 
In practice the accuracy of pumps would require the doses being rounded to one decimal place.

2) Patient weighs 7.2 kg and is prescribed morphine at a dose of 10-20 microgram/kg/hr
The concentration of the available solution is 10 mg in 50 mls.
What range can the infusion be run at in mls/hr?
Dose required per hour = 10 to 20 microgram/kg/hr
= 72 to 144 microgram/hr
Solution contains 200 microgram/ml
Rate should be 0.36 to 0.72 mls/hr
In practice the accuracy of pumps would require the doses being rounded to one decimal place.

3) Patient weighs 3.6 kg and is prescribed dopamine infusion at a rate of 5-10 microgram/kg/min.
How much should be added to 50 mls so that 1 ml/hr = 5 microgram/kg/min?
5 microgram/kg/min = 5 x 3.6 x 60 micrograms/hr = 1080 micrograms/hr
Quantity in 1 ml = 1.08 mg
Quantity in 50 mls = 1.08 x 50 = 54 mg or 15 mg/kg

Using the “rule of three”
3 mg/kg in 50 mls gives 1 ml/hr is equivalent to 1 microgram/kg/min
therefore
15 mg/kg in 50 mls gives 1 ml/hr equivalent to 5 microgram/kg/min

4) Patient weighs 7.2 kg and is prescribed morphine 7.2 mg in 50 mls of Glucose 5%. How much morphine in micrograms/kg /hour will the patient receive if the infusion is running at 1.5mls/hour?
7.2mg in 50mls = 1mg /kg in 50ml
(1.5x1000) /50 microgram/kg in 1.5ml
30 microgram/kg/hr in 1.5ml/hr or 20microgram/kg/hr in 1ml/hr

Using the “rule of three”
3 mg/kg in 50 mls gives 1 ml/hr is equivalent to 1 microgram/kg/min or 60 microgram/kg/hr
therefore
1 mg/kg in 50 mls gives 1 ml/hr equivalent to 0.33 microgram/kg/min or 20 microgram/kg/hr
Infections in Paediatric Intensive Care
Andrea Gill
Revised by Andrea Gill July 2011

Introduction

1. Community-acquired infections
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References
Objectives

- To be able to identify the most likely causative organisms for the types of infection that commonly present on PICU
- To be able to determine an appropriate antibiotic regime for the types of infection that commonly present on PICU
- To be able to identify the parameters which can be used to monitor the progress of an infection
- To understand the mechanism of action, characteristics and use of antibacterial, antiviral, and antifungal agents in the management of infection on PICU
- To understand and be able to describe the process of antimicrobial resistance
- To be able to define sepsis, septic shock and septic inflammatory response syndrome
- To be able to describe local antibiotic prophylaxis for surgical procedures
Introduction

Infection is one of the commonest problems encountered on PICU. Patients may be admitted due to an infection, already have an infection present or develop an infection during their stay. Pharmacists have a vital role in the selection and optimization of the appropriate treatment for these infections. From 1 Jan 2005 to 31 Dec 2007, a primary diagnosis of infection was the reason for admission for 6.2% of the 43,841 patients admitted to PICUs in the UK. Sepsis, bronchiolitis, meningococcal disease and pneumonia were most the most common diagnoses recorded in these patients. This information can be accessed in full on the following website www.picanet.org.uk.

Monitoring Infections

**White cell count (WCC)** WCC is usually raised with a neutrophilia, often with a left shift in bacterial infection and lymphocytosis in viral infection. Severe bacterial infection may also cause thrombocytopenia. Exceptions to this include neutropenia in severe bacterial infection eg meningococcal septicaemia and lymphocytosis in pertussis. A very high neutrophil count usually indicates a collection of pus.

**C-reactive protein (CRP)** CRP is an acute phase protein which is released during acute infection due to bacteria or fungi. It is produced in the liver. During acute bacterial infection levels can rise from <1 to 100mg/l or more and remain raised for a number of days. CRP may be used for differentiation between positive and contaminated blood cultures in children and have been shown to be a better predictor than WCC or absolute neutrophil count (ANC) for this purpose. [1] However it is not sensitive enough to be used to exclude all bacterial infection [2]. As baseline CRP varies enormously between individuals, reviewing trends is often more useful than focusing on actual CRP values.

**Temperature** Measurement of a child’s temperature is the most common assessment method used to monitor progress of infections. The following extract is taken from the NICE guidelines for management of feverish children <5 years of age [3].

Height of body temperature alone should not be used to identify children with serious illness. However, children in the following categories should be recognized as being in a high-risk group for serious illness:

- children younger than 3 months with a temperature of 38 °C or higher.
- children aged 3–6 months with a temperature of 39 °C or higher.

Duration of pre-existing fever should not be used to predict the likelihood of serious illness.

**Cultures and sensitivities** Children with a suspected bacterial infection should have samples taken from the suspected site of infection in order to ensure antibiotic treatment is appropriate. Although growth and identification of bacteria usually takes at least 24 hours, polymerase chain reactions (PCR) and antigen tests can be done much more quickly.
1. Community Acquired Infections

1.1 Community acquired pneumonia (CAP)

**Signs and symptoms** Symptoms of bacterial pneumonia include

- fever of >38.5°C together with chest recession and a respiratory rate of >50/min
- oxygen saturations <92%, cyanosis, difficulty in breathing, intermittent apnoea
- not feeding or signs of dehydration
- empyema may also complicate treatment in a small number of patients [4]

Acute phase reactants such as CRP have not been found to be useful in distinguishing bacterial from viral pneumonia [5].

**Causative organisms** Community acquired pneumonia can be bacterial or viral in origin. Although not serious in the majority of patients, approximately 4% of patients may require intensive care [4]. *Streptococcus pneumoniae* is the most likely causative organism but other potential bacterial causes include mycoplasma and chlamydia. Viral causes include respiratory syncitial virus (RSV), influenza or adenovirus. Severe viral pneumonia is a risk factor for bacterial superinfection. One study found that in children with severe RSV bronchiolitis admitted to PICU, 42% had evidence of bacterial growth in secretions from lower airways and required ventilation for longer than those with only RSV (p<0.01) [6].

**Treatment** Children under 5 years of age are most likely to have a viral cause so antibiotics are not recommended in mild to moderate infections. However, if an antibiotic is required, oral amoxicillin is first choice. Alternatives are co-amoxiclav, cefaclor or a macrolide. In children aged 5 and above macrolide antibiotics should also be used because of the increased risk of mycoplasma infection in this age group [5]. Oral therapy has been shown to be safe and effective in hospitalised children with severe pneumonia who do not have any serious signs or symptoms [7]. Although oral antibiotics are safe and effective for treatment of CAP, IV antibiotics should be used for severe infections but once improving the patient should be switched to oral treatment [5]. In-vitro resistance to penicillin has increased over the past decade however penicillins remain the drugs of choice to treat pneumococcal pneumonia regardless of in-vitro resistance. Combination antimicrobial therapy will likely improve survival of patients with bacteremic pneumococcal pneumonia among the subset of critically ill patients [7]. **Table 2.1** shows appropriate first line treatment for community acquired pneumonia.
<table>
<thead>
<tr>
<th>Age</th>
<th>Likely Causative organism</th>
<th>Choice Of Antibiotic</th>
<th>Duration Of Therapy</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5 years</td>
<td><em>S. pneumoniae</em></td>
<td>Amoxicillin</td>
<td>7-10 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>H. influenzae</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 5 years</td>
<td><em>M. pneumoniae</em></td>
<td>Amoxicillin</td>
<td>7-10 days</td>
<td>M. pneumoniae is more prevalent in older children and macrolide antibiotics should be used. Use in combination with Amoxicillin if unsure of causative organism.</td>
</tr>
<tr>
<td></td>
<td><em>S. pneumoniae</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>C. pneumoniae</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>H. influenzae</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All ages</td>
<td><em>S. pneumoniae</em></td>
<td>Cefuroxime</td>
<td>Based on clinical response and ability to tolerate oral therapy. Total duration of antibiotic (IV and oral) therapy 7-10 days (longer therapy may be required in more severe infections or when atypical organisms)</td>
<td>For empirical therapy use IV Cefuroxime. IV therapy should be considered for patients with severe symptoms and/or those who are unable to absorb or swallow oral antibiotics. For children over 5 years of age, give oral/IV clarithromycin in addition to IV Cefuroxime. For children less than 5 years of age, discuss with a respiratory consultant and consider the addition of clarithromycin.</td>
</tr>
<tr>
<td>(Severe</td>
<td><em>M. pneumoniae</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>condition)</td>
<td><em>H. influenzae</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All ages</td>
<td><em>Staph aureus</em></td>
<td>Flucloxacillin +</td>
<td>10-14 days</td>
<td>Serious condition. Discuss with a respiratory consultant. Monotherapy can be used after microbiological confirmation of organism.</td>
</tr>
<tr>
<td></td>
<td>Clarithromycin</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2.1 Antibiotics recommended for community acquired pneumonia

1.2 Bronchiolitis

Bronchiolitis is a common respiratory infection affecting mainly babies and children less than 2 years of age and is the most frequent cause of acute respiratory failure in children admitted to paediatric intensive care units in the UK. Approximately a third of infants in the UK develop bronchiolitis in their first year of life, and 90% of those who do are less than nine months old. Babies born at < 35 weeks gestation, those with congenital heart disease or chronic lung disease of prematurity, and immunocompromised children are most at risk of developing severe, potentially life-threatening respiratory illness requiring PICU. Peak incidence is seen between October and February.

**Signs and symptoms**  Children usually present with tachypnoea and wheezing. Those with mild to moderate disease will require hospitalisation in order to provide oxygen and IV fluids. Antibiotics are not recommended for bronchiolitis unless there is concern about complications such as secondary bacterial pneumonia [8].
Causative organisms  Bronchiolitis is most commonly caused by RSV, however the human meta-pneumovirus and bocavirus have more recently found to be possible causes, sometimes in combination with RSV.

Treatment  Supportive therapy remains the mainstay of management with limited or no evidence of benefit for most other pharmacological treatments e.g. ribavirin [9] surfactant [10] or steroids [11]. The use of nasal CPAP with heliox may be beneficial [12]. Current evidence suggests nebulized 3% saline may significantly reduce the length of hospital stay and improve the clinical severity score in infants with acute viral bronchiolitis [13] however, this is not routine practice.

Prophylaxis  The main development in bronchiolitis management in recent years relate to the use of prophylactic administration of palivizumab for patients at higher risk of developing severe disease. It is administered monthly for five doses during the season and aims to reduce hospitalization in those patients most at risk of severe RSV. The current recommendations from the Joint Committee on Vaccination and Immunisation which advises the Department of Health in the UK is that its use is restricted to children under 2 with chronic lung disease, on home oxygen or on prolonged use of oxygen; infants less than 6 months of age who have left to right shunt haemodynamically significant congenital heart disease and/or pulmonary hypertension and children under 2 years of age with severe congenital immuno-deficiency. However, due to the cost of this agent and the fact that the evidence for its benefit in individual patients is inconclusive, many Trusts have developed their own criteria for use [14].

TASK 2.1

1. Read the Scottish Intercollegiate Guideline Network (SIGN) guidelines to identify the evidence on which treatment of bronchiolitis is based
http://www.sign.ac.uk/pdf/sign91.pdf
2. Find out the criteria for use of palivizumab in your Trust

1.3 Croup

Croup (laryngotracheitis) is a common childhood disease most commonly affecting children 6 months to 3 years of age, with a peak incidence during the second year of life.

Signs and symptoms  Croup is characterized by the sudden onset of a seal-like barking cough that is usually accompanied by stridor (predominantly inspiratory), hoarse voice, and respiratory distress due to upper airways obstruction.

Causative organisms  Croup is usually caused by the parainfluenza virus (types 1, 2 and 3) although it has also been due to RSV, Influenza A and B and Mycoplasma.

Treatment  Intubation is required in children with severe airway obstruction. 0.5 to 1.5% of children admitted to hospital with croup will require intubation. Oral dexamethasone has been found to be effective in improving symptoms and reducing
length of hospitalization. Oral prednisolone or nebulised budesonide may be used as alternatives to dexamethasone. Nebulised adrenaline is used for severe croup not effectively controlled by corticosteroids [15] in order to try to prevent the need for intubation. 1-5ml of Adrenaline 1:1000 may be used depending upon the age of the child, but the patient should be very closely monitored during this period in case obstruction recurs.

1.4 Epiglottitis

Signs and symptoms Acute epiglottitis is due to localized infection of the supraglottic larynx. This results in swelling of the epiglottis that obstructs the laryngeal inlet and can cause airway obstruction. Patients are usually 2 to 6 years old.

Causative organisms Acute epiglottitis is usually caused by the Haemophilus influenzae

Treatment Patients usually require intubation and antibiotic treatment should be started as soon as possible – see table 2.2 If the infection is found to be caused by H. influenzae then a course of prophylactic rifampicin should be considered for the index patient and close contacts (See BNF-C [16]).

<table>
<thead>
<tr>
<th>Age</th>
<th>Likely causative organism</th>
<th>Choice Of Antibiotic</th>
<th>Duration Of Therapy</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td></td>
<td></td>
<td></td>
<td>Most likely causative organism is H. influenzae, however, this is now much less common since the introduction of the Hib vaccine. Consider oral therapy with Amoxicillin (or Co-amoxiclav depending on sensitivities) if well after 3 days of IV therapy.</td>
</tr>
<tr>
<td>All ages</td>
<td>H. influenzae (99%)</td>
<td>Cefotaxime</td>
<td>5 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S. aureus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>S. pneumoniae</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2.2  Antibiotic treatment of epiglottitis

1.5 Pertussis (whooping cough)

Signs and symptoms Whooping cough is a highly contagious disease and can be life-threatening in infants [17]. The child may develop a characteristic paroxysmal or spasmodic cough followed by a characteristic inspiratory whoop which may be absent in infants.

Causative organisms It is caused by Bordatella pertussis

Treatment The primary aim of treatment is to reduce infectivity and spread. For treatment to affect symptoms it should be started immediately after a sample is taken for culture, or clinical diagnosis is reached on the basis of symptoms and the epidemiological situation suggesting whooping cough. If the patient has exhibited symptoms for over one month, treatment is not usually worthwhile. Should an antibiotic be required, clarithromycin or another macrolide is appropriate for 7 days.
Prophylaxis Although antibiotics are effective in eliminating *B. pertussis*, they did not alter the subsequent clinical course of the illness. There is insufficient evidence to determine the benefit of prophylactic treatment of pertussis contacts [18].

1.6 Influenza

Influenza or “flu” occurs seasonally, every year, around the world. An epidemic is a widespread outbreak of disease occurring in a single community, population or region. A pandemic, occurs on a much greater scale, spreading around the world and affecting many hundreds of thousands of people across many countries. Three influenza pandemics occurred in the last century - 1918 to 1919 (Spanish flu), 1957 to 1958 (Asian flu) and 1968 to 1969 (Hong Kong flu). All affected large numbers of the population, causing many deaths and huge economic and social disruption [19].

Signs and symptoms Children referred to hospital may require PICU if they have the following symptoms [20]

- They are failing to maintain a SaO2 of >92% in FiO2 of >60%
- They are shocked
- They have severe respiratory distress and a raised PaCO2
- They have a rising respiratory rate and pulse rate with clinical evidence of severe respiratory distress with or without a raised PaCO2
- Recurrent apnoea or slow irregular breathing
- Evidence of encephalopathy

Causative organisms There are three main groups of flu viruses: influenza A, B and C. Influenza B and C viruses infect people only, however, influenza A viruses have the ability to cross the species barrier and infect people, birds, and animals such as pigs and horses. Among people, influenza A is the source of most 'ordinary' flu epidemics and has caused all previous flu pandemics. In April 2009 a pandemic associated with the H1N1 strain of virus was announced. For a full summary go to [http://www.cabinetoffice.gov.uk/sites/default/files/resources/the2009influenzapandemic-review.pdf](http://www.cabinetoffice.gov.uk/sites/default/files/resources/the2009influenzapandemic-review.pdf). This pandemic turned out to be a relatively mild illness for most of those affected, though children were particularly severely affected. A total of 457 people died in the UK.

Treatment Treatment of children admitted to hospital with influenza will include oxygen, fluids, antibiotics (eg co-amoxiclav or clarithromycin), oseltamavir and other supportive treatment. Oseltamavir is most effective if given when the patient has had symptoms for less than 2 days.

1.7 Meningitis

Meningitis is defined as inflammation of the membranes (meninges) which cover the brain and spinal cord. Although meningitis is usually due to community-acquired viruses or bacteria, fungal or tuberculous meningitis can also be seen in specific groups of the population e.g. immunocompromised patients. Meningitis can also occur due to infection following trauma or in patients with devices such as ventriculo-
peritoneal shunts. NICE produced a new guideline for Bacterial meningitis and meningococcal septicaemia in June 2010 [42] which details a much more comprehensive outline of the signs and symptoms, assessment, diagnosis and management of the disease than is summarised here. Follow this link to access the full guideline http://www.nice.org.uk/nicemedia/live/13027/49339/49339.pdf

**Signs and symptoms** The symptoms of meningitis can be variable and non-specific making it difficult to diagnose. Young children may have fever and vomiting associated with irritability, drowsiness and confusion. Babies may have a full or bulging fontanelle due to raised intracranial pressure (ICP). They may feel stiff or have jerky movements or be very floppy. Fits are common. Older children are more likely to have fever, vomiting and complain of headache, stiff neck and photophobia. Teenagers may present with symptoms related to a change in behaviour e.g. confusion and aggression. These may mimic the symptoms of alcohol or drug intoxication [22].

A rash may be present, but is more likely to be absent, atypical, scanty or petechial in character than rashes seen in with septicaemia. Many children become suddenly ill with a fever and rigors. Occasionally the shaking, if severe, may be mistaken for fitting. Muscle and joint aches makes children restless and miserable. Vomiting, nausea and poor appetite (poor feeding in babies) are common, abdominal pain and diarrhoea less so.

**Diagnosis** Early diagnosis and prompt institution of treatment is imperative to decrease morbidity and mortality associated with this condition. A lumbar puncture (LP) is a very useful test but has a number of limitations [23]:

- May not be able to culture if antibiotics were given before culture taken – cerebrospinal fluid (CSF) is sterile in 90-100% of patients within 24-36 hours of antibiotics being given although Polymerase Chain Reaction (PCR) testing of CSF allows amplification of minute amounts of DNA from the bacteria and is often much more sensitive than culturing.
- Any suspicion of raised intracranial pressure including fits, focal neurological signs, Glasgow coma score <13, contra-indicates LP due to risk of coning
- LP should not be performed in patients with haemodynamic instability, clotting abnormalities with clinical bleed or thrombocytopenia (platelets < 50 x 10⁹) due to the risk of complications being greater than the benefit gained from the results of the test.

See NICE guideline for full list of contraindications [42].

If an LP is performed, the CSF can be cultured to identify organism and therefore ensure appropriate choice and duration of antibiotic therapy. Biochemical analysis of CSF will show the following if the patient has meningitis

- High protein count
- Low glucose content
- High white blood cell count

**Pathophysiology** Bacterial meningitis is a serious infection which carries a mortality less than 10% for bacterial meningitis and less than 5% for meningococcal meningitis [24]. Bacteria reach the brain from bloodstream and penetrate the blood brain barrier.
Endotoxin and inflammatory mediators cause an inflammatory response in the CSF causing leakage of protein and fluid out of cerebral vasculature. This results in an increase in brain water content and an increase in intracranial pressure (ICP). In serious cases this may lead to a reduction in cerebral perfusion, cerebral infarction and brain death [25].

**Causative organisms**

**Bacterial meningitis** There are a variety of bacteria that can cause meningitis as shown in table 2.3

**Viral meningitis** The most common viral causes of meningitis are the various enterovirus subtypes, but herpes simplex virus 2 (HSV-2) (and less commonly HSV-1), varicella zoster virus, mumps virus and HIV are all possible causes. HSV meningoencephalitis is the most serious (discussed in section on Herpes simplex encephalitis) although mumps infection has recently re-emerged as an important pathogen in young adults in the UK. Viral meningitis is usually self-limited with no serious sequelae although infants and immunocompromised patients are more likely to have complications [26].

**Fungal meningitis** Fungal meningitis is a very rare, life threatening disease and may be caused by a variety of fungi, including most commonly *Cryptococcus neoformans* and *Candida albicans*. Fungal meningitis usually occurs in immunocompromised patients.
### Table 2.3 Likely bacterial causes of meningitis in children

#### Treatment

**Antibiotics** Initial antibiotic treatment should be directed towards the most likely causative organisms in the child’s age group and then altered if positive cultures are obtained (see suggested regimes in Tables 2.4 and 2.5). It is vital that antibiotics are given as soon as possible as delay has been found to correlate with unfavourable outcome [27]. Benzylpenicillin or Ceftriaxone [42] are used as first line empiric treatment for meningitis in the UK as resistance to these agents is rare and they are effective against the most likely causative organisms. Other antibiotics including penicillin, combinations of ampicillin-chloramphenicol or penicillin-chloramphenicol or chloramphenicol alone are also effective agents and are used in countries where use of third-generation cephalosporins is restricted due to cost [28]. NICE recommend

<table>
<thead>
<tr>
<th>Causative organism</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Neiserria meningitidis</em></td>
<td>Most common cause of bacterial meningitis in children and young adults. Meningococcal disease includes both meningitis and septicaemia caused by N meningitidis.</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>Second biggest type of bacterial meningitis in UK and Ireland. Bacteria are commonly carried and more likely to cause earache, pneumonia and less serious illnesses than meningitis. Most common in children &lt; 2 years. Septicaemia does not often accompany meningitis.</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em> group B (HiB)</td>
<td>This used to be the most common type of meningitis in children less than 5 years of aged, however, since the introduction of Hib vaccine in 1992, incidence has reduced by over 90%</td>
</tr>
<tr>
<td><em>Group B streptococcus</em></td>
<td>This organism is the main cause of meningitis in newborn babies. It can cause septicaemia, meningitis and pneumonia. Up to 90% of babies survive with no significant after effects.</td>
</tr>
<tr>
<td><em>Eschericia coli</em></td>
<td>Certain strains of E.coli cause meningitis especially in newborn babies and children with other chronic illness</td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td>Infection occurs mainly in babies and those with immune deficiency</td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td>Tuberculosis (TB) is the seventh leading cause of death and disability worldwide. TB meningitis (TBM) accounts for approx 0.7% of all reported cases of TB. In areas where TB prevalence is high, TB meningitis is most common in children aged 0 - 4 years, and in areas where TB prevalence is low, most cases of TB meningitis are in adults. TBM is rare in the UK</td>
</tr>
</tbody>
</table>
Ceftriaxone is used for treatment of patients with suspected bacterial meningitis or meningococcal septicaemia over 3 months of age. In younger babies or those on calcium infusions use cefotaxime plus amoxicillin/ampicillin [42].

Ceftriaxone is useful because it is secreted into nasal secretions and patients treated with this agent do not need further treatment with rifampicin (see chemoprophylaxis), however it’s use has been associated with biliary sludging and bilirubin encephalopathy (especially in premature neonates) as it can displace bilirubin from its binding to serum albumin. Calcium-containing solutions or products must not be administered within 48 hours of last administration of ceftriaxone in neonates because of the risk fatalities due to calcium-ceftriaxone precipitates in the lungs and kidneys (BNFC)

Vancomycin has been recommended for the treatment of pneumococcal meningitis along with ceftriaxone or cefotaxime, however, a recent study has suggested that early empiric treatment with this drug is not beneficial [29].

A recent report from the Health Protection Agency (HPA) on Antibiotic resistance patterns in England and Wales stated that meningococci remain susceptible to penicillin, cefotaxime, and ciprofloxacin with more than 90% also susceptible to rifampicin and the majority of pneumococci remain susceptible to penicillin and cefotaxime [30].

For the treatment of Tuberculous meningitis the World Health Organisation (WHO) pocket book of hospital care for children recommends a combination of isoniazid, rifampicin and pyrizinamide for treatment of although there is little evidence to support this regime [31a].

<table>
<thead>
<tr>
<th>Age</th>
<th>Likely causative organism</th>
<th>Choice Of Antibiotic</th>
<th>Duration Of Therapy</th>
<th>Notes</th>
</tr>
</thead>
</table>
| Birth-3 months* | **Group B Strep**  
E. coli  
L. mono-cytogenes  
N. meningitidis  
H. Influenzae  
S. pneumoniae | Cefotaxime +  
Ampicillin or  
Amoxicillin | See table below (ages 0-3 months) | Choice of antibiotics for empirical therapy (i.e. causative organism not known). Once causative organism is known (usually possible after 24 hours) therapy must be adjusted according to table below (0-3 months). |
| > 3 months   | N. meningitidis  
H. influenzae  
S. pneumoniae | Ceftriaxone | Unknown organism or  
H. influenza: 10 days  
S. pneumonia: 14 days  
N. meningitidis: 7 days | Broad-spectrum cephalosporins cover likely organisms and penetrate CSF well. |

Table 2.4 Initial antibiotic treatment of meningitis
- Bacteria that cause meningitis in the newborn period are commensals of the human female genital or GI tract and are acquired by the infants during delivery
Organism | Choice Of Antibiotic | Suggested Duration Of therapy | Notes |
--- | --- | --- | --- |
Empirical (organism not known) | Cefotaxime + Ampicillin or Amoxicillin | 14-21 days depending on severity | |
Group B Strep | Cefotaxime | 14 days | If complicated case continue for longer. |
Listeria monocytogenes | Amoxicillin or Ampicillin + Gentamicin | 14 - 21 days Continue Gentamicin for first 7 days | |
Gram negative bacilli | Cefotaxime | 21 days | Longer duration of Cefotaxime if complicated case. If relapse occurs after stopping antibiotics – consult Microbiologist. |
N. Meningitidis | Cefotaxime | 7 days | |

Table 2.5 NICE guideline recommendations for suitable antibiotics once causative organism known in babies 0-3 months of age. [42]

Corticosteroids Dexamethasone has been shown to be effective in protecting against deafness and other neurological sequelae that can occur with meningitis. It acts by reducing the inflammatory response associated with antibiotic-induced bacterial lysis therefore reducing cerebral oedema and ICP. A recent systematic review found that use of corticosteroids in bacterial meningitis was associated, in adults, with a reduced fatality rate, reduced rate of severe hearing loss and improved long-term neurological sequelae. In children corticosteroids reduced severe hearing loss. This review found that the risk for gastro-intestinal tract bleeding was not increased in patients treated with corticosteroids [31]. The beneficial effect of corticosteroids is most apparent in meningitis due to *H. influenzae* and *S. pneumoniae*, however, as it is unlikely that the causative organisms is known when treatment is started, it is recommended that dexamethasone is given regardless of bacterial aetiology [31] except in those <3 months of age or those with meningococcal septicaemia.[42]

NICE recommend dexamethasone (0.15 mg/kg to a maximum dose of 10 mg, four times daily for 4 days) for suspected or confirmed bacterial meningitis as soon as possible if lumbar puncture reveals any of the following:
- frankly purulent CSF
- CSF white blood cell count greater than 1000/microlitre
- raised CSF white blood cell count with protein concentration greater than 1 g/litre
- bacteria on Gram stain.

If dexamethasone was not given before or with the first dose of antibiotics, but was indicated, try to administer the first dose within 4 hours of starting antibiotics, but do not start dexamethasone more than 12 hours after starting antibiotics. In children and young people with meningococcal septicaemia and shock that is unresponsive to vasoactive agents, steroid replacement therapy using low-dose corticosteroids (hydrocortisone 25 mg/m² four times daily) should be used only when directed by a paediatric intensivist [42].
Fluids  Management of fluid and electrolyte balance is important in the treatment of meningitis however, there is controversy over the best method of management. Fluid restriction in the initial management has been recommended [32,33] but other researchers have suggested that maintenance plus replacement is required [34,35]. NICE recommend IV resuscitation in meningococcal septicaemia (see below) [42]. The practice of fluid restriction is based on concerns about hyponatraemia due to increased concentrations of circulating antidiuretic hormone (ADH) and possible associations between this and negative neuro-developmental outcomes [33]. The opponents of this argument suggest that ADH concentrations are increased in children with meningitis because of hypovolaemia and only become normal when sufficient sodium and fluid are given [34]. A systematic review has not been able to demonstrate which of these practices is recommended [36] however NICE guideline states that fluids should not be restricted unless there is evidence of raised intracranial pressure, increased antidiuretic hormone secretion and recommends that full-volume maintenance fluids should be given to avoid hypoglycaemia and maintain electrolyte balance. [42]

Other agents  Oral glycerol (with or without dexamethasone) may be effective in preventing severe neurological sequelae in patients with childhood meningitis [37].

Prophylaxis  Infections due to *N meningitidis* or *H influenzae* necessitates the use of chemoprophylaxis in both the index case and their close contacts (i.e. people in same household who had close, prolonged contact during the previous 7 days) in order to clear carriage of these bacteria [38,39]. The aim of chemoprophylaxis is to reduce the risk of invasive disease by eradicating carriage. Individuals in close contact with cases of meningococcal disease are at increased risk of developing disease. The highest documented relative and absolute risk is for people living in the same household as a case of meningococcal disease, during the first seven days. If prophylaxis is not given, the absolute risk is about 1 in 300 (PHLS), with the risk of contracting the disease increased by a factor of 400 to 800 [40].

Chemoprophylaxis usually consists of rifampicin which is suitable for all ages but side-effects, contraindications and interactions need to be discussed with patients and their contacts. A single dose of ciprofloxacin may be appropriate for those where compliance may be more difficult. A single IM dose of Ceftriaxone may be used in pregnant contacts. Where possible chemoprophylaxis should be commenced within 24 hours but may be started up to 4 weeks after the index case became ill. If the patient attends a nursery, crèche or school, chemoprophylaxis for the other children is only necessary if more than one case within 4 weeks, however, it is important that information is given to other parents on the signs and symptoms to look out for [41].

The most effective antibiotics to achieve eradication of *N meningitidis* are ceftriaxone, rifampicin and ciprofloxacin. Rifampicin is most commonly used but should not be used in pregnancy, liver disease and alcoholism. It is a potent inducer of hepatic metabolism and therefore drug interactions, especially with oral contraceptives, must be considered before this drug is prescribed for contacts. Rifampicin also has a number of side-effects including orange discoloration of urine and staining of contact lenses. Problems with resistance have been identified in some settings. Immunisation campaigns with vaccines against *H influenzae* and *S pneumoniae* have been very effective in reducing the incidence of meningitis due to these bacteria, however, prevention of infection due to *Neisseria meningitidis* will not be possible until a vaccine covering all serotypes is available.
• Group B is poorly immunogenic so no vaccine is currently available
• Meningococcal polysaccharide A&C vaccine - indicated if travelling abroad or for close contacts
• Meningococcal Group C conjugate vaccine - provides long term protection against infection by serogroup C of *N. meningitidis* in children from 3 months
  - Introduced in 1999 as part of childhood primary immunisation schedule
  - Protects against group C only

1.8 Meningococcal disease

Meningococcal disease (MD) includes both meningitis and septicaemia caused by *N. meningitidis*. 15% of cases have meningitis alone, 25% have septicaemia alone, 60% have mixed meningitis and septicaemia. Patients with septicaemia alone have the worst prognosis [42].

**Signs and symptoms**  *Meningococcal meningitis* is described above

The best known symptom of Meningococcal septicaemia is a rash which in the early stages may be blanching and macular or maculopapular, but it nearly always develops into a non-bباحching red, purple or brownish petechial rash or purpura. It is crucial to remember that the underlying meningitis or septicaemia may be very advanced by the time the rash appears. The rapidly evolving haemorrhagic “text book” rash may be a very late sign. It may be too late to save the child’s life by the time this rash is seen

Other symptoms include;
• Fever, although not all patients will be pyrexial
• Rigors
• Aches
• Limb pain
• Gastrointestinal symptoms including vomiting, nausea and poor appetite
• Weakness
• Altered urine output
• Cold hands and feet, mottled skin

**Pathophysiology** 4-25% of the population are carriers. Usually the carrier state is asymptomatic and only occasionally does invasive disease occur when a virulent organism colonises a susceptible host. Mean duration of carriage is 21 months. The majority of adults have some immunity due to nasal carriage. Systemic immunity usually develops within 14 days of acquisition of the meningococci. Rarely acquisition may progress to invasive disease before immunity develops. If carriers don’t develop the illness they become immune but can be a source of infection for others.

The organism resides in the nasopharynx and bacteria are spread by droplets. This incubation period is usually 3-5 days. Disease is likely to occur 2-10 days after contact with the course of the illness being determined by host resistance rather than strain of the organism. Susceptible patients are the non-immune of any age, but peak incidence is from 3 months to 2 years, with most cases occurring in children < 5 years. There is a second peak in teenagers. Although it is not understood why certain patients go on to develop infection rather than remain colonized, the following risk
factors have been identified: male, close contact with case, exposure to parenteral cigarette smoke, winter months, anatomic defects, malnutrition, specific host defence defects e.g. complement deficiency, splenectomy.

Meningococcal septicaemia occurs when, after invading through the nasopharynx, the meningococcus enters bloodstream and releases endotoxin. White blood cells then try to engulf the endotoxin and release pro-inflammatory cytokines e.g. interleukins 1 and 6 (IL-1, IL-6) and tissue necrosis factor (TNF). This results in the endothelial lining of the blood vessels being damaged, the coagulation cascade being activated and death due to multi-organ failure (see section on sepsis).

**Causative organism** *N. meningitidis* are gram negative diplococci and are divided into serogroups based on antigenic differences in their capsular polysaccharides. 13 subgroups are currently recognised. Groups A, B, C, W135 and Y account for most meningococcal disease. In the UK, 70% of cases are due to Group B, most of the remaining due to Group C infection.

**Treatment** Antibiotic treatment is shown in meningitis section. See section below for treatment of sepsis.

**Prophylaxis** See above

**Outcome** Patients with pure septicaemia have the worst prognosis and maximum effort must be made to identify them early. Although a few patients with meningitis will die from raised ICP, most deaths from Meningococcal disease are from shock and multi-organ failure. The fatality rate is approx 7% in meningococcal meningitis and 20-50% in meningococcal septicaemia. This is a notifiable disease so the Health Protection Agency must be informed if a patient is suspected to have an infection due to *N. meningitides*. MD is associated with a significant risk of mortality and long term morbidity and causes more than 100 deaths in the UK each year. Patients who recover may be left with severe disabilities e.g. amputations, scarring, sensory defects, intellectual impairment, epilepsy and a range of less specific cognitive and psychological disorders.

1.9 Sepsis

**Signs and symptoms** International definitions for sepsis related issues are shown below (table 2.6).

**Pathophysiology** Sepsis is the overwhelming systemic disease that results from infection with a microbial pathogen. There is exaggerated stimulation of the normal host responses to the invading pathogen leading to a widespread release of inflammatory mediators and vasodilatation. This is initially compensated for by an increase in cardiac output to help maintain a reasonable blood pressure and adequate organ perfusion, but as the syndrome progresses systemic vascular resistance falls accompanied by reduced cardiac output. This is also accompanied by an increase in the permeability of capillaries, loss of plasma water and a relative hypovolaemic state. The end result is a reduction in arterial blood pressure, inadequate organ perfusion and oxygenation and eventual multiple organ failure [43]. Release of endotoxins and exotoxins from Gram negative bacteria results in activation of macrophages, which produce the lymphokines gamma-interferon and granulocyte macrophage colony stimulating factors, tumour necrosis factors-alpha (TNF–alpha) and IL-1, IL-6. These substances are beneficial to the host in mediating the protective...
inflammatory response but in severe infection an exaggerated, harmful response occurs in which high levels of TNF-alpha and IL-1 lead to serious damage. Acting with the inflammatory mediators prostaglandin E2 released by neutrophils, nitric acid released by macrophages and platelet activating factor, a state of shock can develop. Damage to the endothelial cells of blood vessels results in leakage of plasma from the circulation with consequent vascular collapse. The extrinsic coagulation system is activated causing thrombin to be released which induces the production of endogenous inhibitors of coagulation e.g. protein C. At the same time platelet activation and aggregation occurs resulting in a syndrome similar to disseminated intravascular coagulation (DIC) resulting in an elevated INR, reduced platelet count and elevated APTT. [44]

**Infection** = microbial phenomenon characterized by an inflammatory response to the presence of micro-organisms or the invasion of normally sterile host tissue by those organisms

**Bacteremia** = the presence of viable bacteria in the blood.

**Systemic Inflammatory Response Syndrome (SIRS)** = the systemic inflammatory response to a variety of severe clinical insults. The response is manifested by 2 or more of the following conditions: 1) temperature >38°C or <36°C 2) heart rate > 90 beats per minute; 3) respiratory rate > 20 breaths per minute or PaCO2 < 32 mmHg and 4) WCC>12,000/cu mm, < 4000/cu mm or >10% immature neutrophils (left shift).

**Sepsis** = the systemic response to infection, manifested by 2 or more of the following conditions 1) temperature >38°C or <36°C 2) heart rate > 90 beats per minute; 3) respiratory rate > 20 breaths per minute or PaCO2 < 32 mmHg and 4) WCC>12,000/cu mm, < 4000/cu mm or >10% immature neutrophils (left shift)

**Severe sepsis** = sepsis associated with organ dysfunction, hypoperfusion or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to lactic acidosis, oliguria, or an acute alteration in mental status.

**Septic shock** = sepsis induced with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include but are not limited to lactic acidosis, oliguria or an acute alteration in mental status. Patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.

**Sepsis-induced hypotension** = a systolic blood pressure < 90mmHg or a reduction of >= 40mmHg from baseline in the absence of other causes for hypotension

**Multiple organ dysfunction syndrome (MODS)** = presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention

**Table 2.6 International definitions of sepsis [44]**

**Causative organisms** There are many bacterial causes of sepsis, predominantly Gram negative bacteria, but the incidence of fungal or viral causes of sepsis is increasing. Sepsis due to Gram positive organisms is also increasing in prevalence.
Treatment

**Antibiotics** Blood cultures should be taken prior to starting antibiotics \[45\] and initial treatment should be started as soon as possible based on the likely causative organisms (table 2.7). The Surviving Sepsis campaign recommend that antibiotics are administered to children within 1 hr of the identification of severe sepsis, after appropriate cultures have been obtained \[45\]

<table>
<thead>
<tr>
<th>Age</th>
<th>Likely causative organism</th>
<th>Choice Of Antibiotic</th>
<th>Duration Of Therapy</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intravenous</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth – 3 months</td>
<td>Group B Strep E. coli L. monocytogenes H. influenzae S. pneumoniae Klebsiella sp Salmonella sp Staph aureus Enterococcus sp</td>
<td>Cefotaxime + Benzylpenicillin</td>
<td>5-10 days</td>
<td>Choice of antibiotics for empirical therapy (i.e. causative organism not known). Once causative organism is known (usually within 24 hours) antibiotics should be amended if necessary.</td>
</tr>
<tr>
<td>&gt; 3 months</td>
<td>E. coli H. influenzae S. pneumoniae Klebsiella sp Salmonella sp Staph aureus N. meningitidis</td>
<td>Cefotaxime</td>
<td>5-10 days</td>
<td>Choice of antibiotics for empirical therapy (i.e. causative organism not known). Once causative organism is known (usually within 24 hours) antibiotics should be amended if necessary.</td>
</tr>
</tbody>
</table>

Table 2.7. Suggested antibiotic choices for empirical treatment of sepsis

**Fluids** A recent multi-centre audit involving 17 PICUs and 2 PICU transport services in the UK found that 34/200 (17%) children died following referral and the presence of shock at PICU admission is associated with an increased risk of death. Despite clear consensus guidelines for the emergency management of children with severe sepsis and septic shock, most children received inadequate fluid resuscitation and inotropic support in the crucial few hours following presentation \[46\]. The 2007 American College of Critical Care Medicine (ACCM) guidelines for the resuscitation of pediatric septic shock suggest that 20 mL/kg of bolus intravenous fluid be given within 5 minutes and state that children with septic shock require proportionally larger quantities of fluid compared with adults.\[47\] There is controversy over the appropriate choice of fluid to use following publication of a systematic review in the BMJ in 1998 which suggested that the use of colloids in adults may be associated with increased mortality compared with crystalloids \[48\] however the majority of PICUs continue to use colloids, particularly Human Albumin Solution 4.5% for fluid resuscitation in septic patients and the paediatric recommendations from the Surviving Sepsis Campaign guidelines 2008 recommend either crystalloid or colloid for fluid resuscitation \[45\]. NICE guidance for resuscitation in meningococcal disease
recommend that 20ml/kg boluses of fluid are given if signs of shock are present or persist up to 60ml/kg when intubation and mechanical ventilation is required [42].”

**Vasopressor/Inotropic agents.** If fluids fail to restore adequate arterial pressure and organ perfusion, dopamine or noradrenaline are recommended as first choice for hypotension with dobutamine being added when cardiac output remains low despite fluid resuscitation and combined inotropic/vasopressor therapy [45]. The ACCM recommend that inotropic support is started early and peripheral access used until central access is attained [47]. Vasopressin has been used in patients who do not respond to other treatment.

**Steroids** Adrenal insufficiency is a frequent finding in children with septic shock [49,50]. Low dose hydrocortisone is recommended in children adrenal insufficiency which can be tested using the low dose synacthen test [50,BNF-C] Although the recommended dose of hydrocortisone in shock is yet to be agreed [51], NICE recommend hydrocortisone 25 mg/m² four times daily in meningococcal disease under the supervision of a paediatric intensivist [42].”

**Activated Protein C** This agent is licensed for treatment of adults with severe sepsis who have a high risk of dying. However a recent study in children (RESOLVE (REsearching severe Sepsis and Organ dysfunction in children: a gLobal perspectiVE) found no significant difference between groups in mortality between active and placebo groups but more instances of CNS bleeding in the active group (11 [4.6%], vs 5 [2.1%] in placebo, p=0.13) [52] and so the use of this drug is not recommended in children [45].

**Extracorporeal Membrane Oxygenation (ECMO)** ECMO has been recommended for refractory shock in children [47] however, this is not commonly done in the UK.

**Haemo or Plasma filtration** Early introduction of haemo- or plasma filtration may reduce mortality from sepsis, including meningococcal sepsis, however further studies are required [53,54].

---

**TASK 2.2**

Find a patient with sepsis on your unit.

Prepare a pharmaceutical care plan based on the following problems. Include monitoring parameters in your plan.

- Renal impairment resulting in fluid overload, electrolyte disturbances and metabolic acidosis
- CNS problems including pain, cerebral oedema, reduced level of consciousness
- Respiratory failure
- Hypotension
- Electrolyte disturbances
- Coagulopathy
2. Hospital Acquired infections

A hospital-acquired (nosocomial) infection is defined as an infection of any site with a bacterial or fungal pathogen obtained ≥ 48 hours after admission to hospital. While in the paediatric intensive care unit, 16% of children will develop a nosocomial infection [55].

The risk factors for nosocomial infection in critically ill children include the following:

- Breach of natural defences: immunological, mechanical and immunological barriers
- Immature, inhibited or incapacitated natural host defense to infection
- Clinical condition e.g. immunosuppression, congenital or acquired immunodeficiency, chronic disease, transplantation, history of antibiotic use.
- Indwelling devices e.g. bladder catheters, endotracheal tubes, intravascular devices

2.1 Central venous catheter related infections

Bloodstream infections (BSI) represent a major cause of hospital-acquired infections in PICU patients. Risk factors for development of these infections include being immunocompromised, prolonged length of hospitalization, mechanical ventilation, dialysis and severity of illness. The majority of these infections are due to central venous catheters. Likely organisms include coagulase-negative staphylococci, Klebsiella pneumonia, Candida spp, Pseudomonas aeruginosa and Staphylococcus aureus [56].

A combination of interventions designed to reduce bloodstream infection rates has been described: [57]

- maximal barrier precautions
- antibiotic impregnated central venous catheters
- hand washing campaigns
- using chlorhexidine for skin disinfection rather than povidone-iodine

Novel treatment such as probiotics have not found to be useful and one randomized controlled trial involving Lactobacillus was terminated due to an unexpected statistically non-significant trend toward an increase in the rate of nosocomial infections in the active group [58].

2.2 Ventilator associated pneumonia (VAP)

VAP is the second most common hospital-acquired infection among PICU patients. It is defined as pneumonia occurring ≥48 hours after intubation which was not incubating at the time of admission. Pseudomonas aeruginosa is the most common causative organism occurring in 23.5% of isolates. VAP has been found to be associated with a greater than 4 fold increase in length of stay and a tendency towards increased mortality [59].

The Patient Safety First campaign www.patientsafetyfirst.nhs.uk was launched by the NPSA and NICE in May 2008. Prevention of VAP is one of the interventions they have identified as a priority. Hospitals that sign up to this campaign will implement a set of interventions known as the “Ventilator Care Bundle” and include elevation of the head of the bed to 30-45 degrees as this has been correlated with
reduction in the rate of ventilator-associated pneumonia. [60,61]. The second
intervention this bundle will include is periodic “sedative interruptions” and daily
assessment of readiness to extubate in-order to reduce the duration of mechanical
ventilation and therefore, the risk of VAP [62,63]. Although these interventions are
based on adult populations, extrapolation to paediatrics seems reasonable; however
the use of daily sedation holidays must be weighed against the risk of inadvertent
extubation [64].

Although the use of ranitidine, omeprazole, or sucralfate has been proposed to reduce
the incidence of VAP, none of these agents have been found to reduce the occurrence
of VAP, or affect mortality or stress ulcer bleeding in mechanically ventilated PICU
patients and so use of these agents is not currently recommended [65].

2.3 Urinary tract infections (UTI)
UTIs account for approximately 13% of nosocomial infections in the PICU. The rate
is approximately 4 per 1000 catheter days [66]. The presence of an indwelling
catheter is the major risk factor and early removal reduces the risk of infection. Gram
negative bacteria and yeast account for 82% of pathogens [55].

2.4 Clostridium difficile
Infection with C. difficile is very rare in children; however, a recent study from the
USA estimated the annual incidence of C. difficile-associated disease in paediatric
inpatients has increased from 4.4 to 6.5 cases per 10,000 patient-days over the period
2001-6 [67]. This is much less than the reported incidence in adults over 65 years of
age in England, Wales and Northern Ireland in 2005 of 22 per 10,000 bed days [68].

The 2 main factors which lead to the development of antibiotic-associated colitis are
• alteration of the normal colonic microflora (by antibiotics or
chemotherapeutic agents)
• endogenous or exogenous source of a toxigenic strain of the organism.
Antibiotics most likely to cause C. difficile colitis are broad-spectrum penicillins,
cephalosporins and clindamycin. Oral administration is more likely to cause this than
IV as oral therapy is more likely to be prolonged.
Symptoms vary in severity from simple diarrhoea to colitis with bloody diarrhoea,
abdominal pain, fever, leukocytosis and enteropathy. Diagnosis is based on
• symptoms of diarrhoea occurring whilst on antibiotics (or shortly after a course)
• presence of toxin in stools
• biopsy or sigmoidoscopy where pseudomembranes may be seen
Initial treatment is to stop the causative antibiotic(s) and most cases will then resolve.
However, if this is not possible or symptoms are severe and persistent, metronidazole
or vancomycin can be used for 7-10 days. Metronidazole is usually preferred on the
grounds of cost and because the public health consequences of metronidazole
resistance are less severe than the consequences of vancomycin resistance.
Vancomycin should be reserved for those patients who cannot tolerate or do not
respond to metronidazole. Oral therapy is preferred in order to achieve high
concentrations in the gut lumen. If the patient cannot tolerate oral medication, naso-
gastric administration should be tried. Neither IV metronidazole nor vancomycin
achieve reliable levels in the gut so if IV administration is necessary use of both
agents is recommended.
2.5 Surgical site infections
Patients are admitted to PICU for post-operative care following a large range of surgical procedures. Antibiotic prophylaxis should be based upon the likely causative organisms of infection in these patients.

TASK 2.3
Find 10 patients admitted post-operatively
1. What type of infection are they at risk from?
2. What are the likely causative organisms?
3. Which antibiotics would be appropriate for prophylaxis

3. Viral infections

3.1 Herpes simplex encephalitis (HSE)

Signs and symptoms The classic clinical presentation of HSE includes fever, altered level of consciousness, focal motor seizures, dysphasia, and hemiparesis. Although these are present in the majority of cases in children, other symptoms including ataxia, decreased visual acuity, tremor, or generalized tonic-clonic seizures are also described [69]. Children and adolescents account for approx one third of all cases of HSE. Even with early administration of therapy after the onset of disease, nearly two thirds of survivors will have significant residual neurological deficits [70].

Causative organisms About 90% of cases are due to Herpes Simplex Virus group 1 (HSV-1), while HSV-2 is associated with HSE in neonates, in which there is a disseminated infection, and in immuno-compromised patients such as those with renal transplants or HIV infection [71].

Treatment All suspected cases should be given IV aciclovir at 500 mg/m\(^2\) every 8 hours for 21 days (10 mg/kg 8 hourly for patients > 12 years, 20 mg/kg 8 hourly for neonates - see BNF-C). High doses in inadequately hydrated patients can cause renal impairment so ensure adequate hydration and avoid other nephrotoxic drugs if possible.
As the symptoms of encephalitis are difficult to differentiate from those of meningitis, patients are often started on treatment for both conditions until the diagnosis is clarified. Patients may also require a combination of anti-convulsants as seizures can be particularly difficult to treat.
There have been recent case reports of resistance of HSV to aciclovir. Resistant infections can be managed by foscarnet or cidofovir but both are more toxic than aciclovir [72].

3.2 Varicella

Signs and symptoms Varicella (chicken pox) occurs mainly in young children and is recognised by a characteristic vesicular rash. It is not usually serious but serious
complications can occur including central nervous system involvement, pneumonia, secondary bacterial infections, and death [73].

**Causative organisms** It is caused by Varicella-zoster which is one of the herpes viruses, which after endogenous reactivation can also cause herpes zoster (shingles).

**Treatment** Although aciclovir is the mainstay of treatment, aciclovir-resistant varicella zoster virus infection in a child has been described. In this case, foscarnet was successfully used to treat the infection [74].

### 3.3 Cytomegalovirus (CMV)

CMV virus is a DNA virus of the herpes virus group and as such, after the primary infection causes latent infection with frequent reactivations. Symptomatic infections are most likely in immuno-compromised children or newborns. Treatment is usually with Ganciclovir although if significant bone-marrow suppression occurs, Foscarnet may be used. Cidofovir is also active against CMV.

### 3.4 Antiviral agents

Antiviral agents can be separated into 3 groups

- The nucleoside analogues: acyclovir, ganciclovir, cidofovir and ribavirin
- The prodrug nucleoside analogues: famciclovir and valaciclovir
- Others: foscarnet, amantadine and oseltamavir

**Aciclovir** is a synthetic purine nucleoside analogue with in vitro and in vivo inhibitory activity against human herpes viruses, including Herpes simplex virus (HSV) types 1 and 2 and Varicella zoster virus (VZV), Epstein Barr virus (EBV) and Cytomegalovirus (CMV). Aciclovir inhibits viral DNA replication with resultant chain termination following its incorporation into the viral DNA.

**Valaciclovir** is rapidly and almost completely converted in man to aciclovir and valine, probably by the enzyme referred to as valaciclovir hydrolase.

**Ganciclovir** is a synthetic nucleoside that accumulates in infected cells inhibiting virus replication. Although it is effective against cytomegalovirus (CMV), herpes simplex viruses, Epstein-Barr virus, varicella zoster virus and hepatitis B virus, clinical studies have been limited to assessment of efficacy in patients with CMV infection. Ganciclovir is very poorly absorbed by mouth, and rapidly excreted by the kidney with an average half life of 3 hours.

Use of ganciclovir is limited because of bone marrow suppression. In order to maximize effectiveness and reduce risk of toxicity it is advised that peak and trough levels are monitored.

Resistance to ganciclovir has been described and should be considered in patients who repeatedly show poor clinical response or experience persistent viral excretion during therapy. Resistance can arise after prolonged treatment or prophylaxis with ganciclovir. Other agents that have been used in resistant cases in adults include maribavir, leflunomide and the antimalarial drug, artesunate [75].
Ganciclovir should be handled as a cytotoxic so it is important that nursing staff and parents/carers are aware of how to handle nappies etc

**Cidofovir** is a cytidine analogue with in vitro and in vivo activity against human cytomegalovirus (HCMV). HCMV strains resistant to ganciclovir may still be susceptible to cidofovir. Cidofovir suppresses HCMV replication by selective inhibition of viral DNA synthesis.

**Famciclovir** is the oral form of penciclovir. Famciclovir is rapidly converted in vivo into penciclovir, which has in vivo and in vitro activity against human herpes viruses including varicella zoster virus and herpes simplex types 1 and 2. Penciclovir inhibits replication of viral DNA and has been shown to be active in vitro against a recently isolated aciclovir-resistant herpes simplex virus strain which has an altered DNA polymerase.

**Foscarnet** is an antiviral agent with a broad spectrum inhibiting all known human viruses of the herpes group: herpes simplex virus type 1 and 2; human herpes virus 6; varicella zoster virus; Epstein-Barr virus, cytomegalovirus (CMV), some retroviruses, including human immunodeficiency virus (HIV) and hepatitis B virus. Foscarnet exerts its antiviral activity by a direct inhibition of viral specific DNA polymerase and has been found to be active in vitro against HSV mutants and CMV strains resistant to ganciclovir. Its main toxicity is in the kidney and in inducing electrolyte disturbances.

**Amantadine** inhibits the cellular uptake of influenza-A virus although not all strains are sensitive. Its major indication is for prophylaxis in influenza but central nervous system side-effects limit its use.

**Oseltamivir** is a selective inhibitor of influenza virus enzymes, which are important both for viral entry into uninfected cells and for the release of recently formed virus particles from infected cells, and for the further spread of infectious viruses in the body. Given orally, it inhibits influenza A and B virus replication and pathogenicity.

### 4. Fungal infections

Invasive Candida and Aspergillus infections are the most commonly encountered fungal infections in children and can be life threatening in critically ill patients especially if immuno-compromised.

A recent study found that colonization by Candida species can occur in up to 70% of patients who stay in PICU for more than 5 days and who undergo treatment for severe sepsis or septic shock. In this study oropharyngeal and rectal colonization was more common than skin colonization and 30% of patients developed candidemia [76]. The risk of serious candidemia can be reduced by using shorter courses of antibiotic therapy, undertaking routine surveillance cultures for Candida species and initiating preemptive or empirical antifungal treatment on suspicion of infection.
4.1 Antifungal agents

Polyene macrolide antifungals: amphotericin and nystatin

Intravenous Amphotericin B is the mainstay of treatment against serious Candida and Aspergillus infections in PICU patients. It works by binding to ergosterol in fungal cytoplasmic membranes, creating trans-membrane channels resulting in an increased permeability and leakage of essential nutrients from the fungal cell and ultimately cell death. Its fungicidal activity is concentration-dependent, increasing directly with the amount of drug attained at the site of infection. Nystatin works in a similar way. Amphotericin binds to cholesterol in human cell membranes and causes toxicity in a similar way. Lipid formulations such as Amphotericin B lipid complex (ABLC, Abelcet®), Amphotericin B colloidal dispersion (ABCD, Amphocil®, Amphotec®) and Liposomal amphotericin B (AmBisome®) are better tolerated than the parent drug because they have reduced binding to cholesterol and preferentially bind to serum high-density lipoproteins. This reduces release of the Amphotericin B in the kidneys and means that higher doses can be used which may be better targeted to organs such as the liver, spleen and lungs.

The NPSA released an alert in 2007 highlighting the risk of mixing up preparations of Amphotericin B following reports of 2 fatalities www.npsa.nhs.uk/nrls/alerts-and-directives/rapidrr

Pyrimidine analogues:

5-Flucytosine (5-FC) inhibits fungal protein synthesis. It is not particularly effective against yeast infections and antifungal resistance develops quickly so it should be used in combination with other agents. The combination of amphotericin B plus 5-FC has been found to be more effective than amphotericin B alone in the treatment of cryptococcal meningitis [77]. 5-FC is well absorbed after oral administration and distributes widely, attaining therapeutic concentrations in most body sites. Bone marrow suppression is the most serious problem associated with this drug

Azoles

Fluconazole, Itraconazole, Voriconazole, Posaconazole and ravuconazole

The azole antifungals inhibit enzymes responsible for synthesis of ergosterol resulting in abnormalities in fungal membrane permeability, membrane-bound enzyme activity, and a lack of coordination of chitin synthesis. Fluconazole’s activity is concentration-independent; it does not increase when the maximal fungistatic concentration is attained. It is available as either an oral or an intravenous form, and oral fluconazole is approximately 90% bioavailable so can be used even in serious infections. Unchanged drug is cleared predominantly by the kidneys. Fluconazole passes into tissues and fluids rapidly, probably as a result of its relatively low lipophilicity and limited binding to plasma proteins. Concentrations of fluconazole are 10-fold to 20-fold higher in the urine than in the blood so it is particularly good for treatment of fungal urinary tract infections. Fluconazole pharmacokinetics can be dramatically different in children compared to adults and
higher doses are usually required. Elimination is primarily renal and therefore larger dosing intervals are needed in neonates. It is generally well tolerated [78].

**Itraconazole** is effective in treatment of aspergillosis and in infections due to strains of candida that are fluconazole-resistant. Itraconazole is only available orally and the bioavailability between different formulations can vary considerably. Capsules should be taken with food but the oral suspension is better absorbed on an empty stomach. Itraconazole can also cause a number of significant drug interactions (see BNF-C). It is mainly eliminated by the liver and is well tolerated. It tends not to be used in acute infection but is effective for prophylaxis in patients at risk of developing fungal infections

**Voriconazole** is a second-generation triazole and is fungicidal against Aspergillus and fungistatic against Candida species.[79]. Children require higher doses of voriconazole than adults to attain similar serum concentrations over time [80]. After nearly complete oral absorption, voriconazole is extensively metabolized by the liver. Voriconazole can cause visual disturbances, alterations in liver enzymes and skin reactions and drug interactions need to be considered. Voriconazole is suggested to be superior to amphotericin B in the treatment of infections due to aspergillus [81], equally effective to amphotericin B in invasive candidiasis and more effective than fluconazole [82].

**Posaconazole and ravuconazole.** Posaconazole is a second-generation triazole that is closely related to itraconazole. It is fungicidal in vitro against Aspergillus. It is only available orally at present. Ravuconazole is structurally similar to fluconazole and voriconazole and is also fungicidal. Experience with both of these agents in children is limited.

**Echinocandins – Caspofungin, Micafungin and anidulafungin**

These agents interfere with cell wall biosynthesis by noncompetitive inhibition of 1,3-β-D-glucan synthase, an enzyme present in fungi but absent in mammalian cells. They are fungicidal against Candida but fungistatic against Aspergillus

Caspofungin is excreted primarily by the liver and its half-life is approximately one third less in children than in adults. Because 1,3-β-glucan is a selective target present only in fungal cell walls and not in mammalian cells, caspofungin has few adverse effects. There is little paediatric data on the newer echinocandins Micafungin and Anidulafungin.
5. General information

5.1 Classification of micro-organisms

<table>
<thead>
<tr>
<th>Gram positive organisms</th>
<th>Gram negative organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram-positive cocci</strong></td>
<td><strong>Gram-negative cocci</strong></td>
</tr>
<tr>
<td>Staphylococci</td>
<td>Neisseria</td>
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<td><strong>Gram-positive bacilli</strong></td>
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<td>Bacillus (Aerobic)</td>
<td>Haemophilus and Bordetella</td>
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<td>Clostridium (Anaerobic)</td>
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<td><strong>Spiral bacteria</strong></td>
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</tr>
<tr>
<td>Helicobacter, Campylobacter</td>
<td></td>
</tr>
</tbody>
</table>

5.2 Classification of antibiotics by principal mechanism of action.

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interference with cell wall synthesis</td>
<td>Beta-lactams (e.g. penicillins, cephalosporins,</td>
</tr>
<tr>
<td></td>
<td>carbapenems, monobactams). Glycopeptides (e.g.</td>
</tr>
<tr>
<td></td>
<td>vancomycin, teicoplanin)</td>
</tr>
<tr>
<td>Inhibition of protein synthesis</td>
<td>Macrolides, Tetracyclines, Clindamycin, Aminoglycosides, Chloramphenicol</td>
</tr>
<tr>
<td>Interference with DNA synthesis and</td>
<td>Fluoroquinolones, Quinolones, Rifampin,</td>
</tr>
<tr>
<td>replication</td>
<td>Trimethoprim-sulfamethoxazole</td>
</tr>
<tr>
<td>Disruption of bacterial membrane</td>
<td>Polymyxins, Daptomycin</td>
</tr>
<tr>
<td>structure</td>
<td></td>
</tr>
</tbody>
</table>
5.3 Resistance

Some species of bacteria have innate resistance to some antibiotics so all of that species are resistant to a particular class of antibiotic. Acquired resistance is where initially susceptible populations of bacteria become resistant to an antibiotic by mutation and selection or by acquisition of genetic information from other bacteria. Use of antibiotics allows the resistant organisms to survive and grow and therefore prudent use of antibiotics is vital. The pharmacist is ideally placed to ensure patients receive the appropriate drug at the appropriate dose and for the appropriate duration.

Bacteria have developed ways in which to resist antibiotics [83]:

- **Production of antibiotic-inactivating enzymes.** β-lactamase enzymes cleave the core β-lactamase ring structure of β-lactamase antibiotics thus deactivating them. Both Gram negative and positive organisms can do this. β-lactamase enzymes can be inhibited by the addition of clavulanic acid so the combination agent co-amoxiclav remains effective against organisms that have developed this type of resistance. Extended spectrum β-lactamases (ESBL) are responsible for resistance to penicillin, 3rd generation cephalosporins and aztreonam and are most commonly detected in *E.Coli, Klebsiella pneumoniae* and *Proteus mirabilis*. Bacteria can also produce enzymes to inactivate aminoglycosides and the resistance of Gram negative bacteria to amikacin and tobramycin is increasing.

- **Reduction of concentration of antibiotic within the bacterial cell.** Bacteria can manufacture membrane proteins called efflux pumps that export antibiotics out of the cell. This affects macrolides, tetracyclines and fluoroquinolones and is demonstrated in *Staph aureus, Strep pneumoniae, S. pyogenes* and Enterococcus spp. Gram negative bacteria such as *Enterobacter* and *Pseudomonas aeruginosa* can also reduce the permeability of the cell membrane resulting in reduced concentration of the antibiotic within the cell.

- **Alteration of antibiotic target site.** Bacteria alter target sites so the antibiotic is unable to bind properly. This is one of the mechanisms involved in the methicillin resistance of *Staph aureus* and the pencillin resistance of *strep pneumoniae*. Quinolones and macrolides are also susceptible to this type of resistance mechanism.

- **Elimination of antibiotic target site.** Methicillin resistant *Staph aureus* (MRSA) strains possess a gene which causes an alternative binding site to develop which has low affinity for methicillin.

The development of multi-drug-resistant bacteria (MDRB) is especially problematic. The most clinically relevant MDRB include MRSA, extended-spectrum cephalosporin-resistant Gram-negative bacilli, and vancomycin-resistant enterococci (VRE).

The incidence of MDRB is widely known in adult ICU patients: In Europe MRSA strains account for 5% to 20% of *S aureus* isolates, >20% of *Klebsiella* produce ESBL and the frequency of VRE is estimated to be <1%. However there is less information available about the incidence in children. MRSA is thought to account for 11 - 18% of...
Staph aureus isolated from paediatric units and 14% of Klebsiella strains were ESBL producers [84].

5.4 Specific resistance problems

5.4.1 Methicillin Resistant Staphylococcus aureus (MRSA)

MRSA is very prevalent in many UK hospitals and can be responsible for causing life threatening infections. The incidence of MRSA carriage in children ventilated for $\geq 4$ days over a 4 year period in a PICU in the UK was found to be 2.4%. One third of the children developed MRSA infections and 7% of these patients died [85].

There has been a major national campaign recently to try to reduce the incidence of MRSA bacteraemia. Agreed guidelines suggest the following [86];

- Surveillance of MRSA should be undertaken in a systematic way and should be fed back routinely to healthcare staff.
- The inappropriate or unnecessary use of antibiotics should be avoided in order to reduce the emergence and spread of strains with reduced susceptibility to glycopeptides.
- Screening for MRSA carriage in selected patients and clinical areas should be performed according to locally agreed criteria based upon assessment of the risks and consequences of transmission and infection.
- Nasal and skin decolonization should be considered in certain categories of patients.
- The general principles of infection control should be adopted for patients with MRSA, including patient isolation and the appropriate cleaning and decontamination of clinical areas.

Treatment of MRSA infection usually consists of a regime involving a combination of oral antibiotics (eg trimethoprim, clindamycin, rifampicin or linezolid) and topical preparations (e.g. mupirocin or chlorhexidine). Serious infections are usually treated with IV Vancomycin or Linezolid. Daptomycin has been used in the USA for this indication but experience in the UK with this drug is lacking [87].

It is vital, when using vancomycin that adequate trough plasma concentrations are achieved (i.e. 10-20mg/l) in order to effectively treat the infection and doses much greater than those in the BNF-C may be required to achieve these levels. Pharmacists need to be involved in the measurement and interpretation of plasma levels in order to optimize treatment and ensure that serious infections are treated aggressively. Vancomycin clearance is significantly affected by renal impairment and so levels may need to be measured on a daily basis in some patients in order to prevent accumulation.

5.4.2 Vancomycin Resistant Enterococci (VRE)

Enterococci are amongst the most antibiotic-resistant bacteria in humans. Minor infections can usually be treated orally with penicillins, macrolides or tetracyclines,
however, only IV penicillins, teicoplanin and vancomycin are reliably effective against serious enterococcal infections such as endocarditis or meningitis.

In 1986 the first vancomycin-resistant enterococcus (VRE) was found in France and a year later the first strain was isolated in the UK. Similar strains have now been found world-wide. The genetic material which makes enterococci resistant to vancomycin has probably been passed on from other types of bacteria that do not cause human disease but which are already vancomycin-resistant. Bacteria that are resistant to vancomycin are commonly also resistant to teicoplanin and vice versa.

VRE usually presents in long-stay patients and those who have received antibiotics (especially vancomycin, teicoplanin or cephalosporins). Restricting the use of these antibiotics to those patients who really need should reduce the incidence of VRE. It is also vital that hand-washing and proper cleaning of equipment is carried out. Patients with VRE must be nursed in isolation.

Linezolid is currently the drug of choice for the treatment of VRE in children in the UK. This drug is a monoamine oxidase inhibitor and should therefore be used with great caution in patients with uncontrolled hypertension, phaeochromocytoma, carcinoid, thyrotoxicosis, bipolar depression, schizoaffective disorder, acute confusional states. It can also cause serious drug interactions so careful screening of concomitant medication is required. It has extremely good oral bioavailability so should be used orally whenever possible. There is no need to alter the dose in patients with renal or hepatic insufficiency [88].

5.4.3 Extended spectrum beta lactamases (ESBL)

Patients at high risk for developing colonization or infection with ESBL-producing organisms are often seriously ill patients with prolonged hospital stays and with who have invasive devices (e.g. urinary catheters, endotracheal tubes and central venous lines) in place for a prolonged duration. [89].

Use of antibiotics is also a risk factor for acquisition of an ESBL-producing organism. Ceftazidime has been particularly implicated in this, but other antibiotics have also been linked to development of infections with ESBL-producing organisms including quinolones, co-trimoxazole, amino-glycosides and metronidazole. There is also a strong association between quinolone resistance and ESBL production. Penicillins and carbapenems have not been associated with frequent infections with ESBL-producing organisms and the carbapenems (eg imipenem, meropenem) have the most consistent activity against ESBL-producing organisms.

**TASK 2.5**

Identify 5 patients on your unit who have had resistant organisms identified.

1. Are there any risk factors for resistant organisms present in these patients?
2. Which antibiotics should be used in these patients?
3. Discuss local resistance patterns with your microbiologist
5.5 Panton-Valentine Leukocidin (PVL)

Panton-Valentine Leukocidin (PVL) is a toxin that destroys white blood cells and is excreted by some strains of *Staphylococcus aureus* (SA). Strains of PVL-SA producing a new pattern of infection have emerged in the UK and worldwide and have been associated with virulent transmissible strains of *S. aureus*. As with other strains of *S. aureus*, PVL-SA predominantly cause Skin and Soft Tissue Infections (SSTI), but PVL-SA can also cause severe invasive infections such as septicaemia, osteomyelitis and pneumonia. Necrotising haemorrhagic pneumonia is the most serious clinical feature with a high mortality rate (> 62%). This often follows a “flu-like” illness which may be a genuine viral infection or reflect the bacteraemia, and tends to affect otherwise healthy young people in the community. The Health Protection agency have produced Guidance on the diagnosis and management of PVL-associated *Staphylococcus aureus* infections (PVL-SA) in England [http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1218699411960](http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1218699411960).

Initial treatment of children presenting with necrotising pneumonia should be a high dose, intravenous combination of clindamycin, linezolid (to suppress PVL and alpha toxin production) and rifampicin (for intracellular clearance of staphylococci). Providing the infecting organism is susceptible on testing, this combination should be continued until the patient has improved and is clinically stable, when continuation therapy with linezolid plus rifampicin, or with clindamycin plus rifampicin, may be considered for 10-14 days, guided by the clinical response and infection markers such as CRP. Intravenous Immunoglobulin should be also considered in addition to intensive care support and high dose antimicrobial therapy because of its action in neutralizing exotoxins and superantigens. The dosage of 1-2g/kg of IVIG may be repeated after 48 h if there is still evidence of sepsis, or failure to respond [90].

References


14. Joint Committee on Vaccination and Immunisation. Minutes of the meeting held on Wednesday 22 June 2005.


68. Health Protection Agency. Clostridium difficile. 
http://www.camr.org.uk/web/HPAwebFile/HPAweb_C/1194947309097


82. Kullberg BJ. Voriconazole compared with a strategy of amphotericin B followed by fluconazole for treatment of candidaemia in non-neutropenic patients. In: 14th


88. Pharmacia. Zyvox - Summary of Product Characteristics. 27.3.07


The Genito-urinary system
Rhian Isaac
Revised by Rhian Isaac September 2011

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References
Further Reading
Objectives

- To understand and be able to monitor renal function/ dysfunction (acute and chronic)
- To understand the mechanism of action of diuretics
- To be able to recognise and manage drug therapy that adversely affects renal function
- To understand the pathophysiology of different forms of acute renal failure
- To be able to describe the management options for acute and chronic renal failure
- To be able to describe the different forms of renal replacement therapy in fluid management
- To understand the role of plasmapheresis and plasmapheresis in critical illness
- To understand the mechanics of haemofiltration (or haemodiafiltration) and the implications for anticoagulation, and fluid management
- To be able to monitor and adjust doses of drugs affected by renal dysfunction, including patients who require haemofiltration
1. Introduction

An understanding of renal function and its role in the management of fluid and electrolytes is important for anyone involved in the care of a critically ill child. Renal failure may be a primary cause for admission to PICU but in many cases is part of multi-organ system dysfunction. The manipulation of the renal system for fluid management is part of the standard treatment of most patients and requires knowledge of the roles of diuretics and renal replacement therapies in the PIC settings.

2. Anatomy and Physiology

2.1 Anatomy

The genitourinary system consists of the kidneys, ureters, bladder and the urethra. Usually there are two kidneys, on the left and right of the retroperitoneal region. The renal artery, vein, lymphatic and nerve enter the kidney via the hilus. The ureter emerges from here. See Figure 3.1

The kidney is surrounded by a fibrous renal capsule, to protect the kidney from infection, and adipose tissue. Internally the kidney has a lighter medulla, and surrounding the medulla is the darker cortex. The cortex is where the glomerulus and the proximal and distal tubules of the nephrons are found. The loop of Henle and collecting ducts are in the medulla.

![Figure 3.1 Parts of the urinary system](image-url)
2.2 Physiology

The nephron
The primary function of the nephron is to regulate the concentration of water and solutes, reabsorbing what is required and excreting the waste as urine. The nephron consists of the Bowman’s capsule, the proximal tubule, the descending and ascending limbs of the loop of Henle and the distal tubule. The distal tubule leads into a collecting duct which then unites with others to form larger ducts that empty into the minor calyces.

The Bowman’s capsule
The Bowman’s capsule, containing the glomerular capillaries, starts the nephron. The majority of the nephrons have the glomerulus in the outer cortex with a short loop of Henle (cortical nephrons); the others have the glomerulus close to the medulla/cortex border and have a long loop of Henle (juxtamedullary nephrons).

![Glomerular filtration diagram](image)

Figure 3.2 Glomerular filtration

About 20% of plasma is filtered through the glomerular wall (from the afferent arteriole) into the convoluted proximal tubule. The remainder of the plasma passes out of the kidney via the efferent arteriole. Glomerular filtration depends on hydrostatic and oncotic pressures. **Hydrostatic pressure** is higher in the glomerulus than in other capillaries because the diameter of the efferent arteriole is less than that of the afferent arteriole, enabling the filtrate to flow into the Bowman’s capsule. **Oncotic pressure** is produced because the blood flowing in the glomerulus contains plasma proteins and blood cells that displace the water and its solutes, creating a counter force i.e. water outside the glomerulus equalises with the water inside the glomerulus by osmosis. The hydrostatic force of the glomerulus is greater than the force of the oncotic pressure therefore filtrate is pushed into the Bowman’s capsule. See Figure 3.2
Reabsorption and secretion in the nephron
The convoluted proximal tubule has a brush border wall made up of micro-villi to increase the surface area to maximise its main function of reabsorption of water and electrolytes. See Table 3.1

Sodium is handled along the entire nephron by various mechanisms. In the proximal tubule about 60% of filtered sodium is recovered by transcellular movements and the passive paracellular pathway. The sodium concentration in the filtrate is much higher than in the epithelial cells, therefore favouring the movement of sodium from the tubule into the cells; and at the same time providing the driving force for secondary transport of other solutes. Sodium is coupled to organic or inorganic solutes via these sodium dependent carriers or is exchanged for hydrogen ions (Na+/H+ antiporter). Only about 20% of the transported sodium diffuses into the capillaries due to significant back flux into the lumen of the tubule via the paracellular pathways- this is due to osmotic water flow from the lumen to the blood. In all segments of the tubule sodium is actively pumped out of the cells via the Na/K- ATPase pumps. See Figure 3.3

Glucose is completely and specifically reabsorbed here, but it is a saturatable process i.e. if the amount of glucose delivered to the tubule is less than the maximal capacity of the tubule there will be no glucose in the urine. This is an active process via cotransport channels driven by the sodium in the nephron.
Phosphate is almost exclusively reabsorbed in the proximal tubule, initially by the 2a sodium dependent phosphate transporter (NPT2a). The parathyroid hormone (PTH) controls the NPT2a expression, a decrease in PTH causing an increase in phosphate excretion in the urine.

Urate is both reabsorbed and secreted in the proximal tubule. In Fanconi syndrome there is a decrease in the tubular secretion of urate. A number of drugs interfere with the transport of urate in the proximal tubule e.g. probenecid is used to stimulate urate secretion.

Water is absorbed in the proximal tubule, the thin descending limb and the collecting duct. In the proximal tubule water is moved from the lumen by a process that is iso-osmotic and driven by active solute transporters i.e. the osmotic pressure difference; the more solute there is in the tubule the less water is reabsorbed and therefore produces an osmotic diuresis.

Figure 3.4 Movement of water in the nephron

The loop of Henle’s descending limb is impermeable to sodium and chloride but is permeable to water. As the filtrate travels down the limb and into the hypertonic renal medulla water flows out by osmosis until equilibrium is achieved. The ascending limb is the opposite, it is impermeable to water and no water is reabsorbed in the thick ascending limb or distal tubule. The counter current exchange in the ascending limb actively removes sodium out of the tubule, making the interstitial regions hypertonic. The filtrate therefore becomes more hypotonic as it flows into the distal tubule. See Figure 3.4

The collecting duct has low water permeability in the absence of antidiuretic hormone (ADH) - low ADH will allow the urine to remain dilute. See Figure 3.5
Figure 3.5 Filtrate movement in the nephron

<table>
<thead>
<tr>
<th>Proximal Tubule</th>
<th>Loop of Henle</th>
<th>Distal Tubule</th>
<th>Collecting Tubule</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tonicity of filtrate</strong></td>
<td>Isotonic</td>
<td>Hypotonic</td>
<td>Isotonic or hypotonic</td>
</tr>
<tr>
<td><strong>Solute reabsorbed</strong></td>
<td>Sodium ions Chloride ions</td>
<td>Chloride ions Sodium ions Water Bicarbonate ions</td>
<td>Water Sodium ions Potassium ions Hydrogen ions Ammonium ions Urea</td>
</tr>
<tr>
<td>Chloride ions</td>
<td>Glucose</td>
<td>Potassium ions</td>
<td>Amino acids Bicarbonate ions Phosphate ions Urea Sodium ions Water Uric acid Magnesium ions Calcium ions</td>
</tr>
<tr>
<td><strong>Solute secreted</strong></td>
<td>Sodium ions Chloride ions</td>
<td>Water Potassium ions Urea Hydrogen ions Ammonium ions Uric acid</td>
<td>Urea Sodium ions Potassium ions Hydrogen ions Ammonium ions</td>
</tr>
<tr>
<td>Hydrogen ions</td>
<td>Foreign substances Creatinine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3.1 Summary of reabsorption and secretion in the nephron
2.3 Hormonal influences and the kidney

Erythropoietin is synthesised by the interstitial cells in the cortex and stimulates red blood cell production. It is released from the kidney in response to low blood oxygen levels.

Renin is released from the juxtaglomerular apparatus in response to the baroreceptor reflex stimulated by low blood pressure. Renin converts angiotensinogen to angiotensin I which is converted to angiotensin II by angiotensin converting enzyme. Angiotensin II is a potent vasoconstrictor of the renal arterioles, increasing glomerular filtration rate (GFR). Angiotensin II also stimulates increase in vasopressin release by the hypothalamus and production of aldosterone by the adrenal cortex.

Atrial naturetic peptide (ANP) is released from atrial muscle cells in response to the stretch caused by an increase in blood volume. ANP counteracts the production of renin, aldosterone and vasopressin.

Vasopressin is released in the hypothalamus in response to a rise in plasma osmolality. It stimulates thirst and water reabsorption. Vasopressin also causes vasoconstriction via the renal (and other) V1 receptors.

3. Foetal Development

Homeostasis of fluid and electrolytes in the foetus is maintained by the maternal kidneys via the placenta, therefore if the mother has abnormal kidney function or is unable to maintain fluid, electrolyte or acid-base balance, this will affect the foetus. The foetal kidney maintains the volume of fluid in the amniotic cavity and there is a minimum volume which is essential for foetal lung growth and to allow the foetus to move and develop its joints and muscles. If the foetal kidney becomes oliguric, less fluid is passed into the amniotic cavity and this is associated with pulmonary hypoplasia and joint contractures.

The renal vascular resistance is high in the foetal kidney and the kidney only receives about 2% of the cardiac output, whereas the newborn gets about 15%. The placenta receives about 50% of the maternal cardiac output and as a result the renal filtration fraction is low and the foetal GFR is approximately 25-30 ml/min/1.73m². The tubular function progressively matures towards the end of gestation. Secretory pathways for potassium and organic bases develop and the glucose threshold and the rate of excretion of ammonia and titratable acid improve.[1] Sodium handling differs in the foetus because most reabsorption occurs in the distal tubule rather than the proximal and sodium excretion decreases with increasing gestational and postnatal age i.e. the sodium excretion is higher in a premature than in a term neonate.

The hormonal renin-angiotensin-aldosterone system and vasopressin response mature in early gestation.[2] The main factor preventing urine concentration in the collecting duct of the neonate is the low tonicity of the interstitial medulla, providing a poor osmotic gradient across the tubule membrane.

Nephrogenesis is complete by 36 weeks. The kidneys have a full complement of glomeruli and tubules at birth, but the nephrons need to grow and develop further- this occurs over the first 2 years of life. There is rapid acceleration of glomerular function over the first 2 weeks of life, and continues to increase to completion by 2 years of age. The tubular function matures rapidly in the first year, resulting in an improved
ability to reabsorb sodium, potassium and water. Any changes in the natural function of homeostasis, e.g. dehydration secondary to vomiting, in the first year of life are more pronounced.

Glucosuria is common in premature neonates because the filtered load is too high for the immature nephron. At birth a high-affinity, low-capacity pathway exists to compensate for the reduced activity of high-capacity, low-affinity glucose reabsorption pathway.[3] Later in life glucosuria can be a sign of a number of different conditions involving the kidneys.

Sepsis, hypoxia, hypotension, patent ductus arteriosus, mechanical ventilation, acidosis and catabolism with inadequate renal function provide a PICU neonate with additional renal clearance issues. 79% of newborns in PICU experience a degree of renal impairment[4] and, as a result, drug dosing of renally cleared drugs in premature infants should take both gestation and postnatal age into account when dosing.

4. Assessment of Renal Function in Paediatrics

Renal insufficiency can be defined as a decrease in the GFR. As creatinine is freely filtered by the glomerulus and is almost never reabsorbed throughout the tubules, it is often used as a marker for GFR. The GFR is accepted as the best overall measure of kidney function. Using creatinine as a marker does, however, have some limitations as the level is proportional to muscle mass and will be affected by dietary protein intake and in hepatic disease.

A small percentage of creatinine is actively excreted via tubular secretion and this process can be affected by certain drugs e.g. trimethoprim may inhibit creatinine secretion leading to elevated serum levels and a decrease in creatinine clearance.

The most commonly used method to assess and approximate the GFR in children is the **Schwartz-Counahan method**.[5]

\[
GFR (\text{ml/min/1.73m}^2) = \frac{k \times \text{body length (cm)}}{\text{serum creatinine (micromole/L)}}
\]

where k is a constant that is a function of urinary creatinine per unit of body size. (See Table 3.2).

<table>
<thead>
<tr>
<th>Age Group</th>
<th>k values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm neonates</td>
<td>24</td>
</tr>
<tr>
<td>Term neonates</td>
<td>33</td>
</tr>
<tr>
<td>Infants 0-12 months</td>
<td>40</td>
</tr>
<tr>
<td>Children 2-12yrs</td>
<td>49</td>
</tr>
<tr>
<td>Females 13-21yrs</td>
<td>49</td>
</tr>
<tr>
<td>Males 13-21yrs</td>
<td>60</td>
</tr>
</tbody>
</table>

**Table 3.2** Values of k in paediatric patients

The k values must be adjusted if the patient is malnourished, has short or amputated limbs, or gross musculoskeletal deformities which will limit the accuracy of the equation. For older children the GFR may be calculated by the “adult formula” using the equation of Cockcroft and Gault. Laboratory methods of measuring creatinine
vary from hospital to hospital therefore the local laboratory should be contacted to confirm if any adaptation to the \( k \) values are required.

The Counahan formula can also be used to estimate the GFR in children[6]

\[
\text{GFR (ml/min/1.73m\(^2\))} = \frac{38 \times \text{length (in cm)}}{\text{serum creatinine micromole/L}}
\]

5. Pathology of common diseases  (See case study in renal disease)

5.1 Acute renal failure in ICU

Acute renal failure (ARF), also called acute kidney injury (AKI), is defined as a sudden renal impairment with electrolyte, acid-base and fluid derangements. Classically the criteria include oliguria, an increase in both urea and creatinine and increases in potassium and phosphate serum levels. Oliguria is defined as a urine output of less than 1 ml/kg/hour in infants, 0.5 ml/kg/hour in children and 400 ml/day in adolescents. ARF can occur with normal urine flow. Because of lack of a standard definition for acute renal failure, RIFLE, an international consensus classification, was devised. See Table 3.3

<table>
<thead>
<tr>
<th>Risk</th>
<th>( \downarrow \text{GFR} &gt; 25% ) Or serum creatinine ( \uparrow ) 1.5 times</th>
<th>Urine output (&lt;0.5 \text{ ml/kg/hour for 6 hours} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injury</td>
<td>( \downarrow \text{GFR} &gt; 50% ) Or serum creatinine ( \uparrow ) 2 times</td>
<td>Urine output (&lt;0.5 \text{ ml/kg/hour for 12 hours} )</td>
</tr>
<tr>
<td>Failure</td>
<td>( \downarrow \text{GFR} &gt; 75% ) Or serum creatinine ( \uparrow ) 3 times</td>
<td>Urine output (&lt;0.3 \text{ ml/kg/hour for 24 hours or nil for 12 hours} )</td>
</tr>
<tr>
<td>Loss</td>
<td>Failure for more than 4 weeks</td>
<td></td>
</tr>
<tr>
<td>End Renal Failure (ESRF)</td>
<td>Stage Failure for more than 3 months</td>
<td></td>
</tr>
</tbody>
</table>

Table 3.3 RIFLE multilevel classification for renal failure

The causes of ARF can be divided into three main categories, pre-renal, intra-renal and post renal.

Pre-renal failure occurs when the renal perfusion pressure falls below the autoregulatory threshold needed to maintain normal GFR. Common causes in the ICU are hypovolaemia, hypotension, poor cardiac output or excess vasodilatation. Renal perfusion can be improved by appropriate fluid replacement or by improving the haemodynamics of the patient.

Anatomical causes can be local problems affecting renal perfusion e.g. renal artery stenosis. In pre-renal failure the urine is usually concentrated and the urinary sodium content low. Pre-renal failure due to hepato-renal syndrome can only be managed by treating the failing liver. This will be covered in more detail in the hepatology section.
Abdominal compartment syndrome can be a common cause and should be considered where there is oliguria. The accumulation of blood, gut oedema or ascities can decrease renal blood flow. 

**Intra-renal** can originate from either the glomerular regions or the tubule-interstitial areas. Acute glomerulonephritis can be caused by a number of factors. Tubular/interstitial damage can be caused by nephrotoxins or ischaemia, which lead to acute tubular necrosis. In intra-renal failure the urine is isotonic with high sodium content, and if the glomerulus is involved the urine can contain sediment e.g. fragmented blood cells.

**Post-renal** failure can be caused by obstruction from either the intraluminal or extraluminal areas between the collecting ducts and the urethra. Where anuria is seen, obstruction should be assumed until otherwise proved e.g. blocked catheter. Post renal causes usually require surgical intervention.

**Immediate management of ARF includes:**

- Improving the patient’s haemodynamics and oxygen supply
- Checking for urinary tract obstruction
- Diagnosis/ treating underlying cause
- Medication review- as cause/ dosing/ pharmacodynamic effect
- Correcting any metabolic acidosis
- Use of diuretics
- Consideration for renal replacement therapy in order to correct hyperkalaemia, fluid overload, acidaemia or uraemia (above 35 mmol/L)

Rhabdomyolysis can precipitate acute renal failure through either intra-renal or post-renal causes. Excess myoglobin can precipitate in the glomerular filtrate causing renal tubular obstruction or direct nephrotoxicity to the renal parenchyma. Among the causes of rhabdomyolysis are major trauma, prolonged seizures and infections e.g. necrotizing fasciitis.

### 5.2 Hydronephrosis

Hydronephrosis is the distension and dilation of the renal pelvis and calyces usually caused by obstruction of the free flow of urine from the kidney or due to vesicoureteral reflux (VUR). With VUR the urine abnormally flows backwards from the bladder into the ureters. Increased ureteral pressure results in pyelovenous and pyelolymphatic backflow, leading to dilation within the intra-renal collecting system, which is limited by the surrounding renal parenchyma. Untreated it can lead to sepsis, hypertension and loss of renal function due to atrophy of the kidney.

It can present pre-natally as a finding on ultrasound or may present in the post-natal period or later in life depending on the cause. Urinalysis is used to detect infection or haematuria which may indicate a kidney stone or tumour as the cause. White cell count (WCC) may indicate an infection, and increases in urea, creatinine and potassium may necessitate more urgent treatment. Ultrasound imaging can determine the presence, source and duration of the obstruction (by revealing the extent of dilation).
Treatment
Obstructions are usually treated surgically unless the cause of the obstruction is uric acid stones which can be treated using oral bicarbonate to promote urine alkalisation. Steroids are the mainstay of therapy if retroperitoneal fibrosis is the cause of the blockage.
Surgical management includes placement of urethral stents or insertion of a nephrostomy tube. If the cause is a multicystic kidney, this will be removed, leaving the normal functioning kidney in place.

Complications
Following removal of the obstruction some patients can experience polyuria, more usually in cases of chronic hydronephrosis, bilateral obstruction or considerable dilation of the urinary tract. These patients usually present with hypertension, oedema, congestive heart failure, weight gain and increase serum urea. The diuresis which can last for days (to months in rare cases) can lead to severe volume depletion, hypokalemia, hypophosphataemia, hypocalcaemia and hypomagnesaemia. The treatment is strict fluid balance management, including urine and blood electrolyte monitoring and electrolyte replacement.

5.3 Polycystic Kidney Disease
Polycystic kidney disease (PKD) is a genetic disorder which can be autosomal dominant or recessive, and is characterised by a number of cysts in both kidneys. The disease presents as renal dysfunction, hypertension, or pain in the retroperitoneal area. Other organs such as the liver and pancreas can be affected.
Bilateral progressive dilation of the renal tract by the cysts leads to end stage renal failure. Renal cysts form and enlarge by three processes:
- tubular cell hyperplasia,
- tubular fluid secretion by the proliferated cells
- interstitial inflammation and fibrosis caused by abnormalities in the tubular extracellular matrix.

Signs and symptoms
- Reduced ability to concentrate urine
- Microalbuminuria or haematuria
- Potter facies (low set, flattened ears, short snubbed nose, deep eye creases and micrognathia- Figure 3.6) and abnormal extremities (club footing) can be seen in newborns- due to oligohydraminos.
- Pulmonary hypoplasia is sometimes seen in neonates.
- Abdominal masses or distension may be the presenting signs in older children.
- Recurring urinary tract infections and renal dysfunction e.g. impairment or concentrating defects presenting as polydipsia or polyuria.
- Hypertension with normal renin levels.
- Cardiovascular and hepatic signs may be seen if these organs are affected.
- Ultrasound imaging (pre-natal or during neonatal period) may show echogenic and enlarged kidneys, poor corticomедullary differentiation, and a small or absent bladder.
- In utero, maternal alpha-feto protein is increased.
Treatment

Pharmacotherapy is used to treat the symptoms of the disease, not the condition itself, and can limit its progression. Hypertension requires aggressive treatment with angiotensin converting enzyme (ACE) inhibitors as first choice, followed by calcium channel blockers, beta-blockers and diuretics. Urinary tract infections (UTIs) should be treated. Nephrectomy, unilateral or bilateral, may be required if there is respiratory compromise in the younger child because of the large mass in the abdomen. Concentrating defects should be corrected if present and most infants will require bicarbonate to treat metabolic acidosis. Once ESRF is reached dialysis or renal transplantation are the only options, however if there is hepatic involvement the liver transplant may also be required.

5.4 Renal tubular acidosis

Renal tubular acidosis (RTA) is a condition in which the kidney cannot maintain homeostasis because of impairment of hydrogen ion excretion or bicarbonate ion reabsorption. This can be due to several different derangements of tubular acid transport in the nephron. It is characterised by a normal anion gap with hyperchloraemic metabolic acidosis. RTA is divided into proximal (PRTA-type 2) or distal (DRTA-type 1) tubule defects.

The proximal tubule is the main site of bicarbonate reabsorption and defects will lead to a high urinary bicarbonate loss because of limited bicarbonate re-absorptive capacity in the distal tubule. Hydrogen ions are secreted in the distal tubule and acidosis will result from impairment of this mechanism. PRTA can be due to either a generalised or an isolated transporter e.g. for glucose, whereas DTRA is usually isolated.

The aetiologies of RTA include Fanconi’s syndrome, hyperparathyroidism, some inherited metabolic disorders e.g. Leigh’s, and various drugs, including valproic acid and some chemotherapeutic agents such as cisplatin. The patient may present to PICU requiring correction of severe electrolyte disturbances.
Proximal renal tubular acidosis (PRTA) – Type 2

Because in PRTA there is impairment in bicarbonate reabsorption, urinary bicarbonate wasting is seen with a metabolic acidosis. Bicarbonate can be given as diagnostic tool because it increases the fractional bicarbonate excretion.

\[
\text{Fractional HCO}_3\text{ excretion} = \frac{\text{Urinary HCO}_3 \times \text{plasma Creatinine} \times 100}{\text{Plasma HCO}_3 \times \text{urinary creatinine}}
\]

Potassium wasting is seen because of an increase in aldosterone levels. As the distal acidification process is not affected, the urinary pH can be lowered and ammonium can be produced for excretion.

**Signs and symptoms**
- Failure to thrive, poor growth and vomiting
- Low blood pH, low blood bicarbonate, hypokalaemia
- Urinary pH > 7 with normal blood bicarbonate or urine pH <5.5 with low plasma bicarbonate.
- Some urinary loss of glucose, uric acid, phosphate, amino acid

**Management**
Bicarbonate, lactate or citrate supplements are given in doses ranging between 2 and 20 mmol/kg/day. The variable doses are required because when the plasma bicarbonate is increased and exceeds the renal threshold, the urinary bicarbonate loss increases and therefore only partial correction is possible.

Distal Tubular renal acidosis (DTRA) – Type 1

In DTRA the urinary pH cannot be decreased because there is a lack of hydrogen ion secretion or titratable acid excretion, and as a result ammonium cannot be formed and therefore excreted. Mechanisms for bicarbonate reabsorption are not impaired but as the urinary pH increases some bicarbonate escapes reabsorption. As the patient is always acidotic, metabolic bone disease accompanies DTRA.

**Signs and symptoms**
- Failure to thrive, poor growth, vomiting
- Bone disease
- Increased urinary calcium, nephrocalcinosis
- Hypokalaemia
- Polyuria and polydipsia
- Renal colic.

**Management**
Correction of acidaemia is mainly to prevent bone demineralisation and lower doses of alkali supplementation are required (1-2mmol/kg) than those used in PRTA. Potassium correction is required before correcting the acidosis because of the drop in potassium due to the bicarbonate.
DRTA (type 4) can be caused by a lack of response to aldosterone. Aldosterone is responsible for controlling sodium reabsorption in exchange for potassium and hydrogen. In DRTA type 4 hyperkalaemia, reduced ammonium production and reduced hydrogen ion secretion occurs. Plasma bicarbonate tends to be low to normal and the urine pH is normal. Treatment includes giving mineralocorticoids and/or loop diuretics.

5.5 Glomerulonephritis

Glomerulonephritis is caused by immunological mechanisms which lead to inflammation and proliferation of the glomerular areas resulting in membrane damage. Kidneys appear enlarged, the glomerular tufts swollen and infiltrated with polymorphonucleocytes. It tends to be seen in children aged 5-15 years old, but not exclusively, and is usually preceded, by up to 3 weeks, by an infection, often streptococcal.

Signs and symptoms
- Sudden onset of haematuria, proteinuria and red blood cell casts in urine which may appear dark
- Back pain, weakness, fever
- Oliguria and renal impairment
- Hypertension and oedema
- Erythrocyte sedimentation rate (ESR) is raised

Depending on the underlying cause other signs and symptoms can be seen.
- **Wegners granulomatosis**
  - sinusitis, pulmonary infiltrates and nephritis
- **Henoch-Schonlein purpura**
  - nausea and vomiting, abdominal pain and purpura
- **Goodpastures**
  - haemoptysis
- **Systemic lupus erythematosus (SLE) and vasculitis**
  - skin rashes or hypersensitivity type picture

A renal biopsy should be undertaken to enable diagnosis of the primary renal disease.

Management

Immediate correction of electrolytes, fluid balance and acidosis is required and any underlying infection treated with antibiotics. Hypertensive encephalitis should be treated urgently with IV labetalol or hydralazine. ACE inhibitors and calcium channel blockers can be given orally but ACE inhibitors carry an increased risk of hyperkalaemia. Intravenous Nicardipine can be considered if patient cannot take drugs orally, however it is not readily available in many UK hospitals as it does not have a UK market authorisation. Furosemide should be considered with patients with high urinary protein loses. Steroids and other immunosuppressants may be required in non-streptococcal causes of glomerulonephritis. Renal replacement therapy should be considered.
Complications
Acute glomerulonephritis results in ESRF for up to 2% of patients with a requirement for long term dialysis/listing for renal transplantation. Other end organ damage, e.g. retinopathy, nephrotic syndrome, can occur following encephalopathy, pulmonary oedema and hypertension.

5.6 Haemolytic Uraemic Syndrome
Haemolytic Uraemic Syndrome (HUS) is the most common cause of ARF in children, primarily in infancy and early childhood, presenting mostly between 6 months and 4 years.
The condition is characterised by microangiopathic haemolytic anaemia, thrombocytopenia and ARF. Usually there are precipitating factors of diarrhoea (90%) or upper respiratory infections (10%). The use of anti-motility drugs to reduce diarrhoea is associated with an increased risk of causing HUS. The most common cause is the E.coli toxin, but other common pathogens associated are Shigella, Salmonella, Campylobacter, Varicella, Coxsackie and Strep. pneumonia. Over 85% of children will recover with good supportive care.

Signs and symptoms
- Bloody stools, blood/albumin/casts and white blood cells in the urine
- Neurological symptoms including seizures
- Hypertension
- Petechiae
- Cardiac failure
- Ocular involvement
- Oliguria
- Red blood cells appear fragmented, deformed and irregular

Management
The immediate management requires strict fluid balance, treatment of hyperkalemia and control of blood pressure. Daily plasma exchange should be considered and either haemofiltration or intermittent haemodialysis.

6. Blood pressure management in renal impairment
Increased blood pressure can be a cause of renal impairment or the result of renal failure. Many renal conditions lead to hypertension e.g. glomerularnephritis, obstructive uropathy, renovascular disease and haemolytic uraemic syndrome.
The hypertension can be secondary to volume overload or to the drugs used to treat the underlying condition. Increased blood pressure becomes an emergency where organ damage is imminent. Patients may present in PICU with hypertensive encephalopathy and neurological signs and symptoms, however cardiac failure maybe the first sign in the younger child.
The cause and level of renal function will determine treatment, for example, renin dependent blood pressure will respond to ACE inhibitors, whereas catecholamine influenced blood pressure should be treated with alpha or beta blockers.
Reducing the blood pressure should be managed with care; a large, sharp drop in blood pressure results in increased risk of ischaemic damage to the brain. It is recommended that the aim of the blood pressure drop is to decrease by a third of the
difference between the normal values for that age and the acute value. Therefore shorter acting, titratable agents should be used initially and after a few days longer acting drugs can be introduced. See Table 3.4
Caution is needed to avoid hypotension as this will decrease renal perfusion and stimulate the renin-angiotensin-aldosterone system.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose range</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifedipine orally/sublingual</td>
<td>0.25-0.5mg/kg/dose (max 10 mg)</td>
<td>Risk tachycardias</td>
</tr>
<tr>
<td>Labetalol IV</td>
<td>1-3 mg/kg/hour</td>
<td></td>
</tr>
<tr>
<td>Hydralazine IV</td>
<td>0.1-0.2 mg/kg/dose up to 4 hourly (max 20mg)</td>
<td>Care in SLE type syndromes</td>
</tr>
<tr>
<td>Sodium nitroprusside</td>
<td>0.5-5 microgram/kg/min</td>
<td>Risk of accumulation of thiocyanate</td>
</tr>
<tr>
<td>Glyceryl trinitrate IV</td>
<td>0.1-10 microgram/kg/min</td>
<td>Large volumes to infuse</td>
</tr>
<tr>
<td>Nicardipine IV</td>
<td>0.5-2 microgram/kg/min</td>
<td>Unlicensed in UK</td>
</tr>
</tbody>
</table>

Table 3.4 “Titratable” antihypertensive agents. Further information and details of administration are available in the BNF-C. [7]

7. Diuretics

Diuretics are used to decrease the extracellular fluid volume by increasing urine output as a result of inhibiting tubular reabsorption of sodium and water in the kidney. As a group they either have direct action on the cells of the nephron or indirectly modify the content of the filtrate.

There are several groups of diuretics used in critical care including
- Furosemide
- Thiazides and metolazone
- Potassium sparing diuretics
- Mannitol
- Acetazolamide/ carbonic anhydrase inhibitors

The sites of action of each of these groups are important for understanding the different affects of using them. See Figure 3.7
7.1 Furosemide

Furosemide is one of the loop diuretics and binds at one of the chloride binding sites of the Na/K/2Cl carrier, thereby inhibiting the reabsorption of sodium and chloride in the thick ascending loop of Henle. As potassium and calcium and magnesium are also reabsorbed in this area, these solutes have decreased reabsorptive capacity.

The thick ascending loop reabsorbs sodium, chloride, calcium, magnesium and potassium but it has low permeability to water. The fluid, therefore, in the end of this loop is hypotonic, whilst the reabsorption of the solutes leads to a hypertonic interstitium. This hypertonic reabsorption allows the kidney to excrete concentrated urine via the counter current system which leads to water reabsorption in the collecting ducts. By inhibiting the reabsorption of sodium and chloride the loop diuretics reduce the tonicity of the interstitium and therefore inhibit this reabsorption of water.

The reabsorption process uses the Na/K-ATPase pump in the membrane and, additionally, sodium uptake across the membrane occurs via the Na/K/2Cl- carrier cotransporter system. Potassium is almost completely taken out of the tubule but is recycled across the same membrane with chloride ions via the chloride channels. As the lumen potential becomes more positive, there is a flux of sodium out of the tubule via the paracellular route. As a result

6 chloride ions move across
3 sodium ions removed via the Na/K-ATPase pump
3 sodium ions by paracellular pathway

Furosemide binds to one of the chloride binding sites of the Na/K/2Cl carrier, inhibiting sodium chloride reabsorption here. In addition to this the potential gradient is decreased as there is a decrease in cation (including calcium and magnesium) transport out of the tubule. By preventing reabsorption the hypertonicity of the renal medulla is decreased, and water is excreted.
Furosemide has the added benefit of more solute being delivered to the distal tubule, which is permeable to water. The increased osmotic gradient in the tubule prevents any further water reabsorption. Metabolic alkalosis occurs when the increase in sodium in the distal tubule stimulates aldosterone release and as a result hydrogen ions are exchanged and secreted. If volume loss is not replaced by adequate repletion, renin is released leading to vasoconstriction, decrease renal blood flow and a drop in the GFR. Volume contraction also prevents urate secretion and the result is an increase in serum uric acid. Furosemide works when the GFR is reduced as it is protein bound and is secreted into the proximal tubule by the organic acid transporter mechanism. See Figure 3.8

![Figure 3.8 Mechanism of action of thiazide and loop diuretics](image)

### 7.2 Thiazides and metolazone

The thiazides and metolazone act on the distal tubule and decrease active reabsorption of sodium and accompanying chloride by binding to the electro-neutral Na/Cl co-transporter system and inhibiting the process. Increases in sodium concentration in the collecting duct stimulate aldosterone release, which in turn increases potassium excretion by exchange with sodium and increased luminal permeability to potassium. As chloride reabsorption is decreased, hypochloraemic alkalosis is seen. See Table 3.8

Metolazone has the ability to inhibit reabsorption of sodium in the proximal tubule in addition to the distal section. By the blocking of proximal tubular reabsorption of
sodium and maintenance of substrate delivery to the loop of Henle, metolazone enhances loop diuretic effects.

7.3 Potassium sparing diuretics

The most widely used potassium sparing diuretics are amiloride and spironolactone but these act in slightly different ways. Amiloride works by blocking the sodium selective channels in the late distal tubule and the collecting duct. Only a small amount of sodium is reclaimed in the collecting ducts and sodium entry is paralleled by potassium exit in the process so that the extent of sodium reabsorption determines the potassium secretion. By blocking the sodium reabsorption at these sodium channels amiloride promotes potassium conservation. Spironolactone is an aldosterone antagonist. Aldosterone is a mineralocorticoid which enhances the sodium pump, sodium-hydrogen transporter activity and membrane potassium permeability in the distal tubule. By antagonising aldosterone, spironolactone inhibits potassium secretion, sodium is lost and a diuresis ensues.

7.4 Mannitol

Mannitol acts as an osmotic diuretic. The driving force of an osmotic gradient, created by solute transport across the membrane, causes water movement through the water channels i.e. renal tubular water reabsorption. Mannitol is freely filtered at the glomerulus but is not reabsorbed and increases the osmotic pressure of the tubular fluid. Mannitol, therefore, decreases the osmotic gradient and the reabsorption of water and the luminal Na\(^+\) concentration. The lack of chemical gradient decreases sodium reabsorption and it is lost along with the water. Mannitol diuresis causes a vasodilatation due to the release of prostaglandin and atrial natriuretic peptide. This vasodilatation causes a reduction in the renal medullary hypertonicity by increasing the medullary blood flow, leading to a further breakdown of the osmotic gradient during the water reabsorption in collecting ducts.

7.5 Carbonic anhydrase inhibitors

The most commonly used carbonic anhydrase inhibitor is acetazolamide. They are rarely used for their diuretic actions but are used to correct alkalosis caused by excessive hydrogen loss by other diuretics. Sodium and bicarbonate are reabsorbed, and hydrogen ions secreted, at the luminal surface in the proximal tubule by an antiport mechanism. The bicarbonate is not transported directly but joins with the hydrogen ions to form carbonic acid (H\(_2\)CO\(_3\)), which dissociates to carbon dioxide and water through the enzymatic action of carbonic anhydrase. The carbon dioxide and water diffuse into the tubule cells and recombine to give carbonic acid which breaks down to H\(^+\) ions, which are secreted back into the lumen in exchange for Na\(^+\), and HCO\(_3^-\) which is reabsorbed into the interstitial space. Carbonic anhydrase inhibitors prevent this dissociation/association step and hence bicarbonate is not reabsorbed here.
7.6 Aminophylline

Aminophylline is a methylxantine derivative that is used to promote diuresis in the critically ill. The mechanism of action is postulated to be that as a result of competitively antagonising adenosine-induced preglomerular vasoconstriction, the intrarenal adenosine levels drop which improves the glomerular filtration rate.

8. Renal Replacement Therapy

Renal replacement therapy (RRT) is used for a number of renal and non-renal indications in PICU. These commonly include: persistent hyperkalaemia, fluid overload resistant to diuretics, acidosis, hyperammonaemia, severe hyperuricaemia, tumour lysis, removal of drugs/toxins and to allow space for nutrition. The mode of RRT depends on both patient and unit factors. The commonly seen RRT modes are

- Haemofiltration
- Peritoneal dialysis
- Intermittent Haemodialysis

8.1 Haemofiltration

Haemofiltration is a technique widely used in ICU for the treatment of acute renal failure. It is also used commonly to treat sepsis, acidaemia, and high ammonia in metabolic disorders.

There are two methods; continuous venovenous haemofiltration (CVVH) and continuous arteriovenous haemofiltration (CAVH). CVVH requires a pump whereas CAVH relies on the patient’s perfusion pressure and is therefore difficult to perform in hypotensive patients. CVVH is more commonly used.

Blood passes through an extracorporeal circuit which contains a highly permeable membrane, the haemofilter. Blood under pressure is pumped along the side of the haemofilter and water and solutes pass across the filter by connective flow (as in glomerular filtration). Larger molecules are cleared out at the same rate as smaller molecules.

The removed fluid and solutes from the blood, the filtrate, is discarded and replaced by a crystalloid solution, with electrolytes at physiological levels e.g. sodium 130-140 mmol/L, glucose 5.5 mmol/L, calcium 1.5 mmol/L. The solution is phosphate free and can be potassium free. Most solutions tend to be buffered by bicarbonate rather than lactate. Lactate can be used but when the patient has a lactate acidosis the lactate load, coupled with the bicarbonate removal by the filter, results in further acidosis and an increase in lactate. The rate this fluid is replaced is referred to as the ultrafiltration rate (UFR) or commonly as the ‘turnover’.

If the patient does not need to lose water the filtrate is replaced with the crystalloid solution on a “ml by ml” basis to maintain an “equal balance”. If the patient is fluid overloaded, the crystalloid replacement fluid is replaced at a lower rate than the filtrate so the patient will be ‘running negative at x ml/hour’. Fluid removal is usually kept between 0.5-2 ml/kg/hour. The ‘filtration fraction’ (FF), the fraction of plasma water removed by ultrafiltration, can be calculated from
FF% = \frac{UFR \times 100}{Qp}

\text{Qp} = \text{filter plasma flow rate which is equivalent to blood flow rate x (1-haemocrit level)}

As haemofiltration leads to an increase in the concentration of red blood cells and plasma proteins in the blood in the circuit, there is an increase in the viscosity of the blood with increase in haematocrit and high colloid pressure. As a result the filtration rate, or rate of crystalloid replacement, needs to be greater than 30% of the blood flow. Low blood flow via the circuit is associated with an increase in clotting in the circuit which therefore usually requires anticoagulation although this may not be necessary in very coagulopathic patients. The aim is to anticoagulate the circuit without anticoagulating the patient.

There are several methods used to achieve anticoagulation:

- **Heparin** - an initial bolus of 50 units/kg followed by a continuous infusion in the region of 0-30 units/kg/hour. The aim being to keep the ACT between 120-180 seconds or the aPPT 1.2 to 1.5 normal values.
- **Epoprostenol** can be used if there are contraindications to heparin. The dose is usually in the region of 2-10 nanograms/kg/min
- **Citrate** has been used. The rate is usually 1-2 times the blood flow in \text{ml/\text{min}} but the citrate running in \text{ml/\text{hour}}. Citrate chelates ionised calcium which is required for the clotting cascade, and as a result calcium has to be replaced centrally, post circuit, to avoid systemic anticoagulation.
- Giving the replacement solution pre-filter can improve the rate of clotting in the circuit. However this does decrease the efficiency of the filtration.

Further detail on anticoagulation will be discussed in the haematology section (section 10)

The blood flow for children can be calculated by using 10% of the circulating volume or in the region of 2-6 \text{ml/kg/min}. The circuit requires priming with blood or human albumin in small children, but the dilution is less of a problem in larger children and sodium chloride 0.9% can be used.

**Advantages**

- Controlled with rapid electrolyte and fluid correction
- Good solute clearance
- Corrects acid-base abnormalities
- Achieves reliable and controllable ultrafiltration/ fluid balance
- Causes less haemodynamic instability than Haemodialysis (HD)
- Can be used in neonates

**Disadvantages**

- Anticoagulation required for duration of CVVH
- Filter clotting causing loss of blood volume in the circuit
- Hypotension more likely in smaller patients
Task 3.1
Look at a haemofiltration machine being set-up on your ward. Consider the fluids that are stocked and the methods of anticoagulation used on the unit.

8.2 Acute peritoneal dialysis

Peritoneal dialysis (PD) involves the exchange of water and solutes between the peritoneal membrane capillary blood vessels and the dialysate solution in the peritoneal cavity. The peritoneal membrane surrounds all the loops of the bowel forming a large surface area and space. The area of the membrane is directly proportional to body surface area. In children high transfer rate of solutes and fluid is seen because of the increased surface area in children.

The permeability of a solute across the peritoneal membrane is determined mainly by charge and size. Highly charged solutes e.g. phosphate are less permeable than the less charged e.g. potassium. The smaller and lower molecular weight, the more permeable the substance will be. Small solutes have a biphasic transfer rate i.e. high in the early part of cycle and lower in the later. Conversely larger molecules have a lower but more uniform transfer throughout the cycle. Therefore removal of small molecules such as potassium and urea is more efficient in shorter and frequent cycles. Dialysis fluid/dialysate solutions are commercially available but vary slightly in their composition. Recently there has been increased interest in using the bicarbonate base as a buffer for PD fluids, for reasons similar to haemofiltration solutions. (See Table 3.5)

<table>
<thead>
<tr>
<th>Sodium</th>
<th>132 mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>0</td>
</tr>
<tr>
<td>Calcium</td>
<td>1.2 - 1.7 mmol/L</td>
</tr>
<tr>
<td>Magnesium</td>
<td>0.2 mmol/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>102 mmol/L</td>
</tr>
<tr>
<td>Lactate or Bicarbonate</td>
<td>35 – 40 mmol/L</td>
</tr>
<tr>
<td>Glucose</td>
<td>1.3%, 2.5% or 4.2%</td>
</tr>
</tbody>
</table>

Table 3.5 Typical Dialysate Composition

Ultrafiltration is achieved by the use of glucose as an osmotic agent in the dialysate. The lowest glucose concentration should be used and increased in a stepwise fashion, until the required UFR is reached without being painful or detrimental to the patient. The initial dialysate volume is usually 10 ml/kg, increasing as required to a maximum of 40-50 ml/kg.

In PICU the prescription is likely to vary with each patient depending on the clinical indications for PD and the patient’s condition. See Table 3.6

<table>
<thead>
<tr>
<th>Aim/Result</th>
<th>Potential indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short cycle/dwell times Removal of small molecules</td>
<td>Hyperkalaemia</td>
</tr>
<tr>
<td>Increasing glucose concentrations Removal of fluid/increased UFR</td>
<td>Hyperammonaemia</td>
</tr>
</tbody>
</table>

Table 3.6 Peritoneal dialysis
As there is less shift in circulatory volume in PD than in CVVH, it is more commonly seen in the post cardiac surgery patients or in the smaller neonates, where the blood volume to fill the extra corporeal circuits cause haemodynamic instability. Gastric pathology is a contra-indication to PD and high ventilatory support is a relative contra-indication as the pressures from the full abdomen may affect the movement of the diaphragm and decrease the vital capacity.

**Advantages**
- Suitable for neonates
- Does not cause haemodynamic instability
- Does not require anticoagulation
- Less specialised training required

**Disadvantages**
- Fluid and solute shifts slow
- Catheter obstruction/ drainage failure/ leakage
- Can cause respiratory compromise
- Can cause hyperglycaemia
- May become infected causing peritonitis
- Can be unreliable with regards to fluid balance/ ultrafiltration
- Not suitable for patient with abdominal problems or previous surgery

8.3 Intermittent haemodialysis

In intermittent haemodialysis (IHD) blood flows along one side of a semi permeable membrane, whilst a crystalloid solution is pumped in the opposite direction on the other side of the membrane. Small molecules diffuse across the membrane from an area of high concentration to a lower concentration e.g. urea is a small molecule not contained in the dialysis fluid and therefore will diffuse into the dialysate. The content of the dialysis fluids are designed/ selected depending on which molecules require removal. Rapid ultrafiltration is required as IHD removes fluid volume over several hours rather than in a continuous manner as with CVVH. This may result in cardiovascular instability and hypotension from intravascular depletion.

**Advantages**
- Maximum solute clearance
- Good potassium removal in hyperkalaemia
- Limited anticoagulation time
- Available in most units

**Disadvantages**
- Causes haemodynamic instability
- Causes hypoxemia
- Causes fluid and solute shifts
- Requires equipment/ haemodialysis machines
- Requires trained personnel
- Not suitable for neonates
- Drug administration times must be considered to optimise treatment
8.4 Haemodiafiltration

Haemodiafiltration (CVVHD) combines haemofiltration with a countercurrent flow of dialysate across the filter. By increasing the diffusion gradient solute clearance should rise to a rate proportional to the dialysate flow. In practice sufficient clearance can usually be achieved using CVVH so that CVVHD is not often required.

9. Plasmapheresis and plasma exchange

Whilst quite often interchanged in description, plasmapheresis and plasma exchange are slightly different techniques. They are used in PICU for removal of various toxins including drugs and sepsis mediators.

Plasmapheresis is a two step process. The first step involves the separation of the blood into two compartments by a centrifugal pump i.e. plasma and blood cells. The separated plasma then flows along a column that may contain different absorbent qualities, allowing the selective removal of components in the plasma. The processed plasma is then re-infused into the patient.

Plasma exchange also involves separating the blood components either by pump or filter; however the plasma is removed and replaced by a replacement solution. This solution can be donor plasma or fresh frozen plasma to ensure any substances required for homeostasis are maintained e.g. immunoglobulin and clotting factors, or the replacement can be a combination of fresh frozen plasma (FFP) and albumin.

In each plasma exchange between 40-60 ml/kg of plasma is removed, and approximately 63% of solutes removed from the plasma. As the plasma is removed, circulating drugs from the plasma compartment may be removed or adsorbed onto the column. As a general rule, drugs with a low volume of distribution and a high rate of protein binding are likely to be removed. In addition to drug removal the pharmacodynamic effects of the drug can be altered e.g. removal of auto-antibodies to cholinesterase will prolong the effect of anticholinesterase drugs such as neostigmine.

If a drug has a distribution phase, then this needs to be complete before commencing plasma exchange in order to ensure that drug/metabolite is not removed or pharmacokinetics altered.

Additional problems with plasmapheresis and plasma exchange are similar to other extracorporeal circuits; electrolyte disturbances, the potential drop in body temperature, and the volume of blood in the circuit causes instability to smaller children,

10. Drug Handling Considerations in Renal Dysfunction

10.1 Absorption

Gastrointestinal absorption can be decreased because;

- Salivary urea can be converted to ammonia in certain renal conditions, as a result the stomach pH is increased when the saliva is swallowed
- Gastroparesis is seen more often in uraemic patients
Small bowel absorption of drugs can be decreased in uraemic patients

Subcutaneous absorption can be decreased because;

- Occasionally local pH changes in certain renal conditions affect the acid-base balance.

10.2 Distribution

- An increase of volume of distribution (Vd) is seen in fluid overloaded patients, conversely the Vd is decreased in dehydrated patients
- Uraemia can decrease protein binding by altering the structure of the plasma proteins
- Hypoalbuminaemia seen in certain conditions will increase the fraction of unbound drug which may increase the clearance of a drug
- Acid-base imbalances can affect the ionisation/solubility of some drugs
- Fluctuating fluid status is seen in both acute and chronic renal patients

Drugs with a small volume of distribution may require a larger loading dose, if a loading dose is required.

10.3 Metabolism

- Certain renal conditions and uraemia can decrease hydrolysis reactions, causing either increased levels of an active drug or a delay in metabolising to an active metabolite.
- Concurrent drugs prescribed in renal conditions can induce or inhibit metabolism

10.4 Excretion

- With low GFR drugs, filtration will be decreased, leading to accumulation of the drug or metabolite
- Tubular secreted drugs will accumulate in Acute Tubular Necrosis (ATN) like conditions
- Decreased protein binding can decrease the amount of drugs that are secreted in the tubules
- The higher the proportion of a drug that is renally cleared, the longer the half life will become; the dosing interval will need to be extended or if a certain level is required the dose may require decreasing.

If drug dosing or choice is not altered the pharmacodynamic effects can lead to further problems for the PICU patient. The drug concentration at the receptor needs to be considered as it may be increased or decreased due to absorption changes or changes in free drug availability and the obvious decreased excretion may lead to accumulation.

The drug or metabolite can cause further damage to the kidney, and should be a key consideration where the renal injury is potentially reversible.

It is important to remember to readjust the dosing as the renal impairment improves in PICU; and consideration should be given if there is a lack of clinical response,
especially with antimicrobials, to whether the patient is being under-dosed. In these circumstances the adverse effects versus the benefits should be discussed with the PICU team.

11. Drug Dosing in Renal Replacement Therapy

Published literature should be consulted whenever possible; however in the paediatric setting this is often not available. In order to estimate the doses required, the method of continuous renal replacement therapy (CRRT) and patient factors need to be looked if other data is not available.

Drug factors to consider include:

- Molecular weight
  Haemodialysis removes <500 daltons, where as in CVVH molecules between 20-30,000 daltons may be removed.
- Protein binding
  Only the unbound drug will be removed, therefore highly protein drugs have a lower clearance- see below under patient factors.
- Charge
  The anionic protein on the blood side of filter/membrane exerts forces on certain cations; therefore even if small and unbound they may not be removed
- Volume of distribution (Vd)
  Drugs with a Vd above 0.7l/kg are less likely to be removed, as they are likely to be lipophilic and/or tissue bound.
- Renal clearance of the drug
  If the drug is less than 25% renally cleared then removal/ accumulation by CRRT is considered clinically insignificant.

Factors relating to method of CRRT include:

- Filter composition
  Different filters may have differing sieving co-efficiency of a drug. This information should be sought by the filter company.
- Filter pore size
  The larger the pore size the larger the molecular size that may be removed
- Filter size
  The larger the surface area the greater the removal. Whilst most paediatric units may use the smaller paediatric filter, in shared adult/paediatric units an adult filter may be used with a larger surface area.
- Ultrafiltration rate
  In CVVH clearance of unbound drugs equals the ultrafiltration rate.
- Blood flow
  The higher the blood flow rate the better the clearance by diffusion

Patient factors include:

Protein binding will be affected by acid-base imbalances, concurrent renal impairment or hepatic impairment, low albumin, altered 1-glycoprotein levels and other drugs being used that have a higher affinity for protein binding and that may be displaced
It should be noted that data for intermittent haemodialysis cannot always be extrapolated i.e. if a drug is dialysed it should not be assumed that a drug is removed by haemofiltration.

There are some general points to consider in drug dosing in CVVH when no pharmacokinetic studies are available to guide dosing. See Table 3.7

- Where possible the sieving coefficient should be used to approximate removal of the drug. Where this is not available the percentage protein binding can be used.
- Only non-protein bound drugs can be removed. Note: critically ill patients may have lower albumin levels, but may have higher α 1-glycoproteins.
- Solute removal is achieved by convection through the membrane by the force of water (solvent drag). The greater the solvent drag the greater the removal of molecules.
- Post dilution produces a greater solvent drag and therefore greater removal of molecules.
- Inotropes, sedation/analgesia etc. should be titrated according to clinical effect.
- If the indication for CVVH is acute renal impairment, further dose adjustments may be required when stopping CVVH depending on the degree of renal impairment.

More detail on the pharmacokinetics of drugs in renal replacement therapy is available in Clinical Pharmacokinetics.[8]

<table>
<thead>
<tr>
<th>Drug factors favouring removal by CVVH</th>
<th>CVVH factors favouring drug removal</th>
</tr>
</thead>
<tbody>
<tr>
<td>High % renal eliminated</td>
<td>Synthetic membranes</td>
</tr>
<tr>
<td>Low protein binding</td>
<td>Large membrane surface area</td>
</tr>
<tr>
<td>Low volume of distribution</td>
<td>High ultrafiltration rate</td>
</tr>
<tr>
<td>Molecular weight less than 1500 daltons</td>
<td>Postdilution</td>
</tr>
<tr>
<td>Anions</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient factors that may affect drug removal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver impairment</td>
</tr>
<tr>
<td>Low albumin</td>
</tr>
<tr>
<td>Fluid overload/ potentially larger volume distribution</td>
</tr>
<tr>
<td>Derranged acid/base status</td>
</tr>
</tbody>
</table>

Table 3.7 Factors affecting drug removal in CVVH

References

1. Kesby J, Lumbers E. Factors affecting renal handling of sodium, hydrogen ions and bicarbonate by the fetus. American Journal of Physiology. 251; F226-231


Further reading


Forni L, Hilton P. Continuous haemofiltration in the treatment of acute renal failure. NEJM 1997; 336(18): 1303-1309


Kesby J, Lumbers E. Factors affecting renal handling of sodium, hydrogen ions and bicarbonate by the fetus. American Journal of Physiology. 251; F226-231


UKMI, What factors need to be considered when dosing patients on renal replacement therapies? UKMI Q&A  13.10 2008

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      2.2.1 Neonatal physiology

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Bibliography

References
Objectives

- To understand the effect of maturity on liver function
- To understand the monitoring and treatment of raised bilirubin in the neonatal period
- To understand and monitor liver function/dysfunction (acute or chronic)
- To understand the effect of drugs on liver function
- To understand the effect of different types of liver failure on drug clearance
1. Introduction

The term liver disease is often widely used but poorly understood. There is an enormous range of liver diseases that can affect children - some will have no impact on liver function whilst others may cause anything from mild liver impairment to acute liver failure. What is important for a pharmacist is to understand what impact this may have on the management of the child’s drug therapy - should drugs be stopped, doses changed or treatments started. The key information for a pharmacist looking after a child with a liver problem is to establish the cause of liver dysfunction or what liver disease the child has (if any) and, more importantly, what degree of liver dysfunction they have (if any).

In the PICU setting liver dysfunction can occur for a range of reasons: the child may have presented with acute liver failure, they may have developed liver impairment secondary to multi-organ failure or hypoxia, they may have deranged liver function tests because of drug therapy or they may have an underlying liver disease and be admitted for some other reason. The value of knowing the cause of liver dysfunction is that it helps identify the likely course the child will follow - raised transaminases caused by ischaemia secondary to a prolonged epileptic seizure will probably fall without intervention in a few days with no sequelae although the rise and fall of bilirubin may lag by a few days. However a child with normal transaminases, but underlying cirrhosis and a coagulopathy is likely to get steadily worse and need a liver transplant.

To establish the degree of liver dysfunction three things must be considered along with the cause: the liver function tests (including albumin and clotting), any signs and symptoms of liver dysfunction (such as hepatomegaly, encephalopathy, ascites), and other investigations where available (e.g. ultrasounds, liver biopsy). No one feature can be used in isolation as none give a complete picture. Gathering all this information enables the pharmacist to develop a pharmaceutical care plan.

The following sections provide some background information about liver function and monitoring, and cover some of the common liver conditions seen in children in PICU. The cases illustrate some of these issues. Further reading should include Drugs and the Liver for a fuller understanding of how to adjust doses in patients with liver dysfunction.

2. Anatomy and physiology in children and adolescents

2.1 Anatomy

The liver begins to develop early in foetal life and if it doesn’t develop normally the foetus is unlikely to remain viable, consequently there are almost no congenital structural abnormalities seen at birth. The liver accounts for a high percentage of body weight in the newborn compared to an adult - 5% vs 2%. This large size may reflect the role of the foetal liver in haematopoiesis or may be to provide a greater liver mass available for metabolism of endogenous substances.
The liver is arbitrarily divided into a left and right lobe (not an actual physical divide but everything goes to or leaves each lobe). It receives its blood supply from the hepatic artery (25%, oxygenated) and the portal vein (75%, nutrient rich). The portal vein drains from the spleen, gut and mesentery and contains nutrients (and drugs) absorbed from the stomach and small bowel which are then ‘processed’ by the liver. In terms of drugs this is first pass metabolism. Blood leaves the liver via the hepatic vein and joins the inferior vena cava back to the heart. (See Figure 4.1)

![Figure 4.1 Liver showing the portal vein coming from the spleen, gut and mesentery](image)

The biliary system is like a tree with the trunk (common bile duct) outside the liver draining into the duodenum and splitting just before it enters the liver so that it drains from the left and right lobes. Within the liver the biliary tree further divides into tiny bile ducts and canaliculi that reach throughout the liver. They lie next to hepatocytes and drain the waste products of metabolism as bile into the gut to be excreted in faeces. They also drain bile salts which are made in the liver and transported to the gall bladder, where they are stored until they are excreted into the duodenum in response to food, to solubilise fat. (See Figure 4.2)
2.2 Physiology

The liver has a huge number of roles including:
- synthesis of bile salts and proteins such as albumin and clotting factors
- metabolism of drugs, hormones, waste products e.g. ammonia
- storage and metabolism of vitamins, glycogen, lipid
- immunological function

Without a functioning liver the human body would fail within 48-72 hours. However there is an enormous amount of spare capacity and so liver failure (chronic or acute) has to be severe before life is compromised. In most liver diseases the liver’s functions are largely maintained.

2.2.1 Neonatal Physiology

Neonates have poor liver function due to immaturity of the metabolic enzymes. Some liver enzymes start to be expressed in utero but these are generally different enzymes or in different proportions from those seen in older children or adults. For example cytochrome P450 3A7 is expressed in utero but declines rapidly after birth to be replaced by the CYP 3A4/5 enzymes; sulphotransferases are expressed in utero and continue to be expressed in early childhood but are gradually replaced by glucuronidases in late infancy. Overall, metabolism of exogenous substances by the neonate is poor and it takes many months before adult levels of function are attained.

In keeping with this the neonate has impaired bilirubin metabolism. The enzyme bilirubin uridine diphosphate glucuronyltransferase (bilirubin UGT-1), which is responsible for conjugating bilirubin, takes a few weeks to develop fully and consequently the majority of newborns have a raised unconjugated bilirubin with levels up to 100 micromol/L. This is known as physiological jaundice and it occurs in the first few days of life with no untoward effects. However, it can sometimes become significant with bilirubin levels increasing to 200-300 micromol/L. At this level high concentrations of unconjugated bilirubin can cross the blood brain barrier and cause kernicterus and ultimately brain damage. The neonate’s bilirubin level can
be plotted on a chart to indicate whether or not they are at risk of kernicterus. If they are above the line ultraviolet light therapy is used to conjugate bilirubin through the skin enabling its excretion via the biliary system.

A baby with prolonged hyperbilirubinaemia (more than 2-3 weeks) should have a split bilirubin measured. A high unconjugated fraction suggests immaturity, breast milk jaundice or a pre-liver cause such as haemolysis and requires time +/- UV therapy (or rarely an exchange transfusion) to correct. A high conjugated fraction implies a problem excreting bilirubin from the liver and may suggest a number of liver diseases (metabolic, endocrine or bile duct obstruction) or may be indicative of infection (e.g. CMV, toxoplasmosis, *E.coli* UTI, malaria, HIV). It needs further investigation and possible early referral to a liver unit if biliary atresia is suspected.

### 3. Normal Liver Function Test (LFT) ranges[1]

LFTs are usually thought of as transaminases, alkaline phosphatase and bilirubin, however it is important to consider all of the biochemistry listed below (See Tables 4.1 & 4.2) when assessing a patient’s liver function as the pattern of change helps identify the nature and extent of liver dysfunction.

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Where found</th>
<th>Normal ranges</th>
<th>Implications in liver disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transaminases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransaminase (ALT)</td>
<td>Liver, heart and skeletal muscle</td>
<td>Infants: 10-30 Units/l Children: 10-40 Units/l Newborns: 10-75 Units/l Children: 10-45 Units/l</td>
<td>Raised levels indicate hepatocyte damage/necrosis ALT is more liver specific but has a longer half life, so less sensitive May be normal in compensated liver cirrhosis</td>
</tr>
<tr>
<td>Aspartate aminotransaminase (AST)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase (ALP)</td>
<td>Liver, kidney, bone, placenta and intestine</td>
<td>Newborns and infants: 140-1100 Units/l Children: 250-800 Units/l</td>
<td>Raised levels indicate biliary epithelial damage (biliary inflammation/obstruction), malignant infiltration, cirrhosis, osteopenia secondary to vitamin D deficiency</td>
</tr>
<tr>
<td>Gamma glutamyl transferase (GGT)</td>
<td>Biliary epithelia and hepatocytes</td>
<td>Newborns: &lt;200 Units/l Infants: &lt;120 Units/l Children: &lt;35 Units/l</td>
<td>Raised in many forms of disease Enzyme induction</td>
</tr>
</tbody>
</table>

NB: Check against your own hospital’s reference ranges.

Table 4.1 Enzymes
Biochemical marker | Normal range | Implications in liver disease
--- | --- | ---
Bilirubin (SBr) | 1st 24 hours: <103 micromol/l 2-5 days: <205 micromol/l (nearly all unconjugated) After 1 mth: 1.7 – 26 micromol/l (mainly conjugated) | Raised in hepatocyte dysfunction or biliary obstruction or haemolysis
INR/PT | INR: 0.8-1.2 PT:12-15 secs | Raised levels indicate hepatocyte dysfunction (acute or end stage chronic) or vitamin K deficiency e.g malabsorption in cholestasis
Albumin | Newborns: 25-50 g/l 1 year: 35-50 g/l 4yrs and over: 37-50 g/l | Low indicates: chronic liver disease (poor synthetic function)
Glucose | Newborns: 2.2 – 4.4 mmol/l Infants and children: 3.3 – 5.5 mmol/l (fasting) | Fasting hypoglycaemia indicates poor hepatocyte function. Seen in acute liver failure and some metabolic diseases

Table 4.2 Other biochemical markers of liver function

Task 4.1

Check the normal reference ranges for LFTs for your hospital and compare with tables 4.1 and 4.2.

4. Pathology of common diseases (See case study Acute liver disease)

There are an enormous number of liver diseases that can affect children and on the whole they can be described as hepatitis, cirrhosis, cholestasis or acute liver failure. It is, of course, not as simple as that as a particular disease may start in one category and move into another over time. For example, auto-immune hepatitis may present early with mild inflammation of the liver (hepatitis) but if left untreated it will develop into cirrhosis. It may also present as an apparent acute liver failure as the patient develops decompensated cirrhosis having been unaware of their underlying condition, often for many years.

It is important to understand these terms as they help identify what sort of problems a patient will have in terms of signs and symptoms and managing drug handling, and what sort of supportive treatment they are likely to need.

4.1 Hepatitis

Hepatitis refers to inflammation of the hepatocytes (liver cells). It causes a rise in transaminase levels as the hepatocytes are damaged and release AST and ALT. In its
mildest form the ALT may rise to levels of about 100 as seen in condition such as fatty liver disease. This is unlikely to cause any significant signs or symptoms (but must not be confused with cirrhosis). However hepatitis can be severe and result in an ALT of more than 1000 e.g. acute hepatitis A infection, some drug toxicities or a hypoxic event. In this case there may be problems such as coagulopathy indicating that the hepatocytes are not functioning fully and pain reflecting hepatomegaly. If the inflammation continues the liver cells will become scarred and fibrosis develops. At this stage the scarring is reversible but if it continues cirrhosis can develop.

4.2 Cirrhosis

Cirrhosis is an important condition to understand. The liver cells become irreversibly damaged and the fixed scarring makes the liver small, hard and knobbly. This impedes portal vein blood flow through the liver causing portal hypertension and collateral routes (varices) are formed to avoid it. In its early stages a cirrhotic child may have an ALT of a couple of hundred however as the condition progresses the ALT will fall to apparently normal levels as there are insufficient hepatocytes left to release transaminases. Amazingly a cirrhotic patient can manage with not many functioning liver cells for many months - this is called compensated cirrhosis. However decompensated cirrhosis can be precipitated fairly easily by intercurrent infection, electrolyte disturbance, sedating drugs - the few cells that are left can’t cope with demand. When this happens other complications of chronic liver disease such as coagulopathy (INR usually in the range of 1.5 to 3), encephalopathy and ascites develop and the patient has end stage liver disease.

4.3 Cholestasis

Cholestasis is a different problem altogether. It means a block or stasis of bile salts from exiting the liver. It can be intrahepatic in origin for example Alagille’s syndrome which is a paucity of intrahepatic bile ducts - there just aren’t enough for bile to flow out of, or extrahepatic for example gallstones blocking the common bile duct (CBD) or biliary atresia where the CBD, or a part of it, is missing. A cholestatic patient will have an alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT) that are high reflecting damage to the biliary tree. In some cases the bilirubin may also be high if biliary clearance of bilirubin is affected but it is not necessarily so. Cholestasis has a number of associated complications: the lack of bile salts entering the duodenum impairs the absorption of fats and fat soluble vitamins from the diet and the accumulation of bile salts results in extreme pruritus. These children have poor growth and problems of fat soluble vitamin deficiencies e.g. blindness (vitamin A), osteodystrophy and frequent fractures (vitamin D), poor neurological development (vitamin E) and coagulopathy (vitamin K). If left unchecked the accumulation of bile salts within the liver can cause damage to the hepatocytes and these children will go on to develop a cirrhotic picture as well as a cholestatic one.

4.4 Acute liver failure (ALF).

Acute liver failure (ALF) is the most dramatic presentation of liver dysfunction. This is described as the progression from first presentation of jaundice to encephalopathy within 7 days for hyperacute liver failure, 28 days for acute liver failure or less than 6 months for subacute liver failure. Beyond 6 months it is a chronic liver disease. In
ALF the transaminase levels are extremely high (5-10,000U/L) and the clotting completely deranged (INR>4, sometimes unclottable). Encephalopathy starts as a mild change in behaviour and irritability (grade 1) right through to a coma (grade 4). To protect the child once the encephalopathy score is consistently 2 or above they should be ventilated and sometimes a cerebral bolt is inserted to measure the intracranial pressure. In the neonate, ALF is commonly secondary to infection or a metabolic condition e.g. galactosaemia (presents when first given lactose containing milk) or tyrosinaemia. In older children it is infection and drug toxicity that are the most common causes. The PICU care of these children is basically supportive - cardiovascular support in case of shock, renal support as there is often an associated kidney failure, treatment or prophylaxis of infection and preventing bleeds. Often treating the underlying cause can reverse the liver failure e.g. avoiding lactose or treating the infection. Sometimes it is simply time that the liver needs to get over the poisoning and recover e.g. after a paracetamol overdose (most children do not need a liver transplant for paracetamol overdoses as they seem to have a better capacity for recovery than adults). However sometimes the damage is too great and there isn’t sufficient residual hepatocyte function to give the liver enough time to regenerate. Then liver transplantation is the only option.

Having understood these descriptions of liver disease some of the more common liver diseases that are likely to result in a PICU stay are discussed in greater detail below. These are not necessarily the most common conditions but the ones most likely to require intensive care and specific treatment. The more general complications and their management are described later. (See Table 4.3)

<table>
<thead>
<tr>
<th>Structural</th>
<th>e.g. biliary atresia, choledochal cyst, Alagille’s syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine disorders</td>
<td>e.g. hypopituitarism, hypothyroidism</td>
</tr>
<tr>
<td>Metabolic</td>
<td>e.g. tyrosinaemia, galactosaemia, urea cycle disorders, Wilson’s disease, cystic fibrosis, Gilbert’s syndrome, alpha-1-antitrypsin deficiency</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>e.g. drug induced (paracetamol, anti-tuberculosis therapy, sodium valproate, TPN) or misplacement of an umbilical catheter</td>
</tr>
<tr>
<td>Trauma</td>
<td>e.g. liver laceration following handle bar injury</td>
</tr>
<tr>
<td>Infection</td>
<td>e.g. Hepatitis A, B, C, D, E, CMV, EBV, HSV, coxsackie, rubella, malaria, HIV, tuberculosis</td>
</tr>
<tr>
<td>Circulation/hypoxia</td>
<td>e.g prolonged seizure, post cardiac surgery (by-pass)</td>
</tr>
<tr>
<td>Immunological</td>
<td>e.g. auto-immune hepatitis, primary sclerosing cholangitis</td>
</tr>
</tbody>
</table>

**Table 4.3 Common liver diseases on PICU**

**4.5 Metabolic conditions**

**4.5.1 Tyrosinaemia**

This is a condition where the body is missing the enzyme needed to metabolise tyrosine to its non-toxic metabolites. Instead it is metabolised to maleyl- and fumaryl-acetoacetate both of which are highly hepatotoxic. Tyrosinaemia can present in the
neonatal period as acute liver failure with high INR and transaminases or later in childhood as a more chronic liver disease. Those with ALF require supportive treatment and early instigation of nitisinone. This drug blocks the entire pathway for tyrosine metabolism so no toxic metabolites are formed - it does mean that tyrosine levels in the body increase and a low tyrosine diet has to be given to counteract that. Treatment with nitisinone can reverse the ALF within a day or two, however these children may go on to develop problems with hepatocellular carcinoma in later childhood and may still require liver transplantation.

4.5.2 Galactosaemia

Children missing the enzyme galactose-1-phosphate uridyl transferase (Gal-1-PUT) develop high levels of galactose in the early neonatal period when they first start having lactose containing milk. Galactosaemia presents with hypoglycaemia, encephalopathy and ALF. It can be quickly reversed by stopping all lactose containing foods and it is important to maintain the child on lactose free milk and fluids until a diagnosis is made. There can be long term complications from galactosaemia but close compliance with the diet can improve the child’s quality and length of life.

4.5.3 Wilson’s disease

This is a disorder of copper metabolism which results in copper deposition primarily in the liver but also in the brain and kidneys. Untreated Wilson’s disease can gradually cause cirrhosis and end stage liver failure, however it can sometimes present as acute-on-chronic liver failure i.e. mimicking ALF but actually a sudden decompensation of advanced cirrhosis. Acute Wilson’s disease needs careful management as aggressive use of copper chelating agents (penicillamine or trientine) can precipitate profound neurological symptoms. Most children who present with ALF will require urgent liver transplantation.

4.6 Drug toxicity

4.6.1 Paracetamol overdose

In young children paracetamol overdose (POD) is usually accidental rather than deliberate. It occurs most commonly through misunderstanding of instructions and giving the wrong strength preparation too frequently over 2 or 3 days. In teenagers the POD is usually intentional and the history regarding the timing of the overdose likely to be unreliable. Treatment with acetylcysteine needs instigating as soon as possible, preferably within 15 hours of the overdose, however there is some evidence that even given up to 36 hours post POD acetylcysteine may still have some beneficial effect, reducing the extent of hepatocellular necrosis and the need for transplantation. In staggered overdoses or when the time of the OD is unknown acetylcysteine should be given regardless, paracetamol levels checked and the child reviewed after 24 hours. The treatment schedule in the BNFC should be followed and the child’s ALT, INR and encephalopathy score monitored carefully. Early referral to a liver unit is essential if the child develops worsening coagulopathy, renal failure, hypoglycaemia, acidosis or encephalopathy - any of which may indicate the need for urgent liver transplantation.
4.7 Hypoxia

Prolonged hypoxia following, for example, a long seizure or cardiac by-pass surgery, can cause ischaemic liver damage. It may result in an ALT increase to around 1000-2000 and possibly a derangement in INR. It will usually settle on its own as blood flow is restored. Acetylcysteine is sometimes used at a dose of 100mg/kg/day as a continuous infusion as it has been shown to improve hepatic microcirculation and is an antioxidant, both functions will reduce the risk of free radical damage to the hepatocytes. If the INR and ALT continue to rise the child should be treated as ALF, but in most cases this isn’t necessary and both will fall within a couple of days.

5. Pharmacological treatments

Treatment of liver disease revolves primarily around managing the complications such as varices, ascites, encephalopathy, coagulopathy, pruritus and fat soluble vitamin deficiencies and their consequences e.g. rickets. In the PICU setting the management of acute liver failure is also paramount.

5.1 Oesophageal varices (See case study Hepatology – Varices)

Oesophageal varices occur in patients with cirrhosis or portal vein obstruction i.e. anything that impairs the flow of blood through the portal vein into the liver resulting in portal hypertension. Note: this is not necessarily secondary to liver disease but may reflect a prothrombotic state where the portal vein has been thrombosed. The collaterals form around the gut as a low resistance route into the systemic circulation (see Figure 4.1). However these vessels are not designed for high pressures of blood and are consequently fragile. Bleeds occur when the pressure in the varix is too high or if the varix has been damaged, for example by the use of NSAIDs. Varices can bleed slowly causing malaena (black, tarry stools) or profusely resulting in haematemesis. The latter is a medical emergency. The child needs to be resuscitated and started on an octreotide infusion (1-3 microgram/kg/hour). Octreotide reduces splanchnic blood pressure and thus reduces the pressure in the varix and reduces bleeding. It has a short half life and sudden stopping of the infusion can result in rebound bleeding so generally, once bleeding is under control, the infusion rate is halved for 12 hours, then halved again before stopping.

Some patients will have ongoing problems with oesophageal varices and recurrent bleeding and this group may benefit from the use of propranolol to reduce the splanchnic blood pressure all the time. The usual oral dose is 0.5 mg/kg twice a day but it is adjusted to attain a reduction in heart rate (as a surrogate marker of splanchnic pressure) of 25% from base line.

Oesophageal varices can also be treated by the injection of a sclerosant e.g. ethanolamine, into the varix under endoscopy guidance or, in older children, by the application of a band (literally a tiny rubber band) around the protruding part of the varix. Both methods have good success rates for treating mildly bleeding varices or preventing varices from bleeding. If a varix is bleeding uncontrollably and octreotide is not stopping it then a sengstaken tube can be inserted into the oesophagus. This is a
long rubber tube with a balloon at the end, once the balloon end is in the stomach it is blown up to lodge the tube in place then the long tube which is sitting throughout the oesophagus is blown up to basically apply pressure to the bleeding points. Sengstaken tubes are very uncomfortable for the patient and there is a risk of rebleeding when they are removed.

5.2 Ascites

Ascites occurs when excess fluid accumulates in the peritoneal cavity. There are a number of theories about the mechanism for this but they centre on sodium and water retention and hypoalbuminaemia. In the presence of liver disease it usually implies decompensated cirrhosis. Ascites is managed pharmacologically with spironolactone in doses of 1-4 mg/kg twice a day. If the ascites is severe then it is likely that absorption of spironolactone will be impaired by the ‘boggy’ gut. Potassium canrenoate can be given intravenously instead (divide spironolactone dose by 0.7, maximum 3 mg/kg twice a day). In children with resistant ascites small doses of furosemide can be given (0.5-1mg/kg twice a day) IV or orally, however there is a risk of volume depletion and U & Es need careful monitoring. It is also important to restrict fluid and sodium intake and ensure sodium from drug sources is considered in the total.

Resistant ascites can be treated with albumin infusions using the 20% (salt poor) Human Albumin Solution at a dose of 5 ml/kg. This helps to maintain the plasma oncotic pressure and reduce leakage of fluid into the peritoneal cavity. In severe cases paracentesis can be performed to remove fluid from the peritoneum through a catheter, albumin should be given half way through the procedure to minimise fluid shifts.

5.3 Encephalopathy

Encephalopathy is associated with acute liver failure or decompensated cirrhosis. It reflects the liver’s inability to clear toxins such as ammonia and may reflect altered permeability of the blood-brain barrier with more toxins able to enter the brain. The degree of encephalopathy is related to the severity of liver impairment. It is managed by giving lactulose in large doses (1 ml/kg two or three times a day) in an attempt to produce 3-4 loose stools per day. This is to reduce the ammonia producing gut bacteria by acidifying the gut and ‘flushing’ out bacteria by having loose stools. Some centres also use metronidazole and/or neomycin to reduce the GI bacteria load and there is emerging evidence that rifaximin may be useful, but it is not yet being widely used in paediatrics. Maintaining the child in a quiet and non-stimulating environment, with minimal handling also helps. If encephalopathy worsens the child should be ventilated.

5.4 Coagulopathy

Coagulopathy is treated differently depending on the cause/type of liver dysfunction. In cholestatic liver disease vitamin K deficiency is the cause of coagulopathy and vitamin K supplements should be given. In severe cholestasis this will need to be parenteral to bypass the malabsorption of fat soluble vitamins, alternatively menadiol can be used as a water soluble analogue of phytomenadione. In ALF and cirrhosis the
coagulopathy is usually a result of hepatocyte damage preventing the synthesis of clotting factors. There may be an element of vitamin K deficiency in decompensated cirrhotics who may also have a degree of cholestasis; however it is unlikely that vitamin K will reverse the coagulopathy in these patients.

If a child is bleeding as a result of the coagulopathy then it may be necessary to consider giving fresh frozen plasma (FFP) and/or platelets. In ALF the clotting is a sensitive marker of prognosis as it responds quickly to changes in liver function whereas other LFTs may lag by several hours or days. Using FFP in ALF would mask these changes making it impossible to know if the child was getting worse and needed a liver transplant or improving and could come off the transplant waiting list. Where possible it should be avoided although for safe transfer of a child it is vital to ensure they don’t bleed en route.

5.5 Other complications

Other complications are less likely to be of importance in the PICU setting however children with cholestatic liver disease may be on a range of fat-soluble vitamins, often in large doses, and possibly calcium supplements if they have low vitamin D levels. They may also suffer from pruritus which can be treated with ursodeoxycholic acid, rifampicin, colestyramine or ondansetron. Very occasionally naloxone or naltrexone is also used, although only for short periods of time.

5.6 Acute liver failure (see case study Hepatology- acute liver failure)

Acute liver failure requires a range of specific treatments in addition to normal supportive care (inotropes, renal support etc) (see Table 4.4):

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Co-amoxiclav to cover possible causative organisms and to prevent infection caused by necrotic liver tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antifungal</td>
<td>Fluconazole at 3 mg/kg daily to prevent fungal infection occurring from a necrotic liver. Consider switching to liposomal amphotericin if worsening ALF or development of renal impairment (risk of fungal infection increased)</td>
</tr>
<tr>
<td>Acetylcysteine</td>
<td>100mg/kg/day as a continuous infusion to improve hepatic microcirculation and as an antioxidant to mop up free radicals in necrosis</td>
</tr>
<tr>
<td>Ranitidine or Omeprazole</td>
<td>To prevent or treat GI bleed</td>
</tr>
<tr>
<td>Phytomenadione</td>
<td>300 microgram/kg od IV for 3 days to improve any vitamin K deficiency (unlikely to fully reverse coagulopathy)</td>
</tr>
<tr>
<td>Aciclovir</td>
<td>10 mg/kg (20mg/kg in neonates) or 500 mg/m² tds if HSV could be a cause of the liver failure (caution renal impairment)</td>
</tr>
<tr>
<td>Glucose 5-50%</td>
<td>Hypoglycaemia is a common problem in ALF and high concentrations of glucose are often required to maintain blood sugars.</td>
</tr>
<tr>
<td>Mannitol</td>
<td>May be needed if raised intracranial pressure is contributing to encephalopathy.</td>
</tr>
</tbody>
</table>
### Table 4.4 Treatment of Acute Liver Failure

In the event of worsening ALF a child is likely to need urgent liver transplantation (OLT). When they are listed for an urgent OLT they are put at the top of the national UK transplant waiting list, however it can still sometimes take several days for a suitable organ to become available. If necessary MARS (Molecular Adsorbents Recirculation System) treatment can be used as a bridge to transplant i.e. it helps to keep the child going for a day or two longer. MARS is a CVVHD dialysis circuit with an additional albumin filter attached. This enables large albumin bound molecules to be cleared by the system, in particular unconjugated bilirubin, ammonia, bile acids and other toxins that the liver is unable to metabolise or excrete. MARS cannot take over the whole function of the failed liver so can only provide a very short term stop gap whilst a liver is found.

### 6. Pharmaceutical care

When providing pharmaceutical care to a child with liver dysfunction there is a number of parameters that need to be monitored and drug considerations that need to be taken into account when prescribing. These are outlined below (see Table 4.5).

<table>
<thead>
<tr>
<th>What to monitor</th>
<th>Why</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood sugar</td>
<td>Hepatocytes are responsible for maintaining glucose homeostasis. In ALF this is often impaired and children may need high concentrations of glucose to maintain normal blood sugar levels.</td>
</tr>
<tr>
<td>Liver function tests (including INR and albumin)</td>
<td>To monitor progression of liver dysfunction and identify potential problems with drug handling</td>
</tr>
<tr>
<td>Fluid balance</td>
<td>To ensure a neutral or negative fluid balance is attained - these children often develop ascites</td>
</tr>
<tr>
<td>Sodium intake</td>
<td>If the child has ascites then sodium intake should be minimised</td>
</tr>
<tr>
<td>Renal function</td>
<td>Liver dysfunction, especially ALF, often co-exists with renal failure</td>
</tr>
<tr>
<td>Lactate</td>
<td>Provides an indication of hepatocyte function as does ammonia but lactates are measured on blood gases so are more easily available.</td>
</tr>
<tr>
<td>Sedation score</td>
<td>If the child is ventilated and sedated make sure they are not over sedated as a result of drug accumulation in liver dysfunction</td>
</tr>
<tr>
<td>Drug choice</td>
<td>Some drugs should be avoided or used very cautiously in children with liver dysfunction because their side effect profile may be harmful e.g. NSAIDs (risk of GI bleed and renal impairment), anticoagulants (risk of bleeding), sedating drugs (risk of precipitating encephalopathy), diuretics (risk of electrolyte disturbance precipitating encephalopathy)</td>
</tr>
</tbody>
</table>

### Table 4.5 Monitoring of liver dysfunction
7. Drug handling

Drug handling in children with liver dysfunction is an enormous subject and for a full description of the potential problems ‘Drugs and the Liver’ provides background into pharmacokinetic changes with various types of liver dysfunction, how to assess liver dysfunction and how to apply the basic principles in order to decide what drugs and doses are safe to use.

In the PICU setting a degree of pragmatism is required and the balance of risk vs benefit may be different from a less intensive environment e.g. using a full dose of an antibiotic in a child with septic shock even though the drug is hepatically metabolised and has hepatotoxic side effects.

**Task 4.2**

Use the aide memoire from ‘Drugs and the Liver’ to help adjust drug doses in liver dysfunction.

**Bibliography**


**References**

1. Forfar and Arneil’s Textbook of Paediatrics. 5th edition Edited by AGM Campbell and Neil Mackintosh. Biochemical reference ranges
Cardiovascular Section
Siân Edwards and Sarah Wheeler
Revised by Sara Wheeler July 2011

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      4.2.2.2 Management
    4.2.3 Ventricular tachycardia
      4.2.3.1 Pathophysiology
      4.2.3.2 Management
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      4.2.4.1 Pathophysiology
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Objectives

- To understand the anatomy of foetal circulation and changes in the early neonatal period
- To understand the basic pathophysiology and management options for acute and chronic heart failure
- To understand the mechanism of action, characteristics and clinical use of heart failure treatments
- To understand the basic pathophysiology and medical and surgical management of congenital heart disease
- To understand the basic pathophysiology and management options for the various common arrhythmias
- To understand the role of electrolytes in arrhythmias
- To understand the mechanism of action, characteristics and clinical use of antiarrhythmic treatments
- To understand the basic pathophysiology and management options for pulmonary oedema
- To understand the mechanism of action, characteristics and clinical use of treatments for pulmonary oedema
- To understand the role of extracorporeal membrane oxygenation as cardiovascular support following cardiac surgery
1. Anatomy and Physiology in Children

1.1 The circulation prior to birth

In utero, the baby's lungs are not in use for gas exchange because the baby receives oxygen from the mother via the placenta. In order that oxygenated blood from the mother is delivered to the most important areas of the baby’s body (for example the brain) the heart has developed various bypass systems that avoid the baby’s lungs. (See Figure 5.1)

![Fetal Circulation Diagram](image)

**Figure 5.1 Foetal circulation**

Firstly, oxygenated blood from the placenta enters the inferior vena cava (IVC) via the umbilical vein and ductus venosus in the liver. When it reaches the right atrium, this oxygenated blood is preferentially streamed across the atrial septum into the left atrium via a flap between the two atria called the foramen ovale, which enables oxygenated blood to pass from the right atrium to the left atrium. This is possible because, unlike adult circulations, the foetal systemic circulation resistance is low due to the low resistance placenta, and the pulmonary circuit pressure is high due to the collapsed lungs and the more muscular pulmonary arterioles. Some blood still passes into the right ventricle and on to the pulmonary artery but most of the blood from the placenta will pass through the foramen ovale. In the left atrium this oxygenated blood mixes with pulmonary venous blood and then passes onto the left ventricle and through the ascending aorta to the brain and upper body.
Secondly, deoxygenated blood returns from the superior vena cava (SVC) back into the right atrium and the right ventricle, and then into the pulmonary artery. There is a connection called the ductus arteriosus, which joins the pulmonary artery and the descending aorta. Only a small proportion of this blood passes to the lungs due to the high pulmonary vascular resistance, and so most flows through the ductus arteriosus to the lower body and placenta. Due to mixing at various levels during this process the oxygen saturation of blood in ascending aorta is 65% and 55-60% in descending aorta.

5.2 The Circulation post birth
When the baby is born and uses its lungs for the provision of oxygen, the bypass systems are no longer needed. Clamping the umbilical cord effectively eliminates the placenta from the circulation shortly after birth thereby increasing systemic vascular resistance; and the use of the lungs reduces pulmonary vascular resistance and increases pulmonary blood flow. Consequently the pressure in the left atrium is increased. Since the pressure in the right atrium is conversely decreased due to reduced IVC flow (since the placenta has been removed), the reversal of pressures causes the closure of the foramen ovale a few hours after birth. (See Figure 5.2)
Prostaglandin E2 is produced by the placenta to keep the ductus arteriosus open in utero. Once the placenta has been removed post birth, this duct also closes over a period of days to weeks after the birth, and the circulation is then identical to that of an adult.
2. Heart Failure

Heart failure is the broad term used to describe when the cardiac output of the heart is failing to meet the demands of the body. Whilst this is usually due to an intrinsic problem with the heart e.g. structural abnormalities, it can be due to excessive demands of the body (which may occur in critical illness).

2.1 Pathophysiology

Cardiac output is determined by both stroke volume and heart rate:

\[
\text{Cardiac output} = \text{stroke volume} \times \text{heart rate}
\]

The ability of the heart to increase its contraction in response to the stretching of its fibres is subject to ‘Starling’s Law’ and describes the relationship between ventricular filling (diastolic pressure) and cardiac output. For example if the amount of blood returning to the ventricle is increased (increased pre load) then the stroke volume is increased. According to the equation above this would lead to an increase in cardiac
output. However there is a point where the heart muscle cannot stretch any more and at this point any increase in venous return will not increase the stroke volume. Other factors that affect stroke volume are contractility and afterload. For example if afterload is increased then stroke volume is reduced and vice versa. *(See Figure 5.3)*

In heart failure an increase in ventricular filling produces a much smaller effect on stroke volume, and the point at which no further increases in stroke volume are seen is much lower. In fact if pre load is increased further then stroke volume can fall.

![Cardiac function curve](image)

**Figure 5.3 Cardiac function curve**

There are various compensatory hormonal responses that are associated with a reduction in cardiac output. Although the exact mechanism for the activation of the system is still in debate, it is likely that distension of the ventricles triggers both local and general sympathetic responses, as detailed below. *(See Figure 5.4)*
Figure 5.4 Compensatory mechanisms in heart failure

Chronic activation of the sympathetic nervous system can cause further stress on the ventricular walls and dilatation, causing remodeling and fibrosis of the cardiac tissue. This will eventually cause a worsening of cardiac function.

As well as inadequate systemic oxygen delivery as a result of low cardiac output, pulmonary oedema also manifests with heart failure. This arises as a result of increased left atrial and pulmonary venous pressure. This increase in hydrostatic pressure in the lungs forces fluid out of the pulmonary capillaries into the interstitial spaces and alveoli, leading to pulmonary oedema.

2.2 Causes
The causes of heart failure in children are very different from those in adults. Fundamentally most adults acquire heart failure from diseases such as hypertension and ischaemia, which have significant life-style components. Most paediatric causes are present from birth, although some are acquired from infections, trauma or other critical illness.

The causes of heart failure in children fall into two broad categories:
1) Congenital structural abnormality preventing normal function/blood flow of the heart, causing it to work inefficiently and thus leading to failure. This is the most common cause of heart failure in children.
2) “Pump failure” is when the cardiac muscle itself is not working properly. This can be from a variety of causes (e.g. myocarditis, cardiomyopathy, metabolic disorders and secondary to some chemotherapy drugs). Myocardial dysfunction that might occur in for example cardiogenic shock would also fit into this category.

**Mechanisms of heart failure**

**Increase in the workload of the heart:**

- **Pressure** overload e.g.
  - Aortic stenosis
  - Coarctation of the aorta
  - Pulmonary stenosis
  - Pulmonary hypertension

- **Volume** overload e.g.
  - Left to right shunts e.g. VSD, PDA
  - Valve regurgitation (mitral & aortic)

**Primary myocardial abnormality or insult:**

- Cardiomyopathy
- Myocarditis

**Exhaustion of the compensatory cardiovascular mechanisms**

**Decrease in the work capacity of the heart**

Whatsoever the cause of the heart failure, the condition can be divided into two categories, acute and chronic. Predominantly heart failure in PICU will be acute. It could be caused by a severe congenital abnormality (that necessitates urgent surgery within the first few days/weeks of life) when the child may present to PICU in cardiogenic shock; or develop in the immediate post-operative period. It would also include children with previously normal hearts who have a sudden onset of heart failure e.g. due to infective myocarditis. Chronic heart failure is mostly managed by paediatric cardiologists outside of PICU; however PICU will also look after patients admitted with severe chronic heart failure.

2.2.1 **Structural congenital heart disease**

As the heart develops in utero, there are numerous aspects to its development that can go wrong, and as such there are numerous variations to the “normal” heart that a child can be born with. As the heart is not required to function properly whilst in utero, a child can grow and develop quite normally until the point of birth when their heart is required to function differently to support their own circulation. A few lesions may cause problems in utero, leading to poor foetal growth or oedema (hydrops). Congenital abnormalities have been classified in numerous ways, and there are some that do not fit exactly into any category. However this classification is done from an
intensive care perspective to focus on the effects of the abnormality on the circulation. This list is not exhaustive.

### 2.2.1.1 Left-to-right shunt lesions

These are defined as lesions in which blood from the left side of the heart (LA, LV or aorta) is shunted back to the right side of the heart (RA, RV or pulmonary artery). As the blood on the left side of the heart is under greater pressure than the blood on the right, any “hole” or vessel linking them, will allow the blood to flow down the pressure gradient from left to right.

In the absence of respiratory disease the blood in the left side of the heart is fully oxygenated, so a shunt from left-to-right means that the child will not be cyanotic but will have volume overload on the right side of the heart with an increased blood flow to the lungs.

Common abnormalities that fit in this category are:
- Patent Ductus Arteriosus (PDA)
- Atrial Septal Defect (ASD)
- Ventricular Septal Defect (VSD)
- Atrioventricular Septal Defect (AVSD)

**Task 5.1**
Find out where in the heart each of these lesions is, and identify where the ‘shunt’ is.

### 2.2.1.2 Ventricular Outflow Tract Obstructions

These lesions may obstruct either the right or left side of the heart. Those on the left cause a decreased systemic blood flow, whereas those on the right obstruct blood flow to the lungs. The obstruction imposes a pressure load on the ventricle, due to the increased afterload, causing reduced stroke volume. To compensate, the heart raises its end diastolic pressure (filling pressure) to try to increase stroke volume. Increased pressure in the ventricle will cause hypertrophy and lead to poor contractility. Over time this will cause a congestive heart failure picture and pulmonary oedema.

Abnormalities include:
- Aortic Stenosis
  - Subvalvular aortic stenosis
  - Supravalvular aortic stenosis
- Coarctation of aorta
- Ebstein’s Anomaly
- Tetralogy of Fallots (TOF)
- Interrupted aortic arch
- Pulmonary Stenosis
- Pulmonary Atresia
- Tricuspid Atresia
Task 5.2
For each of the lesions above identify whether the obstruction is on the left or right side of the heart.

2.2.1.3 Single ventricle anomalies
These include lesions with an absent or non-functioning (e.g. hypoplastic) ventricle. The severity of the heart failure is determined by whether it is the left or right ventricle that is affected, but urgent surgery will be required for either. Adequate circulation can usually be maintained with an absent right ventricle as long as there are low pulmonary pressures to allow blood to flow to the lungs. However the systemic circulation requires a “pump” to give sufficient perfusion of organs and tissues so if the left ventricle is absent then major surgery will be required to change the functioning right ventricle into the systemic pump.

- Hypoplastic left heart syndrome (HLHS)
- Hypoplastic right heart

2.2.1.4 Miscellaneous abnormalities: Cyanotic heart disease with increased pulmonary flow (due to altered circulation)
- Transposition of the Great Arteries (TGA)
- Truncus arteriosus
- Total anomalous pulmonary venous drainage (TAPVD)
- Double Outlet Right Ventricle (DORV)

2.2.2 Myocardial pump failure

2.2.2.1 Cardiomyopathy
Cardiomyopathy is a functional term that describes “failure of the heart muscle”. It can be caused by a primary failure of the heart muscle, or be secondary to a systemic disease. Causes are extremely diverse and include myocarditis, metabolic disorders, genetic diseases (including glycogen storage disorders), toxins (including some chemotherapy agents) and nutritional deficiencies.

They are generally categorised into three groups based on the pathology:

- **Dilated cardiomyopathy**
  Left ventricle (sometimes both ventricles) is enlarged and so there is a decrease in systolic function and thus of cardiac output (see Starling curve above). This leads to a cascade of problems which culminate in signs and symptoms of congestive cardiac failure. Arrhythmias are also common. Treatment is largely supportive until the disease process resolves or the heart is transplanted.

- **Hypertrophic obstructive cardiomyopathy (HOCM)**
  Abnormal thickening or hypertrophy of the left ventricle causing diastolic dysfunction and LVOT obstruction.
• **Restrictive cardiomyopathy**

This rare form of cardiomyopathy is due to a restriction of blood flow into the ventricles. This causes the ventricles to become stiff and further worsen the cardiac output. It also leads to increased atrial pressure and enlargement. As the disease progresses there is likely to be a significant pulmonary hypertension too.

### 2.2.2.2 Myocarditis

Myocarditis is defined as inflammation of the heart muscle with cardiac dysfunction. The causes of myocarditis are diverse (including secondary to systemic disease and toxins); but most cases are due to infection and of those viral infections are the most common. The process is not fully understood but it appears to progress through various stages from initial viral infection, to a secondary immune response phase (often subclinical) and culminating in a dilated cardiomyopathy which may be many weeks after the initial infection. Diagnosis is often very difficult as there may be no trace of the initial infection.

Treatment is often supportive until the heart either recovers or is transplanted. Children presenting to PICU with heart failure due to myocarditis will be treated in the usual way with inotropes, diuretics and agents to reduce the afterload. Antimicrobial agents are often of little use by the time the child presents to PICU. Immunoglobulins are controversial in their use in these cases. To date there is no trial proving or disproving their use in paediatric viral myocarditis and so some centres use them. Imunosuppressive therapy is also controversial. Some centres use corticosteroids in an attempt to reduce the secondary immune response phase.

### 2.2.2.3 Metabolic disorders

It is common to see metabolic derangements in a critically ill child on PICU (e.g. acidosis, hyperammonaemia). However primary metabolic disorders (inborn errors of metabolism) are rare, nevertheless they can be a cause of heart failure that requires a rapid diagnosis and specialised treatment or they may be fatal.

### 2.2.3 Low cardiac output syndrome (LCOS)

Low Cardiac output syndrome is commonly seen following paediatric cardiac surgery (but can also feature after acute myocarditis and septic shock). A number of factors contribute to this syndrome following surgery:

- Activation of inflammatory cascade following cardio-pulmonary by-pass (CPB)
- Ischaemia following aorta cross-clamping
- Hypothermia
- Reperfusion injury
- Pericardial tamponade
- Post-operative increase in systemic resistance (afterload)
- Post-operative increase in pulmonary resistance

Treatment has to cover the multitude of causes of LCOS; but minimising the time on by-pass is very important. Pre and post-operative steroids can be used to reduce the inflammation caused by CPB.
2.3 Diagnosis
Acute heart failure (low cardiac output) will generally manifest as:
- Low blood pressure for age
- Poor peripheral perfusion (capillary refill)
- Core – peripheral gap of >3 degrees
- Increased lactates/acidosis
- Poor urine output
- Tachycardia
- Increased left atrial pressure (left sided heart failure)
- Hepatic congestion/ascites (if right sided heart failure)

2.4 Non-Pharmacological treatment

Surgery is the mainstay of treatment for structural congenital disorders; however drug treatment is required to stabilise a patient pre-operatively and to manage them post-operatively. The timing of the surgery is extremely dependent on the severity of the abnormality and the subsequent impact it is having on the child’s growth and development. Whilst a child is growing and developing normally surgery will almost always be delayed as long as it is safe to do so, as generally it is preferable that the child has grown as much as possible so the surgery is less complex and the child has a better recovery. However, there are circumstances where it is not helpful for the child’s body to get used to an abnormal circulation, as then, when it is corrected, there is a significant change in pressures, direction of blood flow etc and this can be difficult to adjust to.

Fluid restriction
Significant restrictions can be in place to reduce the strain on the heart and reduce overload.

Ventilation
Mechanical ventilation will reduce work of breathing and oxygen consumption. It also increases intrathoracacic pressure, thereby reducing venous return and right atrial filling, and can affect ventricular afterload.

Task 5.3

Speak to a member of you PICU team (maybe a physiotherapist, senior nurse or doctor) and ask them to explain how the different modes of ventilation can affect cardiac output.

Nutrition
Children with heart failure require increased calories due to their increased metabolism. Combining this with their reduced fluid intake can make this difficult to achieve. It often requires the use of high calorie feeds and may necessitate NG/NJ feeding or parenteral nutrition.

Temperature control
A raised temperature increases oxygen consumption and can contribute to the development of arrhythmias. It is therefore important to control this when necessary.
2.5 Pharmacological Treatments:

2.5.1 Acute heart failure

**Preload**
- Requirements should be assessed using CVP (assesses filling on right side of the heart); arterial lines (left side of the heart), heart rate and urine output and the pre-load optimised
- Decreased pre-load can be corrected by using small boluses of fluid e.g. sodium chloride 0.9%;
- Increased pre-load can be reduced by using diuretics +/- vasodilators

**Contractility**
- Contractility can be assessed by echocardiogram and the arterial trace (looking at wave form)
- Any reversible causes of reduced contractility e.g. hypoxia; metabolic disturbances or electrolyte imbalance should be corrected.
- Inotropes & inodilators can be used to improve contractility. The choice and combinations will vary from centre to centre e.g. milrinone +/- adrenaline
- Corticosteroids can be administered though there use remains controversial. They can be given as bolus doses or continuous infusion.
- Calcium infusions can be given to correct to above “normal” levels to enhance the inotropic action. Levels should be >1.2 mmol/l ionized calcium.

**Afterload**
- Afterload reduction is generally beneficial in heart failure using vasodilators e.g. Glyceryl Trinitrate (GTN) or Sodium Nitroprusside (SNP), or inodilators such as milrinone. However there are risks attached and it is possible to reduce the afterload too much, which can impair myocardial perfusion during diastole.
- If the patient is tolerating feeds, then captopril can be given.

**Heart rate and rhythm**
Any arrhythmias should be corrected. (See section on arrhythmias)

**Cardiac ECMO** may be used in some centres if the patient is not able to be supported with medication. (See section on ECMO)

**Task 5.4**
Read the PRIMACORP trial which looked at the effects of milrinone in preventing Low Cardiac Output Syndrome in children post cardiac surgery. [1]

2.5.2 Chronic heart failure

**Diuretics** are almost always used in chronic heart failure, post-operatively as well as in pulmonary oedema. Furosemide is the most commonly used and is very useful at “off-loading” excess fluid and thus reducing both pre-load and afterload. Thiazides can also be used.
Amiloride or spironolactone can be used to reduce the potassium loss associated with furosemide. Some centres prefer amiloride due to its cleaner side-effect profile, however spironolactone has been shown to have additional benefits in adult heart
failure due to its inhibition of the renin-angiotensin-aldosterone axis (RAAS) (RALES study)[2] and this benefit has been extrapolated by many paediatric centres, so it is often used instead of amiloride.

**Angiotensin Converting Enzyme Inhibitors (ACE-I)** are very effective at reducing afterload and their use in heart failure has almost completely replaced any vasodilator agents (unless the child is intolerant of an ACE-I). There are long-term benefits of using ACE-I in adults due to the effects on the neurohormonal system (reduction of RAAS) which reduces remodelling and the progressive spiralling down of heart failure. It is therefore generally attempted to get all children with chronic heart failure onto an ACE-I. Most of the research has been done with captopril but many centres have extrapolated adult data to use longer-acting ACE-I such as enalapril and lisinopril, particularly in older children.

**Digoxin** can be used long-term in the more severe heart failure cases which still exhibit signs of failure despite diuretics and ACE-I. The evidence supporting its use in either adults or children still remains controversial and, despite its widespread use, trials have failed to show any real benefit of its use in heart failure.

**Beta Blockers.** Some β-blockers (e.g. carvedilol) can be used in severe chronic heart failure, where failure persists despite diuretics, ACE-I and digoxin. They should only be initiated by an expert paediatric cardiologist. They are used mainly in the treatment of cardiomyopathy.

**Aspirin** is used for a number of indications in paediatric cardiology, mostly for its anti-platelet properties. It can be used post-operatively or following cardiac-catheter stent insertion and post radio-frequency ablation (of arrhythmias). It can also be used at higher anti-inflammatory doses in the treatment of pleural or pericardial effusions or Kawasaki disease.

**Warfarin** is used post-operatively for a number of surgical procedures in children. Most often it will be used life-long for mechanical valve replacements.

### 2.5.3 Patent Ductus Arteriosus (PDA)

PDA is the one structural abnormality that can be treated medically. Initial treatment to close a PDA in a premature neonate will be either ibuprofen or indomethacin, as the duct is sensitive to prostaglandins, however if this fails, or if the child is a little older, they will either have a cardiac catheter or surgical closure of the duct. In some complex cyanotic congenital disorders the PDA may be a necessary part of their circulation, in which case it is necessary to keep this open until surgical correction of the circulation means the child can manage without it. In this case the child will receive prostaglandins (either dinoprostone (prostaglandin E₂) or alprostadil (prostaglandin E₁). Alprostadil is the licensed product for this indication, but considerably more expensive so many centres still use dinoprostone.

### 3. Shock  (see case study – Cardiovascular- shock)

Shock is one of the most dramatic and life-threatening conditions seen in PICU. It can be defined as “acute circulatory failure” in which there is an inadequate delivery of oxygen and metabolic substrates to meet the demands of the tissues. This usually results in an inadequate tissue and organ perfusion which if not treated promptly can
lead rapidly to anaerobic metabolism, metabolic acidosis, organ failure and death. It also results in an inadequate removal of the waste products which can also be damaging to the tissues. There are rarely cases of shock with normal or even high perfusion, where the issue is poor oxygen delivery or uptake.

The causes of shock are extremely diverse and the categorisation can vary but most use broadly the same categories. Sepsis in particular may be classified into one of the other categories, but many now feel because of the unique nature of sepsis that it justifies its own category.

Shock is a rapidly progressive condition and as such, whatever the cause it can be divided into three phases:

- **Compensated**
  Vital organ function is preserved by normal homeostatic mechanisms. Blood pressure, urine output and cardiac function may all appear normal. Previously healthy children can compensate extremely well in hypo-perfusion states and as such this first phase can be very difficult to identify. However due to the nature of shock it is of vital importance that it is identified at this stage as already early cellular metabolic changes are underway.

- **Decompensated / Uncompensated**
  Circulatory compensation now fails because of ischaemia, endothelial injury, toxic materials from the host and microorganisms, and often the deleterious effects of physiological compensations. Eventually cellular function deteriorates and impairment of function of all organs is visible.

- **Irreversible (or terminal)**
  When the process has caused such significant damage to essential organs that death is inevitable despite intensive support.

Speed is essential in the treatment of shock. A rapid diagnosis is required as it is mandatory to treat the underlying cause to prevent the rapid deterioration into the decompensated and then irreversible phase. However the initial treatment of a child in shock of any cause is using the APLS (Advanced Paediatric Life Support) guidelines following the ABC (Airway, Breathing, Circulation) criteria.

### 3.1 Septic shock

Septic shock is the most common type of shock encountered on PICU and remains a major cause of morbidity and mortality in children. There are around 2,000 children admitted to PICUs in the UK each year with presumed sepsis, with approximately 20% mortality. Yet still the disease is not well understood and consequently treatment is not evidence-based and intensivists are always “trying new things” to manage children with septic shock. In 2004 the first “Surviving Sepsis” guidelines were published for adults and a campaign to improve awareness of sepsis and the need to treat promptly was commenced. The guidelines have since been updated in 2008 [3] but are constantly under review as further studies are done. However most studies and all of these guidelines relate to adults.

Definitions

Sepsis is defined as infection plus systemic manifestations of infection. Severe sepsis is sepsis plus acute organ dysfunction or tissue hypoperfusion secondary to infection. Septic shock is severe sepsis plus hypotension that is not reversed with fluid resuscitation.

3.1.1 Pathology

The pathogens responsible for septic shock vary with the age of the patient but may be bacterial, viral or fungal. Meningococcal septicaemia is a common cause of septic shock in children.

In sepsis the cardiac output (CO) is often normal or even raised in the early phase, but then tends to diminish in the uncompensated phase. However even when CO appears normal/raised it may still deliver insufficient oxygen to the tissues because of abnormal distribution. Cells also appear not to utilise oxygen normally (impaired mitochondrial uptake). This impairment is indicative of multiple organ failure.

Bacterial toxins trigger complex haemodynamic and metabolic effects. Inflammatory mediators are released which can cause the “sepsis syndrome” of vasodilatation or vasoconstriction, activation of the clotting cascade or depression of cardiac function. Septic shock is a manifestation of many types of shock that develop as a result of the initial infection:

- Reduced intravascular volume (hypovolaemic shock)
- Peripheral pooling of intravascular fluid (distributive shock)
- Impaired myocardial function and deranged cellular metabolic functions (cardiogenic shock)

Early phase (compensated) or “warm shock” is often not apparent in children. In this phase in adults extremities are usually warm, but cold peripheries are much more common in children.

3.1.2 Treatment

Fluid resuscitation is essential to survival in the management of paediatric septic shock. A large volume of fluid is usually required in septic shock (initial resuscitation often requires 40-60 ml/kg but can be as much as 200 ml/kg), and a mixture of colloids and crystalloids may be satisfactory. Sepsis is one type of shock with some evidence to suggest that colloids are the superior replacement fluid. Gaining access to administer fluid can be very difficult and intraosseous access may be required.

Vasopressors/Inotropes should only be given when there has been appropriate fluid resuscitation but the child remains in a low cardiac output state. The choice will depend on the situation as septic shock may produce low cardiac output and high systemic resistance; high cardiac output and low systemic resistance or low cardiac output and low systemic resistance.

As for adults dobutamine or mid-dose dopamine is the first choice of support if there is ongoing hypotension (low CO) despite adequate fluid resuscitation. However children <12 months old can be less responsive to these agents. If this is ineffective, then adrenaline or noradrenaline can be used. Adrenaline is used far more in paediatric sepsis than in adults. Some places advocate the use of low-dose adrenaline or noradrenaline first-line for cold, hypodynamic shock.
Vasodilators (e.g. SNP or GTN) can be useful when there is low CO and high systemic resistance. Phosphodiesterase inhibitors clearly also have a valuable role here and in many places may be used in preference to a vasodilator.

**Antibiotics / Antiviral / Antifungal**
Rapid treatment with broad spectrum cover is necessary until the cause of the sepsis is identified. It is usual to treat with drugs that cover the most likely causative organisms in a child of that age, taking into account the recent history / possible exposure.

**Steroids**
The use of steroids in septic shock remains controversial; however their use appears rational despite being unproven in trials. In septic shock it is known that a large percentage of patients (>75%) had adrenal insufficiency and this group may benefit from low-dose steroid replacement if adrenal insufficiency is demonstrated (for instance by a synacthen test). Inotrope-resistant patients may also benefit. Children most likely to benefit are those with severe septic shock and purpura, but long term adverse events are not known. Children who have been on steroids previously and those with pituitary or adrenal abnormalities may be unable to increase their endogenous steroid production and should have replacement therapy during any intercurrent illness. Doses suggested for steroid therapy in sepsis vary hugely and no consensus has been reached and can vary from hydrocortisone 1-2 mg/kg up to “shock doses” of 50mg/kg.

**Correction of haematological disorders**
Vitamin K, fresh frozen plasma (FFP) and platelet transfusions are commonly used to correct most coagulopathies. Activated Protein C has been used in children following good trial results in adults and promising early studies in children, however most centres now consider that the potential benefits do not outweigh the risks associated with using it. Indeed some trials have been halted suggesting that outcome is worse in severe sepsis and septic shock in children.

**Gastrointestinal tract management**
In shock a patient is unlikely to be able to feed enterally and is at higher risk of stress ulcers. Ranitidine is most commonly used in prophylaxis.

**Renal support**
Renal impairment is almost inevitable in septic shock although measures should be taken to minimize the damage. Maintaining sufficient circulating volume and blood pressure is crucial to keeping the kidneys well perfused. It may be that renal support in the form of haemofiltration is required. In sepsis some centres have tried haemofiltration to remove the harmful circulating toxins, but to date this is not proven to be effective.

**ECMO**
When conventional maximal critical care measures to ensure adequate ventilation and/or cardiac output have failed then ECMO is the only remaining option. It provides full oxygenation and circulatory support without the need to stress the lungs and heart any further, allowing these organs time to recover. Most centres that do ECMO provide cardiovascular support only for their post-operative patients; however the
bigger national centres take respiratory patients, such as those with acute respiratory distress syndrome (ARDS) and meconium aspiration.

Task 5.5
Familiarise yourself with the Surviving Sepsis Campaign and understand the essence of the guidelines. [3, 4] and www.survivingsepsis.org

3.2 Cardiogenic shock (failure of the heart pump)

3.2.1 Pathology
Cardiogenic shock is not common in children; however it does account for a large number of admissions to PICU. The major cause of this is surgical repair of congenital heart disease. However other causes include: cardiomyopathy, myocarditis, arrhythmias, hypoxic and ischaemic events, prolonged shock, metabolic abnormalities, hypoglycaemia, hypocalcaemia, acidosis, trauma, hypothermia, drugs, and sepsis.

3.2.2 Treatment (see management of acute heart failure)
In addition:
Myocardial contractility – factors impairing contractility should be corrected first, e.g. correcting hypoxia or electrolyte imbalance.

3.3. Hypovolaemic shock (lack of blood volume)

3.3.1 Pathology
Hypovolaemic shock is caused by a decreased intravascular blood volume, which leads to a decreased venous return and myocardial preload (and thus reduced cardiac output). Although one of the most common causes of shock in paediatrics, it is less commonly seen in PICU as it is usually dealt with in emergency settings such as Accident and Emergency (A&E).

Causes of intravascular fluid depletion (lack of blood volume) include;
- Haemorrhage (e.g. trauma, surgery, gastro-intestinal bleeding)
- Water and electrolyte losses (e.g. vomiting, diarrhoea, diabetes insipidus, renal losses, heat stroke, burns)
- Plasma losses (e.g. burns, nephrotic syndrome, sepsis, peritonitis, intestinal obstruction

All of these losses may be external or internal, i.e. third space losses, when intravascular fluid leaks into the interstitial space.

3.3.2 Treatment
Initial treatment is rapid fluid replacement with the choice of fluid that most closely matches the fluid lost.
- Significant blood loss should when possible be replaced by blood
- Water and electrolyte losses should be replaced by crystalloids
- Plasma losses will respond best to albumin solutions
The other essential aspect to the treatment of hypovolaemic shock is treating the cause e.g. for haemorrhage a rapid control of blood loss is necessary and this may mean emergency surgery.

### 3.4 Distributive shock (maldistribution of intravascular fluid)

#### 3.4.1 Pathology

Distributive shock is when, although the intravascular blood volume may be normal, it appears reduced by maldistribution. This means that the intravascular fluid has redistributed/pooled in either the peripheral circulation (e.g. due to vasodilatation as can occur in all of the causes listed below) or when fluid has leaked into the tissues. The difference between distributive shock and hypovolaemic is that the fluid can return to the circulation if the cause of the shift is reversed. With hypovolaemic shock the fluid must be replaced because it has been lost. So although distributive shock can resemble hypovolaemic shock clinically, the causes and subsequent treatment is very different.

Causes of distributive shock include:
- Anaphylaxis
- Neurological injury
  - head injury (brainstem)
  - spinal shock (which occurs with cord transection above T1 causing total loss of sympathetic cardiovascular tone)
- Septic shock (early phase)
- Drugs (barbiturates, phenothiazines, tranquilisers, antihypertensives)

#### 3.4.2 Treatment

Treatment is dependent on the cause:
- Anaphylaxis requires good airway management (most will have rapid onset of bronchoconstriction as well as the maldistribution of the intravascular fluid)
  - Aggressive fluid replacement is needed.
  - The removal of the causative agent if possible.
  - Adrenaline is administered as soon as possible and is the one time in PICU when 1 in 1,000 is given IM. Rarely, in life-threatening shock IV adrenaline will be used if the IM dose has been ineffective.
  - Additional treatment includes steroids (usually hydrocortisone 2-4 mg/kg every six hours) and chlorphenamine IV. Further agents can be used to reverse the bronchoconstriction e.g. nebulised adrenaline, nebulised salbutamol and IV aminophylline.
- Neurological injury is managed by vasoconstrictors e.g. noradrenaline.
- Drugs (overdose) need to be managed by the removal of the drug (e.g. gastric lavage or CVVH), an antidote if one is available and then managing the symptoms.
3.5 Obstructive Shock (obstruction to blood flow from the heart)

3.5.1 Pathology
- Obstructive cardiac and Great Vessel lesions
  Many congenital or acquired structural heart and great vessel lesions are responsible for shock in newborns and young infants (e.g. critical aortic stenosis, atrioventricular valve stenosis, pulmonary valve stenosis, critical coarctation of the aorta, interrupted aortic arch)
- Cardiac tamponade is an emergency situation when there is a leak of fluid into the pericardial sac (membranous sac surrounding the heart). When this fills rapidly with fluid it causes a pressure on the heart which prevents the ventricles from filling and thus blood flow from the heart.
- Pneumothorax. If air enters into the pleural cavity, where there is normally a vacuum it can cause compression of the lungs and can be critical.
- Pulmonary embolism is rare in children, although increasing in frequency with more invasive and aggressive therapy. It is mostly due to venous thromboembolism, however it can also be due to fat or air emboli.

3.5.2 Treatment
For most of the causes of obstructive shock emergency surgery is required to release the obstruction. The only cause treatable medically is venous thromboembolism where heparin can be used (and sometimes streptokinase or alteplase), however if this fails, surgery may be necessary here too.

3.6 Dissociative shock (failure of the circulation to transport oxygen)

3.6.1 Pathology
Causes of dissociative shock include:
- Anaemia
- Methaemoglobinemia
- Carbon monoxide poisoning

Anaemia is the lack of haemoglobin, thus reducing the capacity to transport oxygen in the blood. In methaemoglobinemia and carbon monoxide poisoning there is a loss of the ability of the haemoglobin to transport oxygen in the blood.

3.6.2 Treatment
Treatment will depend on the cause. For severe anaemia it will necessitate urgent blood transfusion (packed red blood cells or whole blood to replace the lack of haemoglobin). Methaemoglobinemia will require 100% oxygen. Methylthionium chloride (methylene blue) and blood transfusions may be required. Carbon monoxide poisoning also requires 100% oxygen and symptomatic management.
4. Arrhythmias (see case study Cardiovascular – arrhythmias)

4.1 Introduction to Arrhythmias

4.1.1 Anatomy and physiology
The normal heart has a number of structures and pathways, which will control the rate, and rhythm of the heart. (See Figure 5.6). Exceptions to these pathways can occur in some congenital conditions.

The Sino-Atrial (SA) node located in the posterior wall of the right atrium near the superior vena cava, controls heart rate and rhythm under normal circumstances, hence the term ‘sinus rhythm’. Electrical impulses are generated spontaneously (also known as automaticity) within the SA node by specialised ‘pacemaker’ cells and are then conducted cell to cell across the atria, leading to atrial contraction.

The Atrio-Ventricular (AV) node, located between the right atria and the ventricles acts as a gate-keeper controlling the passage of electrical impulse form the atria to the ventricles. Also if the automaticity of the SA node was to fail then these pacemaker cells would take over, albeit at a slower rate.

The Bundle of His (or AV bundle) and left and right bundle branches carry the electrical current from the AV node to located at the top of ventricles to the apex (or base) of the ventricles

The Purkinje Fibres, then conduct the current throughout the ventricular tissues, to stimulate contraction of the ventricles from the apex upwards, to ensure efficient ejection of blood during ventricular systole.
4.1.1.1 Understanding an ECG

Figure 5.7 Phases of an ECG

1. **P wave**: atrial depolarisation,
2. **QRS complex**: ventricular depolarisation,
3. **T wave**: repolarisation of the ventricles during diastole.
4. **PR interval**: the distance between the beginning of the P wave and the beginning of the QRS corresponds to the slowing of conduction as the electrical impulse passes through the AV node. For example if there is a block in the AV node then the PR interval will increase.
5. **QT interval**: from the beginning of the Q wave to the end of the T wave, and represents ventricular depolarisation and repolarisation.
6. **ST segment**: from the beginning of the S wave to the beginning of the T wave, represents the period during which the ventricles are depolarised.

**Membrane Potential (See Figure 5.8)**
The movement of electrolytes, in particular potassium, sodium and calcium ions, is key to myocardial contraction. The membrane is most permeable to potassium ions and relatively impermeable to other ions, however there are a number of ion exchange pumps and mechanisms that contribute to the propagation of a membrane potential.

Figure 5.8 Membrane potential

**Phase 4: Resting state**, there is higher concentration of potassium ions inside the cells and more sodium and calcium ions outside cells. This creates a negative electrical charge (membrane potential) across the cell membrane and is associated with diastole.

**Phase 0**: Rapid depolarisation phase. The fast sodium channels open, allowing a large influx of sodium into the cell. This leads to the development of a positive membrane potential. The speed with which this happens determines how quickly the next cell
will depolarise and therefore how quickly the impulse will be propagated across the heart.

**Phase 1:** This occurs with the closure (inactivation) of the fast sodium channels, and the outward movement of potassium ions causes the slight downward deflection of the current. Phases 0 and 1 correspond to the R and S waves of the Electrocardiogram (ECG). The *refractory period* is the time during which another action potential cannot fire, and corresponds directly to the time it takes for the sodium channels to recover from inactivation. It acts as a protection mechanism to allow the heart sufficient time to eject blood from its chambers.

**Phase 2:** Plateau phase. When there is a large enough voltage change across the cell membrane, voltage-sensitive calcium channels open to allow an influx of calcium ions, which prolongs the action potential and refractory period. Potassium also starts to move out of the cells. This corresponds to the ST segment of the ECG.

**Phase 3:** The calcium channels close, but potassium continues to move out of the cells, allowing repolarisation and restoration of the membrane potential. This corresponds to the T wave on the ECG.

Contraction of the myocardial cells occurs at the point of depolarisation. The atria contract significantly earlier than the ventricles because conduction though the AV node is slower than through atrial or ventricular pathways.

Heart rate is adjusted by the autonomic nervous system. For example, during exercise, sympathetic stimulation of the SA node increases the influx of calcium ions. This allows cells to reach threshold potential quicker, and the rate of electrical conduction and contraction therefore increases. Conversely, parasympathetic stimulation via the vagal nerve increases the outflow of potassium ions. Cells therefore take longer to reach the threshold potential and heart rate decreases.

Secondary pacemaker cells in the AV node, the bundle of His and the Purkinje fibres can also generate action potentials spontaneously, but because the SA node generates action potentials more quickly, these impulses are usually overridden by the SA nodal rate.

![Figure 5.9 Normal ECG](image-url)
Task 5.6
If possible, observe a 12 lead ECG being taken. Ask the doctor to explain the ECG to you.

Try to identify the sections on the ECG that correspond to the following:
1. atrial conduction
2. ventricular conduction pathway
3. repolarisation

4.1.2 Pathophysiology

Arrhythmias may arise in children or be the reason for admission to PICU due to a number of causes:
- Congenital abnormalities
- Trauma to the conductive tissue from cardiac surgery
- Drug induced toxicity
- Electrolyte imbalance

A vast array of arrhythmias are possible however the most commonly encountered arrhythmias are Supraventricular Tachycardia (SVT) including Junctional Ectopic Tachycardia (JET), Ventricular Tachycardia (VT), Bradycardia and Heart Block (HB).

The two main mechanisms of arrhythmia are abnormalities in impulse formation e.g. malfunctioning SA node, impulses generated by areas other than the SA node, and abnormalities in impulse conduction e.g. complete or partial block of the conduction pathways or additional electrical (accessory) pathways.

4.1.3 Diagnosis

A 12 lead ECG is essential, however information on the clinical status and haemodynamic stability (e.g. serum magnesium, calcium, potassium and lactate), and the presence or absence of a waveform on the LA or CVP trace, is also important for the diagnosis, and may affect the therapeutic options.

4.1.4 Pharmacological Treatment

Anti-arrhythmic drugs usually aim to restore or maintain sinus rhythm, but can also be used to control the heart rate without resolving the underlying arrhythmia.

Classification of anti-arrhythmic drugs

The Vaughan Williams classification groups drugs according to their electrophysiological effects at a cellular level i.e. their ability to affect the movement of electrolytes during the generation of an action potential.

Class I drugs act by blocking the fast sodium channels, and therefore delay phase 0 of the action potential. This group can be further subdivided into:
Class II drugs act by modifying sympathetic stimulation of heart rate by blocking the beta-receptors. They increase the time taken to reach the threshold potential during phase 4 slowing SA and AV nodal impulses and therefore heart rate. They are useful for SVT’s. Examples include atenolol, esmolol, propranolol.

Class III drugs act by blocking the potassium channels, and therefore prolong the plateau of phase 2, delaying repolarisation and prolonging the action potential. E.g. amiodarone

Class IV agents block the movement of calcium ions during phase 2. Since calcium shifts are the primary determinant of depolarisation in the SA node and AV node they are particularly sensitive to the effects of calcium channel blockers. Only the non-dihydropyridine calcium channel blockers, diltiazem and verapamil, have effects on conduction, however verapamil is rarely used in children due to instances of profound hypotension and death.

Not classified: Digoxin slows conduction in the AV node and prolongs the refractory period that increases AV nodal delay. Adenosine, blocks AV nodal conduction, preventing re-entrant tachycardias through the node.

4.2 Specific arrhythmias

4.2.1 Junctional Ectopic Tachycardia (JET)

4.2.1.1 Pathophysiology

There are 2 types of JET: Congenital and Postoperative. Postoperative JET is the one that is most commonly seen on PICU and is usually associated with trauma to the heart, and is thought to be secondary to trauma, haemorrhage or inflammation of the conduction tissue e.g. resection of the muscle bundles in cardiac surgery, commonly associated with Tetralogy of Fallot (TOF) repair. JET has also been associated with low magnesium levels following cardiopulmonary bypass surgery and the use of dopamine.

JET is characterised by a rapid heart rate for the child’s age (i.e. 180+ beats per minute) that is driven by a focus with abnormal automaticity within or adjacent to the Bundle of His or AV node. There may or may not be ventriculoatrial (VA) dissociation i.e. complete dissociation between the atrial and ventricular rate which may compromise cardiac output.

The incidence varies from 5 – 20%, and is increased in children < 6 months old. It is usually transient and begins in the early postoperative period i.e. hours, and may last up to 72 hours. The combination of postoperative myocardial impairment plus tachycardia, and the potential problem of VA dissociation can result in low cardiac output.
Figure 5.10 Junctional Ectopic Tachycardia

The ECG (See Figure 5.10) will show:

- Narrow QRS complex
- P waves buried within or retrograde to the QRS complex
- Possible complete dissociation between the atrial and ventricular rate

4.2.1 Management

- Correction of electrolyte abnormalities – maintain potassium >4, ionised calcium >1.2 and magnesium >1
- Cooling to 34-35°C to reduce sympathetic stimulus and therefore slow heart rate
- Optimisation of sedation and consider paralysis: to reduce sympathetic stimulus (i.e. catecholamine release) from the body
- Minimising the catecholamine intake e.g. inotropes, where possible
- Treatment of any hypovolaemia
- If the above is not successful in reducing the heart rate sufficiently then IV Amiodarone may be given.
- Pacing of the atria +/- ventricles to allow atrio-ventricular synchrony, once the heart rate is <160 beats per minute.
- ECMO is very occasionally needed if JET (accompanied with low cardiac output) is not managed using the above measures.

4.2.2 Supraventricular Tachycardia (SVT)

4.2.2.1 Pathophysiology

SVT is an all encompassing term for tachycardias arising from above the ventricles and includes atrial tachycardia, atrial flutter, atrial fibrillation, atioventricular nodal re-entry tachycardia and atrioventricular re-entry tachycardia (AVRT). The type of SVT most commonly seen in childhood is AVRT, and usually involves an accessory pathway such as that in Wolff-Parkinson-White syndrome (WPW).

An accessory pathway is an electrical connection between the atrial and ventricular myocardium. AVRT uses this accessory pathway and the AV node as the 2 pathways for the re-entry circuit. The accessory pathway usually has a longer refractory period than the AV node. When an electrical impulse is propagated it passes down these two
pathways, however if the pathway with the longer refractory period (i.e. accessory pathway) has not recovered from the previous impulse then it is not able to pass down it. It will therefore pass down the 2\textsuperscript{nd} pathway. If movement down the 2\textsuperscript{nd} pathway is slow enough to allow the 1\textsuperscript{st} pathway time to recover then the impulse will pass back up the 1\textsuperscript{st} pathway to the original starting point and establish a re-entry circuit. Conduction therefore moves from the atrium to the ventricle (antegrade) through the AV node and then from ventricle to the atrium via the accessory pathway (retrograde), stimulating the atrium and ventricle to beat at 150 – 300 beats per minute (~300 in infants and reduces as age increases).

WPW syndrome has an accessory pathway that conducts more quickly than the AV node. This means that there is early activation of ventricular tissue also known as pre-excitation. This is seen on an ECG as a short PR interval and ‘slurred’ initial portion of the QRS complex (delta wave). (See Figure 5.11)

![Figure 5.11 ECG of Wolf Parkinson White syndrome](image)

Only around 50\% of children with AVRT have any structural heart disease. Idiopathic AVRT is more common in infants than in older children, with a peak incidence in the first 2 months of life. WPW syndrome is present in 10-20\% of patients with AVRT. SVT may be well tolerated in the first instance, however with sustained tachycardia, there will be evidence of cardiac compromise. Sometimes the heart rate will be so fast that it will compromise cardiac output from the start.

The ECG (See Figure 5.12) will show:
- Narrow QRS complexes
- Abnormal or difficult to detect P waves

![Figure 5.12 ECG showing Supraventricular tachycardia](image)

### 4.2.2.2 Management

The aim of treatment is to convert to sinus rhythm.
- Vagal Manoeuvres: stimulating the vagus nerve, sometimes results in slowed conduction of electrical impulses through the AV node of the heart e.g. Valsava manoeuvre – patient forcible exhales against a closed nose (older children); provoking gag reflex; ice to the face.
• IV Adenosine: transient slowing of AV nodal conduction
• If clinically unwell: Cardioversion or IV amiodarone; If well and the heart is structurally normal with good function: IV Flecainide (although such measures should only be taken under the direction of a consultant paediatric cardiologist)
• Digoxin may be used if WPW syndrome has been ruled out

Once in sinus rhythm and to prevent recurrences (and following discussion with paediatric cardiologist):

• If exercise related and/or SVT was well tolerated: propranolol +/- digoxin
• If not then use oral flecainide
• Do not use digoxin if suspect WPW syndrome, as through suppressing AV node conduction it can enhance accessory pathway conduction. Verapamil should also be avoided as collapse and sudden death have been reported with the use of this drug.
• Ablation is an option for refractory cases.

4.2.3 Ventricular Tachycardia (VT)

4.2.3.1 Pathophysiology
Ventricular tachycardia, as its name suggests is a tachycardia that arises directly from the ventricles. Ventricular tachycardia is defined as 5 or more consecutive ventricular ectopics. This is considered sustained VT if the duration is greater than 30 seconds or non-sustained if the VT spontaneously reverts to sinus rhythm within 30 seconds. It may be associated with a number of causes: scarring from previous cardiac surgery, myocarditis, cardiomyopathy, drug toxicity (e.g. digoxin, cocaine, tricyclic antidepressants,) electrolyte abnormalities (Mg, K, Ca), long QT syndrome, and arrhythmogenic right ventricular dysplasia. Similarly to SVT’s the origin of the arrhythmia may be re-entry or automaticity. The heart rate is usually between 120 –180 beats per minute and may be associated with cardiac compromise.
The ECG (See Figure 5.13) will show:
• Prolonged QRS complex
• Absent P waves and AV dissociation

Figure 5.13 ECG showing ventricular tachycardia

4.2.3.2 Management
• Treatment of causes where possible e.g. electrolytes, drug toxicity, hypoxia
• If cardiac output is maintained then IV amiodarone can be given
• Cardioversion can be used where drug therapy is unsuccessful or there is cardiac compromise.
4.2.4 Heart Block (Atrioventricular Block)

4.2.4.1. Pathophysiology

Heart block arises from the malfunction of the AV node with diagnosis made using the ECG. Heart block can be categorised, depending on the severity of this malfunction, into 3 categories.

- **First Degree:** Usually as a result of impaired AV conduction e.g. impulse is delayed, leading to a long PR interval. This may be due to: drugs, trauma to the AV node, ischemia, inflammation, or fibrosis. Although not serious in itself, it may be a warning sign before progression to serious disease.

  ![Figure 5.14 First degree heart block](image)

- **Second Degree:** PR interval is lengthened to the point where some impulses are not transmitted. Some but not all P waves are followed by a QRS complex.

  ![Figure 5.15 Second degree heart block](image)

- **Third Degree (Complete Heart Block):** There is no relation between the atrial and ventricular rhythms. The atrial rate is typically faster than the usually slow ventricular rate (the ventricle are depolarised by an impulse generated within the AV node or ventricle itself). Trauma during cardiac surgery is the most common cause of Complete Heart Block (CHB). They will usually present immediately after surgery with a slow ventricular rates. 40-60% of patients who have CHB post surgery will recover normal AV conduction, though if not, permanent pacing will be needed.

  ![Figure 5.16 Complete heart block](image)

4.2.4.2 Management

- Pacing
4.2.5 Sinus Bradycardia

4.2.5.1 Pathophysiology

Sinus bradycardia arising from sinus node dysfunction i.e. impulse propagation, can result from increased vagal tone, hypoxia, ischaemia, raised intracranial pressure, hypothyroidism, hypothermia, drug toxicity (e.g. beta blockers), and prior cardiac surgery (esp. ‘switch’; Fontan; ASD)

Heart rates are <100 beats per minute in neonates and infants and < 60 beats per minute in the older child.

4.2.5.2 Management

- No intervention is needed if there is no cardiac compromise and the patient is otherwise well
- Treatment of reversible causes e.g. hypoxia; drug toxicity
- Drug therapy can include Atropine: to reduce vagal tone; Isoprenaline to stimulate beta receptors for chronotropic effect (if too much hypotension with this through beta-2 effects, can use adrenaline instead)
- Pacing

5. Extracorporeal Membrane Oxygenation (ECMO)

5.1 Introduction

ECMO may also be known as extracorporeal life support (ECLS), and is essentially temporary mechanical support for patients with heart and/or lung failure that cannot be managed adequately using pharmacological treatment alone.

The aims of ECMO are:

1. To restore adequate oxygen delivery to the vital organs.
2. To provide time and optimal conditions for heart and/or lung recovery.
3. Where appropriate, to provide a ‘bridge to transplant’ in the patient awaiting heart or heart-lung transplantation

Therefore prior to using ECMO, consideration is made as to whether recovery is even possible by using it.
5.2 Anatomy and physiology

This diagram (Figure 5.17) shows a traditional ECMO circuit which most centres have now moved away from using. In this circuit blood is removed from the body via the venous cannula, passes through the bladder box (which is a safety device in the circuit that detects any changes in the flow of blood from the body), then through the roller-pump, which provides return pressure for the blood, through the oxygenator and finally through the heater which re-warms the blood prior to returning the blood to the body via the arterial cannula. The bridge allows recirculation when the patient is clamped off.

There are two kinds of pump that may be used in the ECMO circuits – roller pumps (see figure 5.17) and centrifugal pumps (see Figure 5.18). The latter is now most commonly used, as it generates a ‘sucking force’ which is less destructive to blood cells and has additional safety features. With the use of centrifugal pumps many ECMO centres have also removed the bladder box, so circuits are much shorter and hold much smaller volumes of blood and so have less circuit-associated problems.
ECMO may be referred to as either ‘respiratory or VV’ or ‘cardiac or VA’. This depends on how the circuit is set up, and where the blood is removed and then returned to the body.

In respiratory or VV ECMO only the lungs are bypassed, therefore ECMO provides only oxygenation, with the patients own heart maintaining circulation. In this circumstance a double lumen catheter is usually placed in the internal jugular vein, with deoxygenated blood being taken out of the body at that point, passed through the ECMO circuit to be oxygenated, and then oxygenated blood is returned back into the internal jugular.

In cardiac or VA ECMO both lungs and heart are bypassed with ECMO providing both circulation and oxygenation. Blood may be removed from the neck vessels e.g. internal jugular, and returned to the carotid artery. However, when VA ECMO is used post cardiac surgery it is more common to use the cardiopulmonary bypass cannulae therefore removing blood from the right atrium and returning into the aorta.

In some circumstances where an oxygenator is not required then it may be possible to use a left or right ventricular assist device (L or RVAD) to replace the pumping action of the heart, but utilise the patient own lungs for oxygenation. The ‘Berlin Heart’ now being used in some specialist centres utilises this concept however the device is portable and may be used when bridging a patient to transplant and can be used for much longer periods than ECMO.

In addition to the above many ECMO circuits also run with a haemofilter +/- dialysis to aid urine output and fluid management.
Task 5.7

If you have an ECMO patient on your unit (if your unit doesn’t do ECMO, then consider arranging to visit another trust that does), arrange for the nurse looking after the patient to show you the ECMO circuit, and its components. Find out where they administer drugs to the patient.

5.3 Indications for cardiac ECMO

Cardiac ECMO should be considered when severe circulatory failure is unresponsive to intensive resuscitation and myocardial recovery is likely or cardiac transplantation is an option.

Specific indications include: cardiac failure following open-heart surgery, sometimes referred to as ‘rescue’ ECMO; myocarditis; cardiomyopathy; pulmonary hypertension, and arrhythmias.

Contraindications to cardiac ECMO are child <2kg; <34/40 weeks gestation; irreversible organ dysfunction; and a contraindication to the use of systemic anticoagulation.

5.4 Management

As mentioned previously one of the aims of ECMO is to provide adequate end organ oxygen delivery. Therefore the following measures are used to assess the success of ECMO: lactate; urine output; acid-base balance; mixed venous (not arterial as this would only measure the blood levels after it has been oxygenated by ECMO) oxygen saturations.

Inotropes

Inotropes are not usually necessary when a patient is on full ECMO and would only increase myocardial oxygen demand. However they will be started when a trial off ECMO is deemed appropriate. In this instance usually milrinone + adrenaline or dopamine will be commenced and the flow rate of blood around the ECMO circuit reduced to minimal levels. If the patient tolerates this then the patient will be taken off ECMO. However if the patient becomes haemodynamically compromised, then full ECMO will be recommenced.

Vasodilators

Vasodilators are often necessary to maximise perfusion and reduce afterload, as well as to manage hypertension that arises from the circuit. (mostly associated with VA ECMO). Sodium nitroprusside, glyceryl trinitrate or hydralazine is often used in these circumstances.

Anticoagulation

Systemic anticoagulation, usually using heparin, is necessary to maintain the flow of blood around the circuit. It is administered directly into the circuit, on the venous side and titrated according to activated clotting time (ACT). The target range varies between centres (and is often tailored to the individual patient) but is usually 160 – 200 seconds. ACT is a useful parameter that can be monitored at the bedside, and titration of the heparin infusion is managed using this, in conjunction with the full clotting profile processed in the laboratory by Haematology. As bleeding is often a major problem particularly when ECMO is being used post cardiac surgery, it is
essential that coagulation is tightly controlled at all times to prevent major blood loss, as well as thrombus formation in the circuit.

**Antibiotics**

Prophylactic antibiotics are not routinely necessary, however daily cultures are sent and any signs of infection will be treated quickly and aggressively.

### 5.5 Pharmacokinetics of drugs during ECMO

There is very little data available on the pharmacokinetics of drugs when used in patients on ECMO. What little is available may be extrapolated from effects in cardiopulmonary bypass, which differs in terms of length of time on the circuit e.g. few hours vs. few weeks, and also from small uncontrolled trials and in vitro studies. This is further compounded due to the widely varying practices between centres. For example the ECMO circuits themselves differ, and the point of administration of drugs i.e. directly into patient or into circuit will greatly affect the results of these studies. Subsequently no clear dosing guidelines exist for patients on ECMO.

In light of this, an understanding of the potential effects of ECMO on the pharmacokinetics of drugs will guide use in these patients. To summarise:

1. Flow rates will affect how quickly the drug is distributed and therefore the amount of drug available to exert its effect
2. Haemodilution occurs on connection to the circuit and any drug present in the blood has its total blood concentration reduced (due to increased volume from the priming fluid) e.g. a 3 kg patient will have a 125% increase in circulating volume. (dependent on circuit used). This will affect:
   a. Volume of distribution (Vd), particularly for drugs with a small Vd such as gentamicin. This may lead to a reduced peak concentration but also a reduced elimination.
   b. Plasma protein binding due to reduction in the concentration of circulating proteins. This could lead to an increase in the free fraction of a drug and potentiate effect.
3. Drug sequestration. Some drugs may be adsorbed on to the ECMO circuit tubing, which means that less drug is available to exert an effect. e.g. fentanyl, benzodiazepines
4. Physiological changes, as for a critically ill patient e.g. renal and liver impairment; fluid overload; sepsis.

Practically, initial dosing is the same as for any other critically ill patient on PICU, and taking into account co-morbidities such as renal and liver impairment. This should then be guided by levels wherever possible and patient responses, bearing in mind the potentially altered pharmacokinetics of some drugs in ECMO.

**Further Reading**


Low cardiac output syndrome in children (B Jones, M Hayden, J Fraser, E Janes)

**Bibliography**

Cardiovascular Pediatric Critical Illness and Injury (D S Wheeler, H R Wong, T P Shanley)

Practical Approach to Pediatric Intensive Care (P Khilnani)

Handbook of Pediatric Intensive Care (M C Rogers, M A Helfaer)

Children in Intensive Care: A Survival Guide (J H Davies, L L Hassell)

The Pediatric Cardiology Handbook (M K Park)

Essential Pediatric Cardiology (P Koenig, Z M Hijazi, F Zimmerman)

Care of the Critically Ill Child (A Macnab, D Macrae, R Henning)

Pediatric Heart Failure (R Shaddy, G Wernovsky)

**References:**


3. Dellinger RP et al. Surviving Sepsis Campaign guidelines for management of severe sepsis. Crit Care Med 2008; 36(1); 296-327


**Other Critical Care Guidelines**
University Hospitals of Leicester Paediatric Cardiac ICU Handbook (R Ramaiah)
Respiratory Medicine
Julia Simmons

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References
Objectives

- To be able to understand the basic pathophysiology and management options for respiratory diseases (acute asthma, community acquired pneumonia, hospital acquired pneumonia, ventilator associated pneumonia, acute respiratory distress syndrome, acute lung injury)
- To be able to understand the mechanism of action and characteristics of drugs for the treatment of respiratory diseases (acute asthma, community acquired pneumonia, hospital acquired pneumonia, ventilator associated pneumonia, acute respiratory distress syndrome, acute lung injury)
- To be able to describe the mechanism of action, evidence base and use of mucolytics/mucokinetics
- To be able to understand the basic pathophysiology and management of primary and secondary pulmonary hypertension
Introduction

The aim of this section is to discuss the management of some of the most common respiratory diseases encountered on PICU.

1. Asthma [1,2] (Case study Respiratory – asthma)

1.1 Signs and Symptoms

Asthma is defined as a chronic inflammatory disorder causing recurrent episodes of wheezing, breathlessness, chest tightness and coughing associated with airflow obstruction that is often reversible. Status asthmaticus occurs when the bronchospasm and respiratory dysfunction due to asthma become unresponsive to conventional therapy (including inhaled beta2 agonists, oral or IV steroids and oxygen). These patients may progress to respiratory failure and in turn require mechanical ventilatory support and admission to PICU.

More than 20 chromosomal regions have been linked to asthma, but to date no single asthma gene has been identified.

1.2 Pathophysiology

In status asthmaticus, airway hyperresponsiveness, bronchospasm and airway inflammation with mucosal oedema and mucous plugging of the small airways leads to narrow and obstructed airways. The result is easier air entry during inspiration but airflow obstruction during expiration – causing air trapping with each breath and lung hyperinflation. Gas exchange abnormalities (primarily due to ventilation /perfusion (V/Q) mismatch) occur because of distal airway obstruction. V/Q mismatch describes the condition which occurs when areas of lung are not being appropriately ventilated so that the blood passing through these areas is not able to efficiently exchange oxygen and carbon dioxide.

This initially results in hypoxaemia and hypocarbia then, as intercostal and diaphragmatic muscles fatigue, the progressive hypoxaemia and hypercarbia result in respiratory failure. Hypoxemia (or Hypoxaemia) is generally defined as decreased partial pressure of oxygen in blood, sometimes specifically as less than 60 mmHg (8.0 kPa) or causing hemoglobin oxygen saturation of less than 90%. Hypocarbia is a state of reduced carbon dioxide in the blood.

Most children with asthma who are seen in A&E do not require hospital admission. Some present with mild-moderate status asthmaticus and require inpatient care and treatment with oxygen, inhaled bronchodilators, and systemic corticosteroids. Only a small percentage will require PICU admission. Clinical parameters that suggest the need for PICU admission are poorly defined. These usually include those with past PICU admissions or a history of rapid deterioration, those with severe distress despite initial bronchodilator therapy, altered mental status, respiratory arrest, or a rising PaCO2 coupled with clinical signs of fatigue.

Severe status asthmaticus is a life-threatening disorder that, if recognised and treated aggressively, has an excellent outcome.

1.3 Management [2, 3, 4]

As with all treatment of asthma the British Thoracic Society Guidelines should be followed.[4]
1.3.1 Fluids

Critically ill children with status asthmaticus are often dehydrated as a result of decreased oral intake prior to admission, and increased insensible fluid losses from increased work of breathing. Appropriate fluid resuscitation and ongoing maintenance fluid are required, however, over hydration must be avoided.

1.3.2 Oxygen [1]

Most children with severe status asthmaticus will have some degree of mucous plugging, atelectasis, in which the lungs are not fully inflated, V/Q mismatch and hypoxaemia. All will therefore have a need for oxygen therapy.

1.3.3 Corticosteroids

The overriding physiologic derangement in asthma is airway inflammation, and corticosteroids are a mainstay in the management of both acute and chronic asthma. By suppressing cytokine production, granulocyte-macrophage colony-stimulating factor, and inducible nitric oxide synthase activation, the inflammatory process is suppressed. This results in reduced recruitment together with the activation of inflammatory cells, decreased airway mucous production, and reduced microvascular permeability.

As gastric medications may not be tolerated, often on initial admission to the PICU, corticosteroids are given intravenously. The preferred corticosteroid is hydrocortisone injection, 4mg/kg/dose 6 hourly (under 2 years max 25mg, 2-5years 50mg, 5-18years maximum 100mg)[2] until oral steroids are tolerated. Then the therapy should be changed to prednisolone, 2mg/kg (maximum 40 mg) once daily. (If the child has been taking an oral steroid for more than a few days maximum 60mg)[3] Duration of treatment will depend on the severity of illness, but generally continues until the asthma exacerbation resolves.

Short courses of steroids are usually well-tolerated; the main side effects observed in PICU are hyperglycaemia and hypertension. The incidence of myopathy and weakness from long-term steroid therapy can be increased when neuromuscular blocking agents are concomitantly administered to mechanically ventilated children.

1.3.4 Beta₂ (β₂) agonists [2]

As sympathomimetic agents, these cause direct bronchial smooth muscle relaxation and are the mainstay of all asthma therapy. Bronchial smooth muscles express β₂ adrenergic receptors, which are activated by binding with β₂ agonists.

Regular salbutamol nebulisers (2.5-5mg) are the agent of choice, initially nebuliser therapy may need to be given hourly, and then weaned to 4-6 hourly as the patient improves. In children with severe status asthmaticus, where respiratory air flow is limited, a single intravenous salbutamol bolus (child 1 month-2 years; 5mcg/kg, 2-18 years; 15mcg/kg (max 250mcg)[2] followed by a continuous infusion (1-5mcg/kg/min), may be necessary therapy.

The main side effects to watch out for are sinus tachycardia, hypertension, hyperglycaemia, and hypokalaemia. Potassium levels should be checked regularly with regular salbutamol nebulisation or a continuous infusion, and oral /intravenous
potassium supplementation may be needed. High dose salbutamol infusions may also result in lactic acidosis, therefore lactate levels should be checked to monitor for this (commonly lactate levels can be checked on blood gas analysis).

1.3.5 Methylxanthines [1,2]
Methylxanthines promote relaxation of the bronchial smooth muscles but the exact mechanism of action remains controversial. Suggested mechanisms of action include increase of intracellular cAMP levels by blocking phosphodiesterase 4, control of intracellular calcium flux, inhibition of endogenous catecholamine release, and prostaglandin antagonism.

The use of theophylline has decreased since the 1970’s and recent data has made use in the ICU controversial. It may be useful in those critically ill children who are not responsive to steroids, inhaled and intravenous \(\beta_2\) agonists and oxygen.
Aminophylline (a mixture of theophylline and ethylenediamine, which is 20 times more soluble than theophylline) is administered by a bolus loading dose of 5mg/kg (maximum 500 mg) over 20 minutes followed immediately by a continuous infusion of 0.5-1mg/kg/hr. Infants and adolescents will generally require proportionally smaller doses (i.e. < 0.5 mg/kg/hr) as their theophylline clearance is reduced [3].
Theophylline has a narrow therapeutic window, and toxic concentrations can result in serious side effects such as convulsions and arrhythmias. If the child is already taking regular oral theophylline a loading dose will not be required.

The infusion should be adjusted to serum aminophylline levels (ideally measured 2 hours after the loading dose is complete, and daily thereafter), aiming for levels of 10-20 mg/L. It is important to also be aware of the potential for drug interactions with theophylline which can affect the levels, the most common ones encountered on PICU are erythromycin/clarithromycin and ciprofloxacin.

1.3.6 Anticholinergics [1,2]
Ipratropium bromide promotes bronchodilation without inhibiting mucociliary clearance, as occurs with atropine. Aerosolised ipratropium (125-500 mcg nebules 4-6 hourly) antagonises acetylcholine effects by blocking acetylcholine interactions with the muscarinic receptor on bronchial smooth muscle cells. By this mechanism, intracellular cyclic guanosine monophosphate levels are reduced and bronchial smooth muscle contraction is impaired.

In studies, when administered in A&E ipratropium bromide reduced both hospital admission rates and clinical asthma scores, but for hospitalised children ipratropium has no clinical benefit over inhaled \(\beta_2\) agonists and corticosteroids alone. Inhaled ipratropium has not been evaluated in critically ill children with status asthmaticus. While it has no proven benefit in moderately ill children with asthma, it is felt prudent to add inhaled therapy to the management of critically ill children who are not responding to other measures.
Ipratropium has poor systemic absorption and therefore few unwanted side effects. The most common ones to look out for are dry mouth, bitter taste, flushing, tachycardia, and dizziness.
1.3.7 Magnesium sulphate [1,2]

Magnesium acts as a bronchodilator primarily through its activity as a calcium channel blocker and its role in adenylate cyclase in smooth muscle cells. Through this mechanism, magnesium inhibits calcium-mediated smooth muscle contraction and facilitates bronchodilation. The value of magnesium therapy remains controversial. Some studies in A&E[5] demonstrate that intravenous or aerosol magnesium can reduce hospitalisation rates, improve short-term pulmonary function testing and improve clinical asthma scores over time. Other studies have shown no benefit of magnesium treatment. [6] The usual dose is 40 mg/kg/dose (0.16 mmol/kg/dose) intravenously - maximum 2g-over 20 minutes.[2] Possible side effects of hypotension, CNS depression, muscle weakness and flushing are uncommon. Severe complications such as cardiac arrhythmias may occur in the setting of very high magnesium serum levels (>10-12 mg/dL), therefore levels must be regularly monitored. Magnesium is still an unproven therapy in children with severe asthma on PICU, but due to its low risk profile and demonstrated benefit in the A&E setting, it can be considered as an additional therapy for children on PICU who are not responding to the more conventional treatment measures. All children admitted to PICU with status asthmaticus should have their magnesium levels monitored, and levels kept at the upper range of normal (0.8-1 mmol/l).

1.3.8 Helium – oxygen (Heliox) [1,3]

Helium is a biologically inert, low density gas that, when administered by inhalation in a mixture with oxygen (80% helium, 20% oxygen), reduces air flow resistance in small airways by reducing turbulent flow and enhancing laminar gas flow. There are some small studies in non-intubated children with moderately severe asthma where improvements in lung function and clinical asthma scores have been seen with Heliox therapy. In the PICU, the use of Heliox in mechanically ventilated children reduces peak airway pressure by lowering airway resistance, and may enhance weaning from mechanical ventilation. However, to date, Heliox is an unproven therapy in critically ill children with status asthmaticus. It may have a role in children receiving high pressure mechanical ventilation who are not improving with conventional therapy.

1.3.9 Ventilation [1]

Currently <1% of children with status asthmaticus require mechanical ventilation. Children who receive mechanical ventilation are at increased risk of pulmonary barotrauma, nosocomial infection, pulmonary oedema, circulatory dysfunction, steroid/muscle relaxant induced myopathy, and death. If asthmatic patients are intubated, histamine-producing agents such as morphine or atracurium should be avoided. Ketamine is the common agent used for induction of these patients because of its relatively long half-life, bronchodilating properties, and relative preservation of haemodynamic stability. The opioid of choice while mechanical ventilation is ongoing is fentanyl. Extubation should occur as soon as possible, as the presence of the tube in an awake child may irritate the airway and induce further bronchospasm.
1.3.10 Chest physiotherapy

This may improve airway clearance and encourage resolution of mucous plugging. It should only be considered in children with clear segmental or lobar atelectasis.

1.3.11 Antibiotics

Most asthma exacerbations are triggered by viral infections. Lower respiratory tract infections do occur in children with status asthmaticus, the most common organism is *Mycoplasma pneumoniae*. If fever, chest x-ray and leucocytosis suggest pneumonia, appropriate antibiotics should be started. Sinusitis is a common non-pulmonary infection found in children with status asthmaticus. If the child has a high fever and leucocytosis, but no bacterial pneumonia is present, sinusitis should be considered and appropriate antibiotics considered.

1.3.12 Extracorporeal Membrane Oxygenation Support – ECMO

This should be considered when maximal medical therapy is failing and can only be undertaken in certain specialist PICUs.

1.4 Summary

Mortality rates for children with severe status asthmaticus who arrive at the hospital intact are nearly zero. Nearly all asthma deaths occur in children who suffer a cardiopulmonary arrest prior to arrival to hospital. Improved outpatient management strategies are necessary to reduce these deaths.

2. Pneumonia

2.1 Introduction[1]

Pneumonia is an inflammation of the lung parenchyma. The cause is most commonly infectious, but it may be due to aspiration (of food or gastric juices) or be due to a drug or radiation induced pneumonitis. Pneumonia usually presents with signs of opacity on X-ray. Bronchopneumonia is the term used when there are multiple opacities on X-ray, and is associated with a more severe clinical presentation. Pneumonia is one of the most frequent infections in children and one of the main causes of hospitalisation.

A diagnosis of pneumonia is high on the list of differential diagnoses in children who present with fever, cough, tachypnea and an infiltration on chest x-ray (although other disease processes may also have these signs such as bronchiolitis). Ultrasound may give more detail about pleural effusions, and chest CT scans can be useful to detect an empyema or more complex abnormalities. (An empyema is a collection of pus within the lung pleura.) If symptoms persist despite empiric therapy, bronchoscopy with bronchoalveolar lavage (BAL) can be carried out.

Pneumonia can be classified according to anatomic location (lobar, lobular, alveoli, or interstitial), or the causative organism, or the location where it was acquired community (community acquired pneumonia (CAP)) or nosocomial – (e.g. ventilator-associated pneumonia (VAP)).
2.2 Types of Pneumonia and their Treatment [9] [10]

2.2.1 Community-acquired pneumonia

Community-acquired pneumonia is usually defined as a lung infection with acute symptoms (fever, cough, dyspnoea), associated with altered pulmonary auscultation (crackles) or with the presence of an acute infiltrate in chest X-ray in a child not previously hospitalised for at least 14 days before the first symptoms. In infants <1 year old infection is most likely due to viral causes. Table 6.1 shows the most likely organism and appropriate first line antiviral treatment. Table 6.2 details the most likely bacterial causes and appropriate antibacterial treatment.

<table>
<thead>
<tr>
<th>Age</th>
<th>Likely viral organism</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal period (up to 2 months)</td>
<td>Varicella zoster</td>
<td>Varicella zoster Immunoglobulin + Aciclovir</td>
</tr>
<tr>
<td></td>
<td>Herpes simplex</td>
<td>Aciclovir</td>
</tr>
<tr>
<td></td>
<td>Cytomegalovirus (CMV)</td>
<td>Ganciclovir +/- Foscarnet</td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>Rhinovirus Coronovirus Measles Mumps Rubella</td>
<td>Supportive therapy</td>
</tr>
<tr>
<td></td>
<td>Cytomegalovirus (CMV)</td>
<td>Ganciclovir +/- Foscarnet</td>
</tr>
<tr>
<td></td>
<td>Influenza (including H1N1)</td>
<td>Oseltamivir/zanamivir</td>
</tr>
<tr>
<td></td>
<td>Respiratory Syncytial Virus (RSV) Parainfluenza Adenovirus</td>
<td>If severe- ribavirin (possibly palivizumab for severe RSV)</td>
</tr>
<tr>
<td></td>
<td>Varicella zoster Herpes simplex</td>
<td>Aciclovir</td>
</tr>
</tbody>
</table>

Table 6.1 Causative organisms of viral pneumonia (Modified from Ref 1,11)
<table>
<thead>
<tr>
<th>Age</th>
<th>Likely organism -bacterial</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal period (up to 2 months)</td>
<td><em>Group B streptococcus</em></td>
<td>Benzylpenicillin or cefotaxime + gentamicin</td>
</tr>
<tr>
<td></td>
<td><em>Staph. aureus</em></td>
<td>Flucloxacillin or Vancomycin (if MRSA suspected)</td>
</tr>
<tr>
<td></td>
<td><em>Chlamydia trachomatis</em></td>
<td>Erythromycin</td>
</tr>
<tr>
<td></td>
<td><em>Bordetella pertussis</em></td>
<td>Erythromycin</td>
</tr>
<tr>
<td></td>
<td><em>Listeria monocytogenes</em></td>
<td>Amoxicillin or ampicillin</td>
</tr>
<tr>
<td></td>
<td><em>Congenital syphilis</em></td>
<td>Benzylpenicillin or procaine benzylpenicillin</td>
</tr>
<tr>
<td>2months – 5 years</td>
<td><em>Streptococcus pneumoniae</em></td>
<td>1&lt;sup&gt;st&lt;/sup&gt; line Cefuroxime/co-amoxiclav 2&lt;sup&gt;nd&lt;/sup&gt; line Ceftriaxone</td>
</tr>
<tr>
<td></td>
<td><em>Haemophilus influenzae</em></td>
<td>1&lt;sup&gt;st&lt;/sup&gt; line Cefuroxime/co-amoxiclav 2&lt;sup&gt;nd&lt;/sup&gt; line Ceftriaxone</td>
</tr>
<tr>
<td></td>
<td><em>S. aureus</em></td>
<td>Flucloxacillin or Vancomycin (if MRSA suspected)</td>
</tr>
<tr>
<td></td>
<td><em>Bordetella pertussis</em></td>
<td>Erythromycin or Azithromycin</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td><em>S. pneumoniae</em></td>
<td>1&lt;sup&gt;st&lt;/sup&gt; line Cefuroxime/co-amoxiclav 2&lt;sup&gt;nd&lt;/sup&gt; line Ceftriaxone</td>
</tr>
<tr>
<td></td>
<td><em>Haemophilus influenzae</em></td>
<td>1&lt;sup&gt;st&lt;/sup&gt; line Cefuroxime/co-amoxiclav 2&lt;sup&gt;nd&lt;/sup&gt; line Ceftriaxone</td>
</tr>
<tr>
<td></td>
<td><em>Mycoplasma pneumoniae or Chlamydia pneumoniae</em></td>
<td>Erythromycin or macrolide of choice</td>
</tr>
<tr>
<td>Immunocompromised children (e.g. HIV positive or post-transplant)</td>
<td><em>Pneumocystis carinii (PCP)</em></td>
<td>Co-trimoxazole</td>
</tr>
</tbody>
</table>

Table 6.2 Causative organisms of bacterial pneumonia (Modified from Ref 1,11)
2.2.2 Nosocomial Pneumonia

If a pneumonia is acquired 48-72 hours after hospitalisation it is considered nosocomial in origin. If the patient has been ventilated during this time, the episode will be considered ventilator-associated pneumonia (VAP). Identifying and reducing the incidence of VAP is the focus for infection control teams on many PICUs. The airways are colonised by pathogens from pharyngeal, intestinal sources, and or hospital flora. They include *Pseudomonas aeruginosa*, *Klebsiella spp.*, *Escherichia coli*, *Enterobacter spp.*, *Serratia marcescens*, and *Acinetobacter spp.*. Gram positive agents include *S. aureus* and *S. pneumoniae*, and fungi including *Candida albicans*.

2.2.3 Aspiration Pneumonia

This occurs most commonly in children with obstructive lesions of the gastro-intestinal (GI) tract, diseases with hypotonia, dysautonomia, compromised consciousness or gastro-oesophageal reflux disease (GORD). GI contents are aspirated or regurgitated causing a chemical pneumonitis.

2.3 Pathogenesis

First line defence against respiratory pathogens is the mucous membrane and mucociliary layer. Bacteria get into the respiratory tract either by direct tracheal colonisation (ventilator tubing can take the pathogen straight into the trachea) or by direct invasion of the pulmonary parenchyma. Once the bacteria arrive in the respiratory tract, a normal inflammatory response (including antibodies, complement, phagocytes, and cytokines) begins and causes injury to the pulmonary tissue.

2.4 Signs and symptoms

In the presence of pneumonia, the white cell count can be >25000/mm³. C-reactive protein (CRP) and Erythrocyte sedimentation rate (ESR) are usually raised. Bacterial blood cultures should be sent to determine the causative pathogen. Viral culture or Polymerisation chain reaction (PCR) may be useful to guide treatment in immunocompromised children. If the chest x-ray indicated mycobacterium and/or if the patient has high risk factors for tuberculosis infection, tuberculin PPD test should be performed.

2.5 Treatment [2] [11]

2.5.1 Age-related antibiotic therapy

In the first 3 weeks of life *Group B Streptococci* and gram negative bacteria are most common and respond well to treatment with third generation cephalosporins. Amoxicillin (or ampicillin) should always be added to cover for possible listeria infections.

In children > 5 years a macrolide (erythromycin/clarithromycin/azithromycin) should be added to cover *Mycoplasma* infection. Drug choice will depend on hospital antibiotic guidelines; consideration should be given to the need for good central venous line access if intravenous erythromycin is to be given. Despite the increased
cost, the simplified regime of oral azithromycin once daily for three days may be more straightforward to achieve. Where the patient has a severe infection ceftriaxone, with or without macrolides, is usually used. Neonates are at greater risk of calcium-ceftriaxone precipitation than older children, particularly if born prematurely or if they have impaired bilirubin binding. Therefore cefotaxime should be the drug of choice for neonates and patients who are likely to need IV calcium corrections or TPN.[2] Where there is a likelihood of S. aureus (or a prevalence of MRSA) vancomycin should be added.

2.5.2 Empiric treatment of nosocomial pneumonia

Initial treatment should cover gram positive and gram negative pathogens. Usually cefuroxime/co-amoxiclav will provide adequate cover. If there is no improvement in the patient’s condition a second line agent should be considered e.g. piperacillin-tazobactam. If there are risk factors for fungal infection fluconazole (or Ambisome) will be added. If the patient has received a bone marrow graft, or has lymphoma, leukaemia, or HIV, treatment for PCP should be added (high dose co-trimoxazole – or pentamidine nebulisers may be considered if the patient is already severely neutro and leucopenic).

2.5.3 Specific Pneumonia Treatment

For the treatment of infections caused by C. trachomatis and M. pneumoniae, a macrolide is the drug of choice. For patients where S. pneumoniae is suspected, therapy is driven by local antimicrobial susceptibility patterns and will usually either be ceftriaxone or co-amoxiclav. Occasionally vancomycin may be added for S. pneumoniae if cephalosporin resistance is suspected.

When infection is due to Haemophilus influenzae, co-amoxiclav can be used first-line, or ceftriaxone in severe cases as some H. influenzae strains are now resistant to co-amoxiclav and occasionally to cefuroxime.

The most appropriate length of treatment has not been established for most infections. In S. pneumoniae, treatment should be maintained until the child has no fever for at least 72 hours, and total duration of therapy should be between 10 and 14 days.

2.6 Complications

Complications include pleural effusions, empyema, extrapulmonary infection and sepsis, acute respiratory distress syndrome (ARDS), shock, lung abscess, pneumothorax, atelectasis, and multiple organ system dysfunction. Pleural effusion and empyema are the most common of the complications.

2.6.1 Pleural effusion

Pneumonia with pleural effusion is defined by the presence of fluids in the pleural cavity; it is termed empyema when this fluid contains pus. S. pneumoniae is responsible for most cases, S. aureus and S. pyogenes (Group A streptococcus) are also sometimes responsible. Tuberculosis is another frequent cause of pleural effusion.

If a diagnosis of pleural effusion is made a thoracentesis may be performed to remove fluid from the chest through a needle or tube. Thoracentesis (also known as pleural
tap) is an invasive procedure to remove fluid or air from the pleural space. Conservative treatment of pleural infection consists of isolated antibiotics with or without drainage. Most small parapneumoic effusions respond to antibiotics without the need for additional intervention. However, pleural effusions that compromise breathing in an ill, feverish child must be drained. If the child has a significant pleural infection, a thoracostomy tube should be inserted. This is a flexible plastic tube that is inserted through the side of the chest into the pleural space. It can be used to remove air (pneumothorax) or fluid, or pus from the intrathoracic space.

Initial empiric IV antibiotic therapy should cover *S. pneumoniae*. Broad spectrum antibiotics are needed for nosocomial infections, post surgery, trauma, and aspiration. The antibiotic choice is then guided by microbiologic results. Intrapleural fibrinolytics may shorten length of hospital stay and are recommended if the effusion contains loculated thick fluid or empyema. Only urokinase treatment has been analysed, it should be administered twice a day for 3 consecutive days (10,000 units in 10 ml Sodium chloride 0.9% for children <1 year, 40,000 units in 40ml Sodium Chloride 0.9% in children >1 year old.). Surgical treatment (including thoracotomy and decortication) may be considered for patients who remain septic due to persistent pleural collection despite chest thoracostomy and antibiotics. [9,10] Decortication involves the surgical removal of the surface layer and is usually performed when the lung is covered by a thick, inelastic pleural peel restricting lung expansion.

2.7 Summary

Most children who develop pneumonia do not have long-term sequelae. Children with non-complicated effusions respond well to conservative treatment, without any residual lung lesion. In contrast to adults, children have a better ability to resolve pleural thickness without any subsequent detrimental effect in lung growth and function.

3 Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS)[1]

ALI and ARDS have multiple causes but an important feature in the pathogenesis of both diseases is the inflammatory response of the host.

3.1 Treatment

Currently there are no innovative targets for therapeutic intervention. Drug trials have not identified an agent that improves clinically important outcome measures in the management of all patients with ALI and ARDS. The mainstay of therapy remains supportive care, and most importantly, the application of positive pressure ventilation. Significant reduction in mortality has been shown in studies where low tidal volume mechanical ventilation has been used and this is now part of ICU management. Where conventional ventilation is failing High Frequency Oscillatory Ventilation may be of benefit. Other action including steroids, fluid restriction, surfactant, prone positioning, steroids and inhaled nitric oxide are theoretically beneficial, but will not benefit all patients.
4. Acid Base Balance [12]

Acid-base balance is measured in a PICU setting using arterial blood gas samples. Patients will already have arterial lines in situ and samples can therefore be taken from the line freely and painlessly. There are 3 main measurements obtained that can be used to decide on a patient’s acid base balance.

1. pH and lactate
2. Respiratory function (oxygen, carbon dioxide and saturation)
3. Metabolic measures (bicarbonate, base excess)

4.1 pH (potential hydrogen) and lactate

pH concentration of ions measures acidity and alkalinity. Chemically neutral pH is 7 but human blood is slightly alkaline, normally ranging between 7.35-7.45. pH measures overall acid-base balance of the blood sample. Acid-base balance is affected by both respiratory and metabolic function. An abnormal pH does not identify whether problems are respiratory or metabolic, or both, in origin.

The body will always strive to maintain homeostasis (i.e. a blood pH of 7.35-7.45) and may stimulate an opposing abnormality of the other component (e.g. a metabolic acidosis stimulating a respiratory alkalosis) to maintain a normal pH. This is called compensation and can only be identified by looking at pH together with both respiratory and metabolic results.

Lactic acid can be produced from anaerobic metabolism and poor perfusion (e.g. in shock). High levels can cause a life-threatening metabolic acidosis. Normal blood lactate levels are 1 mmol/l or less.

4.2 Respiratory function

4.2.1 Carbon Dioxide ($P_aCO_2$) (partial pressure of arterial carbon dioxide)

The normal range of $P_aCO_2$ is 4.5-6 kPa.

Carbon dioxide is produced by cells as a waste product of metabolism. The normal response to hypercapnia (> 6 kPa) is via the respiratory centres to increase rate and depth of breathing in order to remove more carbon dioxide. Conversely, hypocapnia (<4.5 kPa) reduces the stimulus to breathe, so decreasing respiratory rate and depth. Therefore, arterial carbon dioxide levels indicate ventilation, the amount of air moving in and out of the alveoli. In a healthy person, respiratory responses can restore a life-threatening pH of 7.0 to 7.2-7.3 within about 10 minutes.

Hypoventilation (which may occur with respiratory failure) can lead to hypercapnia and hypoxia, due to the inability to remove carbon dioxide to maintain normal levels. This is when non-invasive ventilatory support may be needed. Hypocapnia occurs with hyperventilation which can result from artificial over-ventilation or in compensation for metabolic acidosis, which can be treated with bicarbonate or THAM (tris(hydroxymethyl)aminomethane, trometamol.)

When carbon dioxide gas produced by cells diffuses into capillary blood it mixes with water to form carbonic acid. Arterial carbon dioxide therefore indicates the amount of carbonic acid, so hypercapnia creates a respiratory acidosis, while hypocapnia creates a respiratory alkalosis. However, as carbonic acid is a relatively weak acid, relatively
large amounts of carbon dioxide would need to be retained in order for a respiratory acidosis to occur. Carbonic acid usually dissociates back to water (which is removed through urine) and carbon dioxide (which is removed through the lungs).

\[ \text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{H}_2\text{CO}_3. \]

4.2.2 Oxygen (P\textsubscript{a}O\textsubscript{2}) (partial pressure of arterial oxygen)

The normal range of P\textsubscript{a}O\textsubscript{2} is 11.5-13.5 kPa.

Hyperoxia (>13.5 kPa) is extremely rare unless patients are given too high concentrations of oxygen. If this occurs for a sustained amount of time this has the potential to cause toxic damage. More common is hypoxia (<11.5 kPa), occurring as a result of respiratory failure, where patients require supplementary oxygen to maintain adequate tissue oxygenation. For short term use during acute crises, e.g. post cardiac arrest, oxygen toxicity is not an issue and maximal (100%) oxygen can be given. Hypoxia may be caused by hypoventilation, in which case carbon dioxide will be raised, however, as oxygen is far less soluble than carbon dioxide, any disease where the fluid barrier between alveolar air and pulmonary blood is increased (e.g. pulmonary oedema or chest infection,) may cause hypoxia while carbon dioxide remains normal (normocapnia). Hypoxic patients require oxygen.

4.2.2.1. Saturation (S\textsubscript{a}O\textsubscript{2}) of haemoglobin by oxygen

Normal oxygen saturation level is about 97%. The relationship between partial pressure of oxygen in arterial blood (P\textsubscript{a}O\textsubscript{2}) and saturation of haemoglobin in arterial blood by oxygen (S\textsubscript{a}O\textsubscript{2}) is complex, and is represented by the oxygen saturation curve. The S-shaped curve represents significant changes in P\textsubscript{a}O\textsubscript{2} with minimal changes in S\textsubscript{a}O\textsubscript{2} at higher levels while changes in S\textsubscript{a}O\textsubscript{2} accelerate while changes in P\textsubscript{a}O\textsubscript{2} reduce at lower levels.

Saturation measures the percentage of haemoglobin (H\textsubscript{b}) that is saturated by oxygen (it does not actually measure the H\textsubscript{b}). Therefore if two patients have saturations of 97%, but one has an H\textsubscript{b} of 14g/dl and the other an H\textsubscript{b} of 7g/dl, the first has 97% of the 14g/dl saturation and the second 97% of 7g/dl. The first patient therefore has about twice the amount of oxygen in the arterial blood. Therefore H\textsubscript{b} should always be checked when considering the relevance of oxygen saturation results.

4.2.3 Respiratory Failure

Respiratory failure is defined by the British Thoracic Society [14] as an arterial oxygen level below 8 kPa and represents the result of there being inadequate oxygen in the blood.

There are two types of respiratory failure.

**Type 1 respiratory failure** is defined as P\textsubscript{a}O\textsubscript{2} < 8kPa and P\textsubscript{a}CO\textsubscript{2} < 6kPa.

Carbon dioxide is 20 times more soluble than oxygen[15] so diseases that increase the fluid barrier between alveolar air and pulmonary blood, such as pulmonary oedema, may cause hypoxia while carbon dioxide levels remain normal (normocapnia).

**Type 2 respiratory failure** is defined as PaO2 < 8kPa and PaCO2 > 6kPa (BTS 2002).

When breathing is shallow or slow, insufficient carbon dioxide will be removed from the blood, causing high blood carbon dioxide (hypercapnia) in addition to hypoxia.
In summary, in type 1 respiratory failure carbon dioxide remains normal, in type 2 respiratory failure, insufficient carbon dioxide is removed from the blood, resulting in hypercapnia as well as hypoxia.

4.3 Metabolic measures

4.3.1 Bicarbonate (HCO$_3$)

*The normal range is 24-27 mmol/l.*

Bicarbonate is the main chemical buffer in plasma so levels indicate metabolic acid-base status. Bicarbonate is produced in the liver and kidneys so low levels can be due to producing insufficient quantities of buffer e.g. in liver failure. Carbonic acid is the main acid in blood. It can dissociate into bicarbonate and a free hydrogen radical, resulting in production of bicarbonate from respiratory acidosis. Conversely, bicarbonate and a hydrogen free radical can form carbonic acid.

\[
\text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{HCO}_3^- + \text{H}^+
\]

So bicarbonate, used to measure metabolic acid-base balance, can be increased as a result of hypercapnia.

4.3.2 Base Excess (BE)

*The normal level is ±2.*

Metabolic acid-base balance is also represented by base excess. BE measures the number of moles of acid or base needed to return 1 litre of blood to pH 7.4 (assuming P$_a$CO$_2$ remains constant at 5.3kPa). BE means an excess of base (alkali). With metabolic alkalosis there is an excess of base but with metabolic acidosis, there is a negative BE.

4.3.3 Compensation

In health, the body maintains homeostasis which for the blood is pH of 7.35-7.45. When the body remains healthy, imbalance of either respiratory or metabolic function will be compensated for by an opposite imbalance of the other. However, while altering respiratory rate and depth can (with a healthy respiratory system) normalise blood pH in a few minutes, metabolic responses take considerably longer. A patient’s history often helps decide what compensation is occurring.

Compensation when pH in normal range:
- Respiratory acidosis (P$_a$CO$_2$ > 6kPa)
- Respiratory alkalosis (P$_a$CO$_2$ < 4.5kPa)
- Metabolic acidosis (HCO$_3$ < 22, BE < -2)
- Metabolic alkalosis (HCO$_3$ > 28, BE > 2)

Metabolic control relies on:
- Hydrogen loss in urine
- Production and re-absorption of chemical buffers such as bicarbonate, phosphate, and proteins by the liver, kidney and GI tract
- Production of metabolic acids from cells and in the stomach
- Absorption of acids and alkalis from the diet (and/or TPN)
5. Pulmonary Hypertension  (See case Respiratory – Pulmonary hypertension)

Pulmonary hypertension (PH) is a blood vessel disorder of the lung, in which the pressure in the pulmonary artery rises above normal levels and can become life-threatening[15]. It is defined as Pulmonary Artery Pressure \( \geq 25 \) mmHg at rest or 30 mmHg on exercise[16].

There are two main categories of PH, pulmonary venous hypertension and pulmonary arterial hypertension. Pulmonary arterial hypertension is the most common in childhood and can be sub-divided into Idiopathic Pulmonary Arterial Hypertension (IPAH) – formerly known as Primary Pulmonary Hypertension – and Associated Pulmonary Arterial Hypertension (APAHI) usually associated with congenital heart disease.

5.1 Signs and Symptoms

In pulmonary hypertension the muscle fibres in the walls of the arteries thicken and develop hypertrophy. Vasoconstriction occurs as the production of vasodilators such as nitric oxide (NO) and prostacyclin are impaired and expression of vasoconstrictors such as endothelin-1 is increased. This causes a marked increase in pulmonary vascular resistance (PVR). The increase in PVR forces the right ventricle to work harder which reduces blood flow to the lungs, (causing desaturation, and hypoxia) and eventually having an effect on cardiac output.

The PVR can be affected by
- **Endothelins** – potent vasoactive modulators which affect smooth muscle cells in the vascular wall.
- **Carbon dioxide and Hydrogen ion concentration** – acidosis causes pulmonary vasoconstriction and alkalosis pulmonary vasodilatation
- **Oxygen** – hypoxia is a potent pulmonary vasoconstrictor, thus increasing PVR
- **Lung volume** – poorly or over inflated lungs can cause an increase in PVR
- **Nitric Oxide** – relaxes arterial smooth muscle causing pulmonary vasodilatation and reducing PVR

5.2 Therapeutic Options

5.2.1 Inhaled Nitric Oxide

Nitric oxide is a potent and selective pulmonary vasodilator. It acts on cyclic guanosine monophosphate (cGMP), resulting in smooth muscle relaxation. It is delivered in concentrations of 5-10 ppm. Dependency can occur with high doses and prolonged use. To avoid rebound pulmonary hypertension the drug is discontinued slowly and in a controlled manner. If this is problematic it may be helped by the use of sildenafil.

Excess nitric oxide can cause methaemoglobinaemia and methaemoglobin levels should be measured regularly, especially in neonates. Nitric oxide increases the risk of bleeding by inhibiting platelet aggregation, but does not usually cause bleeding.
5.2.2 High Frequency Oscillation Ventilation (HFOV)
Studies have shown that HFOV can be as effective as inhaled nitric oxide in treating PHT. The two therapies can also be combined for more successful results.

5.2.3 Prostaglandins [2]

**Epoprostenol (Flolan)** - A potent non-specific vasodilator. It is a chemically unstable medication with a short half-life which requires continuous intravenous infusion. It can cause systemic hypotension, and it inhibits platelet aggregation, and so patients are at risk of haemorrhage. Ongoing treatment can cause tolerance and patients may require dose increases.

**Iloprost** is a synthetic analogue of epoprostenol. It is more stable and has a longer half-life and is available in an inhaled preparation. Experience in children is limited.

5.2.4 Sildenafil
Sildenafil is a selective phosphodiesterase-5 Inhibitor. It increases intracellular cyclic guanosine monophosphate (cGMP) concentrations which results in smooth muscle relaxation, and pulmonary vasodilatation [2,18]. Sildenafil can also help prevent rebound pulmonary vasoconstriction on withdrawal of NO therapy. It is used orally at doses of up to 2 mg/kg six hourly [2](although starting doses will be smaller). There is no licensed liquid preparation, but extemporaneous preparations can be prepared. [19-24]

5.2.5 Endothelial Antagonists
In pulmonary hypertension the concentration of endothelin (a potent vasoconstrictor) is raised. Drugs such as bosentan block the endothelin A receptors and thus cause pulmonary vasodilatation.[25]

5.2.6 Magnesium
Magnesium is a powerful smooth muscle relaxant acting as a calcium antagonist. It can improve oxygenation and reduce the effects that hypoxia can cause on the PVR.

5.2.7 ECMO
ECMO can be considered for reversible PH which fails to respond to all other therapies. Further information on ECMO is available in the cardiology section.

References:

3. St Mary’s Hospital PICU Clinical Guidelines, Status Asthmaticus, Aug 06
5. Cheuk DKL, Chau TCH, Lee SL. A meta-analysis on intravenous magnesium sulphate for treating acute asthma. Arch Dis Child 2005; 90; 74-77

6. Rowe et al. Magnesium sulphate for treating exacerbations of acute asthma in the emergency department. Cochrane Database of Systematic Reviews 2006 Issue 4

7. Camargo et al. Continuous versus intermittent beta-agonists for acute asthma. Cochrane Database of Systematic Reviews 2006 Issue 4


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Gastro-intestinal system
Venetia Horn

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11. Role of the dietitian

References
Objectives

- To understand the nutritional requirements of children of all ages
- To understand the effects of disease and treatments on the calorie requirements of critically ill children
- To understand the pathophysiology and treatment of congenital gut malformations e.g. exomphalos and gastroschisis
- To understand the pathophysiology and risk factors for the development of necrotising enterocolitis (NEC)
- To understand the basic pathophysiology and risk factors for the development of stress ulceration
- To understand the different options for feeding patients (parenteral and enteral nutrition, percutaneous endoscopically placed gastrostomy etc)
- To understand the indications for different feeding routes and the implications they have for the drug administration (absorption mechanisms, sites of absorption, interactions and side effects)
- To understand the basics of parenteral nutrition (carbohydrate, lipid, protein, electrolytes, and volume)
- To be able to identify and manage refeeding syndrome
- To understand the mechanisms of action, characteristics, and clinical use of antiemetics, prokinetics, laxatives and antidiarrhoeals
- To understand the role of the dietitian
1. Nutrition

1.1 Introduction

In infancy and adolescence, children are particularly sensitive to energy restriction due to high basal anabolic requirements. Therefore these children are at particular risk of nutritional problems occurring due to catabolic states induced by disease or sepsis. Poor nutrition at critical periods of growth results in slowing and stunting of growth, but catch up growth may be exhibited when liberalisation of feeding occurs. Organs may grow and differentiate at one particular time. Substrate intakes modulate the early maturation and differentiation of the developing central nervous system. The neonatal brain accounts for 14% of body weight compared to 2% in adults [1] and have high metabolic demands during early childhood. The brain grows rapidly during the first year of life and during this time it is sensitive to periods of malnutrition and metabolic insult. Malnutrition during infancy may be associated with intellectual impairment.

In utero, there is rapid growth and differentiation. In the third trimester, the body weight is doubled within 6 weeks depending upon substrate availability; energy stores are laid down and accretion of many trace elements occur. For infants, there is rapid growth of tissue and organ development with increased nutritional requirements per kg body weight and limited body stores. There is also immature body function of the gastro-intestinal tract, metabolism and renal function. If there is unbalanced substrate supply, then there is high risk of physiological consequences. The clinical consequence of inadequate nutrition is the failure to gain weight and length. Whilst the body increases in size, there is a regulated change in body structure, composition and function. The growth rate of different organs varies with age in set patterns. The effect of a nutritional insult will vary according to the age of the child. Adverse nutritional events at critical periods of childhood can ‘programme’ nutritional phenotype resulting in irreversible lifelong effects. [1][2] Growth can be divided into three characteristic phases: infancy, childhood and puberty.

1.1.1 Infancy

Growth is at a rapid, but decelerating rate. The time of most rapid growth is during the first few months of life when length increases by 14–22cm/year. Birth weight is approximately doubled by 4-5 months and tripled by 1 year but does not quadruple until 2 years. Birth length increases by 50% in the first year but does not double until 4 years. [3] Head circumference increases by 25% over the first year with the brain growing 200%. [4]

During infancy there is a transition from foetal growth that is driven by maternal nutrition and insulin regulated, to the childhood growth hormone led-growth pattern by 2–3 years of age. [4]

Infants and in particular the newborn have a high body surface area: weight ratio with high relative heat losses and energy requirements. Small infants have minimal nutrient reserves and immaturity of organs that limits their ability to adapt to insufficient or over supply of nutrients. For example, renal immaturity constrains the ability to conserve sodium and water and deal with a high solute load. Healthy infants need approximately three times more energy per kg body weight than adults [1], mainly due to the additional metabolic requirements for growth.
1.1.2 Childhood

This is a relatively slow hormonal-led period of growth. Children from 2 years to puberty gain an average of 2-3kg per year and 5-8cm increase in height per year. Growth closely follows the genetically predetermined centile. Percentile height at about 2 years is closely related to adult height.

1.1.3 Puberty

Growth velocity almost doubles from 5cm/year to 8-10cm/year. The growth spurt imposes an increased demand for calcium, iron, B vitamins and a minor increase in trace elements. [3] Adolescence is characterised by huge increases in lean body tissue particularly in boys and an increased proportion of body fat in girls. Pubertal growth spurt is dependant on sex steroids, insulin growth factors and thyroid hormone. Delayed pubertal growth spurt is due to chronic illness, severe undernutrition or constitutional factors.

1.2 Growth Monitoring

All children admitted to hospital should be weighed and measured and plotted on growth centile charts. Growth should be measured over time and any previous heights and weights (e.g. in hand held red record books) should be plotted and compared with current measurements. The centile is size related to the age-specific population. Deviation from the child’s usual centile will accelerate their growth velocity when recovering from a growth impairing influence.

1.3 Energy requirements

Early metabolic programming of later health is a factor to consider in the role of nutrition in children and infants. There is an association between genetics and the environment during early development, which determines later function in adult life. High weight gain should be avoided in infancy to avoid consequences of diabetes and heart disease in adulthood. [1]

Four factors determine the metabolic demand for energy and nutrients: the genetic makeup of the individual, activity levels, any existing pathology and the stage of growth. Energy is required for maintenance of body, metabolism and growth and requirements vary with age. Infants require more calories if fed enterally compared to parenterally. [5] Different disease states, illness and sepsis will alter energy requirements accordingly. (See parenteral nutrition and nutrition in critical care).

2. Nutrition in critical care

2.1 Anatomy and physiology in children

The body composition of children is quite markedly different from adults with respect to the quality of protein available in times of injury or stress. As a percentage of body weight, the protein stores of adults are approximately twice those of neonates. Lipid stores are also lower though carbohydrate reserves are constant across the age groups.
Not only do neonates and children have reduced stores but they have much higher baseline requirements. Children have a lower percentage of muscle and fat mass but higher resting energy expenditure. The resting energy expenditure for the low birth weight premature infant is 3 times that for adult. Protein requirements for the premature neonate to maintain growth rate approximating those in utero are 3.5 times the requirement for protein balance in the adult. Children are therefore more susceptible to the consequences of prolonged catabolic stress and in particular critically ill children.

2.2 Metabolic response to stress

The body prepares for severe life threatening illness by mounting a hormonal neuroendocrine stress response that is essential for survival and recovery. Neuroendocrine dysfunction is associated with a worsened outcome. Neuroendocrine refers to the hormone signalling between the hypothalamus, pituitary gland and peripheral body systems. The neuroendocrine response to sepsis or stress involves activation of the hypothalamus-pituitary-adrenal axis. Shock and hypoperfusion has a direct effect on pressure and volume receptors in the hypothalamus. Circulating cytokines also stimulate hypothalamus activity and afferent pulses from site of injury. Stimulation of the hypothalamus releases corticotrophin releasing hormone (CRH) and growth releasing hormone (GRH), which in turn stimulates the pituitary gland to release adenocorticotropic hormone (ACTH) and growth hormone. These hormonal stimuli induce α and β adrenergic activity and a rise in catecholamine secretion from the adrenal medulla. Only transient levels are seen with minor injury. For major injury, high levels of catecholamines may be present for days or weeks after the initial insult [8]. See Figure 7.1

![Figure 7.1 Neuroendocrine Response to stress](image)

The neuroendocrine response to injury or stress results in a rise in the secretion of catabolic hormones cortisol, glucagon and catecholamines with insulin resistance and results in the diversion of substrates to healing from formation of new tissue or growth. Cortisol is secreted by the adrenal cortex in response to ACTH and rises for 24-48 hours after surgery or injury. The renal aldosterone and system is also stimulated, which causes water and salt retention. Thyroxine levels may fall largely due to the decrease in levels of binding protein but the change in triiodothyronine (T3)
is more significant. Glucagon increases glucose synthesis and increases protein breakdown. Adrenaline and noradrenaline increase glucose synthesis and increase fat and protein breakdown. There is also a decrease in glucose use, decreased insulin and decreased fat and protein synthesis. Hyperglycaemia increases pro-inflammatory cytokine production. [9] In the flow phase, high insulin levels are accompanied by insulin resistance. Insulin resistance ensures continued carbohydrate production, diminished oxidation and reduced glycogen storage.

The metabolic response is mediated by catabolic hormones, insulin resistance plus cytokines, eicosanoids, oxygen radicals and other local mediators. Insulin and growth hormone resistance results in the catabolism of endogenous stores of protein, carbohydrate and fat to support the ongoing metabolic stress response. During critical illness, changes in growth hormone secretion lead to a growth resistant state with suppressed insulin like growth factors and elevated growth hormones.

Anti-oxidative defences are depleted during response to cytokines increasing the risk of up-regulating inflammatory processes and tissue damage. Pro-inflammatory cytokines interleukin 1, interleukin 6, and TNF-α are produced in response to a wide range of stimuli e.g. infection, cancer, injury, and surgery. Their role is to defeat invading organisms and restore the body to normal but excessive production may result in increased morbidity and mortality.[8] Profound metabolic changes occur due to their actions and these changes influence protein, fat, carbohydrate, energy and micronutrient metabolism and may precipitate malnutrition. For example, TNF-α induces decreased lipoprotein lipase activity leading to increased serum levels of triglycerides, cholesterol and hyperglycaemia. [10][11]

The metabolic response to stress is characterised by an increase in the basal metabolic rate and muscular catabolism commonly observed after complex surgery, severe sepsis, multiple trauma and extensive burns. The stress response can only be reversed with reduction of the causative factor e.g. infection, or inflammation. Nutritional support reduces a negative nitrogen balance but does not reverse catabolism but can reduce the net tissue loss and maintain function. [8]

### 2.3 Protein metabolism

Proteins are in a constant state of flux and exist as either proteins or in the free amino acid pool. In critically ill children, the turnover can be doubled in patients with severe burns or on ECMO due to respiratory failure.

Amino acids are redistributed away from skeletal muscle to injured tissues, cells involved in the inflammatory response and to the liver in times of critical illness. The liver produces more acute phase proteins e.g. CRP, fibrinogen and less nutrient transport proteins such as albumin. Prolonged periods of catabolism lead to an immune system, which is severely compromised and physiological deficit of the body against infection.

A high protein turnover allows immediate synthesis of proteins required for inflammatory response and tissue repair. This process requires energy either by an increase in the resting energy expenditure or by the energy used for growth being redistributed. Patients exhibit both an increase in whole body protein synthesis and protein degradation but degradation dominates leading to a negative protein balance. This may manifest as weight loss, negative nitrogen balance and skeletal muscle wasting.[12] It is usually impossible to achieve positive nitrogen balance due to ongoing cytokine and catabolic hormone cascade preventing adequate anabolism.
Skeletal muscle is catabolised to produce glucose which is the preferred substrate for the brain, red blood cells, renal medulla, immune system and an energy source for injured tissues. Illness increases gluconeogenesis. The catabolism of skeletal muscle is a short term mechanism of providing glucose but because of limited stores, cardiac muscle and respiratory muscle become utilised leading to cardiopulmonary failure. Supplementation improves nitrogen balance but protein degradation rates remain unaffected.

Neonates and children are particularly susceptible to the loss of lean body mass and increased morbidity and mortality. Infants have a higher protein turnover and are avid retainers of nitrogen. They demonstrate a 25% higher protein turnover after surgery, 100% increase in urinary nitrogen excretion with bacterial sepsis and 100% increase in protein breakdown in patients, who are ill enough to require extracorporeal membrane oxygenation. [6]

In critically ill children there is an increased protein, carbohydrate and lipid use and a negative nitrogen balance. The most important nutritional intervention for critically ill children is sufficient dietary protein to optimise protein synthesis, facilitate wound healing and the inflammatory response plus preserve skeletal muscle protein mass. An excessive protein intake should be avoided because of toxicity particularly in renal failure.

For the acute phase, basal protein requirements for parenteral nutrition are 1.5g/kg/day for infants and 1.0g/kg/day for older children. For the recovery phase, normal requirements are used [13] or 2.5-3.5g/kg/day for infants and 1.5-2g/kg/day for older children. Due to the high splanchnic retention of enteral proteins, the requirements are higher than for parenteral; preterms require 3.5g/kg/day, 0-1 years, 2.5g/kg/day, 1-4 years 2g/kg/day and 1.5g/kg/day for children over 4 years.[14] Higher protein loads may be required in patients with burns. Severely stressed states may require additional protein supplementation so monitoring of growth is essential in chronically ill children.

Serum albumin and other transport proteins measure surrogate visceral protein status. Albumin is distributed between the intravascular and extravascular spaces. Serum levels are influenced by synthesis and degradation rates, vascular losses into the interstitial space and losses through the bowel or kidney. Levels drop due to inflammation, trauma and sepsis where high levels of interleukin 6 stimulate acute phase protein production as it inhibits transport protein production. [15] Hypoalbuminaemia is a marker of systemic inflammatory response syndrome and is associated with an increase of morbidity and mortality amongst hospitalised patients. It is a marker of injury and metabolic response to stress but a poor indicator of nutritional status of the critically ill patient and does not reflect current protein status. A pre-operative albumin level is inversely associated with length of stay, infection, and mortality in surgical infants and children.

2.4 Carbohydrate metabolism

Hyperglycaemia and hypoglycaemia are prevalent on PICU. Non-survivors on PICU have a higher peak glucose and longer duration of hyperglycaemia than survivors. Glucose intolerance and insulin resistance occur due to hormonal and metabolic challenges. Under hypoxic conditions such as injury or sepsis, glucose is converted to lactate, which is converted back to glucose in the liver. This process requires energy, which causes further depletion in hepatic gluconeogenesis and insensitivity to negative feedback normally induced by a high glucose load, a decrease in the
synthesis of glycogen in muscles and decreased clearance and secretion of insulin. Glucose production and availability is a priority in critically ill children. A combination of glucose and amino acids improves protein balance in illness but exogenous carbohydrate does not adequately suppress gluconeogenesis during acute metabolic stress therefore breakdown of skeletal muscle and adipose tissue persists. An elevated respiratory quotient increases the ventilatory burden on the child. Tight glycaemic control with insulin infusions has become an important intervention in adult intensive care units due to the potential decrease in morbidity and mortality. The concern for paediatric patients particularly neonates, is the side effects from hypoglycaemia and risk of brain damage. A multi-centre trial for paediatric patients is currently being undertaken.

2.5 Lipid metabolism

Lipid turnover is accelerated by illness, surgery and trauma. In the period post trauma or in early septic shock, lipid utilisation is compromised, with a rise in plasma triglycerides and a decrease in the metabolism of intravenous lipids. Lipolysis is enhanced to provide free fatty acids for energy and glycerol for gluconeogenesis from the turnover of triglycerides. Glycerol may be converted to pyruvate, which can be used as a gluconeogenic precursor. Energy needs are met by mobilising and oxidation of free fatty acids. 30-40% of the fatty acids released from lipid turnover are oxidised for energy. Free fatty acids become an important source of energy in stressed children due to the accelerated lipid turnover and oxidation. Adding in dietary glucose does not decrease glycerol clearance or diminish lipid recycling. Ketone bodies are an energy source for the brain, which cannot oxidise free fatty acids. Production of ketone bodies is suppressed by insulin levels even at low concentrations but insulin concentrations are high due to the stress response of injury and sepsis. The increased demand for lipid use is coupled with limited fat stores and can lead to essential fatty acid deficiency (EFAD) if administered a lipid free diet. Administration of intravenous lipid results in improved protein use, and does not significantly increase CO₂ production or metabolic rate, and reduces risk of EFAD. Excess lipids are stored as triglycerides and do not augment CO₂ production compared to an excess glucose load. Nutrition should provide both glucose and lipids in stressed patients, many of whom are in respiratory failure. Infants and children with SIRS or sepsis are able to oxidise IV lipid without an increase in lipid peroxidation. This does not preclude the use of lipids in these patients, which has been the practice in many units historically, but close monitoring is required to ensure appropriate utilisation.

Main determinants of fat utilisation are carbohydrate intake and resting energy expenditure. Promoting fat utilisation by reducing carbohydrate to fat ratio in intravenous nutrition reduces free radical activity.

2.6 Malnutrition

Significant alterations in metabolism coupled with minimal reserves can lead to malnutrition. This can persist for up to 6 months after discharge in patients with prolonged ICU stay or with chronic diseases. In patients with congenital heart disease, 65% of patients admitted to PICU have pre-existing malnutrition. Growth in these patients, is linear consistent with chronic malnutrition and these patients are more likely to be underfed whilst on intensive care. 25% of non-cardiac PICU patients...
patients are acutely or chronically undernourished on admission to intensive care and nutritional status declines during their stay.[12] It is more common in patients with severe or chronic disease. The highest prevalence is in children less than 5 years old. [18]

Provision of nutrition is compromised on intensive care due to fluid restriction, a reluctance to feed haemodynamically unstable children, increased severity of illness, administration of vasoactive medicines and interruptions to enteral nutrition (EN) for procedures. Inadequate nutrition in the first few days of admission accounts for 50% of cumulative calorie and protein deficits.[14] The inadequate calorie provision results in poor protein retention particularly with poor protein intake, and contributes to a negative nitrogen balance. Protein energy malnutrition leads to increased morbidity, mortality and increased number of ventilator days and length of stay. Malnourished patients are more likely to develop multi-organ failure. Prolonged inadequate nutrition during intensive care stay increases sepsis and causes protein energy malnutrition, which is often associated with physical instability. Measures to improve nutrition on PICU include use of indirect calorimetry to calculate energy balance and requirements, concentration of enteral nutrition, acceptance of higher gastric aspirates, use of prokinetic agents if appropriate, consideration of post pyloric EN if gastric feeds are not tolerated and increase EN after procedural interruptions. Nutrition support of resting energy expenditure should be initiated within 2 days of PICU admission to avoid rapid nutritional depletion. [19]

2.7 Energy Expenditure

At the onset of severe infection or injury, a decreased metabolic rate and stimulation of the neuroendocrine response has been referred to as the ebb phase. [10] There are two phases of injury response. The ebb or acute phase of stress that lasts for 12 to 48 hours and the flow phase, which generally lasts 7-10 days may continue for weeks or months. The duration of injury response is shorter in children compared to adults and children enter the recovery phase usually within one week. Anabolism then returns with a gradual increase in pre-albumin levels and a decrease in CRP.[19]

Data on hypermetabolic stress response and relationship between severity, type and phase of illness is conflicting in children and calorific goals and energy demands are unclear. [20] Most data for energy expenditure in critically ill patients is in children with burns, adults and preterm infants and there is a lack of research in patients on PICU, which makes evidence based guidelines very difficult to compile.[16] Severe paediatric burns and premature infants represent the extremes of critical illness that drastically effect nutritional status. Over and underfeeding is prevalent in PICU and can result in large energy imbalances and those patients who are under or over nourished suffer a worse outcome. Individualised determination of nutrient requirements is the gold standard.

Basal metabolic rate is the minimum amount of energy required to maintain normal metabolic processes but does not include energy for activity or to process food from the diet. In practice resting energy expenditure is used instead of BMR and only differs by 10%. [13] Resting energy expenditure (REE) includes requirements for growth, energy for physical activity and diet induced thermogenesis. In a healthy infant, the total calorie requirements are 100-120kcal/kg/day of which, 50% is used for the BMR and 30% for growth, 10% diet induced thermogenesis and 10% for activity. [19] Critically ill children who are sedated and mechanically ventilated may have significant reduction in energy expenditure due to decreased activity, decreased...
insensible fluid losses and transient absence of growth during the acute illness. [6][16][19] Few patients have REE of more than 110%. These patients can be overfed if they receive concentrated enteral or parenteral nutrition in excess or when the calorie target is based on predictive equations for growth. [7] Energy expenditure is increased in burns, neonatal sepsis, congenital heart disease and head injury.[21] Head injury and neuromuscular drugs decrease energy expenditure but patients react with an increase in resting energy expenditure resulting in lower than predicted total energy expenditure.[9] In traumatic brain injury, children are hypermetabolic and need individualised nutrition support.[7] In the early stages post severe burns, patients are extremely hypermetabolic and their REE is increased by 50% and returns to normal during convalescence.[11] There is under estimation of their REE using predictive equations compared to measured REE. Careful calculation of requirements should be made as over feeding in severe burns of 120% of energy expenditure augments adipose tissue and does not attenuate the loss of lean body mass. Significant liver deposition of lipid may occur following burn injury. There is a poor correlation between predicted and measured energy expenditure.[14] The hypermetabolism seen in adults is not seen in critically ill children except in particular situations such as burns or head injury.[13][19] Overfeeding increases morbidity. Excessive glucose decreases lipid oxidation, promotes hyperglycaemia and prolongs the duration of mechanical ventilation and length of stay. If surgical infants receive more than 50% above energy expenditure, there is an increase in CO₂ production and lipogenesis. This can lead to significant lipid deposition.

2.7.1 Measurement of energy expenditure

The gold standard for measuring energy expenditure is indirect calorimetry. Indirect calorimetry is a non-invasive, highly validated and reliable method to measure energy expenditure and substrate utilisation. Energy expenditure is determined indirectly through the O₂ and CO₂ that is consumed and produced by the oxidation of carbohydrates, fat and protein. It measures the volume of consumed oxygen (VO₂) and the volume of carbon dioxide produced (VCO₂) and the quotient between the VO₂ and VCO₂ is the respiratory quotient (RQ). Indirect calorimetry provides precise measurements except when there is a huge air leak around the ETT, or when FiO₂ is > 60%, during haemodialysis or continuous renal replacement therapy. [7] The RQ for fat is 0.7, 0.85 for protein and 1.00 for carbohydrate, ketone synthesis and gluconeogenesis < 0.7 and lipogenesis is 2.5.[19] A respiratory quotient (RQ) of > 1.0 determines carbohydrate overfeeding and conversion to fat.[22] In the acute phase of critical illness, the RQ is often close to 1 and during basal energy intake, suggestive of overfeeding. The RQ decreases to normal when the stress response is over, which may indicate resumption of growth and the need for more calories. If the respiratory quotient is more than 0.85 then the result excludes underfeeding. The optimum RQ in paediatric patients is 0.87. [19] Less than 0.85 demonstrates hypometabolism and a low metabolic rate. Hypometabolism or energy expenditure < 90% of the predicted basal metabolic rate can be attributed to mechanical ventilation, sedation, neuromuscular blockade, inhibition of anabolism and decreased activity. A low metabolic rate is associated with protein energy malnutrition, increased morbidity, multi-organ failure and mortality.[7]
It is the most accurate measurement of energy expenditure though is not readily available so predictive equations may be used to calculate. Predictive equations are derived from the measurement of resting energy expenditure in healthy patients. The measurement is multiplied by various factors for physical activity, illness, injury and stress, which are extrapolated from adult research. There may be a pronounced difference between measured energy expenditure and predicted energy expenditure with the risk of over feeding. Predictive equations for appropriate age and condition of the patient must be used e.g. Schofield, the calories must be gradually increased until the target is met and the nutrition should be monitored and adjusted as necessary. The ESPGHAN-ESPEN guidelines recommend the use of predictive equations but without the stress factors to avoid over feeding. [12]

2.8 Nutritional requirements in common diseases

2.8.1 Acute renal failure

25% of patients on a paediatric intensive care unit may develop acute renal failure (ARF) and of these 10% will require continuous renal replacement therapy (CRRT)[14] The need for nutritional support for ARF is due to a number of causes; a loss of lean body tissue, toxicity related to symptoms (anorexia, nausea, vomiting and bleeding), loss of amino acids and plasma proteins during dialytic therapy and metabolic disturbances from uraemic toxins. Critically ill adults and children with ARF have high mortality. Malnutrition is a common finding in patients with ARF and also leads to an increased risk of complications and mortality. Good nutrition can improve prognosis. The aim of nutritional support is to maintain or improve the nutritional status of the patient by providing adequate nutrients without exacerbating any metabolic derangement from uraemia. ARF patients have reduced tolerance to EN due to gastrointestinal motility disorders associated with uraemia.

2.8.1.1 Energy

ARF is not associated with increased energy expenditure. The energy requirements for patients with ARF are no more than 30% of resting energy values.[23]

2.8.1.2 Amino acids

Acute renal failure (ARF) occurs in the setting of shock, trauma, sepsis and multi-organ failure. ARF is characterised by profound activation of protein catabolism with stimulation of hepatic gluconeogenesis and ureagenesis and protein synthesis. Amino acid utilisation and elimination is altered and some of the amino acids such as arginine and cysteine become conditionally essential. Nitrogen provision is based upon the clinical condition of the patient, degree of catabolism, extent of impairment of renal function and the route of delivery. CRRT allows nitrogen, fluids and electrolytes similar to patient with critical illness and normal renal function. Protein intake should be restricted in early ARF and adequate provision of non-protein calories to minimise the use of protein for energy and catabolism.[6] For patients not on renal replacement therapy, protein restriction limits...
the rate of urea production and generation of uraemic toxins. In oliguric ARF, fluid, sodium, potassium, phosphate and protein should be restricted.

The use of continuous veno-venous haemofiltration (CVVH) enables unrestricted nutritional support as the fluids and uraemic toxins are removed by the filter. Amino acid losses can be up to 10-15g/day in adults and in individual cases up to 30g/day. Approximately 10-20% of the amino acids infused will be lost to the filter. [24][25] This is seen both in adults and paediatric patients.

For adult patients on CVVH, the daily protein requirements are 1.2-1.5g/kg/day and for those not on filter 0.8-1.2g/kg/day. Some studies have demonstrated high protein loads of 2.5g/kg/day on CVVH is required to promote a positive nitrogen balance.[8] For more than 1.5g/kg/day, there is increased urea and other nitrogenous waste produced. If an intake of more than 2.5g/kg/day of protein is administered, more aggressive haemofiltration is required to control uraemia. Protein requirements for paediatrics are not clear though similar filtration rates are used. One study found that an intake of 1.5g/kg/day of protein and calories of 20-30% REE in paediatric patients did not prevent a negative nitrogen balance.[25]  Patients on PICU are likely to receive inadequate protein to counterbalance filter losses and a catabolic state. [26]

### 2.8.1.3 Carbohydrates

Glucose intolerance and insulin resistance occur in ARF and insulin stimulated glucose transport is reduced by 50%. There is accelerated hepatic gluconeogenesis from conversion of amino acids, which can be reduced by an exogenous glucose infusion.[8] The synthesis of glucogen is deficient and both insulin clearance and secretion is reduced.

If carbohydrate containing dialysate is used, significant amounts can be absorbed (up to 35-45% of the infused carbohydrate)(marin19®). Lactate can also be utilised for energy. 45 mmols of lactate yields 12kcal/L. Carbohydrate provision for nutrition support should be based on the type of CRRT being used.

### 2.8.1.4 Lipids

Hypertriglyceridaemia and a low HDL cholesterol are secondary to a defect in lipolysis, LCT/MCT clearance may be halved by 50% during ARF but can be partially reversed by the administration of glucose and amino acids. [8][24] The lipids should be adjusted according to requirements and tolerance by monitoring triglycerides.

### 2.8.1.5 Loss of nutrients due to CVVH

Water soluble nutrients with low molecular size and low protein binding are lost whilst on CVVH. This includes amino acids and water soluble vitamins. Losses in the ultrafiltrate depend upon the rate of ultrafiltration and the free serum amino acid levels. Losses are greater in patients on continuous veno-venous haemodiafiltration (CVVHD) of amino acids, trace elements and folic acid than on CVVH. [27] Lipids and fat soluble vitamins are not lost by any appreciable degree so do not need extra supplementation. Monitoring of trace elements and vitamins is important for patients who are on CRRT for more than one month. Fat soluble vitamins may accumulate and will require adjustment.
Macronutrients may be lost depending on the dialysate or type of anti-coagulant used for the circuit. If the circuit uses ad-citrate®, a direct calcium infusion is administered to the patient as citrate chelates calcium and can cause hypocalcaemia. Traditional circuits use heparin for anti-coagulation. A phosphate infusion is required when pre-dilution fluid is used i.e. replacement solution administered before the filter or additional phosphate can be added to parenteral nutrition. The first 24 hours on CVVH causes a drop in the blood concentration of water soluble vitamins and trace elements [24] but losses of trace elements after then are negligible. Some plasma levels of micronutrients such as iron, zinc, vitamin A, C, E or selenium may be low as they are used for oxygen scavenger systems rather than because of circuit losses.[8] Low levels of anti-oxidant selenium are due to rapid utilisation rather than circuit loss as selenium is highly protein bound.

2.8.2 Burns

The challenges in providing critical care and nutrition for paediatric burns patients is compounded by a large body surface area relative to weight and an increased susceptibility to hypothermia compared to adults. Renal immaturity results in inefficient handling of fluid overload, immune system leading to an increased risk of infections and haemodynamic compensatory responses allow children to tolerate significant fluid losses followed by decompensation. [28] In burns patients, there is an exaggerated catabolic state with a greatly increased requirement for protein and calories. Enteral nutrition is the preferred option with PN only for patients unable to tolerate EN. The risks of over and underfeeding are important in burns patients. Undernutrition will lead to poor wound healing and increased morbidity. Over feeding will cause steatosis, hyperglycaemia, and increased production of CO₂ and ventilator dependence. Energy expenditure should be measured by indirect calorimetry.

2.8.3 Cardiac

Cardiac surgical patients are at risk of undernutrition. In one study in PICU patients, fluid restriction affected 66.7% of all the patients with a median duration of four days. This was more common in cardiac group. [17] Fluid restriction is part of the pre and post operation management of cardiac patients. Mesenteric perfusion is challenged pre-operatively by an imbalance between systemic and pulmonary circulations and is also challenged during the operation due to hypothermic circulatory arrest. Neonates who require cardiac surgery are at risk of necrotising enterocolitis due to a low cardiac output state.

2.9 Pharmacological treatment

Use of motility agents, laxatives, anti-diarrhoeal and stress ulcer prophylaxis (see Gut motility)

2.9.1 Enteral nutrition

Enteral nutrition (EN) stimulates the immune system, decreases bacterial translocation by preventing intestinal mucosa atrophy and increased permeability, decreases the incidence of sepsis and multisystem failure, and has fewer side effects than parenteral nutrition. EN decreases the risk of hepatobiliary dysfunction, stimulates insulin
secretion, inhibits glucagon secretion and decreases the incidence of hyperglycaemia. Oral or nasogastric feeding is often poorly tolerated in ventilated patients. Severe reduction in haemodynamic instability may lead to a decrease in intestinal blood flow with decreased tolerance to EN. [15]

For critically ill patients, there is risk of rapid nutritional depletion, leading to muscle wasting, impairment of vital organ function, compromised wound healing and decreased immune function. Enteral nutrition (EN) is the preferred nutritional support for gastrointestinal tract function.

Shock reduces splanchnic perfusion, and can induce functional and structural changes in the gastrointestinal tract. Enteral nutrition increases splanchnic metabolic demands and if the gut is hypoperfused it may lead to oxygen or energy mismatch or both. [29] Provision of inadequate enteral nutrition occurs due to gut dysfunction and the need for frequent procedures and diagnostic tests that require a fasted state. Restriction of fluid intake will affect delivery of enteral and parenteral nutrition.

A systematic review of trials looking at clinical outcomes in critically ill children only found one suitable for review in children with burns where early EN was administered (within first 24 hours of admission) versus late (48 hours after admission) and showed no differences in clinical outcomes of mortality, ventilator days, sepsis, and length of hospital stay. There were also no differences in the weekly measurements of resting energy expenditure, nitrogen balance, levels of pre-albumin and albumin.[30] But the early nutrition was well tolerated without detrimental effect.

The use of early EN compared to delayed transpyloric enteral nutrition (TEN) may reduce the incidence of abdominal distension in critically ill children. It is well tolerated even with concomitant vasoactive drugs and improves protein metabolism and calorie deficits.[7] Monitoring of gastric aspirates will identify gastric dysmotility.

The Canadian guidelines for critically ill adults recommend early EN, methods to optimise delivery, benefits of tight glycaemic control, indication for specialised formulas and strategies to reduce the risk of PN. The ACCEPT study found that hospital stay decreased by 10 days with a strong trend towards a decrease in mortality. [7] The frequency of gastrointestinal complications is higher in children with shock, ARF, hypokalemia, hypophosphataemia and in those receiving dopamine, adrenaline (doses higher than 0.3mg/kg/min) and vecuronium. [29] Children with severe burns may have chronic diarrhoea for weeks but the mechanisms are unknown. Severe acute diarrhoea can predict sepsis and increases mortality in these patients. For the complications of EN, see artificial nutritional support. The gastric route is first line for enteral nutrition but if it is not tolerated then TEN should be considered.

The use of standard feeding protocols will facilitate achieving nutritional goals earlier and improves tolerance of enteral regimens.[31]

2.9.2 Transpyloric feeding

Gastric motility is reduced secondary to the administration of drugs or to disease. Distension and gastric aspirates are common. Transpyloric feeding (duodenal or jejunal) is an alternative route of enteral nutrition in the critically ill patient as there is reduced gastric aspirates, less frequent interruptions of nutrition for procedures and enables the prescribed volume of feed to be administered.[29] Patients receiving transpyloric enteral nutrition (TEN) can reach their calorific goal within 48 hours.
2.9.3 Enteral and parenteral

The recommendation in adults is for early EN without supplemental PN due to the increased risk of infection. A meta-analysis based on intention to treat looked at PN versus EN in critically ill adult patients. There was a reduced mortality benefit with PN but an increased risk of infectious complications. EN is the first line choice for nutrition in the critically ill patient but where EN cannot be initiated within 24 hours of admission or injury, PN should be commenced. [34] For paediatric patients due to lack of endogenous reserves, PN should be considered in conjunction with EN while the EN is being graded up to full feeds particularly in the malnourished patient.

2.9.4. Immunonutrition

There are many studies using immunonutrition in critically ill adults but limited data in paediatric patients.

2.9.4.1 Omega 3 Lipids

Omega 3 lipids have anti-inflammatory actions, which help reverse immunosuppression by down regulating eicasonoid production.[8] For omega 3 polyunsaturated fatty acids (PUFAs), there is data for the benefits in critically ill adults, which show an improved course of intensive care stay but limited data in paediatric patients. The adult data shows improved oxygenation, shorter duration of mechanical ventilation, a decreased intensive care stay and fewer new organ failures with formula enriched with EPA, omega 6 linoleic acid plus anti-oxidants.[7] Formulations containing omega 3 PUFAs may be considered for older paediatric patients with ARDS due to the adult data.

2.9.4.2 Glutamine

Glutamine is a non-essential amino acid except in periods of stress or injury when it becomes conditionally essential. It is the precursor for glutathione, which becomes rapidly depleted from the liver, muscle and plasma in critical illness. Glutamine is the most important fuel for cells with rapid turnover such as gastrointestinal and lymphocytes. For one study in critically ill children with enteral glutamine, protein accretion did not improve in the 48 hour study period. The benefits of glutamine have not been demonstrated in very low birth weight infants, in gastrointestinal disease, and gastrointestinal surgery or in malnourished patients but benefits have been seen in severe mucositis in stem cell transplant patients. There is likely to be an improved outcome in doses > 0.2-0.3g/kg/day. For children with burns, trauma and critical illness, there may need to be glutamine supplementation at a dose of 0.3-0.5g/kg/day but more evidence is required. [7]

2.9.4.3 Arginine

Arginine is a non essential amino acid, which plays an important role in the transport, storage and excretion of nitrogen and the disposition of ammonia in the urea cycle. It
has a role in blood flow regulation, immune function, protein synthesis and tissue repair. Arginine becomes indispensable in stress. There may be low levels of arginine in patients with necrotising enterocolitis and supplementation may reduce incidence. [7] Arginine levels are inversely correlated to inflammatory response as measured as C-reactive protein (CRP). There is accelerated degradation and oxidation without an increase in synthesis with critically ill children with severe burns and sepsis. But there is no recommendation for routine use in critically ill patients particularly as there has been an association between an increase in mortality with arginine supplementation in adults.

2.9.4.4 Vitamins and trace elements

Monitoring of nutritional status is a key parameter for assessment of adequate nutrition in intensive care patient (See parenteral nutrition for frequency of monitoring). Trace elements required for normal development are zinc, iron, copper, selenium, manganese and iodide, molybdenum and chromium.[6] Large requirements are only necessary with abnormal losses. Plasma levels are affected by the acute phase response; iron, selenium and zinc levels are decreased and copper are increased. Levels should be interpreted with care to avoid toxicity or over supplementation. Different disease states demand specific micronutrient requirements and adjustment of losses. Critically ill patients with sepsis are at risk of low levels of micronutrients and anti-oxidants, an increase in cysteine oxidation and suppressed synthesis of glutathione compared to healthy controls. Anti-oxidants protect cells and tissues from oxidative stress. Anti-oxidant capacity considerably decreases during catabolic stress with inadequate anti-oxidants to counteract free radicals and subsequent oxidative damage.

Low levels of selenium are associated with oxidative stress, infection, worsening organ failure and higher mortality rates. [33] Decreased levels are due to distribution to other compartments and a move to interstitial compartment by capillary leakage. For patients with systemic inflammatory syndrome, there is a reduction in mortality with selenium supplementation. Low levels of zinc in children with SIRS or sepsis is associated with non-survivors in septic shock. For patients with major burns, low levels of copper and zinc may occur due to wound losses. For children with severe hepatic failure, caution should be used in parenteral vitamin supplementation as copper and manganese accumulate and can cause toxicity. A recent double blinded placebo controlled trial in children with burns demonstrated that when patients were supplemented with extra zinc, vitamin C and E, there was a decrease in lipid peroxidation, an increase in vitamin E concentrations and the time to heal wounds was shorter in the supplemented group.[34]

3. Congenital gut malformations

3.1 Introduction

The survival rate of babies with gastrochisis and exomphalos has steadily improved from the 1970’s when gastrochisis and exomphalos were fatal conditions. Recent survival rates for gastrochisis are 90-95% and for isolated exomphalos 75-95%. [35][36] The observed decline in morbidity and mortality has resulted from improvements in the care of premature babies, particularly those who, because of
open abdominal wounds and extruded intestine (gastroschisis), are especially prone to hypothermia, dehydration, sepsis, and hypoglycaemia. Anaesthetic management and surgical techniques have improved, and the ability to provide parenteral nutrition for patients with gastrointestinal dysfunction has substantially increased their survival.

3.2 Incidence

The incidence for gastroschisis is the UK is 4.4 per 10000 births in 2004. [36a] Worldwide, the incidence of gastroschisis is increasing, and it is associated with young maternal age and low gravidity. Prematurity and low birth weights, secondary to in utero growth retardation, due to placental insufficiency are commonly seen in babies with gastroschisis.

The incidence for exomphalos is 2-3 cases per 100000 births. The incidence of exomphalos has remained constant partially due to termination of foetuses due to associated congenital anomalies including cardiac defects. Exomphalos is associated with increased maternal age.[36][37]

3.3 Anatomy and physiology in children

The human embryo initially has 2 layers and looks like a disc. It becomes cylindrical as it acquires a third cell layer and elongates and invaginates above the umbilical ring. The body folds (cephalic, caudal, and lateral) fuse centrally, where the amnion invests the yolk sac. Defective development at this critical location results in a spectrum of abdominal wall defects. By the sixth week of life, rapid growth of the midgut results in its herniation through the umbilical ring. By the tenth week of life, the abdominal cavity has sufficiently enlarged to accommodate the midgut. As the intestine returns, rotation and fixation occur. This process does not occur in babies with gastroschisis or omphalocle; thus, they are at risk of developing midgut volvulus.

3.4 Gastrochisis

This is an abdominal wall defect located usually to the right of the intact umbilical cord. Prenatal diagnosis by ultrasound is based on demonstration of a normally situated umbilicus and herniated loops of intestine, which are free floating. Most cases of gastrochisis involve the small intestine and a portion of the large intestine spilling out into the amniotic fluid space around the foetus. As a consequence of the herniation, the unprotected bowel may become inflamed and not function well after delivery. See Figure 7.2

Closure of the abdominal wall defect when the intestines are inflamed requires their temporary placement in a silo to allow the inflammation to resolve. As the intestine softens and becomes pliable, reduction can be accomplished. Intestinal dysfunction takes 4-6 weeks to several months to normalise.

An infant with gastrochisis may have malabsorption, either from in utero injury to the intestine or from partial bowel obstruction. Mid-gut volvulus is also a possible complication and short bowel syndrome due to gut necrosis. Gut necrosis may complicate excessively tight closure of the abdominal wall defect by impeding splanchnic blood flow with resultant intestinal ischemia and necrotising enterocolitis (NEC), or it may occur consequentially to closed loop obstruction caused by adhesions.
or midgut volvulus. Loss of intestinal length exacerbates the dysfunction consequent to in utero exposure of the intestine to amniotic fluid.

Figure 7.2  Gastroschisis  
*Photograph courtesy of CATS*

The incidence of chromosomal anomalies is less than 5 percent. Infants may have gastroesophageal reflux disease or Hirschsprung disease, in addition to abnormal intestinal absorption and motility. Long term morbidity from gastroschisis is related to intestinal dysfunction and wound problems. Weight may also be a factor in an increase morbidity and outcome. A recent study demonstrated that infants < 2kg had longer time on ventilators, parenteral nutrition, and time to start and achieve full enteral feeds. [38] Infants with short gut due to gastroschisis account for a significant percentage of children undergoing intestinal transplantation.

3.5 Exomphalos

Exomphalos or omphalocele is where there is incomplete closure of the abdominal wall and persistent herniation of the midgut. The abdominal viscera are contained in a translucent sac, which is composed of amnion, Wharton jelly, and peritoneum. The umbilical vessels radiate onto the wall of the sac. In 50% of cases, the liver, spleen, and ovaries or testes accompany the extruded midgut. In infants with exomphalos, the abdominal wall defect is 4-12 cm, and the defect may be central, epigastric, or hypogastric. The omphalocele sac is usually intact, though it may be ruptured in 10-20% of cases. Rupture may occur in utero or during or after delivery. See figure 7.3

Infants with giant exomphalos have large, central abdominal wall defects. The liver is entirely contained in the omphalocele sac. The abdominal and thoracic cavities are small, bell-shaped and undeveloped. Pulmonary hypoplasia occurs as there is compression of the developing lungs. Reduction and repair of the exomphalos frequently precipitates respiratory failure, which may be chronic and require a tracheotomy and long-term ventilator support. Operative closure is difficult.

Babies with exomphalos have a 35-80% incidence of other clinical problems. These include congenital heart disease, cleft palate, and musculoskeletal and dental occlusion abnormalities. Incidence of associated chromosomal abnormalities is 10-40%. These include trisomies 12, 13, 15, 18, and 21.
3.6 Causes

Factors associated with high-risk pregnancies, such as maternal illness and infection, lower maternal age, drug use, smoking, and genetic abnormalities, can be associated with infants born with omphalocele and gastroschisis. These factors contribute to placental insufficiency and birth of premature or small for gestational age (SGA) babies, in whom gastroschisis and omphalocele are most common. Elevation of maternal serum alpha-fetoprotein (MSAFP) levels requires further ultrasound scans to determine if any structural abnormalities are present in the foetus. If such abnormalities are associated with exomphalos, amniocentesis is indicated to check for an associated genetic abnormality.

3.7 Non-pharmacological treatment

3.7.1 Medical management

3.7.1.1 Gastroschisis

After birth, the exposed intestines are wrapped with plastic wrap and supported to minimize traction on the mesentery and the infant is placed under a radiant heater. Fluid, electrolyte, and heat losses must be minimised and corrected because of significant ongoing insensible fluid losses with an open abdominal wall defect and risk of hypothermia, dehydration and sepsis. The degree of fluid resuscitation is dependent on the ability to successfully enclose the defect and is dependent on the time from birth until surgical intervention. A central venous line needs to be inserted to provide parenteral nutrition and thus minimise catabolic protein loss during the period of gastrointestinal dysfunction. The average duration for parenteral nutrition after closure is 28 days but some patients may need lifelong parenteral nutrition due to short bowel syndrome.[36] Prolonged administration of parenteral nutrition is associated with liver dysfunction and cholestatic jaundice and may become severe enough to warrant liver transplantation. Enteral feeds can be commenced once the first bowel movement has occurred. Initial feeds may be trophic to enhance the growth of intestinal mucosa, enhance release of gastrointestinal hormones and peptides and contribute to the beneficial alteration of enteric flora. There is some evidence to suggest that trophic feeding followed by
gradual increases improves outcome of infants with gastroschisis.[39] Expressed breast milk is the feed of choice if tolerated but if there is malabsorption, a hydrolysed enteral feed should be used. The increase to full enteral feeds is a gradual process, and infants who have undergone gastroschisis repair might experience occasional setbacks, including need for bowel rest or additional surgery.

3.7.1.2 Exomphalos

Exomphalos is medically managed in the same way as gastroschisis. Insensible losses are significantly reduced as the intestines are covered by membrane. The exomphalos acts as a metabolic drain leading to a negative nitrogen balance and poor nutritional state until closure.
Where there is an intact sac, the intestines are protected from the amniotic fluid and enteral feeds can be commenced shortly after surgery. The enteral feeds can be standard as the intestines are normal.

3.7.2 Surgical management

3.7.2.1 Gastroschisis

The main treatment for gastroschisis is surgical closure of the abdominal wall defect. [2] The staged approach to gastroschisis repair begins at the time of delivery, when the exposed abdominal contents are placed in a protective covering prior to encasement in a sterile surgical mesh or ‘silo’. The siro is sutured to the fascia and skin. The closure of the defect can either be a primary gastroschisis repair, or more commonly, a staged repair approach, depending upon assessment of the condition of the exposed bowel after birth. Primary gastroschisis repair entails reduction of the bowel and complete abdominal wall closure in one operation. For a stage repair, the bowel contents in the siro are reduced daily at the bedside until the abdominal contents are level with the skin when primary closure is then possible.

Prenatal exposure of the foetal intestines to the amniotic fluid can be associated with bowel dilatation and inflammation, thus making primary repair not feasible. The intestine may be either normal or abnormal in structure and function. The degree of abnormality depends upon the extent of the inflammatory and ischemic injury, manifested by shortened length and surface exudate (peel), which is related to the duration of the intestine's exposure to, and the composition of, the amniotic fluid (pH 7) and foetal urine. If the patient has intestinal atresia and gastroschisis, both conditions will be repaired if the bowel is in good condition. But if inflammatory peel is present, the gastroschisis will be repaired first and the atresia at a later stage. The bowel is rested for at least 10 days post operation. Further surgery may be required due to strictures or necrotising enterocolitis (NEC).

3.7.2.2 Exomphalos

Closure of a small or moderately sized exomphalos is accomplished without difficulty but larger exomphalos can be a surgical challenge and it may not be possible for primary closure. A large patch is used if there is not enough skin to close the abdomen otherwise the exomphalos is managed as a staged repair as for gastroschisis. The patch used for repair is larger than the abdominal wall defect so that the anterior abdominal wall is concave. The skin flaps are mobilised laterally and approximated.
over the patch. The rigid patch (Gore-Tex®, Vicryl® mesh or Silastic®) is attached to the margins of the abdominal wall defect and stimulates growth of the abdominal wall, elevates the costal arch and expands the thoracic cavity. [35][36] The outcome for patients who do not undergo primary closure may be longer ventilation, longer hospital stay, and a longer period to full enteral feeds.[40]

For immediate closures, complications following surgery include increasing abdominal pressure and pulmonary compromise, wound separation or dehiscence, sepsis and enterocutaneous fistula. In addition, tight closure of the abdominal cavity impedes venous return to the heart, compromising cardiac output and decreasing renal blood flow and glomerular filtration rate. Renal vein thrombosis and renal failure may ensue. An infant with a ruptured exomphalos is managed in the same manner as one with gastroschisis.

4. Necrotising enterocolitis
4.1 Introduction

Necrotising enterocolitis (NEC) is one of the most common reasons for surgery in neonates and affects 90% of preterm infants. The risk is inversely related to birth weight and gestational age. As advances in neonatal intensive care have progressed over the last 30 years, premature infants are surviving long enough for the disease to develop and the incidence of NEC has increased.

With improved supportive intensive care, including ventilation, anaesthetic techniques, and parenteral nutrition, the survival of infants with NEC has steadily increased. The improved prognosis is most notable in critically ill neonates who are younger than 28 weeks' gestational age and who weigh less than 1000 g. These neonates are still at significantly increased risk for pan-involvement and are more likely than other premature infants to require surgery. Despite the improvement in survival, the mortality rate of NEC is 20-40% (up to 50% for babies < 1000g). In England and Wales the mortality rate for 2005 was 0.17 per 1000 ELBW.[41] Of those that survive, approximately 25% suffer long term consequences and recent studies have demonstrated that infants are at an increased risk for neurodevelopmental disorders, as many as 50% have some abnormality in intelligence and motor skills.[42]

4.2 Incidence

The incidence of NEC is approx 0.5-5 cases per 1000 live births.[43] Population studies demonstrate similar rates worldwide.

4.3 Pathophysiology

NEC is an acute inflammatory disease with a multifactorial pathology. NEC is characterised by variable damage to the intestinal tract ranging from mucosal injury to full-thickness necrosis and perforation. Changes can be seen with epithelial regeneration, granulation tissue formation, and fibrosis in as many as two thirds of patients. This indicates an inflammatory process lasting several days with concurrent areas of continuing injury and healing. Advanced disease may result in full-thickness necrosis of the intestinal wall.
4.4 Aetiology

No specific aetiology has been identified but multiple factors are believed to contribute to the development of NEC. The principal factors identified are prematurity, enteral feeds, medical management of patent ductus arteriosis (PDA), and bacterial colonisation. [43][44]

4.4.1 Prematurity and feeding

NEC is principally a disease of premature infants. Although approximately 5-25% of infants with NEC are born full term, studies have found a markedly decreased risk of NEC with increasing gestational age. This finding suggests that the immaturity of the gastrointestinal tract plays an important role in the development of NEC. The premature neonate has numerous physical and immunologic impairments that compromise intestinal integrity. Gastric acid and pepsin production are decreased during the first month of life. Pancreatic exocrine insufficiency is associated with low levels of enterokinase, the enzyme that converts trypsinogen to trypsin, which allows hydrolysis of intestinal toxins. Mucus secretion from immature goblet cells is decreased. Gut motility is impaired, and peristaltic activity is poorly coordinated. Finally, secretory immunoglobulin A (IgA) is deficient in the intestinal tract of premature infants not fed breast milk. The risk for infants fed formula feed is bacterial proliferation due to the carbohydrate substrate and none of the immune protection that breast milk provides is conferred. There is a 3-10 fold risk reduction in infants who are breast fed compared to those fed formula. [43]

4.4.2 Bacteria

Bacteria are thought to play a key role in the development of NEC. An impaired host intestinal defence system and immunologic immaturity combine to allow colonisation of the premature gastrointestinal tract by the bacterial flora present in the NICU. Native flora provides some protection but may be depressed by the antibiotics used to treat respiratory distress. It is not known whether the bacterial infection has a primary inciting role in NEC or whether an initial intestinal mucosal injury allows secondary bacterial invasion. Progressive intestinal damage may occur as bacterial invade through the mucosal injury resulting in full thickness necrosis and subsequent perforation. Positive blood cultures are found in 30% of patients; the most commonly identified organisms are *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus species*, *Clostridium perfringens*, and *Pseudomonas aeruginosa*.

4.4.3 Medications

Medicines used to treat patent ductus arteriosus have been implicated as a risk factor for NEC. Indomethacin or ibuprofen may cause splanchnic vasoconstriction leading to impaired intestinal integrity or spontaneous perforation. Vitamin E used to treat retinopathy of prematurity is known to impair leukocyte function and has been associated with NEC.
4.5 Presentation

NEC typically occurs in the second to third week of life in the infant who is premature and has been formula fed. The clinical presentation of NEC includes non specific symptoms such as vomiting, diarrhoea, feeding intolerance and high gastric aspirates following feeds. The patient may be hyponatraemic from capillary leak and third spacing of fluid within the bowel and peritoneal space. Metabolic acidosis and thrombocytopenia are common. Other symptoms include abdominal distension and frank or occult blood in the stools. With disease progression, abdominal tenderness, abdominal wall oedema, erythema, and palpable bowel loops indicating a fixed and dilated loop of bowel may develop. Systemic signs, such as apnoea, bradycardia, lethargy, labile body temperature, hypoglycaemia, and shock, are indicators of instability and sepsis. See Figure 7.4

Pneumatosis intestinalis (gas in the bowel wall) is present in 70%-80% of patients with NEC, and is a diagnostic early finding but it may be fleeting or intermittent. Distended loops of small bowel are one of the most common, although non specific, radiographic findings in NEC. Pneumoperitoneum (air within the peritoneal cavity) indicates that perforation has occurred. An upper GI contrast can be useful in distinguishing NEC from malrotation with intestinal volvulus. See Table 7.1 for classification of NEC.

NEC most commonly affects the terminal ileum and the proximal ascending colon. However, varying degrees of NEC can affect any segment of the small intestine or colon. The entire bowel may be involved (pan-involvement) and may be irreversibly damaged. [44] The most common histological findings are associated with mucosal injury.
Stage I - Suspected NEC

One or more historical factors related to perinatal stress
Gastrointestinal symptoms, including poor feeding, increasing gastric aspirates, emesis (bilious or test positive for occult blood), mild abdominal distension and occult blood in the stool
Abdominal X-rays reveal distension with mild ileus

Stage II - Definite NEC

One or more historical factors
Signs and symptoms of stage I, plus persistent occult or gross GI bleeding and marked abdominal distension
Abdominal radiographs revealing clinically significant intestinal distension with ileus, small-bowel separation (edema in bowel wall or peritoneal fluid), unchanging or persistent rigid fixed bowel loops, pneumatosis intestinalis, portal-vein gas)

Stage III - Advanced disease

One or more historical factors
Signs and symptoms of stage I and II plus deterioration of vital signs, evidence of septic shock, and or marked GI haemorrhage
Radiographic findings of stage II plus pneumoperitoneum

Table 7.1 Bell Classification of NEC [45]

4.6 Medical management

The mainstay of treatment for patients with stage I or II necrotizing enterocolitis (NEC) is non-operative or conservative management. The initial course of treatment consists of stopping enteral feeds for 7-10 days, performing nasogastric decompression, and initiating broad-spectrum antibiotics consisting of triple antibiotics [44] to cover gram positive, gram negative and anaerobic bacteria. The usual antibiotics include benzylpenicillin or ampicillin, an aminoglycoside and metronidazole. Fungal prophylaxis should be prescribed for infants < 1500g. For all patients who are nil by mouth, parenteral nutrition should be started. It should be administered via a central venous catheter to ensure that all the infant’s nutritional requirements are met.

Patients with stage I disease with improving signs and symptoms and negative results may usually resume feedings in 7-10 days. Once feeding commences, stools may be monitored for reducing substances and occult blood, and feeds should be stopped if a test for either becomes positive.

Patients with stage II NEC are typically treated for 10 days. Clinical improvement after this time should be marked by a normal abdominal examination, normal WBC and platelet counts, and an absence of acidosis.

Patients with stage III NEC and those who do not demonstrate clinical improvement may need intense supportive care, including ventilatory support, aggressive resuscitation, and the initiation of inotropes. These patients require urgent surgical evaluation.
4.7 Surgical management

Surgery is generally indicated in the conservatively managed patient whose clinical condition deteriorates. [46][47] The signs of deterioration include worsening abdominal examination findings, signs of peritonitis, worsening and intractable acidosis, persistent thrombocytopenia, rising leukocytosis or worsening leucopenia, and haemodynamic instability.

After perforation occurs, peritoneal contamination ensues with subsequent intra-abdominal abscess formation. Perforation is not always recognised when it occurs, especially if the area of necrosis is localised and the contamination is contained. These perforations may heal spontaneously or they may be a source of ongoing infection or intestinal obstruction.

If a single area of bowel is resected, a proximal stoma and distal mucus fistula are created. Primary anastomosis is not generally advocated because of the risk of ischemia at the anastomosis, leading to increased incidence of leakage, stricture, fistula, or breakdown. However, intestinal resection with primary anastomosis may be safely performed in select cases but only where there is a clearly demarcated small segment of injured bowel with a normal appearance of the remaining intestine and a patient in a good general condition with no evidence of sepsis, coagulopathy, or physiological compromise.

If multiple segments of intestine are involved because of necrosis or perforation, a decision must be made regarding the course of action. A single proximal stoma may be created and the distal bowel segments anastomosed in continuity, thus avoiding multiple stomas. Clip and drop technique can be used to try and save sections of good bowel amidst necrotic sections.

NEC totalis occurs when less than 25% of the intestinal length is found to be viable at the time of operation. Simple closure of the abdomen is supported by findings that show a 42-100% mortality rate in patients with pan-involvement. Massive resection with excision of the ileocecal valve requires at least 20 cm of residual bowel for any hope of adequate enteral nutrition. Patients with a decreased bowel length require long term parenteral nutrition. After intestinal resection, the length of remaining viable bowel should be measured along the antimesenteric border of the intestine and recorded.

After undergoing an operation for NEC, infants should continue to receive intravenous antibiotics and total parenteral nutrition for at least 2 weeks. Supportive care, including ventilatory support, fluid and electrolyte monitoring and replacement, and correction of anaemia and coagulopathy, should continue. Infants who improve postoperatively should not resume enteral feedings for at least 10-14 days.

An abnormally high stoma output may indicate a need for early stoma closure. A patient with a high jejunostomy may have substantial loss of fluid and electrolytes, with consequences such as failure to thrive and peristomal skin injury. These patients may benefit from early stoma closure with colonic water absorption. However, infants with a high stoma and extensive ileal resection who undergo stoma closure may have considerable secretory diarrhoea after the colon comes in contact with unabsorbed bile salts.

The most common complication after NEC is intestinal stricture. It occurs when an area of intestinal ischemia heals with resultant fibrosis and scar formation that impinges on the diameter of the lumen. The most common site of stricture is the left colon, followed by the terminal ileum. Intestinal stricture should be suspected in any
infant who receives non-operative treatment for NEC and who fails to thrive and/or has bloody stools or bowel obstruction.
Recurrent NEC is an uncommon complication that can occur after either operative or non-operative management. It is seen in only 4-6% of patients with NEC. Recurrent NEC has not been associated with the method of managing the initial episode, the timing of enteral feedings, or the site of initial disease.

4.8 Prevention of NEC

Standardised feeding protocols with slow cautious feeding, and the use of breast milk [48], may decrease the incidence of NEC. Expressed breast milk is the optimum feed for the preterm infant though donor breast milk does not appear to confer the same benefits. [49]
There is some interest in the use of probiotics in preterm neonates to prevent NEC. A recent meta-analysis [50] demonstrated that the rate of sepsis was not different between the patients on probiotics or the control group but the risk of death from NEC was reduced in the probiotic group and time to full feeds was significantly shorter. Further research is needed to determine the optimum dose, duration and type of probiotic supplementation.

5. Stress ulceration

5.1 Anatomy and physiology in children/adolescents

The body and fundus of the stomach is made up of oxyntic glands. The oxyntic glands contain parietal cells, which secrete hydrochloric acid (HCl) and intrinsic factor, and the chief cells, which secrete pepsinogen. Enterochromaffin-like cells (ECL) are located in, and are adjacent to the oxyntic cells. ECL cells secrete histamine when stimulated by gastrin or acetylcholine (Ach) release. [51] See Figure 7.5

![Control of acid release in the stomach](image)
Gastrin is produced by the duodenum and antral G cells in the stomach and circulates via the bloodstream to the parietal and ECL cells. Gastrin stimulates the release of HCl and pepsinogen. Release of hydrochloric acid lowers the pH to less than 3.5, which promotes the conversion of pepsinogen to the active form pepsin. HCl, pepsin and bile acids aid in the digestive process but in certain circumstances such as stress, they can cause mucosal inflammation.

There are 3 major pathways, which regulate parietal acid secretion [52]:
1. Neural stimulation of the vagal nerve to release Ach
2. Endocrine stimulation via gastrin released from antral G cells
3. Paracrine stimulation by local release of histamine from ECL cells

Neural stimulation of the vagal nerves occurs at the sight, smell, taste or thought of food causing Ach to be released from the postganglionic nerves. Mechanical distension of the stomach and ingestion of amino acids and peptides stimulates release of gastrin. Gastrin and acetylcholine stimulate the ECL cells to release histamine and also act directly on the parietal cells to activate calcium sensitive pathways. Histamine activates parietal cell H2 receptors linked to the stimulation of adenyl cyclase, which in turn activates cyclic-AMP (c-AMP) and via c-AMP protein kinase, causes the phosphorylation of the H+ K+- ATPase proton pump. Secretion of acid into the lumen occurs against a concentration gradient, which requires the H+ K+- ATPase proton pump to be activated. The H+ K+- ATPase proton pump exchanges luminal K+ for cellular H+ in the parietal cells.

The mucosa is protected from acid and other compounds by a mucus layer and by the actions of prostaglandins E2 and I2. Mucus is released by the superficial epithelial cells and mucus cells in the stomach. The mucus layer serves as a barrier to luminal pepsin and HCl and prevents access of pepsin to the apical surface of the epithelial cells. It also neutralises acid through the presence of bicarbonate secreted in the mucus layer. Prostaglandins E2 and I2 are synthesised by the gastric mucosa and exert a cytoprotective effect by stimulating the mucosal production of bicarbonate and mucus, inhibit gastric acid secretion and maintain blood flow.

5.2 Common Causes

Stress ulceration is a gastrointestinal mucosal injury related to critical illness where the body is under severe physiological stress. The incidence of clinically significant bleeding appears to be dependent on the severity of illness and the type of patient population studied. The incidence of serious bleeding is low but the accompanying mortality is high. The development of stress ulceration is not related to a history of peptic ulcer disease or Helicobacter infection.

Clinically important bleeding is defined as overt bleeding e.g. haematemesis, gross blood or coffee grounds in nasogastric aspirates or maelena complicated by one of the following within 24 hours after the onset of bleeding: a spontaneous decrease of more than 20 mmHg in systolic blood pressure; an increase of more than 20 beats per minute in heart rate or a decrease in haemoglobin of 2g/dl. [53][54]

Stress related ulceration occurs in the upper body and fundus of the stomach, which is the location of the gastric acid producing areas of the stomach. At fasting conditions, acid is secreted at a low basal rate and large quantities of acid are not a factor in the development of stress ulceration. [59] Bleeding occurs usually in the context of...
concomitant coagulopathy. The rate of upper gastrointestinal bleeding in critically ill children is 1.6 - 5.3% compared to 1.5% in adults. [53]

The cause of stress ulceration is multifactorial and is related to splanchnic hypoperfusion and loss of host defences. The body responds to critical illness by sympathetic nervous system activation, increased catecholamine release and vasoconstriction, hypovolaemia, decreased cardiac output and release of inflammatory cytokines. The mucosa is compromised by ischemia due to decreased blood flow, decreased oxygen delivery and reduced bicarbonate secretion and is attacked by gastric acid, bile and digestive enzymes. The result is reduced production of cytoprotectant factors, such as prostaglandins, mucosal atrophy with increased permeability, and loss of ability to repair and neutralise acid (hydrogen ions). Gastric motility is decreased following splanchnic hypoperfusion, which prolongs exposure of the mucosa to gastric acid and other irritants thus increasing the risk of ulceration. [53][54] Reperfusion injury contributes to mucosal damage when there is restoration of mucosal blood flow resulting in elevated levels of nitric oxide synthetase leading to formation free radicals, which can cause inflammation, cell death and further release of damaging cytokines. [55][56]

5.3 Risk Factors for stress ulceration

The major risk factors are respiratory failure (ventilation for more than 48 hours) and coagulopathy. Other factors include sepsis, hypotension, hepatic failure, renal failure, major surgery lasting more than 4 hours, severe head or spinal injury, burns of more than 35% body surface area, high dose steroids and acute lung injury. [54] For paediatric patients, clinically significant upper gastrointestinal bleeding is most often seen in mechanically ventilated patients with a paediatric risk of mortality (PRISM2) score > 10 and with evidence of systemic coagulopathy. [53][57][58]

5.4 Prophylaxis

Patients with shock, sepsis, respiratory, hepatic or renal failure, or who have a coagulopathy, who are admitted to intensive care, should all be given stress ulcer prophylaxis. If the underlying disease state or physiological condition is treated, then the risk of stress ulceration developing is reduced.

The prevention of stress ulceration has focused on reducing the quantity of luminal acid, using H₂ receptor antagonists (H₂RA), sucralfate or proton pump inhibitors (PPIs). Antacids are no longer used for prophylaxis due to the labour intensive dosing frequency and potential side effects. The overall objective of stress ulcer prophylaxis is to increase the pH of the stomach above 3.5. At pH above 4.5 pepsin is inactivated, above pH 5, 99% of acid is neutralised and at more than pH 7, fibrinolysis is inhibited, which is essential for patients with bleeding ulcers. [56][59] PPIs are the most effective therapy for maintaining the gastric pH at the required level.

Nosocomial pneumonia is common in critically ill patients, and remains the leading cause of death. It has been established that the use of acid suppression therapy promotes gastric colonisation with pathogenic bacteria, and that aspiration of these bacteria may cause nosocomial pneumonia.

The majority of the trials for stress ulceration prophylaxis in adults were undertaken pre PPIs and compared ranitidine to sucralfate or placebo. H₂RA were shown to increase the risk of nosocomial pneumonia but in a recent paediatric cohort there was
no difference between ranitidine, sucralfate, omeprazole or placebo in the rate of ventilator associated pneumonia or mortality. [60]

Stress ulcer prophylaxis should be stopped when risk factors no longer exist and should not be used for non-intensive care patients. A recent study [61] found a 30% increase in the odds of hospital acquired pneumonia in non-ventilated adult patients on acid suppressive therapy and in particular PPIs.

5.5 Pharmacological Treatments

5.5.1 Sucralfate

Sucralfate is a complex of aluminium hydroxide and sulphated sucrose. It is formulated as a gel, which on contact with acid turns into foam and binds to the tissue forming a physical barrier protecting ulcerated tissue against pepsin, acid and bile. Sucralfate stimulates the release of endogenous prostaglandins, stimulates mucus and bicarbonate secretion and improves mucosal blood flow. It is most effective in acid environment though will work in neutral pH. Sucralfate should not be administered into the duodenum or jejunum as it would bypass the site of action in stomach. It is not absorbed systemically but interacts with medicines such as ciprofloxacin, theophylline, phenytoin, levotyroxine, ketoconazole and digoxin. Administration of sucralfate should be 2 hours post dosing with the above medicines. Sucralfate causes bezoars particularly in premature infants and neonates [52]. It should be avoided in renal failure due to the risk of aluminium accumulation and toxicity. For dosing and side effects, refer to BNF-C.

The incidence of nosocomial pneumonia is lower in patients receiving sucralfate as it does not raise the gastric pH.

5.5.2 Histamine 2 receptor antagonists

Histamine 2 receptor antagonists (H2RAs) are the most widely used drugs for stress ulceration. They act by reversible, competitive inhibition of the histamine 2 receptor on the basolateral cell membrane. Acid suppression with H2RA is incomplete due to other pathways including gastrin and acetylcholine still being functional.[55] Tolerance to H2RAs can occur within 72 hours of administration. [54][55] Administration via nasogastric or oral tubes is equally effective in reducing the incidence of stress ulcer bleeding. H2RAs are well tolerated with few minor side effects.

The most regularly studied and used H2RAs is ranitidine. The pharmacokinetics of ranitidine are variable in critically ill children and the dose may need adjustment. [58] Ranitidine is associated with a lower incidence of GI bleeding but a higher risk of nosocomial pneumonia compared to sucralfate. Cimetidine interacts and decreases the clearance of warfarin, ketoconazole, theophylline and phenytoin. For dosage and side effects, refer to the BNF-C.

5.5.3 Proton pump inhibitors

Proton pump inhibitors (PPIs) are substituted benzimidazoles that inhibit gastric secretion in a dose dependent manner. PPIs inhibit both histamine induced and vagally induced gastric acid secretion unlike H2RAs. PPIs can increase and maintain the gastric pH above 6, which is the level to maintain clotting in patients at risk of
rebleeding or ulcer healing. PPIs have a rapid peak time of approximately 15 mins but some anti-secretory effect is still present 72 hours after a dose. The PPIs block the apical membrane proton pumps by irreversible binding to the \( \text{H}^+/\text{K}^+\)-ATPase pump in the parietal cells. Because the proton pump is the final common pathway for acid secretion, the PPIs are more powerful acid suppressants than are the \( \text{H}_2\text{RAs} \). PPIs only inhibit actively secreting proton pumps and so the maximum activity is achieved after 2 days of therapy. [54]

One recent study in patients on paediatric intensive care demonstrated that gastric acid pH of more than 4 was seldom seen with patients on \( \text{H}_2\text{RAs} \) or once daily PPIs, a pH of more than 4 was only seen in twice daily administration of PPIs. [53]. Further studies are required to determine the optimum dosing for paediatric patients.

Some of the PPIs have clinically significant drug interactions as they are metabolised by cytochrome P450 (CP450). Omeprazole inhibits the metabolism of phenytoin, warfarin, and diazepam. The bioavailability of digoxin may be increased by approximately 10% in the antacid conditions produced by omeprazole. Lansoprazole is a weak inducer of cytochrome P450 but can increase the elimination of phenytoin and warfarin. Pantoprazole has a lower affinity than omeprazole/lansoprazole for CP450 with no interactions reported. For dosage and side effects, refer to the BNF-C.

6. Artificial Nutritional support

6.1 Enteral nutrition (EN)

The nutritional goal for paediatric patients should be the provision of nutrients appropriate to the child’s metabolic and physiologic requirements and to promote growth and development. Enteral feeding is a method of maintaining nutritional intake when oral intake is inadequate or when there is restricted access to the gastrointestinal tract. Enteral feeds are more physiological, cost effective and are easier and safer to administer than parenteral nutrition.

The main advantage of enteral feeds is the maintenance of normal intestinal function and structure. Enteral feeds provide a trophic effect on the gut by promoting pancreatic and biliary secretions as well as endocrine, paracrine (growth factors) and neural factors that help promote the integrity of the gastrointestinal tract. [62]

There are 5 broad indications for enteral feeding in children [63]:

- Inability to suck or swallow, or unsafe swallow
- Increased nutritional requirements
- Congenital abnormalities e.g. tracheo-oesophageal fistula
- Gastrointestinal disease e.g. short bowel syndrome, Crohn’s disease
- Metabolic disease

The route of enteral feeding is decided on an individual basis according to clinical indication and nutritional state of the patient.

Enteral feeds may be delivered:

- Directly into the stomach (gastric feeding) via orogastric, nasogastric tube or gastrostomy
- Beyond the stomach (post-pyloric feeding) via a naso-duodenal, naso-jejunal tube or jejunostomy
6.2 Choice of Enteral Feeds

The choice of feed is dependent upon several factors including age, weight, gut function and individual nutrient requirements. There are 4 main categories; whole protein, protein hydrolysate, modular and elemental. Whole protein feeds are used for children with a normal functioning bowel while protein hydrolysate, modular and elemental are used for defective bowel function.

6.3 Complications of Enteral Nutrition

Diarrhoea occurs with enteral feeding when the combined absorptive capacity of the small bowel and salvaging capacity of the colon are exceeded. There should be a slow increase in the rate volume of feed and the use of low osmolarity feeds to minimise this complication.

Bacterial contamination of enteral feeds may cause diarrhoea and vomiting. Contamination may also contribute to more serious infections including pneumonia and septicaemia.

Other complications of enteral nutrition include aspiration, nausea, vomiting and tube related complications and metabolic complications including refeeding syndrome.

6.4 Enteral access

6.4.1 Nasogastric

Nasogastric feeding is the most common route for enteral feeding and unless there is prolonged enteral feeding, it is the route of choice.

6.4.1.1 Nasogastric tubes

Nasogastric tubes tend to be for short term use (< 4 weeks) or in the longer term when other options such as gastrostomy feeding are contraindicated or inappropriate.

Polyvinylchloride (PVC) or Ryles® tubes are recommended for short term use and require changing every 2-3 days as the tubes stiffen over time and may cause tissue damage. PVC tubes are less likely to be displaced than a polyurethane tube so can be useful for children who are prone to vomiting. Fine bore polyurethane or silicone tubes are designed for longer term up to 6 months. Silicone or latex tubes are softer, more flexible and have thicker walls. A latex or silicone tube of the same French size as a polyurethane will have a smaller internal diameter. [63][64]

The external diameter of the feeding tube is expressed using the French unit (Fr) where each ‘French’ is equivalent to 0.33 mm. [64] Size 6-10 Fr are used in paediatrics and are chosen according to the child’s weight and age. [65] The smallest diameter should be used to keep the child comfortable and avoid interference with breathing. The distance between the bridge of the nose to the ear lobe, then from the ear lobe to xiphisternum (lowest part of the sternum), is used as a reference for the length required for the tube. [66]

There may be high risk of tracheal intubation in children who have an impaired swallow or who are ventilated when passing polyurethane tubes. In these patients, a PVC tube may be preferable despite the need for longer term feeding.
All feeding tubes should conform to British Standards BS6314 with a male Luer connection to avoid connection with intravenous lines and wrong route errors. [67] The tubes should be radio-opaque to help confirm correct position.

6.4.1.2 Contra-indications for NG tubes

NG tubes should never be passed in a patient with basal skull fractures as the tube may enter the brain. Other contra-indications include severe gastro-oesophageal reflux disease, recent oral, nasal or oesophageal surgery and patients with an anatomical deformity.

6.4.1.3 Complications

Dislodgement of tubes, poor placement and migration of tubes are complications of NG tubes. There were reports of 11 deaths over a two year period following misplacement of NG tubes, which lead to an alert from the NPSA in 2005. [68] It is vital to confirm that the tube is positioned in the stomach and not the lungs. Liquid must be aspirated from the tube and checked to confirm that the contents are acidic with universal paper. See Table 7.2

<table>
<thead>
<tr>
<th>Position</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric</td>
<td>≤5.5</td>
</tr>
<tr>
<td>Bronchial</td>
<td>6-8</td>
</tr>
<tr>
<td>Small bowel</td>
<td>6-8</td>
</tr>
</tbody>
</table>

Table 7.2 pH of GI tract [66]

It is important to be aware that some medications, such as proton pump inhibitors and H₂ receptor blocking agents, can elevate gastric pH readings, although in the majority of cases a pH of less than 5 has been found. If still unable to confirm position by aspirate, an x-ray may be necessary.

Long term feeding using NG tubes can cause irritation and inflammation to the skin where the tube is fastened. Tube blockage can occur particularly with a fine tube but regular flushing and the choice of medication formulation can help to reduce the occurrence. The characteristics of the tubing material can also have implications for drug adsorption.

The procedure for inserting the tube can be traumatic for the majority of children. Babies and young and uncooperative children are likely to pull out the tube making regular re-insertion necessary.

6.4.2 Gastrostomy

A gastrostomy is an artificial tract between the stomach and the abdominal surface and is commonly used for long term EN. Gastrostomy feeding is generally well accepted in children as it is more comfortable, cosmetically more acceptable and avoids frequent tube changes.
Gastrostomies can be placed surgically, endoscopically or radiologically. Percutaneous endoscopic gastrostomy (PEG) placement is the most popular technique as it does not require open surgery so is completed with a shorter anaesthetic time and therefore has reduced complications compared to a surgically place tube. [67] A gastrostomy is not suitable where there is frank ascites, sepsis or in patients with a history of extensive gastric surgery.

6.4.2.1 PEG Gastrostomy

When inserting a PEG, the tube is passed down the throat into the stomach and the end of the tube is brought out through a small incision in the abdomen to allow access for feeding. The tube is made of polyurethane and the retention disc and fixation plate are silicone. See Figure 7.6

![Figure 7.6 PEG tube](image)

The PEG tubes are held in place by a cross bar or bumper to prevent inadvertent removal. Tract formation occurs within few hours and though it is safe to commence feeding within 4 hours [8] after tube insertion in adults and 6 hours in children [71], water may be passed through the tube before feeds are actually initiated. A feeding adapter may need to be attached for each feed, depending on the type of equipment used. A repeat endoscopy will be required when the tube needs changing or replacement with a gastrostomy button once the tract has formed.

6.4.2.2 Surgical Gastrostomy

Surgical tubes are Malecot® or Foley® catheters and are inserted into the stomach via an insertion in the abdomen. Malecot® tubes are held in place using wide, flat wings inside the stomach, but may need to be temporarily stitched to the skin. See Figure 7.7 The tube must be secured with tape and the position tested before each feed. As these tubes do not have a retention disc, they may migrate into the duodenum.

![Figure 7.7 Surgical tube](image)

The tubes are replaced after 6-8 weeks with a balloon gastrostomy tube. The replacement device of choice is a low profile balloon device or button gastrostomy. If the patient is very small it may be advisable to use a gastrostomy tube as the first replacement device.
6.4.2.3 Balloon or button gastrostomy

A balloon catheter is where there is an end balloon that is inflated with sterile water or sodium chloride 0.9% to hold the tip against the gastric wall following percutaneous insertion. There is also a skin level retention disc preventing migration of the tube. The inflatable balloon allows easy replacement of the tube. See Figure 7.8 A button or Mic-key® has an extension tube detachable from the stoma for a more discreet skin surface and is more popular for children. See Figure 7.9 Button gastrostomy tubes are not suitable for infants and toddlers as their stomachs are too small to fit the balloon inside. Surgically placed tubes are becoming less popular and the balloon type is more usual.

Figure 7.8 Balloon gastrostomy tube

Gastrostomy tubes and buttons require less frequent changes than nasogastric tubes. A balloon gastrostomy can stay in place for approximately 3 months. A button gastrostomy can replace a conventional tube about 3 months after tract formation and will only need replacing after approximately 6-12 months. PEG tubes may last up to 2 years before the tube requires changing. If a tube is inadvertently removed then it should be replaced with 6-8 hours or the tract will begin to close up. [67]

Figure 7.9 Button gastrostomy
6.4.2.4 Contraindications

Although the risks and potential benefits of enteral access tubes must be weighed up for each patient, certain anatomic and pathologic conditions may increase the likelihood of complications. The following are contraindications to percutaneous feeding tube placement:

- Uncorrectable coagulopathy
- Unfavorable anatomy
- Massive ascites
- Active gastritis
- Gastric dysmotility

Examples of unfavourable anatomy include the following:

- Interposition of the colon between the stomach and anterior abdominal wall
- Interposition of the liver between the stomach and anterior abdominal wall
- A high (intrathoracic) position of stomach

Uncorrectable coagulopathy and the absence of a safe access route are the only absolute contra-indications; the remainder are considered relative contra-indications. [70]

6.4.2.5 Complications of gastrostomy tubes

It is quite common to experience a slight serous discharge from around the stoma. Granulation can occur which may not cause any problems however it can cause discomfort or bleeding if rubbing against the gastrostomy device. Sofradex® may be used to gently breakdown the granulation or it may require treatment with silver nitrate.

Blockages of tubes can occur due to medication administration. Occlusion of the tube due to coagulation of feed by syrups or suspensions combined with inadequate flushing of the tubes or obstruction by crushed oral medicines. Tube blockages can be avoided by regular flushing with water, flushing with water after drug administration and use of appropriate formulations. [64]

Peritonitis, perforations, haemorrhage are major complications of gastrostomy tube insertion. There is also the possibility of aspiration with a gastrostomy tube.

6.4.3 Post Pyloric Feeding

6.4.3.1 Nasojejunal

Nasojejunal (NJ) or naso-duodenal (ND) is the route of choice where there is gastric stasis and aspiration risk. Tubes can be placed endoscopically, fluoroscopically or on the ward. Jejunal tubes are made of polyurethane and are designed for use up to 1 month. The tubes are weighted to encourage the tip of the tube to remain in the jejunum once passed. Jejunal tubes can curl back into the stomach or can be pulled back inadvertently. The position of the tube needs to be confirmed on X-ray prior to starting the feed. Placement of a nasojejunal tube can be difficult and maintaining the tube position can cause problems.
6.4.3.2 Indications for jejunal feeding:

- Congenital gastrointestinal anomalies
- Gastric dysmotility
- Severe vomiting resulting in failure to thrive
- Risk of aspiration

For longer term jejunal feeding, a jejunostomy or gastrojejunal tube needs to be placed. A jejunostomy involves a stomal tract between the jejunum and the abdominal surface and is usually a needle catheter jejunostomy. Jejunostomy or gastrojejunal tubes are placed surgically or radiologically. Single lumen tubes are placed beyond the ligament of Trietz. Dual lumen tubes are used for tube feeding and gastric aspirate decompression. These are also known as gastro-jejunal tubes or PEG-J tubes. In this instance, one lumen is placed past the ligament of Trietz and the other in the stomach. The tube can be used within 12 hours of placement. [63]

The stomach acts as a reservoir for food in the normally fed child regulating the amount of food that is delivered into the small intestine. Bolus feeds into the jejunum should be avoided as they can cause abdominal pain and diarrhoea. Dumping syndrome can occur when there is rapid delivery of a hyperosmolar feed into the jejunum. [67]

6.4.3.3 Complications of jejunal feeding

Unintentional removal, bacterial overgrowth, increased infection risk, bowel perforation, leakage around the tube may lead to granulation and tube occlusion may occur due to the small diameter. This is a particular problem if the tube is also being used for drug administration.

6.5 Drug administration via enteral feeding tubes

There are a number of considerations when using enteral feeding tubes to administer medicines. The route of administration is important with respect to site of absorption, the dosage form of the drug, pH and viscosity if the preparation is liquid. Other problems include occlusion of the tube, interactions with the enteral feed, alteration of pharmacokinetics of the drug, adverse drug reactions due to changes in the pharmaceutical dosage form and alteration in the absorption of medicines. [72][73]

Changing the route of drug delivery or using an alternative agent should be considered if there is risk of clinically significant therapy failure.

The incidence of tube occlusion is 6-38% and depends upon the type of enteral feeding tube used, the type of enteral feed and the characteristics of the drug being co-administered along the tube. [72] The tube is more likely to occlude if it is a small bore and a whole protein feed is being used. Casein or whole protein enteral feeds are more likely to clump and coagulate when exposed to acidic pH. Jejunal tubes tend to be a smaller bore than nasogastric tubes and are more prone to drug occlusion. Dissolution occurs in the stomach for most dosage forms, and hydrolysis for other drugs. Delivery into the small bowel may affect absorption and bioavailability of drugs e.g. digoxin bioavailability is reported to be higher if administered to the jejunum compared to the stomach. [72] This is particularly important for drugs with
narrow therapeutic windows. For patients with high stomas, the excipients of the liquid formulations may cause diarrhoea e.g. sorbitol [74] and it may be pertinent to change to the tablet or capsule dosage form if possible or change to an alternative medication.

Drugs may not be available in a form which can be administered via some fine bore tubes. Where possible, liquid preparations should be used but soluble, dispersible and crushed tablets and the extracted contents of capsules can be used. If the medicine is available only in tablet form, the tablet may be crushed and mixed with sterile water for administration. Crushing, dissolving or suspending powder results in an altered pharmaceutical dosage form, which may have adverse effects on efficacy or patient tolerance. [72][74]

However, the contents of some capsules are enteric coated and may not disperse, or the granules may need a solution other than water to disperse them, e.g. omeprazole. [73] Enteric-coated drugs should not be crushed as they may be designed for absorption from the jejunum or the coating is designed to protect the stomach from the drug. Removing the enteric coating may also reduce the efficacy of the drug. [74] Some liquid preparations may need further dilution if they are very thick. High viscosity requires dilution, suspensions tend to coat the tube when thick, the tube needs to be flushed well otherwise occlusion will occur with repeated doses. For drugs with a pH <4, they should be used with caution as clumping is likely to occur. [72] The tube should be flushed well following administration of every drug. If more than one drug is to be administered, the tube should be flushed between each drug with 3-5mls of water. [73]

Some drugs may interact with the nutrients in the feed, which could lead to increased absorption, changes in gut motility or decreased absorption. Therefore understanding the mechanism of a specific drug-nutrient interaction will facilitate choosing the best management option.

The absorption of warfarin, tetracycline, fluoroquinolone antibiotics, and phenytoin are decreased with concomitant enteral feeding. Phenytoin absorption is affected by the presence of enteral feed due to protein binding. [74] Administration at the same time as feeds reduces plasma concentrations and hence the anti-convulsant effect of the drug. Therefore, continuous feeds should be stopped for a period of 2 hours before and after the dose. [74] The majority of trials and case reports that have used continuous enteral feeding with phenytoin administered via the nasogastric tube or jejunostomy have consistently found a reduction in serum phenytoin concentrations requiring dose adjustments, regardless of the type of enteral feeding formulas used. [75] For warfarin, it has been assumed that the reversal of warfarin anti-coagulation is by the Vitamin K in the enteral feeds but the mechanism of interaction may be protein binding with the feeds. [75] Fluoroquinolone antibiotics bind to divalent ions in the enteral feeds. The absorption of ciprofloxacin is reduced by 50% when administered at the same time as enteral feeds. [3] For further information on individual drug monographs and administration via enteral tubes, refer to Handbook of Drug Administration via Enteral Feeding Tubes 2007. [74]

7. Parenteral access

7.1 Introduction

The selection of the site for parenteral access is a very important factor when administering an intravenous drug or nutrition. Small veins have a relatively poor
blood supply and thus are vulnerable to damage. Areas which have small amounts of subcutaneous tissue are the most likely to be problematic should the drug extravasate. Tolerance of the fluids infused into the peripheral veins depends upon the osmolarity, pH, and infusion rate plus the cannula or catheter material.

Central venous access is usually indicated when there are infusions of pH < 5 or pH > 9, administration of vesicant drugs, need for multiple lumen intravenous treatment, parenteral nutrition, dialysis, central venous pressure monitoring, inotrope administration and the requirement for venous access in excess of three months. [76] For neonates, central access is required to allow exchange transfusion, parenteral nutrition, extracorporeal membrane oxygenation, cardiac catheterisation and to enable reliable venous access for fluids and drugs. [77]

Parenteral nutrition requires appropriate vascular access according to the expected duration and nutritional requirements. Peripheral parenteral nutrition is administered using the superficial veins, most often of the upper extremities. Peripheral parenteral nutrition should only be used in the short term and the osmolarity should be less than 850-900 mOsmol/L. [76][78] The addition of lipid and an increase in the fluid volume help to reduce the osmolarity of the solution.

If drugs or parenteral nutrition are administered into central lines, they are very rapidly diluted by a large volume of blood in the right atrium.

7.2 Peripheral cannulae

Cannulae are available in a variety of lengths and bores, and are used to enter the vein for the connection of the infusion set. To aid insertion the cannula has an introducer, which is withdrawn after positioning.

The gauge of cannulae is a measurement of its external diameter. As the diameter increases, the gauge decreases. The size of the cannula is important and should be decided according to the size of vein i.e. the cannula should fit the vein and the smallest diameter for the purpose is preferred as this is less traumatic for the vein. The length of the cannula is not fixed by the gauge, although it tends to increase as the gauge decreases. For neonates and children, the usual cannulae chosen are 24G (yellow needle) with an approximate external diameter of 0.6mm or 22G (blue needle) diameter 0.8mm. For adults, 18G (green needle, 1.2mm) or 20G (pink needle, 1.0mm) are all purpose cannulae for fluids and blood sampling. Gauges 16 and above are used for rapid infusions e.g. blood or fluid resuscitation in adults.

7.2.1 Selecting a site for peripheral cannulation

Preference in decreasing order in adults;

Non-dominant forearm > dominant forearm > dorsum of non-dominant hand > dorsum of dominant hand > anterior upper arm

Alternative peripheral cannula sites for paediatric patients [79]:

If the forearm and hand are not suitable

- Antecubital fossa (elbow crease) and immobilise
- Dorsum of foot
- Greater saphenous vein in leg
- Scalp veins in neonates
In extreme circumstances
- External jugular
- Femoral
- Any other sites

Due to their superior blood flow, the veins in the upper limb are more suitable for cannulation than the lower limb. The hand veins may be used in preference to the antecubital fossa, as a splint has to be applied to the elbow, which can be uncomfortable. Veins of the lower extremities should be considered when inserting a peripheral cannula into a baby, in particular the great saphenous vein whose size and position is advantageous. However, it should be avoided where possible in older children due to the increased risk of thrombi forming and migrating.

Once a vein has been identified the cannula or device can then be chosen.

7.2.2 Peripheral venous cannulae

These are used for short term use for continuous or bolus administration of infusion fluids and or for drug administration.

7.2.3 Peripheral arterial cannulae

Peripheral arterial cannulae are for short term use and monitor haemodynamic status, invasive blood pressure monitoring and can be used to take arterial blood gases to evaluate respiratory and metabolic status. They are usually inserted in the radial artery though can be placed in femoral, axillary, brachial, and posterior tibial arteries. These are associated with a much lower rate of infection than peripheral venous cannulae, possibly because they are exposed to high vascular pressures, making bacterial colonisation difficult.

7.2.4 Complications of peripheral access

Phlebitis, thrombophlebitis, extravasations and bacterial colonisation are some of the complications of peripheral access particularly using cannulae.

7.2.4.1 Phlebitis

Phlebitis is inflammation of the wall of a vein and the entire vein becomes red, swollen and painful. Oedema may develop resulting in a decrease in blood flow. The risk of infection increases when phlebitis occurs. Causes of phlebitis are particulate matter, hyperosmolar infusions, incorrect dilution and rate of administration of the infusion, mechanical irritation by the cannula of the vein, and prolonged infusion at the same site. If phlebitis occurs then the cannula should be removed as soon as possible, the limb should be elevated to reduce any oedema present and another site identified if continued intravenous administration is required. Early identification of phlebitis prevents the development of thrombophlebitis.
7.2.4.2 Thrombophlebitis

Thrombophlebitis is the inflammation of the wall of the vein with accompanied clot formation. The inflamed and damaged endothelium and valves stimulate platelet aggregation and the clotting cascade. The platelets aggregate around the cannula and fibrin is deposited on the surface of the vein. Thrombophlebitis usually occurs more than 12 hours after the start of drug administration. Most common causes of thrombophlebitis are chemical; the high osmolarity and low pH of infusion fluids and mechanical due to vein trauma on insertion.

7.2.4.3 Extravasation

Extravasation is when there is infiltration of the infusion fluid from a blood vessel into the surrounding subcutaneous tissue. Extravasation may occur because of leakage, where the cannula is pushed or pulled through the vein wall. Extravasation may also occur by direct infiltration i.e. the cannula was incorrectly sited and the fluid infused directly into the subcutaneous tissues. An extravasation injury may lead to an inflammatory response and/or pain from the affected tissue, which may be immediate or delayed. Causes of extravasation are cytotoxic drugs, vasoactive drugs such as dopamine, vasopressin, adrenaline, noradrenaline, which have a direct vasoconstrictive action on blood vessels leading to ischaemic injury and drugs with high or low pH or osmolarity.

The antecubital fossa and the dorsum of the hand and foot are the most often implicated in extravasation injury and should be avoided when administering irritant or vasoactive drugs and those capable of causing discharge or blistering. Neonates possess less subcutaneous tissue relative to an adult; hence any extravasated material is more concentrated in the affected area. Further information about specific extravasation problems is available on the national extravasation information website at http://www.extravasation.org.uk/home.html

7.2.4.4 Sepsis

Both bacterial colonisation and thrombophlebitis increase dramatically after the cannula has been in place for 72 hours. The cannula site must be monitored daily for signs of infection or phlebitis and should be flushed regularly before any signs of pain or blockage occurs. It has been recommended that peripheral cannulae should be replaced every 48-72 hours in adults. For children there is no such recommendation possibly because children would find repeated cannulation traumatic – therefore in practice peripheral cannulae tend to be left as long as possible until access for IV therapy is no longer needed. [79]

7.2.5 Catheter material

The ideal catheter should be flexible, strong, chemically inert, non-thrombogenic, radio-opaque and be resistant to kinking. [80] However if the catheter is relatively inflexible, the vein of the wall may be damaged by pressure causing a thrombosis or vein perforation. Polyurethane-hydromer or silicone elastomers (silastic®) are used for PN as they are biologically relatively inert. Silastic® catheters can last up to 10 years. See Table 7.3
### PVC, polypropylene, polyethylene
- Stiffer prone to thrombosis and mechanical complications
- Easier to insert
- Suitable for short term use

### Silicone elastomer (silastic)
- Inert, radio-opaque, soft
- Suitable for long term use

### Polyurethane hydromer
- Less thrombogenic
- Easily damaged
- Suitable for long term use

#### Table 7.3 Choice of catheter materials:

Lines impregnated with chlorhexidine or silver sulfadiazine have been shown to be efficacious in reducing the incidence of catheter related sepsis though this has been demonstrated in catheters for short term use less than 8 days and not for long term use. [78][79] There is limited data for the use of these catheters in paediatric patients. [79]

### 7.3 Central venous lines

#### 7.3.1 Insertion of central lines

The choice of insertion site depends on the risk of infection, mechanical complications, and thrombophlebitis. Options for sites include the external jugular, internal jugular, subclavian, and femoral vein. Basilic or cephalic vein cannulation has high complication rates due to the long large catheters that are used. The use of the subclavian vein has a lower risk of infection and is the route of choice but is associated with a higher complication rate on insertion e.g. pneumothorax. [76] The smaller the child, the greater is the risk of occurrence of complications. Insertion of a central venous line into the internal jugular vein is associated with a lower rate of severe mechanical complications compared with subclavian insertion and can be used for 5-7 days. Use of a femoral line is associated with a higher rate of infection and thrombosis than subclavian catheters. [81] For neonates, direct cannulation of the umbilical vein, which remains potentially patent for the first few days of life, can be the site of choice before a long term catheter is inserted. [77] For peripherally inserted central catheters (PICC), the veins of the antecubital fossa are commonly used; however, the saphenous, axillary, or even scalp veins can be used. Occasionally, none of these sites is available, and innovative approaches must be used, particularly in patients who still need further cardiac surgery. These include the use of small collateral veins, recanalisation of occluded veins, and the use of translumbar or transhepatic approaches to the inferior vena cava.

Insertion of central lines is by surgical cut down technique or external puncture. Surgical lines are inserted after surgical exposure of the vein and direct cannulation of a vein in the neck or upper or lower limb. Surgical cut down can cause narrowing of the venous lumen and subsequent thrombosis. The surgical lines are cut down to a pre-estimated length prior to insertion, and are difficult to adjust later as they have a subcutaneous cuff and a very short intravascular portion.
Percutaneous insertion involves cannulation of a peripheral limb vein, the small catheter then being threaded through the larger cannula until it attains a central position or by percutaneous puncture of a large vein in the neck, groin or chest and direct insertion of a catheter over a guide wire. Catheter insertion may cause thrombosis and venous occlusion. It is essential to preserve venous access points, especially in children who may require life-long parenteral nutrition. Permanent occlusion of a vein may be less likely if the veins are accessed with an image-guided percutaneous technique rather than with a surgical open technique.

7.3.2 Catheter tip position

Regardless of the type of catheter, the tip must lie in a central position. There may be a risk of venous thrombosis if the tip of the catheter is not at the junction of the superior vena cava and right atrium. For patients requiring long term central access, the tip of the central line may be placed in the upper right atrium. This position appears to be associated with a decreased risk of catheter-associated thrombosis than a position along the superior vena cava, and also allows for the shortening of the catheter that occurs with growth in children. But too far inside the right atrium, there is a risk of cardiac tamponade and atrial perforation.

A catheter tip position in the right atrium may be appropriate for older children but for neonates, who receive a percutaneous long line (or PICC), the catheter tip position in the right atrium is not recommended if the line is being used for parenteral nutrition or drug administration. [82] An X-Ray needs to be taken after a central venous catheter has been inserted to check that it has been sited correctly and that a pneumothorax has not occurred.

7.3.3 Central venous catheters

Central venous catheters (CVC) are used for short term access or for long term therapy such as parenteral nutrition or chemotherapy. CVC are made of polyurethane or silicone. Catheters for central use have a diameter between 18 – 12 gauge (5-10 Fr) for adults [83] and for children 2.7-9.6 Fr. The choice of device should be the smallest appropriate size in the largest possible vein to minimise scarring, stricture and distortion.

Medium and long term lines may have more than one lumen. Double, triple and quadruple lumen lines are available though quadruple central lines are only used in adults. In essence these are 2, 3 or 4 lines fused together. They can be regarded as separate catheters as usually each lumen ends at a slightly different place. Even if all lumens exit at the same point, mixing with the blood is so rapid that incompatibilities are assumed not to matter.

Non-tunnelled Central Venous Catheters are the most commonly inserted central venous catheters and also include peripherally inserted central catheters and umbilical catheters. [84][85]

Umbilical lines are made of polyvinyl chloride (PVC) or polyurethane and are used in neonatal care to monitor blood gases, provide parenteral nutrition, central venous pressure monitoring and exchange transfusion. The catheters are 3-5 Fr gauge. Generally the acceptable duration of use of an umbilical catheter is up to 14 days. [79] Peripherally inserted central catheters (PICCs) lines are made of radio-opaque silastic® or polyurethane-hydromer and are single or double lumen 20-22 gauge (1.9-
4.8 Fr). [83] PICCs are inserted into the basilica, median cubital or cephalic veins in the antecubital fossa rather than the chest or neck, and are therefore further away from any nasal or endotracheal secretions. PICCs are also known as percutaneous long lines in neonatal intensive care. Insertion sites in neonates include antecubital fossa, the greater or lesser saphenous veins and scalp veins. [77] The main use of PICCs is for short-term PN and chemotherapy. If a tunnelled central line has been removed due to line sepsis and central venous access is required, a PICC line may be inserted to infuse PN or chemotherapy before another tunnelled line is placed. Although PICCs may be left in place for months if necessary, the PICCs that are used in children have a small lumen, especially the double-lumen, and this may limit their use for PN. PICCs are easier to insert, are associated with fewer insertion complications than centrally placed lines, e.g. pneumothorax, are less expensive than Hickman type catheters and appear to have a lower infection risk. [84][85] The lower infection risk is likely to be due to the site of insertion or the catheter. Complications associated with PICC insertion are infrequent, but include bleeding, tendon or nerve damage, cardiac arrhythmias, chest pain, catheter malposition, and catheter embolism. [86][87] Other complications include dislodgement, effusions, thrombosis and sepsis. PICCs are not cuffed, and can be easily removed without any form of anaesthetic. See Figure 7.10 & 7.11

![Figure 7.10 PICC](image1)

![Figure 7.11 Double lumen PICC](image2)

7.3.4 Long term central venous access

7.3.4.1 Tunnelled CVCs

Broviac® and Hickman® are surgically implanted catheters used for patients requiring long-term nutritional or IV therapy. The end of the catheter is tunneled under the skin away from the site of venepuncture and the Dacron® cuff is half way along the skin tunnel. These catheters are usually associated with a lower infection rate because the cuff inhibits the migration of bacteria down the catheter tract and also prevents accidental removal [9]. The Dacron® cuff fixes the catheter in place as it becomes invaded by a fibrous sheaf and serves as a physical barrier against infection. Cuffed catheters will need surgical removal. See Figure 7.12 and 7.13
7.3.4.2 Total implanted venous access devices

Total implanted venous access devices (TIVAD) consist of a vascular catheter and a subcutaneous port. The port is a cone shaped reservoir made of stainless steel, titanium or plastic, which is covered by a self-sealing compressed silicone septum. The port is designed to be punctured up to 2000 times by a non-coring needle. The port is inserted into the subcutaneous pocket, which has been created in the chest wall. Immediately after insertion, an access needle is placed into the port and heparin added to ensure access to the port is available due to the swelling and inflammation which occurs after insertion. See Figure 7.14

Total implanted venous access devices (TIVAD) are associated with the lowest rate of catheter related infection. This may be due to the inability of microorganisms to infiltrate the system, as only a needle puncturing intact skin can access the device. Ports are rarely used for parenteral nutrition and when catheter related sepsis occurs, the port will need to be removed as it is usually impossible to clear the infection and there is a potential risk of osteomyelitis or endocarditis.
Figure 7.14 TIVAD

Ports are the device of choice for patients requiring long term intermittent drug therapy such as chemotherapy for haematology-oncology patients or for antibiotics in cystic fibrosis. TIVAD are a more cosmetically acceptable choice of central venous device. The main disadvantage of TIVAD is the need to access the port with a needle, which would not be appropriate for a needle phobic patient particularly if using every day for PN. The other main disadvantage is that both insertion and removal require a trip to theatre.

### 7.3.5 Complications of central lines

Complications of central lines are either early, and are related to insertion of the central venous catheter or are late and are due to catheter use. Procedural complications of Hickman catheter insertion are unusual. Potential complications include bleeding, pneumothorax or haemothorax, malposition or failure of insertion. Atria perforation and perforation of the great veins is a recognised complication of any central line in all age groups.

Central veins are a greater risk as a source of serious infection than peripheral veins. Catheter related sepsis is the major cause of morbidity and mortality from use of central venous catheters.

Other complications of central access are cardiac tamponade, (which if left untreated can have a high mortality rate) and airway injury. **See Table 7.4**

<table>
<thead>
<tr>
<th>Early complications</th>
<th>Late complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumothorax</td>
<td>Thrombosis</td>
</tr>
<tr>
<td>Arterial puncture</td>
<td>Sepsis</td>
</tr>
<tr>
<td>Haemothorax</td>
<td>Blockage</td>
</tr>
<tr>
<td>Anaesthetic complications</td>
<td>Fracture or puncture</td>
</tr>
<tr>
<td>Malposition</td>
<td>Cuff exposure</td>
</tr>
<tr>
<td>Air emboli</td>
<td>Inadvertent removal</td>
</tr>
</tbody>
</table>

**Table 7.4 Complications of central lines [83][88]:**
7.3.5.1 Pneumothorax

A pneumothorax is air in the pleural space between the lung and chest wall. It is the most common complication of central venous catheterisation because of the proximity of the visceral pleura and the path of the introducing needle. Pneumothorax occurs in 5% of direct subclavian punctures.

If an x-ray is not performed after the central venous line has been inserted then it can lead to fluids/drugs being infused directly into the lung(s). A small pneumothorax may not require any treatment. For a significant pneumothorax, insertion of a chest drain is necessary.

7.3.5.2 Air Emboli

Air embolism can occur if air bubbles get into the bloodstream. The air bubbles can block the pulmonary capillaries and lead to sudden vascular collapse, cyanosis, hypotension, tachycardia and distension of the neck veins due to raised central venous pressure. Small bubbles in line are not a problem nor are a few mls of air into a vein likely to cause significant problems. Air embolism is a relatively infrequent complication of central venous catheterisation but claims 40 - 50% mortality. Air embolism can be minimised by ensuring any air is removed from syringes and that giving sets are properly primed before administration of drugs or fluids. All connections must be secure and the infusion monitored to ensure it does not run through.

7.3.5.3 Particulate Emboli

Emboli caused by particulate matter can result in chest pain and shortness of breath if the particulates occlude capillaries and vessels in the lungs. Particulate matter can arise from the formation of drug precipitates due to the mixing of incompatible drugs or from glass and other particles being administered intravenously. Precipitates from the mixing of incompatible drugs are usually pharmacologically inactive but can easily occlude capillary veins or cannulae. Therefore it is important to check that incompatible drugs are not administered down the same line and those lines and cannulae are flushed well between drugs. The use of in-line filters should be used where recommended. Infusions and injections should be checked closely for any particulate matter.

7.3.5.4 Catheter Related Sepsis

The major complication of central venous lines is line related sepsis. The incidence of line related sepsis is 4-12 per 1000 catheter days [77][79] in paediatric patients. The rate of bloodstream infections is higher in children compared to adults. [89] The type of device, age of the patient and underlying disease of the patient is important in paediatrics.

The incidence of catheter related sepsis is influenced by the choice of catheter material, frequency of line breaks of infusion change and drug injection, site of insertion of the catheter and multiple lumens. Multi-lumen catheters are associated with much higher infection rates than single lumen catheters. Catheters inserted into the internal jugular vein rather than the subclavian vein are also associated with a
higher rate of infection. A possible reason for this may be due to catheter movement allowing the migration of microorganisms. Other factors include repeated catheterisation, presence of infection in other parts of the body, absence of antibiotic therapy during catheterisation, nature of infusion, number of access points, type of dressing and experience of personnel.

Colonisation can be outer surface (extraluminal) or inside the lumen (intraluminal) or both. The primary causative agents are *Staphylococcus epidermidis*, *Staphylococcus aureus*, and *Candida albicans*. Fever alone is not the indication for removal of a Hickman line. [79][84][85][89] The source of infection should be identified and treated. Empirical therapy should include antibiotics for gram positive bacteria, an aminoglycoside or 3rd generation cephalosporin for gram negative bacteria.

In most cases of non-tunnelled CVC related bacteraemia and fungaemia, the CVC should be removed. Non tunnelled CVC often have extraluminal colonisation of the catheter, which originates from the skin, or intraluminal colonisation of the hub and lumen. For tunnelled lines, contamination of the hub and intraluminal infection is the most common route of infection. The decision to remove a tunnelled central line or port should be based on the severity of the patient’s illness, assessment of the pathogen involved and presence of complications e.g. endocarditis, septic thrombosis. Catheter removal is necessary in children with persistently positive blood cultures or fungal infections. Treatment of catheter associated fungaemia without removal of the line has a low success rate and may be associated with a higher mortality.[89]

Catheter replacement via a guide wire for non-tunnelled central lines is a recognised practice in the UK, yet the benefits of it reducing infection rates remains controversial. It is agreed however that the replacement catheter should be immediately removed via a guide wire if the primary catheter proves to be the source of a catheter related infection.

Prevention is a key part of reducing CVC related infections by aseptic insertion of lines by trained staff. Other preventative measures include use of single lumen lines, appropriate choice of insertion site, ultrasound guided venepuncture, adequate hand washing policy, appropriate dressing of exit site, 2% chlorhexidine for skin disinfection, regular change of administration sets, use of tunnelled and implanted catheters for long term use, and use of peripheral access (PICC) when possible.[76][79][84]

7.3.5.5 Thromboembolism

Predisposing factors to thrombosis include fibrin sheath, vascular endothelial damage, infusion fluid particularly hyper-osmolar, catheter type and position of the catheter tip. The signs and symptoms of thrombosis will depend on its location. There may be engorgement of upper limbs and neck veins, collateral venous distribution on chest wall, cyanosis, breathlessness, oedema, or mottled appearance of the neck and ears.

Thrombosis is common, up to 50% when assessed by ultrasound. Clinical manifestations are uncommon but occasionally cause high morbidity and even death in some cases. [83] Thrombosis can occur around the entry site or at the tip. Treatment is by a plasminogen activator such as alteplase. Prevention of thrombosis is by appropriate selection of insertion site, catheter tip location and infusion practice.
7.3.5.6 Catheter Occlusion

Catheter occlusion is where there is either partial or complete obstruction that limits or prevents the ability to withdraw blood, flush the catheter or administer intravenous solutions or medications. [90] The type of occlusion determines the treatment options. Thrombotic occlusions account for 60% of all occlusions. PICC lines are more prone due to the longer length and smaller diameter. A thrombotic occlusion is a fibrin sheath, which is a collection of fibrin and platelets and starts from where the catheter enters the vein and spreads towards the tip. It will not cause a problem until it surrounds the catheter tip and then acts as a one way valve so that the infusion can be infused but it is not possible to draw back on the catheter. If the catheter is blocked by a fibrin sheath then the line can be treated with tissue plasminogen activator or alteplase. Alteplase is used for unblocking catheters. It is a fibrinolytic that acts as a thrombolytic by activating plasminogen to form plasmin, which degrades fibrin and so breaks up thrombi.

Lipid occlusion can occur in approximately 30% of patients receiving lipid in their parenteral nutrition. There is some data to support the use of ethanol 70% in adults though there is limited data in children. Ethanol locks have also been used to treat persistent bacteraemia of long term intravascular devices. [81] Acidic drug occlusions or mineral precipitates e.g. calcium or phosphate can be treated with hydrochloric acid. Basic medications require sodium bicarbonate or sodium hydroxide. [78][90]

Flushing techniques can help to reduce the incidence of catheter occlusion particularly the pushing-pausing or pulsating action as this creates turbulence in the lumen thus decreasing the risk of fibrin or platelets being deposited.

8. Paediatric parenteral nutrition (see case study Gastro-intestinal- Neonatal TPN )

8.1 Introduction

Adequate nutrition during infancy and early childhood is fundamental to a child’s development. Children differ from adults in that their food intake must provide sufficient nutrients not only for the maintenance of body tissues but also for growth. Stunting of growth will occur if there are periods of poor nutrition at critical stages of development particularly in the last trimester of pregnancy and the first two years of life. [91]

Parenteral nutrition is not indicated in patients with adequate intestinal function where feeding may be maintained by oral tube, gastrostomy or jejunostomy. See Table 7.5

Parenteral nutrition should be initiated when normal metabolic and nutritional needs are not met by the enteral feeding. The therapeutic goal is to ensure that nutritional intake is sufficient to provide nutrients for maintenance of body tissues and balanced somatic growth. Somatic growth spurts occur during early infancy and adolescence. The neonatal brain is sensitive to periods of malnutrition and metabolic insult during a period of rapid growth. Malnutrition in this developmental stage of life may be associated with intellectual impairment. [91] Consequently, starting parenteral nutrition in a small infant who cannot tolerate feeds may be a matter of urgency due to the limited energy reserves. A small preterm infant of 1kg, who has perhaps no more than 10g of storage fat, might survive for only four days if starved, in contrast, it has been estimated that a term infant could survive for 30 days. [92]
Malnutrition is often accompanied by acute or chronic disease and may be present in many hospitalised patients. It may cause clinical problems including suppressed immune response, hypotonia, and loss of ventilatory drive, apnoea, muscle wasting, and reduced cardiac reserve.

### Indications for parenteral nutrition

- Prematurity, necrotising enterocolitis
- Acute pancreatitis
- Intestinal failure:
  - Short bowel and malabsorption syndromes e.g. autoimmune enteropathy
  - Protracted diarrhoea
- Chronic intestinal pseudo-obstruction
- Post-operative abdominal surgery
- Radiation/cytotoxic therapy: severe mucositis, Graft vs Host Disease
- Multi-organ failure
- Hyper-catabolism:
- Extensive burns or major trauma

| Table 7.5 Indications for parenteral nutrition |

**Task 7.1**

What would you need to consider when starting a patient on parenteral nutrition?

### 8.2 Fluid requirements

Fluid requirements are related to calorie expenditure and can be calculated using a formula for body weight. See Table 7.6 The requirement for fluid to body weight is much greater in very small children. Infants have a much larger body surface area relative to weight than older patients and lose more fluid through evaporation and dissipate much more heat per kilogram than their older counterparts, which accounts for the increased requirements. [93] Fluid balance and hydration status can be monitored by regularly weighing the patient.

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10</td>
<td>100ml/kg</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>1000ml + 50ml/kg for each kg above 10kg</td>
</tr>
<tr>
<td>&gt; 20</td>
<td>1500ml + 20ml/kg for each kg above 20kg</td>
</tr>
</tbody>
</table>

| Table 7.6 Daily maintenance fluid requirements |

### 8.3 Energy requirements

Nutritional requirements differ according to age and are affected by the underlying disease and current nutritional status of the child. Energy requirements are increased when the body is under catabolic stress, fever or sepsis or if there is failure to thrive. [94] Fluid restriction is one of the major factors impeding the provision of energy.
requirements particularly in intensive care settings though catch up growth may be exhibited when more liberal volume of fluid is available.

Sufficient non-protein calories, as carbohydrate and fat, must be provided to meet basal metabolic energy demands and to ensure growth and development. [95] Without adequate non-protein calories, the body uses protein from muscle, visceral protein, or protein from PN as a calorie source; conversely excess calories with insufficient protein will be deposited as fat.

For efficient protein anabolism, the energy to nitrogen ratio (kcal: 1g N ratio) should be less than 250 or 30-40kcal per gram of protein. [96][97] See Table 7.7

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Fluid (ml/kg/day)</th>
<th>Energy* (kcal/kg/day)</th>
<th>Nitrogen (g/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm</td>
<td>120 - 180</td>
<td>110 - 120</td>
<td>0.48 – 0.64</td>
</tr>
<tr>
<td>0 - 1</td>
<td>110 - 150</td>
<td>90 – 100</td>
<td>0.34 – 0.46</td>
</tr>
<tr>
<td>1 – 6</td>
<td>80 - 100</td>
<td>75 – 90</td>
<td>0.22 – 0.40</td>
</tr>
<tr>
<td>6 – 12</td>
<td>75 – 80</td>
<td>60 – 75</td>
<td>0.16 – 0.32</td>
</tr>
<tr>
<td>12 - 18</td>
<td>50 – 75</td>
<td>30 - 60</td>
<td>0.16 – 0.32</td>
</tr>
</tbody>
</table>

* Calories include protein

Table 7.7 Estimated Energy and protein requirements [97][98]

8.4 Protein requirements

Protein (nitrogen) is needed for growth and the formation of new tissues (e.g. wound healing) and the synthesis of plasma proteins, enzymes and blood cells. The protein required by the human body is manufactured from 20 different amino acids. Premature infants are unable to synthesise or metabolise some of the non-essential amino acids and are especially vulnerable to amino acid imbalances due to their high nitrogen requirements and enzymatic imbalances. Some of the amino acids are become “conditionally essential” and include cysteine, taurine, glutamine, tyrosine and histidine. [99]

The nitrogen in PN is provided in the form of crystalline L-amino acid solutions. The composition varies according to age of the infant and amino acid requirements. Solutions for infants less than 1 year of age were formulated to contain more branched chain amino acids (leucine, isoleucine, valine) and less phenylalanine, glycine and tyrosine known to cause neurotoxicity in premature infants due to immaturity of metabolic pathways. [100][101] The branched chain amino acids have been shown to produce greater rates of protein synthesis from amino acids. The composition of the amino acid solutions are based on either breast milk amino acids (Vaminolact®) or cord blood amino acid profiles (Primene®). Solutions for infants and children over 6 months of age are based on egg protein profiles. [101]

The goal in the nutritional management of the infant is to provide protein in amounts that maximise synthesis and accretion without causing metabolic acidosis from amino acid excess. Intrauterine accretion rates have been used to estimate protein requirements in the neonate. Neonates have a high rate of whole body protein synthesis and the protein synthesis is very sensitive to insulin. A higher intake is required to achieve physiological protein deposition.

Aggressive and early introduction of amino acids with glucose on day one of life has been found to be safe in premature infants and will decrease protein catabolism and enhances net protein accretion. [102][103][104] Recent studies, have demonstrated...
that premature infants who receive high amino acid intake approaching in-utero accretion rates on day 1 of life achieve better short term growth at 36 weeks and less growth failure. [105][106]
Protein needs in infants and children who are malnourished or acutely stressed by infection or trauma can be increased, while patients who are in renal or liver failure require less protein, depending upon medical management.

8.5 Carbohydrate requirements

Glucose is the carbohydrate of choice for PN as it is utilised by all body tissue and serves as a metabolic fuel for all organs including the brain. It should provide approximately 60-75% of the total non protein calorie intake. Glucose intake should be adapted to age and clinical situation e.g. premature infants, critically ill patients. Premature infants have relatively high requirements due to the large body proportions of metabolically active organs.
In preterm infants, glucose infusion should start with 4-8mg/kg/min (6-12g/kg/day) to suppress hepatic glucose output. It should be introduced slowly (1-3g/kg/day increments) to prevent hyperglycaemia & glycosuria and allow an appropriate response of endogenous insulin. Hyper or hypoglycaemia in an individual previously stable on PN may indicate sepsis.
The majority of the basal glucose requirement is required to maintain adequate energy for the brain. The ability to convert glucose into glycogen starts when the foetus reaches the third trimester. Alternative energy substrates such as ketones are limited in infants at early gestational age due to low fat stores therefore a constant supply of glucose for energy is essential. For persistently high glucose concentrations in very low birth weight infants, insulin can be used to enable administration of adequate glucose loads in the PN but tight control of blood sugars must be maintained to avoid hypoglycaemia and risk of brain hypoxia. [107] Prolonged severe restriction of parenteral glucose may substantially reduce calorie intake and hence growth.
When the glucose intake exceeds oxidative capacity, glucose is converted into fat and deposited in the liver. Net lipogenesis occurs at glucose intakes of more than 18g/kg/day in infants (12.5mg/kg/min). [108][109] The conversion of glucose to fat is an energy inefficient process, which leads to increased energy expenditure, increased oxygen consumption and increased carbon dioxide production. Excessive glucose intake is thought to increase carbon dioxide production, which may have effect on the weaning of infants off artificial ventilation and contribute towards the development of liver impairment due to steatosis.
Cyclical PN may be introduced in older children to improve their quality of life and fit in with other IV medication. The PN must be tapered for the last hour of infusion and blood sugar monitoring should be checked 30 minutes after discontinuation of the infusion to ensure that rebound hypoglycaemia does not occur. The reduction in rate of infusion should be attempted in a stepwise approach to ensure tolerance. Cyclical PN is not suitable for infants less than 3 months of age due to lack of endogenous reserves.
8.6 Lipid requirements

Lipid emulsions are an integral part of paediatric parenteral nutrition in order to provide the high energy needs without carbohydrate overload and to prevent essential fatty acids deficiency. Lipids are incorporated into the structural components of cell and plasma membranes and are used for prostaglandin synthesis and platelet function. Traditional lipid emulsions contain a mixture of egg phospholipids, glycerol and soybean oil. The soybean oil provides essential linoleic (omega 6), alpha-linolenic acid (omega 3) and other long chain polyunsaturated fatty acids. The 20% lipid emulsions are recommended as the 10% emulsions contain a higher phospholipid content resulting in higher triglyceride, fatty acid and plasma cholesterol concentrations [92]. Intravenous lipid has a relatively low osmolality and is well tolerated via a peripheral vein.

Long chain fatty acids (LC-PUFA) are essential to the newborn for brain and retina development and so should be introduced on day 1 of PN. [111][112] Biochemical evidence of essential fatty acid deficiency may develop in 1 to 2 days in the premature neonate, where there are limited fat stores, and a diet without lipid. Lipid intake should usually cover 25-40% of non-protein calories in fully parenterally fed patients. Maximum fat oxidation occurs when lipids provide 40% of the non-protein PN calories in newborns and 50% in infants. [97][112] Small for gestational age neonates and low-birth weight infants may have a limited ability to metabolise fat and should have their serum triglyceride concentrations monitored. Lipid clearance is maximised when the solution is infused over 24 hours. If plasma triglycerides concentrations during infusion exceed 250 mg/dl or 2.82mmol/L, a reduction of lipid intake in newborns, premature and young infants should be considered.

Free fatty acids (FFA) compete with bilirubin on albumin binding sites. A high FFA/albumin ratio is associated with an increased risk of unconjugated hyperbilirubinemia. This could potentially cause kernicterus, a cause of brain damage but in clinical practice it is unlikely to be seen.

There is no evidence to support routine lipid reduction in critically ill or infected patients. Recent studies have suggested that lipid may be the preferred energy source in sepsis. [94][114][115] Lipid emulsions have been shown to inhibit bacterial clearance and depress platelet function. However, white cell function is normal when usual doses of fat are infused over a prolonged period of time. The monitoring of plasma triglyceride levels and dose adjustment in case of lipid intolerance are recommended in these patients.

Newer emulsions contain olive oil and soybean oil, long chain/medium chain triglycerides (LCT/MCT)) or combination lipids (LCT/MCT/Olive oil/Fish oil). Olive oil preparations [115] contain vitamin E, which has antioxidant properties and a mixture of soybean to provide LC-PUFA plus olive oil for monounsaturated fatty acids (63% oleic acid). LCT/MCT lipids provide essential fatty acids and medium chain triglycerides (MCT). MCT is non-carnitine dependent with rapid utilisation for calories and clearance. The use of MCT/LCT is considered to confer advantages with respect to lower incidence of liver dysfunction and improved immune function. Lipid emulsions containing fish oils are rich in long chain, polyunsaturated omega-3 fatty acids. Recent studies have indicated that omega 3 essential fatty acids are more important than omega 6 for neuronal development and promote optimal neurodevelopmental outcome. Docasahexenoic acid and arachnidonic acid accumulate in the developing brain. Preparations have been formulated to contain a
mixture of fish oils, soybean oil, and olive oil and medium chain triglycerides. [116] They are unlicensed in paediatric patients at present. (See Table 7.8)

<table>
<thead>
<tr>
<th>Lipid (g/l)</th>
<th>LCT</th>
<th>MCT</th>
<th>Olive oil</th>
<th>Fish oil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intralipid® 20%</td>
<td>200</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Clinoleic® 20%</td>
<td>160</td>
<td>-</td>
<td>40</td>
<td>-</td>
</tr>
<tr>
<td>Lipofundin® 20%</td>
<td>100</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SMOF®</td>
<td>60</td>
<td>60</td>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>Omegaven®</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 7.8 Lipid preparations

8.7 Electrolytes

Electrolytes are added to PN according to the patient’s individual requirements based on the blood chemistry.

**Task 7.2**

Read individual electrolyte requirements for different age groups in the 2005 ESPGHAN/ESPEN guidelines.

**8.7.1. Sodium**

Approximately 96% of the total body sodium is distributed in the extracellular space. Changes in body sodium probably more accurately reflect changes in fluid balance rather than changes in total body sodium but if the total body sodium is low then weight gain will not be achieved. Aim for a urinary sodium above 20mmol/L. If low plasma sodium is detected, the patient's fluid balance and urinary output should be assessed as the presence of too much fluid will dilute any sodium present in the body, resulting in the appearance of low levels despite the presence of normal levels of sodium in the body. Patients who are dehydrated may appear to have high plasma sodium. If hypo or hypernatraemia is detected in the absence of fluid balance problems the sodium provided in PN should be altered. Urinary sodium should be > 20mmol/L.

Sodium is restricted in the first few days after birth to allow for contraction of the extracellular volume (6-10% loss of body weight), which confers respiratory benefit. However after the first week of life, the premature neonate may have increased sodium requirements, as the immature kidney is unable to effectively regulate urinary sodium losses. Diuretic use may also increase sodium loss. Abnormal losses of
sodium also occur due to hypersecretory states, intestinal malabsorption, and vomiting and nasogastric losses. Sodium imbalance, in the absence of fluid balance problems can have serious consequence. **Hyponatraemia** can slow nerve conduction, reduce excitation of muscle and may cause seizures. The occurrence of neonatal apnoea has also been associated with hyponatraemia. **Hypernatraemia** will produce cellular volume contraction; this may cause the brain to shrink, resulting in intracerebral haemorrhage and thrombosis. Plasma sodium and fluid balance should initially be monitored daily when parenteral nutrition is started and then three times a week.

### 8.7.2 Potassium

Potassium is the most abundant intracellular cation and is responsible for much of the important bioelectrical activity associated with the cell membrane notably nerve and muscle excitation. **Hyperkalaemia** has very serious consequences; levels above 7mmol/l have been associated with cardiac arrest and death. Causes of hyperkalemia include renal failure, potassium sparing diuretics, potassium released from cells (rhabdomyolysis, trauma), and acidosis. Signs of **hypokalaemia** include lethargy, muscle weakness and cardiac arrhythmias. Causes of hypokalemia include immaturity of the kidneys in newborn infants leading to excess potassium being excreted in combination with sodium, renal losses due to diuretic use or other drugs, such as amphotericin, or transcellular shifts (e.g. with salbutamol or insulin), alkalosis.

### 8.7.3 Calcium

Calcium is the most abundant mineral in the human body; most of it is contained in the bones and has many important functions including initiation of muscle contraction, co-enzyme for coagulation factors and as an intracellular second messenger. Neonates require large amounts of calcium for bone and teeth growth. Supply of insufficient calcium is associated with the development of metabolic bone disease, which results in rickets and reduced bone mass and an increased potential for fractures.

In plasma, calcium is present in three forms: bound to protein (mainly albumin); complexes with citrate and phosphate; and free ions. The binding of calcium to protein is pH dependent so the binding increases in acidosis and decreases in alkalosis. Only the ionised form is physiologically active and it is the concentration of ionised calcium which is maintained by homeostatic mechanisms. **See table 7.9**

<table>
<thead>
<tr>
<th>Calculation of 'corrected' plasma calcium concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>For albumin &lt; 40, corrected calcium = Ca$^{2+}$ + 0.02 x (40 – alb)</td>
</tr>
<tr>
<td>For albumin &gt; 45, corrected calcium = Ca$^{2+}$ - 0.02 x (alb – 45)</td>
</tr>
</tbody>
</table>

**Table 7.9** Corrected calcium calculations
Hypercalcaemia  Calcium above 3.5mmol/L requires urgent treatment. Clinical features of hypercalcaemia include a short QT interval on ECG, cardiac arrhythmias & increased blood pressure, renal calculi & nephrocalcinosis, corneal calcification & vascular calcification and mental changes. Causes of hypercalcaemia are malignant disease ± metastases, vitamin D excess, primary hyperparathyroidism, thiazide diuretics, excess absorption and immobilisation.

Hypocalcaemia  Clinical symptoms include tetany, convulsions, and prolonged QT interval on the ECG, numbness and paraesthesia. Causes of hypocalcaemia include Vitamin D deficiency, hypomagnesaemia, hypoparathyroidism, alkalosis and acute pancreatitis.

8.7.4 Magnesium

Magnesium acts as a cofactor for some 300 enzymes, including enzymes involved in protein synthesis, glycolysis and transmembrane transport of ions. Magnesium interacts with calcium and can affect the permeability of excitable membranes leading to hyperexcitability in extracellular magnesium depletion states.

Hypermagnesaemia. Significant hypermagnesaemia is uncommon. Cardiac conduction is affected at concentrations of 2.5-5.0 mmol/l; very high concentrations (> 7.5 mmol/l) cause respiratory paralysis and cardiac arrest. Such extreme hypermagnesaemia may occasionally be seen in renal failure.

Hypomagnesaemia almost always indicates magnesium deficiency. It is related to a number of factors including: malabsorption, malnutrition and fistulae; alcoholism; cirrhosis; diuretic therapy; and renal tubular disorders. Clinical features of hypomagnesaemia include tetany (with normal or decreased calcium), agitation, delirium, ataxia, tremor, choriform movements, convulsions and muscle weakness.

8.7.5 Phosphate

Phosphate is required for the formation of bone, soft tissue growth and urinary buffering. In preterm infants the retention of calcium and phosphate is proportional to growth. Foetal bone mineral accretion rate can be achieved in preterm infants given sufficient supplementation with calcium and phosphate. Supply of too little calcium and phosphate is associated with the development of metabolic bone disease, which results in rickets and reduced bone mass, with increased potential for fractures. Since the introduction of organic phosphate salts, it has been possible to achieve the essential requirements of calcium and phosphate in the PN formulation.

Hyperphosphataemia. The most common cause of hyperphosphataemia is renal failure. Other causes include hypoparathyroidism, excessive phosphate intake or administration, and vitamin D intoxication.

Hypophosphataemia is a common biochemical finding. When mild it is probably of little consequence, but severe hypophosphataemia (<0.3mmol/l) can have important consequences on the function of all cells, particularly muscle cells and red and white blood cells, by limiting the formation of essential phosphate containing compounds.
such as ATP. Causes of phosphate deficiency are vitamin D deficiency, re-feeding syndrome, DKA, hypophosphataemic rickets and phosphate binding agents.

8.8 Vitamins and trace elements

Vitamins and trace elements are an important component of a paediatric PN regimen, because of the intense metabolic activity, growth and development of all organs and systems. The optimal parenteral vitamin and trace element requirements for children and neonates have never been determined. Current recommendations are expert opinions based on observed biochemical responses to variations in parenteral intake and on comparison with enteral recommendations. [118]

A sufficient supply of vitamins is essential for growth and development. Two vitamin preparations are used to provide the daily requirements of fat and water soluble vitamins. Fat soluble vitamins are provided in Vitlipid and water soluble in Solivito. Fat soluble vitamins A, D, E and K have the potential for storage and therefore the potential for toxicity. Water soluble vitamins like ascorbic acid are considered to be relatively non-toxic and are excreted when in excess.

8.8.1 Fat soluble vitamins

Fat soluble vitamins are important for the absorption of calcium (vitamin D), clotting factors (vitamin K), and act as anti-oxidants (vitamin E).

8.8.2 Water soluble vitamins

Water soluble vitamins function as co-factors for enzyme reactions and requirements are dependent upon the energy and protein content of the diet as well as the rate of energy utilisation and renal losses.

8.8.3 Trace elements

Adequate provision of trace elements is essential for optimal utilisation of amino acids and energy substrates; the most important are zinc, copper and selenium. It may be necessary to provide additional trace element supplementation for patients with short bowel syndrome or malabsorption states.

Iron is not routinely added to short term PN but may be necessary for long term therapy to prevent iron deficient anaemia, which can interfere with the growth and development of a child.

8.9 Monitoring

Initial Monitoring
Urea & Electrolytes, Liver function tests

Continued Monitoring (weekly)
Urea & Electrolytes, Liver function tests, FBC
Urinary electrolytes (sodium and potassium)

Continued monitoring (monthly)
Trace elements (copper, zinc and selenium), fat soluble vitamins (A,D & E)
FBC, ferritin
8.10 Complications

The major complication of PN administration involves sepsis of the central line. The primary causative agents are *Staphlococcus aureus*, Coagulase-negative *staphlococcus* and *Candida Albicans*. [119] Treatment is with antibiotics and antifungals.

Cholestasis is commonly seen in long term PN. It is a multifactorial problem and may be due to immaturity of bile acid transport mechanisms, phytosterols in the soybean emulsion, sole use of long chain triglycerides, substrate excess - glucose or lipid overload, lack of enteral feeding, lack of stimulation of the enterohepatic circulation, and sepsis. Measures to help prevent liver disease include minimal enteral or trophic feeding (1-10ml/hour) to maintain intestinal mucosa integrity, reduce bacterial translocation and prevent biliary cholestasis and the use of medium chain triglyceride emulsions. A reduction in overall lipid content of the PN regimen or an alternative lipid source can be beneficial in reversing cholestasis. Lipids containing LCT/MCT (Table 7.8) can be used as a first line alternative or combination lipids containing a proportion of fish oil. [120][121] Lipids containing fish oils alone have been used to reverse cholestasis in patients who had PN associated liver disease. [122] There are concerns regarding the lack of essential fatty acids provided by the fish oils alone. Their place in therapy is unknown at present.

Other measures to reverse cholestasis include prescribing Ursodeoxycholic acid to promote biliary flow as biliary sludge is common in PN associated liver disease. Cyclical PN (12-20 hours overnight) is also recommended to promote clearance.

8.11 Intestinal transplantation

The main criteria for intestinal transplantation are a lack of central access sites and severe PN associated liver disease. Early referral to an intestinal transplantation centre is recommended due to rapid progression of liver disease particularly in the paediatric population. Patients referred with a conjugated bilirubin of > 200µmol/L have a life expectancy without transplantation of around 6 months.

The lack of availability of sized matched organs means that the transplant list is 50-60% children with the majority being less than one year of life and under 10kg. Complications relate to surgical morbidity, rejection of the transplanted organs and opportunistic infections though these complications are becoming less frequent due to better post operation management. The five year survival rate of a combined bowel and liver transplant is 52% compared to approximately 80% at 20 years (local data) on home PN (HPN).

9. Refeeding syndrome

9.1 Introduction

Refeeding syndrome is the metabolic and physiological consequences of the depletion, repletion, and compartmental shifts of phosphate, potassium, magnesium, glucose metabolism, vitamin deficiency and fluid restriction. Refeeding syndrome can occur after initiation of nutrition support via the oral, enteral or parenteral route. It is more likely to occur in malnourished patients who have lost more than 10% of their...
body weight over the previous 2 months. [123] It is not a phenomena restricted to adults, cases have also been reported in children. Refeeding syndrome is associated with [123][124][125]:

- Hypophosphataemia
- Hypomagnesaemia
- Hypokalaemia
- Vitamin deficiency
- Fluid retention

In early starvation, the body switches from using carbohydrate to using fat and protein as the energy source. The basal metabolic rate decreases by up to 20-25%. [125] During prolonged starvation, ketone bodies and fatty acids are utilised as the main energy source; the brain switches to using ketone bodies instead of glucose and muscle and other tissues decrease their use of ketone bodies and use fatty acids as the main energy source. The liver decreases the rate of gluconeogenesis to conserve muscle protein. The loss of fat and lean body mass is accompanied by a proportional loss of phosphate although the plasma concentration remains within the normal range. Normal plasma concentrations of electrolytes are maintained during starvation as there is reduction in renal excretion and contraction of the intracellular compartment. When metabolism switches towards anabolism; carbohydrate intake stimulates insulin release, increased cellular uptake of phosphate, magnesium, water and potassium and synthesis of protein plus increased renal tubular absorption of water and sodium (See Figure 7.15) Insulin stimulates synthesis of glycogen, fat and protein and a decreased secretion of glucagon.

Metabolic manifestations happen at the start of anabolism, which immediately causes rapid alterations in hormone levels and an increase in the basal metabolic rate. Carbohydrate becomes the predominant fuel and if in excess, or if insulin secretion is insufficient to meet the carbohydrate load, then this will lead to hyperglycaemia, glycosuria, and hyperosmotic non-ketotic coma, fatty liver, increased carbon dioxide production, hypercapnia and respiratory failure. [124]

The hallmark biochemical feature of refeeding syndrome is hypophosphataemia. [124][125] Phosphate is essential for many metabolic processes. For example, it is used for adenosine triphosphate (ATP) synthesis, normal function of erythrocytes, leucocytes, platelets, the central nervous system, acid-base balance, has a structural role as a component of phospholipids and is involved in glycolysis.[126]
Phosphate is lost from the intracellular compartment on introduction of glucose with insulin release and the rapid shift of glucose and phosphate into cells. Refeeding hypophosphatemia can be seen within 24-72 hours of initiation of nutrition support. [127] The demand for phosphate is greater in children because it is needed for the formation of new tissues and in a critically ill child with severe malnutrition, the patient will be at a higher risk of developing hypophosphatemia.[126] Phosphate deficiency leads to thrombocytopenia, impaired blood clotting and deficiency of leukocyte function. Poor phosphate intake suppresses secretion of PTH, which increases tubular phosphate reabsorption to more than 80%. Phosphate deficiency leads to renal PTH resistance and therefore reduced excretion in urine.[128] Hypophosphataemia can occur within hours and can lead to depletion of phosphorylated compounds ATP, 2, 3 DPG resulting in cardiac, neuromuscular, haematological and respiratory compromise. At a level of <0.3mmol/L, seizures, cramps, impaired musculo-skeletal function, paraesthesia, hypoventilation and respiratory failure can result. [123] Rarely rhabdomyolysis can occur due to ATP depletion with subsequent renal failure. Therefore homeostasis of phosphate is essential during refeeding in malnourished patients.

Decreased potassium and magnesium can lead to dysrhythmias and cardiac arrest. Cardiac arrest has been reported happen when the patient is < 70% of previous body weight. Glucose refeeding can decrease water and sodium excretion with expansion of the extracellular compartment and subsequent weight gain. Ventricular volume returns to normal but left ventricular mass remains reduced. Fluid retention, oedema formation and congestive heart failure may occur in adults though severely malnourished children tend to increase total body sodium without obvious tissue oedema.[128]
Rapid depletion of thiamine occurs due to consumption in glycolysis as thiamine is a co-factor in glucose metabolism. Deficiency impairs glucose metabolism with subsequent lactic acidosis. [123] Thiamine deficiency can also result in Wernicke’s encephalopathy.

Other symptoms of refeeding syndrome include tachycardia, bradycardia, lethargy and mild elevation of liver function tests.

9.2 Prevention

Not all patients who are re-fed develop refeeding syndrome but patients at risk should be identified on admission to hospital, closely monitored and managed accordingly. Guidelines for adults were published by NICE in 2006 [6] but there is no paediatric guidance of management of refeeding syndrome but if the patient has one or more of the following criteria then they may be at risk of refeeding. See Table 7.10

<table>
<thead>
<tr>
<th>Risk profiles for refeeding syndrome in children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute weigh loss of 10% in past 1-2 months</td>
</tr>
<tr>
<td>Kwashiorkor (decreased protein intake and relatively normal calories)</td>
</tr>
<tr>
<td>Marasmus (decreased energy and protein intake)</td>
</tr>
<tr>
<td>Protein-calorie malnutrition</td>
</tr>
<tr>
<td>Underfeeding / fasting for at least 10-14 days</td>
</tr>
<tr>
<td>Anorexia nervosa</td>
</tr>
<tr>
<td>Morbid obesity with massive weigh loss of 10% in past 2 months</td>
</tr>
<tr>
<td>Prolonged IV hydration without provision of sufficient calories and protein</td>
</tr>
<tr>
<td>&lt; 80% ideal body weight</td>
</tr>
<tr>
<td>Arm anthropometrics less than the fifth percentile</td>
</tr>
</tbody>
</table>

Table 7.10 Risk profiles for re-feeding syndrome in paediatrics [127]

9.3 Management of refeeding syndrome

Circulatory volume should be carefully restored if required and electrolytes corrected if the patient is at risk. Nutritional support should provide both nitrogen and carbohydrate as gluconeogenesis is insufficient to meet requirements following starvation. [128]

Electrolytes need to be supplemented according to plasma levels, requirements and route of administration. A low volume and low sodium enteral or parenteral nutrition is required, and increased amounts of magnesium, potassium and phosphate. There are recommendations for oral supplementation for severely malnourished children being fed enterally [130] but none for parenteral nutrition. Water soluble vitamins are an essential component of the nutrition support; in particular thiamine, folic acid, riboflavin, ascorbic acid, and pyridoxine. Fat soluble vitamins A, D, E and K and trace elements such as selenium may be deficient.

The general recommendation in paediatrics for enteral feeds is 75% of total daily requirements for fluids and calories increased over 3-5 days. This is tailored to the individual patient and may need adjustment by up to 30%. Frequent small feeds are
recommended. [129] Initial protein requirements are 0.6-1g/kg/day increasing to 1.2-1.5g/kg/day for anabolism to occur.[128]

There are few recommendations for calorie provision for parenteral nutrition. One study looking at hospitalised paediatric patients at risk of refeeding syndrome suggested 50-75% of resting energy expenditure (predicted or measured) to a maximum of 100% or 80% of current calorific intake. The current caloric intake was defined as the intake received from oral diet, enteral or parenteral nutrition or IV fluids. The nutritional care plan was to increase the calories by 10-20% per day until the calorific goal was met. This could be achieved within 3-7 days of initiation of nutrition support if the biochemical indices were stable. [127]

Parenteral nutrition regimens are generally built up over a course of 3-4 days depending upon fluid restriction, IV access and tolerance to the constituents. It is unlikely that the calories would start aggressively or be increased excessively in a patient on intensive care due to the above constraints but an initial regimen of a maximum of 50% of energy requirements would seem prudent.

9.4 Monitoring [125][127][128][131]

- Hydration and nutritional status
- Daily weight
- Serum electrolytes
- Daily Na+, K+, Mg2+, Ca2+, P042-, urea, Cr, glucose, albumin
- Cardiac status
- Pulse, ECG, ± ECHO

Nutritional monitoring is an essential part of the management of refeeding syndrome to ensure that appropriate nutrition and supplementation can take place. Daily monitoring is required until full calories are achieved and the patient is stable. Urinary sodium may be useful to determine sodium depletion. Early weight gain may be secondary to fluid retention.

10. Gut motility

10.1 Motility agents

10.1.1 Anatomy and physiology in children/adolescents

Under normal conditions, food is proposed towards the proximal small bowel where there is stimulation of release of cholecystokinin, motilin, peptide YY, glucagon like peptide 1 and ghrelin, which act as a feedback mechanism and cause fundal relaxation and inhibit gastric emptying. Regulation of intraluminal transit is also influenced by dopamine, decreasing gastric emptying and intestinal peristalsis, and motilin. [132]

Motilin is a gastrointestinal hormone that is involved in the induction and amplification of migrating motor complex activities that is initiated almost simultaneously in the stomach and duodenum and characterises the migration of nutrients from the small intestine to the colon. [133][134] Migratory motor complexes (MMC) are a cyclical pattern of electromechanical activity in the smooth muscle that occurs during fasting and are divided in phases. Phase 1 is a period of inactivity, which is followed by a variable period of irregular contractile activity termed phase 2.
Phase 3 comprises a short period (5–10 min) of intense, frequent, regular contractions which migrate down the small bowel and facilitates gastric emptying and accelerates small intestine and colonic transit. Phase 3 activity occurs primarily by activation of motilin receptors. [125] An increase in gastric, biliary and pancreatic secretion is seen in conjunction with the motor activity. 

Muscular contractions of the gut and secretion of acid and enzymes are under the control of the autonomic nervous system. The myenteric plexus is the major nerve supply to the gastrointestinal tract and is located between the longitudinal and circular muscle layers of the gastrointestinal tract. Prokinetics increase gastrointestinal contractions and propulsions by increasing acetylcholine (Ach) activity at smooth muscle muscarinic receptors or by blockade of presynaptic inhibitory dopamine receptors. [133]

10.1.2 Common diseases

In most critically ill patients, motility disorders manifest as inhibition of propulsive gastrointestinal motility such as gastroparesis with high gastric residual volumes, feed intolerance, paralytic ileus and constipation and rarely as hypermotility resulting in diarrhoea.[134] There are diminished migrating motor complexes, antral hypomotility and decreased gastric emptying. [136] Reduced gastric motility is often secondary to the administration of drugs or it may be due to the underlying disease. [137] Abnormal gastrointestinal motility is the major limiting factor for the delivery and success of enteral nutrition on intensive care. Delayed gastric emptying can lead to bacterial overgrowth, gastroesophageal reflux, aspiration, pneumonia and sepsis. (See Table 7.11)

Reduced gastrointestinal motility develops in at least 50% of critically ill children with a delay in gastric emptying and increased risk of nosocomial pneumonia. In children, and particularly in infants, the incidence of gastro-oesophageal reflux and regurgitation is much higher than in adults, mainly due to immaturity of the lower oesophageal sphincter though the incidence of vomiting does not appear higher in critically ill children. [137]

10.1.3 Causes of dysmotility

Abdominal surgery, head and spinal injuries, hyperglycaemia, systemic inflammatory response syndrome (SIRS) and sepsis, electrolyte imbalance, pre-existing co-morbidities, admission diagnosis, and age of the patient contribute to the development of gut dysfunction. [134][136]
### Table 7.11 Summary of pathophysiological disturbances and clinical symptoms

<table>
<thead>
<tr>
<th>Site</th>
<th>Pathophysiological disturbance</th>
<th>Clinical Symptoms</th>
</tr>
</thead>
</table>
| **Oesophagus** | Reduction in frequency and amplitude of propulsion  
Low or absent oesophageal sphincter pressure | Regurgitation, reflux oesophagitis, aspiration (pneumonia) |
| **Stomach**  | Delayed fundal relaxation, reflux, regurgitation, antral hypomotility,  
Poor antropylooduodenal coordination, increased pyloric activity | Vomiting, high gastric residues, gastroparesis |
| **Small intestine** | Delayed gastric emptying  
Increased retrograde activity  
Persistence of MMC phase-3 during enteral feeds | Delayed gastric emptying, paralytic ileus |
| **Colon**    | Reduced flushing of nutrient content, delayed defecation, MMC disorganization | Delayed defaecation, bacterial overgrowth, acute colonic pseudo-obstruction |

To treat excessive gastric residues, the first step would be to minimise the number of drugs which cause a decrease in gastrointestinal motility. There are several main groups of drugs, which include sedatives, muscle relaxants, high dose catecholamines, and opioids.

The incidence of gastrointestinal complications is higher in patients who receive sedatives and muscle relaxants as they reduce gastrointestinal motility. Clonidine affects gastric fundal contractility by acting on α-2 receptors on cholinergic nerves and decreases Ach release, relaxes the stomach, reduces gastric sensation without inhibiting accommodation or emptying. [132] Transpyloric feeding can be used in critically ill patients receiving sedatives and muscle relaxants though careful monitoring for constipation and abdominal distension is required in children receiving continuous infusions of muscle relaxants. [137]

Vasoactive drugs, in particular high dose catecholamines, reduce intestinal perfusion and tolerance to enteral feeds by decreased antral contractions and intestinal transit leading to a longer ICU length of stay. [136] Adrenaline reduces gastric emptying by a β-adrenergic effect. Dopamine reduces antral contractions and also increases phase 3 MMC and slows orocecal transit. [135]
In critically ill adults, sedation, the administration of catecholamines and the presence of gastric residues before the initiation of nutrition are related to a higher volume of gastric residues and intolerance to the nutrition. Opioids are known to play a major role in compromising gastrointestinal motility resulting in fundal relaxation, reduced antral contractions and increased MMC phase-3 frequency via stimulation of peripheral µ-receptors (See laxatives and anti-diarrhoeals).

Other drugs resulting in a delayed gastric emptying have been identified such as anticholinergics, calcium channel blockers, cimetidine and proton pump inhibitors. [134][135]

10.1.4 Pharmacological treatment

Pharmacological treatments should not be used routinely but for symptomatic use only. For adults, the recommendations are for early enteral nutrition, use of prokinetics (metoclopramide or erythromycin) for 3 days only and minimisation of the use of drugs, which affect motility. [134] There are no studies evaluating the efficacy of prokinetic agents in critically ill children.

10.1.4.1 Metoclopramide

Metoclopramide is a dopamine antagonist, has weak 5-HT3 receptor activities and acts as a 5-HT4 receptor agonist. It blocks inhibitory presynaptic D2 receptors of cholinergic motor neurons that innervate smooth muscle thereby increasing release of acetylcholine from nerve terminals. This leads to increased lower oesophageal sphincter tone, increases the force of gastric contractions, improves co-ordination of gastroduodenal contractions and enhances gastric emptying. Metoclopramide has also anti-emetic properties via central effects on dopamine receptors in the area postrema in the CNS. This central activity can cause extrapyramidal dystonic reactions.

10.1.4.2 Domperidone

Domperidone is a dopamine antagonist, which has anti-emetic and prokinetic properties. It interacts with D2 receptors to increase Ach release and improve gastric and small intestine smooth muscle motility. It does not easily pass the blood brain barrier so avoids the extrapyramidal side effects that can occur with metoclopramide. Domperidone is used in infants for gastro-oesophageal reflux but not routinely for dysmotility in critically ill children.

Both metoclopramide and domperidone are associated with QTc prolongation, life threatening ventricular tachycardias such as torsades de pointes and cardiac arrest. [132]

10.1.4.3 Erythromycin

Erythromycin is a motilin receptor agonist on enteric neurons and smooth muscle cells in the gastric antrum and proximal duodenum. It enhances gastrointestinal contractions and increases gastric emptying. Most paediatric studies have focused on the use of erythromycin as a prokinetic agent in premature or low birth-weight babies. These babies are at risk of morbidity and mortality due to gut immaturity, feeding intolerance and the need for prolonged
parenteral nutrition. Foetal gastric emptying matures with gestational age with dominant activity at 35 weeks. Motilin receptors are present but are only functional in the stomach at less than 32 weeks. The lack of migrating motor complex activity could be due to immaturity of either the hormonal system responsible for initiating the migrating motor complex or the receptor system or both. [138] Phase 3 of MMC increases with post natal age, and it is poorly formed in preterms. [132] Although there had been concerns about the development of antimicrobial resistance and torsades de pointes, there is no evidence that short-term administration results in the described adverse events in critical illness. [134][137] There is a lack of randomised placebo-controlled trials for erythromycin in paediatric patients and the existing studies use variable dosing.

10.1.5 Non pharmacological treatment

Transpyloric feeding is well tolerated in the critically ill child with few complications though in preterm neonates there is no evidence of any benefit [137](See enteral nutrition).

10.2 Diarrhoea

Diarrhoea is the passage of loose or watery stools, which may be accompanied with nausea, vomiting and cramps or bloating. In children, the definition of diarrhoea is more complicated as in small infants, they may normally pass up to one stool of semi-liquid consistency after each feed [139] so acute diarrhoea can be defined as the sudden onset of fluid content of the stool above normal. [140] In infants, stool loss may be 10mls/kg/day and for older children and adolescents up to 200g/day. For adults, there is a decrease in consistency and increase in frequency of bowel movements of more than 3 per day or more than 300g/day (soft stools) or 250mls. [141] Diarrhoea is an imbalance of intestinal handling of water and electrolytes. The small intestine absorbs large amounts of sodium, chloride and bicarbonate and secretes hydrogen ions and to a lesser extent bicarbonate and chloride. Water then passively follows net transport of solutes. [140] Absorption is by mature epithelial cells, which line the villi and secretion is predominantly by the crypt cells but absorption and secretion can occur in both. The absorptive capacity of the enterocytes far exceeds secretion leading to a net absorption of water and electrolytes. Sodium (Na+) absorption is driven by Na+ K+ ATPase, which maintains and generates a sodium electrochemical gradient between the gut lumen and the interior of the intestinal epithelial cell. Na+ absorption occurs via three pathways; Na+ coupled to nutrients such as amino acids or glucose, electrogenic amiloride sensitive Na+ absorption, or by neutral sodium chloride absorption. Chloride (Cl-) and bicarbonate (HCO3) are the main anions, which are actively secreted into the gut lumen. Anion secretion of Cl- or HCO3 leads to passive diffusion of a cation (usually Na+) and water into the lumen. [140] Diarrhoea is the change from net absorptive status to secretion. This may be due to osmotic forces drawing water into the gut (osmotic diarrhoea) or an active secretory state. If diarrhoea persists for more than a few hours then stores of potassium, magnesium and zinc can be significantly depleted and must be supplemented.
10.2.1 Osmotic Diarrhoea

For osmotic diarrhoea, the gut mucosa acts as a semi-permeable membrane with fluid entering the bowel if there is a large volume of hypertonic substances in the lumen such as non-absorbable sugars (lactulose, sorbitol), and magnesium salts e.g. magnesium sulphate or magnesium antacids. It may also occur due to malabsorption of carbohydrates or an absorptive defect such as glucose-galactose malabsorption or disaccharidase deficiency. The volume of diarrhoea produced is reduced by absorption of fluid by ileum and the colon. If the offending osmotic agent is stopped, then the diarrhoea will resolve.

10.2.2 Secretory diarrhoea

Secretory diarrhoea is the active intestinal secretion of fluid and electrolytes and decreased absorption. The causes of secretory diarrhoea include endotoxins (cholera toxin, _Clostridium perfringens_, _Staph aureus_, _E.coli_), vasoactive intestinal peptide secreting tumour, which is likely to require hormone therapy, hormones, bile salts and fatty acids malabsorption following ileal resection and drugs (antibiotics, stimulant laxatives). Stool volumes may be very high and fasting does not reduce output.

10.2.3 Inflammatory diarrhoea

Inflammatory diarrhoea involves damage to the intestinal mucosa where there is loss of fluid, blood and defective absorption of fluid and electrolytes. The causes of inflammatory diarrhoea include shigella and ulcerative colitis.

10.2.4 Diarrhoea in the critically ill patient

For critically ill patients, diarrhoea may occur due to the use of high osmolar enteral nutrition, presence of hypoalbuminaemia and sepsis, underlying disease state (shock is an important risk factor), infective causes or the drugs administered. [139][142] Diarrhoea impedes adequate nutritional intake and can lead to electrolyte disturbances.

In general, stool cultures should be taken in patients with bloody diarrhoea, severe symptoms or where there is no improvement within 48 hours. Rotavirus is common in children less than 5 years of age. [143]

The aim of treatment is to enhance the intestinal absorption of water by reducing the content of luminal electrolytes (by increasing active absorption of Na⁺ or decreasing secretion of anions) or by decreasing intestinal motility. Fluid and electrolytes need to be replaced to avoid dehydration.

10.2.5 Non-pharmacological treatment

Na⁺ coupled to glucose absorption is the basis for the treatment of diarrhoea by orally administered rehydration solutions. Rehydration sachets contain glucose, sodium and potassium. The glucose concentration of the solution should be between 80-120mmols/L to optimise sodium absorption in the small intestine. Glucose concentration in excess of 160mmols/L will cause an osmotic gradient resulting in increased fluid and electrolyte loss. Enteral feeds may be replaced with rehydration solution though in severe dehydration, intravenous fluids are required.
Critical illness disturbs the normal gut microflora and may alter the interaction between the gut mucosa. Prebiotics, probiotics and symbiotics (combination of pre and probiotics) have been used to modulate gut flora and prevent or treat diarrhoea in critically ill adult patients. They have to be shown to reduce the incidence and severity in some studies. [141] The use of probiotics is not without controversy as there are reports of bacteraemia secondary to probiotic therapy, which may preclude their use in intensive care. In paediatric patients, there is limited data for use in critical care though some evidence in the prevention of the development of necrotising enterocolitis in neonates. Probiotics have been shown to be safe in one small pilot study in enterally fed critically ill children [144], but in another randomised double blinded controlled trial, the probiotics did not reduce the incidence of nosocomial infection and the trial was concluded early due to safety concerns.[145] Therefore use of probiotics cannot be recommended at present.

10.2.6 Pharmacological treatment

The aim of anti-diarrhoeal treatment is to slow intestinal transit, reduce secretion and stimulate absorption. Anti-diarrhoeals provide symptomatic relief in mild to moderate forms of diarrhoea in adults but are not recommended for use in children.

10.2.6.1 Opioid Agonists

Opioid agonists act on the \( \mu \) receptors on myenteric neurones and cause hyperpolarisation by increasing their potassium conductance. This inhibits acetylcholine release from the myenteric plexus and reduces bowel motility. Activation of \( \mu \) receptors can lead to increased tone of the rectal sphincter, to disruption of normal peristaltic motion and reduced secretion. Activation of \( \delta \) receptors reduces secretory activity. Activation of both receptors may lead to enhanced sodium chloride and water absorption in the small intestine and colon. Opioid agonists for the treatment of diarrhoea include loperamide, diphenoxylate (piperidine opioids), and codeine. Diphenoxylate is a synthetic opioid available in combination with a sub-therapeutic dose of atropine. The anti-cholinergic actions of atropine may account for decreasing intestinal motility. Young children are particularly susceptible to diphenoxylate overdose where as few as 10 tablets can be fatal. [143]

Loperamide is also synthetic opioid agonists, which reduces propulsive peristalsis, increasing intestinal transit time, enhancing reabsorption of water and electrolytes, reducing gut secretions and increasing anal sphincter tone. Loperamide does not cross the blood brain barrier so it exerts local effects in the gut only. Loperamide is also used for reducing high stoma losses in patients with short bowel syndrome and a proximal stoma.

The constipating side effects of codeine may be used to treat diarrhoea though the majority of use of codeine is in short bowel syndrome in adults.

10.2.6.2 Colestyramine

Other agents for the treatment of diarrhoea include colestyramine. Colestyramine (ion exchange resin) binds excess water and bile salts. It may be used post ileal resection.
10.3 Constipation

10.3.1 Anatomy and physiology in children/adolescents

The lower intestinal tract consists of the small intestine (duodenum and jejunum), large intestine (colon), rectum and anus and is responsible for the absorption of nutrients, conservation of body water and electrolytes, drying of faeces and elimination. Undigested food is moved along the gastrointestinal tract by peristaltic waves, which move the faeces from the colon to the rectum and induce the urge to defaecate. The stool should be a firm consistency as most of the water will have been absorbed. There is a net uptake of fluid in the intestine in response to osmotic gradients involving the absorption and secretion of ions. This process is controlled by the autonomic nervous system.

The gastrointestinal tract does not have significant concentrating mechanisms for fluid so the osmolality of the fluid that crosses the upper jejunum is adjusted towards that of plasma. In adults, 9L of fluid enters the intestine per day, 22% of fluid is provided by the diet and 78% from secretions (saliva, gastric, pancreatic and biliary). 8L is absorbed by the small bowel which is approx 50% of its capacity. The jejunum absorbs 7L and the ileum 1-1.5L. 1L of fluid crosses the ileocecal valve into the colon where nearly all of the remainder is absorbed with only approximately 100mls passed in the stool. Any reduction in absorption by the small bowel adds to the burden of the colon, which can absorb 4-5L. In excess of this amount, it will increase the passage of fluid through the anal sphincter and cause diarrhoea. Excessive reabsorption of water will result in desiccated faeces and constipation whereas net secretion results in diarrhoea. [146]

Colonic absorption is secondary to active transport of sodium. The colon absorbs relatively few nutrients except short chain fatty acids (SCFA) by diffusion. The absorption of SCFA also increases the absorption of fluid and electrolytes. Dihydroxy bile acids and long chain FA decrease colonic absorption of fluids and electrolytes and may worsen diarrhoea.

10.3.2 Causes of constipation

Constipation is the symptom of an underlying disease, immobilisation, dehydration, a diet without adequate fibre or caused by the action of drugs [146][147][148]. (See Table 7.12) It is the infrequent and/or difficult passage of hard stool and is characterised by abdominal discomfort, distension and loss of appetite from infrequent defaecation. Passage of stool varies between individuals. Normal size, frequency and consistency of faecal output are difficult to quantify. Acute onset of constipation is likely to be organic obstruction. Chronic constipation indicates intrinsic colonic neuromuscular dysfunction. Motility is largely under cholinergic control (parasympathetic) with stimulation increasing motility while antagonists such as anti-cholinergics or drugs with anti-cholinergic side effects decrease motility and induce constipation (See motility agents).
Causes of constipation

<table>
<thead>
<tr>
<th>Causes of constipation</th>
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<tr>
<td>Inadequate dietary fibre &amp; fermentable carbohydrate</td>
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<tr>
<td>Immobility</td>
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<tr>
<td>Organic obstruction; Neoplasm, Crohn’s disease</td>
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<tr>
<td>Metabolic; Hypothyroidism, hypercalcaemia</td>
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<tr>
<td>Drug therapy; Opiates, anti-cholinergic, iron therapy</td>
</tr>
<tr>
<td>Extrinsic neurological disease</td>
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<tr>
<td>Chronic intrinsic neuromuscular disease of the colon; Hirschprung’s disease, chronic pseudo-obstruction</td>
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<tr>
<td>Functional constipation</td>
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Table 7.12 Causes of constipation [146][149]

There is no definition of constipation in the critically ill paediatric patient. In adults, it has been defined as the absence of the passage of stools for 3 days with an incidence of between 5-83%. For critically ill children, there are few studies and a reported incidence of between 33-50%. [147] Critically ill patients may be constipated because they are often immobile, are dehydrated, are unable to defaecate, suffer drug induced side effects and a diet with inadequate fibre. Causes of constipation in critically ill patients may differ considerably from those in non-critically ill patients, and the efficacy of the laxatives in critically ill patients may be uncertain. These patients will become at risk for pulmonary aspiration and intolerance to enteral feeding after a few days of no defaecation due to delayed gastric emptying and intestinal transit. Constipation may also allow overgrowth of bacteria in the digestive tract and increase the risk of nosocomial infection and sepsis, which prolong the intensive care length of stay and higher mortality. [148]. A recent trial found that defaecation within 6 days after ICU admission was associated with a shorter length of stay, whether or not laxatives were used. [150]

10.3.2.1 Drug induced constipation

Constipation can be a consequence of the pharmacological action of many drugs, including opioids. The reaction occurs at doses used for treatment and is often dose-related in that the higher the dose, the greater the constipating effect, or the sooner the reaction occurs after the administration of the drug. [151]

The administration of vasoactive drugs such as dopamine and noradrenaline along with severity of illness, are implicated in impaired motility of the colon. [150] Other drugs with constipating or reduced gastrointestinal motility effects include anti-convulsants e.g. thiopentone, sucralfate, proton pump inhibitors, cytotoxic drugs, ondansetron, H2 antagonists and calcium channel antagonists e.g.nifedipine. Calcium channel antagonists cause constipation by reducing intestinal (specifically colonic) motility, which in turn leads to increased colonic transfer time, resulting in increased fluid absorption due to longer mucosal contact time. Constipation resolves on cessation of the drug. Clonidine is a α2 receptor agonist and stimulates absorption and inhibits secretion of fluid and electrolytes. It increases intestinal transit time by
interaction with receptors on enteric neurons and enterocytes but is not used for this indication due to its anti-hypertensive activity. [151]

Patients in the paediatric intensive care unit (PICU) commonly require extended exposure to opioid analgesia and are at risk of opioid-induced constipation. Opioids act by several different mechanisms, mediated principally through either µ or δ-opioid receptors on enteric nerves, epithelial cells, and muscle. Activation of these opioid receptors reduces intestinal motility (via µ-receptors), by maintaining or increasing the tone of smooth muscle, suppresses forward peristalsis, delays transit through the small bowel (mainly the jejunum), raises sphincter tone at the ileo-caecal valve and anal sphincter, increases colonic transit time and reduces sensitivity to rectal distension.[151] Opioids reduce intestinal electrolyte and water secretion (via δ-receptors), which together with a slowing of intestinal transit will lead to enhanced dehydration of the stool and increases absorption of water (via µ and δ-receptors), all of which lead to constipation. The early use of laxatives is recommended to improve the intestinal fluid balance by promoting water secretion and preventing excessive water absorption.

10.3.3 Pharmacological treatment

The rationale for the use of laxatives for constipation is to increase the water content of the faeces and to encourage gastrointestinal motility. Laxatives generally work by enhancing retention of intraluminal fluid by hydrophilic and osmotic mechanisms, which lead to a decreasing net absorption of fluid by effects on fluid and electrolyte transport in the small and large bowel. They enhance fluid secretion and alter motility by either inhibiting non-propulsive contractions or stimulating propulsive contractions. [146]

The main agents that are used in intensive care are macrogols, lactulose and enemas (Refer to BNF-C for dosing and side effects).

10.3.3.1 Osmotic laxatives

‘Saline’ laxatives usually contain a cation (e.g. magnesium), an anion (e.g. sulphate or phosphate) or a non-absorbable sugar. Magnesium and sodium salts cause large amounts of water to be retained in the small & large bowel by osmotic pressure. For rectal administration, sodium citrate or phosphate salts are used with a rapid effect seen within 3 hours. Unabsorbable carbohydrates are resistant to digestion by the small intestine. Examples include sorbitol, lactulose, glycerin and mannitol. Lactulose is fermented by colonic bacteria to produce short-chain fatty acids and gases. The acids act as both osmotic and stimulant agents. The low faecal pH reduces absorption of ammonia and causes water to be drawn into the colon, increasing the volume of the stools, and resulting in propulsion of faeces. It takes approximately 2 days to start working and has a modest accumulation of fluid and passage of soft stools.

Glycerin administered rectally acts by its osmotic effect to soften and lubricate the passage of stools and may also stimulate rectal contraction. It promotes colonic evacuation within 30 minutes.

Macrogols e.g. polyethylene glycol (macrogol ‘3350’) are used for faecal impaction. Polyethylene glycol is a mixture of sodium chloride, sodium bicarbonate and potassium chloride in an isotonic solution. The large volume of non-absorbable fluid
results in copious watery diarrhoea and the efficient removal of solid wastes from the gastrointestinal tract.

There is only one study in critically ill adults that has compared the efficacy of lactulose and polyethylene glycol versus placebo to prevent constipation.[152] Lactulose and polyethylene glycol increased the number of defecations compared with placebo and shortened the time to first passage of stools. The trial found that both drugs promoted defaecation with lactulose significantly reducing the length of ICU stay. There was no significant difference in mortality between patients on laxatives compared to placebo. Polyethylene glycol was considered to be the preferred option for opioid induced constipation.

10.3.3.2 Stimulants

Stimulant laxatives promote accumulation of water and electrolytes in the colon and act directly on the neuromuscular apparatus of the colon to stimulate propulsion. Chloride channels open with decreased water & electrolyte reabsorption in the colon. Stimulants are available as both enemas and oral preparations. Enemas are useful for impacted faeces and for intractable long term cases. The therapeutic effect occurs within 6-8 hours post oral intake. The two main stimulant agents that are used are bisacodyl and senna. Bisacodyl acts more quickly when administered rectally.

10.3.3.3 Bulk forming agents

Bulk forming agents are used to establish normal bowel habit in patients with a diet deficient of fibre but are not used in the critically ill child suffering from drug induced constipation. They form non-absorbable hydrophilic masses when taken with water. This increases the volume of the intestinal contents, stimulating peristalsis via the stretch receptors in the mucosa. They take a few days to work. [149]

10.3.3.4 Surfactant laxatives

Anionic surfactants e.g.docusate, act by stool wetting and softening, alter intestinal permeability, increase net water and electrolyte secretions.

10.3.4 Other treatments

Specific therapies aimed at relieving opioid induced constipation such as naloxone are not well studied and remain unproven to date. Naloxone is a competitive antagonist with greater affinity for opioid receptors than analgesic. Oral treatment of opioid induced constipation with naloxone has been studied in critically ill children, but it led to withdrawal symptoms in some patients.[153] Further studies are required to determine if naloxone has a place in therapy.

10.4 Anti-emetics

10.4.1. Anatomy and physiology in children/adolescents

The process of vomiting is co-ordinated by vomiting centre (VC) in the medulla oblongata, which is in the brain stem. The vomiting centre is the final common pathway that mediates all vomiting. It does not directly respond to chemical stimuli.
The VC is activated by input from the chemoreceptor trigger zone (CTZ), the vestibular apparatus via the cerebellum, from higher brainstem and cortical structures and visceral afferents (See Figure 7.16). Stimuli from peripheral tissues (e.g. Stomach, small intestine, gallbladder, and heart), bypasses the CTZ and reaches the VC via the solitary tract nucleus to activate the vomiting centre via the afferent pathways of the vagus, phrenic and other nerves. Sight and emotion from the high centres (limbic cortex) also stimulates the VC. The vomiting centre has 5HT₃, muscarinic cholinergic and H₁ receptors, which provides the basis of directed drug therapy.

**Figure 7.16 Control of vomiting**

The chemoreceptor trigger zone (CTZ) is found in the area postrema in the 4th ventricle and is exposed to both blood and cerebrospinal fluid. It is an important source of stimulation of the vomiting centre. The blood brain barrier is poorly developed in the area postrema, which makes the CTZ readily accessible to emetic substances in the circulation. [154] Emetic inducing drugs stimulate the CTZ and include chemicals, toxins, peptides and neurotransmitters in the CSF and bloodstream. The CTZ possesses dopamine receptors, 5HT₃ and opiate receptors. [154]

There are 3 stages in the act of vomiting [154] (see Table 7.13):

1. **Nausea** is due to dysrhythmias of the gastric antrum and duodenum, which results in cessation of gastric emptying and bloating of the stomach. [155] Emesis is promoted by slow gastric emptying, which is characteristic of gastrointestinal dysfunction in critically ill patients. Nausea often associated with autonomic effects such as hypersalivation, pallor & sweating.
Nausea
Reduced motor activity of the stomach,
Increased activity in the duodenum & jejunum
Reflux of duodenal contents into the stomach

Retching
Contraction of chest muscles & diaphragm with abdominal muscle contraction
Gastric contents flow into lower oesophagus

Vomiting
Powerful, sustained contraction of the abdominal muscles with descent of diaphragm
Large rise in intra-abdominal pressure
Emesis

Table 7.12 Stages in vomiting

The clinical effects of protracted vomiting include hypokalaemia from reduced intake, loss from vomit and renal losses, dehydration, hypochloraemia, hyponatraemia and metabolic alkalosis. The renal loss is due to hyperaldosteronism secondary to electrolyte and water deficiency with contraction of plasma volume. Metabolic alkalosis occurs due to loss of H⁺ in vomit and there is a shift of H⁺ into cells in response to potassium depletion. [154][156]

10.4.2 Common diseases

10.4.2.1 Post-operative nausea and vomiting

The incidence of postoperative nausea and vomiting depends on many factors including the anaesthetic used, and the type and duration of surgery. The incidence of post operative nausea and vomiting (PONV) is higher in children compared to adults and the peak incidence is 34-50% and occurs in children of school age. [157]

There are few trials on the efficacy of drugs controlling established PONV. The majority of trials both in adults and children are based on prophylaxis of PONV. Therapeutic strategies of PONV involve targeting dopamine (D₂), histamine (H₁) and serotonin receptors (5HT₃). [154][156]

Drugs used include some phenothiazines (e.g. prochlorperazine), metoclopramide, 5HT₃ antagonists (e.g. ondansetron), antihistamines (such as cyclizine), and dexamethasone. Corticosteroids have been used for PONV though the mode of action is unknown. They are best used in combination with other anti-emetics. [157] A combination of two antiemetic drugs acting at different sites may be needed in resistant postoperative nausea and vomiting.

10.4.2.2 Opioid induced nausea and vomiting

Cyclizine, ondansetron, and prochlorperazine are used to relieve opioid-induced nausea and vomiting; ondansetron has the advantage of not producing sedation. They
interact with the opioid receptors in the CTZ. [158] Corticosteroids can also be quite beneficial for reducing opioid-induced nausea and vomiting, and in particular have been found to be effective in combination with metoclopramide and ondansetron.

10.4.2.3 Cytotoxic induced nausea and vomiting

Management of cytotoxic induced nausea and vomiting is based on the regime used. Many cytotoxics and radiation cause the release of serotonin from enterochromaffin cells in the gut and this activates 5HT₃ receptors on vagal nerves [159]. Vomiting is characteristic of cisplatin, carboplatin, cyclophosphamides and anthracyclines. Susceptibility to nausea and vomiting may increase with repeated exposure to the cytotoxic drug. Symptoms may be acute, delayed or anticipatory. Acute emesis occurs within 24 hours of treatment though often within 1-2 hours. It peaks within 4-6 hours. Delayed emesis occurs more than 24 hours after treatment. It peaks at 48-72 hours and then subsides over 2-3 days. Anticipatory vomiting is a conditioned response from the patient, who have had previous cytotoxic induced nausea and vomiting. Delayed and anticipatory symptoms are more difficult to control than acute symptoms and require different management. The main anti-emetics used for cytotoxic related nausea and vomiting are 5HT₃ antagonists, metoclopramide, prochlorperazine, domperidone, cyclizine and dexamethasone. [156]

For patients at low risk of emesis, pretreatment with metoclopramide (or less commonly domperidone) continued for up to 24 hours after chemotherapy, is often effective; a 5HT₃ antagonist may also be of benefit. For patients on chemotherapy with high risk emetogenic potential or when other treatment is inadequate, a 5HT₃ antagonist is often highly effective. The addition of dexamethasone and other anti-emetics may also be required. Dexamethasone, given by mouth, is the drug of choice for preventing delayed symptoms; it is used alone or with metoclopramide. The 5HT₃ antagonists may have a role in preventing uncontrolled symptoms.

10.4.3 Pharmacological treatment

Anti-emetics are treatments for symptoms but do not treat underlying causes of vomiting. Drug treatment is based on an understanding of the likely pathophysiology, the receptors involved, available routes of administration and the drug side effects. Treatments are tailored for distinct disease processes and specific data for vomiting in intensive care patients is lacking.

10.4.3.1 Prokinetics

Prokinetics act on the CTZ and increase gastric emptying rate and oesophageal tone. They include metoclopramide and domperidone. Both metoclopramide and domperidone block central dopamine receptors in the CTZ, where they exert an anti-nausea and anti-emetic effect.
10.4.3.1.1 Metoclopramide

Metoclopramide is a D₂ receptor antagonist and works centrally on D₂ receptors on the CTZ to provide effective anti-emesis. It also acts directly on the gastro-intestinal tract and it may be superior to the phenothiazines for emesis associated with gastroduodenal, hepatic, and biliary disease. It is useful to counteract opiate-induced vomiting. Metoclopramide can induce acute dystonic reactions such as facial and skeletal muscle spasms and oculogyric crises particularly in children less than 10kg. The dystonic effects usually occur shortly after starting treatment and subside within 24 hours of stopping it (See BNF-C for dosage and side effects).

10.4.3.1.2 Domperidone

Domperidone acts at the chemoreceptor trigger zone; it has the advantage over metoclopramide and the phenothiazines of being less likely to cause central effects such as sedation and dystonic reactions because it does not readily cross the blood-brain barrier. It is useful for gastrointestinal stasis, migraine and cytotoxic-induced vomiting. (See BNF-C for dosage.

10.4.3.2 5HT₃ receptor antagonists

Granisetron and ondansetron are specific 5HT₃ antagonists for use in children with chemotherapy or radiotherapy induced vomiting. They act on the vomiting centre and decrease sensitivity of the 5HT₃ receptor. It also antagonises the effects on 5HT₃ peripherally as well as in the CTZ. It has few side effects so is popular in oncology (see BNF-C for dosage and side effects). It is also an effective agent for post operative nausea and vomiting. [157]

10.4.3.3 Anti-histamines

Anti-histamines work on the vagal afferents, VC, and the CTZ. There is no evidence that any one antihistamine is superior to another but their duration of action and incidence of side effects are different due to differing potencies on the receptor. They may be considered for the prophylaxis and treatment of nausea and vomiting associated with cancer, radiation sickness, and the emesis caused by drugs such as opioids, general anaesthetics, and cytotoxics. Cyclizine is the anti-histamine used for post operative nausea and vomiting (see BNF-C for dosage and side effects).

10.4.3.4 Phenothiazines

Phenothiazines are dopamine antagonists and act centrally by blocking the chemoreceptor trigger zone. Prochlorperazine may be used for post operative nausea and vomiting and for cytotoxic induced nausea and vomiting. Severe dystonic reactions sometimes occur with phenothiazines (see BNF-C for dosage and side effects).
10.4.3.5 Other treatments

Intravenous dexamethasone may be used after abdominal and other types of surgery and for cytotoxic induced nausea and vomiting. The mechanism of action is unclear, but there may be steroid receptors in area postrema.

11. Role of the dietitian

A multi-disciplinary team approach to nutritional support has been shown to reduce costs and improve patient outcomes for all patients. [160][161] The dietitian is an integral part of this team and provides input into the route and timing of nutritional support, nutritional screening, assessment and calculation of the patients’ requirements, choice of specialised enteral feeds, anthropometric measurements and liaises between enteral and parenteral intakes. [162]

Nutritional screening for malnutrition is an important tool in the identification of the undernourished patient on admission and to identify those patients at risk of becoming malnourished. [163] Screening will also identify the obese patient, which is becoming more frequent on PICU.

Anthropometric measurements are a non-invasive method for evaluating short and long term nutritional status and examine the anatomical changes associated with a change in nutritional status. Body tissues that are catabolised during starvation or stress include muscle, fat and visceral protein stores.[164] The most common anthropometric measurements are body weight, height, triceps skinfold (mainly research) and mid-arm circumference.

Energy expenditure is particularly important to patients on ICU. There are risks associated with both under or over feeding patients. Predictive equations for calculating energy expenditure may be used by the dietitian to estimate the individual requirements as the ‘gold standard’ of measuring energy expenditure; indirect calorimetry, is not readily available. If predictive equations are used, the patient’s requirements need to be regularly monitored, reassessed and adjusted to ensure optimum nutrition without any potential metabolic complications. In practice, 70% of estimated average requirements (EAR) may be used to calculate requirements.

For patients on ICU, the dietitian can provide advice on the type of feed available according to the access chosen for the enteral nutrition (EN). This is based upon the duration of treatment, the risk of aspiration and the patients’ clinical status. The timing of initiation of EN and route of administration still remains controversial especially in adult units. The dietitian may assist in the decision making process of early versus late onset of feeds.

Monitoring of feed tolerance, growth and nutritional monitoring are undertaken by the dietitian as part of the nutritional care plan for each individual patient to maximise effectiveness and reduce the complications of artificial nutrition support. The dietitian provides expertise in optimising enteral nutrition for patients requiring specialised nutritional support as a member of the multidisciplinary intensive care team.
References


5. Guidelines for the use of parenteral and enteral nutrition in adults and paediatric patients. JPEN 2002; 26: 1-150.


European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). JPN 41 Suppl 2: S1-87.


PIC SIG NPPG 262 © NPPG October 2011


Guidelines for the use of parenteral and enteral nutrition in adults and paediatric patients. JPEN 2002; 26: 1-150.


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**Further reading**

**References**
Objectives

- To understand and apply methods of sedation management
- To understand the management of pain and sedation
- To understand and apply methods of neuromuscular blockade management
- To understand the implications of intracranial pressure and methods of drug management
- To understand and manage acute therapy of various forms of epilepsy
- To understand the management options for acute head injury and spinal injury
1. Introduction

Patients will be admitted to PICU with central nervous system (CNS) insults resulting from infection and trauma as well as with neurological diseases. In order to understand the assessment and treatment of these conditions it is important to be aware of the various monitoring techniques which are used. However it is not only in patients with an underlying neurological condition that long term damage can be sustained to the CNS. Presentations with conditions such as diabetic ketoacidosis (DKA), hypoxia and metabolic diseases can result in severe brain injury.

The patient group admitted to a paediatric intensive care unit is highly diverse in respect to:
- the development of the CNS at different ages,
- the underlying acute medical problem (incl. burns, head and brain injuries, infections),
- eventual long-term conditions, co-morbidities and disorders,
- procedures performed pre-admission (incl. drugs administered in theatres, in an acute emergency, chemotherapy, or transfers from other units),
- applied technology, such as ventilation, dialysis.

For these reasons pain management, sedation and neuromuscular blockade become particularly crucial in infants, children or adolescents and frequent assessment and monitoring of administered drug-regimes must be undertaken.

2. Sedation and analgesia

Although sedation and analgesia have different aims there are many aspects in common and some of the most commonly used drugs combine both properties, e.g. morphine is an analgesic drug with sedative properties.

2.1 Analgesia

Analgesia and analgesic techniques refer to pain relief and in intensive care it is important to identify the sources of pain and to match the treatment to the specific requirements of the patient.

Point pain is associated with procedures such as venous or arterial line placement, or insertion or removal of drains.

Postoperative pain may vary from minor pain, for example from a craniotomy, to major pain from a sternotomy, thoracotomy, or laparotomy. This pain is ongoing, intense and may continue for several days.

Discomfort may occur in children who are confined to bed and have invasive lines and an endo-tracheal tube in place even after the acute pain of surgery may have gone.

Chronic pain/hypersensitivity/tolerance may occur in children who have had previous long exposure to sedative and analgesic drugs. Children who have had previous admissions to intensive care, particularly as a neonate, are thought to have some changes in their sensitivity to discomfort and pain.
2.2 Sedation

Sedation and sedative techniques refer to lowering conscious levels or reducing responses to discomfort. It is important to be able to assess sedation in children and there are various scoring systems available, one of the most validated systems being the COMFORT score.[1] This scale, which was designed for intubated PICU patients, scores eight physiological and behavioural parameters from 1 to 5 for a scale range of 8-40. The parameters are alertness, respiratory response, blood pressure, muscle tone, calmness/agitation, physical movement, heart rate and facial tension. The optimal sedation range of 17-26 is based on a comparison of the COMFORT scale with standard clinical assessments of sedation by PICU medical staff. Its advantages for paediatric patients include its utility in all ages and levels of neurodevelopment as well as the absence of an arousal stimulus that repeatedly awakens the child to assess adequacy of sedation. The challenge of sedation is to avoid over-sedation which may lead to cardiovascular depression, withdrawal syndromes and prolonged duration of mechanical ventilation. Adequate sedation will facilitate mechanical ventilation, control agitation, induce amnesia and decrease cellular metabolism. Low doses of sedative drugs may be sufficient to ensure lack of recall and awareness and, if analgesia is sufficient, paralysing the patient for short periods may reduce the longer term effects of high dose sedative drugs. [2]

3. Analgesics and Sedative drugs

Analgesic and sedative drugs are often considered together as there is a cross-over in effect but it is important to ensure patients have adequate levels of analgesia and sedation by understanding the contribution individual drugs have to each aspect of their treatment. Table 1.6 compares the actions of many of the most commonly used drugs which will be discussed further in this section.

3.1 Opioids

The most commonly used opioids in PICU are morphine and fentanyl with some increasing use of remifentanil under certain circumstances. Opioid analgesics mimic endogenous opioid peptides by causing prolonged activation of opioid receptors, usually μ-receptors, and producing analgesia, respiratory depression, euphoria and sedation. Pain acts as an antagonist of respiratory depression so care must be taken if pain is removed by other techniques such as local anaesthesia. Opioids also act on the nerve plexuses in the gut causing constipation. Other side effects often seen with the use of opioids include miosis (pinpoint pupils), postural hypotension caused by depression of the vasomotor centre and nausea and vomiting.

3.1.1 Morphine

Morphine is used for dull visceral pain and also provides some sedation. It is metabolised in the liver by conjugation with glucuronic acid to form morphine-3-glucuronide which is inactive and morphine-6-glucuronide which is a more potent
analgesic than morphine itself. It is well absorbed orally but undergoes first pass metabolism so that its oral bioavailability is only about 30%.

Morphine is renally excreted with approximately 90% of a parenteral dose of morphine appearing in the urine within 24 hours, mainly as the product of glucuronide conjugation with only a small amount as the unchanged drug. 7-10% is excreted in the bile and eliminated in the faeces.

The half life (t½) of morphine varies throughout childhood. In pre-term babies the t½ is 6-12 hours and tissue accumulation can occur with multiple doses. Elimination increases in older babies and the half life in children aged 1 to 6 years is less (about 1 hour) than in adults (about 2 hours). Although babies do not clear the morphine as quickly they may need higher blood levels to achieve an adequate response, reflecting drug receptor differences and also low levels of morphine-6-glucuronide produced by the immature liver.

3.1.2 Fentanyl

Fentanyl is a synthetic, fat soluble opioid which is used for rapid short lived pain relief in surgery. It has few haemodynamic effects and so can be useful in cardiac surgery and intensive care. In infants fentanyl provides sedation and analgesia with haemodynamic stability and stress reduction but in older children it will not provide adequate sedation and other drugs will be required. Because fentanyl is fat soluble it is rapidly redistributed into fat and muscle depots in the body so that in a continuous infusion the drug will accumulate, resulting in prolonged sedation which may delay the patient’s progress in weaning ventilation. However fentanyl is useful in patients with impaired renal function as it is metabolised in the liver. The inactive metabolites of fentanyl are eliminated in the urine following N-dealkylation and hydroxylation. The half life in neonates is increased.

3.1.3 Remifentanil

Remifentanil has a rapid onset (approx 1 minute), a peak effect within 3-5 minutes and a short duration of action. It is inactivated by non-specific esterases. It is important to remember that the patient will require other analgesia in place before discontinuation of the remifentanil. In some pharmacokinetic studies in PIC, it has been shown that younger (smaller) children will require higher remifentanil infusion rates than adults and older (larger) children to achieve equivalent blood concentrations.[6]

3.1.4 Opioid antagonist

Naloxone is used for the reversal of opioid induced central and respiratory depression in non-ventilated patients. It is highly lipid soluble and is rapidly distributed around the body accounting for its short half life. Repeat doses may be required to maintain opioid reversal. It is not often used in intensive care as it is preferable to ensure that the opioids are eliminated completely with no risk of recurrence of the respiratory depression.
3.2 Clonidine

Clonidine is an alpha-2-agonist with some alpha-1-agonist activity and acts by reducing sympathetic outflow. It is used for both its analgesic and sedative actions and can be administered orally or as a continuous intravenous infusion. It is lipid soluble and well absorbed orally with virtually 100% bioavailability. It is metabolised in the liver to inactive metabolites and is excreted renally. Clonidine does not produce respiratory depression and can be used in conjunction with other sedatives and can also be used to prevent withdrawal symptoms when weaning opioids or benzodiazepines. Because clonidine has a relatively long half life (8-12 hours), there may be a requirement for supplemental sedation until adequate levels are achieved. Alternatively a loading dose may be given. Clonidine should be weaned slowly, depending on the length of course, in order to reduce the risk of rebound hypertension.

3.3 Benzodiazepines

Benzodiazepines act by potentiating the action of γ-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the central nervous system (CNS). They are sedative drugs and have amnesic properties by impairing the acquisition and encoding of new information but with little effect on the retention and retrieval of previously stored information. Benzodiazepines have no analgesic activity and so require concomitant administration of an analgesic, usually an opioid.

3.3.1. Midazolam

Midazolam is the most commonly used benzodiazepine on PICU, given by continuous infusion. It is supplied as a water soluble acid salt but at physiological pH midazolam becomes highly lipophilic and rapidly crosses the blood-brain barrier. Midazolam has a quick onset, within 1.5 to 5 minutes, a large volume of distribution, and a half life of 3-4.5 hours. Elimination is prolonged in neonates (3-12 hours) and in patients with liver disorders but is shorter in children aged 3 to 10 years (1-1.5 hours).

The metabolism of midazolam occurs in the liver to produce one active metabolite (1α-hydroxymidazolam) which is less active than midazolam and has a half life of approximately 1 hour. Metabolites are excreted in the urine mainly as glucuronide conjugates. Prolonged infusion can lead to accumulation of metabolite.

Midazolam can also be administered orally, buccally or intranasally. Buccal administration is particularly useful in the initial treatment of status epilepticus. See table 8.1 for details of pharmacokinetics of various routes.

Further discussion concerning the use of benzodiazepines in seizure control will be discussed in section 7.3.2

Midazolam can, in some patients, produce paradoxical reactions including agitation, hyperactivity, hostility, aggressiveness and excitement. It is associated with some of the worst withdrawal problems in PICU and their extent is related to the dose given. High doses should be avoided when used for sedation, preferably no more than 100 micrograms/kg/hour. Higher doses are used in the treatment of refractory status epilepticus.
3.3.2 Other benzodiazepines

Lorazepam and diazepam can also be used for their sedative actions. The longer acting diazepam can be used to reduce some of the withdrawal symptoms associated with midazolam. Lorazepam has an intermediate duration of action with no active metabolites and can be used for longer term maintenance of sedation. It has a slower onset of action than diazepam as lorazepam takes longer to re-distribute.

3.4 Ketamine

Ketamine is a phencyclidine derivative and an NMDA (N-methyl d aspartate) receptor antagonist which produces sedation, immobility, analgesia, and a strong dissociation from the surroundings. Ketamine causes the release of catecholamines and is good in bronchospasm and hypovolaemia as it causes bronchodilatation and hypertension. Ketamine can be given as an intravenous injection for short procedures or by continuous infusion for maintenance of sedation. Following an IV injection it has a fast onset of action of less than 1 minute and produces sedation for approximately 5 to 10 minutes, although analgesia can last for about 40 minutes and the amnesia for 1-2 hours. Awakening is characterised by disagreeable dreams and hallucinations which may last for days. Emergence hallucinations can be reduced by avoiding exposure to bright lights or loud noises and by the co-administration of benzodiazepines.

3.5 Propofol

Propofol is an intravenous anaesthetic which had been used for maintenance of sedation in critical care, because of its association with rapid recovery without a “hangover” effect, until it was shown to cause a rare and often lethal syndrome known as propofol infusion syndrome. This is thought to be due to the disruption of mitochondrial respiratory function and manifests itself as a metabolic acidosis and
cardiac failure. Following an unpublished study showing a higher mortality in a PICU population of children when compared to other standard sedation regimes the Committee of Safety of Medicines (CSM) advised that propofol should not be used for maintenance of sedation in PICU in children under 16 years.

3.6 Chloral hydrate/Triclofos

Chloral hydrate is used as an enteral sedative being available for rectal or oral administration. It is rapidly absorbed and starts to act within 15–60 minutes. It is broken down to trichlorethanol which has an elimination half life of about 8 hours. The duration of action is approximately 60-120 minutes but can last much longer particularly in neonates or in patients with hepatic or renal disease leading to drug accumulation with repeated administration.

3.7 Other drugs

In addition to drugs normally used for sedation and analgesia on PICU, there is still a place for oral drugs including paracetamol, non steroidal anti-inflammatory drugs (NSAIDS), and alimemazine. These drugs can be added in to the standard regimens in order to reduce the risk of withdrawal symptoms related to the use of high doses of opioids and benzodiazepines. The usual restrictions must be considered regarding renal and hepatic function in the use of these drugs.

4. Neuromuscular blocking drugs

Common indications for long-term administration of neuromuscular blocking agents (NMBAs) on PICU are to facilitate mechanical ventilation, decrease oxygen consumption, and ablate muscular activity in patients with elevated intracranial pressure (ICP). They have no analgesic or sedative action and it is important that they are not used without adequate pain relief and sedation. Once a patient has been paralysed the signs of consciousness are lost and so guidance on the level of comfort will be dependent on knowledge of drug doses and observation of cardiovascular responses. When possible, if paralyzing agents are required, intermittent doses or daily “drug holidays” should be used to allow assessment and adjustment of sedation regimens,

Muscle fibres differentiate into one of two main types,
- type-I with oxidative enzymes, corresponding to the slowly contracting muscles (slow-twitch),
- type-II with glycolytic enzymes, corresponding to rapidly contracting muscles

Type-I fibres are relatively resistant to fatigue, whereas type-II are susceptible. By 30 weeks of gestational age a equal number of fibres are present as in the adult, with the exception of the diaphragm which at full term contains only 25 per cent of type-I fibres, and the adult proportion of 50 per cent is not attained until of age 8 months. This lack in the infant diaphragm makes it susceptible to fatigue, and together with a reduced respiratory reserve and an increased oxygen requirement makes it necessary to ensure that the effect of neuromuscular blockers are fully reversed before the end of anaesthesia.
The relaxants are classified into two types based on their mechanism of action, as depolarizing and non-depolarizing agent. The first mimics the action of acetylcholine, whereas the second competitively blocks the action of acetylcholine. The last agents are further classified into the aminosteroid-group comprising pancuronium bromide, rocuronium bromide, and vecuronium bromide, and the benzylisoquinolinium group which includes atracurium besylate, cisatracurium besylate, and mivacurium chloride.

Non-depolarising neuroblockage drugs can also be classified by their duration of action as short acting (15-30 minutes), intermediate-acting (30-40 minutes) and long-acting (60-120 minutes), although the duration of action is dose dependent. The choice of agent depends on the duration of action, method of excretion, side effect profile and speed of onset. The infant’s and child’s response to the agent differs from that of adults because of developmental changes in neuromuscular transmission and body composition. Further details of individual drugs are available in Section 1.

The paralysis sequence is generally as follows: the small rapidly moving muscles such as eyes, then limbs, neck, trunk and upper airway, then intercostals muscles, larynx and face, and the diaphragm. The agents also relax the vocal cords allowing the passage of a tracheal tube.

Regular assessment of the respiratory rate is required to ensure the paralysis has worn off. Monitors of neuromuscular block test neuromuscular transmission via train-of-four, double burst, tetanic and post-tetanic stimulation. Train-of-four stimulation at 2 Hz for 2 seconds repeated every 20 seconds is the preferred method but it is influenced by factors other than relaxant drug concentration. The fourth twitch is usually lower in amplitude than the first in neonates, and hypothermia reduces the height of all twitches but not the ratio.

Neuromuscular blockade may be affected by the clinical condition of the patient and many of these may be common in critical care (Table 8.2).

<table>
<thead>
<tr>
<th>Potentiation</th>
<th>Antagonism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atracurium</td>
<td>Electrolyte abnormalities</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>Severe hyponatraemia</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>Severe hypocalcaemia</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>Severe hypokalaemia</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>Hypermagnesaemia</td>
</tr>
<tr>
<td></td>
<td>Neuromuscular diseases</td>
</tr>
<tr>
<td></td>
<td>Acidosis</td>
</tr>
<tr>
<td></td>
<td>Acute intermittent porphyria</td>
</tr>
<tr>
<td></td>
<td>Renal failure</td>
</tr>
<tr>
<td></td>
<td>Hepatic failure</td>
</tr>
<tr>
<td></td>
<td>Akalosis</td>
</tr>
<tr>
<td></td>
<td>Hypercalcaemia</td>
</tr>
<tr>
<td></td>
<td>Demyelinating lesions</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathies</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
</tr>
</tbody>
</table>

Table 8.2 Clinical conditions affecting neuromuscular blockade

There are some drug interactions which may be important in patients on PICU. Aminoglycosides may cause the block to be deeper and recovery prolonged. This may be a problem if the antibiotic is given at end of surgery as patient is recovering from block, potentially causing apnoea and respiratory depression. The risk is higher in patients with renal disease and hypocalcaemia.
The effects of NMBAs may be reduced and shortened if some anticonvulsants, particularly phenytoin and carbamazepine are given chronically but may be increased if anticonvulsants are given acutely.

5. Central Nervous System Monitoring

Monitoring of the functioning of the brain and CNS is very important for all critically ill patients but unfortunately there is no simple non-invasive system that will give the required information, particularly in patients who have been paralysed and sedated. Some techniques require constant evaluation of the clinical condition of the patient whereas some will only be available occasionally and may have some potential morbidity which requires careful evaluation.

5.1 Physical examination

The Glasgow Coma Scale (GCS) is a scoring system for evaluation of the neurological function of a critically ill child. It is a standardised tool which can provide a objective assessment of the level of consciousness, measured as motor responses, eye opening and verbal response. Table 8.3

<table>
<thead>
<tr>
<th>Response</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Motor Response</strong></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>Extensor response to pain</td>
<td>2</td>
</tr>
<tr>
<td>Abnormal flexion to pain</td>
<td>3</td>
</tr>
<tr>
<td>Withdraws from pain</td>
<td>4</td>
</tr>
<tr>
<td>Localises pain</td>
<td>5</td>
</tr>
<tr>
<td>Responds to commands</td>
<td>6</td>
</tr>
<tr>
<td><strong>Eye Opening</strong></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>Opens to pain</td>
<td>2</td>
</tr>
<tr>
<td>Opens to speech</td>
<td>3</td>
</tr>
<tr>
<td>Spontaneous opening</td>
<td>4</td>
</tr>
<tr>
<td><strong>Best Verbal Response</strong></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>Incomprehensible sounds</td>
<td>2</td>
</tr>
<tr>
<td>Inappropriate words</td>
<td>3</td>
</tr>
<tr>
<td>Appropriate words but confused</td>
<td>4</td>
</tr>
<tr>
<td>Fully orientated</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 8.3 Glasgow Coma Score

The GCS assessment will provide a score with a maximum of 15 and a minimum of 3. The verbal response score has been modified for younger children to provide appropriate age-related assessment.

The GCS has been shown in adults to be predictive of outcome in traumatic brain injury and by tracking changes in the GCS neurological deterioration can be assessed.
5.2 Intracranial pressure monitoring

Intracranial pressure (ICP) management is an important aspect of the treatment of neurological insults and will be discussed further in this section. Monitoring of ICP can be undertaken by monitors in the brain parenchyma or in the ventricular space. Monitors in the intraventricular space allow the drainage of cerebrospinal fluid (CSF) as a therapy for raised ICP. There are potential infection risks with these and some centres have protocols for the administration of intraventricular antibiotics before removal of the monitor and drain.

5.3 Electrophysiology

There are several methods of monitoring brain activity by means of electrophysiological parameters.

5.3.1 Bispectral index monitoring (BIS)

The bispectral index is derived from electrodes placed over the frontal cortex which generate numerical values which correlate with levels of sedation. This has not been standardised for use in children but could potentially be used to maintain adequate levels of sedation without the overdosing which may lead to increased risk of withdrawal.

5.3.2 Electroencephalogram (EEG)

EEGs are surface tracings of the brain’s electrical activity. Rhythm, amplitude and location of waveforms are determined and can be indicative of normal or abnormal function of different brain regions. Monitoring can be as a single EEG or as a continuous recording. Continuous recording can be useful in treatment of status epilepticus when a drug-induced coma can be monitored by the duration of burst suppression that is seen in the EEG.

5.3.3 Evoked potentials

Somatosensory evoked potentials (SSEP), brain stem evoked potentials (BAEP) and visual evoked potentials (VEP) can be used as prognosticators of outcome in coma, spinal cord and brain stem injury patients. Stimuli are applied to the relevant nerves and conduction of the impulses to the cortex is measured. Characteristic waves can be indicative of damage to nerves and pathways. Absence of SSEPs in patients with traumatic brain injury has been associated with poor outcome.

5.4 Lumbar puncture

Obtaining CSF for culture via a lumbar puncture (LP) is the gold standard for diagnosis of meningitis. It is important that the clinical picture is taken into account before undertaking a lumbar puncture as performing one in the presence of raised ICP may cause cerebral herniation. Raised ICP cannot be excluded by normal brain imaging and therefore any respiratory or haemodynamic compromise or focal neurological signs and a fluctuating or reduced GCS (≤ 13) are contra-indications for
an LP. A late LP can give information on causative organisms by polymerase chain reaction (PCR) as this is not affected by antibiotic treatment.

6. Cerebral oedema

The brain is susceptible to damage because it is enclosed in a non-expandable box and assessment of the intracranial pressures is important to protect the brain when there has been an insult, such as infection or trauma, to avoid further damage.

6.1 Cerebrospinal fluid (CSF)

Cerebrospinal fluid production and subsequent absorption is dynamic. The average volume of CSF in children 4-13 years of age is 90 mls and the rate of formation is about 500 mls per day, resulting in a 14% turnover of total volume per hour. The rate of production remains fairly constant and only declines slightly with raised ICP but the rate of absorption increases linearly as pressure increases. As the ICP increases the damage is related to the effects on cerebral blood flow, which is difficult to measure. Cerebral perfusion pressure (CPP) can be used as a surrogate measurement. The CPP is calculated by subtracting the ICP from the mean arterial pressure (MAP). In brain injury, the autoregulation which maintains constant cerebral blood flow within the normal brain is disrupted and ischaemia may occur if the CPP falls. If the intracranial pressures exceed the ability of the brain to compensate, herniation may occur in which the brain is displaced resulting in coma, pupil constriction then dilatation and death (“coning”).

6.2 Pathophysiology of intracranial hypertension

Cerebral oedema can occur because of changes in the capillary permeability and disruption of the blood brain barrier (BBB) following injury. Interstitial damage can occur due to blockage of the drainage of CSF or by increased production.

Cell damage and raised intracranial pressure can be seen in a range of conditions including:

- Metabolic disease including
  - Hepatic encephalopathy
  - Diabetic ketoacidosis
  - Hyperammonaemia
- Hypoxic ischaemic brain injury resulting from
  - Near drowning
  - Seizures
  - Cardiac arrest
- Infection
  - Bacterial, viral and fungal meningitis
  - Abscess
- Neoplastic disease
- Trauma
6.3 Assessment of ICP

The method of imaging the brain will vary, depending on the cause of the ICP, and may include computerised tomography (CT) or magnetic resonance imaging (MRI). Clinical assessment with an awake patient using the Glasgow coma score should be used when ever this is possible.

6.4 Non-pharmacological treatment of raised ICP

The aim of treatment is to avoid damage caused by decreased blood flow. In order to do this it is important to avoid hyperthermia, hypoxia, hypotension, and hypercarbia. Extra-ventricular drains (EVD) can be used to drain CSF for reduction in total intracranial contents and therefore reduction of ICP. Simple manoeuvres should be followed such as elevating the head of the bed to 30° and ensuring that the head is kept in the midline to avoid jugular venous outflow obstruction.

6.5 Pharmacological treatment of raised ICP

Sedation and neuromuscular blockade has been used to reduce cerebral metabolism. Mannitol can be given as an osmotic diuretic which is thought to act by affecting the blood viscosity as well as by promoting the movement of extravascular fluids into the capillaries. Hypertonic saline (3%) also acts to lower ICP and improve cardiac output and increase the mean arterial pressure. Plasma sodium levels should be maintained at the high end of the normal range (145-150 mmol/L). Seizure prophylaxis, usually with phenytoin, should be considered, particularly if the patient has been paralysed.

7. Status epilepticus (SE)  (See Case study – Neurology -Status epilepticus)

Status epilepticus is a condition characterised by frequent and prolonged epileptic seizures which can be either a generalized seizure lasting at least 30 minutes or successive convulsions that occur so frequently that the patient does not recover consciousness between them.

7.1 Pathophysiology

Status epilepticus has two distinct phases with specific neurophysiological changes. Within the first 30 minutes the increased metabolic requirements of abnormally discharging neurons are adequately met. There is an increase in cerebral blood flow and in autonomic activity, resulting in tachycardia, hypertension and an increase in blood glucose levels. After about 30 minutes of seizure activity, the compensatory mechanisms that have maintained adequate cerebral perfusion begin to fail, resulting in a rise in intracranial pressure, systemic hypotension, hypoglycaemia and a rise in systemic and intracranial lactate levels. The aim of treatment of SE is to terminate the seizures before the brain is damaged when the cerebral oxygen requirements exceed supply.
There are many reasons for a patient presenting with status epilepticus including:

- Pre-existing epilepsy
- Tumour
- Trauma
- Infection – febrile fit or CNS infection
- Congenital- pyridoxine dependent, metabolic disease
- Asphyxia- accidental and non-accidental
- Metabolic disease

Among children with epilepsy the incidence of SE may approach 8%, and in 50-86% of such children it will be seen on first presentation. Two metabolic disorders which may present with SE are important to diagnose early as they are treatable with good prognosis.

**Pyridoxine dependent epilepsy** can present in the neonatal period but it usually presents with seizures when the child is a few months old. Treatment with pyridoxine controls the seizures. All children under the age of 18 months with intractable seizures should have a trial of pyridoxine.

**Biotinidase deficiency** is one of the biochemical defects in biotin responsive multiple decarboxylase deficiency. Children develop seizures, ataxia, skin rash and alopecia but may present with seizures alone.

Status epilepticus associated with fever in a neurologically normal child between the age of 6 months and 5 years is considered to have a good prognosis with a low incidence of new neurological deficit or cognitive impairment. The risk of subsequent epilepsy in patients with febrile SE is about 21% - much higher than the population risk of 0.5-1%

The prognosis for a patient with non-febrile SE is primarily dependent on the aetiology which in turn is dependent on the age of the child.

### 7.2 Emergency treatment

The aim of treatment is to achieve seizure control and have some lasting anticonvulsant activity while maintenance therapy is established. Because of the importance of achieving control of the seizures quickly there is an algorithm so that treatment will be consistent (See Table 8.4). The initial treatment should follow the normal resuscitation sequence of checking airway, breathing and circulation. Blood glucose should also be monitored. Appendix C of NICE clinical guideline 20 includes the treatment of SE in adults and children.[4]

Once benzodiazepines have been administered the patient must be monitored as respiratory depression can occur. This may be a particular problem if the patient has been given doses of rectal diazepam or buccal midazolam before reaching the A&E department. If seizures continue after the second dose phenytoin should be given, unless the patient is routinely taking it, but, because of phenytoin cardiotoxicity when given as fast bolus, the infusion must be given over 20 minutes to avoid hypotension and arrhythmias. Blood pressure and ECG should be monitored. In order to help continuing treatment, phenytoin levels should be taken 2 hours after the completion of the loading dose to ensure therapeutic levels achieved.
Table 8.4 Treatment guideline for acute tonic-clonic convulsion [4]
7.3 Refractory status epilepticus

If the seizures continue 20 minutes after the phenytoin dose the patient should be admitted to PICU where treatment can be continued. There are several options for continuing treatment. The patient can be put into an induced coma with a thiopentone infusion or by using high dose intravenous benzodiazepines such as clonazepam or midazolam.

NICE guidance in adults recommends general anaesthesia with propofol, midazolam or thiopentone should be continued for 12-24 hours after the last clinical or electrographic seizure and then the dose should be tapered. The guidance in children only includes thiopentone for induction of anaesthesia although many units prefer the use of benzodiazepines because of the poor side effect profile of thiopentone.

7.3.1 Thiopentone

Thiopentone is lipid soluble and rapidly penetrates the CNS and then redistributes into fat stores. The duration of action after IV bolus is 5-30 minutes and it is metabolised by the liver. It is metabolised mainly to inactive metabolites but a small amount is converted to pentobarbital. Because of the lipid solubility repeated or continuous administration can lead to accumulation in fatty tissue leading to prolonged anaesthesia and respiratory and cardiovascular depression.

In neonates liver elimination is slower, about twice that in adults and accumulation is inevitable if infused for more than a few hours.

Thiopentone is used to induce a coma and produces a characteristic EEG showing “burst suppression”. Burst suppression can be recognised by a periodic pattern of low amplitude and a relatively shorter pattern of higher amplitude complexes.

Thiopentone can also be used in the treatment of neurological insults including head injury, stroke and hepatic encephalopathy as it reduces the metabolic demands of cerebral tissue. The major problem with administration of thiopentone over several days is that there is an association with an impaired immune response and associated chest infections in ventilated patients.

7.3.2 Benzodiazepines

Clonazepam or midazolam can be used as intravenous infusions to try to control refractory seizures. If high doses are required the patient will need to intubated and ventilated. Protocols have been recommended for the use of high dose midazolam in which the doses used are considerably higher than those used for maintenance of sedation. It has been suggested that, following a starting dose of 2 microgram/kg/min or 120 micrograms/kg/hr, there should be a clinical assessment of the patient every 5 minutes and, if seizures persist, a further bolus and an increased of rate of infusion should be given. Following repeated assessments the doses may be increased to a maximum of 24 microgram/kg/min (1440 microgram/kg/hr). Once the patient has been shown to be free of clinical and EEG seizures the infusions are continued to maintain this for 12-24 hours before weaning the midazolam. [5]

Hypotension is the main adverse event associated with the administration of intravenous benzodiazepines.
8. Traumatic brain injury (TBI)

Head injury is most common in young children (< 1 year old) and in adolescents over 15 years. Many injuries in young children occur during falls or are the result of non-accidental injury (NAI). Most head injuries occur because of trauma resulting in skull fractures or intracranial haemorrhages. Contact forces occur when the head is struck or strikes an object and cause scalp lacerations, epidural haematomas and brain surface contusions. Forces which are produced by deceleration of the head cause concussion, subdural haematomas, deeper subcortical or brain stem haemorrhages and diffuse axonal injuries. The injury will depend on the velocity and degree of deceleration.

Patients who have been involved in any trauma resulting in head injury must be carefully assessed for spinal cord damage. Damage to the cord may not be seen on radiological imaging and protective measures must be undertaken until a full clinical assessment can be made when the patient is awake.

8.1 Definitions

**Closed head injury** - caused by a direct or indirect force to the head but the skull remains intact.

**Open head injury** – direct injury to the head with penetration of the skull.

**Diffuse axonal injury** – diffuse cellular injury to the brain occurs from rapid rotational movement. This is often seen in car accidents and in shaking injuries. The axons which compose the white matter of the brain are torn or damaged by the shearing forces.

**Contusion** – bleeding into the tissue.

**Penetrating trauma** – caused by an object entering the brain. There is direct injury by impact and skull fragments pushed in to the brain.

**Secondary injury** – swelling, inflammation and raised intracranial pressure.

8.2 Treatment

Even if no seizures have been witnessed, antiepileptic therapy, usually phenytoin, is recommended in serious head injuries for at least the first seven days. Monitoring of ICP and treatment of raised intracranial pressure should be instituted. Patients with subdural haematomas greater than 5mm should be treated with surgical evacuation to prevent cerebral oedema and a mass effect and shift which can lead to herniation and death.

Patients who are assessed as requiring emergency intracranial surgery should be transferred to the appropriate unit as quickly as possible. Some injuries can cause a trauma victim to decompensate extremely rapidly and therefore the lag time between injury and treatment should ideally be kept to a bare minimum. This time has become known as the “Golden Hour” because it is thought that the potential for recovery is reduced if the time to treatment is extended beyond this.
If the spinal cord has been involved there is some evidence in adults that treatment with methylprednisolone may improve the eventual level of function but there are no trials in children.

**Further reading**

- The central nervous system in pediatric critical illness and injury. Wheeler et al. Springer 2009
- Early Management of children with a head injury, SIGN May 2009

**References**


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   2.2 The adrenal glands
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      4.4.1 Urea cycle defects

Website
References
Objectives
- To understand the effects of blood glucose management in non-diabetic patients and the effects of other drugs on blood glucose control
- To understand the acute treatment of the diabetic patient, including diabetic keto-acidosis, hyper- and hypo-glycaemia
- To understand the effects of different steroids and be able to describe their use and side effects
- To be able to describe the tetracosactide (Synacthen) test and the use of steroids in sepsis
- To understand the mechanisms of water homeostasis and be able to recognise syndrome of inappropriate anti-diuretic hormone (SIADH) and diabetes insipidus in critical care
- To understand the changes in thyroid hormone levels in severe critical illness
- To understand the mechanisms of inborn errors of metabolism and the emergency treatment of hyperammonaemia
1. Introduction

The endocrine system maintains the physiologic functions of numerous other organ systems. Specific endocrine diseases, in particular disorders of energy production and utilisation, fluid and electrolyte balance, and circulatory function, may result in critical illness. Furthermore, critical illness itself can result in specific endocrine diseases. 

Endocrine and metabolic disorders present a complex dilemma, the signs and symptoms are often non-specific making diagnosis difficult but any delay may have adverse consequences. Prompt interpretation of laboratory data is essential to facilitate treatment as quickly as possible.

2. The endocrine system in children and adolescents[1,2]

The endocrine system is a network of glands that typically secrete sequential hormones into the bloodstream until a final hormone reaches its target receptor to exert a physiological effect. It is controlled by feedback cycles which usually have a negative effect, that is, further hormone release is decreased when circulating hormone levels rise. The primary functions of endocrine hormones include regulation of growth and sexual maturation; energy production and utilisation by cells including glucose homeostasis, fluid and electrolyte balance; and a balance of cardiovascular function. The specific functions of the main endocrine glands are described below.

2.1 The Pituitary Gland

The pituitary gland is located at the base of the hypothalamus. The hypothalamus controls the secretion of ‘releasing’ hormones which target the anterior pituitary. In response to these specific hormones are then released from the anterior pituitary (See Table 9.1).

<table>
<thead>
<tr>
<th>Hypothalamic ‘releasing’ Hormones</th>
<th>Effect on Anterior Pituitary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyrotropin-releasing hormone(TRH)</td>
<td>Release of thyroid-stimulating hormone (TSH)</td>
</tr>
<tr>
<td>Gonadotropin-releasing hormone (GnRH)</td>
<td>Release of follicle-stimulating hormone (FSH) and luteinising hormone (LH)</td>
</tr>
<tr>
<td>Growth hormone-releasing hormone (GHRH)</td>
<td>Release of growth hormone (GH)</td>
</tr>
<tr>
<td>Corticotropin-releasing hormone (CRH)</td>
<td>Release of Corticotrophin (ACTH)</td>
</tr>
<tr>
<td>Prolactin-releasing hormone PRH</td>
<td>Release of prolactin</td>
</tr>
<tr>
<td>Somatostatin / growth hormone-inhibiting hormone (GHIH)</td>
<td>Inhibit release of GH and TSH</td>
</tr>
<tr>
<td>Prolactin inhibiting hormone (PIH)</td>
<td>Inhibit release of prolactin and TSH</td>
</tr>
</tbody>
</table>

Table 9.1 Hypothalamic and Pituitary hormones
The hypothalamus also releases antidiuretic hormone (ADH/vasopressin) and oxytocin which are stored and released by the posterior pituitary.

2.2 The Adrenal Glands

The adrenal glands consist of an inner medulla and an outer cortex. The adrenal medulla is related to the sympathetic nervous system and secretes adrenaline and noradrenaline in response to stress. These catecholamines maintain mean arterial blood pressure through their effects on adrenergic receptors by increasing vascular tone, heart rate and myocardial contractility. The adrenal cortex develops throughout infancy and childhood to the adult gland. Initially, the inner foetal zone of the adrenal cortex degenerates during the first two weeks of life until completely absent by the third month of life.[3] The adrenal cortex secretes 3 types of steroid hormones; sex steroids, glucocorticoids and mineralcorticoids, the latter two hormones being the most important in paediatric critical care.

ACTH, released from the anterior pituitary, triggers the secretion of the glucocorticoid hormone, cortisol, in response to stress. Cortisol levels are controlled via a negative feedback mechanism whereby raised plasma cortisol levels then inhibit the secretion of ACTH and CRH. Cortisol also influences the production of catecholamines by the adrenal medulla and increases the sensitivity and number of adrenergic receptors.

Aldosterone is a mineralcorticoid secreted by the adrenal cortex in response to low mean arterial blood pressure and in response to increased serum potassium and decreased serum sodium levels. ACTH also plays a minor role in aldosterone release. Cortisol and aldosterone diffuse into the cells to bind to and activate glucocorticoid receptors producing characteristic actions of these hormones. Aldosterone stimulates sodium and water retention and potassium secretion and cortisol stimulates gluconeogenesis, inhibits glucose uptake in muscle and adipose tissue, and increases protein catabolism. It has anti-inflammatory and immunosuppressive actions in addition to a significant mineralcorticoid effect.

2.3 The Thyroid Gland

TRH release from the hypothalamus triggers TSH from the anterior pituitary and results in thyroxine release from the thyroid gland. Levels of thyroxine (T4) and its active metabolite triiodothyronine (T3) are controlled by a negative feedback system which stimulates TRH release when T3 and T4 levels fall. The thyroid hormones regulate carbohydrate, lipid and protein metabolism and play a crucial role in normal growth and development during childhood and adolescence. Thyroid hormones are especially crucial to the nervous system during the first 6 years of life and deficiency can adversely affect cognitive development. Levels of TSH surge after birth accompanied by a marked increase in T3 and T4 but decline to normal adult levels within a week. Calcitonin which regulates calcium metabolism is also produced in the thyroid.
2.4 The Pancreas

The pancreas regulates glucose homeostasis by the secretion of the hormones insulin and glucagon:

High plasma glucose levels trigger the release of insulin from the β-cells of the islets of langerhans in the pancreas. Insulin lowers plasma glucose levels by enhancing glucose and amino acid uptake, increasing protein synthesis, increasing glycogen synthesis, and increasing adipose tissue.

Low plasma glucose levels stimulate the release of glucagon. Glucagon promotes the breakdown of glycogen stores (glycogenolysis) and increases the production of new glucose molecules from amino acids and fatty acids (gluconeogenesis).


Metabolic pathways are the vast chain of chemical reactions that occur in the body to maintain cell energy balance. Metabolic processes are usually classified as catabolic or anabolic. Catabolism is the process of energy production (adenosine triphosphate (ATP) production) by breaking down large molecules into smaller ones and anabolism is the production of new cell components by the synthesis of large molecules from smaller ones.

The number of metabolic pathways in the body is extensive. A summary of some of the most important metabolic pathways are listed below:

- **Glycolysis** - glucose oxidation in order to produce pyruvic acid and small amounts of ATP.
- **Citric acid cycle (Kreb’s cycle)** - pyruvic acid is used to produce acetyl-Coenzyme A which is oxidised to obtain ATP and valuable intermediates.
- **Oxidative phosphorylation** - disposal of the electrons released by glycolysis and citric acid cycle storing much of the energy released in this process as ATP.
- **Fatty acid oxidation** - fatty acids breakdown into acetyl-Coenzyme A, to be used by the Kreb's cycle.
- **Gluconeogenesis** - glucose synthesis from smaller precursors.
- **Urea Cycle** - detoxifies ammonia by converting it to urea, which is excreted in the urine.

Metabolic pathways interact in a complex way in order to allow an adequate regulation. This interaction includes the enzymatic control of each pathway.

4. Pathology of common endocrine or metabolic disorders.

The signs and symptoms of an endocrine or metabolic disorder are varied and often non-specific. Common symptoms often include an altered level of consciousness and other signs of central nervous system (CNS) defects with a history of poor feeding, weight loss, vomiting, and lethargy. Diagnosis usually depends on the results of laboratory samples which should ideally be obtained before treatment is begun. Due to the non specific symptoms of these disorders, diagnosis is often complicated by samples being taken after treatment (e.g. fluid therapy, electrolytes) has been given. [5]
4.1 Disorders of fluid and sodium balance

4.1.1 Syndrome of inappropriate anti-diuretic hormone secretion (SIADH)[1, 6-9]
The syndrome of inappropriate anti-diuretic hormone secretion results from excess vasopressin (ADH) release from the hypothalamus. Patients are usually hypervolaemic from the subsequent increase in water reabsorption by the kidneys (although in some cases patients can be normovolaemic). This produces symptoms such as weight gain, hypertension, reflex bradycardia, low urine output (< 0.5 ml/kg/hour) and an altered mental status. Neurological complications ranging from drowsiness to seizures and coma may develop particularly in patients with severe acute hyponatraemia; whereas in chronic hyponatraemia, central demyelinating lesions characterised by paraparesis, seizures and coma are more commonly seen. Laboratory results show hyponatraemia (serum sodium < 130 mmol/L), a high urinary sodium, a low serum osmolarity (< 280 mosm/L) and a high urine osmolarity (> 100 mOsm/L). (see Table 9.2) Hyponatraemia is due to the dilutional effect of excess body water.

The causes of SIADH are widespread. SIADH may result from CNS injury or infection, posterior pituitary disease or injury, mid brain hypoplasia, spinal cord injury or surgery, liver disease, or respiratory disease. Drug therapy may also be responsible, for example, chemotherapy, tricyclic antidepressants and carbamazepine have been associated with SIADH.

Non-pharmacological treatment

Fluid restriction should be the initial and main treatment for SIADH. Fluid balance should be monitored closely and although sodium chloride 0.9% may be used as therapy initially, as excess sodium will be excreted, continued use will result in further hyponatraemia due to further water retention. Hypertonic sodium chloride (3%) may be indicated where fluid restriction alone is not effective in increasing sodium levels. A sodium chloride 3% infusion of 0.5ml/kg/hour will correct serum sodium by 0.5 mmol/L/hour.[8] It is critical that sodium levels are increased at a safe rate. Rapid correction will result in a rapid osmotic shifts disrupting the blood brain barrier and causing serious neurological sequelae. In the first 24 hours, sodium levels should not be allowed to rise by more than 10 – 12 mmol/L.[7]

Depending on the underlying cause of SIADH, patients may be receiving many different drug infusions. It will be necessary to consider any fluids used to prepare the patients’ drug infusions when calculating fluid balance and where possible minimum infusion volumes should be used (for example, neat infusions are often possible if a patient has central intravenous access).

Pharmacological treatments

A loop diuretic such as furosemide will increase free water excretion if fluid restriction alone is not effective. In the future, the vasopressin-2 receptor antagonists may be beneficial in the treatment of acute SIADH. Tolvaptan was licensed in 2009 for the treatment of adult patients with hyponatraemia secondary to SIADH. However, there is currently no data to support the use of these agents for the management of acute or severe SIADH or for their use in paediatric patients[10].
4.1.2 Cerebral salt wasting syndrome (CSW) [1, 8, 9]

The exact mechanism of cerebral salt wasting syndrome is unknown but an increase in atrial natriuretic peptide (ANP) is likely to be a major mechanism of this syndrome. ANP controls sodium homeostasis via several mechanisms including increasing glomerular filtration rate to increase sodium secretion. Patients are hypovolaemic with a mild to moderate increase in urine output. Laboratory results show hyponatraemia, a normal (280 – 295 mOsm/L) to mildly elevated urine osmolarity and a high urine sodium concentration (> 80mmol/L). (Table 9.2). Hypovolaemia distinguishes CSW from SIADH.

The causes of CSW are similar to those of SIADH, but additionally congestive heart failure and other endocrine diseases or diuretic therapy may be responsible.

**Non-pharmacological treatment**

Fluid and sodium replacement therapy will be necessary. Fluid balance and sodium concentrations should be monitored carefully to tailor replacement appropriately. An infusion of sodium chloride 3% will often be required to increase sodium levels. A sodium chloride 3% infusion of 0.5 ml/kg/hour will correct serum sodium by 0.5 mmol/L/hour.

As for the treatment of SIADH, sodium levels should be increased slowly to avoid serious neurological adverse effects. Sodium should not be increased by more than 12 mmol/L in the first 24 hours.[7]

4.1.3. Diabetes Insipidus (DI) [1, 6, 8]

Diabetes insipidus results from either a central vasopressin deficiency (cranial DI) or a lack of vasopressin receptor response in the kidneys (nephrogenic DI). Patients become hypovolaemic. They may have symptoms such as tachycardia and hypotension and will have a large urine output (>4 ml/kg/hour). Laboratory results show hypernatraemia (>145 mmol/L) and a low urine osmolarity (50 – 100 mOsm/L).

The causes of DI are similar to those of SIADH but DI is more often associated with a traumatic brain injury.

**Non-pharmacological treatment**

Fluid replacement therapy should be commenced and should include replacement of urinary fluid and electrolytes. Isotonic 0.9% sodium chloride should be used, aiming to correct sodium levels over 36 – 48 hours. As with hyponatraemia, rapid correction
of hypernatraemia may result in cerebral oedema due to water movement into the brain. Ideally sodium levels should not be corrected by more than 0.5mmol/L/hr. [8]

**Pharmacological treatment**

Synthetic vasopressin (desmopressin/DDVAP) may be administered for the treatment of central DI. Desmopressin has a greater antidiuretic activity and a longer duration of action than vasopressin. It is administered most commonly by subcutaneous or intramuscular injection in the paediatric critical care setting but intravenous administration has also been used in children > 1 month.[11] Doses should be tailored to effect and dividing daily doses is often useful to avoid patients becoming anuric.

Hydrochlorothiazide can be used to treat nephrogenic DI.

<table>
<thead>
<tr>
<th></th>
<th>SIADH</th>
<th>CSW</th>
<th>DI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Sodium</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Intravascular volume</td>
<td>hypovolaemia</td>
<td>hypovolaemia or normovolaemia</td>
<td>hypovolaemia</td>
</tr>
<tr>
<td>Urine Output</td>
<td>low</td>
<td>normal to high</td>
<td>high</td>
</tr>
<tr>
<td>Urine osmolality</td>
<td>high</td>
<td>normal to high</td>
<td>low</td>
</tr>
<tr>
<td>Urine sodium</td>
<td>high</td>
<td>high</td>
<td>normal</td>
</tr>
<tr>
<td>Primary treatment</td>
<td>fluid restriction</td>
<td>sodium replacement</td>
<td>vasopressin and fluid replacement</td>
</tr>
</tbody>
</table>

Table 9.2; Differentiating between disorders of fluid and sodium balance

### 4.1.4 Aldosterone deficiency [1]

In critical care this may be seen in patients with an adrenal crisis. Aldosterone stimulates sodium and water retention so patients, deficient of this mineralcorticoid, will have hyponatraemia, hyperkalaemia and hypovolaemia due to increased sodium excretion.

**Non-pharmacological treatment**

As with SIADH and CSW, sodium replacement with sodium chloride 3% may be necessary.

**Pharmacological treatment**

The synthetic mineralcorticoid fludrocortisone should be administered once daily to mimic the effects of aldosterone.

**Practice Note:**

Although reference sources often refer to hypertonic saline 3%, this strength is not readily available in the UK. A sodium chloride 2.7% solution is readily available and can be substituted for the 3% solution. No dose adjustment is necessary.
4.2. Disorders of circulatory function [1-3]

Cortisol plays an important role in maintaining circulatory function as described previously and the hypothalamic-pituitary-adrenal axis is activated in acute illness, leading to increased cortisol secretion. Synthetic glucocorticoids mimic these effects and are used in critical care to suppress inflammation, allergy and immune responses. These synthetic glucocorticoids have been developed to have a higher affinity to steroid receptors and a longer duration of action and a minimal salt retaining effect compared to cortisol. Those most commonly used in PICU are shown in the table below (See Table 9.3)

Due to the wide effects of cortisol, synthetic glucocorticoids will produce many adverse as well as therapeutic anti-inflammatory effects. Those with acute consequence to patients on PICU include;

- Disturbed carbohydrate metabolism which may lead to hyperglycaemia
- Protein loss resulting in muscle wasting and weakness (protein synthesis is inhibited so additional dietary protein is not beneficial)
- Hypokalaemia and water retention, which, if the mineralcorticoid effect is significant, can increase blood pressure
- Increased risk of infection with potential increased severity
- Increased risk of peptic ulcer

The risk of adrenal suppression with subsequent adrenal insufficiency should also be considered. The chronic administration of glucocorticoids reduces ACTH release which eventually produces adrenal atrophy. The abrupt withdrawal of corticosteroids, generally after 3 weeks of treatment, should be avoided and it should be noted that this effect can exist for years after the cessation of glucocorticoid therapy. Refer to the BNF for Children for further advice on corticosteroid withdrawal.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>20mg</td>
<td>significant</td>
<td>Used short term for emergency management. Long term use generally limited by fluid retention</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5mg</td>
<td>low</td>
<td>Most widely used. Administered orally for long term inflammatory suppression</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>750 micrograms</td>
<td>insignificant</td>
<td>Used for high dose therapy where mineralcorticoid effect would be detrimental, e.g. cerebral oedema.</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>750 micrograms</td>
<td>insignificant</td>
<td></td>
</tr>
</tbody>
</table>

Table 9.3 Properties of glucocorticoid steroids
4.2.1 Adrenal insufficiency [1, 5, 6]

Adrenal insufficiency results from a deficiency in cortisol and aldosterone. A lack of cortisol results in a decrease in catecholamine release and adrenergic receptor sensitivity which leads to reduced myocardial contractility, vasodilatation, capillary leak and hypoglycaemia, whereas a lack of aldosterone is associated with hyponatraemia, hyperkalaemia and hypovolaemia. Subsequently patients may present with shock or circulatory failure which is refractory to resuscitation with fluids, inotropes or vasoactive drugs.

Adrenal insufficiency can be classed as primary or secondary. In primary insufficiency, both glucocorticoid and mineralcorticoid levels are reduced and hence ACTH levels are high due to a reduced negative feedback mechanism. However, in secondary (central) insufficiency, CRH or ACTH are initially low causing only cortisol production to be reduced as there is only a minimal effect on mineralcorticoid release. Causes of primary insufficiency include adrenal haemorrhage (a possible result of trauma), adrenal infection, congenital adrenal hyperplasia and familial glucocorticoid deficiency. The cause of secondary insufficiency is most commonly adrenal suppression resulting from glucocorticoid therapy where children are unable to produce an appropriate stress response during periods of crisis. This adrenal crisis should be suspected in any child with refractory shock who has previously been administered corticosteroids. Other secondary causes include intracranial masses, intracranial infection, traumatic brain injury and neurosurgery and critical illness-related corticosteroid insufficiency (CIRCI) has been recognised in both adult and paediatric patients with severe sepsis [13].

Adrenal stimulation tests are used to demonstrate inappropriately low serum cortisol responses following stimulation of the adrenal glands. An inappropriately low random basal cortisol level during ‘stress’ is suggestive of adrenal insufficiency however these levels cannot be relied upon. On PICU, a ‘synaetken’ or ACTH stimulation test is most commonly performed. Serum cortisol is measured at baseline, + 30 minutes and + 60 minutes after the administration of synthetic ACTH. A serum cortisol level of 550 nmol/L at 60 minutes is considered normal.[14] The optimal dosing and timing of an ACTH test is debatable. The standard dose stimulation test (145 micrograms/m² to a maximum dose of 250 micrograms) has raised concerns regarding the use of a supraphysiological dose of ACTH and although the low dose test (300 nanograms/m²) uses a more physiological dose, adult studies have failed to show any superiority over the standard dose test. The advantage of either test in paediatrics has yet to be determined, however some limited data exists to support the use of the low dose test in neonates.[15] and more recently paediatrics. [16] In practice, the use of the ACTH test on PICU is not common. Generally, it is likely that any patient with hypotension unresponsive to inotropes would be empirically treated with hydrocortisone.[17]

Non-pharmacological treatment
IV fluids and glucose will be required for patients in adrenal crisis to correct dehydration and hypoglycaemia. Treatment for hyperkalaemia may also be required.
Pharmacological treatment
Glucocorticoid therapy will be required in both primary and secondary adrenal insufficiency. Hydrocortisone is the glucocorticoid of choice. Doses should be increased two to three fold during periods of stress (e.g. infection, trauma, surgery). Primary deficiency will also require mineralcorticoid therapy with fludrocortisone. During periods of adrenal crisis, hydrocortisone will be required every 6 hours intravenously. Dosing information is available in the BNF for Children.

4.2.2 Use of steroids in critical illness [9, 17]

Currently, in the UK, there is no agreed consensus on the use of corticosteroids in paediatric patients with sepsis. Initial adult studies in the 1970s showed treatment with high dose steroids was associated with lower mortality in septic shock. However, further studies failed to confirm these results and the use of high dose corticosteroids in septic shock was abandoned by the mid 1980s. In 2004, adult guidelines recommending the use of relatively ‘low dose’ steroids for severe sepsis and septic shock were published when a further study showed glucocorticoid replacement had a positive effect on survival. More recently, the Corticosteroid therapy of Septic Shock study [15] and the resulting 2008 Surviving Sepsis guidelines[16] do include paediatric recommendations which state ‘steroids only in children with suspected or proven adrenal insufficiency’. Until results are available from large randomized controlled trials on the use of steroids in critically ill children, there is still no clear evidence to support the use of steroids for this indication[16].

A survey of UK PICUs in 2005 showed that most UK units would appear to consider steroids in patients with refractory shock[17], 42% of units did not perform any endocrine testing before commencing treatment, however all units would discontinue steroids if a synacthen test had been performed and was normal. It is likely that this practice will continue until clear evidence to support or dispute the use of steroids in paediatric patients becomes available. In 2010, the National Institute for Health and Clinical Excellence published clinical guidelines on ‘The management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care’[20]. They support the above findings by recommending the following;

“In children and young people with shock that is unresponsive to vasoactive agents, steroid replacement therapy using low-dose corticosteroids (hydrocortisone 25 mg/m² four times daily) should be used only when directed by a paediatric intensivist.”

Doses for hydrocortisone in the treatment of hypotension resistant to inotropic treatment and volume replacement are also given in the BNF for Children although the limited evidence for this is highlighted[12].

4.3 Disorders of energy metabolism

4.3.1 Hyperthyroidism [8, 9]

Hyperthyroidism is not a common presentation on PICU, however, occasionally, hyperthyroid patients may present with tachycardia and hypertension requiring intensive care. If severe, this hypermetabolic state can lead to cardiovascular collapse, shock and heart failure. Diagnosis is confirmed from a thyroid profile which shows
elevated serum thyroxine (T4) and triiodothyronine (T3) levels with suppressed TSH levels.

Non-pharmacological treatment
Dehydration should be corrected with fluid therapy and hyperthermia with a cooling blanket.

Pharmacological treatment
In the acute period, a β-blocker will be required to relieve cardiovascular symptoms. Propranolol is usually the drug of choice and may be administered intravenously if oral intake is not possible. Intravenous administration will require ECG monitoring to detect any bradycardia or arrhythmias. In severe cases high dose (stress dose) glucocorticoids may be useful as they inhibit the conversion of thyroxine to the more active triiodothyronine metabolite. Appropriate antithyroid therapy (e.g. propylthiouracil) should then be initiated for long term disease management.

4.3.2 Hypothyroidism [1]
As discussed, the thyroid hormones are crucial for infant development. In the UK all newborns are screened for hypothyroidism as the effects of thyroid deficiency on development are irreversible. Congenital hypothyroidism presents in the neonate and if premature, may only be temporary condition as premature neonates have less circulating thyroxine than full term infants. In some cases, symptoms may not present until 6 months of age. Acquired hypothyroidism is associated with various syndromes and autoimmune diseases. It may also occur in any child with a hypothalamic or pituitary abnormality. Sick euthyroid syndrome is an associated condition where thyroid regulation is disrupted. It occurs in prolonged critical illness and contributes to refractory shock. Symptoms of hypothyroidism include hypotonia, hypotension, hypothermia and bradycardia

Pharmacological treatment
Thyroxine replacement is with synthetic thyroxine. Levothyroxine is given enterally and triiodothyronine is given intravenously. A conversion factor is available (2 micrograms of triiodothyronine is approximately equivalent to 8 micrograms of levothyroxine).[12] Interestingly, there has been much debate regarding the most suitable formulation of levothyroxine to administer orally and although suspensions are usually preferred in this patient population, tablets are often administered by clinicians as there are anecdotal reports of treatment failure with levothyroxine suspension.[21-23] Tablets are crushed and mixed with water.

4.3.3 Diabetes Mellitus [1]
Most commonly seen on PICU is Type I diabetes mellitus (insulin dependent diabetes mellitus (IDDM)) which is due to a lack of insulin production. Glucose cannot be
taken up by cells in the absence of insulin and so proteins and lipids are broken down into fatty acids and amino acids to form energy substrates. Patients with type I diabetes mellitus control their disease with regular insulin therapy.

Various complications of IDDM can result in these children being admitted to a paediatric intensive care unit. Diabetic ketoacidosis is a life threatening condition and sudden onset hypoglycaemia can result in seizures and unconsciousness.

4.3.4 Diabetic Ketoacidosis [1, 5, 6, 24, 25] (See Case study Endocrine-Diabetic Ketoacidosis)

When insulin deficiency is prolonged, by-products of fatty acid oxidation are released and accumulate resulting in ketoacidosis. Diabetic ketoacidosis (DKA) therefore occurs in severe hyperglycaemia. This metabolic acidosis is accompanied by electrolyte abnormalities (potassium and phosphate levels are initially high but subsequently drop as they are lost in urine) and hyperosmolarity producing an osmotic diuresis leading to dehydration and hypernatraemia. Laboratory results show hyperglycaemia (plasma glucose >11 mmol/L), metabolic acidosis (pH < 7.3, bicarbonate < 15 mmol/L) and blood ketones > 3mmol/L with the presence of urinary ketones.

Often DKA is the first presentation of type I diabetes mellitus, however a previously diagnosed patient can suffer DKA if non-compliant, if diet or insulin regimen becomes unbalanced or during periods of concurrent infection or stress. Often the underlying cause of DKA is unidentified.

In patients with DKA, metabolic acidosis is characterised by symptoms such as tachypnoea, vomiting and headache leading to serious complications of coma and cerebral oedema. The cause of cerebral oedema is unknown, it is unpredictable and occurs more frequently in younger children and newly diagnosed diabetes. It is therefore important to correct metabolic abnormalities slowly and treatment is aimed at gradually reducing serum glucose levels and maintaining serum glucose levels above 7 mmol/L.

Fluid therapy should be used to correct the acidosis and, as well as total fluid replacement therapy, fluid deficits should be replaced slowly over 48 hours to avoid cerebral oedema from rapid fluid shifts. Bicarbonate therapy should be avoided due to concerns that it may worsen the patient’s consciousness levels and increase the risk of cerebral oedema.

Electrolyte disturbances should be corrected but it is important to note that the presence of metabolic acidosis itself may alter these. For example, potassium is driven out of cells in metabolic acidosis so if a patient has a pH of < 7.3, their potassium will be falsely high (e.g. a level < 4.2 mmol/L would indicate a deficiency due to massive depletion of total body potassium). Ideally potassium levels should be maintained between 4 and 5.5 mmol/L.

As treatment is commenced, patients with DKA will be monitored very closely. Vital signs, neurological status, fluid balance, blood glucose, near patient blood ketones and serum electrolytes will be documented frequently to allow therapy to be titrated carefully.
Non-pharmacological treatment

Fluid resuscitation with boluses of sodium chloride 0.9% will be required immediately in a shocked patient. It is essential that all fluids are documented carefully. Maintenance fluid requirements should then be calculated taking the fluid boluses already administered into account. In addition extra volume will be required to replace the patient fluid deficit (given over 48 hours). If any signs of cerebral oedema are present, IV fluids should be restricted further and deficit fluids replaced over 72 hours rather than 48 hours. A DKA fluid calculator is available at; http://www.bsped.org.uk/professional/guidelines/docs/DKACalculator.pdf.

Initially, sodium chloride 0.9% with 20mmol potassium chloride in 500ml should be commenced at the calculated rate. Glucose should then be added when insulin has reduced the serum glucose to 14 mmol/L to ensure serum glucose is reduced slowly. As sodium depletion is usually present, sodium chloride 0.9% is usually continued with 5% glucose and 20mmol potassium chloride. After a further 12 hours, change to 500ml bags of sodium chloride 0.45% with glucose 5% and 20mmol potassium chloride if plasma sodium levels are stable or increasing.

Oral fluids can be commenced usually after 36 to 48 hours, when the blood glucose is stable and maintained between 7 – 12 mmol/L. Potassium should be added to IV replacement fluids. Even if a patient is not hypokalaemic, potassium levels will drop as insulin therapy is commenced. Some patients may present with hyperkalaemia which should improve as insulin drives potassium into cells. If no improvement is seen however, calcium and sodium bicarbonate therapy may be required.

Pharmacological treatment

A continuous intravenous infusion of insulin should be commenced once intravenous fluids have been running for at least an hour at a low dose (0.1 units/kg/hour). Insulin therapy should be continued to switch off ketogenesis and reverse acidosis and, if glucose levels drop below 4 mmol/L, a 2ml/kg bolus of glucose 10% may be required. The glucose concentration of the infusion fluids should also be increased to 10% and if necessary, the insulin rate can be reduced for short term for 1 hour. Once the pH is >7.3 and blood glucose is < 14mmol/L, the insulin infusion may be reduced for longer to 0.05units/kg/hour. Only once the child is tolerating a good oral intake and blood ketone levels have dropped below 1mmol/L, can IV fluid and insulin therapy be stopped. A subcutaneous insulin regimen would then be commenced for long term maintenance and the IV insulin infusion should be discontinued 60 minutes after the first subcutaneous injection (of soluble or long acting insulin) to avoid rebound hyperglycaemia (10 minutes if using Novorapid or Humalog). Under consultant advice, previously diagnosed DM patients using long-acting insulin may have continued their usual dosage regimen throughout DKA treatment in addition to an IV insulin infusion.

The 2009 BSPED Guidelines for the Management of Diabetic Ketoacidosis also now recommend considering anticoagulant prophylaxis for DKA patients who have femoral lines inserted[24].
4.3.4 Critical Illness hyperglycaemia[9, 26]

Hyperglycaemia is a normal and important physiological response to stress and hence is common in critically ill patients. This is often enhanced by common intensive care drugs such as steroids, catecholamines and thiazides. Increased glucose delivery to cells during periods of illness would be expected to be an advantage but when critically ill, these mechanisms become overwhelmed resulting in persistent hyperglycaemia. In adult critically ill patients, studies have shown that hyperglycaemia is associated with poor outcome for length of stay and higher infection and mortality rates and hence many adult unit patients are being maintained within a strict glucose control. The benefit of tight glycemic control however has not been shown in large, prospective, randomised, controlled, multicenter studies. As preliminary studies in paediatric patients have also shown that prolonged hyperglycaemia is associated with increased length of hospital stay, prolonged ventilation and even increased mortality. It has been suggested that PICU patients should also be maintained under strict glycaemic control [27]. However, although it is recognised that hyperglycaemia in PICU patients needs to be identified, monitored and controlled, the use of strict control is still debatable. Hypoglycaemia, the most common adverse effect of this therapy, is potentially more detrimental in paediatrics than in adults and so the risks of treatment in this population need to be fully evaluated. The results of one large, prospective, randomised controlled study has been published recently and the authors conclude that for infants and children in PICU, ‘targeting blood glucose concentrations to an age-adjusted normal fasting concentration with an insulin infusion throughout intensive care improved morbidity and reduced mortality’. They do however acknowledge that although the short term outcome improved for these patients, the effect on long-term survival, morbidity and neurocognitive development needs to be investigated [28]. Further studies to examine the effects of strict glycaemic control (blood glucose levels maintained between 4 and 7 mmol/L) in critically ill paediatric patients are underway.

4.3.6 Hypoglycaemia[6]

Hypoglycaemia in infants and children is defined as a serum glucose level of less than 2.2 – 2.6 mmol/L. Hypoglycaemia occurs when there is an imbalance between the glucose used by the body and glucose produced by the body, for example from excessive insulin production (or administration) or deficient glucagon production. Neonates and infants often have inadequate glycogen stores resulting in hypoglycaemia although persistent forms of excessive insulin production also exist in this age group. Other causes of hypoglycaemia include congenital adrenal hyperplasia, various metabolic disorders, alcohol poisoning, starvation, sepsis and malabsorption. Hypoglycaemia may also be a complication of patients with diabetes mellitus. The symptoms of hypoglycaemia can be mild but as blood glucose levels drop serious symptoms are more likely, for example, altered level of consciousness, seizures, tachycardia, and hypotonia.

Non-pharmacological treatment
An asymptomatic child should be encouraged to take a glucose drink. Most children on intensive care will require more aggressive treatment. An intravenous bolus
Infusion of glucose will be required (5 – 10 ml/kg of glucose 10%) followed by an infusion of glucose 10% providing 5-8 mg/kg/min (0.05 - 0.08 mls/kg/min).[14]

**Pharmacological treatments**

Glucagon may be administered although this will not work if the patient has low glycogen stores or a glycogen storage disorder. Hyperinsulinism of infancy may be treated with diazoxide.

**4.4 Inborn errors of metabolism (IEM)**[29-33]

(See Case Study – [Metabolic- Hyperammonaemia](#))

IEMs are single gene defects that result in abnormalities in the synthesis or catabolism of proteins, carbohydrates, or fats. To date more than 1400 metabolic diseases have been described. They can be categorised into disorders that give rise to intoxication (e.g. urea cycle disorders), disorders involving energy metabolism (e.g. mitochondrial defects) and disorders involving complex molecules (e.g. lysosomal storage disorders). Nearly every metabolic disease has several forms that vary in age of onset, clinical severity, and often, mode of inheritance.

IEM can present at any age. The onset and severity is exacerbated by environmental factors such as diet or metabolic stress and the symptoms will also vary depending on the age of presentation and the type of metabolic disorder. Generally the pattern of symptoms will include neurological abnormalities, metabolic acidosis, hypoglycaemia, cardiac disease, liver dysfunction and possibly dysmorphism.

**4.4.1 Urea cycle defects**

Urea cycle defects are among the most common inborn errors of metabolism. Neurotoxic ammonia builds up in blood and tissue due to a defect in the urea cycle. Some examples of the specific defects are listed below and depend on the deficient cycle enzyme:

- Ornithine transcarbamylase (OTC) deficiency,
- Citrullinaemia,
- Arginosuccinic aciduria,
- Carbamylphosphate synthase (CPS) deficiency,
- Argininaemia,
- HHH syndrome (hyperammonaemia, hyperornithinaemia, homocitrullinuria),
- \( N \)-acetylglutamate synthetase (NAGS) deficiency.

In all urea cycle disorders the correct diagnosis and early instigation of treatment are critical to avoid permanent neurological injury.

Patients with urea cycle defects commonly present during either the neonatal period, the end of first year (as growth rate slows), during infancy (as protein rich food is introduced) or during puberty (due to changing growth). Symptoms may be precipitated by high protein intake, or present during metabolic stress such as intercurrent infections. The extent of hyperammonaemia and age of presentations will determine the clinical features, for example, a neonate usually has rapidly progressive...
symptoms appearing on the second day of life whereas an adolescent is more likely to present with chronic neurological symptoms. Neonatal symptoms include poor feeding, hyperventilation, seizures and a progressive encephalopathy with deepening coma whereas an adolescent’s symptoms are more likely to include episodes of disorientation, lethargy, psychosis and recurrent encephalopathy.

The most important laboratory test is the plasma ammonia concentration. The time span from the first symptoms to irreversible brain damage from hyperammonaemia is short. Further investigations should be commenced immediately if ammonia is greater than 150 micromol/l in the neonate or 100 micromol/l in older children. Multiple tests will be required and final confirmation of the diagnosis will require measurement of enzyme activity or genetic testing, the results of which may take weeks or months.

In a critically ill patient with a suspected urea cycle disorder, plasma ammonia should be monitored regularly along with the patient’s clinical condition. Ammonia levels change rapidly and should always be considered with the patient’s symptoms. Emergency treatment should be commenced aiming to normalise the patient’s ammonia within 8 to 12 hours and then to maintain the ammonia levels below 50 micromol/l.

Non-pharmacological treatment

The first step in treatment is to stop any further nitrogen load by discontinuing any protein intake. In order to avoid catabolism, a continuous IV infusion of glucose 10 – 20% should then be commenced. Insulin may be required to maintain the blood sugar between 6 – 10 mmol/L and should be commenced rather than reducing the glucose infusion. Dehydration should be corrected slowly with fluid therapy avoiding hypotonic solutions.

If ammonia levels are successfully reduced, amino acids may be introduced cautiously after 48 hours. Additional nutritional requirements should be met with glucose, lipids and vitamins.

Pharmacological treatments

Sodium phenylbutyrate and sodium benzoate should be commenced to reduce ammonia levels by providing an alternative pathway for nitrogen elimination. They are administered by continuous IV infusion. Similarly, a continuous IV infusion of arginine should be commenced to optimise the urea cycle along with, either IV bolus doses, or a continuous IV infusion of carnitine which assists the removal of toxic metabolites as carnitine conjugates. For dosing advice, refer to BNF for Children.[12]

Recently carglumic acid has been licensed for the treatment of hyperammonaemia due to NAGS deficiency. This oral therapy may occasionally be used on initial presentation before IV access is available or therapy may be introduced in addition to the above if ammonia levels fail to drop sufficiently with ‘standard’ therapy. There is minimal evidence to support the use of carglumic acid in these circumstances and there is no information available on the effects of long term administration.

A sodium bicarbonate infusion should be prescribed to partially correct severe acidosis. A mild acidosis should however remain as this is protective against toxicity in hyperammonaemia. Vitamins such as hydroxocobalamin (vitamin B12) and biotin act as co-factors and stimulate residual enzyme activity and may be prescribed in the
initial emergency period. Finally if plasma ammonia levels remain high or acidosis is intractable, continuous renal replacement therapy may be required to remove ammonia.

Useful website

http://www.bimdg.org.uk/emergencyprotocols_disclaimer.asp

References


20. National Institute for Health and Clinical Excellence; Clinical Guideline 102; Bacterial meningitis and meningococcal septicaemia in children. 2010


Haematology
Adam Sutherland

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Objectives

- To be able to understand the clotting physiology and the effects of drugs on it
- To understand the basic physiology of disseminated intravascular coagulation
- To understand the role and dosing of various anti-coagulants
- To understand the pathophysiology of thromboembolism and its management
1. **Introduction**  
(see case studies – [Anticoagulation](#) & [sepsis](#))

For the purposes of critical care, the term “haematology” does not refer to haematological malignancies (though these will frequently be seen in the PICU setting) but instead refers to derangements in the normal processes that lead to the cessation of bleeding. The areas covered will include:
- The clotting cascade,
- The common presentation of disseminated intravascular coagulopathy (DIC),
- Blood products,
- Pharmacological options for influencing clotting and bleeding.

2. **Clotting physiology**

The process of coagulation and clotting in children differs little from that seen in adults, however children are much more responsive to stimuli and it is very common to see “changes” in the coagulopathic picture as the result of an essentially minor insult.

The clotting process is mediated by a number of cellular and microcellular markers:
- **Factors** are serine proteases which cleave their targets into the activated moiety, thus catalysing the clotting cascade.
- **Tissue Factor** is released by damaged cells. It binds to calcium and to Factor VII to become a highly pro-coagulant moiety which drives the initial phases of clotting, and the formation of the first platelet plug.
- **Thrombin** is the glue that holds platelets together in the early clot.
- **Fibrin**

The clotting process can be divided into a three stage process:

2.1 **Initiation (see Figure 7.1)**

In some models of coagulation this is referred to as the extrinsic pathway, whereby cellular damage releases tissue factors which activate Factor VII and calcium. These factors then activate Factor X which in turn activates platelets and fibrinogen to fibrin, forming the first platelet cohesion.

2.2 **Propagation (see Figure 7.2)**

In some models of coagulation, this is referred to as the intrinsic pathway. The presence of a foreign surface (e.g. platelet cohesion, extracorporeal circuit, intravascular catheter) triggers the activation of Factors XII, XI, and IX which also activates Factor X and Prothrombin (NB – Prothrombin is sometimes referred to as Factor II). The pathway of Factor X and Thrombin is sometimes referred to as the “Final Common Pathway” and it is this step that is crucial to the ongoing development of the clot. Interestingly, Factor IXa binds to and activates Factor VIII. However, patients who are deficient in Factor IX do NOT display bleeding disorders, yet patients deficient in Factor VIII do.
Figure 7.1 Initiation of clotting cascade

Figure 7.2 Propagation of clotting cascade
2.3 Termination

Because the clotting cascade is such a massive response and occurs with relative speed, theoretically the process could carry on ad infinitum until all blood products are consumed and clotted. This situation is understandably not compatible with life. Thus there must be a phase in the clotting cascade where the cascade is downregulated and terminates. It has been proposed that this is the role of two anti-coagulant molecules – Protein C (in its activated form) and Antithrombin III (ATIII). Around the site of epithelial damage, there is a relatively higher concentration of pro-coagulant Tissue Factor compared with anti-coagulant ATIII thus ensuring that platelet-fibrin complexes are produced. Upstream of this damage, ATIII is in the greater balance, so passing blood doesn’t clot. Downstream of the clot, excess thrombin is bound to thrombomodulin which activates protein C molecules. Activated protein-C (APC) is strongly anticoagulant, inhibiting factors Va and VIIIa thus preventing the spread of the clotting phenomenon away from the affected area. [1] (See Figure 7.3)

Figure 7.3 Termination of clotting cascade

2.3.1 Protein C and Sepsis

Studies on the use of recombinant human activated Protein C (drotrecogin alpha) in adults have shown a role for it in treatment of acute sepsis. There is a strong correlation between inflammatory response and coagulation, such that there is a positive feedback loop. Inflammatory cytokines stimulate release of tissue factor, triggering the formation of microemboli (the process involved in DIC.) The same tissue factor releasing epithelial cells also release further inflammatory cytokines, stimulating the inflammatory response further. A number of modulatory techniques are proposed for the treatment of sepsis including the application of protein C. Laboratory studies have found that septic patients are deficient in protein C. Early trials with protein C concentrate were promising, but it was already understood then that in sepsis conversion of protein C to its activated moiety was dysfunctional, thus activated Protein C (aPC) was followed closely. The PROWESS study in 2001[1] was a randomised, blinded placebo-controlled multicentre study and found that patients with multi-organ failure who were treated for 96 hours with aPC had a 28-day mortality rate almost 30% less than those patients treated with placebo. There have been similar studies in children with mixed results. Barton et al[2] found that aPC
had similar pharmacokinetic, pharmacodynamic and safety effects in children as in adults. Following on from this study, Nadel et al.[3] began the RESOLVE study. However it was halted early for clinical reasons and as such aPC is not routinely used in paediatric sepsis.

2.4 Dissolution of a Clot

Running concurrently with the final common pathway is the activation of plasminogen to plasmin. Plasmin is another serine protease that is unstable in circulating blood, so is deposited on fibrin surfaces and diffuses into the clot. Plasmin then cleaves fibrin and inhibits factors II, V and VIII terminating the clotting cascade and allowing the clot to disperse and dissolve.

3. Pathology of Common Diseases

3.1 Disseminated Intravascular Coagulopathy (DIC)

DIC is a common problem in Critical Care, and is sometimes referred to as “Consumptive Coagulopathy.” In the presence of sepsis or some other generalized inflammatory process, the coagulation cascade is activated on a massive scale. Thousands of microemboli form in the capillary beds around the body, usually related to hypoperfusion states. These tiny clots consume all available clotting factors and fibrinolytics which then cause a deranged clotting profile. There can also be an impairment of clotting factor synthesis. It can present quite rapidly and severely with bleeding and thromboses happening spontaneously which has lead to DIC being referred to as “Death Is Coming.” This is a rather melodramatic description, with DIC being quite common, and generally self-limiting. On PICU it is commonly associated with sepsis and low cardiac output syndrome (LCOS.)

The deranged clotting seen after periods of cardiopulmonary bypass (CPB) is not DIC but an iatrogenic clotting disorder caused by the process of CPB and the heparin used to prevent the circuit clotting. This transient coagulopathy will usually resolve itself 6 to 12 hours post op. If bleeding is a problem then administration of protamine is indicated to reverse the heparin effect.

Diagnosis
When presented with a clotting profile, the following trends would be indicative of DIC. (SeeTable 7.1)

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>10-20secs</td>
<td>↑</td>
</tr>
<tr>
<td>APTT</td>
<td>20-40secs</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>&gt;2.5gL</td>
<td>↓↓</td>
</tr>
</tbody>
</table>

Table 7.1 Clotting profile of DIC
Management

Generally, the management approach to DIC is to treat the underlying cause and support with clotting factors if necessary. If the patient is septic, then inotropes and fluid therapy will correct the underlying hypoperfusion syndrome and facilitate in moving newly synthesised clotting factors to the microemboli sites. In LCOS, appropriate management and augmentation of the cardiac output will have similar effects. If supportive treatment were to be considered, then first line therapy would be to administer fresh frozen plasma (FFP) to provide more clotting factors.

3.2 Venous Thromboembolism (VTE)

In children idiopathic VTE is rare as there is always an underlying reason such as an organic clotting disorder or an iatrogenic cause. 90% of neonatal VTEs [4] and 60% of paediatric VTEs [5] are caused by indwelling central venous catheters. The formation of catheter related thrombi and subsequent thromboembolism is caused by an activation of the intrinsic pathway as exposure of blood to a foreign surface triggers the activation of Factor XII and subsequent platelet activation and aggregation. In most cases, the thrombus will remain associated with the foreign surface however there is a risk that the thrombus may detach and be propelled under normal blood pressure to vital organs and blood vessels. This is especially common in extracorporeal circuits which often “clot off.” The preferred treatment for venous thromboembolism is with heparin.

3.3 Heparin Induced Thrombocytopenia Syndrome (HITS)

HITS occurs in between 1 and 3% of adult exposures to unfractionated heparin. In the paediatric population it is less well studied, with reviews reporting an incidence of between 0.02% up to 2% of patients [6,7]. In general terms, HITS is an immune-modulated response to exposure to heparin. Heparin Dependent Platelet Antibodies (HDPA) are produced which bind to the surface of activated platelets and destroy them. The condition will usually be observed between 5 and 10 days post-exposure to unfractionated heparin, and is characterised by a rapid fall in platelets to between 20 and 100 x 10^9 cells/mm. A fall in platelets of >50% from baseline should arouse suspicion of HITS and trigger appropriate testing, particularly in cardiac patients who have intravascular shunts in situ and are dependent on anticoagulation.

4. Management of clotting disorders

4.1. Non-pharmacological Therapy

Non-pharmacological management of bleeding

The gold standard in arresting haemorrhage is to locate the source of the bleed and surgically ligate the area. Surgical bleeding is not uncommon, and in the majority of cases would warrant an emergency surgical re-exploration of the site. However some patients will be too unstable to tolerate another surgical procedure and in these cases pharmacological means (anti-fibrinolysis, factor replacement) would be considered before surgical intervention.
Non-pharmacological management of thromboembolism

Prevention

VTE prophylaxis is offered routinely to all adults however, before low molecular weight heparin (LMWH) prophylaxis, there is evidence to support non-pharmacological VTE prophylaxis. This is summarised most concisely in the Scottish Intercollegiate Guideline Network’s 2002 Guideline[20]. Methods of prophylaxis include graduated elasticated compression hosiery (e.g. “TED stockings,”), early mobilisation and leg exercises, to reduce haemostasis, and adequate hydration to maintain blood viscosity at a biological norm.

When dealing with critically ill children, there is no evidence to support offering routine VTE prophylaxis, though some units may offer it to girls around the age of puberty.

Thrombectomy

In the presence of a confirmed thrombus (if the thrombus has been precisely located) it is possible to enter the vessel and physically remove the clot. This process is not definitive nor is it without considerable risk.

4.2 Pharmacological Therapy

4.2.1 Blood products.

Packed Red Blood Cells (PRBC) are produced when a unit of blood is centrifuged leaving just the red blood cells. The plasma supernatant is taken off and frozen. PRBCs are indicated when haemoglobin (Hb) is low. Trigger targets for transfusion are usually below 7g/dL [8] but cardiac surgery patients would usually be topped up when their Hb falls below 9g/dL.

Packed Red Cells are also used in periods of bleeding to augment the circulating volume after a patient has received a substantial quantity of crystalloid/colloid. Packed Red Cells offer no support in encouraging clotting, but will reverse some of the haemodilution caused by large infusions of resuscitation fluid. The dose required to increase Hb by 1g/dL is 5 ml/kg of packed red cells administered over 4 hours. This presents a rather large volume to many smaller children (<10 kg) and neonates, so it is common to administer a dose of furosemide 0.5 mg/kg half way through the infusion. [21]

Fresh Frozen Plasma (FFP) is a straw coloured supernatant that is produced after whole blood has been centrifuged. It is deep frozen (to <-18°C) within six hours of harvest. It is a rich source of clotting factors, notably VII, IX, X and XI and is used most commonly in acute bleeding situations to encourage spontaneous clotting. Usual dose is 10-15 ml/kg given over one hour. [22]

Cryprecipitate (Cryo)

Before the plasma supernatant is frozen, a small volume of methylene blue is added. This acts as a stain and is specific for a number of critical clotting co-factors, notably von Willebrand factor (vWF) and fibrinogen. These low-molecular weight proteins
precipitate out as the plasma freezes and this blue layer is then removed for later use (hence *cryoprecipitate*).

**Risks of Transfusion**

Blood and blood product transfusions are high-risk procedures. Not only is there the risk of anaphylactic reactions on single-unit exposure (minimized by cross matching blood to the rhD antibody status of the patient) but repeated exposure can lead to alloimmunization of the patient. The more units of blood a patient receives, the more antibodies the patient produces so it is common practice to cross match blood every time a request for products is made. Access and administration of blood products is also strictly controlled by law, with the National Blood Transfusion Service (BTS) and the Scottish National Blood Transfusion Services (SNBTS) being responsible for ensuring standards are maintained. All healthcare professions involved in the ordering and administration of donor blood products are required to complete an on-line competency based training package annually (every two years in Scotland.)

4.2.2 Heparin & Low Molecular Weight Heparins (LMWH)

Heparin is a highly sulphated glycosaminoglycan that is derived from mucosal tissues – porcine or bovine. In itself heparin is not intrinsically anticoagulant. Its anticoagulant properties are activated when the glycosaminoglycan portion of the molecule binds to circulating antithrombin III (ATIII). This antithrombin III/heparin complex then inhibits thrombin activation and factor X by occupying the serine active site on the factor, rendering it inactive. This complex is 1000 times the anticoagulant effect of antithrombin alone. Heparin is still the first line parenteral anticoagulant of choice as there is vast experience with its use, and an antagonist is available (protamine sulphate).

However there are some significant drawbacks to its use:

- Continuous infusion and the requirement for definitive vascular access
- Recurrent blood sampling
- 2% risk of bleeding
- Osteoporosis
- Heparin-Induced Thrombocytopenia
- Weight/Age-dependent pharmacokinetics (neonates have much higher heparin requirements.)

Heparin should be used for short term use where anticoagulation is required. For longer term anticoagulation a low molecular weight heparin should be used.

LMWH are fractionated heparins, where only the portion with affinity for antithrombin III is retained. Heparins have much greater affinity for antithrombin III than Factor X directly, and the ATIII/heparin complex is a powerful inhibitor of Factor Xa.

The LMWHs have the advantages of sub-cutaneous administration, longer duration of action, less frequent blood sampling (but blood sampling is still required) and less incidence of bleeding. In the United Kingdom none of the available LMWHs are licensed for use in children however there is a growing experience base in their use and monitoring, such that formal guidelines for the use of LMWHs exist. [9] Dosing of LMWHs, for both treatment and prophylaxis, should always be guided by a haematologist, but the doses expressed in the BNF-C are useful starting points. Note that children up to the age of two have a higher requirement as their clearance...
(especially of enoxaparin) is greater. Therapy with LMWH should always be guided by anti-factor Xa levels. Quoted reference ranges are between 0.5 and 1 unit/mL (normal range is 0.1 – 0.4 unit/mL) and this should be checked at least weekly until stable. Ranges will vary depending on whether LMWH is being used as prophylaxis or treatment.

4.2.3 Hirudins

Hirudins are newer anticoagulants that are derived from the secretions of leeches. They include lepirudin and bivalirudin and are indicated in adults for parenteral anticoagulation of patients with proven HITs. Hirudins act independently of antithrombin III, acting rather as a direct thrombin inhibitor so in patients who are antithrombin III deficient it is possible to adequately anticoagulate without having to administer additional clotting co-factors. The most commonly used hirudin is lepirudin, a recombinant hirudin that is administered as a continuous infusion and titrated according to APTT. It is renally excreted so dosages need to be adjusted for renal impairment. There is no antagonist to any of the hirudins, so in hirudin-induced bleeding only supportive therapy can be offered.

Experience in pediatrics is very limited with only case-reports in the literature.

4.2.4 Oral Vitamin K Antagonists

Parenteral anticoagulants are often not appropriate for longer term therapy post thrombosis (the presence of a venous catheter increases the risk of clotting in itself, as well as infection), and it is necessary to identify an alternative drug to prevent further thrombotic episodes. The first line choice in adults and children are the oral vitamin K antagonists particularly warfarin. Warfarin is rarely used on the PICU as it takes too long to exert its effect, and that effect can take too long to wear off. However, it is necessary to understand the role of vitamin K in the clotting process, and how warfarin antagonises this effect.

During synthesis of prothrombin and Factors VII, IX and X there is a reduction step which changes the glutamic acid residues of these factors to the usable gamma-carboxyglutamic acid residues. This reduction reaction is catalysed by the oxidation of hydroquinone to vitamin K epoxide. An enzyme called vitamin K reductase then restarts the redox cycle so that vitamin K is effectively recycled. Warfarin acts by irreversibly inhibiting vitamin K reductase, reducing the amount of vitamin K available for synthesis of clotting factors. This results in a substantial prolongation of the clotting time. In patients who have had too much warfarin, or where a rapid reversal of effect is required, the administration of exogenous vitamin K (phytomenadione) is sufficient to bypass the inhibition by providing raw substrate for the reduction of newly synthesised factors.

4.2.5 Platelet Aggregation Inhibitors

There are three platelet aggregation inhibitors routinely used on PICU:

- **Aspirin** inhibits the production of arachidonic acid which prevents the aggregation of platelets. The effect is seen at doses of between 1 and 5mg/kg after one or two doses, and the effect can last up to 10 days after cessation of aspirin therapy.
Clopidogrel is sometimes used in combination with aspirin in the prophylaxis of clotting for Blalock-Taussig (BT) shunts, and there are some trials ongoing at present. Clopidogrel inhibits the release of ADP and cGMP that follows activation of platelets. This downregulates the expression of glycoprotein 2b/3a receptors on platelet surfaces and thus slows platelet aggregation. Initial dosing recommendations suggested doses of 1 to 1.5mg/kg however a 2006 trial demonstrated that a dose of 200 micrograms/kg daily had the same effect with fewer adverse bleeding events.[10]

Epoprostenol is an analogue of prostaglandin I\textsubscript{2} and acts both as a direct inhibitor of glycoprotein 2b/3a receptors, resulting in the failure of formation of fibrin cross-links and also by directly inhibiting the aggregation of platelets by reducing surface attraction.

Platelet aggregation inhibitors are useful but all have relative risks. Aspirin is associated with Reyes syndrome (dose related, immune reaction) and an increased risk of gastro-intestinal (GI) bleeds. Clopidogrel is also associated with bleeding. Epoprostenol has to be given as a continuous infusion and is associated with profound hypotension, as it is a potent vasodilator. The choice of platelet aggregation inhibitor is dictated by risk:benefit assessment. Cardiac surgery patients who are palliated with Blalock-Taussig (BT) shunts may receive either aspirin, or clopidogrel (or both) until they have a definitive repair. Some post-surgical circulations are too fragile to be anti-coagulated with anti-platelet therapy alone, so will be therapeutically anti-coagulated with warfarin (e.g.Glen or Fontan circulations).

4.2.6 Anti-fibrinolytic Drugs (including aprotinin)

Most clot formation is natural, and desired. For example, post-surgery it is desirable for the patient to clot appropriately, and thus be supported in doing this with blood products and factors. However, some patients are exposed to thrombolytic drugs (e.g. heparin) at a time where they are still at substantial risk of bleeding, and thus it is necessary to administer anti-fibrinolytic drugs to prevent this inappropriate clot breakdown. There are two anti-fibrinolytic drugs commonly used in PICU.

Tranexamic Acid is a lysine analogue that acts to inhibit plasmin by binding to the lysine active site on plasmin. This prevents plasmin binding to fibrin, preventing the breakdown of fibrin-plugs and renewed bleeding. Tranexamic acid is cheap, can be administered orally or intravenously and is very well tolerated. However, perhaps due to poor availability, tranexamic acid is not well studied in paediatric cardiac surgery patients (tranexamic acid has not been available in North America until very recently).

Aprotinin is currently the subject of some considerable controversy. It has been used liberally in cardiac bypass to reduce the amount of blood products required in theatre[11] and also to reduce the amount of post-surgical bleeding and subsequent blood-product transfusion or surgical re-exploration. Aprotinin is a serine protease inhibitor that directly blocks the transformation of plasminogen to plasmin and the deactivation of numerous clotting factors. It is administered as a continuous infusion, and has been used widely in patients on ECMO both to reduce the amount of blood loss through oozing from cannulation sites, and to reduce the risks of cerebrovascular bleeding. In May 2008 aprotinin was withdrawn from the market voluntarily by Bayer Pharmaceuticals following the publication of the BART study[12]. This study found
that though aprotinin reduced the amount of blood transfusion required by 70% in all patients, all cause mortality in the aprotinin group was 1.5 times higher than in the comparator group. This study followed two papers in 2006 which demonstrated that aprotinin caused renal dysfunction in adults, post-bypass surgery. [13,14]

4.2.7 Recombinant Human Factor VIIa

rFVIIa (Eptacog-alfa, or Novoseven®) is a relatively new treatment in PICU but has some theoretical basis for its use. Referring to Figure 7.1 (Initiation of the clotting cascade) tissue factor binds and activates Factor VII which directly activates Factor X which stimulates the final common pathway. In a patient who is bleeding it is then theoretically feasible to administer more Factor VIIa to induce faster clotting. In the paediatric critical care setting, there is limited evidence to support increasing use of rFVIIa. There have been individual case reports, and case series but there have been no randomised controlled studies undertaken. Doses expressed in children range from 40 micrograms/kg as a single dose up to 120 micrograms/kg as a single dose. Haematologists will usually recommend a dose of 60-90 micrograms/kg for intractable bleeding, repeated if necessary after two hours.

The risks of using rFVIIa are mainly an increased risk of thrombotic events (particular intracranial thrombosis.) This risk is particularly worrying when using rFVIIa in patients on ECMO who are bleeding, because they are already hypercoagulable. However, rFVIIa has been used safely in patients on ECMO[15] when the following precautions are taken:

- A fresh, blood-primed ECMO circuit is available immediately
- Perfusionists and ECMO team are on standby for urgent circuit change
- The drug is NOT injected DIRECTLY into the circuit, but injected into a vessel away from the circuit.

4.2.8 Citrate anticoagulation

The single most important component in the clotting cascade is the calcium ion. Calcium is consumed during the clotting process, and without it, clots will not form. Citrate chelates with calcium removing it from the circulation, and small quantities are added to blood products to prevent clotting. As a result of this there is
considerable interest in using citrate as an anticoagulant. Citrate anticoagulation was first described by Ward and Mehta in 1993[16]. Subsequently it has been studied in the anticoagulation of extracorporeal circuits during continuous renal replacement therapy.

In order to achieve citrate anticoagulation the following process is undertaken [17].

1. Measure the ionised calcium level of the patient (this can be done simply using a blood gas analyser.) Ionised calcium (iCa) is the only useful measure of citrate activity, as ionised calcium is available for chelation. Total calcium (as reported in formal blood results) includes protein bound calcium which is NOT available for citrate chelation.

2. Run a continuous infusion of acidified citrated dextrose (ACD) solution into the afferent limb of the filtration circuit. The dose and rate should be determined by the ionised calcium levels. iCa levels of <0.35 mmol/L will inhibit coagulation.

3. Calcium-citrate complexes are freely cleared by the filter.

4. Measure ionised calcium levels in the blood post-filter.

5. Infuse calcium into the efferent (“return”) limb of the filter circuit to replace calcium stores.

By removing calcium, the effect is a prolongation in the APTT, without the risks associated with systemic exposure to heparin which include auto-immune reactions, systemic anticoagulation and risk of bleeding. There are however limitations to using citrate anticoagulation:

- A small amount of citrate passes into the patient, but citrate dissociates to form citric acid which is rapidly metabolised in the liver and kidneys. Under normal functional circumstances, this metabolic process is so rapid, and the quantities of citrate in the systemic circulation so small that there is no detectable effect of citrate toxicity. However, in patients with a degree of hepatic impairment, citrate accumulation occurs characterised by metabolic acidosis OR alkalosis (citrate is metabolised to bicarbonate), hypocalcaemia and systemic anticoagulation.

- Logistical issues in the United Kingdom currently include the lack of a calcium-free haemofiltration fluid, and the difficulty in obtaining ACD solutions. There are some companies however who are currently developing solutions for citrate anticoagulation.

5. Monitoring Coagulation

The monitoring and measurement of coagulation has been standardised for many years. Most readily available markers are crude ratios of patient specific clotting characteristics measured against a laboratory standard. There are however some developments in the monitoring of coagulation, most interestingly in the near-patient setting.

**Prothrombin Time (PT)**

The PT is a measurement of the tissue factor pathway of the clotting cascade. Whole blood or plasma is taken and tissue factor is added. The time taken for the sample to clot is then measured optically. The usual time taken to clot is between 10 and 20 seconds. The PT is then used to calculate the INR.
International Normalised Ratio (INR)
The INR is a derived value using the PT of the patient (PT-test) and the PT of the laboratory standard (PT-normal.) The equation is:

\[
\text{INR} = \frac{\text{PT-test}}{\text{PT-normal}}
\]

Activated Partial Thromboplastin Time (APTT)
This measures both the contact activation pathway and the final common pathway. In the lab, an activator is added to trigger the contact activation pathway (usually kaolin) and the time taken for a thrombus to form is recorded. An APTT of between 20 and 40 seconds is considered “normal.” If on the first sample the APTT is raised, it’s fairly non-specific, thus further “mixing tests” are carried out. The first of the mixing tests is to dilute the sample 1:1 with fresh plasma. If on retest the APTT is still raised, then there is likely to be an inhibitor of the contact activation pathway present, usually heparin or antiphospholipid antibodies. If the clotting abnormality reverses on mixing, then there is likely a factor deficiency.

Aggregated Clotting Time
ACT is a near patient test that gives a crude clotting time in seconds. It tends to be used when clotting information is needed quicker than a lab can turn around formal tests and as such it tends to be used in those patients who are dependent on extracorporeal circulations (ECMO, Ventricular assist device (VAD) or CRRT.) A small quantity of blood is drawn up into a capillary tube containing an activator such as kaolin. The tube is inserted into a colorimeter with a digital read out. The ACT is the time taken for the blood to clot. Its on-going application as a clinically useful measurement is under some debate at present as research has shown that the ACT correlates poorly with the APTT, and newer more accurate technologies such as thromboelastography give much better information about the clotting process on a patient-by-patient basis.

Further Reading

Perioperative Systemic Haemostatic Agents
Mahdy AM, Webster NR; Br J Anaesth 2004; 93(6):842-858

Disseminated Intravascular Coagulation
Levi M; Crit Care Med 2007; 35(9):2191-2195

Bibliography

Monagle P, Chalmers E, Chan A et al.
Chest 2008 133:887-968

Rang & Dale’s Essential Pharmacology Chapter 23 – Coagulation and Haemostasis
Churchill Livingstone, 7th edition 2008
References


10. Li JS, Yow E, Berezny KY et al. “Dosing of Clopidogrel for Platelet Inhibition in Infants and Young Children (PICOLO Trial)” Circulation 2008 117:553-559


PIC SIG NPPG 322 © NPPG October 2011


19. Prophylaxis of Venous Thromboembolism SIGN Publication No. 62 October 2002


Case Studies

 Disclaimer
 All cases are only representative of patients who may present on PICU. The answers may be unit dependant and are only an indication of potential treatments and are the opinions of the authors. All treatments should be reviewed in line with your individual unit policies.

1. Cardiovascular – arrhythmias  Siân Edwards
2. Cardiovascular – shock  Siân Edwards
3. Renal – acute interstitial nephritis  Rhian Isaac
4. Endocrine – Diabetic ketoacidosis  Karen Bourne
5. Metabolic – Hyperammonaemia  Karen Bourne
6. Haematology - Anticoagulation  Adam Sutherland
7. Haematology- Sepsis  Adam Sutherland
8. Neurology – Status epilepticus  Sue Jarvis
9. Gastro-intestinal – Neonatal TPN  Venetia Horn
10. Respiratory – asthma  Siân Edwards
11. Respiratory – Pulmonary hypertension  Siân Edwards
12. Hepatology – acute liver failure  Penny North-Lewis
13. Hepatology – Varices  Penny North-Lewis
1. Cardiovascular Case – Arrhythmias

A 6 week old baby boy, ER, weighing 3.8 kg is admitted to your PICU with a mean blood pressure of 50 mm Hg and a heart rate between 250 - 300 bpm. His ECG looks like this:

Looking at his ECG, can you identify what sort of arrhythmia he may have?

What are the key features from this baby’s ECG, which can help with this diagnosis?

**The PICU medical team confirm the diagnosis of supraventricular tachycardia.**

What do you think they will try first?

If this doesn’t work, what treatment would be tried next?

**Adenosine is tried.** How does it work? When it is NOT recommended and why? How is it administered? And what drugs interact with adenosine?
ER successfully converts to sinus rhythm after the 3rd dose of adenosine. His ECG now looks like this:

Is this a normal ECG? If not, what are the abnormal features; and together with ER’s history what diagnosis may this lead you to?

Unfortunately after 12 hours his heart rate is back at 280 bpm, and his mean blood pressure is now lower at 25-30 mmHg.

The SHO mentions using digoxin, what is your response? What other options are there for treating his arrhythmia?

The SHO writes up a loading dose and then continuous IV infusion of amiodarone. The nurse looking after ER, wants some advice on how to administer amiodarone.

What do you advise?
Specimen answer

All cases are only representative of patients who may present on PICU. The answers may be unit dependant and are only an indication of potential treatments and are the opinions of the authors. All treatments should be reviewed in line with your individual unit policies.

Looking at his ECG, can you identify what sort of arrhythmia he may have?

Supraventricular Tachycardia

What are the key features from this baby’s ECG, which can help with this diagnosis?

- Heart rate 250 bpm +
- Narrow QRS complexes
- Abnormal or difficult to detect P waves

What do you think they will try first?

Vagal Manoeuvres: stimulating the vagus nerve - for an infant suggest ice to the mid-face

This doesn’t work, what treatment would be tried next?

IV Adenosine – it is not negatively inotropic so can be used safely in patients with hypotension

Adenosine is tried. How does it work? When it is NOT recommended and why? How is it administered? And what drugs interact with adenosine?

Adenosine blocks conduction through the AV node and breaks any re-entry circuit operating through the node, causing a period of asystole lasting 5 –15 seconds followed by sinus rhythm.

Adenosine should not be used in patients with second or third degree AV block and sick sinus syndrome (except in patients with a permanent pacemaker). It should be used with caution in patients with asthma due to the risk of severe bronchospasm. It is thought that adenosine can produce bronchoconstriction by enhancing IgE-dependent release of pre-formed mediators from mast cells. Adenosine should be used carefully in heart transplant patients as they are extremely sensitive to the effects of adenosine.
Due to the rapid metabolism of adenosine, it is usual to administer the dose rapidly over 2 to 3 seconds followed with a rapid saline (0.9%) flush to promote flow towards the central circulation (in the IV closest to the heart, as a rapid push with a 'saline chaser').

Central administration is preferred wherever possible, as due to its rapid metabolism adenosine is more effective and acts more quickly when administered in this way. Larger doses may be needed if given peripherally.

Doses will be escalated up (usually starting at 100 micrograms/kg and increase by 100 micrograms/kg per dose) given every 2 mins until either the SVT is terminated or the maximum dose is reached (<1month 300micrograms/kg; >1month 500 micrograms/kg)

Dipyridamole prevents adenosine degradation by blocking the uptake into cells and can potentiate the clinical effects of adenosine. Use 25% of the usual dose of adenosine.

Xanthines (theophylline, aminophylline and caffeine) antagonise the effects of adenosine.

Is this a normal ECG? If not, what are the abnormal features; and together with ER’s history what diagnosis may this lead you to?

*Not normal ECG.*

*Abnormal features: Presence of delta waves, Short PR interval*

*History:*
  *Age (most likely to have SVT associated with WPW in first 6 months)*
  *Sex (males> females)*

*Diagnosis: Wolff-Parkinson-White Syndrome (pre excitation)*

The SHO mentions using digoxin, what is your response? What other options are there for treating his arrhythmia?

*The SHO needs to talk to a consultant paediatric cardiologist as there are many issues to address.*

Digoxin should be avoided or used with extreme caution in patients with WPW syndrome as by shortening the refractory period in the accessory pathway, it may produce a "paradoxical" increase in ventricular fibrillation.

*IV amiodarone is the drug of choice in this situation as it is unlikely to compromise this patient’s cardiac function further. It works by prolonging the refractory period in the atria, ventricles and AV node.*

*If IV amiodarone is unsuccessful then cardioversion is an option.*
IV flecainide may be mentioned / used if the heart is structurally normal however is negatively inotropic, so in a patient who is haemodynamically compromised is best avoided.

The nurse looking after ER, wants some advice on how to administer amiodarone. What do you advise?

Amiodarone is usually administered by continuous infusion following a loading dose. This is necessary due to the long half life and large volume of distribution of amiodarone. The loading dose should be given over at least 30 minutes due to the risk of hypotension and bradycardia associated with fast rates of infusion, with many centres opting to administer over 2 – 4 hours. Amiodarone can only be diluted in 5% glucose and where possible should be given via a central line. It is recommended that amiodarone infusions be administered through non-PVC containing equipment. This is to minimise patient exposure to a substance called DEHP (di-2-ethylhexylphthalate) that may leach out of PVC-containing equipment in the presence of amiodarone. Plastipak® syringes do not contain PVC and PVC free giving sets are available.

Be aware that Amiodarone contains benzyl alcohol. There have been reports of fatal 'gasing syndrome' in neonates (hypotension, bradycardia and cardiovascular collapse) following the administration of intravenous solutions containing this preservative, and is particularly important if the child is on other medications that contain this preservative.
2. Cardiovascular - Shock

A 5 day old baby girl, AM, weighing 3kg is admitted to your PICU, intubated and ventilated.

PMH:
Normal vaginal delivery at 39 weeks (no prolonged rupture of the membranes); APGAR scores normal and feeding well.
Mother had no signs of sepsis
Day 4 became progressively more irritable, tachypnoeic and disinterested in feeding

Presented to A&E day 5:
Pale and sweaty, tachypnoeic (RR 80 – 90), tachycardic (HR 150), chest clear
Brachial pulses present, femoral pulses difficult to palpate
4 limb blood pressure, upper extremities easily recordable, lower extremities difficult to record
Resuscitated with fluid & antibiotics (IV ampicillin and gentamicin)
AM continued to deteriorate so intubated and transferred to PICU.

On admission to PICU:
On examination: pale, peripherally cool, centrally warm, poor urine output (<1ml/kg/hour), liver 3cm,
Right arm mean blood pressure 35 - 40mmHg & HR 170 in sinus rhythm
Toe – core gap of 10 degrees
Saturations: Pre duct (right hand) normal; Post duct (right foot) reduced

Blood gas:
- pH 7.19
- pCO2: 6.9mmHg
- HCO3: 18.0mmol/l
- Base excess: -9mmol/l
- Lactate 7.3mmol/l

What are the differential diagnoses for shock, and what are the clinical parameters that indicate that AM is suffering from shock?

Of these which are most likely in AM’s case? With this in mind, what steps should be taken to stabilise her condition?

An echocardiogram confirms that AM has a ‘coarctation of the aorta,’ and she is started on a dinoprostone infusion at 5 nanograms/kg/minute

What is a ‘coarctation’ of the aorta, and how will it have caused shock in this baby?
How will dinoprostone help to support her circulation?

What is the definitive treatment for this condition?

What post operative problems may she encounter?
Specimen Answer

All cases are only representative of patients who may present on PICU. The answers may be unit dependant and are only an indication of potential treatments and are the opinions of the authors. All treatments should be reviewed in line with your individual unit policies.

What are the differential diagnoses for shock, and what are the clinical parameters that indicate that AM is suffering from shock?

- Septic
- Cardiac
- Metabolic

Pale, peripherally cool (wide Toe Core gap; normal < 2 degrees), poor urine output, low blood pressure (normal mean 45 mmHg), Acidotic (normal pH: 7.3 – 7.45; base: -2 to +2; HCO3 22 - 26); High lactate (normal <2);

Of these which are most likely in AM’s case? With this in mind, what steps should be taken to stabilise her condition?

Metabolic causes of shock are relatively rare, so this leaves cardiac and sepsis as the differential diagnoses at this stage.

Treat possible underlying causes

AM is already on broad spectrum antibiotics which will cover infection as a cause, though minimal risk factors i.e. uncomplicated delivery; no maternal risk factors of note.

Cardiac conditions must be considered, so suggest starting a prostaglandin infusion.

Treatment of the resultant shock

The definitive treatment for shock is re-opening of the duct and reperfusion of distal (abdominal) organs (via dinoprostone or emergency surgery).

In the meantime support the heart:

(i) Optimise pre load (note that fluid resuscitation was carried out in A&E)
(ii) Inotropes should be used to support the heart. Choice will vary from centre to centre but usually dopamine or low dose adrenaline, dependant on line access
(iii) Correction of the acidosis (pH 7.19; base excess -9mmo/l) is indicated in severe shock. Acidosis impairs cardiac contractility and reduces inotropic affect of catecholamines It is probable that a decline in the number of beta-receptors on the cell surface contributes to contractile hyporesponsiveness to catecholamines during acidosis. Really you need to treat the underlying cause of the acidosis so that the body is then able to correct itself. As the PaCO2 is high this can be treated with ventilation. If all other measures fail administration of sodium bicarbonate will correct the pH but it will also result in an acute rise in pCO2 and respiratory support must be adequate to compensate for this.
An echocardiogram confirms that AM has a ‘coarctation of the aorta,’ and she is started on a dinoprostone infusion at 5 nanograms/kg/minute

What is a ‘coarctation’ of the aorta, and how will it have caused shock in this baby?

A coarctation is a narrowing of the aorta usually around the area where the ductus arteriosus meets the descending aorta (which supplies blood to the lower half of the body) from the pulmonary artery. Blood flow via the ductus bypasses the coarctation and therefore maintains adequate flow to the lower half of the body. In addition, the proximity of the open duct to the coarctation widens this narrow area reducing the ‘obstruction’ to flow and maintaining systemic blood flow.

Once the duct starts to close (anything from a few days to 2 weeks after birth) the coarctation becomes narrower, causing an obstruction to blood flow to the lower half of the body (right foot cold). In contrast blood flow to the upper half of the body (right hand normal) is maintained as the ascending aorta and arch (supplying the upper half of the body) come off before the narrowing. Cardiogenic shock may present when the ductus starts to close, as the left ventricle has to pump +++ against the obstruction. This increase in pressure can be poorly tolerated leading to acute heart failure and shock.

How will dinoprostone help to support her circulation?

Prostaglandin E2 is produced by the placenta to keep the ductus arteriosus open in utero. Therefore is follows that by exogenously administering this to the infant we can maintain the patency of the ductus arteriosus post birth. By keeping the ductus arteriosus open, we are able to reduce the obstruction maintaining a reasonable blood supply to the lower half of the body, and reduce the pressure on the left ventricle, thereby improving blood pressure and blood flow to the end organs.
What is the definitive treatment for this condition?

*Surgery (most commonly the treatment in severely ill infants, so likely necessary in this patient)*

---

**Surgical procedures for the correction of COA**

- End-to-end technique
- Left subclavian flap aortoplasty
- Aorta patch augmentation


*Percutaneous balloon angioplasty (rarely) can be used in some cases to good effect, but tend to be older children or adults with milder symptoms*  

What post operative problems may she encounter?

- Low cardiac output, particularly if pre operative LV failure
- Renal impairment: due to preoperative hypoperfusion of end organs
- Necrotising enterocolitis: risk of feeding in first 24 hours due to pre operative hypoperfusion of the gut
- Hypertension: Rare in neonates - tends to be in older children where the LV has been pumping against obstruction for some time (conditioned) & renin-angiotensin system activated by poor renal blood flow.
3. Renal – acute interstitial nephritis

**Patient:** Bobby 4 year old male, weight 15kg

**PC:** Rash, fever, ‘generalised aching’, very little urine output for last 24 hour, mum says that he has been passing blood yesterday.

**HPC:** Been to GP for ? chest infection

**PMH:** Nil of note

**DH:** amoxicillin course from GP 2 days ago, paracetamol and ibuprofen OTC

**Allergies:** Nil known

**OE:** Generalised rash- looks like hypersensitivity type reaction, Pyrexial, slightly confused

**Urinalysis:** white blood cells, red blood cells, eosinophils

**Relevant lab results:**
- Potassium 5.4mmol/L,
- Phosphate 3.2mmol/L,
- Urea 14.3mmol/L,
- Creatinine 183mmol/L

**Diagnosis:** acute interstitial nephritis

What should the clinician’s immediate actions be?

What is the estimated GFR?

What is the likely cause of the acute interstitial nephritis?

**The junior doctor asks you to recommend pain relief for Bobby.**

What would be your choice and why?

What advice should be given to the carer about future medication?

Would steroids be appropriate in this patient?
Specimen answer
All cases are only representative of patients who may present on PICU. The answers may be unit dependant and are only an indication of potential treatments and are the opinions of the authors. All treatments should be reviewed in line with your individual unit policies.

What should the clinician’s immediate actions be?
Fluid should be administered as necessary
Amoxicillin and the OTC ibuprofen should be stopped
The electrolyte disturbances will need correcting. ECG changes need to be assessed to decide on hyperkalemia treatment. Calcium resonium and potassium restrictions can be used if there are no ECG changes but if ECG then calcium gluconate and insulin/glucose therapy should be started.

What is the estimated GFR?

GFR can be calculated from the formula

\[ \text{GFR (ml/min/1.73m}^2) = \frac{49 \times \text{body length (cm)}}{\text{serum creatinine (micromole/L)}} \]

What is the likely cause of the acute interstitial nephritis?

Amoxicillin is the more likely as eosinophils are not usually seen in AIN due to NSAIDS

The junior doctor asks you to recommend pain relief for Bobby- what would be your choice and why?

NSAIDs should be avoided due to risk of further nephrotoxicity
Opioids metabolite are renally cleared so should not be recommended
Paracetamol is the drug of choice but if renal function deteriorates further need to cap frequency at TDS.

What advice should be given to the carer about future medication?

The carers should be advised to avoid pencillins, and be cautious with cephalosporins

Would steroids be appropriate in this patient?

If no improvement after removing the causative agent, a short course of prednisolone 1mg/kg/day should be considered.
4. Endocrine - Diabetic ketoacidosis

Patient: 11 year old male (TJ) 28kg

Past Medical History: Previously fit and well

Presenting History: 4 day history of lethargy and vomiting. Increasing confusion over last 24 hours.

On admission: GCS 13/15 on presentation to the Emergency Department. Diagnosis of DKA made following urinalysis results (++++ketones and glucose). A 10ml/kg sodium chloride 0.9% bolus was given for shock and this was repeated a further 3 times over the next hour (40 ml/kg in total). Dehydration was calculated at 5% and a maintenance infusion of sodium chloride 0.9% with 0.3% potassium was commenced at 75ml/hr. An insulin infusion was commenced at 0.1unit/kg/hour.

The patient was admitted to the ward but over the next few hours his GCS deteriorated to 9/15 which necessitated intubation for ventilation with transfer to PICU. A Mannitol 20% 5ml/kg (1g/kg) bolus was given before intubation and 2 further 10ml/kg sodium chloride 0.9% boluses after intubation. His dehydration was re-assessed and calculated at 7.5%.

The patient remained stable and over the next 24 hours, he improved and was extubated. He was discharged from PICU back to the ward the following day.

Blood Results:

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>8am</td>
<td>1pm</td>
<td>6pm</td>
</tr>
<tr>
<td>pH</td>
<td>6.8</td>
<td>6.99</td>
</tr>
<tr>
<td>K+</td>
<td>4.6</td>
<td>5.6</td>
</tr>
<tr>
<td>Glucose</td>
<td>35</td>
<td>24</td>
</tr>
</tbody>
</table>

Fluid therapy:
Day 1: Sodium Chloride 0.9% with 0.3% K+ @ 65.4ml/hr
Day 1/2: Sodium chloride 0.45% with glucose 5% with 0.3% K+ @ 48mls/hr
Day 2&3: Sodium chloride 0.45% with glucose 10% with 0.3% K+ @ 48mls/hr then 75mls/hr

Insulin Infusion;
Commenced at 0.1unit/kg/hr on day 1
Changed to 0.05units/kg/hour on day 2 (am)

Are the fluid rates correct?
Why was a mannitol bolus given?
What factors may have influenced the changing fluids and fluid rates?
What is the next step for insulin therapy?
Specimen answer

All cases are only representative of patients who may present on PICU. The answers may be unit dependant and are only an indication of potential treatments and are the opinions of the authors. All treatments should be reviewed in line with your individual unit policies.

Comment on the initial maintenance fluids. Are the fluid rates correct?

Fluid resuscitation with boluses of sodium chloride 0.9% will be required immediately. Maintenance fluid therapy should then be calculated taking the fluid boluses already administered into account. In addition extra volume will be required to replace the patient fluid deficit (given over 48 hours). Fluid deficit in litres can be calculated by multiplying the percentage of dehydration by the body weight (kg).

Replace over 48 hours, therefore

Maintenance fluids = 1660ml/day x 2 = 3320mls

Plus:

Deficit fluids for 5% dehydration (0.05 x 28 x1000) = 1400mls
Less resus fluids (40ml/kg) = 1120mls

= 280mls

= 3600mls over 48 hours = 75ml/hour.

Sodium chloride 0.9% is commenced initially. Glucose is then added when the serum glucose falls to below 14 mmol/L as can be seen on day 2 when the fluids are changed to sodium chloride 0.45% and glucose 5%. Potassium should be added to IV replacement fluids. Even if patient is not hypokalaemic, potassium levels will drop as insulin therapy is commenced.

Why was a mannitol bolus given?

Cerebral oedema is a serious consequence of DKA. The cause of cerebral oedema in children is not known as study results are inconsistent. It has been associated with the correction of acidosis using sodium bicarbonate and also with overhydration, for example, cerebral oedema presenting within hours of the onset of treatment is probably associated with fluid shifts into the CNS when extracellular osmolarity is reduced too quickly.

Intravenous mannitol is therefore given if mental status is worsening for the symptomatic treatment of cerebral oedema. It is an osmotic diuretic, increasing plasma osmolarity and maintaining the osmotic gradient between the brain and plasma.

What factors may have influenced the changing fluids and fluid rates?

Sodium chloride 0.45% with glucose 5% and 0.3% K+ was changed to glucose 10% to increase blood glucose levels. This allows the insulin infusion to be continued which is essential to ‘switch off’ ketogenesis.

When the patients GCS dropped on day 1, the replacement of deficit fluids was changed to be given over 72 hours after the suspicion of cerebral oedema.
Maintenance fluids were also restricted to 2/3 maintenance for this indication as overhydration has been indicated as a cause of cerebral oedema.

Replace over 72 hours, therefore
\[
\text{2/3 x Maintenance fluids} = 1106\text{ml/day} \times 3 = 3318\text{mls}
\]
\[
\text{Plus;}
\]
\[
\text{Deficit fluids for 7.5% dehydration} (0.075 \times 28 \times 1000) = 2100\text{mls}
\]
\[
\text{Less resus fluids (60ml/kg)} = 1680\text{mls}
\]
\[
= 420\text{mls}
\]
\[
= 3738\text{mls over 72 hours} = 51.9\text{ml/hour.}
\]

Consider other drug treatment e.g. morphine and midazolam were commenced to facilitate ventilation both infusions running at 1ml/hour. This volume should also be subtracted from fluid allowance. Also 2.8ml/hour insulin.

Post extubation, the patient’s fluid allowance was increased back to 100% of maintenance. Further increases in the hourly fluid rate were also made as the morphine and midazolam infusions were stopped.

What is the next step for insulin therapy?

Intravenous insulin is usually continued until the patients pH is >7.3. or bicarbonate levels are > 15 mmol/L. This will take longer than the normalisation of blood glucose levels. Once the pH is > 7.3 and blood glucose is < 14mmol/L, the insulin infusion may be reduced to 0.05units/kg/hour, oral fluids may then be introduced when the patient has improved and wants to eat. When food is tolerated, a subcutaneous insulin regimen should be commenced and IV fluids stopped. The insulin infusion should be discontinued 10 - 60 minutes after the first subcutaneous injection (depending on the type of SC insulin given) to avoid rebound hyperglycaemia.
5. Endocrine - Hyperammonaemia

Patient: 4 day old male infant, 3.5kg
Past Medical History: born at term in good condition, discharged after 24 hours. Uncomplicated pregnancy,
Presenting History: Poor feeding and reduced level of consciousness
Seizures and apnoeas developed and the patient was transferred to PICU

On PICU admission:
The patient became less responsive and had gasping respiration. He was ventilated and stabilised. Phenobarbitone was commenced following a further twitching episode and cefotaxime, aciclovir and amoxicillin were commenced to cover for neonatal meningitis/encephalitis. Investigations revealed raised ammonia levels and the following therapy was commenced;

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arginine</td>
<td>2100mg in 21ml glucose 10% over 90 mins, then 700mg in 12 ml glucose 10% @ 1.5ml/hr</td>
</tr>
<tr>
<td>Sodium benzoate</td>
<td>875mg in 18ml glucose 10% over 90 mins, then 1750mg in 36ml glucose 10% @ 1.5ml/hr</td>
</tr>
<tr>
<td>Sodium phenylbutyrate</td>
<td>875mg in 18ml glucose 10% over 90 mins, then 1750mg in 36ml glucose 10% @ 1.5ml/hr</td>
</tr>
</tbody>
</table>

A full septic screen was performed and was negative. Ammonia levels remained initially increased and CVVH was performed for ~ 36 hours.

<table>
<thead>
<tr>
<th>Day (time)</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ammonia</td>
<td>742 (12.00)</td>
<td>490 (8.15)</td>
<td>60 (11.30)</td>
<td>24 (13.55)</td>
<td>14 (8.15)</td>
</tr>
<tr>
<td>CVVH</td>
<td>start 22.45</td>
<td>-------------</td>
<td>stop 09.30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Further investigations led to a diagnosis of citrullinaemia. He was weaned off ventilation on day 3 of his PICU admission. Suitable oral feeds were introduced and his drugs were changed to oral therapy. He was discharged to a medical ward on day 5.

Why are arginine, sodium benzoate and sodium phenylbutyrate commenced? Are the doses appropriate?
How will these drugs be prepared and administered? Consider potential problems with fluid restriction and limited IV access.
What are the main side effects of arginine, sodium benzoate and sodium phenylbutyrate?
What role does CVVH have?
What oral therapy should be commenced? Is there a role for carglumic acid in this patient?
Specimen Answer

All cases are only representative of patients who may present on PICU. The answers may be unit dependant and are only an indication of potential treatments and are the opinions of the authors. All treatments should be reviewed in line with your individual unit policies.

Why are arginine, sodium benzoate and sodium phenylbutyrate commenced? Are the doses appropriate?

In all urea cycle disorders the early instigation of treatment is critical to avoid permanent neurological injury. The time span from the first symptoms to irreversible brain damage is short (may be less than 1 day), and therapy to reduce ammonia levels should be commenced immediately if ammonia is greater than 200micromol/l. The aim of initial treatment is to normalise ammonia levels within 8 to 12 hours. Arginine will optimise the function of the urea cycle whereas sodium phenylbutyrate and sodium benzoate provide an alternative pathway for nitrogen elimination.

Doses for initial treatment are stated in the BNFc;

Arginine; 600mg/kg over 90 minutes then 600mg/kg/day
Sodium benzoate; 250mg/kg over 90 minutes then 500mg/kg/day
Sodium phenylbutyrate; 250mg/kg over 90 minutes then 500mg/kg/day

The doses prescribed are therefore appropriate. A diagnosis of citrullinaemia was suspected and so arginine was commenced at this higher dose. If a diagnosis is unknown then it may have been more appropriate to prescribe a loading dose of 200mg/kg followed by 200mg/kg/day until further results were available.

How will these drugs be prepared and administered? Consider potential problems with fluid restriction and limited IV access.

Arginine;
The BNFc recommends that arginine is diluted to a concentration of 20mg/ml with a maximum concentration of 100mg/ml. It is our practice at Sheffield Children’s Hospital to dilute the loading dose to 100mg/ml and then the continuous infusion to 20mg/ml. If fluid volumes are too high then the continuous infusion can be concentrated to 100mg/ml.

Sodium benzoate and sodium phenylbutyrate;
The BNFc recommends that these drugs are diluted to a concentration of 20mg/ml with a maximum concentration of 50mg/ml. It is our practice at Sheffield Children’s Hospital to dilute the loading dose to 50mg/ml and then the continuous infusion to 20mg/ml. If fluid volumes are too high then the continuous infusion can be concentrated to 50mg/ml.
Although various infusion fluids are compatible with these drugs, it is desirable to use glucose 10% as a diluent. Glucose 10% (or a higher concentration of glucose if central access is available) should be used for maintenance fluids to interrupt the catabolic state present in these patients and promote anabolism.

Fluid volumes are unlikely to be a problem initially in this patient as any excess fluid can be removed through the CVVH circuit.

It is likely this patient will not have enough IV access to allow each drug to be administered via a single lumen. For example, this patient is receiving IV boluses (e.g. antibiotics), short IV infusions (e.g. aciclovir) and numerous continuous IV infusions (e.g. morphine and midazolam to facilitate ventilation). It may therefore be advantageous to run these drugs together to free up IV lumens. There is anecdotal evidence to suggest that arginine can be infused at Y-site with sodium benzoate and sodium phenylbutyrate.

What are the main side effects of arginine, sodium benzoate and sodium phenylbutyrate?

**Sodium Benzoate;**
The most common side effects are nausea, vomiting, anorexia, irritability, lethargy, coma. Reported symptoms of overdose include renal tubular dysfunction, hypokalaemia, hypocalcaemia, and metabolic acidosis. Premature infants have been reported to be at risk of metabolic acidosis and kernicterus.

**Sodium Phenylbutyrate;**
Reported side effects include decreased appetite, body odour, taste disturbances; less commonly nausea, vomiting, abdominal pain, peptic ulcer, pancreatitis, rectal bleeding, arrhythmia, oedema, syncope, depression, headache, rash, weight gain, renal tubular acidosis, aplastic anaemia, ecchymoses

Sodium benzoate and sodium phenylbutyrate contain significant amounts of sodium; therefore, they should be used with caution in children with congestive heart failure, renal insufficiency and clinical conditions involving sodium retention with oedema.

Sodium benzoate 500mg contains 3.5mmol sodium
Sodium phenylbutyrate 500mg contains 2.7mmol sodium

**Arginine;**
Nausea, vomiting, flushing, headache, numbness, hypotension, headache, hyperchloraemic metabolic acidosis and local venous irritation have been associated with intravenous therapy. Elevated plasma-potassium concentrations have been reported in uraemic patients and arginine should therefore be used with caution in patients with renal disease or anuria.
What role does CVVH have?

Continuous renal replacement therapy with continuous veno-venous haemofiltration (CVVH) is commenced to assist with the removal of toxins, in this case ammonia. It can be initiated rapidly and will achieve glomerular filtration rates of up to 30mls/min (depending on the circuit used). Generally CVVH will be commenced if the ammonia level fails to fall in the first 4 hours after the start of therapy and is usually continued until the ammonia levels fall below 50 micromol/l.

If the patients’ renal function remains normal, then drug doses will not have to be reduced while the patient is on CVVH. In fact there is an argument to suggest that doses should actually be increased to account for the additive glomerular filtration rate from the patient and CVVH circuit. Due to a lack of data in practice, as long as the patient does not have impaired renal function, drug doses are left the same as pre CVVH.

Fluid balance is not so critical while the patient is on CVVH as excess fluid volumes can be removed during haemofiltration.

Electrolytes must be monitored carefully and replacements made for those lost in the ultrafiltrate solution.

What oral therapy should be commenced? Is there a role for carglumic acid in this patient?

In this case, all three drugs can be converted to oral therapy. Doses are given in the BNF for children. These oral preparations however are not licensed and liquids will have to be purchased from a specials manufacturer. Plans will therefore have to be made for attaining further supplies on a long term basis.

Sodium benzoate, sodium phenylbutyrate and arginine all have an unpleasant taste. They may need to be mixed with milk, fruit juice or feeds to be made more palatable.

Carglumic acid is an oral drug licensed for the treatment of hyperammonaemia due to N-acetyl glutamate synthase (NAGS) deficiency. NAGS deficiency is not strictly a urea cycle disorder but it is a related disorder of ammonia detoxification. Carglumic acid is an analogue of N-acetylglutamate which is the activator of carbamoyl phosphate synthetase, the first enzyme of the urea cycle.

There are anecdotal reports to support the administration of carglumic acid in related urea cycle disorders although the evidence is limited and hard to evaluate due to the effects of co-administered hyperammonaemia therapy. Carglumic acid may have a role in the initial emergency period if, for example intravenous access is unavailable but as there is no information on long term administration, its use long term for urea cycle disorders cannot be recommended.
6. Haematology - Anticoagulation

JB is a 7-month old male who returned from cardiac theatre last night following a definitive repair of pulmonary atresia. There was intra-operative coronary damage which was noticed on reperfusion diagnosed by ST elevation on ECG and an epicardial ECHO. A coronary stent was placed to maintain perfusion to the myocardium. The patient was returned from theatre with the chest open and a PD catheter in situ, but not on ECMO. You are seeing him for the first time the morning after surgery. He is stable on the following therapy:

- Alfentanil 1mcg/kg/min
- Midazolam 100mcg/kg/hr
- Sodium nitroprusside 2mcg/kg/min
- Adrenaline 0.02mcg/kg/min
- Inhaled Nitric Oxide therapy
- Heparin 25units/kg/hr. The last APTT was 40s

Propose a heparin sliding scale for APTT range 20 up to 100.

After two dose increments in 10 hours, the APTT is low at 30.
What action testing would you suggest?

Day 2: The chest is closed, but quickly reopened due to excessive bleeding and a cardiac tamponade. The APTT is only 40, so is not thought to be related to anticoagulation. The cardiac surgeon refuses to take the patient back to theatre for re-exploration and suggests antifibrinolytics.
Which anti-fibrinolytic you would choose
How would you adjust your anticoagulant strategy?
How long would you continue antifibrinolytics for?

Day 2, 12 hours later. Antifibrinolytics haven’t worked, the surgeon is still unwilling to re-explore and blood loss continues. JB has required 100ml/kg of blood products in the last 8 hours.
What medical treatment options are likely?
What precautions should be taken?

Day 6: Everything is more settled, and heparin is providing adequate anticoagulation. Ventilation is being weaned, feeds are being restarted and his chest was closed 24 hours ago. This morning’s blood count shows a drop in platelets from 180 to 65. The suspicion is Heparin Induced Thrombocytopenia, and further investigations have been requested.
Plan for a change in anticoagulation

Day 10: The HITS screen was negative. Heparin therapy was continued. Ventilation has weaned JB has been extubated and started on oral anticoagulation
Which oral anticoagulants will be chosen?
How will they be monitored?
How long will they be continued?
Specimen Answer

All cases are only representative of patients who may present on PICU. The answers may be unit dependant and are only an indication of potential treatments and are the opinions of the authors. All treatments should be reviewed in line with your individual unit policies.

Propose a heparin sliding scale for APTT range 20 up to 100

Loading dose of 50-75 units/kg over 20 minutes, followed by a continuous infusion of 20 units/kg/hr. Check APTT after four hours and make the following changes:

<table>
<thead>
<tr>
<th>APTT ratio</th>
<th>Infusion</th>
<th>Recheck APTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5</td>
<td>STOP for 1-2hrs then restart at 50% previous rate</td>
<td>4hrs</td>
</tr>
<tr>
<td>4.1 – 5</td>
<td>Reduce by 20%</td>
<td>4hrs</td>
</tr>
<tr>
<td>3.1 – 4</td>
<td>Reduce by 10%</td>
<td>4hrs</td>
</tr>
<tr>
<td>2.6 – 3</td>
<td>Reduce by 5%</td>
<td>4hrs</td>
</tr>
<tr>
<td>1.5 – 2.5</td>
<td>No change</td>
<td>24hrs</td>
</tr>
<tr>
<td>1.2 – 1.4</td>
<td>Bolus 50 units/kg then increase by 10%</td>
<td>4hrs</td>
</tr>
<tr>
<td>&lt;1.2</td>
<td>Bolus 50 units/kg then increase by 30%</td>
<td>4hrs</td>
</tr>
</tbody>
</table>

What action testing would you suggest?

Antithrombin III levels (should be at least 80% of lab standard)

Which anti-fibrinolytic would you choose?

Risk benefit assessment – is the patient at high risk of bleeding complications and how much blood product has been required in the last 4-6 hrs. Would defer aprotinin on risk:benefit. Therefore Tranexamic acid

How would you adjust your anticoagulant strategy?

Though there are warnings about heparin and antifibrinolytics (increased risk of bleeding) in practice this is seldom clinically significant. Monitor.

How long would you continue antifibrinolytics for?

Review 24hrly. Minimum period necessary

What medical treatment options are likely?

Novo7 90mcg/kg stat. Repeat in two hours if necessary

What precautions should be taken?

Consultant decision and present at point of administration

If on extracorporeal circuit, do not administer bolus into the circuit – have perfusionist and replacement circuit on standby.
Plan for a change in anticoagulation

Hirudin – dependent on formulary. Most common is lepirudin: 400mcg/kg stat then 150mcg/kg/hr adjusted according to APTT:
  APTT <2.5 then increase by 20%
  APTT >2.5 stop infusion for 2hrs and restart at 50% of previous rate.

Which oral anticoagulants will be chosen?

  Aspirin +/- clopidogrel

How will they be monitored?

  No monitoring required

How long will they be continued?

  6-12 months to allow epithelialisation
7. Haematology – sepsis

AS is a 12 year old, 40kg girl admitted overnight with frank meningococcal sepsis. She is profoundly hypotensive requiring multiple inotropes and fluid. She has florid *purpura fulminans* across her lower extremities which have required bilateral fasciotomies. She has not passed urine for 8 hours, and she is on CVVHD-F running at 90ml/kg/hr for “toxin clearance.” Her medication is as follows:

- Adrenaline 0.5mcg/kg/min
- Noradrenaline 1mcg/kg/min
- Vasopressin 0.015units/kg/min
- Alfentanil 2mcg/kg/min
- Midazolam 70mcg/kg/hr
- Atracurium 5mcg/kg/min
- Maintenance fluid (0.9% sodium chloride, 5% glucose)
- Cefotaxime 2g QDS
- Heparin 40units/kg/hr into filter (avoiding systemic anticoagulation.)

18 hrs post-admission: She is deteriorating and has DIC. The consultant looking after her asks about Activated Protein C (Xigris®) (aPC)

Does this patient fit the NICE recommendations for aPC?

Review the literature pertaining to aPC in adults and children and formulate advice for your consultant.

**Having been successfully talked out of aPC he decides on a heparin-free strategy for the extracorporeal circuit.**

What are the options?
Outline administration, monitoring and management the methods.

**Day 2: The extracorporeal circuit keeps clotting off. Conventional heparin-free anti-coagulation is abandoned. The consultant wants to use citrate but this has not been previously used on this unit.**
Discuss the pros and cons of citrate anti-coagulation.
What considerations need to be taken into account before you try to source the materials to do it?
Which professional groups in your hospital would you liaise with?

**Day 4: AS’s monitoring parameters are improving and CVVHD-F is stopped. Inotropes are weaned, but there is still a residual prolongation of the clotting time, with the PT raised. Fibrinogen is normal.**
What does the raised PT, normal fibrinogen indicate?
How would you expect this to be managed?
How long would therapy continue?

**Day 7: AS has weaned off ventilation and inotropes. She is now ready to be extubated and discharged to the infectious diseases unit.**
Specimen Answer
All cases are only representative of patients who may present on PICU. The answers may be unit dependant and are only an indication of potential treatments and are the opinions of the authors. All treatments should be reviewed in line with your individual unit policies.

Does this patient fit the NICE recommendations for aPC?

She is under 18, so no.
However if AS was an adult then she would probably qualify for APC as she has
Multiorgan failure
Fair chance of survival
Maximal intensive care
No history of major surgery, recent traumatic CPR, brain bleeds or other major contraindication.

Review the literature pertaining to aPC in adults and children and formulate advice for your consultant.

PROWESS
Statistically significant improvement in 28 day survival post APC, with a NNT of 15.

ADDRESS
No benefit in patients with a low risk of death (APACHE II score <25 with 1 organ failure) and an increased risk of bleeding.

RESOLVE
Higher blood product requirement in aPC group resulted in early closure of trial before sufficient numbers recruited for evidence of efficacy. Note that blood product limit was only 10ml/kg/24hrs

Having been successfully talked out of aPC he decides on a heparin-free strategy for the extracorporeal circuit

What are the options?

Insulating the filter
Pre-dilution, high flux
Epoprostenol

Outline administration, monitoring and management the methods involving a medicine.

Epoprostenol at 2nanog/kg/min titrating to 5nanog/kg/min maximum if required into the arterial side of the filter. Stop at end of dialysis. Monitor blood pressure and heart rate. Monitor for signs of extravasation (pH = 10.5)

Discuss the pros and cons of citrate anti-coagulation.

Pro: Heparin free, easy to reverse effect
Con: Requires close monitoring of calcium
Requires source of citrate
Requires calcium free dialysate

What considerations need to be taken into account before you try to source the materials to do it?

Arrangements for monitoring – labs, nursing/medical staff (do your blood gas analysers do ionised calcium?)

Which professional groups in your hospital would you liaise with?
Renal team, pharmacy procurement, chair of the Medicines Committee, Haematology, Biochemistry

What does the raised PT, normal fibrinogen indicate?

DIC

How would you expect this to be managed?

Products and vitamin K as required.

How long would therapy continue?

Blood products as indicated

72hrs (1-3 doses) vitamin K
8. Neurology - Status epilepticus

AB is a 4 years and 10 months old boy who has been brought to Accident and Emergency by ambulance following a 999 call by his mother. He has had a prolonged generalised convulsion which had started approximately 20 minutes before his arrival in A & E. He has been given 1 dose of rectal diazepam by the ambulance crew just prior to admission.

Past Medical History
AB has no previous history of seizures
He attends infant school and has normal development having reached all milestones at an appropriate time
No known allergies
All vaccinations have been given as recommended schedule
There has been no recent travel abroad

Family History
AB lives with his mother, father and one elder sister who are all well.
There is no family history of seizures.

Current medication
He is not on any regular medications

On examination in A&E
Weight 18Kg
Height 108cm

AB is still fitting on arrival in A & E. There are no signs of rash
The patient was treated according to the status epilepticus algorithm in the NICE guidance and his seizures stopped after 36 minutes but he was showing signs of respiratory compromise and was admitted to PICU for further observation.

What drugs will he have received?

What investigations should be undertaken and what treatment considered on his admission?

Which drugs would you expect to be prescribed on admission to PICU?

What investigations would you expect to be undertaken to help with diagnosis?
Specimen Answer – Status epilepticus

All cases are only representative of patients who may present on PICU. The answers may be unit dependant and are only an indication of potential treatments and are the opinions of the authors. All treatments should be reviewed in line with your individual unit policies.

There is a detailed algorithm for the treatment of children with prolonged seizures and it is important that this is followed because there is evidence that permanent brain damage can occur in patients who have seizures lasting over 60 minutes and potentially after 30 minutes. When cerebral metabolic needs exceed available oxygen, glucose, and metabolic substrates, neuronal destruction can occur and may be irreversible.

This patient was admitted by ambulance and had been given one dose of rectal diazepam and it is important to realise that this patient has already reached the second step in the algorithm. (See below). The important parts to be recognised from a pharmaceutical aspect are the method of delivery of each drug and the dose. Once the patient has arrived in A&E intravenous access is needed in order to administer some of the drugs. There are two pathways dependent on the success at obtaining IV access and if this has not been achieved within 10 minutes of the initial dose of diazepam, a dose of rectal paraldehyde should be given.

As IV access was obtained, the second dose of a benzodiazepine would be given as lorazepam 1.8mg over 30-60 seconds (0.1mg/kg). The administration of a second dose of benzodiazepines should prompt the monitoring of respiration as respiratory depression can occur.

The seizures still continued 10 minutes after the administration of the lorazepam, and so phenytoin 18mg/kg as an IV infusion should be given over 20 minutes. The dose should be 324mg or 6.48mls of 50mg/ml injection which will need to be given via a syringe driver over 20 minutes (maximum rate of infusion is 1mg/kg/min).

Patients being given IV phenytoin should have blood pressure and ECG monitoring in place as phenytoin can cause arrhythmias, hypotension and cardiovascular collapse. Respiratory rate monitoring also needs to continue as phenytoin can add to the reduction in respiratory function from the benzodiazepines. The injection site should be examined as phenytoin is alkaline and can cause tissue damage.

The patient should receive a dose of rectal paraldehyde at the same time as the phenytoin infusion. The dose of 0.4ml/kg (7.2mls) should be diluted with an equal volume of olive oil and given rectally. Arachis oil should be avoided because of the risk of anaphylaxis in patients with a peanut allergy.

The seizures stopped 36 minutes after arrival at A&E and so the patient did not receive thiopentone and was not anaesthetised for assisted ventilation. He was admitted to Paediatric Intensive Care as he had respiratory compromise.

Following the administration of a loading dose of phenytoin it is good practice to take blood to ensure that a therapeutic level has been achieved. The recommendation is for a level to be taken 2 hours after the completion of the infusion. If this level is within range (10-20mg/L) then maintenance dose of 2.5 to 5mg/kg twice a day should be started 12 hours after loading dose is complete. If the level is <10mg/L a further loading dose of 5mg/kg over 20 minutes should be given at once and the maintenance dose started after 8 hours.
This patient had no previous history of seizures and therefore the ambulance and A&E staff did not need to take into consideration any previous medications that he may have been on. Caution should be taken with patients who have had convulsions previously as they may already be taking phenytoin and will therefore need loading with phenobarbitone instead of phenytoin. Many parents of children with epilepsy may have supplies of rectal diazepam or buccal midazolam at home so that they can administer immediately to try to avoid prolonged seizures. This may result in large doses of benzodiazepines and respiratory depression. A medication history should be taken from carers accompanying the child to A&E when possible.

Because of the seriousness of delaying treatment in cases of meningitis and encephalitis, treatment needs to be started as soon as the diagnosis is suspected. Any patient admitted with status epilepticus has to be treated for both these diseases until another diagnosis is confirmed or there is good evidence to stop the treatment.

One UK study showed that of patients presenting with their first episode of febrile convulsive status epilepticus 17% have bacterial meningitis. The causative organisms that could be responsible for this in a child (excluding neonatal infections) are Haemophilus influenzae (HiB), Streptococcal pneumoniae (Pneumococcus), or Neisseria menigitidis (Meningococcus).

Of these HiB, meningococcal C and, since 2006, pneumococcus vaccines are part of the primary immunisation schedule but this does not exclude the possibility that patients can present with meningitis resulting from infections from these organisms. Vaccination failures can happen and only approximately 90% of patients will receive their full vaccination course. It is important to check the immunisation status of patients so that vaccination failures can be reported. Meningococcal and pneumococcal both have several serotypes and the vaccines do not provide protection against all of them.

In the UK the recommended antibiotics used to treat meningitis with all three of these organisms is cefotaxime (or ceftriaxone) alone. Ceftriaxone should be avoided in unstable patients, particularly neonates, who may require infusions containing calcium, including TPN. Patients who have travelled abroad just before presentation may be infected with organisms with a different resistance pattern and the microbiologist should be consulted for continuing treatment.

In the acute situation in which a patient has presented in A&E with convulsive status epilepticus the treatment should include cefotaxime at a high dose of 50mg/kg four times a day. AB would receive 900mg four times a day by IV injection. The treatment should be started immediately without waiting for cultures and sensitivities as delay in treating can lead to major morbidity and mortality.

Herpes simplex encephalitis should also be included in the differential diagnosis for patients being admitted with decreased level of consciousness. The symptoms of this are more difficult to identify and many patients will be treated with a short course of IV aciclovir without having a herpes infection. However the long-term morbidity of this disease is greatly reduced if aciclovir is started early. Studies to determine the dose have shown that a higher dose is required and the recommended dose for a patient of AB’s age is 500mg/m2 every 8 hours. The surface area can be calculated
from nomograms (available in the BNF for children) and for AB will be 0.73 m² which will give a dose of 365 mg every 8 hours. This must be diluted to 5 mg/ml and given over one hour. The concentration can be higher (25 mg/ml) if there is central access.

Phenytoin maintenance should be continued until the patient has been assessed by a neurologist and other causes of his prolonged seizure have been eliminated. For a first prolonged febrile convulsion the recommendation is that anti-epileptic treatment should not be given on discharge from hospital.

Paracetamol can be given when required if the patient is distressed on waking and shows sign of discomfort. This should be given orally if possible or alternatively as a suppository or as an IV infusion. The rectal dose is less reliable and has a longer onset of action and the IV infusion should only be used when neither of the other routes is available as it is expensive and needs to be given over 20 minutes.

Lumbar puncture is only undertaken if the patient is clinically appropriate as well as having no signs of cerebral oedema because there is a risk of causing brain herniation “coning”. Some of the contraindications for lumbar puncture are

- Coma
- Signs of raised intracranial pressure
- Cardiovascular compromise / shock
- Respiratory compromise
- Focal neurological signs or seizures
- Recent seizures (within 30 minutes).
- Coagulopathy/thrombocytopenia
- Local infection (in the area where an LP would be performed)

The febrile child with purpura where meningococcal infection is suspected.

The advantage of an early lumbar puncture is the possibility of having specimens of the infecting organism which can be identified by culture. Once the antibiotics have been given the chances of growing the bacteria are greatly reduced. However the use of PCR (polymerase chain reaction) to identify organisms from their DNA after they have been killed allows the LP to be delayed until the patient can be seen to behave appropriately and respond normally. Although CT scan can show some abnormalities in the brain it is not good at demonstrating raised intracranial pressure and therefore a lumbar puncture should not be done until the patient is awake. The PCR results may take several days to be available and the aciclovir should be continued until a negative result is obtained. Bacterial meningitis can be excluded if there are no white cells in the CSF on lumbar puncture and the glucose and protein are normal. If there are signs of bacterial infection in the CSF then again a PCR should be requested looking for the causative organism as this is important for epidemiological data as well as helping to decide the length of course of the antibiotics and the potential for the disease to result from a vaccine failure. In the long term it is important to know if the patient has had meningitis as there are implications for long term sequelae such as hearing loss, which should be monitored.
9. Gastrointestinal - Neonatal parenteral nutrition

ST is a neonate delivered at 34 weeks gestation by emergency caesarean section due to severe IUGR. He develops NEC at the age of 4 weeks and is treated conservatively for NEC with IV antibiotics, NBM for at least 10 days and commenced on TPN.

Weight 1.77kg

What is the most appropriate TPN formulation for this patient?

What would be the most appropriate IV access for this patient?

How long will it take build up to full requirements?

After 2 weeks, enteral feeds are recommenced.

What enteral feed would you suggest and why?

Unfortunately on starting enteral feeds the ST develops a distended abdomen and recurrence of NEC. The patient undergoes surgery where intermittent NEC is found along the length of the small intestine. The necrotic intestine is resected, the ileocaecal valve is left intact and an end to end anastomosis performed. Approx 30cm of small intestine remain after surgery.

What is the long term prognosis for this infant?
What parameters would you want to monitor closely and supplement in the TPN?
What measures would you use to help prevent liver damage?
What drugs may this infant to be prescribed?
Specimen answer – Neonatal TPN

All cases are only representative of patients who may present on PICU. The answers may be unit dependant and are only an indication of potential treatments and are the opinions of the authors. All treatments should be reviewed in line with your individual unit policies.

What is the most appropriate TPN formulation for this patient?

Tailor made regimen to ensure full complement of calories, electrolytes, trace elements and vitamins

What is the most appropriate IV access for this patient?

Central IV access would be the most appropriate for this patient to enable full nutritional requirements to be met and to reduce any potential risks from peripheral administration of PN. Thrombophlebitis and extravasation injuries can occur from peripheral administration of high glucose and electrolyte concentrations.

How long will it take build up to full requirements?

This depends on local policy but at GOS, it takes four days to build up to full requirements. This does depend on fluid requirements, glucose tolerance and IV access.

E.g. day 1, 1g/kg lipid, 11g/kg carbohydrate, 0.2g/kg nitrogen
   Day 2, 2g/kg lipid, 14g/kg glucose, 0.32g/kg nitrogen
   Day 3, 3g/kg lipid, 16g/kg glucose, 0.4g/kg nitrogen
   Day 4, 3g/kg lipid, 18g/kg glucose, and 0.48g/kg nitrogen

Check lipid tolerance by triglyceride and cholesterol monitoring- most prems and neonates at GOS receive 3g/kg/day.

What enteral feed would you suggest and why?

Expressed breast milk (EBM) or hydrolysed feeds e. g Neocate
Breast milk is rich in immunoprotective factors and growth factors

What is the long-term prognosis for this infant?

In a premature infant < 30 weeks gestation, normal length of small intestine is between 100-120cm
In a term infant, the small bowel length is 200-250cm. In adults the small bowel length is thought to be between 250-800cm in length
Up to 2 years of age, there will be growth as well as adaptation of the small bowel
Prognosis for this patient is ok but depends on the adaptation post resection
Generally < 25cm have a poor prognosis but there are case reports of infants surviving with as little as 11cm of proximal small bowel but only if the ileocaecal valve was still intact
Clinical factors associated with prolonged parenteral nutrition requirements include the following:

- If there is < 40cm of small bowel intact
- No ileocaecal valve. (The ileocaecal valve is important in preventing bacterial overgrowth as it stops bacteria refluxing from the large bowel into the small)
- Bowel adaptation (ileum has greater adaptability than the jejunum)
- Dysmotility
- Residual bowel
- Colon resection
- Bacterial overgrowth (Bacterial overgrowth is associated with translocation and sepsis)

What parameters would you want to monitor closely and supplement in the TPN?

- Urine and electrolytes especially urine sodium (to maintain growth and to check total body stores of sodium) to counterbalance stoma or gut losses.
- Magnesium and calcium may also need adjusting
- Liver function tests as cholestatic liver disease common in infants on long term parenteral nutrition
- Trace elements especially zinc, selenium, copper. Supplementation depends on area resected
- If the terminal ileum has been resected, B12 will need to be supplemented as it is absorbed in this area of the small bowel but additional supplementation should not be necessary until approximately 2 years of life due to neonatal reserves and reasonable levels of B12 in TPN
- Bile salts are absorbed at the terminal ileum so there will be an increased requirement for fat soluble vitamins if this area is resected

What measures would you use to help prevent liver damage?

- Trophic feeds from 1ml per hour, to maintain the integrity of gut mucosa and prevent bacterial translocation
- Cyclical PN over between 12 – 16 hours
- Ursodeoxycholic acid to improve biliary flow in cholestatic liver disease
- Lipids three times per week in cholestatic liver disease to promote lipid clearance

What drugs may this infant to be prescribed?

- Ranitidine or Omeprazole/Lansoprazole as increased acid very common in the first year post resection
- Loperamide to enhance small bowel absorption due to decreased transit time
- Antibiotics to reduce bacterial overgrowth and perhaps bacterial translocation
- Prokinetics e.g. Domperidone for dysmotile guts
- Ursodeoxycholic acid as above
10. Respiratory - Status Asthmaticus

JM, a 4yr old, 16 kg, known asthmatic girl is transferred to PICU. She initially presented to A&E with significant audible wheeze, breathless and tachycardia. In A&E she received Oxygen via a close fitting facemask and inhaled salbutamol via an MDI + spacer + facemask up to 10 puffs. Inhaled salbutamol was repeated 30 minutes later with no response. Nebulised ipratropium was added every 30 minutes, and she was given a bolus dose of IV salbutamol and a dose of IV hydrocortisone. Her condition did not improve so she was admitted to PICU.

Following a normal blood count and chest X-ray, a preliminary diagnosis of status asthmaticus is made.

What is Status Asthmaticus?

What is the evidence for giving inhaled versus nebulised B2 agonist?

What is your opinion on the addition of multiple doses of a nebulised anticholinergic in this scenario?

On PICU a course of IV hydrocortisone is continued as well as IV salbutamol infusion at a dose of 1 – 5 mcg/kg/min via a peripheral line. She was also commenced on antibiotics due to suspicion of community-acquired pneumonia. Due to her penicillin allergy they decide on a one week course of erythromycin.

Discuss the use of IV versus oral steroids and the length of course needed.

Regarding salbutamol, what problems can you foresee with this patient?

JM fails to improve and the registrar asks your advice on the addition of aminophylline.

How does it exert its effect?
What potential problems might there be in JM?

There is also talk on the ward round of magnesium sulphate.

What is your experience of using magnesium?
Which route and dose do you recommend? Alone or in combination? What is the evidence?
Do you agree with the use of an antibiotic in acute asthma attack? Any comments on the choice of erythromycin?
Specimen answer – status asthmaticus

All cases are only representative of patients who may present on PICU. The answers may be unit dependant and are only an indication of potential treatments and are the opinions of the authors. All treatments should be reviewed in line with your individual unit policies.

What is Status Asthmaticus?

A prolonged, severe asthma attack that does not respond to standard treatment, which can be life threatening. In practical terms it is a child not responding to initial doses of nebulised bronchodilators and corticosteroids.

What is the evidence for giving inhaled versus nebulised B2 agonist?

Continuous nebulised B2 agonists are of no greater benefit than the use of frequent intermittent doses in the same total hourly dosage. Children receiving B2 agonists via MDI + spacer are less likely to suffer tachycardia and hypoxia compared with children given the same agent via the nebulised route. By using spacer and mask parents can see that treatment can be started at home, a nebuliser is not necessary.

What is your opinion on the addition of multiple doses of a nebulised anticholinergic in this scenario?

The role of simultaneous and repeated use of inhaled anticholinergics and B2 agonists in the acute phase is well established. Repeated nebulised doses are recommended early in treatment repeated every 20-30 mins. Frequency should be reduced as clinical improvement occurs.

Discuss the use of IV versus oral steroids and the length of course needed.

Early use of steroids is recommended. Oral and IV steroids are reported to be of similar efficacy with IV route recommended particularly in severely affected children unable to retain oral medication, critically ill or unconscious.

Dose = 50mg three times daily adjusted according to response, can increase to 4 hourly.

Short course of up to 3 days should be sufficient and with this short length there is no need to taper the dose at the end of treatment.

Inhaled steroids should only be initiated as part of long-term management plan and not in preference to short course.

Change to oral steroids (prednisolone 2mg/kg mane) once patient is tolerating oral feeds.

Regarding salbutamol, what problems can you foresee with this patient?

The patient has a peripheral line inserted but no central venous access, so the maximum concentration allowed for solution is 200micrograms/ml:
PICU preference is to dilute 3mg/kg i.e. 48mg in 50ml and run at 1ml/hr = 1mcg/kg/min but unless a central line is inserted the maximum concentration that should be used is 10mg in 50ml. To give 1mcg/kg/min you would need to run the infusion at 4.8ml/hr. This volume of fluid sometimes becomes unacceptable and often a central line needs to be inserted if treatment needs to continue.

Salbutamol is compatible with saline and glucose and incompatible with aminophylline.

Salbutamol is compatible with potassium chloride at a Y site or in a well mixed bag, though avoid adding to salbutamol in the same solution as it is more difficult to titrate doses of potassium and salbutamol accordingly. Potassium infusion may be run at a maximum rate of 0.5mmol/kg/hr.

Hypokalaemia is always a risk with salbutamol but especially with high intravenous doses. Careful monitoring of arterial blood gases is warranted. Commence potassium infusion concurrently and recheck potassium gas after three hours. Particular caution is advised in acute severe asthma as this effect may be potentiated by hypoxia and by concomitant treatment with xanthine derivatives such as aminophylline, steroids and diuretics.

Tachycardia may limit the dose used.

JM fails to improve and the registrar asks your advice on the addition of aminophylline. How does it exert its effect? What potential problems might there be in JM?

Aminophylline is a xanthine derivative which competitively inhibits phosphodiesterase resulting in increased levels of cyclic adenine monophosphate (cAMP). This is thought to be responsible for most of its effects; including: relaxation of the smooth muscle of the respiratory tract, suppression of the response of airways to stimuli and pulmonary dilation.

Evidence suggests addition of aminophylline to salbutamol and steroids improves lung function in the acute phase. However there is no apparent reduction in symptoms, number of nebulised treatment or length of hospital stay. There is no clear consensus on its place in therapy i.e. whether it should be used first or second line compared with the addition of salbutamol but generally the role of aminophylline is most likely in severe acute exacerbations where response to maximized therapy is poor.

When initiating aminophylline it is important to consider whether JM was previously been taking theophylline as a loading dose may not be required. In addition JM has been prescribed erythromycin, which is an enzyme inhibitor. This may elevate levels of aminophylline so it is important to monitor levels. Levels may be taken 6 hours after starting the infusion (aiming for 10-20mg/l). Nausea and vomiting and tachycardias are common signs of toxicity.

Other potential problems for JM are the fact that salbutamol and aminophylline are incompatible so lines may become an issue, and potentiation of hypokalaemia with salbutamol.
There is also talk on the ward round of magnesium sulphate. What is your experience of using magnesium? Which route and dose do you recommend? Alone or in combination? What is the evidence?

*Use of magnesium sulphate is another of numerous treatment options available during acute exacerbations.* Current evidence does not support routine use in all patients but it does appear safe and beneficial in patients who present with severe acute asthma. However less is known about the inhaled route. It is thought to work by causing upregulation of beta-receptors, thus regularly used in combination with salbutamol. It may also cause a reduction in the neutrophilic burst associated with the inflammatory response. Benefits include improved pulmonary function and reduced hospital admissions but quality good quality evidence is lacking to provide a definitive conclusion.

Do you agree with the use of an antibiotic in acute asthma attack? Any comments on the choice of erythromycin?

*An acute asthma attack may be exacerbated by a viral URTI, and so antibiotics are often prescribed despite questionable efficacy.* Evidence is lacking as to whether treatment with antibiotics is effective without proven evidence of infection such as abnormal white cell count or signs of consolidation on the chest X-ray.

*Azithromycin is better tolerated with less potential for interaction with aminophylline but is only available as an oral preparation, which the patient may not tolerate.*
11. Respiratory - Pulmonary Hypertension

PG is an 8 month old girl with Down’s Syndrome. She has just undergone surgery for an Atrioventricular Septal Defect (AVSD) and been admitted to PICU. Prior to her surgery she had pulmonary arterial hypertension as a result of her heart condition and upper airway obstruction.

On the ward round the following morning you hear that she still has pulmonary hypertension.

How would you define pulmonary hypertension?

PG had pulmonary arterial hypertension pre-surgery secondary to congenital heart disease (AVSD) and a degree of upper airway obstruction.

Explain how this causes pulmonary hypertension.

What are the other causes of pulmonary hypertension?

PG still has pulmonary hypertension post op. Why?

PG is not absorbing at present.

What options are there to manage PG’s pulmonary hypertension whilst she is acutely unwell? Consider sedation, ventilation etc. as well as specific therapies.

After 72 hours PG’s condition starts to stabilise and she is tolerating enteral feeds. However the cardiologists feel there is still a degree of pulmonary hypertension that needs treating. What oral therapies are available to treat pulmonary hypertension?
Specimen answer- Pulmonary hypertension

All cases are only representative of patients who may present on PICU. The answers may be unit dependant and are only an indication of potential treatments and are the opinions of the authors. All treatments should be reviewed in line with your individual unit policies.

How would you define pulmonary hypertension?

_Pulmonary hypertension is defined as a mean pulmonary artery pressure greater than 25mm Hg at rest, or greater than 30mm Hg during exercise (WHO 1998)_

PG had pulmonary arterial hypertension pre-surgery secondary to congenital heart disease (AVSD) and a degree of upper airway obstruction. Explain how this causes pulmonary hypertension

An AVSD is the most common congenital heart defect found in children with Down’s Syndrome, accounting for 50% of the total. In its complete form there is a hole in the wall between the atria and a hole in the wall between the ventricles, and one common valve between the two atria and the two ventricles. Because of the high pressure in the left ventricle, blood is forced through the holes in the septum when the ventricle contracts, thus increasing the pressure in the right ventricle. This increased pressure results in excess blood flow to the lungs and the body’s natural reaction to this, is to constrict the blood vessels in the lungs in an effort to limit this excess blood flow.
pulmonary hypertension. The longer it takes for the defect to be repaired the more chance that the pulmonary hypertension will be irreversible. This occurs because over a period of time, this narrowing of the pulmonary arteries increases due to thickening in the surrounding muscle due to the increased workload, and also the closure of smaller lung arteries. These changes reduce the blood flow into the lungs, and increase the pressure needed by the right ventricle to pump blood into the lungs to be oxygenated. This will cause progressive RV failure and eventually death. There is also the fact that the high pulmonary blood flow creates shear stress and subsequent endothelial dysfunction (imbalance between endogenous vasodilators e.g. prostacyclin and nitric oxide and vasoconstrictors e.g. Thromboxane A2 and Endothelin). Other complications include arrhythmias and emboli.

PG also has a degree of upper airway obstruction (associated with Down’s), this results in retention of CO2 in the lungs, which in itself acts as pulmonary vasoconstrictor, further increasing the pressure in the pulmonary arteries.

And finally PG has Down’s Syndrome which in itself is thought to increase the risk of pulmonary hypertension.

What are the other causes of pulmonary hypertension?
As mentioned previously the musculature within the pulmonary vasculature would have developed to the extent that even with the lesion corrected and the pulmonary blood flow reduced the pressure within the vessels would not reduce immediately. This is coupled with the effects of cardiopulmonary bypass that also serve to raise pulmonary vascular resistance e.g. cytokines causing endothelial dysfunction, microemboli, vasoconstriction, atelectasis and adrenergic events.

PG is not absorbing at present.

What options are there to manage PG’s pulmonary hypertension whilst she is acutely unwell? Consider sedation, ventilation etc. as well as specific therapies.
Sedation/Neuromuscular Blockade is used to minimise anxiety and stress that can precipitate pulmonary hypertensive crisis, by reducing sympathetic outflow and therefore reducing pulmonary vascular resistance (PVR). Fentanyl is often used instead of Morphine in this situation as it is more potent and because histamine release is less. It is also good practice to give a bolus dose before suctioning to prevent a sudden rise in PVR. However there is no evidence comparing the two opioids in this situation and therefore this practice is only based on experience.

Ventilation should be used to minimise acidosis and ‘blow off’ excess CO₂, which is a vasoconstrictor. This is usually attained using conventional ventilation and aiming for normocapnia. It is important that the tidal volume is not too high as the pressure generated will collapse the vessels, and not too low that the lungs collapse. Historically “hyperventilation” was used to aggressively lower the CO₂ however the significant lung damage that occurred as a result means this is not now done. Remember oxygen is a pulmonary vasodilator, though sustained high oxygen levels should be avoided. High Frequency Oscillation is used when conventional ventilation fails (e.g. if atelectasis or acute lung injury) as this minimises further injury caused by pressures and aims to recruit more of the lung in gas exchange.

Sodium bicarbonate. As mentioned above CO₂ is a vasoconstrictor, so ideally a moderate alkalosis is permitted aiming for pH 7.45 – 7.55. Generally this is a respiratory alkalosis, but if needed sodium bicarbonate infusions may be used.

Nitric oxide is a vasodilator that when delivered by inhalation selectively distributes across the alveoli to the pulmonary vascular smooth muscle. Because of its rapid inactivation by haemoglobin, inhaled NO (iNO) can achieve selective pulmonary vasodilatation without the unwanted effect of systemic hypotension.

There is good physiological data and clinical experience to support a trial of iNO as a specific pulmonary vasodilator in patients experiencing acute, severe pulmonary hypertension following congenital heart surgery. There is insufficient evidence to support the prophylactic use of iNO in children thought to be at risk of pulmonary hypertension following congenital heart surgery.

Response to iNO treatment should be gauged by evidence of immediate haemodynamic improvement, by a substantial fall in PA pressure, fall in transpulmonary gradient. In some centres iNO is discontinued within 30 minutes for any child in whom positive haemodynamic responses are not elicited. The recommended starting dose is 20 ppm, weaned rapidly down to 5 –10 ppm. Thereafter reverse dose-response titration should be undertaken daily and the child maintained on lowest effective dose. Abrupt discontinuation of iNO can lead to rebound pulmonary hypertension. It is thought that this effect may be due to a reduced production of endogenous NO and reduced capacity to rapidly generate cGMP when iNO is stopped. This may be caused by negative feedback inhibition by iNO therefore the dose should be weaned. When dose is approximately 1ppm a trial off iNO should be attempted with 5 minutes pre-oxygenation at a higher FiO₂.
Milrinone, Dobutamine, Epoprostenol and Dipyridamole are systemic vasodilators that can be given intravenously. However their use on PICU for pulmonary hypertension is often limited by systemic hypotension

Alternatively Iloprost/Epoprostenol may be nebulised. This achieves selective vasodilation to the lungs, however systemic hypotension can still occur and is dose limiting. Care should also be taken in administration as staff may experience side effects from the drug released into the environment e.g. headaches. For this reason it should be vented out of a window using elephant tubing, as it cannot be scavenged and filters have doubtful efficacy. Iloprost is more stable then epoprostenol and has a longer half-life.

ECMO can also be considered in a suitable centre.

After 72 hours PG’s condition starts to stabilise and she is tolerating enteral feeds. However the cardiologists feel there is still a degree of pulmonary hypertension that needs treating. What oral therapies are available to treat pulmonary hypertension?

Calcium channel blockers such as nifedipine and amlodipine, may be useful but have largely been superseded by the newer more selective therapies. Use may be limited by systemic hypotension

Sildenafil is a selective inhibitor of Phosphodiesterase-5 (PDE-5). PDE-5 catalyses the hydrolysis of cGMP to GMP thereby lowering cGMP levels. By inhibiting this enzyme, cellular levels of cGMP are increased potentiating vascular smooth muscle relaxation, particularly in the lungs where PDE-5 is found in high concentrations\(^1\). This is thought to result in a selective reduction in pulmonary blood pressure without affecting the systemic blood pressure.

There are no randomised controlled trials investigating the use of sildenafil for pulmonary hypertension in children, however a few case reports/series have noted that sildenafil appears to be safe and may be beneficial.

Sildenafil may also be useful in ameliorating the effects of inhaled nitric oxide (iNO) withdrawal – rebound pulmonary hypertension

Bosentan acts as a competitive antagonist and blocks endothelin receptors on vascular endothelium and smooth muscle. Patients with PAH have elevated lung tissue and plasma concentrations of endothelin, a potent vasoconstrictor. According to the results of a retrospective analysis of 86 patients in WHO functional classes I to IV; either idiopathic or associated with congenital heart or connective tissue disease bosentan appears effective and safe for treating pulmonary arterial hypertension (PAH) in children. Unlicensed in children under 12 years. Cost Implications!! 62.5 mg, net price 56-tab pack = £1541.00; 125 mg, 56-tab pack = £1541.00

Interactions

Bosentan may increase the metabolism, via CYP isoenzymes, of Sildenafil. Sildenafil may increase the serum concentration of Bosentan
12. Hepatology – acute liver failure

A 10 year old boy with known epilepsy who has been on phenytoin for the last 18 months is admitted to PICU on a Sunday evening following multiple prolonged seizures needing sedation and ventilatory support. His LFTs the next morning show a markedly raised ALT of 2450 IU/L and an INR of 1.7. His serum bilirubin, alkaline phosphatase and albumin are within the normal range.

What type of liver picture does a raised ALT and INR suggest?

Why might his ALT be raised?

What clinical course would you expect him to follow in terms of his liver function?

What drugs should be started in a child with this picture of acute liver failure?

What considerations need to be given to the choice and dose of anticonvulsant therapy?
Specimen answer – Acute liver failure

All cases are only representative of patients who may present on PICU. The answers may be unit dependant and are only an indication of potential treatments and are the opinions of the authors. All treatments should be reviewed in line with your individual unit policies.

What type of liver picture does a raised ALT and INR suggest?

Raised transaminases occur when hepatocytes are damaged and the cell contents released. A level of 2450 IU/L suggests an acute insult to the liver which has damaged a large number of hepatocytes in one go - i.e. acute hepatitis. The increase in INR reflects the hepatocyte damage - hepatocytes are essential for the production of clotting factors and the INR will increase very quickly in response to hepatocyte damage. If the INR and ALT continued to rise then this would be acute liver failure.

Why might his ALT be raised?

Some antiepileptics are known to cause hepatotoxicity and this should be considered e.g. phenytoin can cause acute hepatitis but this is extremely rare and would be most likely in the first couple of months of treatment.

In this child the most likely cause would be the prolonged fit causing hypoxic damage to the liver. Acute hypoxia causes a rapid destruction of hepatocytes and a high ALT.

What clinical course would you expect him to follow in terms of his liver function?

Acute hypoxic damage to the liver is usually quick to resolve once blood flow is restored. The liver has an amazing ability to regenerate and within 24-48 hours the ALT should start to fall. This type of liver damage is sometimes followed by a secondary rise in bilirubin caused by the hepatocytes having been temporarily out of action and so not excreting bilirubin or bile salts properly. The bili may rise up to 200 or so and will then fall over the next few days. Assuming nutrition is maintained the albumin should remain normal.

What drugs should be started in a child with this picture of acute liver failure?

Acetylcysteine 100mg/kg/day to improve hepatic microcirculation and as an antioxidant

Vitamin K 0.3mg/kg od IV for 3 days to correct clotting (unlikely to help in the context of acute liver failure as the problem isn’t related to vitamin K deficiency but to hepatocyte failure, but do it anyway)

Ranitidine 1mg/kg tds IV for gastric protection whilst clotting deranged

Antibiotics and antifungals are unlikely to be needed for this patient as the cause of ALF is known and isn’t related to infection (unless there is something else to indicate that it is). However if the LFTs worsen then consider adding in to prevent infection if the liver becomes necrotic.

What considerations need to be given to the choice and dose of anticonvulsant therapy?

In the initial phase any drug which is hepatically metabolised may have reduced clearance due to hepatocyte failure, however it is more important to ensure that therapeutic levels of anticonvulsants are attained to stop the fitting and prevent further hypoxic damage and allow the liver to recover. I would use normal doses
of drugs in this child being very aware of the likely side effects that might occur in the event of poor clearance i.e. increased sedation with benzodiazepines, and titrate against those effects.
13. Hepatology – Varices

James is a 4 year old boy with alpha-1-antitrypsin deficiency. He is under the regular review of a liver unit and is known to have cirrhosis. He is brought into A&E by ambulance because of a severe episode of haematemesis caused by a variceal bleed. He is ventilated and sedated and sent for an emergency OGD where the bleeding points on his oesophagus are sclerosed. His mother says he has been unwell with a cold for the last 2 or 3 days.

What drug treatment should be started in light of his bleeding varices?

His LFTs on the day of admission are:
ALT 65IU/L, SBr 89micromol/L, ALP 370IU/L, INR 2.1, Albumin 31g/L
And the next day are:
ALT 64IU/L, SBr 105micromol/L, ALP 345 IU/L, INR 2.3, Albumin 29g/L

Can you explain these numbers?

How might the standard PICU drugs (sedation, analgesia) be affected by his liver disease and what amendments might you recommend?
Specimen answer - Varices

All cases are only representative of patients who may present on PICU. The answers may be unit dependant and are only an indication of potential treatments and are the opinions of the authors. All treatments should be reviewed in line with your individual unit policies.

What drug treatment should be started in light of his bleeding varices?
- **Octreotide 1mcg/kg bolus then 1-3mcg/kg/hour** (reduces splanchnic blood pressure and helps stop variceal bleeding in children)
- **Omeprazole 0.5-1mg/kg bd IV**
- **Antibiotics – co-amoxiclav** - high risk of infection

His LFTs on the day of admission are:
- ALT 65IU/L, SBr 89micromol/L, ALP 370IU/L, INR 2.1, Albumin 31g/L
And the next day are:
- ALT 64IU/L, SBr 105micromol/L, ALP 345 IU/L, INR 2.3, Albumin 29g/L

Can you explain these numbers?
- His ALT is nearly normal but this reflects cirrhosis - the liver has insufficient hepatocytes left to release large amounts of ALT.
- The bilirubin is high because he is cirrhotic and the liver is unable to clear bilirubin normally. It rises following an oesophageal bleed because the breakdown of a large amount of haemoglobin cause an increase in the production of bilirubin which the liver is unable to deal with.
- The Alk Phos is normal for his age because this disease is not a biliary disorder, however as the cirrhosis progresses it will start to affect the biliary tree and the Alk Phos is likely to go up in time.
- The INR is raised indicating that the liver cells are not synthesising enough clotting factors.
- The albumin is low suggesting a chronic liver disease with long term cirrhosis.

A cirrhotic patient can be ‘compensated’ for a long time despite severe cirrhosis which means that the remaining hepatocytes are just about managing to perform all the functions of the liver. However an event such as an infection (a cold in this case) can put just enough pressure on the liver to push the patient into ‘decompensated cirrhosis’. When this happens the child reaches end stage liver failure and the clotting goes off and they may bleed, the albumin falls further and they may develop ascites, they may become encephalopathic. If the underlying cause is removed e.g the infection is treated, then a child may revert to compensated cirrhosis.

How might the standard PICU drugs (sedation, analgesia) be affected by his liver disease and what amendments might you recommend?
- We know that this child has deranged synthetic function (raised INR and bilirubin and low albumin) and is therefore likely to have impaired metabolic function. He also has portal hypertension (hence the variceal bleed) which would impair first pass metabolism of some oral drugs. His albumin is low which would have an impact on protein binding. He is also at risk of side effects of some drugs due to
his coagulopathy and the fact that he is cirrhotic which makes him at risk of developing encephalopathy. Morphine and midazolam are both hepatically metabolised and both have sedating side effects (obviously!). It is likely that James will have impaired metabolism of both drugs and consequently delayed clearance. Children like this may take 2-3 times longer to wake up from standard PICU sedation if the doses are not adjusted. Suggest loading with the normal dose then running at the lowest possible dose to maintain sedation scores as required. May even occasionally stop sedation to see how long it takes for them to wake up. Whilst he is ventilated being overdosed is unlikely to be a problem, however delays in getting him off the ventilator because he takes so long to wake up could be.