Mind Maps for Medical Students

This brand new revision aid has been designed specifically to help medical students memorise essential clinical facts, invaluable throughout medical studies and particularly useful in the pressurised run-up to final exams. Over 100 maps are organised by body system, with a concluding section of miscellaneous examples.

Key features:
• Proven – content presented as mind maps, an established tool in education and known to improve memory recall among students
• Flexible – ideal when preparing to study a topic for the first time, when reviewing it at the end of a module or attachment, and for making project and revision plans
• Adaptable – use the maps in the book directly, or as a guide to prepare your own
• Systems-based – in line with medical course structure
• Relevant – by a medical student for medical students

Olivia Smith is a fourth year medical student, The Hull York Medical School, UK
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In memory of Michael J. Webb

It would be wrong for me not to acknowledge the man to whom this book is dedicated. I know that without Michael’s care and tireless patience I would never have undertaken, nor believed that I could complete, a project such as this.
Mind Maps for Medical Students represents an industrious and valuable piece of work from an undergraduate student. But perhaps I should start by saying what it is not. It is neither a textbook nor a definitive information source for students encountering a topic for the first time. It cannot give a comprehensive account of every topic listed and some information will change as the world of medicine rapidly evolves.

So what does Mind Maps for Medical Students offer? The author has provided rapid revision notes covering a broad range of medical topics, ideally suited to students and early postgraduates revising for exams. This distillation of knowledge will save many hours of note taking for other students. The format will appeal to those who construct their knowledge in logical sequences and the layout will allow the reader to add notes and annotations as information changes or to add a local context.

The author is to be congratulated on providing so much information in such a concise format and I hope that many others will be rewarded by her endeavours.

Colin H. Jones
MBChB, MD, FRCP, Master of Education
Associate Dean of Assessment, The Hull York Medical School, UK
I am extremely grateful to Dr. A.G.W. Smith and Dr. D. Maleknasr for their continued support, help and guidance with this project.
The idea for this book began when I was in my second year of medical school. It was only then that I truly realised the full enormity of knowledge that medical students have to retain.

I envisaged a book presenting relevant material in a simplified way that would only enhance and consolidate what I had already learned from textbooks, lectures and the ward, particularly in the countdown to exams. Then, as chance would have it, I was granted the opportunity to make this a reality.

This book is an attempt to cover the main topics faced by medical students from day one, capturing and presenting the facts in a clear manner that is even sufficient for final year level. Even its format has been designed with the student in mind – it is pocket sized and has titles covering the definition of the disease, causes, investigations, treatments and complications to aid recall. The intention of Mind Maps for Medical Students is not to substitute for larger texts but to complement them and, with that in mind, I hope that it assists your understanding.

Finally, I hope that readers enjoy this book and I wish you all the best of luck with your medical and future studies.

Olivia Smith
Fourth year medical student, The Hull York Medical School, UK
5-ASA  5-aminosalicylic acid
ABG  arterial blood gas
ACE  angiotensin converting enzyme
ACE-III  Addenbrooke's Cognitive Examination
ACTH  adrenocorticotrophic hormone
ADH  antidiuretic hormone
ADL  activity of daily living
ADP  adenosine diphosphate
ADPKD  autosomal dominant polycystic kidney disease
AF  atrial fibrillation
Ag  antigen
AIDS  acquired immunodeficiency syndrome
AKI  acute kidney injury
ALL  acute lymphoblastic leukaemia
AML  acute myeloid leukaemia
ANA  antinuclear antibody
ANCA  antineutrophil cytoplasmic antibody
APML  acute promyelocytic leukaemia
Apo  apolipoprotein
APP  amyloid precursor protein
ARB  angiotensin receptor blocker
ARDS  acute respiratory distress syndrome
ARPKD  autosomal recessive polycystic kidney disease
ASD  atrial septal defect
ATP  adenosine triphosphate
AV  atrioventricular
BBB  blood–brain barrier
BMI  body mass index
BNP  brain natriuretic peptide
BP  blood pressure
BPH  benign prostatic hypertrophy
CABG  coronary artery bypass graft
CADASIL  cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy
CCP  cyclic citrullinated peptide
CEA  carcinoembryonic antigen
CHF  congestive heart failure
CJD  Creutzfeldt–Jakob disease
CKI  chronic kidney injury
CLI  chronic lymphocytic leukaemia
CML  chronic myeloid leukaemia
CMV  cytomegalovirus
CNS  central nervous system
COPD  chronic obstructive pulmonary disease
CRC  colorectal cancer
CRP  C-reactive protein
CSF  cerebrospinal fluid
CT  computed tomography
CTS  carpal tunnel syndrome
CXR  chest X-ray
DaTSCAN  ioflupane ^{123}I for injection
DCIS  ductal carcinoma in situ
DEXA  dual-energy X-ray scan
DFA  direct fluorescent antibody test
DHT  dihydrotestosterone
DI  diabetes insipidus
DIC  disseminated intravascular coagulation
DIP  distal interphalangeal (joint)
DM  diabetes mellitus
DMARD  disease modifying antirheumatic drug
DNA  deoxyribonucleic acid
DPP  dipeptidyl peptidase
<table>
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<td>diffusion-weighted MRI</td>
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<td>Epstein–Barr virus</td>
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<td>electrocardiography</td>
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<td>echocardiography</td>
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<td>electroencephalography</td>
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<td>enzyme immunoassay</td>
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<td>ELISA</td>
<td>enzyme linked immunosorbent assay</td>
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<td>EMB</td>
<td>eosin methylene blue</td>
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<td>EMG</td>
<td>electromyography</td>
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<td>EPEC</td>
<td>enteropathogenic <em>E. coli</em></td>
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<td>EPO</td>
<td>erythropoietin</td>
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<td>ERCP</td>
<td>endoscopic retrograde cholangiopancreatography</td>
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<td>ESKD</td>
<td>end-stage kidney disease</td>
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<td>ESR</td>
<td>erythrocyte sedimentation rate</td>
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<td>ESWL</td>
<td>extracorporeal shock wave lithotripsy</td>
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<td>FAP</td>
<td>familial adenomatous polyposis</td>
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<td>FBC</td>
<td>full blood count</td>
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<td>FEV1</td>
<td>forced expiratory volume</td>
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<tr>
<td>FSH</td>
<td>follicle stimulating hormone</td>
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<td>FTA</td>
<td>fluorescent treponemal antibody absorption</td>
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<td>FVC</td>
<td>forced vital capacity</td>
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<td>GABA</td>
<td>gamma-aminobutyric acid</td>
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<td>GBM</td>
<td>glomerular basement membrane</td>
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<tr>
<td>(c)GFR</td>
<td>(calculated) glomerular filtration rate</td>
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<td>GH</td>
<td>growth hormone</td>
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<tr>
<td>GHRH</td>
<td>growth hormone releasing hormone</td>
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<td>GI</td>
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<td>gastrointestinal tract</td>
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<td>GLP</td>
<td>glucagon-like peptide</td>
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<td>GnRH</td>
<td>gonadotrophin releasing hormone</td>
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<td>glycoprotein</td>
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<tr>
<td>GTN</td>
<td>glyceryl trinitrate</td>
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<td>HAART</td>
<td>highly active antiretroviral therapy</td>
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<td>HAV</td>
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<tr>
<td>Hb</td>
<td>haemoglobin</td>
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<td>HbAlc</td>
<td>glycated haemoglobin</td>
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<td>HBV</td>
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<td>hepatocellular carcinoma</td>
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<td>HCV</td>
<td>hepatitis C virus</td>
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<tr>
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<td>hepatitis D virus</td>
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<tr>
<td>HEV</td>
<td>hepatitis E virus</td>
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<td>HGPRT</td>
<td>hypoxanthine–guanine phosphoribosyltransferase</td>
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<tr>
<td>HHV</td>
<td>human herpes virus</td>
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<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
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<td>HNPCC</td>
<td>hereditary nonpolyposis colorectal cancer</td>
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<td>HPV</td>
<td>human papilloma virus</td>
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<td>HTLV-1</td>
<td>human T-lymphotrophic virus-1</td>
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<td>HUS</td>
<td>haemolytic uraemic syndrome</td>
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<td>IBD</td>
<td>inflammatory bowel disease</td>
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<td>IBS</td>
<td>irritable bowel syndrome</td>
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<td>ICU</td>
<td>intensive care unit</td>
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<td>IFA</td>
<td>immunofluorescence assay</td>
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<td>Ig</td>
<td>immunoglobulin</td>
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<td>IGF</td>
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<td>IL</td>
<td>interleukin</td>
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<tr>
<td>IPSS</td>
<td>International Prostate Symptom Score</td>
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<td>IV</td>
<td>intravenous</td>
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<td>IVU</td>
<td>intravenous urogram</td>
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<td>JVP</td>
<td>jugular venous pressure</td>
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### Abbreviations

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<tr>
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<td>KUB</td>
<td>kidney, ureter, bladder</td>
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<td>LBBB</td>
<td>left bundle branch block</td>
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<td>LFTs</td>
<td>liver function tests</td>
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<td>LH</td>
<td>luteinising hormone</td>
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<tr>
<td>LHRH</td>
<td>luteinising hormone-releasing hormone</td>
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<tr>
<td>LMN</td>
<td>lower motor neuron</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>LTOT</td>
<td>long-term oxygen therapy</td>
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<td>LVF</td>
<td>left ventricular failure</td>
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<td>MALT</td>
<td>mucosa-associated lymphoid tissue (lymphoma)</td>
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<td>MAO</td>
<td>monoamine oxidase</td>
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<td>MCH</td>
<td>mean corpuscular haemoglobin</td>
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<td>MCPJ</td>
<td>metacarpophalangeal joint</td>
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<tr>
<td>MCV</td>
<td>mean corpuscular volume</td>
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<tr>
<td>MEN</td>
<td>multiple endocrine neoplasia (syndrome)</td>
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<td>MI</td>
<td>myocardial infarction</td>
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<td>MLCK</td>
<td>myosin light chain kinase</td>
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<td>MMR</td>
<td>mumps, measles, rubella</td>
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<td>MND</td>
<td>motor neuron disease</td>
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<td>MOA</td>
<td>mode of action</td>
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<td>magnetic resonance imaging</td>
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<td>multiple sclerosis</td>
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<td>NICE</td>
<td>National Institute for Health and Care Excellence</td>
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<td>noninvasive ventilation</td>
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<td>non-nucleoside reverse transcriptase inhibitor</td>
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<td>NPI</td>
<td>Nottingham Prognostic Index</td>
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<td>NRTI</td>
<td>nucleoside reverse transcriptase inhibitor</td>
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<td>non small cell carcinoma</td>
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<td>NSTEMI</td>
<td>non-ST elevation myocardial infarction</td>
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<td>OA</td>
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<td>PaCO₂</td>
<td>arterial partial pressure of carbon dioxide</td>
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<td>PaO₂</td>
<td>arterial partial pressure of oxygen</td>
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<td>PAH</td>
<td>phenylalanine hydroxylase</td>
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<td>PCI</td>
<td>percutaneous coronary intervention</td>
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<td>PCR</td>
<td>polymerase chain reaction</td>
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<td>PE</td>
<td>pulmonary embolus</td>
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<td>PET</td>
<td>positron emission tomography</td>
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<td>PG</td>
<td>prostaglandin</td>
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<td>PI</td>
<td>protease inhibitor</td>
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<td>PIP</td>
<td>proximal interphalangeal</td>
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<td>PPAR</td>
<td>peroxisome proliferator-activated receptor</td>
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<td>PPI</td>
<td>proton pump inhibitor</td>
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<td>PR</td>
<td>per rectum</td>
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<td>PSA</td>
<td>prostate specific antigen</td>
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<td>PT</td>
<td>prothrombin time</td>
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<td>PTH</td>
<td>parathyroid hormone</td>
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<td>PTT</td>
<td>partial thromboplastin time</td>
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<td>rheumatoid arthritis</td>
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<td>renin angiotensin aldosterone system</td>
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<td>renal cell carcinoma</td>
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<td>respiratory distress syndrome</td>
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<td>ribonucleic acid</td>
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<td>RPR</td>
<td>rapid plasma regain</td>
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<td>RVF</td>
<td>right ventricular failure</td>
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<td>SCC</td>
<td>small cell carcinoma</td>
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<td>SERM</td>
<td>selective oestrogen receptor modulator</td>
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<tr>
<td>SLE</td>
<td>systemic lupus erythematous</td>
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<td>SPECT</td>
<td>single photon emission computed tomography</td>
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<td>SSRI</td>
<td>selective serotonin reuptake inhibitor</td>
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<td>STEMI</td>
<td>ST elevation myocardial infarction</td>
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<td>STI</td>
<td>sexually transmitted infection</td>
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<td>SUDEP</td>
<td>sudden unexplained death in epilepsy</td>
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<td>T3</td>
<td>triiodothyronine</td>
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<td>thyroxine</td>
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<tr>
<td>TB</td>
<td>tuberculosis</td>
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<td>TCC</td>
<td>transitional cell carcinoma</td>
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<td>TFTs</td>
<td>thyroid function tests</td>
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<tr>
<td>Th</td>
<td>T helper (cell)</td>
</tr>
<tr>
<td>TIA</td>
<td>transient ischaemic attack</td>
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<tr>
<td>TIBC</td>
<td>total iron binding capacity</td>
</tr>
<tr>
<td>TNF</td>
<td>tumour necrosis factor</td>
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<tr>
<td>TOF</td>
<td>tetralogy of Fallot</td>
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<td>TPHA</td>
<td>Treponema pallidum haemagglutination test</td>
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<td>TPPA</td>
<td>Treponema pallidum particle agglutination test</td>
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<td>TSH</td>
<td>thyroid stimulating hormone</td>
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<td>transurethral resection of the prostate</td>
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<td>U&amp;Es</td>
<td>urine and electrolytes</td>
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<td>upper motor neuron</td>
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<td>UPEC</td>
<td>uropathogenic E. coli</td>
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<td>UTI</td>
<td>urinary tract infection</td>
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<td>VDRL</td>
<td>Venereal Disease Research Laboratory</td>
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<td>V/Q</td>
<td>ventilation/perfusion</td>
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<td>VSD</td>
<td>ventricular septal defect</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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</table>
Chapter One The Cardiovascular System

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What is heart failure?
This may be defined as the inability of cardiac output to meet the physiological demands of the body. It can be classified in several ways:
- Left ventricular failure (LVF): Symptoms of LVF: paroxysmal nocturnal dyspnoea, wheeze, nocturnal cough with pink sputum caused by pulmonary oedema.
- Right ventricular failure (RVF): Symptoms of RVF, which is usually caused by LVF or lung disease, peripheral oedema and ascites.
- Low output and high output heart failure. This is due to excessive afterload, excessive preload or pump failure.

Pathophysiology
See page 4.

Causes
Anything that causes myocardial damage may lead to heart failure. Examples include:
- Coronary artery disease.
- Hypertension.
- Atrial fibrillation.
- Valve disease.
- Cardiomyopathies.
- Infective endocarditis.
- Anaemia.
- Endocrine disorders.
- Cor pulmonale: this is right ventricular failure secondary to pulmonary disease.

Classification
Framingham Criteria for Congestive Heart Failure: 2 major criteria or 1 major criteria and 2 minor criteria:
- Major criteria: PAINS
  - Paroxysmal nocturnal dyspnoea.
  - Acute pulmonary oedema.
  - Increased heart size, increased central venous pressure.
  - Neck vein dilation.
  - S3 gallop.
- Minor criteria: PAIN
  - Pleural effusion.
  - Ankle oedema (bilateral).
  - Increased heart rate >120 beats/min.
  - Nocturnal cough.

New York Heart Association Classification for Heart Failure
I: No limitation of physical activity.
II: Slight limitation of physical activity.
III: Marked limitation of physical activity.
IV: Inability to carry out physical activity.
The Cardiovascular System

Causes
Anything that causes myocardial damage may lead to heart failure. Examples include:
- Coronary artery disease.
- Hypertension.
- Atrial fibrillation.
- Valve disease.
- Cardiomyopathies.
- Infective endocarditis.
- Anaemia.
- Endocrine disorders.
- Cor pulmonale: this is right ventricular failure secondary to pulmonary disease.

Treatment
- Conservative: smoking cessation advice, weight loss, promotion of healthy diet and exercise.
- Medical:
  - Angiotensin converting enzyme (ACE) inhibitors.
  - Beta-blockers: currently only two are licensed in the UK, bisoprolol and carvedilol.
  - Candesartan: an angiotensin receptor blocker (if intolerant to ACE inhibitors).
  - Digoxin: a cardiac glycoside.
  - Diuretics, e.g. furosemide.
  - Spironolactone: an aldosterone receptor antagonist.
- Surgical: heart transplantation.

Complications
- Renal failure.
- Valve dysfunction.
- Stroke.

Investigations
- Bloods:
  - FBC, U&Es, LFTs, TFTs, lipid profile.
  - BNP (brain natriuretic peptide). It suggests how much the myocytes are stretched. BNP is arguably cardioprotective as it causes Na+ ion and H2O excretion in addition to vasodilation. A concentration >400 pg/mL (>116 pmol/L) is suggestive of heart failure.
- CXR: ABCDE
  - Alveolar oedema.
  - Kerley B lines.
  - Cardiomegaly.
  - Dilated upper lobe vessels.
  - pleural Effusion.
- ECHO: aims to identify cause and assess function of the heart.
- ECG.

Framingham Criteria for Congestive Heart Failure:
- 2 major criteria or 1 major criteria and 2 minor criteria:
  - Major criteria:
    - PAINS
    - P: paroxysmal nocturnal dyspnoea.
    - A: acute pulmonary oedema.
    - I: increased heart size, increased central venous pressure.
    - N: neck vein dilation.
    - S: S3 gallop.
  - Minor criteria:
    - PAIN
    - P: pleural effusion.
    - A: ankle oedema (bilateral).
    - I: increased heart rate >120 beats/min.
    - N: nocturnal cough.

New York Heart Association Classification for Heart Failure
- I: No limitation of physical activity.
- II: Slight limitation of physical activity.
- III: Marked limitation of physical activity.
- IV: Inability to carry out physical activity.

Pathophysiology
See page 4.
Map 1.2 Pathophysiology of Congestive Heart Failure (CHF)

Causes of left-sided heart failure
- Coronary artery disease.
- Hypertension.
- Aortic valve disease.
- Mitral valve disease.
- Myocardial disease.

Ischaemic injury
- Reduced myocardial efficiency.

Causes of right-sided heart failure
- Left-sided heart failure.
- Tricuspid valve disease.
- Pulmonary valve disease.
- Pulmonary vascular disease.

MAP 1.2 Pathophysiology of Congestive Heart Failure (CHF)

- Increased workload.
- ↓ Cardiac output.
- ↓ Contractility.
The Cardiovascular System

Map 1.2 Pathophysiology of Congestive Heart Failure (CHF)

**Activates compensatory mechanisms**
- Activation of the renin angiotensin aldosterone system (RAAS) causes Na$^+$ ion and H$_2$O retention, and peripheral vasoconstriction. This increases preload.
- Activation of the sympathetic nervous system increases heart rate and causes peripheral vasoconstriction. This increases afterload.
- ↑ Myocyte size.

Chronic activation of these compensatory mechanisms worsens heart failure and leads to increased cardiac damage.

**Remember that:**
- The cause of cardiac dilation is increased end-diastolic volume.
- The raised jugular venous pressure (JVP) is related to right-sided heart failure and fluid overload.
- Hepatomegaly is caused by congestion of the hepatic portal circulation.
What is MI?
Also known as a heart attack. It occurs when there is myocardial necrosis following atherosclerotic plaque rupture, which occludes one or more of the coronary arteries. MI is part of the acute coronary syndromes. The acute coronary syndromes comprise:
- ST elevation MI (STEMI).
- Non-ST elevation MI (NSTEMI).
- Unstable angina.

Causes
- Atherosclerosis.

Symptoms
- Nausea, sweating, palpitations.
- Crushing chest pain for more than 20 minutes.
- N.B. Can be silent in diabetics.

Signs
Remember these as RIP:
- Raised jugular venous pressure (JVP).
- Increased pulse, blood pressure changes.
- Pallor, anxiety.

Pathophysiology
See page 9 for the pathophysiology of atherosclerosis.

Type of infarct
- Transmural:
  - Affects all of the myocardial wall.
  - ST elevation and Q waves.
- Subendocardial:
  - Necrosis of <50% of the myocardial wall.
  - ST depression.

Investigations
- ECG: this may show:
  - ST elevation, ST depression, inverted T waves.
  - New left bundle branch block (LBBB).
  - Pathological Q waves.
- CXR: this may show:
  - Cardiomegaly.
  - Pulmonary oedema.
  - Widening of the mediastinum.
- Bloods: look for cardiac biomarkers:
  - Troponin I.
  - Troponin T.
- Angiography with the view to perform percutaneous coronary intervention (PCI).
The Cardiovascular System

### The Cardiovascular System

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Conservative: lifestyle measures such as smoking cessation and increased exercise.</td>
<td></td>
</tr>
<tr>
<td>• Medical – <strong>MONA B</strong> for immediate management:</td>
<td><strong>Complications</strong> Remember this as <strong>C PEAR DROP</strong>:</td>
</tr>
<tr>
<td>o Morphine.</td>
<td>• Cardiogenic shock, Cardiac arrhythmia.</td>
</tr>
<tr>
<td>o Oxygen (if hypoxic).</td>
<td></td>
</tr>
<tr>
<td>o Nitrates (glyceryl trinitrate [GTN]).</td>
<td></td>
</tr>
<tr>
<td>o Anticoagulants, e.g. aspirin and an antiemetic.</td>
<td>N.B. Atrial fibrillation (AF) increases a patient’s risk of stroke. AF presents with an irregularly irregular pulse and an ECG with absent P waves, irregular RR intervals, an undulating baseline and narrow QRS complexes. Start anticoagulation therapy.</td>
</tr>
<tr>
<td>o Beta-blockers if no contraindication.</td>
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</tbody>
</table>

On discharge all patients should be prescribed: aspirin, an angiotensin converting enzyme (ACE) inhibitor, a beta-blocker (if no contraindication; calcium channel blockers are good alternatives) and a statin.

| Surgical: reperfusion with PCI if STEMI. PCI may also be used in NSTEMI but if NSTEMI patients are not having immediate PCI, fondaparinux (a factor Xa inhibitor) or a low molecular weight heparin (LMWH) may be given subcutaneously. |

<table>
<thead>
<tr>
<th>Pericarditis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emboli.</td>
</tr>
<tr>
<td>Aneurysm formation.</td>
</tr>
<tr>
<td>Rupture of ventricle.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dressler’s syndrome: an autoimmune pericarditis that develops 2–10 weeks post MI. This is a triad of: 1) fever; 2) pleuritic pain; 3) pericardial effusion.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rupture of free wall.</td>
</tr>
<tr>
<td>O Papillary muscle rupture.</td>
</tr>
</tbody>
</table>
Angina pectoris may be defined as substernal discomfort that is precipitated by exercise but relieved by rest or GTN spray.

**Causes**
- Atherosclerosis.
- Rarely anaemia and tachyarrhythmia.

**Precipitants**
- Exercise.
- Cold weather.
- Heavy meals.

**Types of angina**
- Stable angina: precipitated by exercise but relieved by rest.
  - **ST DEPRESSION**
- Unstable angina: pain at rest, worsening symptoms.
  - **ST DEPRESSION**
- Decubitus angina: triggered by lying flat.
  - **ST DEPRESSION**
- Prinzmetal angina: due to coronary artery spasm.
  - **ST ELEVATION**

**Investigations: ECG**
- ECG for signs of ST depression or ST elevation. Exercise ECG is no longer recommended by NICE guidelines.
- CT scan, Coronary Calcium Score (this is measured on CT) and Coronary angiography.
- Go for thallium scan.
Pathophysiology of atherosclerosis
Atherosclerosis is a slowly progressive disease and is the underlying cause of ischaemic heart disease when it occurs in the coronary arteries.

There are 3 stages of atheroma formation:

1 **Fatty streak formation**
   Lipids are deposited in the intimal layer of the artery. This, coupled with vascular injury, causes inflammation, increased permeability and white blood cell recruitment. Macrophages phagocytose the lipid and become foam cells. These form the fatty streak.

2 **Fibrolipid plaque formation**
   Lipid within the intimal layer stimulates the formation of fibrocollagenous tissue. This eventually causes thinning of the muscular media.

3 **Complicated atheroma**
   This occurs when the plaque is extensive and prone to rupture. The plaque may be calcified due to lipid acquisition of calcium. Rupture activates clot formation and thrombosis. If the coronary artery is partially occluded the result is myocardial ischaemia and therefore angina. If the coronary artery is completely occluded then the result is myocardial necrosis and MI.

Complications
- MI.
- Stroke.

Treatment
- Conservative: modify risk factors, e.g. control cholesterol, control diabetes, smoking cessation advice, weight loss, increase exercise and control hypertension.
- Medical:
  - Nitrites: glyceryl trinitrate (GTN) spray. Side-effects include headache and hypotension.
  - **A** – Aspirin.
  - **B** – Beta-blockers but contraindicated in asthma and chronic obstructive pulmonary disease (COPD).
  - **C** – Ca²⁺ antagonists especially if beta-blockers are contraindicated.
  - K⁺ channel activator, e.g. nicorandil.
- Surgery: percutaneous transluminal coronary angioplasty or coronary artery bypass graft (CABG).
What is infective endocarditis?
It is an infection of the endocardium usually involving the heart valves, with ‘vegetation’ of the infectious agent.

The mitral valve is more commonly affected but the tricuspid valve is implicated in IV drug users.

Risk factors
- IV drug abuse.
- Cardiac lesions.
- Rheumatic heart disease.
- Dental treatment: requires antibiotic prophylaxis.

Causative agents
- *Streptococcus viridans.*
- *Staphylococcus aureus.*
- *Staphylococcus epidermidis.*
- Diphtheroids.
- Microaerophilic streptococci.
- HACEK group: *Haemophilus, Actinobacillus, Cardiobacterium, Eikenella and Kingella.*

Pathophysiology
Infective endocarditis is a rare infection that usually affects patients who already have a structural valve abnormality. The reason why heart valves are targeted is because the valves of the heart have limited blood supply and consequently white blood cells cannot reach the valves through the blood. Circulating bacteria adhere to the valve causing vegetations.

Classification of infective endocarditis
**Duke Criteria:** 2 major criteria or 1 major and 3 minor criteria or 5 minor criteria.
- Major criteria:
  - 2 separate positive blood cultures.
  - Endocardial involvement.
- Minor criteria: **FIVE**
  - Fever >38°C.
  - IV drug user or predisposing heart condition, and
  - Immunological phenomena, e.g. Osler’s nodes or Roth’s spots.
  - Vascular phenomena, e.g. mycotic aneurysm or Janeway lesions.
  - Echocardiograph findings.

Signs and symptoms
Remember this as **FROM JANE**:
- Fever.
- Roth’s spots (seen on fundoscopy).
- Osler’s nodes (painful nodules seen on the fingers and toes).
- New murmur.
- Janeway lesions (painless papules seen on the palms and plantars).
- Anaemia.
- Nails: splinter haemorrhages.
- Emboli.

Investigations
- Blood cultures: take 3 separate cultures from 3 peripheral sites.
- Bloods for anaemia.
- Urinalysis; microscopic haematuria.
- CXR.
- Transoesophageal/ transthoracic ECHO for vegetations.
**The Cardiovascular System**

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- Staphylococcus epidermidis.
- Diphtheroids.
- Microaerophilic streptococci.
- HACEK group: *Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella* and *Kingella*.

**Complications**
- Heart failure.
- Arrhythmias.
- Abscess formation in the cardiac muscle.
- Emboli formation: may cause stroke, vision loss or spread the infection to other regions of the body.

**Investigations**
- Blood cultures: take 3 separate cultures from 3 peripheral sites.
- Bloods for anaemia.
- Urinalysis: microscopic haematuria.
- CXR.
- Transoesophageal/ transthoracic ECHO for vegetations.

**Treatment**
Depends on the causative agent. Check hospital antibiotic guidelines.
- Conservative: maintain good oral hygiene.
- Medical: empirical therapy is **benzylpenicillin** and **gentamicin**.
  - Streptococci: **benzylpenicillin** and **amoxicillin**.
  - Staphylococci: **flucloxacillin** and **gentamicin**.
  - Aspergillus: **miconazole**.
- Surgical: valve repair or valve replacement.

**Pathophysiology**
Infective endocarditis is a rare infection that usually affects patients who already have a structural valve abnormality. The reason why heart valves are targeted is because the valves of the heart have limited blood supply and consequently white blood cells cannot reach the valves through the blood. Circulating bacteria adhere to the valve causing vegetations.

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It is an infection of the endocardium usually involving the heart valves, with 'vegetation' of the infectious agent. The mitral valve is more commonly affected but the tricuspid valve is implicated in IV drug users.

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- Anaemia.
- Nails: splinter haemorrhages.
- Emboli.

**FIGURE 1.1 Heart Valves**
Remember the heart valves as: All Prostitutes Take Money (Aortic, Pulmonary, Tricuspid, Mitral).
## TABLE 1.1 Aortic Valve Disease

<table>
<thead>
<tr>
<th>Valve lesion</th>
<th>Causes</th>
<th>Symptoms</th>
<th>Signs</th>
<th>Murmur</th>
<th>Investigations</th>
<th>Treatment</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aortic stenosis</strong></td>
<td>Atherosclerotic-like calcific degeneration Congenital bicuspid valve Rheumatic heart disease</td>
<td>Syncope Syncope Dyspnoea Dyspnoea Angina Angina</td>
<td>Narrow pulse pressure Narrow pulse pressure Slow rising pulse Slow rising pulse</td>
<td>Crescendo-decrescendo ejection systolic murmur, which radiates to the carotids Crescendo-decrescendo ejection systolic murmur, which radiates to the carotids</td>
<td>ECG: left ventricular hypertrophy; AV block CXR: poststenotic dilation of the ascending aorta; may see calcification of valve on lateral view ECHO: confirms diagnosis; allows severity and valve area to be assessed</td>
<td>Conservative: manage cardiovascular risk factors, e.g. smoking cessation Medical: manage cardiovascular risk factors, e.g. control blood pressure Surgical: valve replacement is the treatment of choice</td>
<td>Sudden death Arrhythmia Heart failure Infective endocarditis</td>
</tr>
<tr>
<td><strong>Aortic regurgitation</strong></td>
<td>Acute Cusp rupture Connective tissue disorders, e.g. Marfan’s syndrome Aortic dissection Perforation secondary to infection Acute Cusp rupture Connective tissue disorders, e.g. Marfan’s syndrome Aortic dissection Perforation secondary to infection Chronic Rheumatoid arthritis Ankylosing spondylitis Syphilis</td>
<td>Dyspnoea Dyspnoea Angina Angina Heart failure Heart failure</td>
<td>Waterhammer pulse Waterhammer pulse pressure Waterhammer pulse pressure</td>
<td>Decrescendo early diastolic murmur Decrescendo early diastolic murmur</td>
<td>ECG: left ventricular hypertrophy</td>
<td>Conservative: manage cardiovascular risk factors, e.g. smoking cessation Medical: manage cardiovascular risk factors, e.g. control blood pressure Surgical: valve replacement is the treatment of choice</td>
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<table>
<thead>
<tr>
<th>Cause</th>
<th>Symptoms</th>
<th>Signs</th>
<th>Murmur Description</th>
<th>Investigations</th>
<th>Treatment</th>
<th>Complications</th>
</tr>
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<td>Narrow pulse</td>
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<td>Conservative: manage cardiovascular risk factors, e.g. smoking cessation</td>
<td>Sudden death</td>
</tr>
<tr>
<td>Atherosclerotic-like calcific degeneration</td>
<td>Dyspnoea</td>
<td>Slow rising pulse</td>
<td></td>
<td>CXR: poststenotic dilation of the ascending aorta; may see calcification of valve on lateral view</td>
<td>Medical: manage cardiovascular risk factors, e.g. control blood pressure</td>
<td>Arrhythmia</td>
</tr>
<tr>
<td>Congenital bicuspid valve</td>
<td>Angina</td>
<td></td>
<td></td>
<td>ECHO: confirms diagnosis; allows severity and aortic root to be assessed</td>
<td>Surgical: valve replacement is the treatment of choice</td>
<td>Heart failure</td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td></td>
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<td></td>
<td>Infection</td>
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<tr>
<td>Connective tissue disorders, e.g. Marfan’s syndrome</td>
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<tr>
<td>Aortic dissection</td>
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<tr>
<td>Perforation secondary to infection</td>
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<tr>
<td>Chronic</td>
<td>Dyspnoea</td>
<td>Waterhammer pulse</td>
<td>Decrescendo early diastolic murmur</td>
<td>ECG: left ventricular hypertrophy</td>
<td>Conservative: manage cardiovascular risk factors, e.g. smoking cessation</td>
<td>Heart failure</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Angina</td>
<td></td>
<td></td>
<td></td>
<td>Medical: manage heart failure by following NICE guidelines</td>
<td>Arrhythmia</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>Heart failure</td>
<td></td>
<td></td>
<td></td>
<td>Surgical: valve replacement is the treatment of choice</td>
<td></td>
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<tr>
<td>Syphilis</td>
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<tr>
<td>Traube’s sign: a ‘pistol shot’ heard over the femoral artery</td>
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<tr>
<td>De Musset’s sign: head nodding in time with heart beat</td>
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<tr>
<td>Quincke’s sign: pulse felt in the nail</td>
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<tr>
<td>Signs of systemic disease</td>
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<td></td>
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<tr>
<td>CXR: may see cardiomegaly and pulmonary oedema if patient has heart failure</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>ECHO: confirms diagnosis; allows severity and aortic root to be assessed</td>
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</tbody>
</table>

**Table 1.1 Aortic Valve Disease**
### Mitral Valve Disease

<table>
<thead>
<tr>
<th>Valve lesion</th>
<th>Causes</th>
<th>Symptoms</th>
<th>Signs</th>
<th>Murmur</th>
<th>Investigations</th>
<th>Treatment</th>
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</tr>
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<tr>
<td><strong>Mitral stenosis</strong></td>
<td>Rheumatic heart disease</td>
<td>Dyspnoea</td>
<td>Malar flush</td>
<td>Low pitch mid-diastolic murmur with opening snap</td>
<td>ECG: atrial fibrillation; bifid P waves</td>
<td>Conservative: manage cardiovascular risk factors, e.g. smoking cessation</td>
<td>AF Heart failure</td>
</tr>
<tr>
<td></td>
<td>Calcification of valve</td>
<td>Palpitations if in atrial fibrillation (AF)</td>
<td>Tapping apex beat</td>
<td></td>
<td>CXR: pulmonary oedema and enlarged left atrium may be seen</td>
<td>Medical: manage AF and heart failure by following NICE guidelines</td>
<td>Infective endocarditis</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid arthritis</td>
<td>Heart failure</td>
<td>Hoarse voice (Ortner’s syndrome)</td>
<td></td>
<td>ECHO: confirms diagnosis; allows severity and valve area to be assessed</td>
<td>Surgical: valve replacement is the treatment of choice</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ankylosing spondylitis</td>
<td></td>
<td>Irregularly irregular pulse if in AF</td>
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<tr>
<td></td>
<td>Systemic lupus erythematosus</td>
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<td></td>
<td>(SLE)</td>
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<tr>
<td></td>
<td>Malignant carcinoid</td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mitral regurgitation</strong></td>
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<td>Irregularly irregular pulse</td>
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<tr>
<td></td>
<td>Papillary muscle rupture</td>
<td>Palpitations if in AF</td>
<td>Irregularly irregular pulse if in AF</td>
<td></td>
<td>CXR: may see cardiomegaly and pulmonary oedema if patient has heart failure</td>
<td>Medical: manage AF and heart failure by following NICE guidelines</td>
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<tr>
<td></td>
<td>Infective endocarditis</td>
<td>Heart failure</td>
<td>Displaced apex beat</td>
<td></td>
<td></td>
<td>Surgical: valve replacement is the treatment of choice</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td></td>
<td>Prolapse</td>
<td>Symptoms of infective endocarditis</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**TABLE 1.2 Mitral Valve Disease**
### Valve lesion Causes

- Mitral stenosis
- Rheumatic heart disease
- Calcification of valve
- Rheumatoid arthritis
- Ankylosing spondylitis
- Systemic lupus erythematosus (SLE)
- Malignant carcinoid

### Symptoms

- Dyspnoea
- Palpitations if in atrial fibrillation (AF)
- Heart failure
- Haemoptysis

### Signs

- Malar flush
- Tapping apex beat
- Hoarse voice (Ortner's syndrome)
- Irregularly irregular pulse if in AF

### Murmur

- Low pitch mid-diastolic murmur with opening snap

### Investigations

- ECG: atrial fibrillation; bifid P waves
- CXR: pulmonary oedema and enlarged left atrium may be seen
- ECHO: confirms diagnosis; allows severity to be assessed

### Treatment

- **Conservative:**
  - manage cardiovascular risk factors, e.g. smoking cessation
- **Medical:**
  - manage AF and heart failure by following NICE guidelines
- **Surgical:**
  - valve replacement is the treatment of choice

### Complications

- AF
- Heart failure
- Infective endocarditis

### Table 1.2

<table>
<thead>
<tr>
<th>Condition</th>
<th>Symptoms</th>
<th>Signs</th>
<th>Murmur</th>
<th>Investigations</th>
<th>Treatment</th>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Papillary muscle rupture</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Infective endocarditis</td>
<td>Symptom of infective endocarditis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolapse</td>
<td>Dyspnoea</td>
<td>Displaced apex beat</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
What is hypertension?
This is a clinic blood pressure that is >140/90 mmHg.

Pathophysiology
There is much uncertainty as to the cause of hypertension but it is likely multifactorial. ~95% of cases have no known cause and, in these cases, patients are said to have ‘essential hypertension’.

More rarely, patients will have secondary hypertension. This should be considered in young patients with an acute onset of hypertension, any history that is suggestive of a renal or endocrine cause and when the patient fails to respond to medical therapy. Examples include renovascular disease, Conn’s syndrome, Cushing’s disease and phaeochromocytoma.

Blood pressure is controlled by several mechanisms, e.g. the autonomic nervous system, the capillary fluid shift mechanism, the renin angiotensin aldosterone system and adrenaline. A problem with one of these mechanisms may result in high blood pressure.

Lifestyle factors such as smoking, alcohol intake, obesity and stress also play a role in increasing blood pressure.

Investigations
- Clinic blood pressure readings (with ambulatory blood pressure monitoring to confirm). Stages of hypertension are listed below:

<table>
<thead>
<tr>
<th>Blood pressure (mmHg)</th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Pre-hypertension</td>
<td>120–139</td>
<td>80–89</td>
</tr>
<tr>
<td>Stage 1</td>
<td>140–159</td>
<td>90–99</td>
</tr>
<tr>
<td>Stage 2</td>
<td>160–179</td>
<td>100–109</td>
</tr>
<tr>
<td>Severe hypertension</td>
<td>≥180</td>
<td>≥110</td>
</tr>
</tbody>
</table>

- Bloods: FBC, LFTs, U&Es, creatinine, serum urea, cGFR, lipid levels and glucose.
- ECG: left ventricular hypertrophy.
- Urine dipstick: haematuria and proteinuria.
**The Cardiovascular System**

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<td>&gt;160</td>
<td>&gt;100</td>
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Lifestyle factors such as smoking, alcohol intake, obesity and stress also play a role in increasing blood pressure.

**Complications**
- MI.
- Heart failure.
- Renal impairment.
- Stroke.
- Hypertensive retinopathy.

**Causes**
- Unknown: ‘essential hypertension’.
- Secondary causes: renal and endocrine disease.
- Contributory lifestyle factors such as increased stress, smoking and obesity.

**Treatment**
- Conservative: lifestyle advice including smoking cessation, encouraging weight loss, decreased alcohol consumption and a salt restricted diet.
- Medical: this is split into 4 steps according to NICE guidelines:

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>A C D</td>
<td>A A C D</td>
<td>A C D</td>
<td>Refer for add-on therapy</td>
</tr>
</tbody>
</table>

**Key:**
- A: angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) if ACE inhibitor is not tolerated by patient;
- C: calcium channel blocker;
- D: thiazide-type diuretic;
- add-on therapy: spironolactone (side-effect: hyperkalaemia), alpha-blocker or beta-blocker.

- Surgical: surgical excision (if related to cause).

**FIGURE 1.2 The Renin Angiotensin System**

- Angiotensin II stimulates:
  - Aldosterone secretion from the zona glomerulosa of the adrenal cortex.
  - Vasoconstriction.
  - Antidiuretic hormone (ADH) release from the posterior pituitary gland.
  - The sympathetic system.

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Atrial Fibrillation (AF)

What is AF?
This is the most common tachyarrhythmia, characterised by an irregularly irregular pulse, rapid heart rate and ECG changes.

Signs and symptoms
- None.
- Palpitations.
- Dyspnoea.
- Syncope.
- Exercise intolerance.
- Fatigue.
- Heart failure.
- Irregularly irregular pulse.

Pathophysiology
Atrial ectopic beats, thought to originate in the pulmonary veins, lead to dysfunction of the cardiac electrical signalling pathway. As a result the atria no longer contract in a coordinated manner. Instead they fibrillate and contract irregularly. Due to the irregular contractions, the atria fail to empty adequately. This may result in stagnant blood accumulating within the atrial appendage, increasing the risk of clot formation and therefore embolic stroke.

Complications
- Stroke.
- Heart failure.
- Sudden death.

Investigations
- ECG: absent P waves, irregular RR intervals, an undulating baseline and narrow QRS complexes.
- Holter monitoring: ambulatory ECG device.
- ECHO.
- TFTs.
- CXR.

Causes
- Idiopathic.
- Ischaemic heart disease.
- Heart failure.
- Valve disease: mitral stenosis and mitral regurgitation.
- Hypertension.
- Hyperthyroidism.
- Alcohol induced.
- Familial.

Treatment
- Conservative: patient education and management of cardiovascular risk factors, e.g. smoking cessation and decreasing alcohol intake.
- Medical: treat underlying cause and:
  - Restore rate: beta-blocker, calcium antagonist, digoxin, amiodarone.
  - Restore rhythm: beta-blocker, cardioversion, amiodarone.
  - Anticoagulant, e.g. warfarin, apixaban, dabigatran and rivaroxaban (see Appendix 2).
Chapter Two The Respiratory System

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What is pneumonia?
Pneumonia is inflammation of the lung parenchyma caused by a lower respiratory tract infection. It often occurs after a viral infection in the upper respiratory tract. It is uncertain how the bacteria reach the lower respiratory tract after attaching to disaccharide receptors on pharyngeal epithelial cells.

Pathophysiology
Debatable methods of invasion include:
- The inhibition of IgA.
- Pneumolysins, which inhibit ciliary beating.
- Damage of the epithelial cells by prior infection.
- Hijacking the platelet aggregating factor receptor pathway to reach the alveoli.

Symptoms
- Fever.
- Cough with purulent sputum.
- Dyspnoea.
- Pleuritic pain.

Signs
- Percussion: dull.
- Auscultation: crackles, bronchial breathing.
- Respiratory failure: cyanosis, tachypnoea.
- Septicaemia: rigors.

Causative organisms

<table>
<thead>
<tr>
<th>Children</th>
<th>Community acquired pneumonia</th>
<th>Hospital acquired pneumonia</th>
<th>HIV patients or immunocompromised patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viruses</td>
<td><em>Streptococcus pneumoniae</em></td>
<td>Gram-negative bacteria</td>
<td><em>Pneumocystis jirovecii</em></td>
</tr>
<tr>
<td>Pneumococcus</td>
<td><em>Haemophilus influenzae</em></td>
<td><em>Staphylococcus aureus</em></td>
<td><em>Cytomegalovirus</em></td>
</tr>
<tr>
<td>Mycoplasma</td>
<td><em>Moraxella catarrhalis</em></td>
<td><em>Streptococcus pneumoniae</em></td>
<td><em>Adenovirus</em></td>
</tr>
<tr>
<td>Chlamydia pneumoniae (A)</td>
<td>Anaerobes</td>
<td></td>
<td><em>Herpes simplex virus</em></td>
</tr>
<tr>
<td>Mycoplasma pneumoniae (A)</td>
<td>Fungi</td>
<td></td>
<td><em>Mycobacterium tuberculosis</em></td>
</tr>
<tr>
<td>Legionella pneumophila (A)</td>
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<td>Bacterial infection, e.g. <em>Staphylococcus aureus</em></td>
<td></td>
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\( A \) = Atypical
The Respiratory System

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Treatment
Remember this as BAPP:
• Breathing: maintain oxygen saturation levels.
• Antibiotics: treat the underlying cause (check hospital guidelines).
• Pain: give analgesics.
• Pneumococcal vaccines for those at risk, e.g. diabetics, the immunosuppressed and those over 65 years old.

Complications
• Respiratory failure: by causing acute respiratory distress syndrome (ARDS).
• Septic shock: the causative agent enters the patient’s bloodstream, releasing cytokines.
• Pleural effusion.
• Empyema.
• Lung abscess.
• Hypotension: sepsis or dehydration is usually the underlying cause.

Investigations
• CXR: look for infiltrates.
• Identify the causative organism by assessing a sputum sample.
• Monitor oxygen saturation.
• Bloods: look for raised WCC and raised inflammatory markers.
• Urinary antigen test: for pneumococcal or Legionella antigen.
• Arterial blood gas (ABG).

Assess severity using CURB-65
• Confusion.
• Urea >7 mmol/L.
• Respiratory rate >30/min.
• BP <90/<60 mmHg.
• >65 years old.

Each section of the CURB-65 is worth 1 point:
1 = Outpatient care.
2 = Admission.
>3 = Requires ICU admission.

Causative organisms

Children
Community acquired pneumonia
Hospital acquired pneumonia
HIV patients or immunocompromised patients

Viruses
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Gram-negative bacteria
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Pneumococcus
Staphylococcus aureus
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Anaerobes
Herpes simplex virus
Fungi
Mycobacterium tuberculosis
Legionella pneumophila
Bacterial infection, e.g. Staphylococcus aureus

MAP 2.1 Pneumonia
What is bronchiectasis?
Bronchiectasis is permanent dilation of the airways caused by chronic inflammation and inability to clear secretions.

Pathophysiology
This is dependent on the cause. Initially, there is infection of the smaller distal airways that results in inflammation and the release of inflammatory mediators. This impairs ciliary action, allows for bacterial proliferation and tissue damage and causes bronchial dilation.

Causative organisms
- Streptococcus pneumoniae.
- Haemophilus influenzae.
- Staphylococcus aureus.
- Pseudomonas aeruginosa: common in patients with cystic fibrosis.

Causes
- Congenital:
  - Cystic fibrosis.
  - Young’s syndrome: associated with azoospermia.
  - Kartagener’s syndrome: causes cilia to become immobile, thus removing the defence mechanism of the respiratory tract; also associated with situs inversus.
- Acquired:
  - Tumours.
  - Rheumatoid arthritis.
  - Inflammatory bowel disease.

Complications
- Massive haemoptysis: this is a medical emergency.

What is cystic fibrosis?
This is an autosomal recessive condition that occurs in approximately 1 in 2500 births.

Causes
- Mutation of the cystic fibrosis transmembrane conductance regulator gene (CFTR), located on chromosome 7.

Investigations
- Diagnosed by sweat test.
- In the neonatal period diagnosed by Guthrie’s test, which detects raised serum immunoreactive trypsinogen.
The Respiratory System

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Symptoms
• Purulent sputum.
• Persistent cough.
• Fever.

Signs
• Clubbing.
• Crepitations.
• Coarse inspiratory crackles.

Treatment
Remember this as ABCDS:
• Antibiotics.
• Bronchodilators.
• Corticosteroids.
• postural Drainage.
• Surgery (if indicated).

Investigations
• Bloods: FBC, WCC, U&Es, LFTs, TFTs, CRP, ESR.
• CXR: shows tram track opacities of bronchi and bronchioles.
• Sputum culture and sensitivity.
• Aspergillus screen if cause suspected.

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Investigations
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Associations
• Lung disease, pancreatic insufficiency, diabetes and infertility in males.
What is asthma?
Asthma is a chronic, inflammatory disease that is characterised by reversible airway obstruction.

Signs and symptoms
- Wheezing.
- Shortness of breath.
- Coughing.

Remember to ask if the patient has a history of atopy, e.g. hay fever and eczema.

Triggering factors include:
- Dust/pets/vapours.
- Emotion.
- Drugs, e.g. beta-blockers.

Investigations
- Peak expiratory flow rate: note diurnal variation.
- Sputum sample.
- ABG: in emergency.
- Spirometry: for obstructive defects.
- Bloods: increased IgE, FBC.
- CXR: pneumothorax, consolidation.

Pathophysiology
- Copious mucus secretion.
- Inflammation.
- Contraction of bronchial muscle.

Interleukin (IL)-4: stimulates eosinophils and stimulates B lymphocytes. B lymphocytes produce IgE, which causes mast cells to degranulate. When mast cells degranulate, they release histamine and this histamine causes bronchoconstriction.
- IL-5: stimulates eosinophils.
- IL-13: stimulates mucus secretion.
The Respiratory System

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- CXR: pneumothorax, consolidation.

Treatment
- Conservative: patient education; advice on inhaler technique and avoidance of triggering factors; annual asthma review and influenza vaccine required.
- Medical: refer to British Thoracic Society Guidelines:
  - Step 1: salbutamol (a short-acting beta-2 receptor agonist).
  - Step 2: step 1 + beclometasone (inhaled steroid).
  - Step 3: steps 1, 2 + salmeterol (a long-acting beta-2 receptor agonist) + increased total dose of inhaled steroid.
  - Step 4: steps 1–3 + increased dose of inhaled steroid + consider adding additional therapy, e.g.:
    - Theophylline (a xanthine derived bronchodilator that inhibits phosphodiesterase).
    - Montelukast (a leukotriene receptor antagonist).
  - Step 5: oral prednisolone (steroid) + high-dose inhaled steroid; refer to specialist.

Treatment of acute asthma
Remember as O SHIT:
- Oxygen.
- Salbutamol.
- Hydrocortisone.
- Ipratropium.
- Theophylline.

Complications
- Death.
- Disturbed sleep.
- Persistent cough.
- Side-effects of steroids:
  - Weight gain.
  - Thinning of the skin.
  - Striae formation.
  - Cataracts.
  - Cushing’s syndrome.

Pathophysiology
- Copious mucus secretion.
- Inflammation.
- Contraction of bronchial muscle.
- Interleukin (IL)-4: stimulates eosinophils and stimulates B lymphocytes. B lymphocytes produce IgE, which causes mast cells to degranulate. When mast cells degranulate, they release histamine and this histamine causes bronchoconstriction.
- IL-5: stimulates eosinophils.
- IL-13: stimulates mucus secretion.
The Respiratory System

What is COPD?
This is a chronic obstructive airway disease that is characterised by its irreversibility. It is closely linked to smoking.

- Chronic bronchitis: cough with sputum production for at least 3 months in 2 consecutive years.
- Emphysema: this encompasses permanently dilated airways distal to the terminal bronchioles with alveolar destruction and bullae formation. It is defined histologically and is associated with alpha-1 antitrypsin deficiency and increased elastase activity.

Causes
Remember this as GASES:
- Genetics: alpha-1 antitrypsin deficiency results in the loss of protection against proteases.
- Air pollution.
- Smoking.
- Exposure through occupation, e.g. coal mining.
- Secondhand smoke exposure.

Pathophysiology
- Chronic bronchitis: chronic infection results in the chronic infiltration of the respiratory submucosa by inflammatory cells. This results in mucous gland hyperplasia and smooth muscle hypertrophy, causing bronchial lumen narrowing. ‘Blue bloaters’ are patients where this pathology dominates.
- Emphysema: alveolar walls are destroyed resulting in bullae formation and the fusion of adjacent alveoli. This ultimately results in a decreased surface area for gas exchange and decreased elastic recoil with subsequent air trapping. ‘Pink puffers’ are patients where this pathology dominates.

MAP 2.4 Chronic Obstructive Pulmonary Disease (COPD)
The Respiratory System

Complications

Remember this as **CLIPPer**:

- **Cor pulmonale**: right-sided heart failure due to chronic pulmonary hypertension.
- **Lung cancer**.
- **Infections**: usually treat with macrolide antibiotics.
- **Pneumothorax**.
- **Polycythaemia**.
- **Respiratory failure**.

Investigations

- Diagnosis is confirmed by spirometry, which has a FEV₁ value <80% predicted and FEV₁/FVC <0.7.
- **CXR** shows lung hyperinflation, emphysematous change and diaphragmatic flattening.
- **Bloods**: FBC, U&Es, WCC, ESR, CRP, alpha-1 antitrypsin levels.
- **ECG**: for cor pulmonale.
- **Sputum culture**.

The **GOLD scale** assesses severity of COPD:
- **Stage I**: mild COPD.
- **Stage II**: moderate COPD.
- **Stage III**: severe COPD.
- **Stage IV**: very severe COPD.

Treatment

Remember this as **ABCS, oxygen therapy and pulmonary rehabilitation**:

- **Anticholinergics**, e.g. ipratropium.
- **Bronchodilators**, e.g. salmeterol.
- **Corticosteroids**.
- **Smoking cessation** is imperative.
- **Oxygen therapy**: long-term oxygen therapy (LTOT) or noninvasive ventilation (NIV).
<table>
<thead>
<tr>
<th>TABLE 2.1 Type 1 vs. Type 2 Respiratory Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 1: hypoventilation with V/Q mismatch</strong></td>
</tr>
<tr>
<td>‘Pink puffer’ – thin and hyperinflated</td>
</tr>
<tr>
<td><strong>Cause</strong></td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Pulmonary oedema</td>
</tr>
<tr>
<td>Fibrosing alveolitis</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
</tr>
<tr>
<td>Remember this as <strong>ABCD:</strong></td>
</tr>
<tr>
<td>Agitation</td>
</tr>
<tr>
<td>Breathlessness</td>
</tr>
<tr>
<td>Confusion</td>
</tr>
<tr>
<td>Drowsiness and fatigue</td>
</tr>
<tr>
<td><strong>Signs</strong></td>
</tr>
<tr>
<td>Central cyanosis</td>
</tr>
<tr>
<td><strong>PaO₂</strong></td>
</tr>
<tr>
<td>↓ (&lt;8.0 kPa)</td>
</tr>
<tr>
<td><strong>PaCO₂</strong></td>
</tr>
<tr>
<td>Normal (~6.7 kPa)</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td>Oxygen replacement therapy</td>
</tr>
<tr>
<td>Treatment of underlying cause</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
</tr>
<tr>
<td>Nosocomial infections, e.g. pneumonia</td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>Arrhythmia</td>
</tr>
<tr>
<td>Pericarditis</td>
</tr>
<tr>
<td><strong>Type 2: hypoventilation with or without V/Q mismatch</strong></td>
</tr>
<tr>
<td>‘Blue bloater’ – strong build and wheezy</td>
</tr>
<tr>
<td><strong>Cause</strong></td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease (COPD)</td>
</tr>
<tr>
<td>and asthma</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td>Opiate overdose</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>Motor neuron disease</td>
</tr>
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<tr>
<td><strong>Signs</strong></td>
</tr>
<tr>
<td>Remember this as <strong>ABC:</strong></td>
</tr>
<tr>
<td>A flapping tremor</td>
</tr>
<tr>
<td>Bounding pulse</td>
</tr>
<tr>
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</table>
**Coal workers pneumoconiosis**
- Caused by inhaling coal dust.
- The dust particles accumulate in the lung parenchyma and are engulfed by macrophages. These macrophages then die, releasing enzymes resulting in tissue fibrosis.

**Bauxite fibrosis**
- This is also known as Shaver’s disease.
- Caused by inhaling bauxite fumes.

**Berylliosis**
- Caused by inhaling beryllium.
- It causes granuloma formation, made up of:
  - Giant cells
  - Macrophages
  - Epithelioid cells

Other granulomatous conditions include: tuberculosis, leprosy, cat-scratch disease and sarcoidosis.

**Asbestosis**
- Caused by inhaling asbestos fibres. The fusiform rods are found inside macrophages.
- Associated with malignant mesothelioma.
- Pleural plaques are apparent on CXR.
- White asbestos has the lowest fibrogenicity, whereas blue asbestos has the highest.

**Siderosis**
- Caused by inhaling iron particles.
- Benign with no apparent respiratory symptoms or altered lung function.

**Silicosis**
- This is also known as Potter’s rot.
- Caused by inhaling silica particles, which cannot be removed by respiratory defences.
- Macrophages engulf the silica particles releasing tumour necrosis factor (TNF) and cytokines that induce fibroblasts, resulting in fibrosis and collagen deposition.
- Associated with increased tuberculosis (TB) infection.
- Eggshell calcification of hilar lymph nodes is apparent on CXR, along with nodular lesions in the upper lobes.
**Squamous cell carcinoma**
- Associated with smoking.
- Paraneoplastic parathyroid-like actions.
- Keratin pearls are seen histologically.

**Pancoast’s tumour**
- Results in Horner’s syndrome, a triad of:
  1. Miosis.
  2. Ptosis.
  3. Anhidrosis.

**Adenocarcinoma**
- NOT associated with smoking.
- More common in women.
- Associated with hypertrophic osteoarthropathy.
- Mucin-positive staining seen on histology.

**Small cell carcinoma**
- Also known as oat cell carcinoma.
- Very aggressive, therefore treat solely with chemotherapy regime.
- Adrenocorticotropic hormone (ACTH) and antidiuretic hormone (ADH) are generated ectopically.
- Associated with Lambert–Eaton syndrome.
- Kulchitsky cells are seen histologically.
- Non small cell carcinomas (NSCC) are any epithelial derived lung cancers that are not small cell carcinoma (SCC). They are relatively insensitive to chemotherapy.

**Mesothelioma**
- Associated with asbestos.
- Psammoma bodies are seen histologically.

**Large cell carcinoma**
- Patient is likely to have a poor outcome.
- Lack light microscopic features of other tumour types.
- Larger sized anaplastic cells.
- High cytoplasmic-to-nuclear size ratio.
- Treated by surgical excision of tumour.
What is a DVT?
A DVT is a clot that usually develops in one of the deep veins. It usually occurs in the leg.

Signs and symptoms
- Asymptomatic.
- Pain.
- Oedema.
- Erythema/discolouration.
- Increased temperature of symptomatic leg.
- Engorgement of surface veins.

Investigations
- D-dimer: this is sensitive but not specific, i.e. if the result is negative then the cause is unlikely to be DVT.
- B-mode venous compression ultrasonography: for DVT above the knee.
- Investigations to uncover cause of DVT.
- The Modified Wells Score may be used to calculate probability of DVT (for a full description of the Wells Score and NICE guidelines please follow the website link provided at the end of the book).

Differential diagnosis
Remember as ABC:
- A musculoskeletal injury.
- Baker’s cyst rupture.
- Cellulitis.

Pathophysiology
The pathophysiology of DVT may be summarised by Virchow’s triad. This comprises 3 predisposing factors for DVT formation (the causes of each factor are listed):

Hypercoagulability
- Malignancy.
- Surgery.
- Trauma.
- Oral contraceptive pill.
- Clotting abnormalities.

Venous stasis
- Immobility, e.g. after surgery.
- Pregnancy.
- Heart failure.

Trauma
- Inflammation.
- Previous thrombosis.

Complications
- Pulmonary embolism.
- Post-thrombotic syndrome.

Treatment
Anticoagulation therapy with unfractionated heparin or a low molecular weight heparin, e.g. dalteparin, and secondary management with a vitamin K antagonist, e.g. warfarin.
What is a PE?
This is occlusion of the pulmonary vasculature by a clot. Often it occurs from a deep vein thrombosis (DVT) that has become dislodged and forms an embolus that lodges in the pulmonary arterial vasculature, blocking the vessels.

Signs and symptoms
- Breathlessness: this may be of sudden onset or progressive.
- Tachypnoea.
- Pleuritic chest pain.
- Cyanosis.
- Haemoptysis.

Causes
- DVT.
- Air embolus.
- Fat embolus.
- Amniotic fluid embolus.
- Foreign material introduced via IV drug use.

Pathophysiology
The extent of thrombus may be classified into small-medium, multiple and massive PE. Symptom correlation depends on where the pulmonary circulation is occluded.

There are 3 pathways involved in the pathophysiology of PE:
1. Platelet factor release: serotonin and thromboxane A2 cause vasoconstriction.
2. Decreased alveolar perfusion: lung is underperfused and this leads to diminished gas exchange.
3. Decreased surfactant: this leads to ventilation/perfusion mismatch, hypoxaemia and dyspnoea.
The Respiratory System

33

The extent of thrombus may be classified into small-medium, multiple and massive PE. Symptom correlation depends on where the pulmonary circulation is occluded. There are 3 pathways involved in the pathophysiology of PE:

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2. Decreased alveolar perfusion: lung is underperfused and this leads to diminished gas exchange.
3. Decreased surfactant: this leads to ventilation/perfusion mismatch, hypoxaemia and dyspnoea.

Investigations

- D-dimer: sensitive but not specific; negative result used to rule out PE.
- Thrombophilia screening: in patients <50 years with recurrent PE.
- CXR: usually normal.
- ECG: sinus tachycardia, S1Q3T3 pattern is classical but rare; excludes MI.
- ABG: hypoxaemia.
- CT, pulmonary angiography.
- V/Q scan.
- The Wells Score may be used to calculate risk of PE.

Treatment

- Acute:
  - Oxygen.
  - IV fluids.
  - Thrombolysis therapy if indicated, e.g. alteplase if massive PE or haemodynamically unstable.
  - Low molecular weight heparin.
- Long-term management:
  - Anticoagulation.
  - Inferior vena cava filter.

Complications

- Sudden death.
- Arrhythmia.
- Pulmonary infarction.
- Pleural effusion.
- Paradoxical embolism.
- Pulmonary hypertension.

Signs and symptoms

- Breathlessness: this may be of sudden onset or progressive.
- Tachypnoea.
- Pleuritic chest pain.
- Cyanosis.
- Haemoptysis.

Causes

- DVT.
- Air embolus.
- Fat embolus.
- Amniotic fluid embolus.
- Foreign material introduced via IV drug use.

Investigations

- D-dimer: sensitive but not specific; negative result used to rule out PE.
- Thrombophilia screening: in patients <50 years with recurrent PE.
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- Long-term management:
  - Anticoagulation.
  - Inferior vena cava filter.

Complications

- Sudden death.
- Arrhythmia.
- Pulmonary infarction.
- Pleural effusion.
- Paradoxical embolism.
- Pulmonary hypertension.
What is a pneumothorax?
A pneumothorax is air within the pleural space.

Signs and symptoms
- Ipsilateral chest pain.
- Shoulder tip pain.
- Dyspnoea.
- Tachypnoea.
- Hypoxia.
- Cyanosis.
- Auscultation: decreased on affected side.
- Percussion: hyper-resonant or normal.

Causes
- Ruptured pleural bleb.
- Chronic obstructive pulmonary disease (COPD).
- Tuberculosis.
- Sarcoïdosis.
- Idiopathic pulmonary fibrosis.
- Rheumatoid arthritis.
- Ankylosing spondylitis.
- Lung cancer.
- Trauma, e.g. stab wound.

Pathophysiology
The pathophysiology of pneumothorax is directly linked to cause, outlined below.
- Primary spontaneous pneumothorax:
  - Idiopathic/rupture of pleural bleb.
  - Usually found in young, tall, slim men.
- Secondary spontaneous pneumothorax:
  - In patients with prior lung disease, e.g. COPD, sarcoïdosis or idiopathic pulmonary fibrosis.
- Tension pneumothorax:
  - Due to blunt, traumatic injuries, e.g. a stab wound.
  - Air cannot be removed on expiration due to one-way valve mechanism. This leads to mediastinal shift and lung collapse.

Investigations
- CXR: pleural line; may show tracheal deviation away from lesion.
- CT scan.
- ABG: hypoxia.

Treatment
- If pneumothorax on CXR <2 cm then no treatment is required; advise patients not to travel by air or to dive.
- If >2 cm then aspirate air +/- intercostal drain.
- Tension pneumothorax requires immediate decompression with a large bore needle inserted into the 2nd intercostal space mid-clavicular line.

Complications
- Risk of future pneumothorax.
- Respiratory failure.
- Cardiac arrest.
Chapter Three The Gastrointestinal System

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TABLE 3.1 Microbiology of the Gastrointestinal (GI) Tract 52

The Gastrointestinal System
Map 3.1 Causes of Regional Abdominal Pain

**Right hypochondriac region**
- Pancreatitis.
- Ulcer (gastric).
- Gallstones.
- Biliary colic.

**Epigastric region**
- Heartburn.
- Pancreatitis.
- Epigastric hernia.
- Gallstones.
- Ulcer (gastric).

**Left hypochondriac region**
- Pancreatitis.
- Ulcer (gastric or duodenal).

**Right lumbar region**
- Kidney stones.
- Urinary tract infection.
- Constipation.
- Inflammatory bowel disease (IBD).
- Diverticular disease.

**Umbilical region**
- Gastric ulcer.
- Early stages of appendicitis.
- Aortic aneurysm.
- Ruptured aortic aneurysm.
- Pancreatitis.
- IBD.

**Left lumbar region**
- Kidney stones.
- Urinary tract infection.
- Constipation.
- Inflammatory bowel disease (IBD).
- Diverticular disease.

**Right iliac region**
- Appendicitis.
- Ectopic pregnancy.
- Ovarian torsion.
- Inguinal or femoral hernias.

**Hypogastric region**
- Urinary tract infection.
- Appendicitis.
- IBD.
- Diverticular disease.

**Left iliac region**
- Diverticular disease.
- IBD.
- Ectopic pregnancy.
- Ovarian torsion.
- Inguinal or femoral hernias.
Causes of Gastrointestinal (GI) Bleeding

- Crohn's disease
- Ulcerative colitis
- Gastritis
- Peptic ulcers
- Oesophageal varices
- Peptic ulcers
- Upper GI bleeds
- Diverticulitis
- Malignancy
- Polyps
- Mallory–Weiss tear
- Malignancy
- Lower GI bleeds
- Malignancy
- Angiodysplasia
- Infectious diarrhoea
- Malignancy
GASTRITIS
What is gastritis?
This is inflammation of the stomach lining. Gastritis may be acute or chronic.
- Acute gastritis, caused by:
  - Stress.
  - Uraemia.
  - Alcohol.
  - NSAIDs.
  - Burns: Curling’s ulcer.
- Chronic gastritis:
  - Type A:
    - Autoimmune: autoantibodies are present to parietal cells.
    - Presents with pernicious anaemia.
    - Occurs in the fundus or body of the stomach.
  - Type B:
    - Most common.
    - Associated with Helicobacter pylori infection.

Investigate for H. pylori infection:
- Bloods: anaemia and H. pylori.
- Urinalysis.
- Blood test – measures antibodies to H. pylori.
- Carbon isotope–urea breath test.
- Endoscopy with biopsy of stomach lining.
- Stool microscopy and culture – may detect trace amounts of H. pylori.

Treatment
- Triple therapy to eradicate H. pylori: proton pump inhibitor (PPI), with amoxicillin 1g and clarithromycin 500 mg or metronidazole 400 mg and clarithromycin 250 mg, taken twice daily.
- Step-wise approach to treating gastritis:
  - Mild – antacids or H2 receptor antagonists.
  - Moderate/severe – PPI.

Complications
- Peptic ulcers, anaemia (from bleeding ulcers), stricture formation, mucosa-associated lymphoid tissue (MALT) lymphoma.

IRRITABLE BOWEL SYNDROME (IBS)
What is IBS?
This is a common functional disorder of the bowel.

Signs and symptoms
Recurrent abdominal pain, which improves with defaecation; there is a change in bowel habit, i.e. increased or decreased frequency.

Investigations
This is a clinical diagnosis.

Treatment
- Conservative: education and avoidance of triggering factors, e.g. decrease stress.
- Medical: depends on symptoms; antimuscarinics, laxatives, stool softeners, antispasmodics and antidepressants may play a role.

Complications
- Depression and anxiety.
**APPENDICITIS**

**What is appendicitis?**
This is inflammation of the appendix that presents with pain that can originate in the umbilical area before migrating to the right iliac fossa.

**Investigations**
Diagnosis is clinical:
- Bloods: FBC, U&Es, CRP.
- Ultrasound.
- Pregnancy test in females of child bearing age to rule out ectopic pregnancy.

**Treatment**
- Surgical excision.

**Complications**
- Peritonitis.

---

**IRRITABLE BOWEL SYNDROME (IBS)**

**What is IBS?**
This is a common functional disorder of the bowel.

**Signs and symptoms**
Recurrence abdominal pain, which improves with defaecation; there is a change in bowel habit, i.e. increased or decreased frequency.

---

**GASTRITIS**

**What is gastritis?**
This is inflammation of the stomach lining. Gastritis may be acute or chronic.

- **Acute gastritis**, caused by:
  - Stress.
  - Uraemia.
  - Alcohol.
  - NSAIDs.
  - Burns: Curling’s ulcer.

- **Chronic gastritis**:
  - **Type A**: Autoimmune: autoantibodies are present to parietal cells. Presents with pernicious anaemia. Occurs in the fundus or body of the stomach.
  - **Type B**: Most common. Associated with *Helicobacter pylori* infection. Investigate for *H. pylori* infection:
    - Bloods: anaemia and *H. pylori*.
    - Urinalysis.
    - Blood test – measures antibodies to *H. pylori*.
    - Carbon isotope–urea breath test.
    - Endoscopy with biopsy of stomach lining.
    - Stool microscopy and culture – may detect trace amounts of *H. pylori*.

**Treatment**
- **Triple therapy** to eradicate *H. pylori*:
  - Proton pump inhibitor (PPI), with amoxicillin 1g and clarithromycin 500 mg or metronidazole 400 mg and clarithromycin 250 mg, taken twice daily.

**Step-wise approach to treating gastritis**:
- **Mild** – antacids or H2 receptor antagonists.
- **Moderate/severe** – PPI.

**Complications**
- Peptic ulcers, anaemia (from bleeding ulcers), stricture formation, mucosa-associated lymphoid tissue (MALT) lymphoma.

---

**Inflammatory bowel disease (IBD)**

(Continued overleaf)
ULCERATIVE COLITIS
What is ulcerative colitis?
This is a relapsing remitting autoimmune condition that is not associated with granulomas. It affects the colon and rarely the terminal ileum (backwash ileitis).

Signs and symptoms
Remember the 5Ps:
- Pyrexia.
- Pseudopolyps.
- Lead Pipe radiological appearances.
- Poo (bloody diarrhoea).
- Proctitis.

Investigations
- These are the same as Crohn’s disease.

Treatment
- Conservative: patient education; smoking has been shown to be protective but is not advised.
- Medical: corticosteroids, 5-aminosalicylic acid (5-ASA) analogues (sulfasalazine), mesalazine, 6-mercaptopurine, azathioprine.
- Surgical: colectomy.

Complications
- Toxic megacolon, increased incidence of colon cancer, primary sclerosing cholangitis and osteoporosis (from steroid use).

CROHN’S DISEASE
What is Crohn’s disease?
This is a disordered response to intestinal bacteria with transmural inflammation. It may affect any part of the gastrointestinal tract but often targets the terminal ileum. It is associated with granuloma formation.

Signs and symptoms
- Weight loss, abdominal pain (with palpable mass), diarrhoea, fever, skip lesions, clubbing, cobblestone mucosa, fistula formation, fissure formation and linear ulceration.

Investigations
- Bloods: FBC and platelets, U&Es, LFTs and albumin, ESR and CRP.
- Colonoscopy (with biopsy): diagnostic.
- Radiology: small bowel follow through (diagnostic) and abdominal X-ray (for toxic megacolon and excluding perforation).

Treatment
- Conservative: smoking cessation, low residue diet may be encouraged but usually diet is normal.
- Medical: corticosteroids, infliximab, 5-ASA analogues (sulfasalazine), azathioprine, methotrexate.
- Surgical: remove strictured or obstructed region of bowel.

Complications
- Stricture formation, fistula formation, obstruction, pyoderma gangrenosum, anaemia and osteoporosis.
The Gastrointestinal System

Causes of Gastrointestinal (GI) Malabsorption

- **Tropical sprue**
  - Cause unknown.
  - Can affect all of the small intestine.
  - Treatment: folic acid and tetracycline.

- **Coeliac disease**
  - Cause: autoantibodies to gliadin.
  - Proximal small intestine mainly affected.
  - Treatment: gluten-free diet.

- **A-beta-lipoproteinaemia**
  - Cause: autosomal recessive disorder.
  - Results in the inability to synthesise chylomicrons.
  - Treatment: vitamin E.

- **Whipple’s disease**
  - Cause: *Tropheryma whippelii*.
  - This is a Gram-positive bacterium.
  - Treatment: antibiotics for 1–2 years.

- **Disaccharidase deficiency**
  - Cause: a deficiency in enzymes required for digestion and absorption, e.g. beta-glycosidase complex.
  - Treatment: restricted diet.

- **Pancreatic insufficiency**
  - Cause: diseases such as cystic fibrosis, cancer and pancreatitis.
  - Results in deficiency of vitamins A, D, E, K (these are fat soluble vitamins).
  - Treatment: pancrelipase (CREON®).

- **A-beta-lipoproteinaemia**
  - Cause: autosomal recessive disorder.
  - Results in the inability to synthesise chylomicrons.
  - Treatment: vitamin E.

Remember as These Definitely Cause Absorption Problems:
- Tropical sprue.
- Disaccharidase deficiency.
- Coeliac disease and Crohn’s disease.
- Pancreatic insufficiency.
**What is GORD?**
This is abnormal reflux where acid from the stomach refluxes into the oesophagus subsequently damaging the squamous oesophageal lining, causing discomfort.

**Signs and symptoms**
- Heartburn – pain is worse in certain positions, e.g. lying down/stooping and is worse after heavy meals.
- Acid taste in mouth.
- Regurgitation.
- Water brash (excess salivation).
- Dysphagia.
- Nocturnal asthma/chronic cough.
- Laryngitis.

**Causes**
- Genetic inheritance of angle of lower oesophageal sphincter.
- Oesophagitis.
- Sliding hiatus hernia.
- Rolling hiatus hernia.

**Risk factors**
- Smoking.
- Excessive alcohol.
- Excessive coffee.
- Obesity.
- Pregnancy.
- Drugs, e.g. calcium channel blockers, antimuscarinics and tricyclic antidepressants.

**Investigations**
Age dependent:
- If the patient is <55 years old:
  - Proceed to treatment unless they have ALARM symptoms, e.g. unintentional weight loss, dysphagia, haematemesis, melaena and anorexia.
- If >55 years old:
  - Send patient to endoscopy: diagnostic and allows for biopsy.
  - 24-h pH monitoring.

**What is Barrett’s oesophagus?**
This is metaplasia of the normal squamous epithelium of the lower oesophagus to columnar epithelium. This occurs in patients who suffer with GORD for several years. It is a premalignant lesion.

**MAP 3.5 Gastro-Oesophageal Reflux Disease (GORD)**
The Gastrointestinal System

Treatment

- Conservative: education, weight loss, raising head of bed at night and avoidance of precipitating factors, e.g. smoking, large meals.
- Medical:
  - Antacids, e.g. aluminium hydroxide.
  - H$_2$ receptor antagonists, e.g. ranitidine.
  - Proton pump inhibitors, e.g. omeprazole.
- Surgical: Nissen’s fundoplication.

Complications: Barrett’s oesophagus

What is Barrett’s oesophagus?
This is metaplasia of the normal squamous epithelium of the lower oesophagus to columnar epithelium. This occurs in patients who suffer with GORD for several years. It is a premalignant lesion.

Investigations
- Endoscopy with biopsy in all 4 quadrants.

Treatment
- HALO® system radiofrequency ablation or mucosal resection for highly dysplastic lesions.

Complications
- Adenocarcinoma of the oesophagus.
The Gastrointestinal System

What is jaundice?
Jaundice, also known as icterus, is the yellow discolouration of mucous membranes, sclera and skin. This happens due to the accumulation of bilirubin. Jaundice may be seen at a bilirubin concentration >2.5–3.0 mg/dL (42.8–51.3 mmol/L).

Causes
The causes of jaundice may be split into 3 categories (see Table below):
1. Prehepatic jaundice.
2. Intrahepatic jaundice.
3. Posthepatic jaundice.

Treatment
Treat the underlying cause.

Complications
- Liver failure.
- Renal failure.
- Sepsis.
- Pancreatitis.
- Biliary cirrhosis
- Cholangitis
- Kernicterus (a serious complication of jaundice in neonates).

Investigations
You must determine underlying cause. Use these tests to determine the type of jaundice:
- Appearance of urine and stool.
- LFTs.
- Bilirubin levels.
- Alkaline phosphatase levels.

The different blood results for different types of jaundice:

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Prehepatic jaundice</th>
<th>Intrahepatic jaundice</th>
<th>Posthepatic jaundice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance of urine</td>
<td>Normal</td>
<td>Dark</td>
<td>Dark</td>
</tr>
<tr>
<td>Appearance of stool</td>
<td>Normal</td>
<td>Pale</td>
<td>Pale</td>
</tr>
<tr>
<td>Conjugated bilirubin</td>
<td>Normal</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Unconjugated bilirubin</td>
<td>Normal or ↑</td>
<td>↑</td>
<td>Normal</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>Normal or ↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>Normal</td>
<td>↑</td>
<td>↑</td>
</tr>
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</table>
Jaundice

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<tr>
<th>Jaundice Type</th>
<th>Appearance of Urine</th>
<th>Appearance of Stool</th>
<th>Bilirubin Levels</th>
<th>Alkaline Phosphatase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posthepatic</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Prehepatic</td>
<td>Normal</td>
<td>Conjugated bilirubin</td>
<td>Unconjugated</td>
<td>↑</td>
</tr>
<tr>
<td>Intrahepatic</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal or ↑</td>
<td>Normal or ↑</td>
</tr>
</tbody>
</table>

The causes of different types of jaundice

<table>
<thead>
<tr>
<th>Prehepatic jaundice</th>
<th>Intrahepatic jaundice</th>
<th>Posthepatic jaundice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crigler–Najjar syndrome</td>
<td>Viral and drug induced hepatitis</td>
<td>Gallstones in common bile duct</td>
</tr>
<tr>
<td>Gilbert's syndrome</td>
<td>Alcoholic liver disease</td>
<td>Pancreatic cancer</td>
</tr>
<tr>
<td>Haemolysis, e.g. thalassaemia, sickle cell anaemia</td>
<td>Hepatic cirrhosis</td>
<td>Schistosomiasis</td>
</tr>
<tr>
<td>Drugs, e.g. rifampicin</td>
<td>Primary biliary cirrhosis</td>
<td>Biliary atresia</td>
</tr>
<tr>
<td>Malaria</td>
<td>Leptospirosis</td>
<td>Cholangiocarcinoma</td>
</tr>
<tr>
<td>Haemolytic uraemic syndrome</td>
<td>Physiological neonatal jaundice</td>
<td>Mirizzi's syndrome</td>
</tr>
</tbody>
</table>
**HEPATITIS A (HAV)**

**What is HAV?**
It is a RNA picornavirus.

**Transmission**
Faecal–oral transmission, associated with contaminated shellfish. The virus passes into bile after replication within liver cells. The immune system is activated by this process and leads to necrosis predominantly in zone 3 of the hepatic lobule.

**Incubation period**
- 2–3 weeks.

**Investigations**
- Anti-HAV IgM in serum.

**Treatment**
- Conservative: vaccine for travellers to endemic areas.
- Medical: supportive since HAV is often self-resolving.

**Complications**
- Rarely acute liver failure.

---

**HEPATITIS B (HBV)**

**What is HBV?**
A partially stranded, enveloped DNA virus. It has an e-antigen that indicates increased infectivity.

**Transmission**
- Vertical transmission.
- Contaminated needles.
- Infected blood products.
- Sexual intercourse.

**Incubation period**
- 1–5 months.

**Investigations**
- HBV DNA in serum, HBsAg, HBeAg, anti-HBc; HBsAg presents on histology with a ‘ground glass’ appearance.

**Treatment**
- Conservative: education and prevention of disease; vaccine for at-risk groups, e.g. health workers.
- Medical: antiviral medications, e.g. pegylated alpha-2a interferon, adefovir, entecavir, lamivudine, tenofovir, telbivudine.

**Complications**
- Hepatic cirrhosis, hepatocellular carcinoma (HCC), fulminant hepatitis B.
HEPATITIS A (HAV)
What is HAV?
It is a RNA picornavirus.

Transmission
- Faecal–oral transmission, associated with contaminated shellfish. The virus passes into bile after replication within liver cells. The immune system is activated by this process and leads to necrosis predominantly in zone 3 of the hepatic lobule.

Incubation period
- 2–3 weeks.

Investigations
- Anti-HAV IgM in serum.

Treatment
- Conservative: vaccine for travellers to endemic areas.
- Medical: supportive since HAV is often self-resolving.

Complications
- Rarely acute liver failure.

HEPATITIS B (HBV)
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- Contaminated needles.
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- Sexual intercourse.

Incubation period
- 1–5 months.

Investigations
- HBV DNA in serum, HBsAg, HBeAg, anti-HBc; HBsAg presents on histology with a ‘ground glass’ appearance.

Treatment
- Conservative: education and prevention of disease; vaccine for at-risk groups, e.g. health workers.
- Medical: antiviral medications, e.g. pegylated alpha-2a interferon, adefovir, entecavir, lamivudine, tenofovir, telbivudine.

Complications
- Hepatic cirrhosis, HCC, fulminant hepatitis B.

HEPATITIS C (HCV)
What is HCV?
It is a single stranded, enveloped RNA virus and a member of the flavivirus family.

Transmission
- Vertical transmission (occasionally).
- Contaminated needles.
- Infected blood products.

Incubation period
- Intermediate (6–9 weeks).

Investigations
- Antibody to HCV in the serum.

Treatment
- Conservative: education and prevention of disease.
- Medical: antiviral medications, e.g. pegylated alpha-2a interferon, ribavirin, taribavirin, telaprevir.

Complications
- Hepatic cirrhosis, HCC, liver failure.

HEPATITIS D (HDV)
What is HDV?
It is a single stranded defective RNA virus that co-infects with hepatitis B virus. Co-infectivity with HDV leads to an increased chance of liver failure.

Transmission
- Contaminated needles.
- Infected blood products.
- Sexual intercourse (rare).

Incubation period
- 1–5 months.

Investigations
- Serum IgM anti-D.

Treatment
- Pegylated alpha-2a interferon.

Complications
- Hepatic cirrhosis, HCC.

Hepatitis E (HEV)
What is HEV?
It is a single stranded RNA virus.

Transmission
- Faecal–oral transmission, associated with contaminated water.

Incubation period
- 2–3 weeks.

Investigations
- IgG and IgM anti-HEV.

Treatment
- Usually self-limiting.

Complications
- High mortality of pregnant women (~20%).
What is CRC?
This is cancer of the colon and rectum and is the third most common malignancy. Usually adenocarcinoma on histology.

Signs and symptoms
- Abdominal pain.
- Unintentional weight loss.
- Altered bowel habit.
- Faecal occult blood.
- Anaemia.
- Fatigue.

Causes
Multifactorial and often unknown. There are risk factors that may predispose an individual to develop CRC (see risk factor box).

Investigations
- Bowel Cancer Screening Programme: faecal occult blood test in men and women aged 60–69 years.
- Bloods: FBC for iron deficiency anaemia and carcinoembryonic antigen (CEA) tumour marker.
- Endoscopy: colonoscopy/sigmoidoscopy.
- Imaging: double contrast barium enema study ‘apple core’ sign; virtual colonoscopy.

Treatment
Depends on the extent of disease. This is assessed using Dukes staging system or TNM system.
- Conservative: patient education and referral to Macmillan nurses.

Risk factors
- Smoking.
- Increased age.
- Family history of CRC.
- Inflammatory bowel disease (IBD).
- Streptococcus bovis bacteraemia.
- Congenital polyposis syndromes:
  - Juvenile polyposis syndrome:
    - Autosomal dominant but it may occur spontaneously.
    - Not malignant.
  - Peutz–Jeghers syndrome:
    - Autosomal dominant.
    - Increases risk of CRC.
    - Melanosis is present on the oral mucosa.
- Genetic predisposition:
  - Familial adenomatous polyposis (FAP):
    - Autosomal dominant.
    - Mutation of APC gene on chromosome 5.
    - 100% lead to CRC.
  - Hereditary nonpolyposis colorectal cancer (HNPCC):
    - Autosomal dominant.
    - Mutation of DNA mismatch repair gene.
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- Endoscopy: colonoscopy/sigmoidoscopy.
- Imaging: double contrast barium enema study 'apple core' sign; virtual colonoscopy.

Treatment
Depends on the extent of disease. This is assessed using Dukes staging system or TNM system.
- Conservative: patient education and referral to Macmillan nurses.
- Medical: chemotherapy (oxaliplatin, folinic acid and 5-fluorouracil is the most common regime); radiotherapy may also be used.
- Surgery: surgical resection is usually treatment of choice.

Complications
- Obstruction and metastasis.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Confined to muscularis mucosa</td>
<td>90%</td>
</tr>
<tr>
<td>B</td>
<td>Extends through muscularis mucosa</td>
<td>65%</td>
</tr>
<tr>
<td>C</td>
<td>Lymph node involvement</td>
<td>30%</td>
</tr>
<tr>
<td>D</td>
<td>Distant metastases</td>
<td>&lt;10%</td>
</tr>
</tbody>
</table>

Duke’s staging system

TNM system
- T – Carcinoma in situ
- T1 – Submucosa invaded
- T2 – Muscularis mucosa invaded
- T3 – Tumour has invaded subserosa but other organs have not been penetrated
- T4 – Adjacent organs invaded
- N1 – Metastatic spread to 1–3 regional lymph nodes
- N2 – Metastatic spread to ≥4 regional lymph nodes
- M0 – No distant metastases present
- M1 – Distant metastases present
ACUTE PANCREATITIS
What is acute pancreatitis?
This is inflammation of the pancreatic parenchyma, with biochemical associations of increased amylase and raised lipase enzymes on blood test.

Signs and symptoms
Remember these as PAN:
- Epigastric Pain that radiates to the back.
- Anorexia.
- Nausea and vomiting.
- Grey Turner’s sign: flank bruising.
- Cullen’s sign: periumbilical bruising.

Causes
Remember these as GET SMASHED:
- Gallstones.
- Ethanol.
- Trauma.

CHRONIC PANCREATITIS
What is chronic pancreatitis?
This is where the structural integrity of the pancreas is permanently altered as a direct result of chronic inflammation.

Signs and symptoms
Pain! The pain is:
- Epigastric in origin.
- Recurrent.
- Radiates to the back.
- Relieved by sitting forward.
- Worse when eating/drinking heavily.

Causes
Remember these as CAMP:
- Cystic fibrosis.
- Alcohol.
- Malnourishment.
- Pancreatic duct obstruction.
The Gastrointestinal System

Pancreatitis

ACUTE PANCREATITIS

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This is inflammation of the pancreatic parenchyma, with biochemical associations of increased amylase and raised lipase enzymes on blood test.

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• Grey Turner’s sign: flank bruising.
• Cullen’s sign: periumbilical bruising.

Causes
Remember these as GET SMASHED:
• Gallstones.
• Ethanol.
• Trauma.
• Cystic fibrosis.
• Alcohol.
• Malnourishment.
• Pancreatic duct obstruction.
• Scorpion sting (Tityus trinitatis).
• Mumps.
• Autoimmune disease.
• Steroids.
• Hyperlipidaemia/Hypercalcaemia.
• Endoscopic retrograde cholangiopancreatography (ERCP).
• Drugs, e.g. azathioprine.

CHRONIC PANCREATITIS

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• Mumps.
• Autoimmune disease.
• Steroids.
• Hyperlipidaemia/Hypercalcaemia.
• Endoscopic retrograde cholangiopancreatography (ERCP).
• Drugs, e.g. azathioprine.

Investigations
• Raised serum amylase and lipase.
• Detect cause, e.g. ultrasound scan to detect presence of gallstones.
• CT scan to rule out complications (not within <72 h of acute presentation unless clinically indicated).

Treatment
• This is usually symptomatic relief. Keep ‘nil by mouth’ (NBM), IV fluids and analgesia, e.g. tramadol
• Treat underlying causes, e.g. ERCP to remove gallstones.

Complications
Remember these as HDAMN:
• Haemorrhage.
• Disseminated intravascular coagulation (DIC).
• Acute respiratory distress syndrome (ARDS).
• Multiorgan failure.
• Necrosis.

Investigations
• Decreased faecal elastase.
• CT scan: shows calcification (may also be seen on abdominal X-ray).
• Magnetic resonance cholangiopancreatography (MRCP).

Treatment
• Conservative: alcohol cessation.
• Medical: analgesia, e.g. tramadol and pancreatic enzyme replacement therapy; start insulin therapy if diabetes has developed.

Complications
Remember these as PODS:
• Pseudocysts.
• Obstruction (pancreatic).
• Diabetes mellitus.
• Steatorrhoea.
<table>
<thead>
<tr>
<th>Organism</th>
<th>Illness caused</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Vibrio vulnificus</em></td>
<td>Food poisoning</td>
<td>Found in seafood; Gram-negative bacterium</td>
</tr>
<tr>
<td><em>Bacillus cereus</em></td>
<td>Food poisoning</td>
<td>Found in reheated rice; Gram-positive bacterium</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>Food poisoning</td>
<td>Found in contaminated meat and mayonnaise; Gram-positive bacterium</td>
</tr>
<tr>
<td><em>Clostridium botulinum</em></td>
<td>Food poisoning</td>
<td>Found in poorly canned foods; Gram-positive bacterium</td>
</tr>
<tr>
<td><em>Escherichia coli</em> O157:H7</td>
<td>Food poisoning and diarrhoea</td>
<td>Found in meat that is undercooked; enteropathogenic <em>E. coli</em> causes diarrhoea in children; also causes haemolytic uraemic syndrome (HUS); Gram-negative bacterium</td>
</tr>
<tr>
<td><em>Campylobacter jejuni</em></td>
<td>Bloody diarrhoea</td>
<td>Found in animal faeces and poultry; it is associated with Guillain–Barré syndrome, which is an ascending paralysis; Gram-negative bacterium</td>
</tr>
<tr>
<td><em>Salmonella</em></td>
<td>Bloody diarrhoea</td>
<td>Found in contaminated food; Gram-negative bacterium</td>
</tr>
<tr>
<td><em>Shigella</em></td>
<td>Bloody diarrhoea</td>
<td>Produces shiga toxin; Gram-negative bacterium</td>
</tr>
<tr>
<td><em>Yersinia enterocolitica</em></td>
<td>Bloody diarrhoea</td>
<td>Associated with outbreaks in nurseries; Gram-negative bacterium</td>
</tr>
<tr>
<td>Enterotoxic <em>Escherichia coli</em></td>
<td>Traveller’s diarrhoea</td>
<td>Traveller’s diarrhoea is usually self-limiting; Gram-negative bacterium</td>
</tr>
<tr>
<td><em>Vibrio cholerae</em></td>
<td>Rice water diarrhoea</td>
<td>Produces cholera toxin; Gram-negative bacterium</td>
</tr>
<tr>
<td><em>Cryptosporidium</em></td>
<td>Cryptosporidiosis</td>
<td>Associated with AIDS patients; protozoon</td>
</tr>
<tr>
<td><em>Norwalk virus</em></td>
<td>Gastroenteritis</td>
<td>Most common viral cause of nausea and vomiting</td>
</tr>
<tr>
<td><em>Helicobacter pylori</em></td>
<td>Risk factors for peptic ulcers, gastritis and gastric adenocarcinoma</td>
<td>Produces urease; treat with ‘triple therapy’, i.e. a proton pump inhibitor (PPI) with either clarithromycin and amoxicillin or clarithromycin and metronidazole; Gram-negative bacterium</td>
</tr>
<tr>
<td><em>Toxoplasma gondii</em></td>
<td>Toxoplasmosis</td>
<td>Cysts are found in meat or cat faeces; causes brain abscesses in AIDS patients; protozoon</td>
</tr>
<tr>
<td><em>Taenia solium</em></td>
<td>Intestinal tapeworms</td>
<td>Found in undercooked pork; cestode</td>
</tr>
</tbody>
</table>
### FIGURE 4.1 Nephron Physiology

#### MAP 4.1 Renal Calculi

#### MAP 4.2 Urinary Tract Infection (UTI)

#### MAP 4.3 Renal Cancers

#### MAP 4.4 Kidney Injury

#### MAP 4.5 Nephritic vs. Nephrotic Syndrome

#### MAP 4.6 Cystic Disease

#### MAP 4.7 Congenital Kidney Abnormalities

### TABLE 4.1 Diuretics
### FIGURE 4.1 Nephron Physiology

<table>
<thead>
<tr>
<th>Component</th>
<th>Function and Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proximal convoluted tubule</strong></td>
<td>• Reabsorbs glucose, amino acids, water, bicarbonate ions, Na(^+) and Cl(^-) ions</td>
</tr>
<tr>
<td></td>
<td>• Contains a brush border</td>
</tr>
<tr>
<td><strong>Distal convoluted tubule</strong></td>
<td>• Actively reabsorbs Na(^+) and Cl(^-) ions</td>
</tr>
<tr>
<td></td>
<td>• Simple cuboidal epithelium</td>
</tr>
<tr>
<td><strong>Collecting tubule</strong></td>
<td>• Aldosterone: increases the number of Na(^+) ion channel in the collecting tubules</td>
</tr>
<tr>
<td></td>
<td>• Antidiuretic hormone (ADH): binds to V(_2) receptors and consequently increases the</td>
</tr>
<tr>
<td></td>
<td>number of aquaporins</td>
</tr>
<tr>
<td><strong>Thin descending loop of Henle</strong></td>
<td>• Reabsorbs water by medullary hypertonicity</td>
</tr>
<tr>
<td></td>
<td>• It is impermeable to Na(^+) ions</td>
</tr>
<tr>
<td><strong>Thick ascending loop of Henle</strong></td>
<td>• Permeable to Na(^+) ions</td>
</tr>
<tr>
<td></td>
<td>• Impermeable to water</td>
</tr>
<tr>
<td></td>
<td>• Contains the Na(^+)/K(^+)/2Cl(^-) transporter</td>
</tr>
</tbody>
</table>

---

**Figure 4.1** Nephron Physiology

[Diagram illustration of nephron physiology with annotations for each section.]
The Renin Angiotensin Aldosterone System (RAAS)

Angiotensinogen (LIVER)

Angiotensin I

Angiotensin converting enzyme (ACE) (LUNGS)

Angiotensin II

Renin (KIDNEY)

Renin secretion is stimulated by:
- ↓ Blood pressure
- ↓ Na⁺ ion and H₂O delivery to the macula densa
- ↑ Sympathetic activity

↑ Blood pressure by:
- Vasoconstriction of smooth muscle
- Stimulating aldosterone → ↑ Na⁺ ion and H₂O retention
- Stimulating antidiuretic hormone (ADH) (posterior pituitary gland) → ↑ H₂O reabsorption
- ↑ Thirst by stimulating the hypothalamus
<table>
<thead>
<tr>
<th>Class of diuretic</th>
<th>Example</th>
<th>Mechanism of action</th>
<th>Uses</th>
<th>Side-effects</th>
<th>Contraindications</th>
<th>Drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazide diuretic</td>
<td>Bendroflumethiazide</td>
<td>Blocks Na⁺/Cl⁻ ion symporter in the distal convoluted tubule</td>
<td>Hypertension</td>
<td>Hyponatraemia</td>
<td>Gout</td>
<td>Hypokalaemia may increase the risk of digoxin toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Heart failure</td>
<td>Hypokalaemia</td>
<td>Liver failure</td>
<td>Decreased lithium excretion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ascites</td>
<td>Hypercalcaemia</td>
<td>Renal failure</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hyperglycaemia</td>
<td>May worsen diabetes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hyperlipidaemia</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hyperuricaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>Furosemide</td>
<td>Blocks Na⁺/K⁺/2Cl⁻ co-transporter in the ascending loop of Henle</td>
<td>Heart failure (symptomatic treatment of oedema)</td>
<td>Hyponatraemia</td>
<td>Renal failure</td>
<td>Hypokalaemia may increase the risk of digoxin toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severe hypercalcaemia</td>
<td>Hypokalaemia</td>
<td></td>
<td>Decreased lithium excretion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypocalcaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ototoxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K⁺ sparing diuretic</td>
<td>Spironolactone</td>
<td>Aldosterone receptor antagonist</td>
<td>Heart failure (in combination with furosemide)</td>
<td>Hyperkalaemia</td>
<td>Addison’s disease</td>
<td>Decreased lithium excretion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oedema</td>
<td>Gynaecomastia</td>
<td>Hyperkalaemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ascites</td>
<td>(alternatively, eplerenone can be given as a more selective aldosterone antagonist)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Refractory hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Conn’s syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osmotic diuretic</td>
<td>Mannitol</td>
<td>Increases plasma osmolarity</td>
<td>Cerebral oedema</td>
<td>Fever</td>
<td>Heart failure</td>
<td>Increases levels of tobramycin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rhabdomyolysis</td>
<td>Hyponatraemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Haemolysis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
What are renal calculi?
These are stones that form within the renal tract. Most stones are made from calcium (radiopaque), but others are made from struvite (staghorn calculus) and uric acid crystals (radiolucent).

Signs and symptoms
- Asymptomatic.
- Pain (suprapubic and loin pain that may radiate to the genital region).
- Dysuria.
- Urinary tract infection (UTI).
- Haematuria.

Causes
- Idiopathic.
- Hypercalcaemia.
- Hyperuricaemia.
- Hyperoxaluria.
- Recurrent UTI.
- Drugs, e.g. loop diuretics.
- Hereditary conditions increase risk, e.g. polycystic kidney disease.

Investigations
- 24-h urine analysis: assess levels of calcium, uric acid, oxalate and citrate.
- CT kidney, ureter, bladder (KUB): for radiopaque stones.
- Ultrasound and IVU can also be utilised.
- Chemical analysis of stone composition.

Complications
- Recurrent UTI.
- Recurrent calculi.
- Obstruction.
- Trauma to ureter/ureteric stricture.

Treatment
- Conservative: prevent cause, e.g. low calcium diet. Education about risk factors.

Medical:

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Analgesia and tamsulosin</td>
</tr>
<tr>
<td>Dehydration</td>
<td>IV and oral fluids</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>Antiemetics</td>
</tr>
<tr>
<td>↑ Calcium</td>
<td>Low calcium diet and stop thiazide diuretics if possible</td>
</tr>
<tr>
<td>↑ Oxalate</td>
<td>Low oxalate diet</td>
</tr>
<tr>
<td>↑ Uric acid</td>
<td>Allopurinol</td>
</tr>
</tbody>
</table>

- Radiology:
  - Nephrostomy insertion.
  - Antegrade ureteric stent insertion.
- Surgical:
  - Antegrade or retrograde removal of large stones or staghorn calculus.
  - Extracorporeal shock wave lithotripsy (ESWL) for the treatment of larger stones (>0.5 cm).
What is a UTI?
This is an infection of the urinary tract with typical signs and symptoms. It may be classified as either a lower or upper (acute pyelonephritis) UTI.

Signs and symptoms of lower UTI
- Dysuria.
- Frequency.
- Urgency.
- Suprapubic pain.

Signs and symptoms of upper UTI
- Fever/chills.
- Flank pain.
- Haematuria.

Risk factors
- Female gender.
- Sexual intercourse.
- Catheterisation.
- Pregnancy.
- Menopause.
- Diabetes.
- Genitourinary malformation.
- Immunosuppression.
- Urinary tract obstruction, e.g. stones.

Pathophysiology
The urinary system has many defences to prevent UTI such as:
- Micturition.
- Urine: osmolarity, pH and organic acids are antibacterial.
- Secreted factors:
  - Tamm–Horsfall protein: binds bacteria nonspecifically; produced by cells of the thick ascending loop of Henle; mutations in the gene that codes for this protein are associated with progressive renal failure and medullary cysts.
  - IgA: against specific bacteria.
  - Lactoferrin: hoovers up free iron.
- Mucosal defences: mucopolysaccharides coat the mucosal surfaces of the bladder.
- If these defence mechanisms are overcome by bacterial virulence factors then the patient is prone to developing a UTI. Some virulence factors worth noting are:
  - For uropathogenic *E. coli* (UPEC):
    - Type 1 fimbriae: binds to mannose residues; associated with cystitis.
    - Type P fimbriae: binds to glycolipid residues; associated with pyelonephritis.
    - Bacterial capsule: aka antigen K, resists phagocytosis; associated with pyelonephritis.
  - For *Proteus mirabilis*:
    - Produces urease.
    - Increases pH of urine.
    - *Proteus mirabilis* is associated with staghorn calculi.

Causative organisms
- *Escherichia coli*: leading cause of UTI in the community and also nosocomial infection. Metallic sheen on eosin methylene blue (EMB).
- *Staphylococcus saprophyticus*: 2nd leading cause in sexually active females.
- *Pseudomonas aeruginosa*: bile green pigment and fruity odour. Usually nosocomial and drug resistant.
- Adenovirus: haemorrhagic cystitis.
- BK and JC viruses: associated with graft failure after transplant.
- *Schistosoma haematobium*: parasitic infection.

Investigations
- Urine dipstick: positive for leucocytes and nitrites.
- Urine culture: for diagnosis for causative organism (>10^5 organisms per mL of midstream urine).
- Radiology: consider ultrasound scan or cystoscopy if UTI occurs in children, in men or if UTI is recurrent.

Treatment
- Conservative: education about the condition and avoidance of predisposing risk factors.
- Medical: trimethoprim twice daily. Consider prophylactic antibiotics if UTI is recurrent.
- If recurrent, i.e. >4 UTIs per year, seek to exclude anatomical variant or abnormality of the renal tract.

Complications
- Pyelonephritis.
- Renal failure.
- Sepsis.
**What is a UTI?**
This is an infection of the urinary tract with typical signs and symptoms. It may be classified as either a lower or upper (acute pyelonephritis) UTI.

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- Dysuria.
- Frequency.
- Urgency.
- Suprapubic pain.

**Signs and symptoms of upper UTI**
- Fever/chills.
- Flank pain.
- Haematuria.

**Risk factors**
- Female gender.
- Sexual intercourse.
- Catheterisation.
- Pregnancy.
- Menopause.
- Diabetes.
- Genitourinary malformation.
- Immunosuppression.
- Urinary tract obstruction, e.g. stones.

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- *Escherichia coli*: leading cause of UTI in the community and also nosocomial infection. Metallic sheen on eosin methylene blue (EMB).
- *Staphylococcus saprophyticus*: 2nd leading cause in sexually active females.
- *Pseudomonas aeruginosa*: bile green pigment and fruity odour. Usually nosocomial and drug resistant.
- *Adenovirus*: haemorrhagic cystitis.
- BK and JC viruses: associated with graft failure after transplant.
- *Schistosoma haematobium*: parasitic infection.

**Investigations**
- Urine dipstick: positive for leucocytes and nitrites.
- Urine culture: for diagnosis for causative organism (>10^5 organisms per mL of midstream urine).
- Radiology: consider ultrasound scan or cystoscopy if UTI occurs in children, in men or if UTI is recurrent.

**Treatment**
- Conservative: education about the condition and avoidance of predisposing risk factors.
- Medical: trimethoprim twice daily. Consider prophylactic antibiotics if UTI is recurrent.
- If recurrent, i.e. >4 UTIs per year, seek to exclude anatomical variant or abnormality of the renal tract.

**Complications**
- Pyelonephritis.
- Renal failure.
- Sepsis.
### Renal Cell Carcinoma (RCC)

**What is RCC?**
This is an adenocarcinoma originating from the cells that line the proximal convoluted tubule.

**Risk factors**
- Male.
- Age 50–70 years.
- Smoking.
- Obesity.
- Mutation of the Von Hippel–Lindau tumour suppressor gene on chromosome 3.

**Signs and symptoms**
- Unintentional weight loss.
- Loin pain.
- Haematuria.
- Palpable mass.
- Fever.
- Hypertension.

### Transitional Cell Carcinoma (TCC)

**What is TCC?**
This is a cancer that arises from transitional urothelium. It is more common in men.

**Risk factors**
Remember these as CAPS:
- Cyclophosphamide.
- Aniline dyes.
- Phenacetin.
- Smoking.

**Signs and symptoms**
Depends on the location of the cancer but is usually associated with painless haematuria and lower urinary tract symptoms, e.g. frequency and urgency.
RENAL CELL CARCINOMA (RCC)

What is RCC?
This is an adenocarcinoma originating from the cells that line the proximal convoluted tubule.

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Signs and symptoms
- Unintentional weight loss.
- Loin pain.
- Haematuria.
- Palpable mass.
- Fever.
- Hypertension.

Paraneoplastic syndromes involved
- Secretion of adrenocorticotrophic hormone (ACTH): may produce symptoms of hypercalcaemia.
- Secretion of erythropoietin (EPO): may produce symptoms of polycythaemia.

Investigations
- Radiology (ultrasound scan, CT scan, MRI scan).

Treatment
- Medical: interferon alpha, sunitinib, sorafenib, bevacizumab.
- Surgical: partial or total nephrectomy is the treatment of choice; radiofrequency ablation may be considered.

Complications
- Metastasis: to brain, bone, lung, liver, adrenal glands and lymph nodes.
- Hypercalcaemia.
- Hypertension.
- Polycythaemia.

TRANSITIONAL CELL CARCINOMA (TCC)

What is TCC?
This is a cancer that arises from transitional urothelium. It is more common in men.

Risk factors
Remember these as CAPS:
- Cyclophosphamide.
- Aminopterin.
- Phenacetin.
- Smoking.

Signs and symptoms
Depends on the location of the cancer but is usually associated with painless haematuria and lower urinary tract symptoms, e.g. frequency and urgency.

Investigations
- Cystoscopy and ureteroscopy with biopsy.
- Retrograde pyelography.
- CT scan.
- MRI scan.

Treatment
- Conservative: supportive counselling and monitoring of psychological wellbeing (depression). Refer patients to Macmillan nurses.
- Medical: mitomycin, GC regimen (gemcitabine and cisplatin) or MVAC regimen (methotrexate, vinblastine, adriamycin and cisplatin).
- Surgical: nephroureterectomy, cystectomy; radiofrequency ablation may be considered.

Complications
- Metastasis, usually to bone.
## CHRONIC KIDNEY INJURY (CKI)
### What is CKI?
This is well-established renal impairment and is irreversible. Renal function progressively worsens with time. Without treatment the patient will eventually develop end-stage kidney disease (ESKD).

### Causes
- Any renal disease may lead to CKI.
- Glomerulonephritis.
- Hypertension.
- Diabetes mellitus.
- Malignancy.
- Anatomical abnormality of the renal tract.
- Hereditary disease, e.g. polycystic kidney disease.

## ACUTE KIDNEY INJURY (AKI)
### What is AKI?
This is when the kidney fails over a short time period (days to weeks) and is characterised by a rapid fall in glomerular filtration rate (GFR) and an increase in creatinine and urea levels. It may be reversible. AKI may be subdivided into prerenal, intrinsic renal and postrenal failure and these have many different causes.

### Causes

<table>
<thead>
<tr>
<th>Prerenal</th>
<th>Intrinsic</th>
<th>Postrenal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolaemia</td>
<td>Glomerular disease</td>
<td>Obstruction of the ureter</td>
</tr>
<tr>
<td>- Haemorrhage</td>
<td>- Glomerulonephritis</td>
<td>- Stones</td>
</tr>
<tr>
<td>- Burns</td>
<td>- Vasculitis</td>
<td>- Tumour</td>
</tr>
<tr>
<td>- Diuretic use</td>
<td>- Immune complex disease, e.g. systemic lupus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>erythmatosus (SLE)</td>
<td></td>
</tr>
<tr>
<td>Shock</td>
<td>Vascular lesions</td>
<td>Obstruction of the bladder neck</td>
</tr>
<tr>
<td>- Sepsis</td>
<td>- Bilateral renal artery stenosis</td>
<td>- Stones</td>
</tr>
<tr>
<td>- Cardiogenic</td>
<td>- Microangiopathy</td>
<td>- Tumour</td>
</tr>
<tr>
<td></td>
<td>- Malignant hypertension</td>
<td>- Benign prostatic hypertrophy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Prostate cancer</td>
</tr>
<tr>
<td>Hypoperfusion</td>
<td>Tubulointerstitial disease</td>
<td>Obstruction of the urethra</td>
</tr>
<tr>
<td>- Hepatorenal syndrome</td>
<td>- Acute tubular necrosis</td>
<td>- Tumour</td>
</tr>
<tr>
<td>- NSAID use</td>
<td>- Acute tubulo-interstitial nephritis</td>
<td>- Stricture</td>
</tr>
</tbody>
</table>

### Signs and symptoms
Oliguria/anuria/polyuria, nausea and vomiting, confusion, hypertension, oedema (peripheral and pulmonary), fatigue, metallic taste in mouth, unintentional weight loss, itchy skin, skin pigmentation, Kussmaul breathing (metabolic acidosis), anaemia.
The Renal System

Map 4.4

Kidney Injury

**CHRONIC KIDNEY INJURY (CKI)**

What is CKI?
This is well-established renal impairment and is irreversible. Renal function progressively worsens with time. Without treatment the patient will eventually develop end-stage kidney disease (ESKD).

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Investigations
- GFR.
- Bloods: FBC, U&Es, creatinine, calcium and phosphate levels, ESR, CRP, immunology, virology.
- Urinalysis: blood, protein, glucose, leucocytes and nitrates, Bence Jones proteinuria (multiple myeloma).
- Imaging: ultrasound scan.

Treatment
- Conservative: smoking cessation, low salt diet, maintain psychological wellbeing.
- Medical:
  - Treat underlying cause and complications.
  - Control blood pressure.
  - Treat anaemia.
  - Treat acidosis (with sodium bicarbonate).
  - Treat hyperphosphataemia (with phosphate binders).
- Surgical: dialysis (haemodialysis or peritoneal dialysis), renal transplantation.

Complications
- Anaemia.
- Hypertension.
- Renal bone disease.
- Metabolic acidosis.
- Stroke.
- Peripheral nerve damage.
- Carpal tunnel syndrome.
- Oedematous states.
- Depression.

**ACUTE KIDNEY INJURY (AKI)**

What is AKI?
This is when the kidney fails over a short time period (days to weeks) and is characterised by a rapid fall in glomerular filtration rate (GFR) and an increase in creatinine and urea levels. It may be reversible. AKI may be subdivided into prerenal, intrinsic renal and postrenal failure and these have many different causes.

Causes

Signs and symptoms
- Oliguria/anuria, nausea and vomiting, confusion, hypertension, abdominal/flank pain, signs of fluid overload, e.g. ↑ jugular venous pressure (JVP).

Investigations
- GFR.
- Bloods: FBC and platelets, U&Es, creatinine, calcium and phosphate levels, ESR, CRP, immunology, virology.
- Urinalysis: blood, protein, glucose, leucocytes and nitrates, Bence Jones protein.
- Imaging: ultrasound scan.

Treatment
- Maintain renal blood flow and fluid balance.
- Monitor electrolytes.
- Treat underlying cause; classify AKI with **RIFLE** criteria (Risk, Injury, Failure, Loss, End-stage renal disease).
- Stop all nephrotoxic drugs.

Complications
- Metabolic acidosis.
- Hyperkalaemia.
- Hyperphosphataemia.
- Pulmonary oedema.
## NEPHRITIC SYNDROME

### What is nephritic syndrome?
This is a group of signs of varying diseases.

### Signs
Remember these as PHARAOH:
- Proteinuria.
- Haematuria.
- Azotaemia.
- Red blood cell casts.
- Antistreptolysin O titres.
- Oliguria.
- Hypertension.

### Causes
These may be split broadly into 2 categories: focal proliferative and diffuse proliferative causes.

<table>
<thead>
<tr>
<th>Focal proliferative</th>
<th>Diffuse proliferative</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA nephropathy</td>
<td>Rapidly progressive glomerulonephritis, e.g. Goodpasture's syndrome</td>
</tr>
<tr>
<td>Systemic lupus erythematosus (SLE)</td>
<td>SLE</td>
</tr>
<tr>
<td>Henoch–Schönlein purpura</td>
<td>Membranoproliferative glomerulonephritis</td>
</tr>
<tr>
<td>Alport's syndrome</td>
<td>Cryoglobulinaemia</td>
</tr>
</tbody>
</table>

## NEPHROTIC SYNDROME

### What is nephrotic syndrome?
This is a group of signs of varying diseases.

### Signs
Remember these as PHHO:
- Proteinuria >3 g daily.
- Hypoalbuminaemia <30 g/L.
- Hyperlipidaemia, occurs because:
  - Hypoproteinaemia stimulates the production of more proteins from the liver, which results in the synthesis of more lipoproteins.
  - Decreased levels of lipoprotein lipase means that lipid catabolism decreases.
- Oedema.

### Causes
- Minimal change disease.
- Focal segmental glomerulosclerosis.
- Membranous glomerulonephritis.
- Diabetic nephropathy.
- Amyloidosis.
**Investigations**
- Bloods: FBC, WCC and platelets, U&Es, LFTs, creatinine, urea, CRP, ESR, glucose, lipid profile.
- Urinalysis: blood, protein, glucose, leucocytes, nitrites and Bence Jones protein.
- Nephritic screen: serum complement (C3 and C4), antinuclear antibody (ANA), double stranded DNA, antineutrophil cytoplasmic antibody (ANCA), antiglomerular basement membrane (GBM), HIV serology, HBV and HCV serology, blood cultures, Venereal Disease Research Laboratory Test (VDRL) for syphilis.
- Renal biopsy.
- Radiology: ultrasound scan.

**Treatment**
- Conservative: lifestyle advice, low salt diet.
- Medical: treatment depends on cause:
  - Treat hypertension.
  - Treat proteinuria.
  - Treat hypercholesterolaemia.
  - Give prophylactic anticoagulation therapy.
  - Immunotherapy regimen, e.g. prednisolone, cyclophosphamide and azathioprine.
  - Dialysis if severe.

**Complications**
- Nephrotic syndrome.
- Chronic glomerulonephritis.
- Heart failure.

**Investigations**
- Bloods: FBC, WCC and platelets, U&Es, LFTs, creatinine, urea, CRP, ESR, glucose, lipid profile.
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  - Dialysis if severe.

**Complications**
- Hypertension.
- Acute kidney injury.
- Chronic kidney injury.
- Infection.
**ADPKD**

**What is ADPKD?**
This is a dominantly inherited polycystic disease found in adults.

**Causes**
Mutations in the genes encoding a membrane protein called polycystin result in this condition. Two genes code for this protein:
- **PKD1** on chromosome 16 (encodes polycystin 1).
- **PKD2** on chromosome 4 (encodes polycystin 2).

**Signs and symptoms**
- Pain (due to renal cyst haemorrhage).
- Hypertension.
- Haematuria.
- Palpable bilateral flank masses.
- Hepatomegaly.

**Investigations**
- Bloods: FBC, U&Es, calcium and phosphate, PTH.
- Urinalysis and culture.
- Imaging: ultrasound scan is diagnostic.
- Genetic screening and monitoring of blood pressure.

**Remember cystic disease as CAAR**
- Cystic renal dysplasia.
- Autosomal dominant polycystic kidney disease (ADPKD).
- Autosomal recessive polycystic kidney disease (ARPKD).
- Cystic diseases of the Renal medulla.

**ARPKD**

**What is ARPKD?**
This is a recessively inherited polycystic disease found in children presenting with varying levels of kidney and liver disease.

**Causes**
- **PKHD1** on chromosome 6.

**Signs and symptoms**
- Hypertension.
- Those of chronic kidney injury.
- Chronic respiratory infections.
- Those of portal hypertension: ascites, caput medusae and oesophageal varices.
- Failure to thrive.
- Recurrent UTI.
- Polyuria.

**Investigations**
- Antenatal screening is diagnostic.
- Bloods: FBC, U&Es, LFTs.
- Urinalysis and culture.
- Imaging: ultrasound scan (shows enlarged kidney with or without oligohydramnios), CT scan, MRI scan.
**The Renal System**

### Treatment
- Conservative: patient support.
- Medical:
  - Treat hypertension.
  - Antibiotic therapy for urinary tract infection (UTI).
- Surgical: cyst decompression.

### Complications
- Development of chronic kidney injury.
- Remember **LAMB**:
  - Liver cysts.
  - Aneurysms.
  - Mitral valve prolapse.
  - Berry aneurysm rupture leading to subarachnoid haemorrhage.

---

**Cystic diseases of the renal medulla**

Remember **NAMS**:
- **N**ephronophthisis medullary cystic disease.
- **A**cquired cystic disease: usually from dialysis.
- **M**edullary sponge kidney.
- **S**imple cysts.

---

**Treatment**
- Conservative: parental and patient support.
- Medical:
  - Ventilation and long-term oxygen therapy.
  - Treat hypertension (angiotensin converting enzyme [ACE] inhibitors).
  - Antibiotics for UTI.
  - Diuretics for fluid overload.
- Surgical:
  - Nephrectomy.
  - Combined renal and liver transplant.

### Complications
- Hepatic cysts.
- Congenital hepatic fibrosis.
- Proliferative bile ducts.

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**Complications**
- Hepatic cysts.
- Congenital hepatic fibrosis.
- Proliferative bile ducts.
HORSESHOE KIDNEY
What is a horseshoe kidney?
This occurs during development when the lower poles of both kidneys fuse, resulting in the formation of one horseshoe-shaped kidney. This cannot ascend to the normal anatomical position due to the central fused portion catching the inferior mesenteric artery.

Signs and symptoms
- Asymptomatic.
- Recurrent urinary tract infection (UTI).
- Renal calculi.
- Obstructive uropathy.

Causes
- Congenital abnormality.

Investigations
- Ultrasound scan is diagnostic.

Treatment
- Treatment of complications.

Complications
- Susceptible to trauma.
- Renal calculi formation.
- Increased risk of transitional cell carcinoma of the renal pelvis.

Remember these as HERD
- Horseshoe kidney.
- Ecotopic kidney.
- Renal agenesis.
- Duplex ureters.

ECTOPIC KIDNEY
What is an ectopic kidney?
This is a congenital abnormality in which the kidney lies above the pelvic brim or within the pelvis.

Signs and symptoms
- Usually asymptomatic.

Causes
- Genetic abnormalities.
- Poor development of the metanephrogenic diverticulum.
- Teratogen exposure.

Investigations
- Ultrasound scan is diagnostic.

Treatment
- None; treat complications should they develop.

Complications
- UTI.
- Renal calculi.
DUPLEX URETERS
What are duplex ureters?
This occurs when the ureteric bud splits during embryonic development and results in the development of 2 ureters, which drain 1 kidney.

Signs and symptoms
- Asymptomatic.
- Recurrent UTI.

Causes
- Splitting of the ureteric bud.

Investigations
- Ultrasound scan and excretory urography is diagnostic.

Treatment
- Treatment of complications.

Complications
- Vesicoureteral reflux.
- Ureterocele.
- UTI.

RENAL AGENESIS
What is renal agenesis?
Bilateral or unilateral absence of the kidney.

Signs and symptoms

<table>
<thead>
<tr>
<th>Bilateral absence (Potter's syndrome)</th>
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<tr>
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Causes
- Failure of the ureteric bud development.

Investigations
- Antenatal screening.

Treatment
This depends on whether there is bilateral or unilateral absence of the kidney.

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Complications
- Susceptible to trauma (unilateral).
- Death.

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Signs and symptoms
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- Treatment of complications.

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MAP 5.10  Acromegaly 92
What is hyperthyroidism?
This occurs when there is too much circulating thyroid hormone in the body. There are many different causes of hyperthyroidism.

### Causes

<table>
<thead>
<tr>
<th>Cause</th>
<th>Comment</th>
</tr>
</thead>
</table>
| Graves’ disease                 | • This is the most common cause of hyperthyroidism  
• It is an autoimmune condition  
• May be distinguished from other causes of hyperthyroidism by ocular changes, e.g. exophthalmos, and other signs, e.g. pretibial myxoedema  
• It is associated with other autoimmune conditions such as pernicious anaemia |
| Toxic multinodular goitre and toxic solitary nodule goitre | • This is the second most common cause of hyperthyroidism  
• Risk increases with age  
• More common in females  
• A single nodule is suggestive of thyroid neoplasia |
| De Quervain’s thyroiditis       | • This is transient hyperthyroidism that develops after a viral infection  
• Goitre is often painful  
• A period of hypothyroidism may follow |

Signs and symptoms
- Weight loss.
- Warm skin/heat intolerance.
- Diarrhoea.
- Exophthalmos (Graves’ disease).
- Lid lag.
- Palpitations.
- Anxiety.
- Tremor.
- Goitre +/- bruit.
- Brisk reflexes.
The Endocrine System

Hyperthyroidism

**Complications**
- Atrial fibrillation.
- High output heart failure.
- Cardiomyopathy.
- Osteoporosis.

**Treatment**
- Conservative: patient education, smoking cessation.
- Medical:
  - Symptomatic control: Palpitations and tremor: beta-blockers
    Eye symptoms: eye drops for lubrication
  - Antithyroid medication: Carbimazole
    Propylthiouracil
    Side-effects: agranulocytosis (monitor patient’s bloods carefully)
  - Radioactive iodine ablation: Definitive treatment; patients must be euthyroid before commencing treatment
  - Surgical: subtotal thyroidectomy; patients must be euthyroid before the procedure. Give the patient potassium iodide before surgery since it decreases thyroid gland vascularity.

**Investigations**
- TFTs (↓TSH, ↑T3 and ↑T4).
- Ultrasound scan of nodules.
- Fine needle aspiration of solitary nodules to exclude malignancy.
- Isotope scan to assess hot and cold thyroid nodules.

**Causes**
- **Graves' disease**
  - The second most common cause of hyperthyroidism
  - Risk increases with age
  - More common in females
  - A single nodule is suggestive of thyroid neoplasia
- **Toxic multinodular goitre and toxic solitary nodule goitre**
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  - A period of hypothyroidism may follow

**What is hyperthyroidism?**
This occurs when there is too much circulating thyroid hormone in the body.

**Signs and symptoms**
- Weight loss.
- Warm skin/heat intolerance.
- Diarrhoea.
- Exophthalmos (Graves’ disease).
- Lid lag.
- Palpitations.
- Anxiety.
- Tremor.
- Goitre +/– bruit.
- Brisk reflexes.

**Investigations**
- TFTs (↓TSH, ↑T3 and ↑T4).
- Ultrasound scan of nodules.
- Fine needle aspiration of solitary nodules to exclude malignancy.
- Isotope scan to assess hot and cold thyroid nodules.
What is hypothyroidism?
This occurs when there is too little circulating thyroid hormone in the body. There are many different causes of hypothyroidism.

<table>
<thead>
<tr>
<th>Causes</th>
<th>Type of hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iodine deficiency</td>
<td>Primary hypothyroidism</td>
</tr>
<tr>
<td>Hashimoto’s autoimmune thyroiditis</td>
<td></td>
</tr>
<tr>
<td>Post-thyroidectomy/radioactive iodine therapy</td>
<td></td>
</tr>
<tr>
<td>Drug induced, e.g. lithium, overtreatment of hyperthyroidism</td>
<td></td>
</tr>
<tr>
<td>Dysfunction of the hypothalamic–pituitary axis</td>
<td>Secondary hypothyroidism</td>
</tr>
<tr>
<td>Pituitary adenoma</td>
<td></td>
</tr>
<tr>
<td>Sheehan’s syndrome (ischaemic necrosis of the pituitary gland after childbirth)</td>
<td></td>
</tr>
<tr>
<td>Infiltrative disease, e.g. tuberculosis and haemochromatosis</td>
<td></td>
</tr>
</tbody>
</table>
The Endocrine System

**MAP 5.2 Hypothyroidism**

**Complications**
- Hypercholesterolaemia.
- Complications in pregnancy, e.g. pre-eclampsia.
- Hyperthyroidism from overtreatment of hypothyroidism.
- Myxoedema coma.

**Treatment**
- Conservative: patient education.
- Medical: lifelong replacement of thyroid hormone with levothyroxine.

**Investigations**
- TFTs (↑ TSH, ↓ T3 and ↓ T4).
- Thyroid antibodies.
- FBC (anaemia).
- U&E.
- LFTs.
- Creatinine.
- Cholesterol.
- Guthrie test for congenital screening.

**Signs and symptoms**
- Weight gain.
- Cold skin/cold intolerance.
- Constipation.
- Dry skin.
- Thinning of hair.
- Bradycardia.
- Depression.
- Delayed reflexes.

**Causes**

<table>
<thead>
<tr>
<th>Type of hypothyroidism</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary hypothyroidism</td>
<td>• Dysfunction of the hypothalamic–pituitary axis</td>
</tr>
<tr>
<td></td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>• Hashimoto's autoimmune thyroiditis</td>
</tr>
<tr>
<td></td>
<td>• Post-thyroidectomy/radioactive iodine therapy</td>
</tr>
<tr>
<td></td>
<td>• Drug induced, e.g. lithium, overtreatment of hyperthyroidism</td>
</tr>
</tbody>
</table>

**Investigations**
- TFTs (TSH, T3, T4).
- Thyroid antibodies.
- FBC (anaemia).
- U&E.
- LFTs.
- Creatinine.
- Cholesterol.
- Guthrie test for congenital screening.
What is thyroid carcinoma?
This is cancer that originates from follicular or parafollicular cells.

Causes
Malignant neoplasm. Increased risk with childhood neck irradiation.

Thyroid carcinomas may be classified histopathologically.

<table>
<thead>
<tr>
<th>Histological appearance</th>
<th>% of thyroid cancer</th>
<th>Comment</th>
</tr>
</thead>
</table>
| Papillary               | 70%                 | ● Affects younger patients  
                          |                     | ● Spreads to cervical lymph nodes  
                          |                     | ● Good prognosis         |
| Follicular              | 20%                 | ● More common in low iodine areas  
                          |                     | ● Spreads to bone and lungs    |
|                        |                     | ● Good prognosis           |
| Medullary               | 5%                  | ● Arises from parafollicular cells  
                          |                     | ● Calcitonin is a biochemical marker    |
|                        |                     | ● Associated with MEN syndrome  
                          |                     | ● Spreads to lymph nodes         |
| Anaplastic              | <5%                 | ● Affects older patients    
                          |                     | ● Aggressive                   |
|                        |                     | ● Spreads to lymph nodes    
                          |                     | ● Poor prognosis               |
| Other                   | -                   | ● Lymphoma of the thyroid   
                          |                     | ● Sarcoma of the thyroid       |
|                        |                     | ● Hürthle cell carcinoma (a variant of follicular carcinoma) |

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**MAP 5.3 Thyroid Carcinoma**

**Signs and symptoms**
- Thyroid nodules/solitary nodule.
- Signs and symptoms of hyperthyroidism (rarely).
- Signs and symptoms of hypothyroidism (rarely).

**Investigations**
- Bloods: TFTs to assess thyroid status.
- Fine needle aspiration cytology.
- Diagnostic lobectomy.
- Radiology:
  - Ultrasound scan of thyroid.
  - Thyroid isotope scan (hot nodules are less likely to indicate malignancy).

**Complications**
- Death: anaplastic carcinoma.
- Metastasis.
- Recurrence.
- Complications of surgery:
  - Haemorrhage.
  - Infection.
  - Damage to the recurrent laryngeal nerve.
  - Hypoparathyroidism.
- Hypothyroidism.

**Treatment**
This depends on histological classification.

<table>
<thead>
<tr>
<th>Histological appearance</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| Papillary               | Lesion <1 cm: thyroid lobectomy, then lifelong levothyroxine and annual thyroglobulin measurements  
  | Lesion >1 cm: total thyroidectomy, radio-iodine ablation then lifelong levothyroxine and annual thyroglobulin measurements |
| Follicular              | Lesion <1 cm: thyroid lobectomy, then lifelong levothyroxine and annual thyroglobulin measurements  
  | Lesion >1 cm: total thyroidectomy, radio-iodine ablation then lifelong levothyroxine and annual thyroglobulin measurements |
| Medullary               | Total thyroidectomy then lifelong levothyroxine; screen family members for multiple endocrine neoplasia (MEN) syndrome and thyroid cancer |
| Anaplastic              | Debulking surgery and palliative care |

**What is thyroid carcinoma?**
This is cancer that originates from follicular or parafollicular cells.

**Causes**
Malignant neoplasm. Increased risk with childhood neck irradiation.

**Thyroid carcinomas may be classified histopathologically.**

<table>
<thead>
<tr>
<th>Histological appearance</th>
<th>% of thyroid cancer</th>
<th>Comment</th>
</tr>
</thead>
</table>
| Papillary               | 70%                 | Affects younger patients  
  |                       | Spreads to cervical lymph nodes  
  |                       | More common in low iodine areas  
  |                       | Arises from parafollicular cells |
| Follicular              | 20%                 | Calcitonin is a biochemical marker |
| Medullary               | 5%                  | Associated with MEN syndrome and thyroid cancer |
| Anaplastic              | <5%                 | Affects older patients  
  |                       | Aggressive  
  | Other                   | Lymphoma of the thyroid  
  |                       | Sarcoma of the thyroid  
  |                       | Good prognosis  
  |                       | Good prognosis  
  |                       | Poor prognosis  
  |                       | Hürthle cell carcinoma (a variant of follicular carcinoma) |
### What is DM?
This is a metabolic condition in which the patient has hyperglycaemia due to insulin insensitivity or decreased insulin secretion.

- **Type 1 DM**: this is an autoimmune condition, which results in the destruction of the pancreatic beta cells resulting in no insulin production. This condition has a juvenile onset and is associated with HLA-DR3 and HLA-DR4. Patients are at risk of ketoacidosis.

- **Type 2 DM**: this occurs when patients gradually become insulin resistant or when the pancreatic beta cells fail to secrete enough insulin or both. It usually has a later life onset; however, the incidence is increasing in young populations due to environmental factors such as increasing obesity and sedentary lifestyle. Patients are at risk of developing a hyperosmolar state.

- **Other cause of DM include**: chronic pancreatitis, gestational DM and cystic fibrosis.

### Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Type 1 DM</th>
<th>Type 2 DM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conservative</strong></td>
<td><a href="#">Dietary advice</a>, BMI measurement, Smoking cessation, Decrease alcohol intake, Regular blood glucose and HbA1c monitoring, Encourage exercise</td>
<td><a href="#">Dietary advice: high in complex carbohydrates, low in fat</a>, BMI measurement, Smoking cessation, Decrease alcohol intake, Regular blood glucose and HbA1c monitoring, Encourage exercise</td>
</tr>
<tr>
<td><strong>Medical</strong></td>
<td>See pages 80–82 for antidiabetic agents</td>
<td>See pages 80–82 for antidiabetic agents</td>
</tr>
</tbody>
</table>
**Diabetes Mellitus (DM)**

**What is DM?**
This is a metabolic condition in which the patient has hyperglycaemia due to insulin insensitivity or decreased insulin secretion.

- **Type 1 DM**: this is an autoimmune condition, which results in the destruction of the pancreatic beta cells resulting in no insulin production. This condition has a juvenile onset and is associated with HLA-DR3 and HLA-DR4. Patients are at risk of ketoacidosis.

- **Type 2 DM**: this occurs when patients gradually become insulin resistant or when the pancreatic beta cells fail to secrete enough insulin or both. It usually has a later life onset; however, the incidence is increasing in young populations due to environmental factors such as increasing obesity and sedentary lifestyle. Patients are at risk of developing a hyperosmolar state.

- **Other cause of DM include**: chronic pancreatitis, gestational DM and cystic fibrosis.

**Treatment**

**Type 1 DM**
- Conservative Dietary advice
- BMI measurement
- Smoking cessation
- Decrease alcohol intake
- Regular blood glucose and HbA1c monitoring
- Encourage exercise
- See pages 80–82 for antidiabetic agents

**Type 2 DM**
- Dietary advice: high in complex carbohydrates, low in fat
- BMI measurement
- Smoking cessation
- Decrease alcohol intake
- Regular blood glucose and HbA1c monitoring
- Encourage exercise
- See pages 80–82 for antidiabetic agents

**Signs and symptoms**

- **General**: polyuria, polyphagia, polydipsia, blurred vision, glycosuria, signs of macrovascular and microvascular disease.

- **More common in type 1 DM**: acetone breath, weight loss, Kussmaul breathing, nausea and vomiting.

**Complications**

- **Macrovascular**: hypertension, increased risk of stroke, myocardial infarction, diabetic foot.

- **Microvascular**: nephropathy, peripheral neuropathy (glove and stocking distribution), retinopathy, erectile dysfunction.

- **Psychological**: depression.

**Investigations**

Diagnostic investigations include:

- Fasting plasma glucose: >7 mmol/L (126 mg/dL).
- Random plasma glucose (plus DM symptoms): >11.1 mmol/L (200 mg/dL).
- HbA1c: >6.5% (48 mmol/mol).

Other tests include:

- Impaired glucose tolerance test (for borderline cases):
  - Fasting plasma glucose: <7 mmol/L (126 mg/dL) and at 2 h, after a 75 g oral glucose load, a level of 7.8–11 mmol/L (140–200 mg/dL).
  - Plasma glucose at 2 h: >11.1 mmol/L (>200 mg/dL).
- Impaired fasting glucose: plasma glucose: 5.6–6.9 mmol/L (110–126 mg/dL).

**Investigations**

Diagnostic investigations include:

- Fasting plasma glucose: >7 mmol/L (126 mg/dL).
- Random plasma glucose (plus DM symptoms): >11.1 mmol/L (200 mg/dL).
- HbA1c: >6.5% (48 mmol/mol).

Other tests include:

- Impaired glucose tolerance test (for borderline cases):
  - Fasting plasma glucose: <7 mmol/L (126 mg/dL) and at 2 h, after a 75 g oral glucose load, a level of 7.8–11 mmol/L (140–200 mg/dL).
  - Plasma glucose at 2 h: >11.1 mmol/L (>200 mg/dL).
- Impaired fasting glucose: plasma glucose: 5.6–6.9 mmol/L (110–126 mg/dL).
### TABLE 5.1 Antidiabetic Agents

For a full description of diabetes mellitus (DM) management and which drugs to use first line, please follow the website link provided for NICE guidelines in Appendix 2

<table>
<thead>
<tr>
<th>Class of antidiabetic agent</th>
<th>Example</th>
<th>Mechanism of action</th>
<th>Uses</th>
<th>Side-effects</th>
<th>Contraindications</th>
<th>Drug interactions</th>
</tr>
</thead>
</table>
| Biguanides                 | Metformin | ↑ Peripheral insulin sensitivity  
↑ Glucose uptake into and use by skeletal muscle  
↓ Hepatic gluconeogenesis  
↓ Intestinal glucose absorption | Type 2 DM (first choice in overweight patients)  
Polycystic ovarian syndrome | Gastrointestinal tract (GIT) disturbance, e.g. diarrhoea  
Nausea  
Vomiting  
Lactic acidosis | Renal failure  
Cardiac failure  
Respiratory failure  
Hepatic failure (The above increase the risk of developing lactic acidosis) | Contrast agents  
Angiotensin converting enzyme (ACE) inhibitors  
Alcohol  
Nonsteroidal anti-inflammatory drugs (NSAIDs)  
Steroids |
| Sulphonylureas             | Glipizide | Block potassium channels on the pancreatic beta cells, thus stimulating insulin release | Type 2 DM | GIT disturbance  
Hypoglycaemia  
Weight gain | Renal failure  
Hepatic failure  
Porphyria  
Pregnancy  
Breastfeeding | ACE inhibitors  
Alcohol  
NSAIDs  
Steroids |
| Meglitinides (glinides)    | Repaglinide | Block potassium channels on the pancreatic beta cells, thus stimulating insulin release | Type 2 DM | Weight gain  
Hypoglycaemia | Hepatic failure  
Pregnancy  
Breastfeeding | Ciclosporin  
Trimethoprim  
Clarithromycin |
<table>
<thead>
<tr>
<th>Class of antidiabetic agent</th>
<th>Antidiabetic Agents</th>
<th>Mechanism of action</th>
<th>Uses</th>
<th>Side-effects</th>
<th>Contraindications</th>
<th>Drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>Metformin</td>
<td>Peripheral insulin sensitivity/Glucose uptake into and use by skeletal muscle/Hepatic gluconeogenesis/Intestinal glucose absorption</td>
<td>Type 2 DM (first choice in overweight patients)/Polycystic ovarian syndrome</td>
<td>Gastrointestinal tract disturbance, e.g. diarrhoea/Nausea/Vomiting</td>
<td>Renal failure/Cardiac failure/Respiratory failure/Hepatic failure (The above increase the risk of developing lactic acidosis)</td>
<td>Contrast agents/Angiotensin converting enzyme (ACE) inhibitors/Alcohol/Nonsteroidal anti-inflammatory drugs (NSAIDs)/Steroids</td>
</tr>
<tr>
<td>Sulphonylureas</td>
<td>Glipizide</td>
<td>Block potassium channels on the pancreatic beta cells, thus stimulating insulin release</td>
<td>Type 2 DM</td>
<td>GIT disturbance</td>
<td>Renal failure/Hepatic failure/Porphyria/Pregnancy/Breastfeeding</td>
<td>ACE inhibitors/Alcohol/NSAIDs/ Steroids/Ciclosporin/Trimethoprim/Clarithromycin</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>(glinides)</td>
<td>Repaglinide</td>
<td>Type 2 DM</td>
<td>GIT disturbance</td>
<td>Hypoglycaemia/Weight gain</td>
<td>Hepatic failure/Pregnancy/Breastfeeding</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>(glitazones)</td>
<td>Pioglitazone</td>
<td>Type 2 DM</td>
<td>GIT disturbance</td>
<td>Hypoglycaemia/Weight gain/Hepatotoxicity</td>
<td>Fracture risk/Pregnancy/Heart failure/Bladder cancer</td>
</tr>
<tr>
<td>Incretins</td>
<td>Exenatide</td>
<td>Analogue of glucagon-like peptide (GLP)-1</td>
<td>Type 2 DM</td>
<td>GIT disturbance, e.g. diarrhoea/Acute pancreatitis</td>
<td>Thyroid cancer/Multiple endocrine neoplasia (MEN) 2 syndrome</td>
<td>Bexarotene</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>Inhibits dipeptidyl peptidase (DPP)-4</td>
<td>Type 2 DM</td>
<td>GIT disturbance, e.g. diarrhoea/Infection of the respiratory and urinary tract/Hepatotoxicity/Peripheral oedema</td>
<td>History of serious hypersensitivity reaction</td>
<td>Thiazolidinedione</td>
<td></td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitors</td>
<td>Acarbose</td>
<td>Inhibits alpha-glucosidase</td>
<td>Type 2 DM</td>
<td>GIT disturbance, e.g. diarrhoea</td>
<td>Inflammatory bowel disease (IBD)/Intestinal obstruction/Hepatic cirrhosis</td>
<td>Orlistat/Pancreatin</td>
</tr>
<tr>
<td>Amylin analogues</td>
<td>Pramlintide</td>
<td>Analogue of amylin</td>
<td>Type 1 DM/Type 2 DM</td>
<td>Severe hypoglycaemia/Gastroparestis</td>
<td>Hypersensitivity to pramlintide/Acute pancreatitis</td>
<td>Acarbose</td>
</tr>
</tbody>
</table>

Continued overleaf
**TABLE 5.1 Antidiabetic Agents (Continued)**

<table>
<thead>
<tr>
<th>Class of antidiabetic agent</th>
<th>Example</th>
<th>Mechanism of action</th>
<th>Uses</th>
<th>Side-effects</th>
<th>Contraindications</th>
<th>Drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin therapy</td>
<td>Rapid acting, e.g. insulin lispro</td>
<td>Replaces insulin <strong>Mechanism of action of insulin:</strong> Insulin binds to tyrosine kinase receptors where it initiates 2 pathways by phosphorylation: 1 The MAP kinase signalling pathway: this is responsible for cell growth and proliferation. 2 The PI-3K signalling pathway: this is responsible for the transport of GLUT-4 receptors to the cell surface membrane; GLUT-4 transports glucose into the cell; this pathway is also responsible for protein, lipid and glycogen synthesis</td>
<td>Type 1 DM</td>
<td>Weight gain Hypoglycaemia Localised lipoatrophy Hypokalaemia</td>
<td>Hypersensitivity to any of the therapy ingredients Hypoglycaemia</td>
<td>Repaglinide increases risk of myocardial infarction (MI) and hypoglycaemia Monoamine oxidase inhibitors may increase insulin secretion Corticosteroids decrease the effect of insulin Levothyroxine decreases the effect of insulin Thiazide diuretics decrease the effects of insulin</td>
</tr>
<tr>
<td></td>
<td>Short acting, e.g. soluble insulin</td>
<td>Intermediate acting, e.g. isophane insulin Long acting, e.g. insulin glargine Biphasic, e.g. biphasic isophane insulin</td>
<td>Type 2 DM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
What is DI?
A disorder caused by low levels of or insensitivity to antidiuretic hormone (ADH) leading to polyuria. This can be cranial or nephrogenic in origin.

Causes
- Cranial: decreased ADH is released by the posterior pituitary gland. Remember this as CIVIT:
  - Congenital defect in ADH gene.
  - Idiopathic.
  - Vascular.
  - Infection: meningoencephalitis.
  - Tumour(e.g. pituitary adenoma), Tuberculosis and Trauma.
- Nephrogenic: the kidney does not respond to ADH. Remember this as DIMC:
  - Drugs, e.g. lithium.
  - Inherited.
  - Metabolic ↓ potassium, ↑ calcium.
  - Chronic renal disease.
(See also Figure 5.1.)

Signs and symptoms
- Polydypsia.
- Polyuria.
- Dehydration.
Diabetes Insipidus (DI)

Treatment
This depends on the cause:
- Conservative: patient education. Education on how to monitor fluid levels and dietary salt levels. Advise patients to wear a MedicAlert® bracelet.
- Medical:

<table>
<thead>
<tr>
<th>Cranial cause</th>
<th>Nephrogenic cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desmopressin – a synthetic replacement for vasopressin; it increases the number of aquaporin-2 channels in the distal convoluted tubules and the collecting ducts. This increases water reabsorption</td>
<td>High-dose desmopressin</td>
</tr>
<tr>
<td>Correction of electrolyte imbalances</td>
<td>Thiazide diuretics</td>
</tr>
<tr>
<td>Prostaglandin synthase inhibitors</td>
<td></td>
</tr>
</tbody>
</table>

Complications
- Electrolyte imbalance.
- Dehydration.

Investigations

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Cranial cause</th>
<th>Nephrogenic cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma osmolality</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Urine osmolality</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Plasma Na⁺</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>24-h urine volume</td>
<td>&gt;2 L</td>
<td>&gt;2 L</td>
</tr>
<tr>
<td>Water deprivation test</td>
<td>Urine does not concentrate</td>
<td>Urine does not concentrate</td>
</tr>
<tr>
<td>After treatment with desmopressin</td>
<td>Urine becomes concentrated</td>
<td>Urine does not concentrate</td>
</tr>
<tr>
<td>MRI scan</td>
<td>Look for abnormality of the pituitary gland, e.g. tumour</td>
<td></td>
</tr>
</tbody>
</table>
**HYPOPARATHYROIDISM**

**What is it?**
This occurs when too little PTH is produced from the parathyroid gland. It may be categorised into congenital, acquired, transient and inherited causes.

<table>
<thead>
<tr>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
</tr>
<tr>
<td>Congenital</td>
</tr>
<tr>
<td>Acquired</td>
</tr>
<tr>
<td>Transient</td>
</tr>
<tr>
<td>Inherited</td>
</tr>
</tbody>
</table>

**Signs and symptoms**
These depend on the cause: abdominal pain, myalgia, muscle spasm, seizures, fatigue, headaches, carpopedal spasm, Chvostek’s sign, Trousseau’s sign.

**Investigations**

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Hypoparathyroidism</th>
<th>Pseudohypoparathyroidism</th>
<th>Pseudopseudohypoparathyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH level</td>
<td>↓</td>
<td>↑</td>
<td>Normal</td>
</tr>
<tr>
<td>Serum calcium</td>
<td>↓</td>
<td>↓</td>
<td>Normal</td>
</tr>
<tr>
<td>Serum phosphate</td>
<td>↑</td>
<td>↑</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Other investigations include:
- Bloods: FBC, U&Es, LFTs, creatinine, urea.
- ECG: arrhythmias.
- ECHO: cardiac structural defects (DiGeorge syndrome).
- Radiology: X-ray of hand (pseudohypoparathyroidism patients have shorter 4th and 5th metacarpals).

**Treatment**
- Conservative: diet high in calcium and low in phosphate. Support for parents.
- Medical: calcium and vitamin D supplements.

**Complications**
- Renal calculi.
- Arrhythmias.
- Cataract formation.
- Dental problems.
**HYPERPARATHYROIDISM**

**What is it?**
This occurs when too much parathyroid hormone (PTH) is produced from the parathyroid gland. It may be categorised into primary, secondary and tertiary causes.

<table>
<thead>
<tr>
<th>Type</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Parathyroid adenoma</td>
</tr>
<tr>
<td></td>
<td>Parathyroid hyperplasia</td>
</tr>
<tr>
<td></td>
<td>Parathyroid carcinoma</td>
</tr>
<tr>
<td></td>
<td>Drug induced, e.g. lithium</td>
</tr>
<tr>
<td>Secondary</td>
<td>Vitamin D deficiency</td>
</tr>
<tr>
<td></td>
<td>Chronic kidney injury</td>
</tr>
<tr>
<td>Tertiary</td>
<td>Prolonged secondary hyperparathyroidism</td>
</tr>
</tbody>
</table>

**Signs and symptoms**
These depend on the cause.

<table>
<thead>
<tr>
<th>Primary – ‘Bones, moans, groans and stones’</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>Osteomalacia</td>
</tr>
<tr>
<td>Bones, e.g. pain, osteoporosis</td>
<td>Rickets</td>
</tr>
<tr>
<td>Moans, e.g. depression, fatigue</td>
<td>Renal osteodystrophy</td>
</tr>
<tr>
<td>Groans, e.g. myalgia</td>
<td></td>
</tr>
<tr>
<td>Stones, e.g. kidney stones</td>
<td></td>
</tr>
</tbody>
</table>

**Investigations**

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Primary</th>
<th>Secondary</th>
<th>Tertiary</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH level</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Serum calcium</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Serum phosphate</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>

Other investigations include:
- Bloods: FBC, U&Es, LFTs, creatinine.
- Urine calcium level.
- Dual energy X-ray (DEXA) scan.
- Radiology:
  - Ultrasound scan of kidneys and neck.
  - Plain X-ray (for bone changes).
  - Parathyroid gland biopsy.
Hyperparathyroidism

Type | Cause |
--- | --- |
Primary | Parathyroid adenoma, Parathyroid hyperplasia, Parathyroid carcinoma, Drug induced (e.g. lithium), Vitamin D deficiency, Chronic kidney injury, Prolonged secondary hyperparathyroidism |
Secondary | |
Tertiary | |

Signs and symptoms:
- Primary: ‘Bones, moans, groans and stones’
- Secondary: Asymptomatic, Bones, e.g. pain, osteoporosis, Moans, e.g. depression, fatigue, Groans, e.g. myalgia, Stones, e.g. kidney stones
- Tertiary: Osteomalacia, Rickets, Renal osteodystrophy

Investigations:
- Primary: PTH level
- Secondary: Serum calcium, Serum phosphate
- Tertiary: Other investigations include:
  - Bloods: FBC, U&Es, LFTs, creatinine
  - Urine calcium level
  - Dual energy X-ray (DEXA) scan
  - Radiology:
    - Ultrasound scan of kidneys and neck
    - Plain X-ray (for bone changes)
    - Parathyroid gland biopsy

Type of treatment:
- Primary: Conservative (Monitoring, Increase oral fluid intake)
- Secondary: Medical (Bisphosphonates), Secondary Tertiary: Medical (Calcimimetics, e.g. cinacalcet)
- Tertiary: Medical (Parathyroidectomy if unresponsive to medical therapy), Surgical (Parathyroidectomy)

Complications:
- Renal calculi
- Acute pancreatitis
- Peptic ulceration
- Calcification of the cornea
What is Cushing’s syndrome?
This is a collection of signs and symptoms that occur when a patient has long-term exposure to cortisol. There are many causes of Cushing’s syndrome and they may be classified as exogenous or endogenous causes.

### Causes

<table>
<thead>
<tr>
<th>Type</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exogenous</td>
<td>Iatrogenic, e.g. prescription of glucocorticoids for asthma</td>
</tr>
<tr>
<td>Endogenous</td>
<td>This may be split into adrenocorticotropic hormone (ACTH) dependent and ACTH independent causes:</td>
</tr>
<tr>
<td></td>
<td>• ACTH dependent:</td>
</tr>
<tr>
<td></td>
<td>○ Cushing’s disease: this occurs when ACTH is produced from a pituitary adenoma. Use a low-dose dexamethasone test to confirm.</td>
</tr>
<tr>
<td></td>
<td>○ Ectopic ACTH production (usually from small cell lung cancer).</td>
</tr>
<tr>
<td></td>
<td>• ACTH independent: <strong>CARS</strong>:</td>
</tr>
<tr>
<td></td>
<td>○ Cancer: adrenal adenoma.</td>
</tr>
<tr>
<td></td>
<td>○ Adrenal nodular hyperplasia.</td>
</tr>
<tr>
<td></td>
<td>○ Rare causes: McCune–Albright syndrome.</td>
</tr>
<tr>
<td></td>
<td>○ Steroid use.</td>
</tr>
</tbody>
</table>

### Signs and symptoms
- Moon face.
- Central obesity.
- Buffalo hump.
- Acne.
- Hypertension.
- Hyperglycaemia.
- Striae.
- Vertebral collapse.
- Proximal muscle wasting.
- Psychosis.

### Investigations
- Diagnostic tests: urinary free cortisol, low-dose and high-dose dexamethasone suppression test.
- Bloods: FBC, U&Es, LFTs, glucose, lipid levels.
- Other: dual energy X-ray (DEXA) scan.

### Complications
- Osteoporosis.
- Diabetes mellitus.
- Hypertension.
- Immunosuppression.
- Cataracts.
- Striae formation.
- Ulcers.

### Treatment
- Conservative: education about the condition. Advise patient to decrease alcohol consumption since alcohol increases cortisol levels.
- Medical: ketoconazole, metyrapone, mitotane.
  Treat complications such as hypertension and diabetes mellitus.
- Surgical: trans-sphenoidal surgery to remove pituitary adenoma or bilateral adrenalectomy to remove adrenal adenoma, if indicated.
The Endocrine System

Figure 5.2 The Hypothalamic–Pituitary–Adrenal Axis

- **Conservative**: patient education. Patient must carry a steroid alert card.
- **Medical**: replace glucocorticoids and mineralocorticoids with hydrocortisone and fludrocortisone; treat complications.
- **Surgery**: surgical excision of tumour, if indicated.

**Complications**
- Adrenal crisis.
- Hyperkalaemia.
- Hypoglycaemia.
- Eosinophilia.
- Alopecia.
- Addison's disease is associated with other conditions such as 3PGH:
  - Pernicious anaemia.
  - Primary ovarian failure.
  - Polyglandular syndrome.
  - Graves' disease.
  - Hashimoto's thyroiditis.

**Investigations**
- **Diagnostic tests**: Adrenocorticotrophic hormone (ACTH) and cortisol measurements. Insulin tolerance test. Short tetracosactide test aka Short Synacthen test.
- **Bloods**: FBC, U&Es (\(_{Na^+}, _{K^+}\)), LFTs, glucose, lipid levels, serum calcium.

**Signs and symptoms**
- Unintentional weight loss.
- Myalgia.
- Weakness.
- Fatigue.
- Postural hypotension.
- Abdominal pain.

**What is adrenal insufficiency?**
This occurs when the adrenal glands fail to produce sufficient steroid hormone. The causes of adrenal insufficiency may be categorised into primary and secondary adrenal failure.

**Type** | **Cause**
---|---
**Primary**
- Addison's disease; causes:
  - MAIL:
    - Metastases from breast, lung and renal cancers.
    - Autoimmune.
    - Infections, e.g. tuberculosis (commonest cause) and opportunistic infections, such as cytomegalovirus (CMV) in HIV patients.
    - Lymphomas.
- Idiopathic.
- Postadrenalectomy.
- Prolonged prednisolone use.
- Pituitary adenoma.
- Sheehan's syndrome.

**Secondary**
- Destruction of the adrenal cortex leads to cortisol deficiency.
What is adrenal insufficiency?
This occurs when the adrenal glands fail to produce sufficient steroid hormone. The causes of adrenal insufficiency may be categorised into primary and secondary adrenal failure.

<table>
<thead>
<tr>
<th>Type</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>• Addison’s disease; causes: MAIL:</td>
</tr>
<tr>
<td></td>
<td>o Metastases from breast, lung and renal cancers.</td>
</tr>
<tr>
<td></td>
<td>o Autoimmune.</td>
</tr>
<tr>
<td></td>
<td>o Infections, e.g. tuberculosis (commonest cause) and opportunistic infections, such as cytomegalovirus (CMV) in HIV patients.</td>
</tr>
<tr>
<td></td>
<td>o Lymphomas.</td>
</tr>
<tr>
<td></td>
<td>• Idiopathic.</td>
</tr>
<tr>
<td></td>
<td>• Postadrenalectomy.</td>
</tr>
<tr>
<td>Secondary</td>
<td>• Prolonged prednisolone use.</td>
</tr>
<tr>
<td></td>
<td>• Pituitary adenoma.</td>
</tr>
<tr>
<td></td>
<td>• Sheehan’s syndrome.</td>
</tr>
</tbody>
</table>

Signs and symptoms
• Unintentional weight loss.
• Myalgia.
• Weakness.
• Fatigue.
• Postural hypotension.
• Abdominal pain.
• Skin pigmentation.
• Body hair loss.
• Diarrhoea.
• Nausea.
• Vomiting.
• Depression.

Investigations
• Diagnostic tests:
  o Adrenocorticotropic hormone (ACTH) and cortisol measurements.
  o Insulin tolerance test.
  o Short tetracosactide test aka Short Synacthen test.
• Bloods: FBC, U&Es (Na⁺, K⁺), LFTs, glucose, lipid levels, serum calcium.
• Radiology:
  o CXR (look for lung cancer).
  o CT and MRI scan of the adrenal glands.

Treatment
• Conservative: patient education. Patient must carry a steroid alert card.
• Medical: replace glucocorticoids and mineralocorticoids with hydrocortisone and fludrocortisone; treat complications.
• Surgery: surgical excision of tumour, if indicated.
The Endocrine System

MAP 5.9 Adrenal Insufficiency

**Treatment**
- **Conservative:** patient education. Patient must carry a steroid alert card.
- **Medical:** replace glucocorticoids and mineralocorticoids with hydrocortisone and fludrocortisone; treat complications.
- **Surgery:** surgical excision of tumour, if indicated.

**Complications**
- Adrenal crisis.
- Hyperkalaemia.
- Hypoglycaemia.
- Eosinophilia.
- Alopecia.
- Addison’s disease is associated with other conditions such as 3PGH:
  - Pernicious anaemia.
  - Primary ovarian failure.
  - Polyglandular syndrome.
  - Graves’ disease.
  - Hashimoto’s thyroiditis.

**Signs and symptoms**
- Unintentional weight loss.
- Myalgia.
- Weakness.
- Fatigue.
- Postural hypotension.
- Abdominal pain.

**What is adrenal insufficiency?**
This occurs when the adrenal glands fail to produce sufficient steroid hormone. The causes of adrenal insufficiency may be categorised into primary and secondary adrenal failure.

**Type** | **Cause**
--- | ---
Primary | Addison’s disease:
- M: Metastases from breast, lung and renal cancers.
- A: Autoimmune.
- I: Infections, e.g. tuberculosis (commonest cause) and opportunistic infections, such as cytomegalovirus (CMV) in HIV patients.
- L: Lymphomas.
- Idiopathic.
- Postadrenalectomy.

Secondary | Prolonged prednisolone use.
- Pituitary adenoma.
- Sheehan’s syndrome.

**Investigations**
- **Diagnostic tests:**
  - Adrenocorticotrophic hormone (ACTH) and cortisol measurements.
  - Insulin tolerance test.
  - Short tetracosactide test aka Short Synacthen test.
- **Bloods:** FBC, U&Es (Na+, K+), LFTs, glucose, lipid levels, serum calcium.
- **Radiology:**
  - CXR (look for lung cancer).
  - CT and MRI scan of the adrenal glands.

**FIGURE 5.2 The Hypothalamic–Pituitary–Adrenal Axis**

**FIGURE 5.3 Anatomy of the Adrenal Cortex and Adrenal Medulla**

- Mesoderm → Capsule
  - Zona glomerulosa → Aldosterone
  - Zona fascicularis → Cortisol
  - Zona reticularis → Androgens
- Neural crest → Medulla → Adrenaline Noradrenaline
**What is acromegaly?**
Acromegaly is a syndrome that results from excessive growth hormone (GH) production after fusion of the epiphyseal plates. Excess GH produced before epiphyseal plate fusion causes gigantism.

**Causes**
- Pituitary adenoma (most common).
- GH releasing hormone (GHRH) production from bronchial carcinoid.

**Signs and symptoms**
- Increased jaw size.
- Increased hand size.
- Macroglossia.
- Lower pitch of voice.
- Carpal tunnel syndrome.
- Ask to see old photographs of the patient and note changes in appearance.

**Complications**
- Increased risk of cardiovascular disease.
- Hypertension.
- Diabetes mellitus.
- Increased risk of colon cancer.
- Erectile dysfunction.
- Postsurgical, e.g. infection, cerebrospinal fluid (CSF) leak.

**Investigations**
- Bloods: FBC, U&Es, creatinine, LFTs, glucose, lipid levels, GH levels, glucose tolerance test, insulin-like growth factor (IGF)-1 levels (raised), prolactin levels.
- Radiology:
  - CXR.
  - CT and MRI scan.
- ECG and ECHO: assess for cardiac complications, e.g. cardiomyopathy.
- Visual field testing: bilateral hemianopia.

**Treatment**
- Conservative: patient education. Inform the patient that bone changes will not revert after treatment.
- Medical:
  - Somatostatin analogues, e.g. octreotide.
  - Dopamine agonists, e.g. cabergoline.
  - GH receptor antagonists, e.g. pegvisomant.
- Surgery: trans-sphenoidal surgical excision of the adenoma is the treatment of choice.
### What is anaemia?
Anaemia occurs when the haemoglobin (Hb) concentration is low. This condition may be classified as microcytic, macrocytic or normocytic.

### TABLE 6.1 Anaemia

<table>
<thead>
<tr>
<th>Type of anaemia</th>
<th>Causes</th>
<th>Symptoms</th>
<th>Signs</th>
<th>Investigations</th>
<th>Treatment</th>
<th>Complications</th>
</tr>
</thead>
</table>
| Microcytic     | Iron deficiency of varying cause, e.g.  
Menorrhagia  
Pregnancy  
Gastrointestinal tract malignancy  
Oesophagitis  
Gastro-oesophageal reflux disease  
Coeliac disease  
Hookworm  
Schistosomiasis  
Diet low in iron  
Thalassaemia: see page 96 | Fatigue  
Palpitations  
Headache  
Dyspnoea | Pallor  
Nail changes, e.g. koilonychia  
Angular cheilitis  
Atrophic glossitis | FBC  
- Microcytic, hypochromic anaemia  
- ↓ MCV (<80 fL)  
- ↓ MCH  
- ↓ Ferritin  
- ↓ Iron  
- ↑ Total iron binding capacity (TIBC)  
Blood film: anisocytosis and poikilocytosis  
Investigate causes, e.g. endoscopy, stool microscopy, barium enema | Treat cause  
Ferrous sulphate | Fatigue  
Increased risk of infection  
Heart failure |
| Macrocytic     | Remember these as FAT RBC:  
Folate deficiency  
Alcohol  
Thyroid (hypothyroidism) | Fatigue  
Palpitations  
Headache  
Dyspnoea  
Irritability  
Depression | Pallor  
Glossitis  
Angular cheilitis  
Paraesthesiae  
Subacute degeneration of the spinal cord | FBC  
- ↓ Hb  
- ↑ MCV (>96 fL)  
- ↓ Vitamin B₁₂  
- ↓ Folate  
- ↓ Reticulocytes  
- ↓ Platelets (if severe) | Treat cause  
If pernicious anaemia then treat with hydroxocobalamin injections | Fatigue  
Heart failure  
Splenomegaly  
Neuropsychiatric and neurological complications |
<table>
<thead>
<tr>
<th>Type of Anaemia</th>
<th>Causes</th>
<th>Symptoms</th>
<th>Signs</th>
<th>Investigations</th>
<th>Treatment</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcytic</td>
<td>Iron deficiency of varying cause, e.g. Menorrhagia, Pregnancy, Gastrointestinal tract malignancy, Oesophagitis, Gastro-oesophageal reflux disease, Coeliac disease, Hookworm, Schistosomiasis, Diet low in iron</td>
<td>Fatigue, Palpitations, Headache, Dyspnoea, Irritability, Depression</td>
<td>Pallor, Nail changes, e.g. koilonychia, Angular cheilitis, Atrophic glossitis, Paraesthesiae, Subacute degeneration of the spinal cord</td>
<td>FBC • Microcytic, hypochromic anaemia • MCV (&lt;80 fL) • MCH • Ferritin • Iron • Total iron binding capacity (TIBC)</td>
<td>Treat cause</td>
<td>Fatigue, Increased risk of infection, Heart failure, Splenomegaly, Neuropsychiatric and neurological complications</td>
</tr>
<tr>
<td>Macrocytic</td>
<td>Haemolytic anaemia of varying cause, e.g. Glucose-6-phosphate dehydrogenase deficiency, Hereditary spherocytosis, Erythroblastosis fetalis, Sickle cell disease, Warm antibody autoimmune haemolytic anaemia and cold agglutinin disease, Anaemia of chronic disease, e.g. rheumatoid arthritis Aplastic anaemia</td>
<td>Fatigue, Palpitations, Headache, Dyspnoea, Symptoms of underlying disease</td>
<td>Pallor, Signs of underlying disease</td>
<td>FBC • Hb • MCV • Vitamin B12 • Folate • Reticulocytes • Platelets</td>
<td>Treat cause</td>
<td>Fatigue, Heart failure</td>
</tr>
<tr>
<td>Normocytic</td>
<td>Haemolytic anaemia of varying cause, e.g. Glucose-6-phosphate dehydrogenase deficiency, Hereditary spherocytosis, Erythroblastosis fetalis, Sickle cell disease, Warm antibody autoimmune haemolytic anaemia and cold agglutinin disease, Anaemia of chronic disease, e.g. rheumatoid arthritis Aplastic anaemia</td>
<td>Fatigue, Palpitations, Headache, Dyspnoea, Symptoms of underlying disease</td>
<td>Pallor, Signs of underlying disease</td>
<td>FBC • Normal MCV • Normal or ferritin</td>
<td>Treat cause</td>
<td>Fatigue, Heart failure</td>
</tr>
</tbody>
</table>

**TABLE 6.1 Anaemia**

**Remember these as FAT RBC:**
- Folate deficiency
- Alcohol
- Thyroid (hypothyroidism)
- Reticulocytosis
- B12 (vitamin B12 deficiency)/pernicious anaemia
- Cytotoxic drugs
### What is thalassaemia?
Thalassaemias are genetic conditions, inherited in an autosomal recessive pattern, that produce a picture of microcytic anaemia due to a problem in globin chain production. This subsequently alters haemoglobin (Hb) synthesis. Thalassaemia may be classified into α-thalassaemia and β-thalassaemia.

### TABLE 6.2 Thalassaemia

<table>
<thead>
<tr>
<th>Types of thalassaemia</th>
<th>Populations affected</th>
<th>Causes</th>
<th>Investigations</th>
<th>Treatment</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-thalassaemia</td>
<td>More prominent in African and Asian populations</td>
<td>↓ α-globin synthesis due to α-globin gene mutation on chromosome 16; this subsequently results in excess β-globin production</td>
<td>Blood films: in α-thalassaemia target cells (or Mexican hat cells) may be seen&lt;br&gt;FBC:&lt;br&gt;• Microcytic, hypochromic anaemia&lt;br&gt;• ↓ MCV&lt;br&gt;• ↓ MCH&lt;br&gt;• Ferritin normal&lt;br&gt;• Iron normal&lt;br&gt;Hb electrophoresis: ↑ HbA₂ and ↑ Hbf&lt;br&gt;High performance liquid chromatography&lt;br&gt;Radiology: X-ray for bone abnormalities, e.g. frontal bossing</td>
<td>Conservative: patient education, genetic counselling</td>
<td>Iron overload&lt;br&gt;Splenomegaly&lt;br&gt;Increased risk of infection&lt;br&gt;Heart failure&lt;br&gt;Arrhythmias&lt;br&gt;Bone abnormalities, e.g. cranial bossing&lt;br&gt;Gallstones</td>
</tr>
</tbody>
</table>
| β-thalassaemia        | More prominent in European populations | Point mutatioin in β-globin chain on chromosome 11; this subsequently results in excess α-globin production | β-thalassaemia may be subdivided into 3 different traits:<br>1. Minor: usually asymptomatic; carrier state; mild anaemia<br>2. Intermediate: moderate anaemia; no blood transfusions required<br>3. Major: aka Cooley’s anaemia; abnormalities in all β-globin chains results in severe anaemia; characteristic cranial bossing seen due to extramedullary haematopoiesis | Medical:<br>• Management of α-thalassaemia and β-thalassaemia is based on patient symptoms and overall state of health<br>• Transfusions are usually required when Hb <7 g/dL or when the patient is highly symptomatic | }
<table>
<thead>
<tr>
<th>Type of Thalassaemia</th>
<th>Populations Affected</th>
<th>Causes</th>
<th>Investigations</th>
<th>Treatment</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>α-thalassaemia</strong></td>
<td>More prominent in African and Asian populations</td>
<td>a-globin synthesis due to <strong>α-globin</strong> gene mutation on chromosome 16; this subsequently results in excess <strong>β</strong>-globin production</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>β-thalassaemia</strong></td>
<td>More prominent in European populations</td>
<td>Point mutation in <strong>β</strong>-globin chain on chromosome 11; this subsequently results in excess <strong>α</strong>-globin production</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>β-thalassaemia</strong></td>
<td>May be subdivided into 3 different traits:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor: usually asymptomatic; carrier state; mild anaemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Intermediate: moderate anaemia; no blood transfusions required</td>
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</tr>
<tr>
<td>Major: aka Cooley’s anaemia; abnormalities in all <strong>β</strong>-globin chains results in severe anaemia; characteristic cranial bossing seen due to extramedullary haematopoiesis</td>
<td></td>
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</tr>
</tbody>
</table>

**Patients who have repeated blood transfusions are at risk of haemochromatosis and, therefore, require iron chelation therapy, e.g. desferroxamine.**

**Surgical:**
- Splenectomy
- Stem cell transplant

**Table 6.2 Thalassaemia**
BERNARD–SOULIER SYNDROME
What is Bernard–Soulier syndrome?
This is an autosomal recessive bleeding disorder.

Causes
This is a hereditary condition that leads to deficiency of glycoprotein (Gp) Ib.

Investigations
• ↑ Bleeding time, normal or ↓ platelet count.

Treatment
• Conservative: patient education.
• Medical:
  ○ Desmopressin may decrease bleeding time.
  ○ Recombinant activated factor VII.

CLOT FORMATION
This consists of 4 steps. Defects in steps 2–4 may lead to a bleeding disorder.
1 Vessel constriction.
2 Platelet adhesion and aggregation: Glanzmann’s thrombasthenia, von Willebrand disease, Bernard–Soulier syndrome.
3 Blood coagulation: haemophilia.
4 Fibrinolysis: antiplasmin deficiency.

HAEMOPHILIA
What is haemophilia?
This is an inherited condition that impairs the body’s ability to coagulate the blood.

Causes
This is a hereditary condition. There are two forms of haemophilia:
• Type A: lack of factor VIII.
• Type B: lack of factor IX.

Investigations
• Normal prothrombin time, ↑ partial thromboplastin time.

Treatment
• Conservative: patient education. Avoid aspirin, NSAIDs, heparin and warfarin.
• Medical: replace deficient clotting factor with regular infusions.
VITAMIN K INSUFFICIENCY
What is vitamin K insufficiency?
This avitaminosis occurs when there is decreased vitamin K₁ or vitamin K₂ or both. This results in:
- ↓ Synthesis of factors II, VII, IX and X.
- ↓ Synthesis of proteins C and S.

Causes
- Drugs, e.g. warfarin.
- Malnutrition.
- Malabsorption.
- Alcoholism.
- Cystic fibrosis.
- Chronic kidney injury.
- Cholestatic disease.

Investigations
- ↑ Prothrombin time, normal or ↑ partial thromboplastin time.

Treatment
- Conservative – patient education. Dietary advice about food rich in vitamin K
- Medical – treat cause. Vitamin K supplements.

GLANZMANN’S THROMBASTHENIA
What is Glanzmann’s thrombasthenia?
This is a rare autosomal recessive or acquired autoimmune condition in which platelets are deficient of GpIIb/IIIa. GpIIb/IIIa binds fibrinogen.

Causes
Disease of hereditary or acquired autoimmune cause.

Investigations
- ↑ Bleeding time.

Treatment
- Medical:
  - Desmopressin.
  - Recombinant activated factor VII.

VON WILLEBRAND DISEASE
What is von Willebrand disease?
This is the most common hereditary coagulation disorder, which involves a defect in von Willebrand factor (VWF). The function of von Willebrand factor is to bind GpIb receptor on platelets to subendothelial collagen.

Causes
Hereditary condition. There are many different types of von Willebrand disease, but the most common are type 1, type 2, type 3 and type Normandy.

Investigations
- ↑ Activated partial thromboplastin time,
- ↑ Bleeding time, normal prothrombin time,
- ↓ VWF antigen, ↓ factor VIIIc.

Treatment
- Conservative: patient education. Avoid aspirin and NSAIDs.
- Medical: desmopressin may be useful, but is not helpful in type 3 von Willebrand disease.
What is leukaemia?
This is a rare neoplasm of the blood or bone marrow. It is classified into lymphoid and myeloid neoplasms that may present chronically or acutely. These 4 classifications are:
1. Acute lymphoblastic leukaemia (ALL).
2. Chronic lymphocytic leukaemia (CLL).
3. Acute myeloid leukaemia (AML).
4. Chronic myeloid leukaemia (CML).

Signs and symptoms

<table>
<thead>
<tr>
<th>Neoplasm</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>Bone marrow failure</td>
</tr>
<tr>
<td></td>
<td>Bruising</td>
</tr>
<tr>
<td></td>
<td>Shortness of breath</td>
</tr>
<tr>
<td></td>
<td>Purpura</td>
</tr>
<tr>
<td></td>
<td>Malaise</td>
</tr>
<tr>
<td></td>
<td>Weight loss</td>
</tr>
<tr>
<td></td>
<td>Night sweats</td>
</tr>
<tr>
<td>CLL</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td></td>
<td>Bone marrow failure</td>
</tr>
<tr>
<td></td>
<td>Nontender lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td>Hepatosplenomegaly</td>
</tr>
<tr>
<td></td>
<td>Malaise</td>
</tr>
<tr>
<td></td>
<td>Weight loss</td>
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<tr>
<td></td>
<td>Night sweats</td>
</tr>
</tbody>
</table>

Causes

<table>
<thead>
<tr>
<th>Neoplasm</th>
<th>Cause</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>Possibly a genetic susceptibility coupled with an environmental trigger</td>
<td>Commonest cancer in children Often spreads to central nervous system Associations – DIP: Down’s syndrome Ionising radiation Pregnancy</td>
</tr>
<tr>
<td>CLL</td>
<td>Exact cause unknown</td>
<td>Usually affects adults over 60 years old Affects B lymphocytes Positive ZAP-70 marker is associated with a worse prognosis</td>
</tr>
<tr>
<td>AML</td>
<td>Exact cause unknown</td>
<td>Commonest leukaemia in adults Rapidly progressing Auer rods on microscopy are diagnostic</td>
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<tr>
<td></td>
<td>Risk factors include:</td>
<td></td>
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<tr>
<td></td>
<td>Myeloproliferative disease</td>
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<td></td>
<td>Alkylation agents</td>
<td></td>
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<tr>
<td></td>
<td>Ionising radiation exposure</td>
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<tr>
<td></td>
<td>Down’s syndrome</td>
<td></td>
</tr>
<tr>
<td>CML</td>
<td>Exact cause unknown</td>
<td>Usually affects males 40–60 years old 80% associated with the Philadelphia chromosome t(9;22), forming bcr-abl fusion gene</td>
</tr>
<tr>
<td></td>
<td>Risk factor: ionising radiation exposure</td>
<td></td>
</tr>
</tbody>
</table>
Causes and Comment

**ALL**
- Possibly a genetic susceptibility coupled with an environmental trigger
- Exact cause unknown
- Commonest cancer in children
- Often spreads to the central nervous system
- Associations:
  - DIP:
    - Down’s syndrome
    - Ionising radiation
    - Pregnancy

**AML**
- Exact cause unknown
- Risk factors include:
  - Myeloproliferative disease
  - Alkylating agents
  - Ionising radiation exposure
  - Down’s syndrome
- Commonest leukaemia in adults
- Rapidly progressing
- Auer rods on microscopy are diagnostic

**CML**
- Exact cause unknown
- Risk factor: ionising radiation exposure
- Usually affects males 40–60 years old
- 80% associated with the Philadelphia chromosome t[9;22], forming bcr-abl fusion gene

### Signs and Symptoms

**Neoplasm**

**Clinical features**

**ALL**
- Bone marrow failure
- Malaise
- Weight loss
- Night sweats

**CML**
- Bone marrow failure
- Hepatosplenomegaly
- Malaise
- Weight loss
- Night sweats

**Signs and symptoms**

**Neoplasm**

**Investigations**
- Bloods: FBC, WCC, platelets, U&Es, LFTs, ESR, CRP.
- Bone marrow biopsy, lymph node biopsy.
- Radiology: X-ray, ultrasound scan, CT scan, MRI.
- AML and ALL are classified using the French–American–British (FAB) classification.

### Treatment

**All**

**Conservative**
- Patient education; refer to Macmillan nurses

**Medical**
- Induce remission and maintenance
  - To induce remission:
    - Dexamethasone
    - Vincristine
    - Anthracycline antibiotics
    - Cyclophosphamide
  - Maintenance:
    - Methotrexate
    - Mercaptopurine
    - Cytarabine
    - Hydrocortisone

**Chlorambucil**
- Fludarabine
- Rituximab
- Prednisolone
- Cyclophosphamide

**Patients <60 years:**
- chemotherapy with an anthracycline and cytarabine or methotrexate

**Patients >60 years:**
- palliative anthracycline, cytarabine or mitoxantrone

**If M3 type AML, i.e. acute promyelocytic leukaemia (APML), then add all-trans retinoic acid to the therapeutic regime**

**AML**

- Patients <60 years:
  - chemotherapy with an anthracycline and cytarabine or methotrexate
- Imatinib
- Patients <60 years may be considered for allogeneic stem cell transplantation
- Other treatments include alpha-interferon, vincristine, prednisolone, cytarabine and daunorubicin

**CML**

- Imatinib
- Patients <60 years may be considered for allogeneic stem cell transplantation
- Other treatments include alpha-interferon, vincristine, prednisolone, cytarabine and daunorubicin

### Complications
- Death
- Increased risk of infection
- Haemorrhage: pulmonary, intracranial
- Depression
- Complication of chemotherapy

### Investigations
- Bloods: FBC, WCC, platelets, U&Es, LFTs, ESR, CRP.
- Bone marrow biopsy, lymph node biopsy.
- Radiology: X-ray, ultrasound scan, CT scan, MRI.
HODGKIN’S LYMPHOMA
What is Hodgkin’s lymphoma?
This is a group of uncommon malignancies; the 4 most common histological subtypes are:
1. Lymphocyte-predominant.
2. Nodular sclerosing.
4. Lymphocyte-depleted.

Cause
Exact cause is unknown.
Risk factors include:
- Male sex.
- Infection with Epstein–Barr virus (EBV).
- Immunosuppression, e.g. HIV patients.
- Exotoxin exposure.

Signs and symptoms
- Painless lymphadenopathy.
- Unintentional weight loss.
- Fever (constitutional ‘B signs’: fever >38°C, night sweats, weight loss).

NON-HODGKIN’S LYMPHOMA
What is non-Hodgkin’s lymphoma?
This is a group of malignancies that are either B cell or T cell in origin.

<table>
<thead>
<tr>
<th>B cell neoplasms</th>
<th>T cell neoplasms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burkitt’s lymphoma:</td>
<td>Adult T cell lymphoma; caused by human</td>
</tr>
<tr>
<td>• Associated with EBV</td>
<td>T-lymphotrophic virus-1 (HTLV-1)</td>
</tr>
<tr>
<td>• t[8;14]</td>
<td>Sézary syndrome</td>
</tr>
<tr>
<td>Diffuse large B cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>Mantle cell lymphoma: t[11;14]</td>
<td></td>
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<tr>
<td>Follicular lymphoma:</td>
<td></td>
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<tr>
<td>• t[14;18]</td>
<td></td>
</tr>
<tr>
<td>• bcl-2 expression</td>
<td></td>
</tr>
</tbody>
</table>

Cause
Exact cause is unknown.
Risk factors include:
- Male sex.
- Infection, e.g. EBV, Helicobacter pylori, human herpes virus (HHV)-8, hepatitis C.
- Immunosuppression, e.g. HIV patients.
Hodgkin’s Lymphoma

What is Hodgkin’s lymphoma?

This is a group of uncommon malignancies; the 4 most common histological subtypes are:

1. Lymphocyte-predominant.
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Cause

Exact cause is unknown. Risk factors include:

• Male sex.
• Infection with Epstein–Barr virus (EBV).
• Immunosuppression, e.g. HIV patients.
• Exotoxin exposure.

Signs and symptoms

• Painless lymphadenopathy.
• Unintentional weight loss.
• Fever (constitutional ‘B’ signs: fever >38˚C, night sweats, weight loss).

Investigations

• Bloods: FBC, WCC, U&Es, CRP, ESR, lactate dehydrogenase, creatinine, alkaline phosphatase, serum cytokine levels.
• Histology: Reed–Sternberg cells are seen.
• Radiology: X-ray, CT scan, PET scan.
• Other: lymph node biopsy (Ann Arbor classification).

Treatment

• Conservative: patient education and referral to Macmillan nurses.
• Medical: depends on Ann Arbor classification; AVBD regimen: doxorubicin, vinblastine, bleomycin, dacarbazine; BEACOPP regimen: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone.

Complications

• Increased risk of infection.
• Recurrence and metastasis.
• Increased risk of cardiovascular disease.
• Complications of chemotherapy.
• Neurological complications.

Non-Hodgkin’s Lymphoma

What is non-Hodgkin’s lymphoma?

This is a group of malignancies that are either B cell or T cell in origin.

Cause

Exact cause is unknown. Risk factors include:

• Male sex.
• Infection, e.g. EBV, Helicobacter pylori, human herpes virus (HHV)-8, hepatitis C.
• Immunosuppression, e.g. HIV patients.

Signs and symptoms

• Painless lymphadenopathy.
• Unintentional weight loss.
• Fever.
• Dyspnoea.
• Splenomegaly.
• Hepatomegaly.

Investigations

• Bloods: FBC, WCC, U&Es, CRP, ESR, lactate dehydrogenase, creatinine, alkaline phosphatase, serum cytokine levels, soluble CD25 level.
• Radiology: X-ray, CT scan, PET scan.
• Other: lymph node biopsy (Ann Arbor classification).

Treatment

• Conservative: patient education and referral to Macmillan nurses.
• Medical: depends on Ann Arbor classification; R-CHOP regimen: rituximab, cyclophosphamide, hydroxydaunomycin, vincristine, prednisolone; other agents used are cisplatin, etoposide and methotrexate.

Complications

• Increased risk of infection.
• Recurrence and metastasis.
• Increased risk of cardiovascular disease.
• Complications of chemotherapy.
• Neurological complications.
What is myeloma?
This is a malignant neoplasm of the plasma cells.

Causes
Exact cause is unknown.
Risk factors include:
- Monoclonal gammopathy of unknown significance.
- Pernicious anaemia.
- History of thyroid cancer.
- Exposure to certain exotoxins, e.g. benzene, Agent Orange.
- Past history of radiation exposure.

Signs and symptoms
- Fatigue.
- Unintentional weight loss.
- Pathological fractures.
- Vertebral collapse (may lead to spinal cord compression).
- Hypercalcaemia.
- Anaemia.
- Infection.
- Renal impairment.
- Bruising.

Investigations
- Bloods: FBC (normocytic, normochromic anaemia), U&Es, creatinine, LFTs, ESR, CRP, calcium levels, alkaline phosphatase, beta-2 microglobulin.
- Blood film: rouleaux formation.
- Serum and urine electrophoresis: paraprotein (M protein), Bence Jones proteinuria.
- Bone marrow biopsy.
- Radiology:
  - X-ray for bone deformities, e.g. pepper pot skull and generalised skeletal osteopaenia.
  - MRI scan may be useful.

Treatment
- Medical: medical therapy in multiple myeloma depends on the age of the patient and their state of health. If they are <70 years and without significant co-morbidities then they are eligible for autologous bone marrow transplant, which is the most effective treatment. This involves an induction phase using the VAD regimen: vincristine, adriamycin, dexamethasone. After transplant the patient receives long-term therapy with melphalan.
  - Patients who are ineligible for autologous bone marrow transplant receive long-term treatment with melphalan and prednisolone.
  - Other medical therapy is targeted to treating symptoms: analgesia, bisphosphonates, prednisolone, blood transfusion.
  - Radiotherapy may be required to treat bone pain and spinal cord compression.
- Surgical: kyphoplasty may be required.

Complications
- Spinal cord compression.
- Pathological fracture.
- Hypercalcaemia.
- Acute kidney injury.
- Increased risk of infection.
- Anaemia.
Chapter Seven Infectious Disease

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What is malaria?
This is an infectious disease caused by parasitic Plasmodium, which is spread by the female Anopheles mosquito.

Causes
- *P. ovale*: may lie dormant within the liver as hypnozoites.
- *P. vivax*: may lie dormant within the liver as hypnozoites.
- *P. malariae*.
- *P. knowlesi*: very rare.

Signs and symptoms
- Fatigue.
- Night sweats.
- Flu-like symptoms.
- Diarrhoea.
- Nausea.
- Vomiting.
- Anaemia.
- Splenomegaly.
- Seizures (cerebral malaria or secondary to fever).

Complications
- Cerebral malaria.
- Anaemia.
- Hepatic failure.
- Splenomegaly.
- Shock.
- Acute kidney injury.
- Dehydration.
- Acute respiratory distress syndrome (ARDS).

Treatment
- Conservative; patient education. Prevention of disease, e.g. mosquito nets and repellent sprays.
- Medical: prophylactic and therapeutic.
  Treatment is dependent on Plasmodium species:
  1. Inhibit haem polymerase:
     - Chloroquine.
     - Quinine.
  2. Blood schizonticide:
     - Mefloquine (Lariam).
     - Primaquine.
     - Malarone.
  3. Inhibits plasmodial protein synthesis: doxycycline.
  4. Inhibits dihydrofolate reductase: pyrimethamine.
  5. Inhibits falciparum sarcoplasmic–endoplasmic reticulum calcium ATPase: artemether (always used with lumefantrine).
- Surgical: splenectomy, if indicated.

Investigations
- Bloods: FBC, U&Es, creatinine, LFTs, ESR, CRP.
- Blood film.
- Real-time PCR.
- Antigen detection kits.

Malaria lifecycle: transmitted by female Anopheles mosquito

MAP 7.1 Malaria
Infectious Disease

Figure 7.1 Malaria Lifecycle

**FIGURE 7.1 Malaria Lifecycle**

Infected mosquito bites human host

Sporozoites enter the circulatory system

The sporozoites travel in the blood to the liver where they infect hepatocytes

Within the hepatocyte the sporozoites mature into schizonts, which produce many merozoites. *P. vivax* has an additional dormant stage where the sporozoites become hypnozoites.

Malaria lifecycle: transmitted by female *Anopheles* mosquito

Within the red blood cells merozoites continue to replicate until the red blood cells rupture

These merozoites replicate until their vast numbers eventually rupture the hepatocytes. In doing this the merozoites enter the bloodstream and infect red blood cells

Some of these red blood cells become gametocytes, which remain in the blood for a few days. During this time the gametocytes may be transferred to a mosquito that feeds on this infected human

Within the mosquito the gametocytes turn into sporozoites and the mosquito is now a vector of disease

Infected mosquito bites human host
What is TB?
TB is a granulomatous disease that may affect any organ, but most commonly affects the lungs since it is transmitted via aerosol droplets.

Causes
*Mycobacterium tuberculosis* (acid-fast bacillus).

Pathophysiology
- **Primary pulmonary TB:**
  - Initial TB infection.
  - Ghon focus formation in upper lobes.
  - Hilar lymphadenopathy.
- **Secondary pulmonary TB:**
  - Occurs after primary infection.
  - Dormant TB is reactivated.
  - Fibrocaseous lesions.
- **Other forms of TB:**
  - Miliary.
  - Genitourinary.
  - Bone, e.g. Pott’s disease of the spine.
  - Peritoneal.
  - Meningitis.

Treatment
- Conservative: patient education, especially the importance of complying with medical therapy.
- Medical — remember **RIPE**:
  - Rifampicin.
  - Isoniazid.
  - Pyrazinamide.
  - Ethambutol.

Other drugs that may be used in therapy include: streptomycin, quinolones, amikacin and capreomycin.

- Surgical: depends on location, e.g. for pulmonary TB consider lobectomy.

Signs and symptoms
- Cough.
- Haemoptysis.
- Weight loss.
- Night sweats.
- Fever.

Complications
- Dissemination to other organs.
- Death.

Investigations
- Sputum culture: Ogawa/Löwenstein–Jensen medium.
- Sputum stain: Ziehl–Neelsen stain.
- Transbronchial biopsy: granulomas are diagnostic.
- Pleural fluid analysis and biopsy.
- Radiology: X-ray for infiltrates and cavitations. Lesions described as millet seeds in miliary TB.

Mode of infection
- Droplets inhaled
- Bacteria colonise alveoli
- Bacteria engulfed by macrophages
- Multiplication of bacteria within macrophages
- Granulomas form around *M. tuberculosis* (caseous necrosis)

MAP 7.2 *Tuberculosis (TB)*
What is TB?

TB is a granulomatous disease that may affect any organ, but most commonly affects the lungs since it is transmitted via aerosol droplets.

Causes

- Mycobacterium tuberculosis (acid-fast bacillus).

Pathophysiology

- **Primary pulmonary TB:**
  - Initial TB infection.
  - Ghon focus formation in upper lobes.
  - Hilar lymphadenopathy.
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  - Miliary.
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  - Peritoneal.
  - Meningitis.

Signs and symptoms

- Cough.
- Haemoptysis.
- Weight loss.
- Night sweats.
- Fever.

Investigations

- Sputum culture: Ogawa/Löwenstein–Jensen medium.
- Sputum stain: Ziehl–Neelsen stain.
- Transbronchial biopsy: granulomas are diagnostic.
- Pleural fluid analysis and biopsy.
- Radiology: X-ray for infiltrates and cavitations. Lesions described as millet seeds in miliary TB.

Complications

- Dissemination to other organs.
- Death.

Treatment

- **Conservative:** patient education, especially the importance of complying with medical therapy.
- **Medical – remember RIPE:**
  - Rifampicin.
  - Isoniazid.
  - Pyrazinamide.
  - Ethambutol.
- Other drugs that may be used in therapy include: streptomycin, quinolones, amikacin and capreomycin.
- **Surgical:** depends on location, e.g. for pulmonary TB consider lobectomy.

Nonimmunocompetent patients – granuloma formation does not contain bacteria

Liquefaction of necrotic tissue

Coughing of infectious droplets since the liquified necrotic tissue drains into the bronchus

Immunocompetent patients – caseous necrosis produces conditions that decrease the growth of bacteria, e.g. lowered oxygen and pH levels

Granulomas form around *M. tuberculosis* (caseous necrosis)

Latency

**FIGURE 7.2 Mode of Infection of Pulmonary TB**
**HHV-8**
- Kaposi’s sarcoma (associated with HIV).

**HHV-7**
- Belongs to the subfamily betaherpesviridae.
- It is closely related to HHV-6.

**HHV-6**
- Roseola infantum.

**HHV-1**
- Herpes labialis.

**HHV-2**
- Herpes genitalis.

**HHV-3**
- Chickenpox.
- Shingles.

**HHV-4**
- Infectious mononucleosis – ‘kissing disease’ (positive Monospot test).
- Associated with Burkitt’s lymphoma.
- Associated with nasopharyngeal carcinoma.
- Transmitted via droplet infection and saliva.

**HHV-5**
- Mononucleosis (negative Monospot test).
- Typically seen in immunocompromised patients.
- Transmitted via sexual contact, saliva, urine, transplant, transfusion and congenitally.

**HHV-8**
- Kaposi’s sarcoma (associated with HIV).

**HHV-7**
- Belongs to the subfamily betaherpesviridae.
- It is closely related to HHV-6.

**HHV-6**
- Roseola infantum.

**HHV-1**
- Herpes labialis.

**Note**
HHV-1 and HHV-2 may affect both the mouth and the genitals.

**Investigations**
A clinical diagnosis, which may be confirmed by culturing the virus and by immunofluorescence.

**Treatment**
- Conservative: patient education and methods to reduce spread.
- Medical: antiviral medications, e.g. aciclovir and famciclovir.

**Epstein–Barr virus (HHV-4)**
- Infectious mononucleosis – ‘kissing disease’ (positive Monospot test).
- Associated with Burkitt’s lymphoma.
- Associated with nasopharyngeal carcinoma.
- Transmitted via droplet infection and saliva.
**Cytomegalovirus (HHV-5)**
- Mononucleosis (negative Monospot test).
- Typically seen in immunocompromised patients.
- Transmitted via sexual contact, saliva, urine, transplant, transfusion and congenitally.

**Epstein–Barr virus (HHV-4)**
- Infectious mononucleosis—‘kissing disease’ (positive Monospot test).
- Associated with Burkitt’s lymphoma.
- Associated with nasopharyngeal carcinoma.
- Transmitted via droplet infection and saliva.

**Varicella zoster virus (HHV-3)**
- Chickenpox.
- Shingles.
What is HIV?
HIV is an RNA retrovirus of the lentivirus genus. This virus causes acquired immunodeficiency syndrome (AIDS).

Causes
There are two types of HIV:
1. HIV-1:
   - Type M: A-J prevalent in Europe, America, Australia and sub-Saharan Africa.
   - Type O: mainly in Cameroon.
2. HIV-2: predominantly confined to West Africa.

Transmission
- Unprotected sexual intercourse.
- Shared contaminated needles.
- Contaminated blood transfusions.
- Vertical transmission from mother to child. The virus crosses the placenta and is transmitted through breast milk.

Investigations
- Bloods: FBC, U&Es, LFTs, lipids, glucose, HLA-B*5701 status, lymphocyte subsets.
- HIV specific:
  - Enzyme-linked immunosorbent assay (ELISA).
  - Western blot test.
  - Immunofluorescence assay (IFA).
  - Nucleic acid testing.
- Virology screen: HIV antibody, HIV viral load, HIV genotype, hepatitis serology, cytomegalovirus (CMV) antibody, syphilis screen.
- Other infection, e.g. tuberculosis if indicated.

Complications
- Increased risk of opportunistic infections:
  - Toxoplasmosis.
  - CMV, e.g. retinitis.
  - Pneumocystis jiroveci pneumonia.
  - Cryptococcal meningitis.
  - Mycobacterium avium complex.
  - Candida.
  - Aspergillosis.
- Increased risk of malignancies:
  - Kaposi’s sarcoma.
  - Non-Hodgkin’s lymphoma.
  - Cervical cancer.
  - Anal cancer.

MAP 7.4 Human Immunodeficiency Virus (HIV)
Infectious Disease

**Map 7.4 Human Immunodeficiency Virus (HIV)**

**What is HIV?**
HIV is an RNA retrovirus of the lentivirus genus. This virus causes acquired immunodeficiency syndrome (AIDS).

**Causes**
- There are two types of HIV:
  - HIV-1:
    - Type M: A-J prevalent in Europe, America, Australia and sub-Saharan Africa.
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**Transmission**
- Unprotected sexual intercourse.
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- Contaminated blood transfusions.
- Vertical transmission from mother to child.
  - The virus crosses the placenta and is transmitted through breast milk.

**Investigations**
- Bloods: FBC, U&Es, LFTs, lipids, glucose, HLA-B*5701 status, lymphocyte subsets.
- HIV specific:
  - Enzyme-linked immunosorbent assay (ELISA).
  - Western blot test.
  - Immunofluorescence assay (IFA).
  - Nucleic acid testing.
- Virology screen: HIV antibody, HIV viral load, HIV genotype, hepatitis serology, cytomegalovirus (CMV) antibody, syphilis screen.
- Other infection, e.g. tuberculosis if indicated.

**Treatment**
- Conservative: patient education including transmission reduction advice. Contact tracing. Psychological support.
- Medical: highly active antiretroviral therapy (HAART): either 2 × NRTIs combined with 1 × NNRTI or 2 × NRTIs combined with 1 × PIs or 1 × II:
  - Nucleoside reverse transcriptase inhibitor (NRTI), e.g. zidovudine.
  - Non-nucleoside reverse transcriptase inhibitor (NNRTI), e.g. nevirapine.
  - Protease inhibitor (PI), e.g. indinavir.
  - Integrase inhibitor (II), e.g. raltegravir.
- Highly active antiretroviral therapy (HAART):
  - Nucleoside reverse transcriptase inhibitor (NRTI), e.g. zidovudine.
  - Non-nucleoside reverse transcriptase inhibitor (NNRTI), e.g. nevirapine.
  - Protease inhibitor (PI), e.g. indinavir.
  - Integrase inhibitor (II), e.g. raltegravir.

**Infection process**
- gp120 antigen on HIV binds to CD4+ receptors on the T cell.
- This process produces a conformational change and the need to bind to a co-receptor: CCR5 or CXCR4.
- gp41 binds to the co-receptor.
- This binding causes ‘six-helix bundle formation’ and fusion of the viral and host membranes.
- Disintegration of the viral capsid occurs causing viral RNA to be released into the human cell.
- Double-stranded RNA is produced and this process is catalysed by viral reverse transcriptase.
- Double-stranded RNA is integrated into host DNA using integrase enzyme.
- Host cell now manufactures new virions by long terminal repeat sequences and genes tat and rev.

**Complications**
- Increased risk of opportunistic infections:
  - Toxoplasmosis.
  - CMV, e.g. retinitis.
  - Pneumocystis jiroveci pneumonia.
  - Cryptococcal meningitis.
  - Mycobacterium avium complex.
  - Candida.
  - Aspergillosis.
- Increased risk of malignancies:
  - Kaposi’s sarcoma.
  - Non-Hodgkin’s lymphoma.
  - Cervical cancer.
  - Anal cancer.

**Genes required for viral replication**
**Remember PEG**
- **pol**: encodes reverse transcriptase and integrase.
- **env**: encodes envelope proteins, e.g. gp120.
- **gag**: encodes viral structural proteins.
**TRICHOMONAS VAGINALIS**

**What is Trichomonas vaginalis?**
It is an anaerobic protozoon, which causes trichomoniasis. Symptoms include a fishy bubbly thin discharge and on speculum examination ‘strawberry’ cervix is visible.

**Investigations**
- Cervical smear.
- Rapid antigen testing.
- PCR technique.

**Treatment**
- Metronidazole. Intravaginal clotrimazole during pregnancy.

**Complications**
- Increased risk of HIV infection
- Increased risk of cervical cancer.
- Increased risk of preterm delivery.

---

**GARDNERELLA VAGINALIS**

**What is Gardnerella vaginalis?**
This is a facultative anaerobic coccobacillus that causes bacterial vaginosis (‘fishy odour’ and grey discharge). N.B. This is NOT an STI but does cause vaginal discharge and, as such, is included in differential diagnosis with chlamydia and gonorrhoea.

**Investigations**
- Microscopy – clue cells observed.

**Treatment**
- Metronidazole or clindamycin.

**Complications**
- Rarely causes complications.

---

**TREPONEMA PALLIDUM**

**What is Treponema pallidum?**
This is a spirochaete that causes syphilis. Infection occurs in 3 stages:
1. **Chancre**: painless superficial ulceration.
2. **Disseminated disease**: systemic involvement, rash seen on palms and soles.
3. **Cardiac and neurological involvement**.

**Investigations**
- Venereal Disease Research Laboratory (VDRL) test.
- Rapid plasma regain (RPR) test.
- Treponema pallidum particle agglutination.
- Fluorescent treponemal antibody absorption (FTA) test.
- Treponema pallidum haemagglutination (TPHA) test.
- Treponema pallidum particle agglutination (TPPA) test.
- Treponemal enzyme immunoassay (EIA).

**Treatment**
- Procaine penicillin G, doxycycline, erythromycin, azithromycin.
- N.B. If the patient has neurosyphilis then give them prophylactic prednisolone to avoid the Jarisch–Herxheimer reaction. This reaction may occur after antibacterial treatment, which causes the death of the spirochaete and subsequent endotoxin release. Endotoxins cause the Jarisch–Herxheimer reaction.
**CHLAMYDIA TRACHOMATIS**

**What is Chlamydia trachomatis?**
This is an Gram-negative bacterium that causes chlamydia.

**Investigations**
- Chlamydia cell culture.
- Nucleic acid amplification test (NAAT).
- Direct fluorescent antibody test (DFA).

**Treatment**
- Azithromycin (single dose) or doxycycline (for 7 days).

**Complications**
- Pelvic inflammatory disease.
- Urethritis.
- Infertility.
- Postpartum endometritis.

---

**GARDNERELLA VAGINALIS**

**What is Gardnerella vaginalis?**
This is a facultative anaerobic coccobacillus that causes bacterial vaginosis ('fishy odour' and grey discharge). N.B. This is NOT an STI but does cause vaginal discharge and, as such, is included in differential diagnosis with chlamydia and gonorrhoea.

**Investigations**
- Microscopy – clue cells observed.

**Treatment**
- Metronidazole or clindamycin.

**Complications**
- Rarely causes complications.

---

**CHLAMYDIA TRACHOMATIS**

**Investigations**
- Chlamydia cell culture.
- Nucleic acid amplification test (NAAT).
- Direct fluorescent antibody test (DFA).

**Treatment**
- Azithromycin (single dose) or doxycycline (for 7 days).

**Complications**
- Pelvic inflammatory disease.
- Urethritis.
- Infertility.
- Postpartum endometritis.

---

**TRICHOMONAS VAGINALIS**

**What is Trichomonas vaginalis?**
It is an anaerobic protozoon, which causes trichomoniasis. Symptoms include a fishy bubbly thin discharge and on speculum examination 'strawberry' cervix is visible.

**Investigations**
- Cervical smear.
- Rapid antigen testing.
- PCR technique.

**Treatment**
- Metronidazole. Intravaginal clotrimazole during pregnancy.

**Complications**
- Increased risk of HIV infection
- Increased risk of cervical cancer.
- Increased risk of preterm delivery.

---

**NEISSERIA GONORRHOEAE**

**What is Neisseria gonorrhoeae?**
This is a Gram-negative diplococcus that causes gonorrhoea. It is sometimes asymptomatic or presents with discharge.

**Investigations**
- NAAT.
- Cultured on chocolate agar.

**Treatment**
- Azithromycin (single dose) and ceftriaxone (single dose).

**Complications**
- Pelvic inflammatory disease.
- Infertility.
- Dissemination of bacteria.

---

**TREPONEMA PALLIDUM**

**What is Treponema pallidum?**
This is a spirochaete that causes syphilis. Infection occurs in 3 stages:
1. Chancre: painless superficial ulceration.
2. Disseminated disease: systemic involvement, rash seen on palms and soles.
3. Cardiac and neurological involvement.

**Investigations**
- Venereal Disease Research Laboratory (VDRL) test.
- Rapid plasma regain (RPR) test.
- Treponema pallidum particle agglutination.
- Fluorescent treponemal antibody absorption (FTA) test.
- Treponema pallidum haemagglutination (TPHA) test.
- Treponemal enzyme immunoassay (EIA).

**Treatment**
- Procaine penicillin G, doxycycline, erythromycin, azithromycin.

**Complications**
- Gumma formation.
- Meningitis.
- Stroke.
- Heart valve damage.

---

**Remember 3Hs**
- Hepatitis see page 46.
- Herpes see page 110.
- HIV see page 112.
**Staphylococcal infections**
*Staphylococcus aureus* causes:
- Skin infections.
- Osteomyelitis.
- Pneumonia.
- Endocarditis.
- Toxic shock syndrome.

Virulence factors – remember **SET**:
- Surface proteins for adherence.
- Enzymes.
- Toxins.

Grow in clusters.

**Gram-positive bacteria stain blue and pink with Gram stain. This is retained when washed with ethanol and water.**

**Whooping cough**
*Bordetella pertussis*, a coccobacillus.

**Gram-negative bacteria do not retain Gram stain when washed with ethanol and acetone.**

**Streptococcal infections**
Facultative or obligate anaerobes.

- **Streptococcus pneumoniae**: acquired pneumonia, see page 20 and meningitis.
- Enterococci: urinary tract infection and endocarditis.

**Virulence factors:**
- Capsules, which resist phagocytosis.
- **M** protein, which inhibits the alternative pathway of the complement system.
- Pneumolysin, which destroys the membranes of host cells.

Grow in pairs or chains.

**Diphtheria**
*Corynebacterium diphtheriae*.
- Rod shaped.
- Exotoxin causes damage to the heart and nerves.

**Pseudomonas infection**
*Pseudomonas aeruginosa* is an opportunistic aerobic bacillus.

**Neisserial infections**
- *Neisseria meningitidis*: meningitis.
- *N. gonorrhoeae*: sexually transmitted infection (STI), see page 114.

**Anthrax**
Spore forming bacillus.

**MAP 7.6 Bacterial Infections**
**Gram-positive**
**Gram-negative**
**Staphylococcal infections**
- Facultative or obligate anaerobes.
- *Streptococcus pneumoniae*: acquired pneumonia, see page 20 and meningitis.
- Enterococci: urinary tract infection and endocarditis.

Virulence factors:
- Capsules, which resist phagocytosis.
- M protein, which inhibits the alternative pathway of the complement system.
- Pneumolysin, which destroys the membranes of host cells.

Grow in pairs or chains.

**Listeriosis**
- *Listeria monocytogenes*.
- Aerobic.
- Grows in branched chains.
- Causes opportunistic respiratory infections with central nervous system involvement.

**Nocardia**
- *Nocardia asteroides*.
- Aerobic.
- Grows in branched chains.
- Causes opportunistic respiratory infections with central nervous system involvement.

**Granuloma inguinale**
- *Klebsiella granulomatis*.
- An encapsulated coccobacillus.
- Causes ulcerative genital infection.

**Chancroid**
- *Haemophilus ducreyi*.
- Causes ulcerative genital infection.

**Streptococcal infections**
- Facultative or obligate anaerobes.
- *Streptococcus pneumoniae*: acquired pneumonia, see page 20 and meningitis.
- Enterococci: urinary tract infection and endocarditis.

Virulence factors:
- Capsules, which resist phagocytosis.
- M protein, which inhibits the alternative pathway of the complement system.
- Pneumolysin, which destroys the membranes of host cells.

Grow in pairs or chains.
TRANSIENT INFECTIONS

Rhinovirus
- Enterovirus.
- Causes the common cold.

Influenza
- RNA virus.
- Causes the flu.
- Classified into 3 types: A, B and C.

Polio virus
- Unencapsulated RNA enterovirus.

Measles
- RNA paramyxovirus.
- Host cells develop T cell-mediated immunity to control this viral infection.
- Rash is caused by hypersensitivity to the viral antigens within the skin.

Mumps
- Paramyxovirus.
- Causes inflammation of the parotid glands.
- Sometimes travels to central nervous system (CNS), pancreas and testes.

West Nile virus
- Arthropod virus of the flavivirus group.
- Invades the CNS causing meningitis and encephalitis.
- Seen in the elderly and immunosuppressed.

Chronic latent infections
- Human herpes virus (HHV): see page 110.
- Cytomegalovirus (CMV): see page 111.
- Varicella zoster virus (VZV): see page 111.
Viral Infections

**TRANSIENT INFECTIONS**

- **Rhinovirus**
  - Causes the common cold.
- **Enterovirus**
  - Causes the common cold.
- **Influenza**
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  - Invades the CNS causing meningitis and encephalitis.
  - Seen in the elderly and immunosuppressed.

**CHRONIC LATENT INFECTIONS**

- **Human herpes virus (HHV):** see page 110.
- **Cytomegalovirus (CMV):** see page 111.
- **Varicella zoster virus (VZV):** see page 111.

**TRANSFORMING INFECTIONS**

- **Human immunodeficiency virus (HIV)**
  - See page 112.
- **Human papillomavirus (HPV)**
  - This is associated with cervical cancer (this is because the HPV E6 and HPV E7 gene products dysregulate the cell cycle).
- **Epstein–Barr virus (EBV)**
  - Causes infectious mononucleosis.
  - Usually self-limiting.
  - Presents with fever and sore throat.
  - Associated with Burkitt’s lymphoma (8;14 translocation of c-myc oncogene), see page 102.

**CHRONIC PRODUCTIVE INFECTIONS**

- **Hepatitis virus,** see page 46.
**DNA vaccines**
- Potentially in the future.
- Usually a harmless virus which has a gene for a protective antigen spliced into it.
- This protective antigen is generated within the vaccine recipient and elicits an immune response.

Advantages:
- Plasmids are easily manufactured and do not replicate.
- DNA is stable and sequencing may be changed.
- Temperature extremes are resisted; therefore, it is easily transported and stored.
- Cheap.

Disadvantages:
- Plasmids could integrate into the host genome.
- Immunological tolerance.

**Subunit**
- E.g. hepatitis B, tetanus, diphtheria.
- This is a vaccine containing purified components of the virus.
- Example components include the surface antigen.

**Inactivated**
- E.g. polio (Salk), rabies, hepatitis A, influenza.
- Preparations of the wild type virus.
- The virus is nonpathogenic because of chemical treatment (e.g. with formalin).
- This chemical treatment cross-links viral proteins.

Advantages:
- Sufficient humoral immunity if boosters given.
- Good for immunosuppressed patients.
- No mutations of virus.
- Good for those living in tropical areas.

Disadvantages:
- Some do not increase immunity.
- Boosters are required.
- Expensive.
- Potential failure of viral inactivation process.
- Little local immunity.
Infectious Disease

### Vaccines

#### Subunit
- E.g. hepatitis B, tetanus, diphtheria.
- This is a vaccine containing purified components of the virus.
- Example components include the surface antigen.

#### DNA vaccines
- Potentially in the future.
- Usually a harmless virus which has a gene for a protective antigen spliced into it.
- This protective antigen is generated within the vaccine recipient and elicits an immune response.

**Advantages:**
- Plasmids are easily manufactured and do not replicate.
- DNA is stable and sequencing may be changed.
- Temperature extremes are resisted; therefore, it is easily transported and stored.
- Cheap.

**Disadvantages:**
- Plasmids could integrate into the host genome.
- Immunological tolerance.

#### Attenuated
- E.g. polio (Sabin), mumps, measles, rubella (MMR), varicella, rotavirus, yellow fever.
- Live virus particles grow in the vaccine recipient.
- However, these particles do not cause disease because the virus has been mutated to a form that is nonpathogenic, e.g. the virus tropism has been altered.

**Advantages:**
- Activates all phases of the immune system.
- It stimulates antibodies against multiple epitopes.
- Provides cheap and fast immunity.
- It has the potential to eliminate the wild type virus from the community.
- Easily transported.

**Disadvantages:**
- If the mutation fails then the virus will revert to its virulent form.
- Potential spread of the mutated viral form.
- Do NOT give to immunocompromised patients.
- Not good for those living in tropical areas.

#### Inactivated
- E.g. polio (Salk), rabies, hepatitis A, influenza.
- Preparations of the wild type virus.
- The virus is nonpathogenic because of chemical treatment (e.g. with formalin).
- This chemical treatment cross-links viral proteins.

**Advantages:**
- Sufficient humoral immunity if boosters given.
- Good for immunosuppressed patients.
- No mutations of virus.
- Good for those living in tropical areas.

**Disadvantages:**
- Some do not increase immunity.
- Boosters are required.
- Expensive.
- Potential failure of viral inactivation process.
- Little local immunity.
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Chapter Eight

The Immune System

MAP 8.1 Cells of the Immune System  124
MAP 8.2 Antibodies  126
MAP 8.3 The Complement System  127
MAP 8.4 Activation of the Complement System  128
MAP 8.5 Hypersensitivity Reactions and Disorders  129
MAP 8.6 Systemic Lupus Erythematosus (SLE)  130
**T lymphocytes**
- Arise from bone marrow but mature in thymus.
- Different types:
  - Cytotoxic CD8+ cells.
  - Helper CD4+ cells.
  - Suppressor cells.

**B lymphocytes**
- Part of the humoral immune system.
- Arise from bone marrow and mature there.

**Mast cells**
- Involved in allergic reactions.
- Degranulate producing histamine, heparin and chemotactic factors (for eosinophils).

**Dendritic cells**
- Antigen presenting cells.
- In skin they are referred to as Langerhans cells.

**Lymphocytes**

**Leucocytes**

**Myeloid progenitor cells**

**MAP 8.1 Cells of the Immune System**
Plasma cells
- B cells differentiate into plasma cells when they come across an antigen.
- Plasma cells produce specific antibodies.

Myeloblasts → Granulocytes

Basophils
- Allergic reactions.
- Bilobate nucleus.

Eosinophils
- Bilobate nucleus.
- In allergic reactions and parasite infections.

Neutrophils
- Acute inflammatory response.
- Multilobed nucleus.

Monocytes
- Kidney shaped nucleus.
- Differentiate into macrophages.

Macrophages
- Phagocytic.
- Scavenger cells: they scavenge and destroy.
- γ-interferon activates macrophages.
**IgA**
- Dimer (when secreted).
- Prevents bacteria and viruses from attaching to and colonising mucosal surfaces.
- Found in colostrum, breast milk, saliva, mucosal surfaces and tears.

**IgM**
- Pentamer (when secreted).
- Fixes complement.
- Involved in primary immune response.

**IgG**
- Monomer.
- Only immunoglobulin to cross the placenta.
- Involved in secondary immune response.
- Largest concentration of immunoglobulin in the blood.
- Fixes complement system.

**IgD**
- Monomer.
- Activates basophils.
- Activates mast cells.

**IgE**
- Monomer.
- Binds to allergens and causes mast cells to degranulate. This results in histamine release.
- Binds to basophils, also causing histamine release.
- Activates eosinophils.
- IgE plays a role in protection against parasitic worm infection.
The Complement System

Part of the innate immune system

Consists of 3 pathways
Remember CAL:
- Classical complement pathway.
- Alternative complement pathway.
- Lectin complement pathway.

Functions
Remember COCA:
- Chemotaxis.
- Opsonisation.
- Cell lysis.
- Antigen bearing agents are clumped together.
Antibody–antigen complex → Classical complement pathway

Spontaneous reaction to microbial surface → Alternative complement pathway

Lectin binds to mannose residues on microbial surface → Lectin complement pathway

**MAP 8.4 Activation of the Complement System**

**Response**
- C3a
  - Chemotaxis
  - Activates leucocytes
  - Stimulates histamine release
- C3b
  - Opsonisation
- C5b-9
  - Opsonisation
- C5a
  - Chemotaxis
  - Stimulates arachidonic acid metabolism
Hypersensitivity Reactions and Disorders

**Type I (immediate hypersensitivity)**
- E.g. Hay fever, allergic reaction to a wasp sting.
- Anaphylactic reaction.
- IgE involvement.
- Antigen presents to CD4+ cells, which stimulates IgE production.
- IgE causes mast cells to degranulate, resulting in histamine release.

**Type II (cytotoxic hypersensitivity)**
- E.g. Graves' disease, see page 72, myasthenia gravis, rheumatic fever.
- Antibody-mediated reaction.
- IgM, IgG and complement (classical pathway) involvement.

**Type III (immune-complex reactions)**
- E.g. Systemic lupus erythematosus, see page 130, rheumatoid arthritis, see page 157.
- Immune complex reaction.
- IgG and complement involvement.

**Type IV (delayed hypersensitivity)**
- E.g. Hashimoto's thyroiditis, see page 74, multiple sclerosis, see page 153.
- Cell-mediated reaction.
- T cell involvement.
Signs and symptoms
- Fatigue.
- Myalgia.
- Rashes: malar (butterfly) rash, discoid rash.
- Raynaud’s phenomenon.
- Arthritis.
- Central nervous system disorders: epilepsy, headache.
- Haematological disorders: haemolytic anaemia.
- Immunological disorders.
- Nephritis.
- Oral ulcers.
- Photosensitivity.
- Pericarditis.
- Pleuritis.

What is SLE?
SLE is a multisystemic autoimmune disease that usually affects females of childbearing age.

Causes
The exact cause of SLE is unknown. It is thought to be an autoimmune reaction in genetically susceptible individuals.

Investigations
- Antinuclear antibody (ANA).
- Anti-Smith antibodies and antidouble-stranded DNA.
- Bloods: FBC, U&Es, LFTs, TFTs, glucose.
- Pulmonary function tests.

MAP 8.6 Systemic Lupus Erythematosus (SLE)
Signs and symptoms

- Fatigue.
- Myalgia.
- Rashes: malar (butterfly) rash, discoid rash.
- Raynaud's phenomenon.
- Arthritis.
- Central nervous system disorders: epilepsy, headache.
- Haematological disorders: haemolytic anaemia.
- Immunological disorders.
- Nephritis.
- Oral ulcers.
- Photosensitivity.
- Pericarditis.
- Pleuritis.

Investigations

- Antinuclear antibody (ANA).
- Anti-Smith antibodies and antidouble-stranded DNA.
- Bloods: FBC, U&Es, LFTs, TFTs, glucose.
- Pulmonary function tests.

What is SLE?

SLE is a multisystemic autoimmune disease that usually affects females of childbearing age.

Causes

The exact cause of SLE is unknown. It is thought to be an autoimmune reaction in genetically susceptible individuals.

Complications

- Increased risk of atherosclerosis.
- Increased risk of stroke.
- Increased risk of myocardial infarction.
- Risk of lupus nephritis.
- Increased risk of other autoimmune conditions.
- Depression.

Revised criteria for diagnosing SLE

≥4/11 is diagnostic. Remember this as I AM PORN HSD:

- Immunological disorder.
- ANA positive.
- Malar rash.
- Photosensitivity.
- Oral ulcers.
- Renal disorder.
- Nonerosive arthritis, neurological disorder.
- Haematological disorder.
- Serositis.
- Discoid rash.

Treatment

- Medical:
  - Analgesia (nonsteroidal anti-inflammatory drugs).
  - Steroid therapy.
  - Immunosuppressive therapy, e.g. azathioprine, cyclophosphamide.
  - Monoclonal antibodies, e.g. rituximab.

Revised criteria for diagnosing SLE
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**Frontal lobe**
- Is responsible for motor control of the opposite side of the body, e.g., the left frontal lobe has motor control of the right side of the body.
- Controls emotion and insight.
- The dominant hemisphere is responsible for speech output (Broca's area).
- Primary motor cortex: located in the posterior portion of the frontal lobe. This area plans and executes movement.
- Broca's area: located in the frontal lobe, just superior to the lateral fissure. It is responsible for the formation of speech.

**Basal ganglia**
- Is an interconnection of deep nuclei:
  - Putamen and globus pallidus: together they form the lentiform nucleus.
  - Caudate nucleus.
  - Substantia nigra.
  - Subthalamus nucleus.
- Integrates motor and sensory inputs.

**Parietal lobe**
- Is responsible for sensation of the opposite side of the body.
- It is also responsible for spatial awareness.
- Somatosensory cortex: located in the anterior cortex of the parietal lobe. It processes pain, pressure and touch.

**Cerebellum**
- This is split into 3 lobes:
  1. The paleocerebellum: maintains gait.
  2. The neocerebellum: maintains postural tone and is responsible for the co-ordination of fine motor skills.
  3. The archicerebellum: maintains balance.

**Occipital lobe**
- Is responsible for vision.
- Primary visual cortex is located within this lobe.

**Temporal lobe**
- Is responsible for memory and emotion.
- In the dominant hemisphere it is responsible for the comprehension of speech (Wernicke's area).
- Wernicke's area: allows spoken and written language to be comprehended. It is located just posterior to the superior temporal gyrus.
- Primary auditory complex: responsible for hearing. It is located within the temporal lobe bilaterally.
FIGURE 9.1 The Blood Supply of the Brain

Circle of Willis

- Anterior communicating artery
- Internal carotid artery
- Superior cerebellar artery
- Vertebral artery
- Posterior inferior cerebellar artery
- Anterior cerebral artery
- Middle cerebral artery
- Posterior communicating artery
- Posterior cerebral artery
- Pontine branches
- Basilar artery
- Anterior inferior cerebellar artery
- Anterior spinal artery
### Table 9.1 The Cranial Nerves and their Lesions

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Sensory or motor</th>
<th>Location</th>
<th>Function</th>
<th>Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: Olfactory</td>
<td>Sensory</td>
<td>Cribriform plate of the ethmoid bone</td>
<td>Sense of smell</td>
<td>Loss of smell (anosmia)</td>
</tr>
<tr>
<td>II: Optic</td>
<td>Sensory</td>
<td>Optic canal</td>
<td>Sight</td>
<td>Different visual field losses depending on the location of the lesion</td>
</tr>
<tr>
<td>III: Oculomotor</td>
<td>Motor</td>
<td>Superior orbital fissure</td>
<td>Innervates the superior, medial and inferior rectus muscles as well as the levator palpebrae superioris, inferior oblique and sphincter pupillae</td>
<td>Eye moves down and out due to unopposed action of the superior oblique and lateral rectus muscles; ptosis (drooping eyelid) and mydriasis (dilated pupil) are observed</td>
</tr>
<tr>
<td>IV: Trochlear</td>
<td>Motor</td>
<td>Superior orbital fissure</td>
<td>Innervates the superior oblique muscle</td>
<td>Diplopia and eye moves down and in</td>
</tr>
</tbody>
</table>
| V: Trigeminal        | Motor and sensory | V1: ophthalmic nerve: superior orbital fissure  
V2: maxillary nerve: foramen rotundum  
V3: mandibular nerve: foramen ovale | Sensation of the face and innervates the muscles of mastication; test corneal reflex | Decreased facial sensation and jaw weakness                              |
<p>| VI: Abducens         | Motor           | Superior orbital fissure        | Innervates the lateral rectus muscle                                    | Eye deviates medially                                                   |</p>
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<td>Inferior orbit</td>
<td>Eye moves down and out due to unopposed action of the superior oblique and lateral rectus muscles; ptosis (drooping eyelid) and mydriasis (dilated pupil)</td>
<td>Decreased lacrimation due to irritation</td>
</tr>
<tr>
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<td>Superior oblique muscle</td>
<td>Diplopia and eye moves down and in</td>
<td></td>
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<td>VI: Abducens</td>
<td>Motor</td>
<td>Lateral rectus muscle</td>
<td>Eye deviates medially</td>
<td></td>
</tr>
<tr>
<td>VII: Facial</td>
<td>Motor and sensory</td>
<td>Internal acoustic canal and exits through the stylomastoid foramen</td>
<td>Innervates the muscles of facial expression, stapedius, posterior belly of the digastric muscle, stylohyoid, taste anterior 2/3 tongue, the lacrimal gland and the salivary glands (not parotids)</td>
<td>Upper motor neuron (UMN): asymmetry of lower face with forehead sparing Lower motor neuron (LMN): asymmetry of upper and lower face; loss of taste, hyperacusis and eye irritation due to decreased lacrimation</td>
</tr>
<tr>
<td>VIII: Vestibulocochlear</td>
<td>Sensory</td>
<td>Internal acoustic canal</td>
<td>Sense of sound and balance</td>
<td>Deafness and vertigo</td>
</tr>
<tr>
<td>IX: Glossopharyngeal</td>
<td>Motor and sensory</td>
<td>Jugular foramen</td>
<td>Supplies taste to posterior 1/3 tongue and innervates the parotid as well as the stylohyoid</td>
<td>Decreased gag reflex, uvular deviation away from lesion</td>
</tr>
<tr>
<td>X: Vagus</td>
<td>Motor and sensory</td>
<td>Jugular foramen</td>
<td>Innervates laryngeal and pharyngeal muscles (not stylohyoid) and parasympathetic supply to thoracic and abdominal viscera</td>
<td>Dysphagia, recurrent laryngeal nerve palsies and pseudobulbar palsies</td>
</tr>
<tr>
<td>XI: Spinal Accessory</td>
<td>Motor</td>
<td>Jugular foramen</td>
<td>Innervates trapezius and sternocleidomastoid muscles</td>
<td>Patient cannot shrug and displays weak head movement</td>
</tr>
<tr>
<td>XII: Hypoglossal</td>
<td>Motor</td>
<td>Hypoglossal canal</td>
<td>Innervates the muscles of the tongue (except for the palatoglossal, which is supplied by the vagus nerve)</td>
<td>Tongue deviates towards the side of weakness during protrusion</td>
</tr>
</tbody>
</table>
Fasciculus gracilis and fasciculus cuneatus make up the dorsal columns. They are responsible for:
- Proprioception
- Fine touch
- The pathways decussate in the medulla
- Ascend through the medial lemniscus pathway

The dorsal and ventral spinocerebellar tracts are responsible for:
- Posture
- Co-ordination of movement

Fasciculus gracilis (below T6)
Fasciculus cuneatus (above T6)
Lateral corticospinal tract (80%)
Rubrospinal tract
Medullary reticulospinal tract
Lateral vestibulospinal tract
Pontine reticulospinal tract
Tectospinal tract
Ventral corticospinal tract (20%)
Spinothalamic tract
Dorsal spinocerebellar tract
Ventral spinocerebellar tract
Medial longitudinal fasciculus
**Neurology**

**Figure 9.2 Ascending and Descending Spinal Pathways**

**Dorsal spinocerebellar tract**
- Originates from Clarke’s column
- Location: inferior cerebellar peduncle
- Ipsilateral

**Lateral corticospinal tract (80%)**
- Voluntary skilled movements at the DISTAL parts of limbs

**Rubrospinal tract**
- Location: red nucleus of the midbrain
- Afferent fibres are received from the cerebellum and motor cortex
- Responsible for:
  - Control of limb flexor muscles

**Ventral spinocerebellar tract**
- Location: superior cerebellar peduncle
- Contralateral

**Spinothalamic tract**
- Decussate at level of entry
- Anterior: crude touch
- Posterior: pain and temperature
- Responsible for:
  - Pain
  - Pressure
  - Nondiscriminative touch

**Tectospinal tract**
- Originates in the superior colliculus
- Reflective movements of the head in response to visual/auditory stimuli

**Medullary reticulospinal tract**
- Bilateral
- Responsible for:
  - Reflex activity
  - Control of breathing
  - Control of alpha and gamma neurons

**Lateral vestibulospinal tract**
- From vestibular nucleus in pons and medulla
- Responsible for:
  - EXTENSOR muscle tone
  - Posture

**Pontine reticulospinal tract**
- Ipsilateral
**What is a stroke?**
A stroke is a vascular insult to the brain causing a focal neurological deficit. This occurs due to ischaemic infarct or haemorrhage, which disrupts the blood supply to the brain.

**Signs and symptoms**
These vary depending on the circulation affected by the infarct or haemorrhage.

Acute signs and symptoms may be remembered as **FAST**:
- **F**ace: unilateral drooping.
- **A**rms: these may feel weak and numb. Patient may not be able to lift them.
- **S**peech: slurring of speech.
- **T**ime: time for emergency medical attention, call 999 (UK) immediately.

Stroke may also be associated with transient ischaemic attack (TIA). This is a focal neurological deficit where symptoms last <24 h due to temporary occlusion of the cerebral circulation. Patients may describe amaurosis fugax – loss of sight described as ‘curtains descending’. The phenomenon lasts <24 h and is usually followed by stroke within 90 days.

**Risk factors**
- ↑ Blood pressure.
- Atrial fibrillation (AF).
- Diabetes mellitus.
- Smoking.
- Alcohol.
- Previous stroke.
- The oral contraceptive pill.
- Disorder that increases clotting.
- Cocaine use.
- ↑ Cholesterol.

**Investigations**
- Bloods: FBC, U&Es, LFTs, PTT, glucose, cholesterol levels.
- Other: ECG for AF and ECHO for structural abnormalities.
- Glasgow Coma Scale to assess level of consciousness.
- Radiology: CT head and diffusion-weighted MRI (DWI) immediately if any indication of stroke. It is important to distinguish between haemorrhagic and ischaemic stroke since treatment options differ.

**Complications**
- Hydrocephalus.
- Increased risk of deep vein thrombosis (DVT).
- Aphasia.
- Dysphagia.
- Decreased muscle movement.
- Amnesia.
- Depression.

**Causes**
- **Haemorrhagic causes:**
  - Central nervous system bleeds from trauma.
  - Ruptured aneurysm.
- **Ishcaemic causes:**
  - Small vessel occlusion.
  - Atherothromboembolism.
  - Cardiac emboli.
  - Emboli secondary to AF.
What is a stroke?
A stroke is a vascular insult to the brain causing a focal neurological deficit. This occurs due to ischaemic infarct or haemorrhage, which disrupts the blood supply to the brain.

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These vary depending on the circulation affected by the infarct or haemorrhage.

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- Bloods: FBC, U&Es, LFTs, PTT, glucose, cholesterol levels.
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Causes
- Haemorrhagic causes:
  - Central nervous system bleeds from trauma.
  - Ruptured aneurysm.
- Ischaemic causes:
  - Small vessel occlusion.
  - Atherothromboembolism.
  - Cardiac emboli.
  - Emboli secondary to AF.

Treatment
- Conservative: patient and family education, initiate early mobilisation, commence stroke rehabilitation, assess speech and swallowing. Assess impact of activities of daily living (ADLs) using Barthel index.
- Medical:
  - TIA patients:
    - Assess risk of subsequent stroke using ABCD² (high risk is a score >6, low risk is a score <4).
    - ABCD²: Age >60 years (1 point); Blood pressure >140/90 mmHg (1 point); Clinical features: unilateral weakness (2 points), isolated speech disturbance (1 point); Duration of symptoms: >60 min (2 points), 10–59 min (1 point); Diabetes (1 point).
    - Start aspirin 300 mg.
  - Ischaemic stroke patients without haemorrhage:
    - Thrombolysis with alteplase within 3 h (patients >80 years) and within 4.5 h (patients <80 years).
    - Start aspirin 300 mg (unless contraindications).
  - Haemorrhagic stroke patients:
    - Prothrombin complex concentrate.
    - Intravenous vitamin K.
- Surgical:
  - Referral for acute intracerebral haemorrhage.
  - Referral for decompressive hemicraniectomy.

Risk factors
- ↑ Blood pressure.
- Atrial fibrillation (AF).
- Diabetes mellitus.
- Smoking.
- Alcohol.
- Previous stroke.
- The oral contraceptive pill.
- Disorder that increases clotting.
- Cocaine use.
- ↑ Cholesterol.
# Table 9.2 Dementia

This is a syndrome of a progressive global decline in cognitive function.

<table>
<thead>
<tr>
<th>Type of dementia</th>
<th>Causes</th>
<th>Signs and symptoms</th>
<th>Investigations</th>
<th>Treatment</th>
<th>Complications</th>
</tr>
</thead>
</table>
| **Alzheimer’s disease** | Exact cause unknown Risk factors include:  
- Down’s syndrome due to ↑ APP gene load  
- Familial gene associations:  
  - Amyloid precursor protein (APP): chromosome 21  
  - Presenilin-1: chromosome 14  
  - Presenilin-2: chromosome 1  
  - Apolipoprotein E4 (ApoE4) alleles: chromosome 19  
  - Hypothyroidism  
  - Previous head trauma  
  - Family history of Alzheimer’s disease | Amnesia  
Disorientation  
Changes in personality  
Decreasing self care  
Aphasia  
Agnosia  
Lexical anomia  
Paranoid delusions  
Depression  
Wandering  
Aggression  
Sexual disinhibition | Mental state examination  
Addenbrooke’s Cognitive Examination (ACE-III)  
Bloods: FBC, U&Es, LFTs, TFTs, CRP, ESR, glucose, calcium, magnesium, phosphate, VDRL, HIV serology, vitamin B12 and folate levels, blood culture, ECG, lumbar puncture, CXR, CT scan, MRI scan, SPECT  
3 main findings on histology – **BAT**:  
- Beta amyloid plaques  
- ↓ Acetylcholine  
- neurofibrillary Tangles | Memantine: inhibits glutamate by blocking N-methyl-D-aspartate (NMDA) receptors  
Donepezil: acetylcholinesterase inhibitor  
Rivastigmine: acetylcholinesterase inhibitor | Amnesia  
Increased risk of infection  
Dysphagia  
Urinary incontinence  
Increased risk of falls |
| **Vascular dementia** | Is the second most common cause of dementia  
It is caused by infarcts of small and medium sized vessels in the brain  
Genetic association with cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) on chromosome 19 | It follows a deteriorating stepwise progression. There are 3 types:  
1. Vascular dementia following stroke  
2. Multi-infarct dementia | Mental state examination  
ACE-III  
Bloods: FBC, U&Es, LFTs, TFTs CRP, ESR, glucose, calcium, magnesium, phosphate, | Dietary advice  
Smoking cessation  
Treat diabetes mellitus and hypertension  
Aspirin | Significant co-morbidity, e.g. cardiovascular disease and renal disease |
### Table 9.2 Dementia

**Type of dementia**

- Alzheimer’s disease
  - Exact cause unknown
  - Risk factors include:
    - Down’s syndrome due to APP gene load
    - Familial gene associations:
      - Amyloid precursor protein (APP): chromosome 21
      - Presenilin-1: chromosome 14
      - Presenilin-2: chromosome 1
      - Apolipoprotein E4 (ApoE4) alleles: chromosome 19
    - Hypothyroidism
    - Previous head trauma
    - Family history of Alzheimer’s disease

**Signs and symptoms**

- Amnesia
- Disorientation
- Changes in personality
- Decreasing self care
- Apraxia
- Agnosia
- Aphasia
- Lexical anomia
- Paranoid delusions
- Depression
- Wandering
- Aggression
- Sexual disinhibition

**Investigations**

- Mental state examination
- Addenbrooke’s Cognitive Examination (ACE-III)
- Bloods: FBC, U&Es, LFTs, TFTs, CRP, ESR, glucose, calcium, magnesium, phosphate, VDRL, HIV serology, vitamin B12 and folate levels, blood culture, ECG, lumbar puncture, CXR, CT scan, MRI scan, SPECT

**3 main findings on histology – BAT**:

- Beta amyloid plaques
- Acetylcholine
- Neurofibrillary tangles

**Treatment**

- Memantine: inhibits glutamate by blocking N-methyl-D-aspartate (NMDA) receptors
- Donepezil: acetylcholinesterase inhibitor
- Rivastigmine: acetylcholinesterase inhibitor

**Complications**

- Amnesia
- Increased risk of infection
- Dysphagia
- Urinary incontinence
- Increased risk of falls

---

**Dementia with Lewy bodies**

- Associated with Parkinson’s disease
- Avoid antipsychotic drugs in these patients

Is a triad of:

1. Parkinsonism: bradykinesia, gait disorder
2. Hallucinations: predominantly visual hallucinations, usually of animals and people
3. Disease process follows a fluctuating course

**Mental state examination**

- ACE-III
- CT scan, MRI scan, SPECT scan

**ApoE genotype**

- Lewy bodies, ubiquitin proteins and alpha-synuclein found on histology

**AVOID**

- ANTIPSYCHOTICS: causes hypersensitivity to neuroleptics
- Levodopa may be used to treat Parkinson’s symptoms but these may worsen psychotic symptoms

**Avoid neuroleptic hypersensitivity**

- Autonomic dysfunction
- Fluctuating blood pressure
- Arrhythmias
- Urinary incontinence
- Dysphagia
- Increased risk of falls

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*Continued overleaf*
### Table 9.2 Dementia (Continued)

This is a syndrome of a progressive global decline in cognitive function.

<table>
<thead>
<tr>
<th>Type of dementia</th>
<th>Causes</th>
<th>Signs and symptoms</th>
<th>Investigations</th>
<th>Treatment</th>
<th>Complications</th>
</tr>
</thead>
</table>
| **Frontotemporal dementia (Pick’s disease)** | Genetic association with chromosome 17q21 – 22 and tau 3 gene mutations | Amnesia
Disorientation
Changes in personality
Decreasing self care
Mutism
Echolalia
Overeating
Parkinsonism
Disinhibition | Mental state examination
ACE-III
CT scan, MRI scan, SPECT scan
Histology – depends on subtype:
- Microvacuolar type: microvacuolation
- Pick type: widespread gliosis, no microvacuolation
- Motor neuron disease (MND) type: histological changes like MND | Currently none. Only supportive treatment available | Increased risk of falls
Increased risk of infection |
| **Huntington’s dementia** | A complication of Huntington’s disease (see page 204), which is an autosomal dominant disorder where there is a defective gene on chromosome 4 Causes uncontrollable choreiform movements and dementia | Uncontrollable choreiform movements
Depression
Irritability
Anxiety
Psychosis
Obsessive compulsive behaviour | Diagnostic genetic testing | No cure. Treat symptoms:
- Chorea: an atypical antipsychotic agent
- Obsessive compulsive thoughts and irritability: selective serotonin reuptake inhibitors (SSRIs) | Dysphagia
Increased risk of falls
Increased risk of infection |
### Table 9.2  Dementia

<table>
<thead>
<tr>
<th>Disease</th>
<th>Causes</th>
<th>Signs and Symptoms</th>
<th>Investigations</th>
<th>Treatment</th>
<th>Complications</th>
</tr>
</thead>
</table>
| **Creutzfeldt-Jakob disease (CJD)** | Caused by prions
Progressive and without cure
There is also variant CJD (vCJD), which has an earlier onset of death | Rapidly progressive dementia (4–5 months)
Amnesia
Disorientation
Changes in personality
Depression
Psychosis
Ataxia
Seizures | EEG: triphasic spikes seen
Lumbar puncture (LP): for
14-3-3 protein
CT scan
MRI scan | No cure | Increased risk of infection
Coma
Heart failure
Respiratory failure |
| **Other causes**            | HIV
Vitamin B₁₂ deficiency
Syphilis
Wilson’s disease: autosomal recessive condition where copper accumulates within the tissues
Dementia pugilistica: seen in boxers and patients who suffer multiple concussions; also known as ‘punch drunk’ syndrome | | | | |
What is epilepsy?
This is a condition in which the brain is affected by recurrent seizures. These seizures may be defined in many different ways:
- Partial seizures: this is a seizure that occurs in one discrete part of the brain. These seizures may be simple (without alteration in consciousness) or complex (with alteration in consciousness).
- Generalised seizures: these seizures affect the brain globally. Consciousness is always altered. Examples include:
  - Absence seizures: often picked up in children who ‘stare into space’. The seizure usually only lasts seconds.
  - Tonic–clonic seizures: involves convulsions and muscle rigidity. Usually last minutes.
  - Atonic seizures: involves a loss of muscle tone.
  - Myotonic: involves jerky muscle movements.
  - Secondary generalised: this is a generalised seizure that originates from a partial seizure.

Investigations
- Bloods: FBC, U&Es, LFTs, CRP, ESR, glucose, calcium levels.
- Radiology: CT scan, MRI scan.
- Other: ECG, LP, EEG.

Signs and symptoms
These depend on the region of the brain affected.
- Frontal lobe, remember JAM:
  - Jacksonian march.
  - pAlsy (postictal Todd’s palsy).
  - Motor features.
- Temporal lobe, remember ADD FAT:
  - Aura that the epileptic attack will occur.
  - Dégà vu.
  - Delusional behaviour.
  - Fear/panic: hippocampal involvement.
  - Automatisms.
  - Taste/smell: uncal involvement.
- Parietal and occipital lobe: visual and sensory disturbances.
- Others include: partial or generalised seizure with or without convulsions, tongue biting, migraines and depression.
**Causes**
Seizures are caused by abnormal paroxysmal neuronal discharges in the brain, which are usually a result of some form of traumatic brain injury. These discharges display hypersynchronisation. The causes of epilepsy may be broadly classified into 3 types:
1. Idiopathic: cause for epilepsy is unknown.
2. Cryptogenic: cause for epilepsy is unknown, but there are signs suggesting it may be linked to brain injury, e.g. patient has autism or learning difficulties.
3. Symptomatic: cause known. Some causes of symptomatic epilepsy include:

**VINDICATE:**
- Vascular: history of stroke.
- Infection: history of meningitis or malaria.
- Neoplasms: brain tumour.
- Drugs: alcohol and illicit drug use.
- Iatrogenic: drug withdrawal.
- Congenital: family history of epilepsy.
- Autoimmune: vasculitis.
- Trauma: history of brain injury.
- Endocrine: ↓ Na⁺, ↓ Ca²⁺, ↓ or ↑ glucose.

**Complications**
- Injuries whilst having seizure.
- Depression.
- Anxiety.
- Brain damage.
- Sudden unexplained death in epilepsy (SUDEP).

**Treatment**
- Medical: anticonvulsant therapy, see Table 9.3.
- Surgical: anterior temporal lobe resection, corpus callosotomy, tumour removal.

*Neurology* Map 9.3 Epilepsy
### Table 9.3 Anticonvulsant Drugs

N.B. for a full description of epilepsy management and which drugs to use as first line, please follow the website link provided for NICE guidelines (Appendix 2).

<table>
<thead>
<tr>
<th>Anticonvulsant agent</th>
<th>Mechanism of action</th>
<th>Uses</th>
<th>Side-effects</th>
<th>Contraindications</th>
<th>Drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carbamazepine</strong></td>
<td>Blocks voltage dependent Na(^+) channels</td>
<td>All seizures except absence seizures Neurpathic pain, e.g. trigeminal neuralgia Manic–depressive illness</td>
<td>Rash Sedation Drowsiness Hyponatraemia Dry mouth Blurring of vision Neutropenia Hallucinations</td>
<td>Pregnancy (it is teratogenic) Past history of bone marrow depression Acute porphyria</td>
<td>Alters metabolism of oral contraceptive pill Alters metabolism of warfarin Alters metabolism of corticosteroids</td>
</tr>
<tr>
<td><strong>Phenytoin</strong></td>
<td>Blocks voltage dependent Na(^+) channels</td>
<td>All seizures except pure absence seizures Seizure prevention post neurosurgery Trigeminal neuralgia Arrhythmia</td>
<td>Rash Hypersensitivity reactions Ataxia Megaloblastic anaemia Hirsutism Gum hypertrophy Purple glove syndrome</td>
<td>Pregnancy (it is teratogenic) Sinus bradycardia Stokes–Adams syndrome Sinoatrial block Second degree heart block Third degree heart block</td>
<td>Sodium valproate alters (increases or decreases) phenytoin concentration Phenytoin increases metabolism of drugs like anticoagulants by enzyme induction Phenytoin reduces concentration of mirtazapine N.B. This drug has a narrow therapeutic index</td>
</tr>
<tr>
<td>Anticonvulsant Drug</td>
<td>Mechanism of Action</td>
<td>Uses</td>
<td>Side-effects</td>
<td>Contraindications</td>
<td>Drug Interactions</td>
</tr>
<tr>
<td>---------------------</td>
<td>---------------------</td>
<td>------</td>
<td>--------------</td>
<td>-----------------</td>
<td>------------------</td>
</tr>
<tr>
<td><strong>Sodium valproate</strong></td>
<td>Blocks voltage dependent Na⁺ channels</td>
<td>All seizures except absence seizures, manic-depressive illness</td>
<td>Rash, sedation, drowsiness, hyponatraemia, dry mouth, blurring of vision, neutropenia, hallucinations</td>
<td>Pregnancy (it is teratogenic), history of bone marrow depression, acute porphyria</td>
<td>Phenytoin increases levels of sodium valproate, sodium valproate may enhance effects of anticoagulant coumarins, sodium valproate decreases levels of sodium valproate</td>
</tr>
<tr>
<td><strong>Ethosuximide</strong></td>
<td>Inhibits T-type Ca²⁺ channels</td>
<td>Absence seizures (used more frequently in children)</td>
<td>Nausea, vomiting, anorexia, hypersensitivity reactions, blood dyscrasias, ataxia</td>
<td>Pregnancy (it is teratogenic), hepatic failure, affective disorders, systemic lupus erythematosus</td>
<td>Metabolism is inhibited by isoniazid, sodium valproate increases the level of ethosuximide, phenytoin and carbamazepine decrease the level of ethosuximide</td>
</tr>
<tr>
<td><strong>Phenobarbital</strong></td>
<td>Acts on GABA_A receptors, enhancing synaptic inhibition</td>
<td>All seizures except absence seizures, status epilepticus (third line), anaesthesia, neonatal seizures, cyclical vomiting syndrome, crigler–najjar syndrome, gilbert syndrome</td>
<td>Rash, sedation, depression, ataxia, amelogenesis imperfecta</td>
<td>Pregnancy (it is teratogenic), history of porphyria</td>
<td>Phenobarbital increases metabolism of coumarins, carbamazepine increases concentration of phenobarbital, phenobarbital decreases levels of itraconazole</td>
</tr>
</tbody>
</table>

Continued overleaf
### TABLE 9.3 Anticonvulsant Drugs (Continued)

N.B. for a full description of epilepsy management and which drugs to use as first line, please follow the website link provided for NICE guidelines (Appendix 2)

<table>
<thead>
<tr>
<th>Anticonvulsant agent</th>
<th>Mechanism of action</th>
<th>Uses</th>
<th>Side-effects</th>
<th>Contraindications</th>
<th>Drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td>Allosterically modifies GABA&lt;sub&gt;A&lt;/sub&gt; receptor, thereby increasing Cl&lt;sup&gt;−&lt;/sup&gt; conductance</td>
<td>Lorazepam used to treat status epilepticus (first line) Anxiety disorders Insomnia Seizures Alcohol withdrawal</td>
<td>Sedation Withdrawal syndrome Respiratory depression</td>
<td>Chronic obstructive pulmonary disease Sleep apnoea Myasthenia gravis Severe depression (increased suicidal tendencies)</td>
<td>Use cautiously with other central nervous system depressants, e.g. opioids and barbiturates Increasing sedative effect when used with antihistamines Increasing sedative effect when used with antipsychotics</td>
</tr>
<tr>
<td><strong>Vigabatrin</strong></td>
<td>Inhibits GABA transaminase</td>
<td>All seizures Seizures in patients who are resistant to other anticonvulsant medication</td>
<td>Sedation Headache Peripheral visual field defect Depression Psychosis Hallucinations</td>
<td>Hypersensitivity</td>
<td>Vigabatrin increases clearance of carbamazepine Vigabatrin decreases levels of phenytoin</td>
</tr>
</tbody>
</table>
### Table 9.3 Anticonvulsant Drugs (Continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Uses</th>
<th>Side-effects</th>
<th>Contraindications</th>
<th>Drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lamotrigine</strong></td>
<td>Blocks voltage</td>
<td>All seizures</td>
<td>Stevens–Johnson syndrome</td>
<td>Hypersensitivity</td>
<td>The oral contraceptive pill decreases levels of lamotrigine</td>
</tr>
<tr>
<td></td>
<td>dependent Na⁺</td>
<td>Manic–depressive illness</td>
<td>Toxic epidermal necrolysis (Lyell’s syndrome)</td>
<td>Hepatic failure</td>
<td>Carbemazepine decreases lamotrigine levels</td>
</tr>
<tr>
<td></td>
<td>channels</td>
<td>Severe depression</td>
<td>Rashes</td>
<td></td>
<td>Rifampicin decreases levels of lamotrigine</td>
</tr>
<tr>
<td></td>
<td>Inhibits L-, N- and P-type Ca²⁺ channels</td>
<td>Neuropathic pain, e.g. trigeminal neuralgia</td>
<td>Nausea</td>
<td></td>
<td>Valproate increases levels of lamotrigine</td>
</tr>
<tr>
<td>Gabapentin and pregabalin</td>
<td>Gapapentin is a GABA analogue</td>
<td>All seizures</td>
<td>Sedation</td>
<td>Hypersensitivity</td>
<td>When used with propoxyphene patients are more at risk of side-effects such as dizziness and confusion</td>
</tr>
<tr>
<td></td>
<td>Pregabalin is an analogue of gabapentin</td>
<td>Neuropathic pain</td>
<td>Ataxia</td>
<td></td>
<td>Bioavailability of gabapentin increased by morphine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Manic–depressive illness</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
What is Parkinson’s disease?
This is a progressive disorder of the central nervous system, which is due to dopamine depletion.

Causes
The exact cause of this degenerative disease is unknown but some postulated risk factors include:
- Male gender.
- Genetic component.
- Environmental exposure to insecticides, pesticides and herbicides.

Pathophysiology
- \( \downarrow \) Dopamine producing cells in the pars compacta region of the substantia nigra, located in the midbrain.
- Dopamine produced is secreted to the putamen and caudate nucleus.
- \( \uparrow \) Lewy bodies in the substantia nigra.

Signs and symptoms
Remember Facial TRAPS:
- Facial: expressionless face.
- Tremor (pill rolling tremor).
- Rigidity (cog wheel rigidity).
- Akinesia.
- Posture (stooped).
- Shuffling gait.

Investigations
There is no specific test for Parkinson’s disease. It is a clinical diagnosis.
- CT scan and MRI scan may be arranged but these are usually normal.
- PET, SPECT and ioflupane (DaTSCAN) may measure basal ganglia dopaminergic function.

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- Rigidity (cog wheel rigidity).
- Akinesia.
- Posture (stooped).
- Shuffling gait.

Treatment
- Medical:
  - Levodopa: crosses the blood–brain barrier (BBB) where it is converted to dopamine.
  - Carbidopa; always given with levodopa. It is a dopa decarboxylase inhibitor and prevents levodopa from being metabolised to dopamine in other regions of the body. Therefore, it acts to decrease peripheral side-effects.
  - Selegiline; inhibits monoamine oxidase B (MAO-B). This enzyme breaks down dopamine.
  - Amantadine; dopamine agonist. Decreases Parkinsonian symptoms.
- Surgical: this option is unlikely since drug regimens have improved.

Complications
- Dysphagia.
- Dementia.
- Increased risk of falls.
- Erectile dysfunction.
What is MS?
This is thought to be a progressive autoimmune condition in which the neurons of the central nervous system demyelinate. Its progression may be classified into 4 subtypes:
1. Relapsing remitting.
2. Primary progressive.
4. Benign.

Causes
The exact cause of MS is not known but there are several factors that are thought to contribute:
- It is thought to be a type IV T cell-mediated immune response.
- Location: those who live further from the equator and Sardinians are at greater risk than other populations.
- Viruses may play a role, e.g. Epstein–Barr virus (EBV).
- Smoking is a risk factor.

Pathophysiology
- Plaques of demyelination, disseminated in time and space, interfere with neuronal transmission.
- Often patients enter remission but then relapse. This is because the demyelinated neurons do not heal fully.

Signs and symptoms
- Usually monosymptomatic.
- Symptoms relate to the location where plaques of demyelination occur. Remember these as DOTS:
  - Diplopia, Dysaesthesia.
  - Optic neuritis: this is often a presenting symptom and patients complain of double vision (diplopia).
  - Trigeminal neuralgia, Trunk and limb ataxia.
  - ↓ Sense of vibration.
- Uhthoff’s phenomenon: symptoms worsen in hot conditions.

Investigations
- LP: some proteins are altered in MS, e.g. oligoclonal bands.
- MRI scan: shows regions affected by inflammation and scarring, e.g. Dawson’s fingers.

Treatment
- Conservative: patient education. Use diagnostic McDonald criteria and regularly assess ADLs as well as psychosocial impact of disease.
- Medical:
  - Interferon.
  - Methylprednisolone, a corticosteroid.
  - Glatiramer acetate, an immunomodulator.
  - Natalizumab, a monoclonal antibody.
  - Alemtuzumab, a monoclonal antibody.
  - Azathioprine, a purine analogue (immunosuppressant).
  - Mitoxantrone, a doxorubicin analogue.

Complications
- Urinary incontinence.
- Bowel incontinence.
- Depression.
- Epilepsy.
- Paralysis.
Mechanism of skeletal and cardiac muscle contraction

- **Depolarisation:**
  - Action potential causes voltage gated Ca\(^{2+}\) ion channels to open.
  - Neurotransmitter released.
- **Spread of depolarisation:**
  - Down the T-tubules to dihydropyridine receptors in skeletal muscle.
  - In cardiac muscle, this process involves calcium-induced calcium release from the sarcoplasmic reticulum.
- **Conformational change:**
  - ↑ Ca\(^{2+}\) ions from calcium-induced calcium release.
  - Ca\(^{2+}\) ions bind to troponin C.
- **Cross bridge formation:**
  - Myosin head binds to actin when tropomyosin moves due to conformational change.
- **Power stroke:**
  - ADP released.
  - Muscle contracts.
- **Myosin head released and cycle repeats.**

Mechanism of smooth muscle contraction

- **Depolarisation:**
  - Caused by action potential.
  - Voltage gated Ca\(^{2+}\) ion channels open.
- **Calmodulin binding:** Ca\(^{2+}\) ions bind to calmodulin.
- **Myosin light chain kinase (MLCK) activated.**
- **The role of myosin: actin coupled with myosin P causes contraction.**
OSTEOARTHRITIS (OA)

What is OA?
This is a degenerative arthritis affecting synovial joints and is characterised by cartilage degeneration, the associated response of the periarticular tissue and pain that is typically worse at the end of the day.

Causes
Damage to the joints and general wear and tear of the joint over time is thought to be the primary cause of OA. There are certain factors that increase the risk of OA such as:
- Increased age.
- Obesity.
- Trauma to the joint.
- Conditions such as haemochromatosis and Ehlers–Danlos syndrome.

Signs and symptoms
- Pain and stiffness.
- Swelling around the joints involved.
- Crepitus.
- Heberden’s nodes at distal interphalangeal (DIP) joints. Remember they are the ‘outer Hebrides’.
- Bouchard’s nodes at proximal interphalangeal (PIP) joints.

Investigations
- Bloods: usually are not diagnostic but may be relevant when OA is related to another condition such as haemochromatosis.
- Radiology: radiological signs:
  - Loss of joint space.
  - Osteophytes.
  - Subchondral cysts.
  - Sclerosis.

Treatment
- Medical:
  - Analgesia, e.g. paracetamol or nonsteroidal anti-inflammatory drugs.
  - Gels such as capsaicin may be useful.
  - Steroid injections.
- Surgical: arthroplasty.

Complications
- Increased risk of gout.
- Chondrocalcinosis.
- Cervical myopathy.
- Tendon rupture.
- Sjögren’s syndrome.

Continued overleaf
Musculoskeletal System

Arthritis

OSTEOARTHRITIS (OA)
What is OA?
This is a degenerative arthritis affecting synovial joints and is characterised by cartilage degeneration, the associated response of the periarticular tissue and pain that is typically worse at the end of the day.

Causes
Damage to the joints and general wear and tear of the joint over time is thought to be the primary cause of OA. There are certain factors that increase the risk of OA such as:
- Increased age.
- Obesity.
- Trauma to the joint.
- Conditions such as haemochromatosis and Ehlers–Danlos syndrome.

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- Pain and stiffness.
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  - Loss of joint space.
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  - Subchondral cysts.
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Treatment
- Medical:
  - Analgesia, e.g. paracetamol or nonsteroidal anti-inflammatory drugs.
  - Gels such as capsaicin may be useful.
  - Steroid injections.
- Surgical: arthroplasty.

Complications
- Increased risk of gout.
- Chondrocalcinosis.

RHEUMATOID ARTHRITIS (RA)
What is RA?
This is a chronic, autoimmune type III hypersensitivity reaction that principally affects the joints but may also affect other organs. Joint involvement is characterised by symmetrical deformation with pain that is worse in the morning.

Cause
The exact cause of RA is unknown, but it is thought to involve a type III hypersensitivity reaction. This condition is associated with HLA DR4 and HLA DR1.

Signs and symptoms
- Hands: Z deformity, boutonnière deformity, swan neck deformity, ulnar deviation, subluxation of the fingers, Raynaud’s phenomenon.
- Wrist: carpal tunnel syndrome.
- Feet: subluxation of the toes, hammer toe deformity.
- Skin: rheumatoid nodule, vasculitis.
- Cardiovascular: atherosclerosis is increased in RA.
- Respiratory: pulmonary fibrosis.
- Bones: osteoporosis.
- Pain and stiffness.

Investigations
- Bloods:
  - 80% test positive for rheumatoid factor.
  - ESR and CRP raised.
  - Cyclic citrullinated peptide (CCP) antibodies. If positive this is suggestive of erosive disease.
- Radiology: radiological signs of RA are visualised on plain film:
  - Bony erosion.
  - Subluxation.
  - Carpal instability.
  - Joint involvement of metacarpophalangeal joint (MCPJ) and metatarsophalangeal joint (MTPJ).
  - Periarticular osteoporosis.

Treatment
- Medical: glucocorticoids, disease modifying antirheumatic drugs (DMARDs), e.g. gold salts, methotrexate, sulfasalazine. Anticytokine therapies may be considered in patients intolerant of methotrexate.
- Surgery: excision arthroplasty or replacement may be considered in severely affected joints.

Complications
- Carpal tunnel syndrome.
- Pericarditis.
- Cervical myopathy.
- Tendon rupture.
- Sjögren’s syndrome.
- Increased risk of gout.
- Chondrocalcinosis.
**REACTIVE ARTHRITIS**

**What is reactive arthritis?**
This is an asymmetrical arthritis that occurs post gastrointestinal or urogenital infection.

**Causes**
The exact cause and pathophysiology of this condition is not known. However, it often occurs after an infection, typically, a sexually transmitted infection or an infection of the gastrointestinal tract.

**Signs and symptoms**
- Urethritis.
- Arthritis: pain and stiffness.
- Uveitis/conjunctivitis.

**Investigations**
- Radiology: X-ray of affected joint (assesses severity).

**Treatment**
- Conservative: patient education. Refer to physiotherapy.
- Medical: analgesia nonsteroidal anti-inflammatory drugs (NSAIDs) and disease modifying antirheumatic drugs (DMARDs), e.g. sulphasalzine (first line).

**Complications**
- Arrhythmia.
- Aortic insufficiency.
- Uveitis.

*Remember PEAR:*
- Psoriatic arthritis.
- Enteropathic arthropathies.
- Ankylosing spondylitis.
- Reactive arthritis.
PSORIATIC ARTHRITIS
What is psoriatic arthritis?
This is an inflammatory arthritis that is associated with the skin condition psoriasis. It is associated with HLA B27. The signs and symptoms also depend on how and where the joints are affected. Accordingly, psoriatic arthritis may be split into 5 subtypes:
1. Asymmetrical oligoarthritis (distal and proximal interphalangeal joints).
2. Symmetrical rheumatoid-like arthropathy.
3. Ankylosing spondylitis variant.
4. Polyarteritis with skin and nail changes.
5. Arthritis mutilans.

Causes
The exact cause is unknown. It is thought to be due to an inflammatory process coupled with genetic involvement of the HLA B27 gene. The greatest risk factor is a family history of psoriasis.

Signs and symptoms
- Psoriasis: well-demarcated salmon-pink plaques with evidence of scaling. These plaques are usually present on the extensor surfaces (chronic plaque psoriasis) but sometimes smaller plaques may occur in a raindrop pattern over the torso. This is called guttate psoriasis and is often preceded by an upper respiratory tract infection/sore throat that is caused by Streptococcus.
- Joint pain and stiffness.
- Swelling of affected joints.
- Nail changes: there are 4 nail changes noted in psoriasis: yellowing of the nail, onycholysis, pitting and subungual hyperkeratosis.

ENTEROPATHIC ARTHROPATHIES
What are enteropathic arthropathies?
This is an arthritis that develops in association with inflammatory bowel disease (IBD). It is indistinguishable from reactive arthritis.

Causes
The exact cause and pathophysiology of this condition are not known. However, it is thought to be associated with HLA B27.

Signs and symptoms
- Those of IBD, see page 40.
- Spondylitis.
- Sacroiliitis.
- Peripheral arthritis: usually of large joints.

Investigations
- Those for IBD, see page 40.

Treatment
- Analgesia (NSAIDs).
- Treatment of IBD, see page 40.

Complications
- Severely decreased mobility with axial involvement.
**Investigations**
- Psoriasis is a clinical diagnosis.
- Bloods: seronegative for rheumatoid factor.

**Treatment**
- Conservative: patient education. Refer to physiotherapy. Explain to patients that psoriasis does not have a cure and control of the disease is more realistic.
- Medical: analgesia (nonsteroidal anti-inflammatory drugs [NSAIDs]) and disease modifying antirheumatic drugs (DMARDs), e.g. methotrexate (first line). Manage psoriasis.
- Surgery: rarely joint replacement.

**Complications**
- Neurological manifestations if atlanto–axial joint involvement.
- Joint destruction.

---

**ANKYLOSING SPONDYLITIS**

**What is ankylosing spondylitis?**
This is a chronic inflammatory disease of the spine and sacroiliac joints. There is predominance in young males and the condition is associated with HLA B27 (positive in 95%).

**Causes**
The exact cause and pathophysiology of this condition are not known. However, it is thought to be associated with HLA B27.

**Signs and symptoms**
- Question mark posture.
- Bamboo spine: due to calcification of ligaments.
- Pain and stiffness: symptoms improve with exercise.

**Investigations**
- Bloods: seronegative for rheumatoid factor.
- Radiology: CXR and MRI scan assess changes in the spine.

**Treatment**
- Conservative: patient education. Refer to physiotherapy.
- Medical: analgesia (NSAIDs) and DMARDs, e.g. sulphasalzine (first line).
- Surgery: corrective spinal surgery.

**Complications**
- Osteoprosis.
- Spinal fractures.
- Increased risk of cardiovascular disease, e.g. stroke and myocardial infarction.
What is gout?
Gout is an inflammatory crystal monoarthropathy caused by the deposition of urate crystals. These monosodium urate crystals often precipitate in the metatarsophalangeal joint (MTPJ). Gout involving the big toe is known as a podagra.

Causes
There are many causes of gout but essentially anything that increases urate levels may be the underlying cause. Some examples include,

**Horrific DELAY:**
- Hyperuricaemia, Hereditary.
- Diuretics (thiazides).
- Ethanol.
- Leukaemia.
- renAl impairment.
- associated with Lesch–Nyhan syndrome.

Signs and symptoms
- Calor, dolor, rubor and tumour (heat, pain, redness and swelling) of the affected joint, which is usually the MTPJ in 50% of patients.
- Tophi (urate deposits) may be present on tendon surfaces, e.g. the elbow, or visible on the ear.
- Patients may have symptoms of renal calculi.

Investigations
- Bloods: serum urate levels, FBC, WCC, U&Es, creatinine, ESR, CRP.
- GFR: assess kidney function.
- Synovial fluid analysis: positive if birefringent monosodium urate crystals seen.
What is gout?

Gout is an inflammatory crystal monoarthropathy caused by the deposition of urate crystals. These monosodium urate crystals often precipitate in the metatarsophalangeal joint (MTPJ). Gout involving the big toe is known as a podagra.

Causes

There are many causes of gout but essentially anything that increases urate levels may be the underlying cause. Some examples include:

- Hyperuricaemia
- Hyperuricaemia
- Diuretics (thiazides)
- Alcohol
- Leukaemia
- Renal impairment
- Associated with Lesch–Nyhan syndrome.

Signs and symptoms

- Calor, dolor, rubor and tumour (heat, pain, redness and swelling) of the affected joint, which is usually the MTPJ in 50% of patients.
- Tophi (urate deposits) may be present on tendon surfaces, e.g. the elbow, or visible on the ear.
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Investigations

- Bloods: serum urate levels, FBC, WCC, U&Es, creatinine, ESR, CRP.
- GFR: assess kidney function.
- Synovial fluid analysis: positive if birefringent monosodium urate crystals seen.

Pseudogout vs. gout

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pseudogout</th>
<th>Gout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joints affected</td>
<td>Larger proximal</td>
<td>Classically 1st MTPJ</td>
</tr>
<tr>
<td>Crystal type</td>
<td>Calcium pyrophosphate crystals</td>
<td>Sodium urate crystals</td>
</tr>
<tr>
<td>Crystal shape</td>
<td>Rhomboid</td>
<td>Needle</td>
</tr>
<tr>
<td>Light microscopy</td>
<td>Negative birefringence</td>
<td>Strongly positive birefringence</td>
</tr>
</tbody>
</table>

Treatment

- Conservative: patient education. Lifestyle advice, e.g. encourage alcohol reduction and a low purine diet. Review medications that the patient is taking and stop causative agents, e.g. thiazide diuretics, if possible.
- Medical:
  - Analgesia.
  - Acute: colchicine and steroids.
  - Chronic: allopurinol. Febuxostat may be used if allopurinol is not tolerated by the patient.

Complications

- Joint damage.
- Renal calculi.
- Tophi formation.
**Osteoma**
- Location: skull.
- Associated with Gardner’s syndrome (this syndrome is associated with the *APC* gene on chromosome 5).

**Osteoblastoma**
- Location: vertebrae.
- Similar to osteoid osteoma.

**Giant cell tumour**
- Location: epiphysis (long bones).
- Soap bubble appearance.

**Ewing’s sarcoma**
- Location: diaphysis (long bones), pelvis, scapula, ribs.
- Onion skin appearance.
- Very aggressive.
- Predominance in children.

**Enchondroma**
- Location: intramedullary bone.
- Cartilaginous neoplasm.
- Seen in phalanges.

**Osteoid osteoma**
- Location: femur and tibia, phalanges and vertebrae.
- Intracortical lesion best differentiated on CT.
- Nidus.

**Osteosarcoma**
- Location: metaphysis (long bones).
- Risk factors: Paget’s disease, radiation, familial retinoblastoma.
- Predominance in children.
- Bimodal: 75% <20 years; increases >60 years.

**Chondrosarcoma**
- Location: medullary cavity of femur, humerus, tibia, pelvis, scapula, spine, skull and craniofacial area.

**Osteochondroma**
- Location: metaphysis (long bones).
- Most common benign bone lesion.

**Benign**

**Malignant**

**MAP 10.5 Bone Tumours**
Osteoma
- Location: skull.
- Associated with Gardner's syndrome (this syndrome is associated with the APC gene on chromosome 5).

Giant cell tumour
- Location: epiphysis (long bones).
- Soap bubble appearance.

Ewing's sarcoma
- Location: diaphysis (long bones), pelvis, scapula, ribs.
- Onion skin appearance.
- Very aggressive.
- Predominance in children.

Osteoblastoma
- Location: vertebrae.
- Similar to osteoid osteoma.

Benign Malignant

Enchondroma
- Location: intramedullary bone.
- Cartilaginous neoplasm.
- Seen in phalanges.

Osteochondroma
- Location: metaphysis (long bones).
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- Location: femur and tibia, phalanges and vertebrae.
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Osteosarcoma
- Location: metaphysis (long bones).
- Risk factors: Paget's disease, radiation, familial retinoblastoma.
- Predominance in children.
- Bimodal: 75% <20 years; increases >60 years.
OSTEOPOROSIS
What is osteoporosis?
This is a bone disorder that is characterised by loss of trabecular bone and increased fracture risk. It is more common in postmenopausal women due to ↓ oestrogen levels and ↑ bone resorption.

Causes
There is no single cause of osteoporosis but there are risk factors that predispose patients to this condition. These include:
- Loss of protective oestrogen in postmenopausal women.
- Prolonged steroid use.
- Increasing age.
- Excessive alcohol intake.
- Smoking.
- Positive family history.
- Diet deficient in calcium.
- Endocrine disorders such as diabetes mellitus and hyperthyroidism.

Signs and symptoms
This is often asymptomatic until the patient presents with pathological fracture. Patients may report loss in height, back pain and have a dowager’s hump (hyperkyphosis) on physical examination.

OSTEOMALACIA
What is osteomalacia?
This is a metabolic bone disorder characterised by low mineral bone content and deficient vitamin D. This leads to soft bones; however, the amount of bone is normal. In children this condition is called rickets.

Causes
Remember REVOLT:
- RESistance to vitamin D.
- Vitamin D deficiency.
- Osteodystrophy (renal).
- Liver disease.
- Tumour-induced osteomalacia.

Signs and symptoms
- Bone pain.
- Myalgia.
- Pathological fracture.

Investigations
- Bloods: FBC, U&Es, LFTs, TFTs, glucose, serum calcium, serum phosphate, alkaline phosphatase, PTH and vitamin D levels.
- Radiology: X-ray to assess fractures.
Osteoporosis

What is osteoporosis?
This is a bone disorder that is characterised by loss of trabecular bone and increased fracture risk. It is more common in postmenopausal women due to reduced estrogen levels and bone resorption.

Causes
There is no single cause of osteoporosis but there are risk factors that predispose patients to this condition. These include:

- Loss of protective estrogen in postmenopausal women.
- Prolonged steroid use.
- Increasing age.
- Excessive alcohol intake.
- Smoking.
- Positive family history.
- Diet deficient in calcium.
- Endocrine disorders such as diabetes mellitus and hyperthyroidism.

Signs and symptoms
This is often asymptomatic until the patient presents with pathological fracture. Patients may report loss in height, back pain and have a dowager's hump (hyperkyphosis) on physical examination.

Investigations
- Bloods: FBC, U&Es, LFTs, TFTs, glucose, serum calcium, serum phosphate, alkaline phosphatase levels and PTH.
- Dual-energy X-ray (DEXA) scan: a T-score >–2.5 is diagnostic.
- Radiology: X-ray, CT and MRI scan to assess fractures.

Treatment
- Medical: selective oestrogen receptor modulators (SERMs), calcitonin and bisphosphonates.

Osteomalacia

What is osteomalacia?
This is a metabolic bone disorder characterised by low mineral bone content and deficient vitamin D. This leads to soft bones; however, the amount of bone is normal. In children this condition is called rickets.

Causes
Remember REVOLT:

- Resistance to vitamin D.
- Vitamin D deficiency.
- Osteodystrophy (renal).
- Liver disease.
- Tumour-induced osteomalacia.

Signs and symptoms

- Bone pain.
- Myalgia.
- Pathological fracture.

Investigations
- Bloods: FBC, U&Es, LFTs, TFTs, glucose, serum calcium, serum phosphate, alkaline phosphatase, PTH and vitamin D levels.
- Radiology: X-ray to assess fractures.

Treatment
- Medical: vitamin D supplements, e.g. cholecalciferol and calcitriol.

Complications
- Increased risk of fracture.
OSTEOPETROSIS
What is osteopetrosis?
This condition, also known as marble bone disease, occurs when osteoclasts do not function properly. As such bone is no longer resorbed. This means that bones are thick and fracture easily.

**Causes**
- Osteoclast dysfunction.

**Signs and symptoms**
- Asymptomatic.
- Hepatomegaly.
- Splenomegaly.
- Anaemia.

**Investigations**
- Bloods: FBC, U&Es, LFTs, TFTs, glucose, serum calcium, serum phosphate, alkaline phosphatase and PTH.
- Radiology: X-ray to assess fractures.

**Treatment**
- Conservative: patient education. Refer to physiotherapy.
- Medical: vitamin D, calcitriol, erythropoietin, corticosteroids, gamma interferon, bone marrow transplant.

**Complications**
- Increased fracture risk.
- Neurological involvement due to nerve impingement.

PAGET’S DISEASE
What is Paget’s disease?
This is a chronic remodelling disorder of bone that results in abnormal bone architecture.

**Causes**
The exact cause is unknown but it this thought to have a viral and genetic aetiology.

**Signs and symptoms**
- Asymptomatic.
- Bone pain.
- Pathological fracture.
- Hearing loss (if skull affected).

**Investigations**
- Bloods: FBC, U&Es, LFTs, TFTs, glucose, serum calcium, serum phosphate, alkaline phosphatase and PTH.
- Radiology: X-ray to assess fractures.

**Treatment**
- Conservative: patient education and management of complications.
- Medical: bisphosphonates such as zoledronate injections.

**Complications**
- Osteogenic sarcoma.
- Heart failure.
- Increased risk of renal calculi.
### TABLE 10.1 Biochemical Profiling in Different Metabolic Bone Diseases

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Osteoporosis</th>
<th>Osteomalacia</th>
<th>Osteopetrosis</th>
<th>Paget’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum calcium</td>
<td>Normal</td>
<td>✅↓</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Serum phosphate</td>
<td>Normal</td>
<td>✅↓</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>Normal</td>
<td>✅↑</td>
<td>✅↑</td>
<td>Varies with evolution of disease</td>
</tr>
<tr>
<td>PTH</td>
<td>Normal</td>
<td>✅↑</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>
TABLE 10.2 Brachial Plexus Injury

<table>
<thead>
<tr>
<th>Nerve and nerve origin</th>
<th>Lesion</th>
<th>Cause</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axillary nerve (C5–C6)</td>
<td>Deltoid muscle paralysis</td>
<td>Shoulder dislocation Humeral neck fracture</td>
<td>Atrophy of the deltoid muscle seen</td>
</tr>
<tr>
<td>Musculocutaneous nerve (C5–C7)</td>
<td>Paralysis of biceps, brachialis and coracobrachialis muscles</td>
<td>Rarely occurs Complication of surgery Dislocation</td>
<td>↓ Sensation of lateral forearm</td>
</tr>
<tr>
<td>Median nerve (C5–T1)</td>
<td>Above antecubital fossa</td>
<td>Supracondylar fractures Neuropathy</td>
<td>Papal sign of benediction Ape hand deformity (at rest) Loss of sensation over thenar eminence</td>
</tr>
<tr>
<td></td>
<td>Below antecubital fossa</td>
<td>Injury to the anterior interosseous branch of the median nerve</td>
<td>Anterior interosseous syndrome Inability to pronate the forearm</td>
</tr>
<tr>
<td></td>
<td>At the wrist</td>
<td>Laceration of the wrist</td>
<td>Papal sign of benediction Ape hand deformity (at rest) Loss of sensation over thenar eminence</td>
</tr>
<tr>
<td></td>
<td>Within the wrist</td>
<td>Carpal tunnel syndrome (CTS)</td>
<td>Parasthesiae in median nerve distribution, i.e. lateral 2.5 fingers Pain often worse at night Wasting seen over the thenar eminence Special tests may be used in the diagnosis of CTS: Phalen’s test and Tinel’s test CTS is associated with pregnancy, the oral contraceptive pill, diabetes, heart failure, acromegaly, rheumatoid arthritis and gout</td>
</tr>
<tr>
<td>Ulnar nerve (C8–T1)</td>
<td>Ulnar clawing</td>
<td>Cubital tunnel syndrome</td>
<td>Ulnar clawing is more pronounced the more distal the lesion. This is known as the ulnar paradox.</td>
</tr>
<tr>
<td>---------------------</td>
<td>---------------</td>
<td>-------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Radial nerve (C5–C8)</td>
<td>Wrist drop</td>
<td>Trauma: fracture of the humerus, Lead poisoning</td>
<td>If lesion is located at the axilla it is sometimes called Saturday night palsy.</td>
</tr>
</tbody>
</table>
| C5 and C6 roots     | Erb–Duchenne palsy, aka waiter’s tip palsy | Dystocia (difficult childbirth) | Paralysis of lateral rotators: infraspinatus, teres minor  
Paralysis of abductors: supraspinatus, deltoid  
Paralysis of supinators: biceps  
Paralysis of flexors: brachialis          |
| C8 and T1           | Klumpke’s palsy | Dystocia                | Atrophy of interosseous muscles  
Atrophy of thenar muscles  
Atrophy of hypothenar muscles  
↓ Sensation of medial hand and medial forearm |
### PROGESTERONE
**Secreted by**
- Corpus luteum, placenta, adrenal cortex and testes.

**Function**
- Maintains pregnancy.
- Produces cervical mucus.
- Increases body temperature.
- Inhibits LH and FSH.
- Relaxes uterine smooth muscle.
- Downregulates oestrogen receptors.
- Increases endometrial gland secretion.
- Increases spiral artery development.
- Softens ligaments during pregnancy.

---

### OESTROGEN
**Secreted by**
- Ovaries and placenta.

**Function**
- Genital development.
- Breast development.
- Follicle growth.
- Endometrial growth.
- Upregulates oestrogen, LH and progesterone receptors.
- Inhibits FSH and LH through feedback mechanism.
- Stimulates prolactin secretion.
- Stimulates LH surge, which causes ovulation.
- Increases protein transport.

---

### INHIBIN
**Secreted by**
- Sertoli cells.

**Function**
- Inhibits FSH.
**PROGESTERONE**
- Secreted by: Corpus luteum, placenta, adrenal cortex and testes.
- Function:
  - Maintains pregnancy.
  - Produces cervical mucus.
  - Increases body temperature.
  - Inhibits LH and FSH.
  - Relaxes uterine smooth muscle.
  - Downregulates oestrogen receptors.
  - Increases endometrial gland secretion.
  - Increases spiral artery development.
  - Softens ligaments during pregnancy.

**OESTROGEN**
- Secreted by: Ovaries and placenta.
- Function:
  - Genital development.
  - Breast development.
  - Follicle growth.
  - Endometrial growth.
  - Upregulates oestrogen, LH and progesterone receptors.
  - Inhibits FSH and LH through feedback mechanism.
  - Stimulates prolactin secretion.
  - Stimulates LH surge, which causes ovulation.
  - Increases protein transport.

**TESTOSTERONE**
- Secreted by: Leydig cells of the testes and adrenal cortex.
- Function:
  - Male secondary sexual characteristics.
  - Penile and muscular development.
  - Growth of seminal vesicles.
  - Epiphyseal plate closure.
  - Differentiation of vas deferens, seminal vesicles and epididymis.

**LUTEINISING HORMONE (LH)**
- Secreted by: Anterior pituitary gland.
- Function:
  - Stimulates Leydig cells to produce testosterone.
  - Surge causes ovulation.
FIGURE 11.1 The Menstrual Cycle

Step 1: Increased oestrogen levels cause endometrial proliferation whilst Graafian follicle matures

Step 2: An increase in oestrogen levels causes an increased expression of gonadotrophin releasing hormone (GnRH) receptors on the anterior pituitary gland.
A further increase in oestrogen causes a luteinising hormone (LH) surge

Step 3: LH surge causes ovulation around day 14

Step 4: Corpus luteum secretes progesterone, which maintains the endometrial lining for implantation

Step 5: When a fertilised egg does not implant, the corpus luteum regresses meaning that progesterone levels decrease

Step 6: Progesterone levels no longer maintain the endometrium, and so the endometrium is shed
FIGURE 11.2 The Lactation Pathway

CNS

Anterior pituitary

Prolactin

Milk production

Suckling

Posterior pituitary

Oxytocin

Milk ejection

Supraoptic and paraventricular nuclei of the hypothalamus

4th–6th intercostal nerve
**MATERNAL CHANGES DURING PREGNANCY**

**Respiratory system**
- Elevated diaphragm by 4 cm.
- ↓ Expiratory reserve volume.
- ↑ Tidal volume.

**Cardiovascular system**
- ↓ BP because progesterone decreases vascular resistance by increasing spiral artery formation.
- ↑ Cardiac output.
- ↑ Blood volume since renin angiotensin aldosterone system (RAAS) is stimulated by lowered BP.
- Constriction of peripheral circulation (this is why some pregnant women experience Raynaud’s phenomenon).

**Renal system**
- ↑ Kidney size.
- ↑ Frequency of urination.
- ↑ Glomerular filtration rate (GFR).
- ↑ Urinary tract infection risk due to dilated, elongated ureters.

**Musculoskeletal system**
- Gait changes.
- Lower back pain.
- Ligaments soften.
- Symphysis pubis dysfunction.

**MASTITIS**

**What is mastitis?**
This is inflammation of the breast tissue.

**Causes**
Milk stasis or overproduction causes regional infection of the breast parenchyma with *Staphylococcus aureus*, which enters the breast via trauma to the nipple. This in turn causes mastitis.

**Signs and symptoms**
- Calor, dolor, rubor and tumour (heat, pain, redness and swelling) of the breast tissue.
- Nipple discharge.
- Fever.

**Investigations**
- This is a clinical diagnosis.

**Treatment**
- Conservative: patient education. Encourage mother to continue breastfeeding since this will help to overcome the obstruction.
- Medical: flucloxacillin.
**The Reproductive System**

**Dermatology**
- Linea nigra.
- Palmar erythema.
- Spider angioma.

**Gastrointestinal system**
- Constipation.
- Gastro-oesophageal reflux disease.
- ↑ Risk of gallstones.
- Gestational diabetes.

**Reproductive system**
- ↑ Uterus size.
- Thickening of uterine ligaments.
- Softening of cervix.
- ↑ Vaginal secretions.

**Immune system**
- Weakened.

---

**MAP 11.2 Pregnancy and Lactation**

**Dermatology**
- Linea nigra.
- Palmar erythema.
- Spider angioma.

**Gastrointestinal system**
- Constipation.
- Gastro-oesophageal reflux disease.
- ↑ Risk of gallstones.
- Gestational diabetes.

**Reproductive system**
- ↑ Uterus size.
- Thickening of uterine ligaments.
- Softening of cervix.
- ↑ Vaginal secretions.

**Immune system**
- Weakened.
<table>
<thead>
<tr>
<th>Breast tumour</th>
<th>Benign or malignant</th>
<th>Characteristics</th>
<th>Investigations</th>
<th>Treatment</th>
<th>Complications</th>
</tr>
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<tbody>
<tr>
<td>Fibroadenoma</td>
<td>Benign</td>
<td>Small&lt;br&gt;Also known as ‘breast mouse’ due to tumour not being tethered&lt;br&gt;Sharp edges&lt;br&gt;Most common type of benign breast tumour in young women</td>
<td>Undergo triple assessment: 1 Examination 2 Imaging 3 Biopsy</td>
<td>Treatment depends on the cause of the breast tumour and whether it is benign or malignant; treatment may be split into 3 modalities:</td>
<td>Death&lt;br&gt;Metastasis&lt;br&gt;Complications of chemotherapy regimen&lt;br&gt;Complications of radiotherapy regimen&lt;br&gt;Depression</td>
</tr>
<tr>
<td>Intraductal papilloma</td>
<td>Benign</td>
<td>Small&lt;br&gt;Under areola&lt;br&gt;Bloody discharge from nipple</td>
<td>Physical examination for lumps and masses&lt;br&gt;Bloods: FBC, WCC, U&amp;Es, LFTs, TFTs&lt;br&gt;Radiology: mammogram, ultrasound scan, fine needle biopsy under ultrasound guidance (core needle biopsy may be required). Look for metastasis with CXR, CT scan and MRI scan</td>
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<tr>
<td>Phyllodes tumour</td>
<td>Benign</td>
<td>Large&lt;br&gt;Leaf-like projections&lt;br&gt;Rapid growing</td>
<td>Physical examination for lumps and masses&lt;br&gt;Bloods: FBC, WCC, U&amp;Es, LFTs, TFTs&lt;br&gt;Radiology: mammogram, ultrasound scan, fine needle biopsy under ultrasound guidance (core needle biopsy may be required). Look for metastasis with CXR, CT scan and MRI scan</td>
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<tr>
<td>Ductal carcinoma in situ (DCIS)</td>
<td>Malignant</td>
<td>From ductal hyperplasia&lt;br&gt;Cheesy discharge, confined to ducts</td>
<td>Risk factors for breast cancer:  • Female  • Increasing age  • Family history of breast cancer</td>
<td></td>
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<tr>
<td>Comedocarcinoma</td>
<td>Malignant</td>
<td>High-grade DCIS&lt;br&gt;Characterised by central necrosis&lt;br&gt;Cheesy discharge</td>
<td>Physical examination for lumps and masses&lt;br&gt;Bloods: FBC, WCC, U&amp;Es, LFTs, TFTs&lt;br&gt;Radiology: mammogram, ultrasound scan, fine needle biopsy under ultrasound guidance (core needle biopsy may be required). Look for metastasis with CXR, CT scan and MRI scan</td>
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</tr>
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<tr>
<td>Invasive ductal</td>
<td>Malignant</td>
<td>A hard mass, sharp edges, most common, very aggressive</td>
<td></td>
<td>HER2 directed therapy, depending on the type of tumour</td>
<td>Hormone treatment: premenopausal women are treated with tamoxifen (a selective oestrogen receptor modulator); postmenopausal women are treated with anastrazole (an aromatase inhibitor). This is because trials such as the ATAC trial have suggested that aromatase inhibitors are superior to tamoxifen in postmenopausal women. If a woman becomes menopausal during treatment she will benefit from switching medications. Chemotherapy and radiotherapy regimens: vary depending on tumour type.</td>
</tr>
<tr>
<td>Invasive lobular</td>
<td>Malignant</td>
<td>Bilateral presentation</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Medullary</td>
<td>Malignant</td>
<td>Well differentiated, lacks desmoplastic reaction, lymphatic infiltrate, good prognosis</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Inflammatory</td>
<td>Malignant</td>
<td>Invades the dermis and lymphatic system, peau d'orange appearance, retracted nipple</td>
<td></td>
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</tr>
<tr>
<td>Paget's disease of the breast</td>
<td>Malignant</td>
<td>Epidermal infiltration of ductal carcinoma, eczematoid nipple changes</td>
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Table 11.1 Breast Tumours (Continued)
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<table>
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<tr>
<th>Breast tumour</th>
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<th>Treatment</th>
<th>Complications</th>
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<tr>
<td>HER2 directed therapy:</td>
<td>treatment with trastuzumab (herceptin). This is a monoclonal antibody against the extracellular domain of the HER2 receptor</td>
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<tr>
<td>Surgical: the primary aim of surgery is to remove the invasive and noninvasive cancer with clear margins. Lumpectomy followed by a radiotherapy regime has been shown to be as effective as mastectomy, but mastectomy may be recommended in certain circumstances such as multifocal breast disease. The ipsilateral axilla should also be assessed with ultrasound, fine needle aspiration or core biopsy.</td>
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### Table 11.1 Breast Tumours

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<td>Risk factors for breast cancer: Female, Increasing age, Family history of breast cancer, Genetic involvement, e.g. BRCA 1 (chromosome 17) and BRCA 2 (chromosome 13), Alcohol, Obesity, Increased oestrogen exposure, e.g.: Early menarche, Late menopause, Oral contraceptive pill use, Hormone replacement therapy, Decreased parity, Not breastfeeding.</td>
<td>Treatment depends on the cause of the breast tumour and whether it is benign or malignant; treatment may be split into 3 modalities. 1 Conservative: patient and family education; refer to Macmillan nurses; offer genetic counselling; provide psychological assessment and support. 2 Medical: prognosis of disease is assessed using the Nottingham Prognostic Index (NPI): ( NPI = (0.2 \times \text{invasive size}) + \text{lymph node stage} + \text{grade of tumour} ). Medical therapy may be split into adjuvant hormone therapy, chemotherapy or HER2 directed therapy, depending on the type of tumour. Hormone treatment: premenopausal women are treated with tamoxifen (a selective oestrogen receptor modulator); postmenopausal women are treated with anastrazole (an aromatase inhibitor). This is because trials such as the ATAC trial have suggested that aromatase inhibitors are superior to tamoxifen in postmenopausal women. If a woman becomes menopausal during treatment she will benefit from switching medications. Chemotherapy and radiotherapy regimens: vary depending on tumour type. HER2 directed therapy: treatment with trastuzumab (herceptin). This is a monoclonal antibody against the extracellular domain of the HER2 receptor. 3 Surgical: the primary aim of surgery is to remove the invasive and noninvasive cancer with clear margins. Lumpectomy followed by a radiotherapy regime has been shown to be as effective as mastectomy, but mastectomy may be recommended in certain circumstances such as multifocal breast disease. The ipsilateral axilla should also be assessed with ultrasound, fine needle aspiration or core biopsy. Clinical staging of the axilla should also be assessed by sentinel lymph node biopsy. The reason for this is to avoid unnecessary axillary clearance in patients.</td>
</tr>
</tbody>
</table>
Benign Prostatic Hyperplasia (BPH)

What is BPH?
This is a benign enlargement of the prostate gland, particularly in the transitional zone. It is common with increasing age.

Causes
There is hypertrophy of the epithelial and stromal cells of the prostate gland. This classically occurs in the transitional zone of the prostate gland and is thought to be driven by the androgen dihydrotestosterone.

Signs and symptoms
Remember FUN BOO:
- Frequency.
- Urgency.
- Nocturia.
- Those of bladder outflow obstruction (BOO):
  - Hesitancy.
  - Intermittent flow/poor urine stream/dribbling.
  - Incomplete bladder emptying.

Investigations
- Per rectum (PR) examination: an enlarged but smooth prostate gland with a palpable midline sulcus.
- Urine dipstick, microscopy and culture.
- Bloods: FBCs, U&Es and creatinine (renal function), LFTs.
- Prostate specific antigen (PSA) – usually raised.
- Radiology: ultrasound scan of the urinary tract, transrectal ultrasound scan.

Management
- Conservative: watchful waiting is usually adopted in mild disease.
- Completion of the International Prostate Symptom Score (IPSS). Completion of a voiding diary to see if patient is bothered by their symptoms.
- Medical:
  - α1-adrenoreceptor blockers, e.g. tamsulosin.
  - 5α-reductase inhibitors, e.g. finasteride.
- Surgical:
  - Transurethral resection of the prostate (TURP).

Complications
- Urinary retention.
- Recurrent urinary tract infections.
- Impaired renal function.
- Haematuria.
FIGURE 11.3 Zones of the Prostate Gland

- **Transitional zone**
  - 10–20% of prostate cancers
  - Benign prostatic hypertrophy (BPH)

- **Peripheral zone**
  - 70–80% of prostate cancers

- **Central zone**
  - 2.5% of prostate cancers
  - Aggressive
  - Spread to seminal vesicles

- **Fibromuscular zone**

- **Seminal vesicles**

**Figure 11.3 Zones of the Prostate Gland**
What is prostate cancer?
This is usually an adenocarcinoma that arises from the peripheral zone of the prostate gland.

Risk factors
- Increasing age.
- Family history of prostate cancer.
- More common in African populations.

Signs and symptoms
- Those of benign prostatic hyperplasia – FUN BOO (see page 184).
- Those of metastatic disease:
  - Weight loss.
  - Malaise and fatigue.
  - Usually spreads to bone, therefore bone pain, pathological fracture.

Investigations
- Per rectum (PR) examination: an enlarged prostate gland that may be uninodular or multinodular. The midline sulcus is usually no longer palpable.
- Urine dipstick, microscopy and culture.
- Bloods: FBCs, U&Es and creatinine (renal function), LFTs.
- Prostate specific antigen (PSA) – usually raised.
- Radiology: transrectal ultrasound and biopsy. If this procedure diagnoses a malignancy then the patient should be sent for a MRI and bone scan to look for distant metastases. Prostate cancer is staged using the TMN system. Since there may also be symptoms of BOO an ultrasound scan of the urinary tract may also be required.

Complications
- Metastasis.
- Death.
- Urinary incontinence.
- Erectile dysfunction.

Management
- Conservative: involvement of Macmillan nurses and psychological support.
- Medical:
  - Radiotherapy.
  - Brachytherapy.
  - Goserelin (Zoladex) – a luteinising hormone-releasing hormone (LHRH) agonist.
  - Antiandrogens, e.g. cyproterone.
- Surgical:
  - Laparoscopic radical prostatectomy.
  - Transurethral resection of the prostate (TURP).
### Chapter Twelve: Embryology

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**Important dates to remember**
- Day 6: implantation.
- Day 9:
  - Blastocyst embedded in the endometrium.
  - Lacunae formation.
- Day 15: gastrulation.

**The germ layers and their derivatives**
- Ectoderm → epidermis, nervous system.
- Mesoderm → muscles, bones, connective tissue.
- Endoderm → other organs, e.g. GIT, respiratory tract.
**FIGURE 12.1 Development of the Embryo**

**Hypoblast**
- Exocoelomic membrane (Heuser’s membrane)
- The hypoblast and exocoelomic membrane form the yolk sac

**Epiblast**
- The small cavity within the epiblast is the amniotic cavity which fills with amniotic fluid
- Amniotic fluid acts as a shock absorber and serves to regulate fetal temperature

**Syncytiotrophoblast**
- No distinct cell boundaries
- Creates enzymes during implantation

**Cytotrophoblast**
- Distinct cell boundaries
- Between embryoblast and syncytiotrophoblast

- **Zygote** → **4 cells** → **64 cells (morula)** → **Blastocyst (day 5)** → **Entrace uterine cavity** → **Day 8: embryoblast (forms embryo)** → **Day 8: trophoblast (forms chorionic sac)**
**Development of the heart**
- Develops during week 3 from cardiac progenitor cells.
- The heart tube forms from 2 endocardial tubes at day 21 and the heart begins to beat on day 22. Note that blood flows through the endocardial tube caudocranially:
  - Truncus arteriosus → aorta and pulmonary trunk.
  - Bulbus cordis → smooth part of right ventricle (conus arteriosus); smooth part of left ventricle (aortic vestibule).
  - Primative ventricle → Trabeculated part of right and left ventricle.
  - Primative atrium → Trabeculated part of right and left atrium.
  - Sinus venosus → Smooth part of right atrium; coronary sinus; oblique vein of left atrium.
- The ventricle grows at a faster rate than the other areas causing the cardiac loop to fold in a U shape.
- The cardiac septa form between the 27th and 37th day.

**Molecular regulation**
- NKX-2.5: induces heart formation and also plays a role in expression of HAND1 and HAND2, which are important regulators of ventricle differentiation.
- WNT inhibitors.
- BMP2 and BMP4 along with WNT inhibitors are responsible for NKX-2.5 expression.
- Laterality-inducing genes NODAL and LEFTY2 cause PITX2 expression: plays a role in cardiac loop formation.

**Examples of defects**
- Atrial septal defect (ASD): ostium secundum defect.
- Ostium primum defect.
- Tricuspid atresia.
- Ebstein’s anomaly.
- Ventricular septal defect (VSD).
- Tetralogy of Fallot (TOF):
  - Pulmonary stenosis.
  - Overriding aorta.
  - VSD
  - Right ventricular hypertrophy.
- Transposition of the great vessels.
- Persistent truncus arteriosus.

**Cardiovascular teratogens**
Avoid **RAT**:
- Retinoic acid, Rubella virus.
- Alcohol.
- Thalidomide.
**Abnormalities**
- Respiratory distress syndrome (RDS).
- Insufficient surfactant produced.
- Congenital lung cysts.
- Ectopic lobes.
- Tracheo–oesophageal fistula.

**Development of the lungs**
- During week 4 the lung bud or respiratory diverticulum develops from the foregut.
- Endoderm → respiratory epithelium.
- Splanchnic mesoderm → connective tissue, cartilage and muscle.

**Lung maturation**
- 2 months before birth marks an increase in terminal sac number.
- Type 1 alveolar epithelial cells → form blood–air barrier.
- Type 2 alveolar epithelial cells → produce pulmonary surfactant.
- Surfactant decreases surface tension.
- Alveoli are only fully mature after birth.

**Molecular regulation**
- Lung bud formation is caused by an increase in retinoic acid, which causes TBX4 expression.
- TBX4 is responsible for respiratory development.

**VACTERL association**
If you find one of these on examination then always assess if the others are present:
- Vertebral anomalies.
- Anal atresia.
- Cardiac defects.
- Tracheo–oesophageal fistula.
- Oesophageal atresia.
- Renal anomalies.
- Limb defects.
Abnormalities
- Oesophageal atresia.
- Congenital hiatus hernia.
- Pyloric stenosis.
- Accessory hepatic ducts.
- Duplication of gallbladder.
- Extrahepatic biliary atresia.
- Annular pancreas.
- Omphalocele.
- Gastrochisis.
- Rectourethral fistula.
- Rectovaginal fistula.
- Hirschsprung’s disease.

Development of the GIT
There are 4 parts to the primitive gut. These are the:
1. Pharyngeal gut.
2. Foregut.
3. Midgut.
4. Hindgut.
- Endoderm → epithelial lining, pancreatic endocrine glands, pancreatic exocrine glands and hepatocytes.
- Visceral mesoderm → connective tissue and muscle.

Molecular regulation

<table>
<thead>
<tr>
<th>Region of GIT</th>
<th>Gene involved</th>
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<tr>
<td>Oesophagus</td>
<td>SOX-2</td>
</tr>
<tr>
<td>Stomach</td>
<td>SOX-2</td>
</tr>
<tr>
<td>Small intestine</td>
<td>CDXC&lt;br&gt;HOX 9, 10</td>
</tr>
<tr>
<td>Caecum</td>
<td>HOX 9–11</td>
</tr>
<tr>
<td>Large intestine</td>
<td>CDXA&lt;br&gt;HOX 9–12</td>
</tr>
<tr>
<td>Cloaca</td>
<td>HOX 9–13</td>
</tr>
<tr>
<td>Rectum</td>
<td>CDXA</td>
</tr>
<tr>
<td>Liver</td>
<td>HOX</td>
</tr>
<tr>
<td>Duodenum</td>
<td>PDX1</td>
</tr>
</tbody>
</table>

Sonic hedgehog (SHH) gene causes epithelial–mesenchymal interaction and HOX gene expression.
Development of the kidneys
3 sets of kidneys form during development:
1. Pronephros: nonfunctional.

The kidneys develop from intermediate mesoderm.

Abnormalities
- Autosomal recessive polycystic kidney disease (ARPKD).
- Autosomal dominant polycystic kidney disease (ADPKD).
- Wilms’ tumour.
- Denys–Drash syndrome.
- Renal agenesis.
- Pelvic kidney.
- Horseshoe kidney.

FIGURE 12.2 Molecular Regulation of Kidney Development

WT1

Ureteric bud formation

Mesenchyme induction via:
- FGF2
- BMP7

Nephron formation via:
- WNT9B
- WNT6
- PAX2
- WNT4

FIGURE 12.3 Kidney Development

Mesonephric bud → Ureteric bud → Renal pelvis → Cranial and caudal major calyces → 2 × buds → 12+ generations → Minor calyces
Embryology

Development of the male and female reproductive system
- From intermediate mesoderm.
- Male gender is determined by sex determining region on Y chromosome (SRY gene).
- Without SRY gene expression the embryo is female.

Abnormalities
- Androgen insensitivity syndrome.
- Congenital adrenal hyperplasia.
- Hermaphroditism.
- Vaginal agenesis.
- Ambiguous genitalia.
- Intersex syndromes.
- Cryptorchidism.
- Hypospadias.

Molecular development
- Male: SRY gene → SOX9 → SP1 → testes.
- Female: WNT4 → DAX1 → ovaries.

MAP 12.6 Genital Development

Female development:
- Paramesonephric (Müllerian) ducts develop
- No tunica albuginea
- Uterus, vagina, clitoris and labia develop

Male development:
- Mesonephric (Wolffian) ducts develop
- Thick tunica albuginea
- Müllerian inhibiting substance secreted from Sertoli cells
- Dihydrotestosterone (DHT) – penile and scrotal development

FIGURE 12.5 Development of the Reproductive System
Embryology

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Development of the male and female reproductive system

- From intermediate mesoderm.
- Male gender is determined by sex determining region on Y chromosome (SRY gene).
- Without SRY gene expression the embryo is female.

Abnormalities

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- Congenital adrenal hyperplasia.
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**FIGURE 12.5 Development of the Reproductive System**

**Male development:**
- Mesonephric (Wolffian) ducts develop
- Thick tunica albuginea
- Müllerian inhibiting substance secreted from Sertoli cells
- Dihydrotestosterone (DHT) – penile and scrotal development

**Female development:**
- Paramesonephric (Müllerian) ducts develop
- No tunica albuginea
- Uterus, vagina, clitoris and labia develop

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HAEMOPHILIA A
What is haemophilia A?
This is an X-linked recessive bleeding and bruising disorder.

Causes
• Deficiency of factor VIII.

Signs and symptoms
These vary depending on disease severity. Bleeding is the main feature and this is prolonged, resulting in the need for investigations to uncover the cause. Positive family history may tailor diagnosis.

Investigations
• Low factor VIII levels: the lower the level, the more severe the disease.
• Coagulation factor assay.
• Increased PTT but normal PT.

Treatment
• Conservative: patient and parent education. Genetic counselling and testing is now available. Avoid anticoagulant medication, e.g. nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, aspirin.
• Medical:
  o Mild: desmopressin.
  o Severe: require IV replacement with plasma concentrate factor VIII.

Complications
• Patient’s immune system may start to reject the IV plasma concentrate factor VIII by making inhibitors.
• Joint destruction by recurrent bleeding.
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What is haemophilia A?
This is an X-linked recessive bleeding and bruising disorder.

Causes
• Deficiency of factor VIII.

Signs and symptoms
These vary depending on disease severity. Bleeding is the main feature and this is prolonged, resulting in the need for investigations to uncover the cause. Positive family history may tailor diagnosis.

Investigations
• Low factor VIII levels: the lower the level, the more severe the disease.
• Coagulation factor assay.
• Increased PTT but normal PT.

Treatment
• Conservative: patient and parent education. Genetic counselling and testing is now available. Avoid anticoagulant medication, e.g. NSAIDs, warfarin, aspirin.
• Medical: IV replacement with plasma concentrate factor VIII.

Complications
• Joint destruction by recurrent bleeding.

HAEMOPHILIA B
What is haemophilia B?
Haemophilia B, also known as Christmas disease, is an X-linked recessive bleeding and bruising disorder.

Causes
• Deficiency of factor IX.

Signs and symptoms
These vary depending on disease severity. Bleeding is the main feature of this disease and this is prolonged, resulting in the need for tests to uncover the cause. Positive family history may tailor diagnosis.

Investigations
• Low factor IX levels: the lower the level, the more severe the disease.
• Coagulation factor assay.
• Increased PTT but normal PT.

Treatment
• Conservative: patient and parent education. Genetic counselling and testing is now available. Avoid anticoagulant medication, e.g. NSAIDs, warfarin, aspirin.
• Medical: IV infusion of factor IX.

Complications
• Joint destruction by recurrent bleeding.
DUCHENNE MUSCULAR DYSTROPHY

What is Duchenne muscular dystrophy?
This is a form of muscular dystrophy.

Causes
• Mutated dystrophin gene at locus Xp21.

Signs and symptoms
• Patient falls frequently.
• Fatigue.
• Toe walking/difficulty walking.
• Muscle weakness.
• Muscle pseudohypertrophy.
• Muscle fibrosis.
• Positive Gower’s test.

Investigations
• DNA testing: confirms mutation of dystrophin gene.
• Creatine phosphokinase test. Results show increased levels.
• Muscle biopsy: confirms mutation of dystrophin gene.
• Electromyography (EMG): analyses muscle destruction.

Treatment
There is no specific treatment for this disease. Prednisolone and creatinine replacement may be considered. Patient will be wheelchair bound at ~12 years; refer to occupational therapy and physiotherapy. Patient and parent education and support is essential since this condition is very debilitating and life expectancy is ~25–30 years.

Complications
• Scoliosis.
• Respiratory complications and increased risk of respiratory infections.
• Cardiomyopathy.
• Osteoporosis.
**LESCH–NYHAN SYNDROME**  
**What is Lesch–Nyhan syndrome?**  
This is a rare X-linked recessive disorder that causes a build-up of uric acid in the body.

**Causes**  
- Deficiency of hypoxanthine–guanine phosphoribosyltransferase (HGPRT).

**Signs and symptoms**  
- Behavioural problems.  
- Intellectual impairment.  
- Self-harming behaviour.  
- Poor muscle control.  
- Symptoms of gout, see page 162.

**Investigations**  
- Bloods: FBC, U&Es, LFTs, creatinine, uric acid, HGPRT.  
- Radiology: ultrasound scan of kidneys for radiolucent urate renal calculi.

**Treatment**  
- Conservative: parent education.  
- Medical: allopurinol (to decrease uric acid levels). For neurological and behavioural problems consider benzodiazepines and baclofen.

**Complications**  
- Gout.  
- Renal calculi.  
- Self harm.
RETT’S SYNDROME
What is Rett’s syndrome?
This is a neurodevelopmental disorder of brain grey matter.

Causes
- Mutation of the methyl-CpG binding protein-2 (MECP2) gene.

Signs and symptoms
- Neurological dysfunction, e.g.:
  - Ataxia.
  - Hypotonia.
  - Inability to walk or altered gait.
  - Chorea.
- Autistic behaviour, e.g.:
  - Lack of eye contact.
  - Lack of theory of mind.
  - Decreased social interaction.
  - Speech deficit.
  - Screaming.

Investigations
- DNA sequencing of MECP2 gene is diagnostic.

Treatment
- Conservative: parent education.
- Medical: treatment of complications.

AICARDI SYNDROME
What is Aicardi syndrome?
This is an X-linked recessive condition in which there is partial or a complete absence of the corpus callosum. Retinal abnormalities and seizures are also present.

Causes
The exact cause remains unknown but it is thought to be due to new mutations that are passed genetically to offspring via X-linked recessive inheritance.

Signs and symptoms
- Infantile spasms.

Investigations
- Radiology: CT or MRI scan confirming corpus callosum agenesis.

Treatment
- Conservative: parent education. Referral to speech and language therapy, neuropsychologist, neurology and physiotherapy.
- Medical: there is no specific treatment. Manage epilepsy, see pages 146–151.

Complications
- Hydrocephalus.
- Porencephalic cysts.
**Genetic Disorders**

**KLINEFELTER'S SYNDROME**

**What is Klinefelter’s syndrome?**
This is a syndrome in which males have an extra X chromosome. Chromosomally, patients are XXY.

**Causes**
- An additional X chromosome.

**Signs and symptoms**
- Hypogonadism.
- Long limbs.
- Late onset of puberty.
- Gynaecomastia.
- Infertility.

**Investigations**
- Prenatal diagnosis.
- Follicle stimulating hormone (FSH) and luteinising hormone (LH) levels.

**Treatment**
- Medical: no specific medical therapy. Treat comorbidities such as depression, which is common in this group.

**Complications**
- Infertility.
- Depression.

**Complications**
- Arrhythmias.
- Epilepsy.
- Gastro-oesophageal reflux disease.
- Osteoporosis.

**AICARDI SYNDROME**

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**Causes**
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**Signs and symptoms**
- Infantile spasms.

**Investigations**
- Radiology: CT or MRI scan confirming corpus callosum agenesis.

**Treatment**
- Conservative: parent education. Referral to speech and language therapy, neuropsychologist, neurology and physiotherapy.
- Medical: there is no specific treatment. Manage epilepsy, see pages 146–151.

**Complications**
- Hydrocephalus.
- Porencephalic cysts.
**HUNTINGTON’S DISEASE**
What is Huntington’s disease?
This is an autosomal dominant inherited neurodegenerative disorder.

**Causes**
- Abnormal *huntingtin* gene on chromosome 4.
- Leads to (CAG)$_n$ repeats.
- The longer the (CAG)$_n$ repeats, the earlier the onset of disease.

**Signs and symptoms**
- Present at ~35 years of age.
- Progressive decline in motor coordination.
- Chorea.
- Cognitive decline.
- Personality change.

**Investigations**
- Genetic testing confirms diagnosis.

**Treatment**
- Medical: there is no specific treatment. Manage complications.

**Complications**
- Chorea.
- Dementia.
- Dysphagia.
- Depression.
- Anxiety.
**FAMILIAL ADENOMATOUS POLYPOSIS (FAP)**

*What is FAP?*
This is an autosomal dominant condition that causes thousands of polyps to develop in the large intestine. It predisposes patients to colon cancer.

**Causes**
- Mutation in the *APC* gene on chromosome 5.

**Signs and symptoms**
- Blood in stool.
- Signs of malignancy, see page 48.

**Investigations**
See page 48.
- Genetic testing and colonoscopy are diagnostic.

**Treatment**
- Surgical resection of the affected bowel is the treatment of choice.

**Complications**
- Colon cancer.

---

**EHLERS–DANLOS SYNDROME**

*What is Ehlers–Danlos syndrome?*
This is a type of connective tissue disorder that results from defective collagen.

**Causes**
- Defect in type I and type III collagen synthesis.

**Signs and symptoms**
Remember these as HBO:
- Hyperextension.
- Bruise easily.
- Osteoarthritis (early onset).

**Investigations**
- Collagen gene mutation testing.
- Skin biopsy for collagen typing.
- ECHO for valvular heart disease and aortic dilation.

**Treatment**
- Conservative: patient education.
- Medical: there is no specific treatment for this condition. Manage complications.

**Complications**
- Valvular heart disease.
- Joint deformities, e.g. osteoarthritis and scoliosis.
- Anal prolapse.
- Complications during pregnancy.
TUBEROUS SCLEROSIS

**What is tuberous sclerosis?**
This condition causes nonmalignant tumours to grow in a variety of organs.

**Causes**
- Mutation of TSC1 and TSC2 genes. TSC1 gene codes for hamartin protein. TSC2 gene codes for tuberin protein.

**Signs and symptoms**
These depend on where the tumours form. Some examples include:
- Renal angiomyolipomas: haematuria.
- Rhabdomyomas: cardiac arrhythmias.
- Facial angiofibromas: butterfly distribution on face.
- Ash leaf spots.
- Coloboma.

**Investigations**
- Fundoscopy.
- Examine skin with Wood’s lamp for ash leaf spots and angiofibromas.
- Radiology: CT scan, MRI scan, ECHO (rhabdomyoma), renal ultrasound scan (angiomyolipoma).

MARFAN’S SYNDROME

**What is Marfan’s syndrome?**
This is a disorder of connective tissue due to abnormal fibrillin-1 formation.

**Causes**
- Mutated FBN1 gene.

**Signs and symptoms**
A – Arachnodactyly, Astigmatism, Angina, Aortic Aneurysm/dissection.
B – Bullae, Bronchiectasis.
C – Cyanosis, Cysts (spinal), Coarctation of the aorta.
D – Dolicostenomelia, Dislocation of lens.
P – Pectus carinatum/excavatum, high Palate, Palpitations.

**Investigations**
- This is a clinical diagnosis.
- ECG and ECHO to monitor cardiac complications.
- MRI scan of spinal cord to monitor neurological complications.
**TUBEROUS SCLEROSIS**

**What is tuberous sclerosis?**
This condition causes nonmalignant tumours to grow in a variety of organs.

**Causes**
- Mutation of **TSC1** and **TSC2** genes.
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These depend on where the tumours form. Some examples include:
- Renal angiomyolipomas: haematuria.
- Rhabdomyomas: cardiac arrhythmias.
- Facial angiofibromas: butterfly distribution on face.
- Ash leaf spots.
- Coloboma.

**Investigations**
- Fundoscopy.
- Examine skin with Wood’s lamp for ash leaf spots and angiofibromas.
- Radiology: CT scan, MRI scan, ECHO (rhabdomyoma), renal ultrasound.

**Treatment**
- Conservative: patient education.
- Medical: there is no specific treatment. Manage complications.

**Complications**
- Renal failure.
- Status epilepticus.
- Sudden unexpected death in epilepsy (SUDEP).

---

**MARFAN’S SYNDROME**

**What is Marfan’s syndrome?**
This is a disorder of connective tissue due to abnormal fibrillin-1 formation.

**Causes**
- Mutated **FBN1** gene.

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A – A rachnodactyly, A stigmatism, A ngina, Aortic A neurysm/dissection.

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C – Cyanosis, Cysts (spinal), C oarctation of the aorta.

D – Dolichostenomelia, D islocation of lens.

P – Pectus carinatum/excavatum, high P alate, P alpitations.

**Investigations**
- This is a clinical diagnosis.
- ECG and ECHO to monitor cardiac complications.
- MRI scan of spinal cord to monitor neurological complications.

**Treatment**
- Medical: there is no specific treatment. Manage complications, e.g. prescribe a beta-blocker (if not contraindicated) to reduce blood pressure.
- Surgery: to manage complications.

**Complications**
- Aortic dissection/aneurysm.
- Valvular disease.
- Glaucoma.
- Scoliosis.
- Depression.
**FRIEDREICH’S ATAXIA**

**What is Friedreich’s ataxia?**
This is an autosomal recessive condition that causes neural degeneration.

**Causes**
- Mutation of *FXN* gene on chromosome 9 causes GAA repeats and abnormal frataxin production.

**Signs and symptoms**
- Abnormal gait.
- Speech disturbance.
- Cardiomyopathy.

**Investigations**
- Genetic testing.
- Nerve conduction studies.
- ECG for cardiac complications.
- Vitamin E levels: rule out vitamin E deficiency as a differential diagnosis.

**Treatment**
- Conservative: patient and parent education. Refer to physiotherapy and speech and language therapy.
- Medical: there is no specific treatment for this condition. Manage complications.

**PHENYLKETONURIA**

**What is phenylketonuria?**
This is an autosomal recessive disease in which levels of phenylalanine increase due to the lack of phenylalanine hydroxylase (PAH). Phenylalanine is subsequently converted to phenylpyruvate instead of tyrosine.

**Causes**
- Mutation in the gene that codes for PAH.

**Signs and symptoms**
- Asymptomatic at birth.
- Severe learning difficulties.
- Seizures.

**Investigations**
- Guthrie heel pricking test is diagnostic.

**Treatment**
- Patients are on lifelong low phenylalanine diet.

**Complications**
- Neurobehavioural problems.
- Seizures.
Complications
- Cardiomyopathy.
- Scoliosis.
- Pes cavus (high instep).
- Diabetes mellitus.
- Hearing loss.

FRIEDREICH'S ATAXIA
What is Friedreich's ataxia?
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Causes
- Mutation of FXN gene on chromosome 9 causes GAA repeats and abnormal frataxin production.

Signs and symptoms
- Abnormal gait.
- Speech disturbance.
- Cardiomyopathy.

Investigations
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- ECG for cardiac complications.
- Vitamin E levels: rule out vitamin E deficiency as a differential diagnosis.

Treatment
- Conservative: patient and parent education. Refer to physiotherapy and speech and language therapy.
- Medical: there is no specific treatment for this condition. Manage complications.

Complications
- Cardiomyopathy.
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- Pes cavus (high instep).
- Diabetes mellitus.
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- Severe learning difficulties.
- Seizures.

Investigations
- Guthrie heel prick test is diagnostic.

Treatment
- Patients are on lifelong low phenylalanine diet.

Complications
- Neurobehavioural problems.
- Seizures.

Sickle cell anaemia
See page 94.

Thalassaemia
See page 96.

Cystic fibrosis
See page 22.

Map 13.6
Autosomal Recessive Conditions
DOWN’S SYNDROME
What is Down’s syndrome?
Down’s syndrome is the most common trisomy abnormality, which is characterised by specific signs and symptoms.

Causes
- Trisomy 21.

Signs and symptoms
- Learning difficulties.
- Short stature.
- Flattened nose.
- Slanted eyes.
- Simian crease.
- Gap between 1st and 2nd toe.

Investigations
- Antenatal testing: ultrasound for nuchal translucency.
- Radiology: pelvic X-ray shows dysplastic pelvis.
- ECG and ECHO for cardiac complications.

Treatment
- Conservative: parent education.
- Medical: management of complications.
- Surgical: management of complications.

Complications
- Atrial septal defects.

EDWARD’S SYNDROME
What is Edward’s syndrome?
Edward’s syndrome is the second most common trisomy abnormality.

Causes
- Trisomy 18.

Signs and symptoms
- Rocker bottom feet.
- Learning difficulties.
- Clenched hands.
- Low set ears.
- Micrognathia.
- Cleft lip or cleft palate.
- Undescended testicles.

Investigations
- Chromosomal analysis confirms diagnosis.
- ECG and ECHO for cardiac complications.

Treatment
- Conservative: parent education and support particularly since life expectancy is 4 months – 1 year.

Complications
- Coarctation of the aorta.
- Atrial septal defects.
- Atrial septal defects.
- Atrial septal defects.
- Atrial septal defects.
- Atrial septal defects.
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- Trisomy 21.

Signs and symptoms
- Learning difficulties.
- Short stature.
- Flattened nose.
- Slanted eyes.
- Simian crease.
- Gap between 1st and 2nd toe.

Investigations
- Antenatal testing: ultrasound for nuchal translucency.
- Radiology: pelvic X-ray shows dysplastic pelvis.
- ECG and ECHO for cardiac complications.

Treatment
- Conservative: parent education.
- Medical: management of complications.
- Surgical: management of complications.

Complications

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What is Edward’s syndrome?
Edward’s syndrome is the second most common trisomy abnormality.

Causes
- Trisomy 18.

Signs and symptoms
- Rocker bottom feet.
- Learning difficulties.
- Clenched hands.
- Low set ears.
- Micrognathia.
- Cleft lip or cleft palate.
- Undescended testicles.

Investigations
- Chromosomal analysis confirms diagnosis.
- ECG and ECHO for cardiac complications.

Treatment
- Conservative: parent education and support particularly since life expectancy is 4 months – 1 year.

Complications
- Atrial septal defects.
- Coarctation of the aorta.
- Ventricular septal defects.
- Duodenal atresia.
- Acute lymphoblastic leukaemia.
- Alzheimer’s disease.
- Hypothyroidism.
- Inguinal hernia.
- Omphalocele.
- Renal agenesis.

**PATAU’S SYNDROME**

What is Patau’s syndrome?
This is a chromosomal abnormality.

Causes
- Trisomy 13.

Signs and symptoms
- Learning difficulties.
- Congenital heart disease.
- Cleft lip/palate.
- Microcephaly.
- Polydactyly.
- Rocker bottom feet.

Investigations
- Chromosomal analysis confirms diagnosis.
- ECG and ECHO for cardiac complications.

Treatment
- Conservative: parent education and support particularly since life expectancy is <1 year.

Complications
- Omphalocele.
- Polycystic kidneys.
- Ventricular septal defects.
- Inguinal hernia.
### TABLE 14.1 Issues in Preterm Infants

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Comment</th>
</tr>
</thead>
</table>
| Patent ductus arteriosus      | Continuous machinery murmur  
|                               | Bounding pulse  
|                               | Treatment: Prostaglandin synthase inhibitor, indomethacin and ibuprofen |
| Vulnerable to heat loss       | Due to:  
|                               | ↓ Subcutaneous fat  
|                               | Heat loss through thin skin  
|                               | Large surface area to volume ratio |
| Increased infection risk      | This is because most IgG is transferred in the last trimester           |
| Necrotising enterocolitis     | Bacterial invasion of ischaemic bowel  
|                               | X-ray visualises distended bowel loops due to intramural gas and thickened walls  
|                               | Treat with antibiotics and supportive treatment; may require surgical intervention |
| Retinopathy of prematurity    | Affects blood vessels of the retina and may lead to blindness           |
| Bronchopulmonary dysplasia    | CXR shows opacification                                                 |
# TABLE 14.2 Issues in Term Infants

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk aspiration</td>
<td>↑ Risk with cleft palate</td>
</tr>
<tr>
<td>Transient tachypnoea of the newborn</td>
<td>CXR shows fluid in the horizontal fissure</td>
</tr>
<tr>
<td>Meconium aspiration</td>
<td>CXR visualises overinflated lungs, areas of consolidation and evidence of collapse</td>
</tr>
</tbody>
</table>
| Infection                                     | Common examples:  
- Group B *Streptococcus*  
- Meningitis  
- Conjunctivitis:  
  - Group B *Streptococcus*  
  - *Listeria monocytogenes*  
  - *Escherichia coli*  
- Hepatitis B                                    |
| Persistent pulmonary hypertension of the newborn | This condition is life threatening  
Treat with nitric oxide inhalation and sildenafil |
What is a hernia?
A hernia is the protrusion of a viscus or part of a viscus through a weakening in its containing cavity.

There are many different types of hernia, e.g.:
- Inguinal hernia.
- Femoral hernia.
- Hiatus hernia.
- Umbilical hernia: this is a hernia that is more common in males and is due to weakness of the umbilicus. It is usually self-resolving.
- Incisional hernia: weakness caused by a surgical repair that has not fully healed.

INGUINAL Types
There are two types of inguinal hernia:
- Direct:
  - Causes: due to weakness in the abdominal wall.
  - Located medial to the inferior epigastric vessels.
- Indirect:
  - Causes: due to a congenital weakness of the internal inguinal ring.
  - Located lateral to the inferior epigastric vessels.
  - More common than direct hernias.

Signs and symptoms
- Mass in the groin.
- Hernia accentuated by certain situations such as coughing or on standing.
- Reducible.
- Pain: hernia likely to be strangulated, i.e. the blood supply is compromised.

Investigations
- This is a clinical diagnosis.
- Radiology: ultrasound scan of hernia.

Treatment
- Surgical hernia repair is the treatment of choice.

Complications
- Strangulation.
- Incarceration.
**Hernia**

*What is a hernia?*
The protrusion of a viscus or part of a viscus through a weakening in its containing cavity.

There are many different types of hernia, e.g.:

- **Inguinal hernia.**
- **Femoral hernia.**
- **Hiatus hernia.**
- **Umbilical hernia:** This is a hernia that is more common in males and is due to weakness of the umbilicus. It is usually self-resolving.
- **Incisional hernia:** Weakness caused by a surgical repair that has not fully healed.

### Inguinal Types

- **Direct:**
  - Causes: due to weakness in the abdominal wall.
  - Located medial to the inferior epigastric vessels.

- **Indirect:**
  - Causes: due to a congenital weakness of the internal inguinal ring.
  - Located lateral to the inferior epigastric vessels.
  - More common than direct hernias.

### Signs and symptoms

- Mass in the groin.
- Hernia accentuated by certain situations such as coughing or on standing.
-Reducible.
- Pain: hernia likely to be strangulated, i.e. the blood supply is compromised.

### Investigations

- This is a clinical diagnosis.
- Radiology: ultrasound scan of hernia.

### Treatment

- Surgical hernia repair is the treatment of choice.

### Complications

- Strangulation.
- Incarceration.

---

**Femoral**

*Causes*

Due to a weakness in the femoral canal.

- Located inferior and lateral to the pubic tubercle.
- More common in females.
- High risk of strangulation.

*Signs and symptoms*

- Mass in the groin.
- Tends to be irreducible.

*Investigations*

- This is a clinical diagnosis.
- Radiology: ultrasound scan of hernia.

*Treatment*

- Surgical hernia repair is the treatment of choice.

*Complications*

- Strangulation.
- Fistula formation.

---

**Hiatus**

*Types*

There are two types of hiatus hernia: sliding and rolling.

*Causes*

Weakness in the diaphragm that allows the stomach and intestines to move into the chest cavity. There are certain risk factors that make this more likely, e.g. obesity and constipation.

*Signs and symptoms*

- Those of gastro-oesophageal reflux disease (GORD), see page 42.

*Investigations*

- Endoscopy.
- Barium study.

*Treatment*

- Those of GORD, see page 42.

*Complications*

- Strangulation.
- Gastric volvulus.
- Those of GORD, see page 42.
What is glaucoma?
Glaucoma is a group of eye disorders that are characterised by visual field loss, alterations to the optic disc and damage to the optic nerve. Intraocular pressure (IOP) is usually increased but it may, in some cases, be normal.

Open angle
- Causes: MYOC mutation. A secondary cause is obstruction of the trabecular meshwork by trauma.
  - Most common.
  - ↑ IOP.
  - Painless.

Closed angle
- Causes: may be split into primary and secondary causes:
  - Primary causes: shallow anterior chambers.
  - Secondary causes: trauma and tumours of the ciliary body.
- This is a medical emergency.
- Peripheral zone of iris adheres to the trabecular meshwork.
- ↑ IOP since aqueous outflow is impeded.
- Painful.

Treatment
- Medical:
  - Prostaglandin analogues, e.g. latanoprost:
    - MOA: ↑ uveoscleral outflow of aqueous humour.
  - Beta-receptor antagonists, e.g. betaxolol:
    - MOA: ↓ aqueous humour production.
  - Alpha-2 agonists, e.g. brimonidine:
    - MOA: ↓ aqueous humour production and ↑ uveoscleral outflow of aqueous humour.
  - Less selective alpha agonists, e.g. adrenaline:
    - MOA: ↓ aqueous humour production.
    - Do not use in closed angle glaucoma.
  - Miotic agents (parasympathomimetics), e.g. pilocarpine:
    - MOA: ↓ uveoscleral outflow of aqueous humour by causing the ciliary muscles to contract and open the trabecular meshwork.
  - Carbonic anhydrase inhibitors, e.g. dorzolamide:
    - MOA: ↓ aqueous humour secretion by inhibiting carbonic anhydrase in the ciliary body.
  - Cholinesterase inhibitors, e.g. physostigmine.
Glaucoma

What is glaucoma?
Glaucoma is a group of eye disorders that are characterised by visual field loss, alterations to the optic disc and damage to the optic nerve. Intraocular pressure (IOP) is usually increased but it may, in some cases, be normal.

Open angle
- Causes:
  - MYOC mutation. A secondary cause is obstruction of the trabecular meshwork by trauma.
  - Most common.
  - /-IOP.
  - Painless.

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- This is a medical emergency.
- Peripheral zone of iris adheres to the trabecular meshwork.
- IOP since aqueous outflow is impeded.
- Painful.

Treatment
- Medical:
  - Prostaglandin analogues, e.g. latanoprost: – mode of action (MOA): /-uveoscleral outflow of aqueous humour.
  - Beta-receptor antagonists, e.g. betaxolol: – MOA:¯aqueous humour production.
  - Alpha-2 agonists, e.g. brimonidine: – MOA:¯aqueous humour production and/-uveoscleral outflow of aqueous humour.
  - Less selective alpha agonists, e.g. adrenaline: – MOA:¯aqueous humour production.
    - Do not use in closed angle glaucoma.
  - Miotic agents (parasympathomimetics), e.g. pilocarpine: – MOA:/-uveoscleral outflow of aqueous humour by causing the ciliary muscles to contract and open the trabecular meshwork.
  - Carbonic anhydrase inhibitors, e.g. dorzolamide: – MOA:¯aqueous humour secretion by inhibiting carbonic anhydrase in the ciliary body.
  - Cholinesterase inhibitors, e.g. physostigmine.

Complications
- Blindness.

Characteristics
Remember VIA:
- Visual field changes due to peripheral field loss.
- IOP.
- Alterations to the optic nerve cup.

Investigations
- Tonometry: measures IOP.
- Fundoscopy.
- Visual field test: tunnel vision is a late feature.
- Gonioscopy: assesses the iridocorneal angle.
- Scanning laser ophthalmoscopy.
- Scanning laser polarimetry.
### SENSORINEURAL

**What is sensorineural hearing loss?**
This is hearing loss that occurs due to a problem within the inner ear or involving the vestibulocochlear nerve.

**Causes**
- **Congenital:**
  - Rubella.
  - Genetic causes, e.g. Alport’s syndrome.
- **Acquired:**
  - Noise injury.
  - Head injury.
  - Infection, e.g. meningitis, measles, mumps, syphilis.
  - Presbycusis.
  - Tumour, e.g. acoustic neuroma.
  - Ototoxic drugs, e.g. aminoglycosides, furosemide.
  - Ménière’s disease.

**Treatment**
- Conservative: patient and parent education. Advise about sign language programmes if appropriate. Hearing aids (if these are not suitable or do not work then consider middle ear and cochlear implants).
- Medical: antivirals, antifungals or antibiotics if indicated.

### CONDUCTIVE

**What is conductive hearing loss?**
This is hearing loss that occurs due to abnormalities/blockage of the middle ear or of the auditory canal. It may be reversible.

**Causes**
- **Congenital:**
  - Abnormalities of the ossicles.
  - Ear atresia.
  - Complications of Down’s syndrome and Pierre Robin sequence.
- **Acquired:**
  - Wax.
  - Otitis externa.
  - Glue ear.
  - Perforated drum.
  - Otosclerosis.
  - Eustachian tube dysfunction.

**Treatment**
- Treatment of underlying cause.

**Investigations**
- Bloods: look for underlying cause if indicated.
- Audiometric hearing test.
- Weber test.
- Rinne test.

**Complications**
- Depression.
- Anxiety.
### Appendix One

**List of Useful Disease Diagnostic Criteria**

<table>
<thead>
<tr>
<th><strong>Name of criteria</strong></th>
<th><strong>Name of disease</strong></th>
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</thead>
<tbody>
<tr>
<td>Framingham Criteria</td>
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<td>New York Heart Association Classification</td>
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<td>Duke Criteria</td>
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<td>The Los Angeles Classification</td>
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<td>The Rome III Criteria</td>
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<td>The Rockall Risk Scoring Criteria</td>
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<tr>
<td>The Child–Pugh Grading System</td>
<td>Cirrhosis and risk of variceal bleeding</td>
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<tr>
<td>The Truelove and Witts Criteria</td>
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<td>The Vienna Criteria</td>
<td>Crohn’s disease</td>
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<td>The Rifle Criteria</td>
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<td>MRC Classification</td>
<td>Grading for muscle power</td>
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<td>The McDonald Criteria</td>
<td>Multiple sclerosis</td>
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<td>Duke’s Criteria</td>
<td>Colorectal cancer</td>
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<tr>
<td>Ann Arbor Staging</td>
<td>Hodgkin and non-Hodgkin lymphoma</td>
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<td>Beighton Criteria</td>
<td>Joint hypermobility</td>
</tr>
<tr>
<td>Psoriasis Area and Severity Index</td>
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<tr>
<td>Cardiac Failure, Hypertension, Age, Diabetes, Stroke system (CHADS2) Score</td>
<td>Calculates risk of stroke in patients with AF</td>
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<td>QRISK Score</td>
<td>Calculates 10-year cardiovascular risk</td>
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## Appendix Two Useful Websites

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## Useful Websites

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### Useful Websites

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Mind Maps for Medical Students

This brand new revision aid has been designed specifically to help medical students memorise essential clinical facts, invaluable throughout medical studies and particularly useful in the pressured run-up to final exams. Over 100 maps are organised by body system, with a concluding section of miscellaneous examples.

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Olivia Smith is a fourth year medical student, The Hull York Medical School, UK

Olivia Smith

Mind Maps for Medical Students