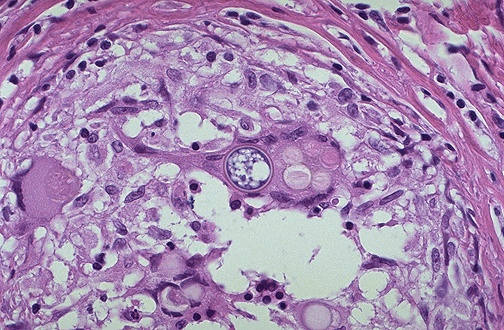
School of Medicine

Year 5 2012/13

PATHOLOGY THEME GUIDE

Volume 3 – Week 3

****

Theme leaders

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PATHOLOGY THEME

Year 5 – Study Guide – Week 3

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SOLE FEEDBACK – PATHOLOGY Week 3

The following pages provide you with templates on which you can record your thoughts as the course proceeds. At the end of the course you can enter your views onto SOLE.

Please answer all questions by selecting the response which best reflects your view.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Strongly Agree | Agree | Neutral | Disagree | Strongly Disagree |
| The content of this module is useful. |  |  |  |  |  |
| The support materials available for this module (e.g. handouts, web pages, problem sheets) are helpful. |  |  |  |  |  |
| I receive sufficient feedback and guidance. |  |  |  |  |  |
| Overall, I am satisfied with this module. |  |  |  |  |  |

Please use this box for constructive feedback and suggestions for improvement.

|  |
| --- |
|  |

SOLE FEEDBACK - INDIVIDUAL LECTURERS – Week 3

Please note that for SOLE, a Lecturer’s name will only appear once. This template gives you the opportunity to record your comments about each lecture in the order of delivery.

On the following section, you have an opportunity to record any comments and constructive feedback you have for each lecturer.

|  | **The lecture(s) are well structured** | | | | | **The lecturer explains concepts clearly** | | | | | **The lecturer engages well with the students** | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Lecturer and Lecture Title** | Strongly Agree | Agree | Neutral | Disagree | Strongly Disagree | Strongly Agree | Agree | Neutral | Disagree | Strongly Disagree | Strongly Agree | Agree | Neutral | Disagree | Strongly Disagree |
| Dr Ann Sandison  Metabolic bone disease |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Ben Jones  Calcium handling, bones and stones |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Ann Sandison  Neoplastic Bone Disease |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Amir Sam  Sodium and Fluid balanace, |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Amir Sam  Potassium handling |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Yehani Wedatilake  Uric Acid Metabolism |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Corrina Wright  Cytopathology |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Kirsty Lloyd  Consent, confidentially, Coronial law & The Human Tissue Act |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Prof Karim Meeran  EMQs – bugs etc |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Paul Lewis  Clinical Chemistry CPC |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Prof Karim Meeran  Clinical Chemistry CPC |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Ann Sandison  Clinical Chemistry CPC |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Jaimini Cegla  Acid-base |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Michael Petrou  Fungal infections |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Marjorie Walker  Skin Pathology |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr James Carton  Disease of the Pancreas |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Carolyn Millar  Obstetric Haematology |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Monica Nijher  Porphyrias |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Prof Terry Cook  Endocrine disease |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Prof Gilbert Thompson  Obesity & cardiovascular update |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Emilie Sanchez  Opportunistic viral infections |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Luke Moore  CNS Infection |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Claire Thomas  PUO & Endocarditis |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Claire Thomas  Zoonoses |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Donald Macdonald  Lymphoma |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Sasha Marks  Lymphoma |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Alex Rice  Lymphoma |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Rathi Ramakrishnan  Urological pathology |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Michael Petrou  Fungal infections |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Prof Karim Meeran  EMQs – enzymes |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Dunisha Samarasinghe  Wound, bone, joint |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Wing May Kong  Human Rights and Global Justice |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

| **Lecturer and Lecture Title** | **Please use this box for additional constructive feedback** |
| --- | --- |
| Dr Ann Sandison  Metabolic bone |  |
| Dr Ben Jones  Calcium handling, |  |
| Dr Ann Sandison  Neoplastic Bone |  |
| Dr Amir Sam  Sodium and Fluid balance |  |
| Dr Amir Sam  Potassium handling |  |
| Dr Corrina Wright  Cytopathology |  |
| Dr Yehani Wedatilake  Uric Acid Metabolism |  |
| Dr Kirsty Lloyd  Consent, confidentially, Coronal law and HTA |  |
| Prof Karim Meeran  EMQs – bugs |  |
| Dr Paul Lewis  Clinical Chemistry CPC |  |
| Prof Karim Meeran  Clinical Chemistry CPC |  |
| Dr Ann Sandison  Clinical Chemistry CPC |  |
| Dr Jaimini Cegla  Acid-base |  |
| Dr Michael Petrou  Fungal infections |  |
| Dr Marjorie Walker  Skin Pathology |  |
| Dr Ann Sandison  Non-neoplastic bone |  |
| Dr Carolyn Millar  Obstetric Haematology |  |
| Prof Jane Apperley  Haemopoetic Stem Cell  Transplanation |  |
| Dr Monica Nigher  The porphyrias |  |
| Dr Amir Sam  Sodium & Fluid Balance |  |
| **Lecturer and Lecture Title** | **Please use this box for additional constructive feedback** |
| Dr Monica Nijher  Porphyrias |  |
| Prof Terry Cook  Endocrine Disease |  |
| Prof Gilbert Thompson  Obesity & cardiovascular update |  |
| Dr Emilie Sanchez  Opportunistic viral infections |  |
| Dr Donald Macdonald  Lymphoma |  |
| Dr Sasha Marks  Lymphoma |  |
| Dr Sasha Marks  Lymphoma |  |
| Dr Alex Rice  Lymphoma |  |
| Dr Rathi Ramakrishnan  Urological pathology |  |
| Dr Michael Petrou  Fungal infection |  |
| Prof Karim Meeran  EMQs – enzymes |  |
| Dr Dunisha Samarasinghe  Wound, bone, joint |  |
| Dr Wing May Kong  Human Rights and Global Justice |  |

TIMETABLE Week 3 – Charing Cross Campus

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
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| |  |  |  |  | | --- | --- | --- | --- | | **Monday 16th July** | | | | | 9.00-9.45 | Hi | | Metabolic bone disease (Dr Ann Sandison) | | 9.45-10.30 | CP | | Calcium handling, bones and renal stones (Dr Ben Jones) | | 10.30-11.15 | CP | | Neoplastic bone disease (Dr Ann Sandison) | | 11.15-11.30 |  | | BREAK | | 11.30-12.15 | CP | | Sodium and fluid balance (Dr Amir Sam) | | 12.15-13.15 |  | | LUNCH | | 13.15-14.00 | CP | | Potassium (Dr Amir Sam) | | 14.00-14.45 | CP | | Uric Acid Metabolism (Dr Yehani Wedatilake) | | 14.45-15.00 |  | | BREAK | | 15.00-15.45 | Hi | | Cytopathology (Dr Corrina Wright) | | 15.45-16.30 | EL | | Consent, Confidentiality, Coronial law and the Human Tissue Act (Dr Kirsty Lloyd) | | 16.30-17.15 | CP | | EMQ examples – bugs and others (Prof Karim Meeran) | | **Tuesday 17th July** | | | | | 9.00-10.00 | CP | Clinical chemistry CPC (Dr Paul Lewis/Prof Karim Meeran/Dr Ann Sandison) | | | 10.00-11.00 | CP | Acid-Base Handling (Dr Jaimini Cegla) | | | 11.00-11.15 |  | BREAK | | | 11.15-12.15 | Mi | Opportunistic viral infections (Dr Emilie Sanchez) | | | 12.15-13.15 |  | LUNCH | | | 13.15-14.30 | Ha | Haemolytic anaemias (Dr Mark Layton)) | | | 14.30-14.45 |  | BREAK | | | 14.45-15.30 | Hi | Disease of the Pancreas (Dr James Carton) | | | 15.45-16.45 | Hi | Upper Gastrointestinal Disease (Dr Marjorie Walker) | | | **Wednesday 18th July** | | | | | 9.00-10.00 | Hi | Skin pathology (Dr Marjorie Walker) | | | 10.00-10.45 | Hi | Non-neoplastic bone and joint disease (Dr Ann Sandison) | | | 10.45-11.00 |  | BREAK | | | 11.00-12.15 | Ha | Obstetric Haematology (Dr Carolyn Millar) | | | **Thursday 19th July** | | | | | 9.00-10.00 | CP | Endocrine disease (Prof Terry Cook) | | | 10.00-10.15 |  | BREAK | | | 10.15-11.15 | CP | Obesity & cardiovascular update, Lipoprotein metabolism, Lipid Cases  (Prof Gilbert Thompson) | | | 11.15-12.15 | Mi | CNS infection & Meningitis (Dr Luke Moore) | | | 12.15-13.15 |  | LUNCH | | | 13.15-15.15 | Ha | Lymphoma: multidisciplinary afternoon (Dr Donald Macdonald, Dr Alex Rice,  Dr Sasha Marks) | | | 15.15-15.30 |  | BREAK | | | 15.30-16.30 | Ha | Haemopoetic stem cell transplantation (Prof Jane Apperley) | | | 16.30-17.00 | Ha | The Porphyrias (Dr Monia Nigher) | | | **Friday 20th July** | | | | | 9.00-9.45 | Mi | PUO & Endocarditis (Dr Claire Thomas) | | | 9.45-10.30 | Mi | Zoonoses (Dr Claire Thomas) | | | 10.30-10.45 |  | BREAK | | | 10.45-12.00 | Hi | Urological pathology (Dr Rathi Ramakrishnan) | | | 12.00-12.45 | Mi | Fungal infections and their Diagnosis (Dr Michael Petrou) | | | 12.45-13.45 |  | LUNCH | | | 13.45-14.45 | CP | Wound, bone and joint infections (Dr Dunisha Samarasinghe) | | | 14.45-15.45 | Mi | EMQ on enzymes, chemistry and zoonoses (Prof Karim Meeran) | | | 15.45-16.00 |  | BREAK | | | 16.00-17.00 | EL | Human Rights and Global Justice (Dr Wing May Kong) | | |

CONTACT DETAILS

Theme leaders

Prof Karim Meeran ([k.meeran@imperial.ac.uk](mailto:k.meeran@imperial.ac.uk))

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*Immunology*

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*Microbiology*

Dr Hugo Donaldson (h.donaldson@imperial.ac.uk)

Course administration

Mrs Chandra Tambimuttu ([c tambimuttu@imperial.ac.uk](mailto:c%20tambimuttu@imperial.ac.uk))

**Please use the discussion board for any questions wherever possible, rather than emailing staff directly.**

HANDOUTS FOR INDIVIDUAL LECTURES

The page numbering continues from the previous volume.

Metabolic Bone Histopathology

Dr Ann Sandison

***Structure of Bone***

Bone needs to be strong for protection and support of soft tissues and light for mobility. It is the main storage site for calcium and the chief site for haematopoiesis.

Periosteum covers cortical surface and delivers blood supply. Bones have geographical regions i.e. epiphysis, metaphysis, diaphysis

**Types of bone include: -**

**Compact** bone (cortex) - function mainly mechanical support and protection. Cancellous (spongy, trabecular) bone (e.g. in vertebra) – large surface area, main function in calcium metabolism.

**Lamellar** bone is characteristic of adult bone, compact and cancellous. It is ‘mature’.

**Woven** bone is immature and usually pathological.

***Bone Cells***

Osteocytes are osteoblasts, which have become trapped in bone matrix. They are in contact with other bone cells and bone surface

Osteoblasts are bone forming cells, which line endosteal surfaces (blasts build bone). They deposit osteoid at a rate of about 1um a day.

Osteoclasts are multinucleate cells part of the macrophage family, involved in bone resorption (clasts chew bone).

These cells comprise the ‘Basic Multicellular Unit’. Each cell type is formed from osteprogenitor cells in marrow. Osteoclast differentiation is regulated via RANK gene product (**r**eceptor **a**ctivator for **n**uclear factor **k**β ) that adheres to RANK ligand on osteoclast cells and activates the cell; osteoprotegerin (OPG) inhibits RANK ligand and deactivates the osteoclast. The cells work in concert and regulation is multifactorial via eg mechanical factors, hormones (eg PTH), cytokines.

Bone homeostasis depends on the finely controlled coupling of bone resorption and bone formation whereby osteoclasts and osteoblasts exert critical stimulatory and inhibitory control over each other via molecules such as RANKL, TGFβ, PDGF, BMP2 and Mim-1.

***Bone Biopsy***

**Types:-**

Needle biopsy with/without imaging

Open biopsy

**Indications:-**

Suspected tumour or infection

Suspected metabolic bone disease e.g. osteomalacia or Paget’s disease

Diagnostic classification of renal osteodystrophy

Evaluation of therapy

Research

Usual biopsy for the investigation of metabolic bone disease is needle biopsy from the anterior iliac crest.

To achieve diagnostic accuracy with such small tissue samples, full and accurate clinical information is essential to the pathologist, as are specialist laboratory techniques. To investigate metabolic bone disease, a patient is given 2 doses of demeclocycline 10 –14 days apart before bone biopsy as mineralisation lags behind osteoid formation by about 10 days. The specimen must not be decalcified and needs to be embedded in resin to cut sections. Special stains are then used to demonstrate osteoid or uncalcified bone matrix. Histomorphometry is the quantitative analysis of undecalcified bone.

***METABOLIC BONE DISEASE***

**A.  *Osteoporosis***. Bone is normal in quality but reduced in quantity (density). May be generalised - aetiology age related in particular post-menopausal females – decreased oestrogen results in increased IL1 which subsequently causes increased IL6 release by osteoblasts which activates osteoclasts. Can be secondary to drugs or systemic disease (Cushing’s, hyperparathyroidism). May be localised e.g. following immobilisation post-fracture or adjacent to a rheumatoid joint. Max. bone density is in 3rd decade. Rate of loss averages 0.7% per year. Greatest loss in spine and femoral neck.

**B. *Osteomalacia****.* Defective bone mineralisation. Two types 1)- deficiency of Vitamin D 2) deficiency of phosphate (PO4 ). Sequelae are bone pain, fracture, proximal weakness and bone deformity. Causes are inadequate diet, malabsorption, lack of exposure to sunlight, chronic liver disease, chronic renal disease, anticonvulsant therapy.

**C. *Hyperparathyroidism****.* Caused by excess PTH. Increased Ca and PO4 excretion in urine. Hypercalcaemia, hypophosphataemia. Skeletal changes of osteitis fibrosa cystica.

Aetiology 1° - adenoma (85-90%) or chief cell hyperplasia. 2° - chronic renal insufficiency, vitamin D deficiency, malabsorption. PTH increases osteoclast activation which increases resorbtion of calcium by renal tubule, also increases synthesis of 1,25(OH)2 D by kidney and increases resorbtion of Ca from gut. Hallmark of the disease is increased osteoclast activity and bone resorption.

**D. *Paget’s Disease of bone*** - a disorder of bone turnover common in middle aged and elderly. Characterised by both lytic and sclerotic lesions. Divided into 3 stages:

1) osteolytic, 2) osteolytic-osteosclerotic, 3) quiescent osteosclerotic.

Onset >40y, equal sex incidence, rare in Asians and Africans. Monostotic 15% remainder polyostotic. Clinical - pain, microfractures, nerve compression including spinal nerves and cord. Skull changes may put medulla at risk, +/- haemodynamic changes- cardiac failure. Development of sarcoma in area of involvement (1%). Aetiology unknown. Research suggests infection by paramyxovirus like organisms may induce IL6 and increase osteoclast activity. Mutations in the SQSTM1 gene on chromosome 5 are associated with classical Paget’s disease in bone but mutations in this gene are infrequently associated with familial Paget’s therefore other genes are likely to be involved.

Blood tests show raised serum alk. Phos with normal Ca and PO4.

**E. *Renal Osteodystrophy*** *-* progressive bone disease associated with chronic renal failure. Pathological effects mainly secondary to hyperparathyroidism although marked increase in unmineralised matrix also present. 54% show features of hyperparathyroidism alone while 34% show features of both hyperparathyroidism and osteomalacia.

**References**

**General**

Robbins & Cotran Pathologic Basis of Disease 7th Ed. Chapter 26. Edited by Kumar, Abbas & Fausto (Elsevier Saunders 2005 )

The New Aird’s Companion in Surgical Studies 3rd Ed. Chapter 41. Edited by KG Burnand, A EYoung, J Lucas (Elsevier Churchill Livingstone 2005)

**Specialist text**

Bone Histomorphometry by Eriksen, Axelrod and Melsen (Raven Press 1994)

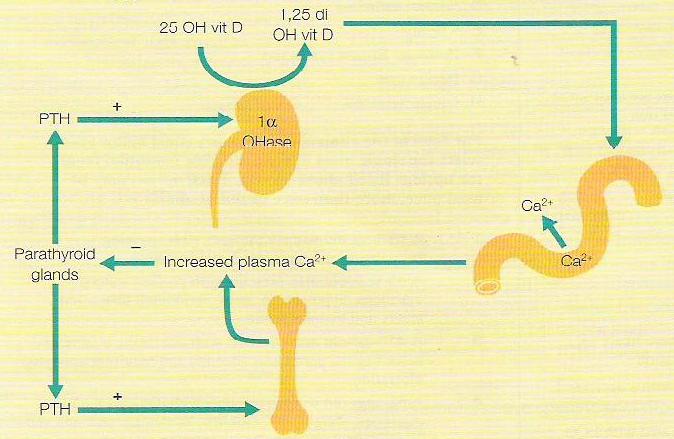
Calcium Handling, Bones and Renal Stones

Dr Ben Jones

**THE BASICS**

1. **Daily Ca2+ Flux**
2. 1g/day in diet, 0.2g/day net absorption
3. 0.5g of Ca circulating at any one time
4. 1.5Kg of Ca in the skeleton
5. **Serum Ca2+**
6. 2.2 - 2.6 mmol/L
7. 50% ionized (free) / 40% protein-bound / 10% complexed
8. ~~Corrected~~ Adjusted Ca(mmol/L) = Ca(mmol/L)+0.02(40 - alb(g/L)) - **depends on lab method**

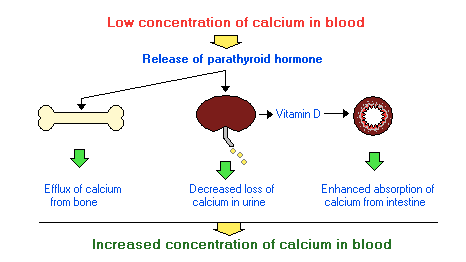
**SUMMARY OF Ca2+ HOMEOSTASIS**



**PARATHYROID HORMONE**

84 aa peptide hormone

Exclusively secreted from parathyroids



Also stimulates renal Pi wasting

**PRIMARY HYPERPARATHYROIDISM**

Commonest cause of hypercalcaemia

Biochemistry: ↑Ca, ↑ or inappropriately N PTH, ↓Phos

Note – urine Ca is high despite PTH action (due to high serum Ca)

**Sx**: “Bones, (renal) stones, (abdominal) groans, (psychiatric) moans”

**Rx**: Parathyroidectomy if symptomatic

**REGULATION OF PTH RELEASE - CALCIUM SENSING RECEPTOR**

|  |  |
| --- | --- |
| Picture 2  **[PTH]**   * 1088 aa GPCR * Expressed on parathyroids and kidneys * Responds to extracellular [Ca] Mutations cause FHH **(familial hypocalciuric hypercalcaemia)**   + In FHH abnormal renal CSR -> hypocalciuria | **[Ca2+]**  Normal  FBH  **Inactivating Mutation causes R shift of curve** |

**NOMENCLATURE IN HYPER & HYPOPARATHYROIDISM**

**Hyper**

1. 10 Adenoma
2. 20 Response to hypocalcaemia. Vit D deficiency, CKD.
3. 30 Autonomous PTH production after longstanding 20 hyperPTH. CKD.

**Hypo**

Hypoparathyroidism – low PTH, low / inappropriately N Ca

*Pseudo*hypoparathyroidism – resistance to PTH -> high PTH, low / inappropriately N Ca, characteristic physical appearance

*Pseudopseudo*hypoparathyroidism..! – characteristic physical appearance, but biochemistry normal..

**VITAMIN D METABOLISM**



Cholecalciferol (D3)

UV

7-dehydrocholesterol



**25-OH-D3**

**1,25-(OH)2-D3**

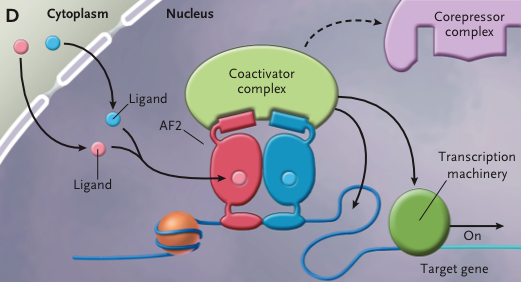
PTH

+

1α OHase

**ACTIONS OF VITAMIN D**

1. Intestinal Ca absorbtion
2. Bone calcification
3. Muscle strength
4. Immune regulation
5. Vit. D receptor = Nuclear hormone receptor, like thyroxine receptor, glucocorticoid receptor, etc., ligand-dependent transcription factor



**VITAMIN D DEFICIENCY**

1. Childhood = Rickets
2. Adulthood = Osteomalacia = Metabolic bone disease   
    in which there is inadequate mineralisation of the boney  
    osteoid (cf Osteoporosis, quality of bone ok, amount decreased)

**CLINICAL FEATURES OF VIT D DEFICIENCY**

|  |  |
| --- | --- |
| 1. Osteomalacia 2. Bone pain 3. Myopathy 4. Looser’s zones (pseudo#s) 5. Biochem abnormality 6. ↑# risk | 1. Rickets 2. Bowed legs 3. Chostrochondral swelling 4. Widened epiphyses at the wrists 5. Myopathy |

**HYPERCALCAEMIA**

**Sx –** polyuria / polydipsia, constipation, neuro – confusion, seizures

**Rx** – fluids ++, bisphosphonates, treat underlying cause

**Causes:** (first exclude “spurious”)

**Is PTH suppressed?**

**No -** 10 hyperPTH (commonest cause)

Raised or inappropriately normal PTH

Low phosphate

“bones, stones, (psychiatric) moans, (abdominal) groans”

familial hypocalciuric hypocalcaemia

Mild hyperCa

LOW urine Ca (differentiate from hyperPTH)

**Yes -** Malignancy (2nd commonest cause)

Bony mets (high ALP)

PTHrp

Haematological – cytokine mediated, ALP normal (except after #)

Sarcoidosis, VitD intoxication, thyrotoxicosis, milk alkali syndrome,

**HYPOCALCAEMIA**

**Sx** - Neuromuscular excitability, Chvostek’s sign, Trouseau’s sign, seizures

**Rx** – Ca infusion (acutely), Ca + vit D supplements (chronic); activated vit D used in most

cases except simple vit D deficiency

**Causes**

1. **Lack of vitamin D action** – esp vit D deficiency & CKD

Common, hypocalcaemia often mild

Causes 2ary hyperPTH

1. **Lack of PTH** – parathyroidectomy, DiGeorge, autoimmune hypoPTH

**BONES**

|  |  |  |
| --- | --- | --- |
| Picture 3 | 1. Approx’ 1.5 kg of calcium in the skeleton 2. From a metabolic point of view, skeleton = huge reservoir of Ca 3. Highly active tissue 4. “remodeling cycle” | Picture 1 |

**OSTEOPOROSIS - INTRODUCTION**

Osteoporosis is defined as *“a progressive systemic disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture”* (WHO 1994)

* 2.1 million women in UK with osteoporosis
* 200,000 osteoporotic #s in UK annually
* £940 million annual cost to NHS alone
* 1/3 of all women will sustain at least 1 osteoporotic #
* NOF #s account for 20% of orthopaedic bed occupancy in the NHS

**DEFINITIONS:**

1. T-score: BMD relative to young adult
2. Z-score: BMD relative to age related mean
3. Osteopaenia: T between -1 & -2.5
4. Osteoporosis: T below -2.5

**TREATMENTS FOR OSTEOPOROSIS**

1. Lifestyle - exercise/smoking/alcohol
2. Drugs
3. Bisphosphonates - etidronate/alendronate, etc.
4. Vitamin D/Ca
5. PTH derivative - teriparatide
6. Strontium
7. Oestrogens - HRT
8. SERMs e.g. raloxifene

**PAGET’S DISEASE**

|  |  |
| --- | --- |
| 1. Focal disorder of bone remodeling, the normally tightly controlled link between deposition and resorption is lost. 2. Primary defect = Osteoclast 3. ? Viral in origin 4. PAIN, warmth, deformity, fracture, compression, malignancy, 5. Pelvis, femur, skull and tibia 6. Elevated Alkaline phosphatase 7. Treatment = Bisphosphonates for pain |  |

**COMPOSITION OF RENAL STONES % of stones Characteristics**

**Crystals**

Calcium oxalate 40-60% Radio-opaque  
 Well circumscribed

Calcium phosphate (apatite: Ca10[PO4]6[OH]2) 20-60%

Calcium phosphate (brushite: CaHPO4 2H2O) 2-4%

Uric acid 5-10% Radiolucent; Rarely staghorn

Struvite (magnesium ammonium phosphate) 5-15% Can be staghorn

Cystine 1.0-2.5% Mildly opaque; Can be staghorn

Ammonium urate 0.5-1.0%

**Mixed Stones**

Mixed calcium oxalate-phosphate 35-40%

Mixed uric acid-calcium oxalate 5%

**RENAL CALCIUM STONES**

1. RFs: FH, Dehydration, hypercalciuria (>6mmol Ca/day), hypercalcaemia, HPTH
2. Presentation: Pain (colic), haematuria, recurrent infection, renal failure
3. Ix: KUB, stone analysis, urine and serum biochemistry
4. Natural Hx: Most stones pass
5. Mx: Lithotrypsy, cystoscopy, lithotomy

Prevention: Drink more water, treat hypercalciuria (e.g. thiazides) &/or   
 hypercalcaemia as necessary

**PRINCIPAL DISORDERS, CALCIUM HANDLING**

**Disorder 1o defect Ca Pi PTH AlkP VitD**

10 Hyper-parathryoidism ↑ PTH ↑ ↓ ↑/N ↑/N N

Hypo-parathryoidism ↓PTH ↓ ↑ ↓/N N N

Rickets / Osteomalacia ↓ VitD ↓/N ↓ ↑ ↑ ↓

Pagets Remodelling N N N ↑ N

Osteoporosis Bone loss N N N N N

Neoplastic Bone Disease

Dr Ann Sandison

Primary bone tumours are uncommon, but are among the more common tumours in the young (<30 years). Classification is based on cytological appearance and the matrix or product of the tumour cells. Very few malignant tumours arise from benign counterparts.

Secondary (metastatic) tumours are far more common, but occur in a much older age group

(>50 years).

Most common site forprimary tumours of bone is around the knee. However, specific entities have their own patterns of distribution**.**

***Bone Tumours Non-neoplastic***:

These lesions are best regarded as disorder of bone development or maturation.

***Fibrous Dysplasia***

Hamartomatous disorder characterised by fibro-osseous dysplasia.

Mostly < 30 years age.

Single or multiple lesions. Multiple can be part of Albright’s Syndrome, characterised by precocious puberty, fibrous dysplasia, and brown skin patches. Affects mainly long bones, ribs and skull. Radiologically characteristic ground glass appearance. Histologically, characterised by loose fibrous tissue with haphazardly arranged, misshapen metaplastic bone trabeculae. Bone trabeculae may lack osteoblastic rimming. Benign course but may cause severe deformity.

***Simple Bone Cyst***

Benign, fluid filled, unilocular cyst. Age < 20 years. Usually affects the proximal metaphyses of the humerus or femur. Radiology - lytic, well defined. Natural history is one of migration down the shaft from the original growth plate site.

***Osteochondroma***

Cartilage capped bony protuberance of the metaphysis or diaphysis. Developmental abnormality. Grows by virtue of enchondral ossification of the cartilage cap. Occurs in the young (growth plate derived). May be asymptomatic or be noticed as a lump +/- pain.

Multiple osteochondromas = osteochondromatosis with very rarely, malignant transformation. Diaphyseal aclasia is a separate entity with a greater risk of malignant transformation, associated with mesomelic dwarfism.

***Neoplastic Bone Tumours - Benign***

***Enchondroma***

Benign, tumour composed of cartilage, arising in the medulla of the bone. Can occur at any age. Average 40 years. Radiological - lytic, with “cotton wool” calcification.

Multiple enchondromata = Ollier’s Syndrome. Multiple enchondromata + multiple haemangiomas = Maffucci’s Syndrome. Benign hyaline cartilage on histological examination. Significant risk of malignant transformation.

***Osteoid Osteoma***

Small (<1cm), benign bone forming lesion. Very painful - relieved by aspirin.

<30 years age. Usually occurs in diaphyseal cortex of lower limb. It is a more difficult diagnosis when the lesion is intraarticular or intramedullary sites. Radiologically a lytic lesion with a central nidus and a sclerotic rim on X- ray. Histology shows an active, well-defined, woven bone-forming lesion. Highly vascular.

Sodium and fluid balance

Dr Amir H. Sam, Clinical Lecturer

**Learning objectives**

* To describe the hormonal regulation of water balance
* To discuss the underlying pathophysiology of hypo and hypernatraemia
* To state the main causes of hypo and hypernatraemia
* To outline the main points in the management of hypo and hypernatraemia

1. **What is the commonest electrolyte abnormality in hospitalized patients?**

Answer: -

1. **What is the underlying pathogenesis of hyponatraemia?**

Answer: -

1. **Which hormone controls water balance?**

Answer: -

1. **What are the two main stimuli for ADH secretion?**

Answer: -

-

1. **What is the effect of increased ADH secretion on serum sodium?**

Answer: -

1. **What is the first step in the clinical assessment of a patient with hyponatraemia?**

Answer: -

1. **What are the clinical signs of hypovolaemia?**

Answer: -

-

-

-

-

-

1. **What are the clinical signs hypervolaemia?**

Answer: -

-

-

1. **What are the causes of hyponatraemia in a hypovolaemic patient?**

Answer: -

-

1. **What are the causes of hyponatraemia if a hypervolaemic patient?**

Answer: -

-

-

1. **What are the causes of hyponatraemia in a euvolaemic patient?**

Answer: -

-

-

1. **What are the causes of Syndrome of Inappropriate ADH secretion (SIADH)?**

Answer: -

-

-

-

1. **What investigations would you order in a patient with euvolaemic hyponatraemia?**

Answer: -

-

-

1. **How would you manage a hypovolaemic patient with hyponatraemia?**

Answer: -

-

1. **How would you manage a hypervolaemic patient with hyponatraemia?**

Answer: -

-

1. **How would you manage a euvolaemic patient with hyponatraemia?**

Answer: -

-

1. **What is the most important point to remember while correcting hyponatraemia?**

Answer: -

1. **What are the main causes of hypernatraemia?**

Answer: -

-

1. **What investigations would you order in a patient with suspected diabetes insipidus?**

Answer: -

-

-

-

-

1. **How would you treat hypernatraemia?**

Answer: -

-

**21. What are the effects of diabetes mellitus on serum sodium?**

Answer: -

Potassium handing

Dr Amir H. Sam, Clinical Lecturer

**Learning objectives**

* To describe the hormones involved in the renal regulation of potassium
* To discuss the underlying pathophysiology and main causes of hyper and hypokalaemia
* To outline the main points in the management of hyper and hypokalaemia

1. **Which hormones are involved in renal regulation of potassium?**

Answer: -

-

1. **What are the stimuli for aldosterone secretion?**

Answer: -

-

1. **What are the main causes of hyperkalaemia?**

Answer: -

-

-

-

-

-

-

1. **What is the main the ECG change associated with hyperkalaemia?**

Answer: -

1. **How would you manage a patient with hyperkalaemia?**

Answer: -

-

-

-

1. **What are the causes of hypokalaemia?**

Answer: -

-

-

-

-

-

1. **What are the clinical features hypokalaemia?**

Answer: -

-

-

1. **What screening test would you order in a patient with hypokalaemia and hypertension?**

Answer: -

1. **How would you manage a patient with hypokalaemia?**

Answer: -

Uric Acid Metabolism

**Hyperuricaemia and Gout**

Dr Yehani Wedatilake

(Handout by Dr Jeremy Turner)

**Monosodium Urate, Plasma concentrations.**

Men 0.12 – 0.42 mmol/l, Women 0.12 – 0.36 mmol/l

Solubility in saline at 37oC= 0.40 mmol/l

At 30oC = 0.27 mmol/l

pH dependent

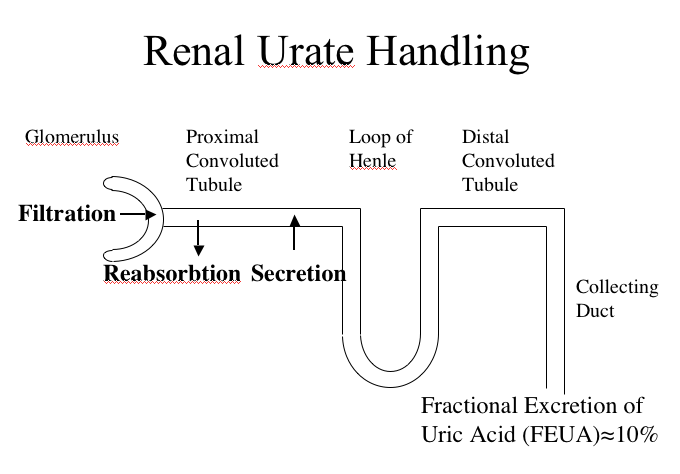


FIGURE 1

**Purine metabolic pathways**.

Metabolites are in non-bold text and enzymes are in bold text.

dAMP, deoxyadenosine monophosphate; PAT, phosphoribosyl pyrophosphate amidotransferase; 5’NT, 5’-nucleotidase; ADA, adenosine deaminase; NP, nucleoside phosphorylase; XO, xanthine oxidase; HPRT, hypoxanthine phospho ribosyltransferase; APRT, adenine phospho ribosyltransferase; PRPS, purine phosphoribosylpyrophosphate synthetase.

Green; *de-novo* pathway of purine synthesis

Blue; salvage pathway.

**HGPRT deficiency**

Complete: Lesch Nyhan syndrome.

Normal at birth

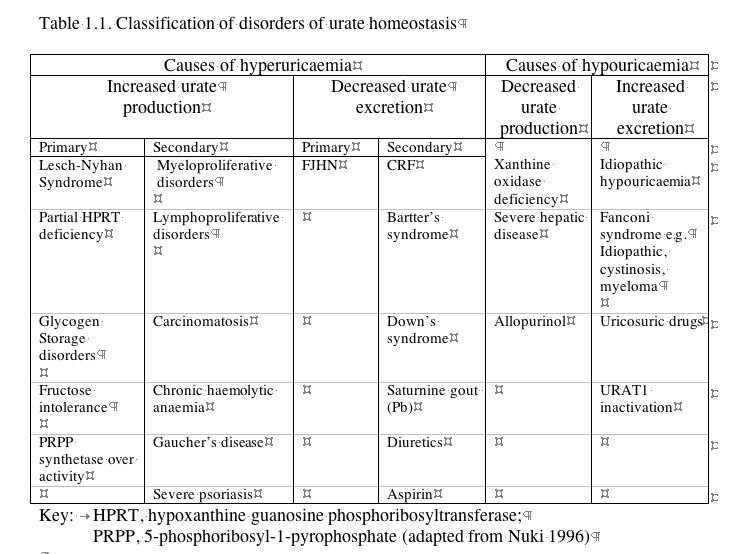
Developmental delay apparent at 6/12

Hyperuricaemia

Choreiform movements (1 year)

Spasticity, mental retardation

Self mutilation (85%) aged 1-16



**Gout**

Monosodium urate crystals

Can be acute or chronic

Males 0.5 – 3% prevalence

Females 0.1 – 0.6% prevalence

Post pubertal males and post menopausal females

**Acute Gout clinical features**

Rapid build up of pain

“Exquisite”

Affected joint red, hot and swollen

1st MTP joint first site in 50%

This joint is involved in 90% overall

**Management**

Important to distinguish between therapy for reducing inflammation and that for managing hyperuricaemia

**Treatment: General Principles**

Acute gout.

NSAIDs

Colchicine

Do NOT attempt to modify plasma urate concentration

**General Principles**

Interval (non acute) gout.

Drink plenty

Reverse factors putting up urate

modify plasma urate concentration

(reduce synthesis with allopurinol)

(increase renal excretion with probenecid): “uricosuric”

**Side effects of allopurinol**

Interacts with azathioprine, making it more toxic on bone marrow etc.

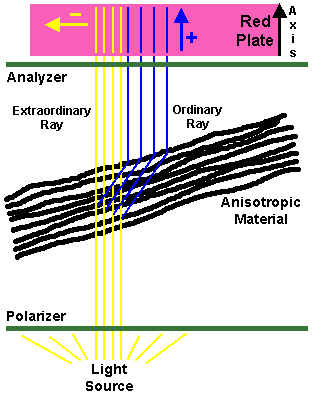
Azathioprine is metabolised to mercaptopurine and then to thioinosinate which interferes with purine metabolism.

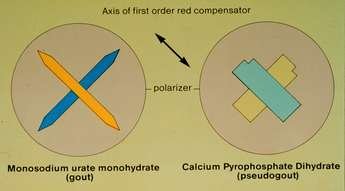
Allopurinol makes the mercaptopurine last longer.

**Diagnosis of gout**

Tap effusion

View under polarised light

Use red filter



**Negatively birefringent**

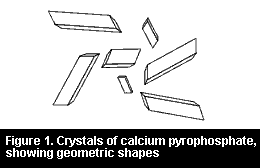
*Monosodium Urate crystals viewed under polarized light with a red plate that makes those in the plane of the long axis of the red plate yellow, which indicates that they are negatively birefringent.*

**Pseudogout**

Occurs in patients with osteoarthritis

Pyrophosphate crystals

Self limiting 1 – 3 weeks



**Summary**

Look at the direction of the axis of the filter.

Negatively birefringent crystals will be yellow in that direction and blue perpendicularly.

Cytopathology

Dr Corrina Wright   
(handout courtesy Dr Julie McCarthy)

**What is cytopathology ?**

1. The study of cell morphology to establish underlying disease processes
2. Gynae and non-gynae samples
3. Non-gynae: Exfoliative samples (brushes, washes, scrapes, fluids) and FNAs
4. Gynae: NHSCSP Cervical screening programme

**Back-to-basics**

1. Take sample
2. Place in fluid medium / smear onto glass slide
3. Stain sample
4. Examine microscopically
5. Write a report

**Gynaecological samples – NHS Cervical Screening Programme NHSCSP**

1. Cervical cytology underpins the cervical screening programme
2. Women between the ages of 25 – 65 years are invited for screening
3. Cervical scrape sample taken, now Liquid Based Cytology (LBC)
4. Sample viewed microscopically at lab looking for precancer and cancer cells
5. Repeated every 3-5 years
6. Ability to test for HPV and STDs from the vial
7. Significantly reduced the incidence of invasive squamous cell carcinoma

**Non-Gynae samples**

1. Benign vs malignant diagnosis
2. Inflammatory lesions - ? specific cause
3. Something other
4. Quick, easy and cheap test

Non-gynae samples are either exfoliative or fine needle aspirations

**Exfoliative Cytology**

This is when cells are dislodged or spontaneously shed from a surface ie. Bronchial washings and brushings, serous cavity effusions etc etc

**Fine needle aspirate**

Rapid, cheap and accurate method to achieve diagnosis of nature of mass lesions

1. May be done by hand or under radiologist control
2. Pathologists get better results with a low inadequate rate and optimisation of the diagnostic potential of each sample (i.e. microbiology samples, immunocytochemistry)

**Equipment**

1. Syringe and needles
2. +/- Cameco syringe holder

**Common sites for FNA**

1. Head and neck lesions
2. Breast lesions
3. Lung

**Advantages of FNA**

Accurate

Quick

Acceptable to patient

Rapid turnaround time

Organised into fast access clinics run by cytopathologists for aspiration of palpable swellings

Can prevent further surgical intervention

**Current applications of FNA**

Diagnosis of benign lesions (reactive lymph nodes, etc)

Diagnosis of malignancy (lymphoma, carcinoma, melanoma)

Diagnosis of thyroid malignancy and triage of nodules requiring surgical excision

Diagnosis of benign breast lesions as part of triple assessment, diagnosis of breast malignancy

**Less common applications of FNA**

EUSFNA

TBNA

Immunocytochemistry

Provision of cytospun material for molecular studies (ie FISH)

**Side effects of FNA**

1. Typically nothing
2. Bruising
3. Fainting
4. (Pneumothorax – site dependent!)
5. (Infarction of lesion)

**Why do cytology?**

1. Accurate
2. Cheap
3. Acceptable to patient
4. Pathologist / patient contact

Consent, Confidentiality, Coronial law and   
The Human Tissue Act

Dr Kirsty Lloyd

**Objectives:**

* Overview of the Human Tissue Act & human tissue authority in respect to autopsy practice
* Overview of the coronial & death certification system in England and Wales
* Know how to write a death certificate
* Know who the coroner is
* Understand what the HTA covers in terms of permissions.

**Outline**

* Consent
* Confidentiality
* Role of the coroner
* Coroner’s Act
* Coroner’s Rules

**CONSENT**

* All consent forms for investigations and treatments comply with 2001 DOH guidelines
* GMC requirement “Good Medical Practice”
* Pts have a fundamental legal and ethical right to determine what happens to their own bodies
* Seeking consent is a matter of common courtesy between health professionals and patients
* CONSENT is a patient’s agreement for a health professional to provide care. Patients may indicate consent implicitly / orally / in writing
* For consent to be VALID, the patient must be :
  + COMPETENT to take the decision
  + Received sufficient information to take it
  + Not be acting under duress
* A signature on a consent form does not imply valid consent
* Patients may withdraw consent after they have signed a form (not a binding contract)

**Who is Consenting?**

* Legally: the healthcare professional performing the procedure carries ultimate responsibility
* The health professional providing the information must be competent to do so because

1. they themselves can carry out the procedure
2. they have received specialist training in advising patients about this procedure, have been assessed, are aware of their own knowledge limitations

**Consent in pathology**

* The post mortem examination (**nominated representative**) storage/use of tissues for research or teaching

**Hierarchy of qualifying relationships**  
**1/ Spouse or partner (including civil or same sex partner)**   
*The HT Act states that, for these purposes, a person is another person's partner if   
the two of them (whether of different sexes or the same sex) live as partners in   
an enduring family relationship.*

**2/ Parent or child**   
(in this context a child may be of any age and means a biological or adopted child)

**3/ Brother or sister**

**4/ Grandparent or grandchild**

**5/ Niece or nephew**

**6/ Stepfather or stepmother**

**7/ Half-brother or half-sister**

**8/ Friend of long standing**

**CONFIDENTIALITY**

* Doctors hold sensitive and private information about patients
* This must NOT be given to others unless the patient consents OR you can justify the disclosure

**Justifications**

1. Best interest of patient / safeguarding wellbeing of others
2. Statutory Requirements e.g.

Road Traffic Act 1988

Prevention of Terrorism Act 1989

Public Health (Control of Disease) Act 1984

1. Public Interest

Public good *vs* obligation of confidentiality to the patient.

Protection of confidence is a public interest

**Disclosure in the Public Interest**

* Protecting the public from crime
* Protecting third parties

**Protecting the public from crime**

* No legal *duty* by doctors to disclose information even if requested by police.
* Except in certain circumstances e.g:
  + Motoring offences (road traffic act 1988)
  + Terrorist activities (terrorism act 1989)
* However, use your own discretion re: crime prevention

**Beyond death…**

GMC and BMA and DOH say that confidentiality **must continue** beyond death.   
Otherwise, a doctor could face disciplinary action.

**Exceptions**

* To assist Coroner / officer involved with inquest
* National Confidential Inquiries
* On death certificates
* Public health surveillance
* Parent seeking info re: cause of child’s death
* Insurance companies (lawfully)
* Partner/close relative/friend ...if you have no reason to believe the pt would have objected

**PART 1 QUESTION**

A secretary in your department asks you repeatedly whether she can she have a printout of the pathology report for her niece. **WHAT DO YOU DO?**

**AUTOPSIES IN THE UK**

**CONSENT AUTOPSIES** <10% of all autopsies in the UK

* Cause of death
* Extent of disease
* Effect of treatment

**Medico-legal autopsies**

* > 90% of all autopsies in the UK
* Identity of deceased
* When they died
* Where they died
* Cause of death

**Role of the coroner**

In regard to dead bodies lying in their geographical jurisdiction:

WHO?

WHEN?

WHERE?

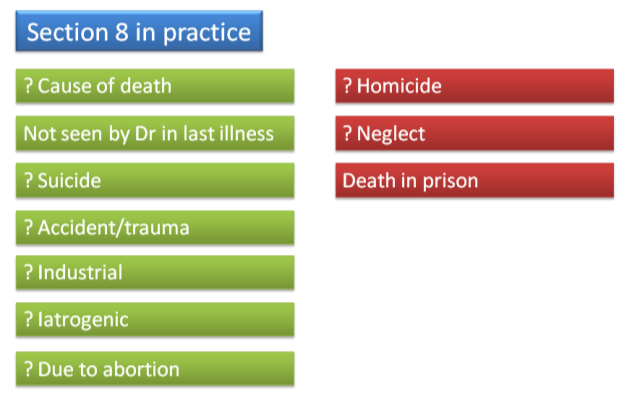
HOW?

**Who can refer?**

**UK Common Law:**

* All citizens of England and Wales have a common law duty ‘to give information which may lead to the coroner having notice of circumstances requiring the holding of an inquest’

**THE CORONERS ACT 1988**



**Section 8**

Sets out the coroner’s right to take jurisdiction over a death

Requires the coroner to hold an INQUEST if there is cause to suspect that death:

Was violent or unnatural, OR

Was sudden and of unknown cause, OR

Occurred in prison

**Section 22**

Allows coroner to order removal of a body from where it lies to a mortuary.

*R v. Bristol Coroner ex p Kerr [1974] 2 All ER 719*

Allows the coroner to take possession of a body for a post mortem examination until the inquest is concluded.

**Section 19**

Allows coroner to order an autopsy where it may prove an **inquest is unnecessary** by establishing a **natural cause of death**

*Coroner can direct “any legally qualified medical practitioner” to make a post mortem examination of the body and report the result of the examination in writing.*

DOES NOT allow the coroner to pay for “Special Examinations” such as:

* + Toxicology
  + Microbiology
  + Neuropathology
  + Etc

**Section 20**

Allows coroner to order an autopsy where it is clear that an **inquest will be needed** because the cause of death is clearly **unnatural**

*Coroner can direct “any legally qualified medical practitioner” to make a post mortem examination of the body.*

**The Coroners Rules 1984**

**Rule 5**

Any post mortem is to be made as soon after death as reasonably practicable.

**Rule 6**

Examination by a pathologist with suitable qualifications and experience

Coroner must consult with Chief officer of Police as to identity of pathologist if death is suspicious

Coroner must NOT instruct a pathologist on the staff of a hospital if the death occurred there and the conduct of any staff member is likely to be called into question, unless this will cause undue delay.

**Rule 10**

Sets out a schedule of the major organs of the body which should be included in the post mortem examination report.

*10 (2). Unless authorised by the coroner the pathologist must NOT supply a copy of the report to any person other than the coroner.*

**Rule 57(1)**

Coroner must, on payment of the appropriate fee, supply a copy of the post mortem report to any person who in his or her opinion is a properly interested person.

**Rule 11**

Forbids a post mortem from being performed in a dwelling house or in licensed premises.

Post mortem must be performed in adequately equipped premises

**What coronial legislation does NOT make provision for:**

* Teaching
* Public display
* Research
* Audit
* Clinical governance

**The Human Tissue Authority (HTA)**

HTA is a watchdog that supports public confidence by licensing organisations that store and use human tissue for purposes such as research, patient treatment, post-mortem examination, teaching, and public exhibitions.

**The Human Tissue Act, 2004**

* Established by Human Tissue Authority
* Came into effect September 2006
* Deals with consent, performance of autopsies and storage of material retained, as well as the collection and retention of material taken from the living

**Key principles**

* Replaces Human Tissue Act 1961 (no penalty for breaking the 1961 Act.)
* Breaking the 2004 Act can result in a FINE and/or CUSTODIAL SENTENCE

**Regarding dead bodies:**

You need consent for examination, removal, storage and ANY type of use – teaching, research, audit, clinical governance etc

These activities can only take place under the authority of a license:

**16 (2) b** – The making of a post mortem examination

**16 (2) c** – The removal from the body of a deceased person of relevant material of which the body consists or which it contains for a scheduled purpose other than transplantation

**16 (2) e** – The storage of the body of a deceased person or relevant material which has come from a human body for use for a scheduled purpose.

**Scheduled purposes**

**Purposes requiring consent: deceased persons**

1. Clinical audit
2. Education or training related to human health
3. Performance assessment
4. Public health monitoring
5. Quality assurance

**Purposes requiring consent: general**

1. Anatomical examination
2. Determining the cause of death
3. Establishing after a person’s death the efficacy of any drug or other treatment administered to him/her
4. Obtaining scientific or medical information about a living or deceased person that may be relevant to any other person (including a future person)
5. Public display
6. Research in connection with disorders or the functioning of the human body
7. Transplantation

**The coronial autopsy report**

* Demographics
* Clinical history
* External examination
* Internal examination
* Further investigations
* Summary of findings
* Discussion
* **Cause of death**

**Office of National Statistics Format:**

1a. Ischaemic and hypertensive heart disease

1b. Diabetes mellitus

1c. -

2. -

**Summary and where to find more information**

**The Coroners Act (1988):** <http://www.opsi.gov.uk/acts/acts1988/ukpga_19880013_en_1>

**The Coroners' Rules (1984) :** <http://www.kcl.ac.uk/depsta/law/research/coroners/1984rules.html>

**The 2005 amendment rules :** <http://www.opsi.gov.uk/si/si2005/20050420.htm>

**Human Tissue Act (2004):** <http://legislation.gov.uk/ukpga/2004/30/contents>

**Further references**

* The Hospital Autopsy, Burton and Rutty
* GMC Good Medical Practice Guidelines

Thanks to Dr Mears, Dr Burton and Dr Osborn for use of teaching material

EMQ examples – bugs and others

Prof Karim Meeran

**Theme: Bugs**

**OPTION LIST**

|  |  |  |  |
| --- | --- | --- | --- |
| A | E-coli |  |  |
| B | Haemophilus Influenzae |  |  |
| C | Mycoplasma |  |  |
| D | Neisseria |  |  |
| E | Staphylococcus aureus |  |  |
| F | Streptococcus pneumoniae |  |  |
| T | Streptococcus viridans |  |  |

**For each scenario below, choose the most appropriate answer from the list above. Each option may be used once, more than once or not at all.**

1. A 19-year-old man returns from holiday in Spain. Four weeks later, he develops a hot, swollen, painful red knee joint, with an effusion. The knee is tapped, and 20 ml of cloudy yellow fluid is withdrawn. Microbiology reveals Gram-negative intracellular diplococci.

2. A 19-year-old student arrives in casualty, septic, pyrexial and confused with a pyrexia of 39oC. He has a stiff neck, and a lumbar puncture reveals Gram-negative intracellular diplococci.

3. A 6-year-old boy arrives in casualty, septic, pyrexial and confused with a pyrexia of 39oC. He has a stiff neck, and a lumbar puncture reveals gram-negative rods.

4. A 19-year-old student arrives in casualty, septic, pyrexial and confused with a pyrexia of 39oC and blood cultures grew Gram-positive diplococci

5. A 19-year-old student arrives in casualty, septic, pyrexial and confused with a pyrexia of 39oC and blood cultures fail to culture any organisms. Cold agglutinins are positive.

6. A 19-year-old student has a boil on his leg which is 2cm in diameter, and painful. It is drained and some of the pus sent to microbiology. Eventually it grows Gram-positive cocci in clusters.

7. A 19-year-old has a mild fever for several months, and no cause can be found. After 2 months, blood cultures come back positive for Gram-positive cocci.

ANSWERS

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 1. | 2. | 3. | 4. | 5. | 6 | 7 |

**Theme: Acute Renal Failure**

**OPTION LIST**

|  |  |  |  |
| --- | --- | --- | --- |
| A | Acute tubular necrosis |  |  |
| B | Acute glomerulonephritis |  |  |
| C | Acute interstitial nephritis |  |  |
| D | Myeloma associated ARF |  |  |
| E | Renal obstruction |  |  |
| F | Renal artery stenosis |  |  |
| T | Wegner’s granulomatous |  |  |
|  |  |  |  |

**For each scenario below, choose the most appropriate answer from the list above. Each option may be used once, more than once or not at all.**

1. A 65 yr old lady with ischaemic heart disease and peripheral vascular disease presents to casualty with increasing confusion, hiccups and pruritus. She was started on ACE inhibitors a week ago.

2. A 21 yr old man is admitted to hospital with multiple fractures after his motorcycle collided into a lorry on the motorway. There is myoglobin in his urine.

3. A 50 yr old lady with A BMI of 24 who had intermittent pain in the loin, with nausea and vomiting now has a low urine output and urinalysis shows microscopic haematuria.

4. A 45 yr old man with known renal problems has bilateral leg oedema. There is blood in his urine, and urine stix testing also confirms the presence of protein. Microscopy also reveals red cell casts.

5. A 25 yr old man presents to his GP with a cough, nasal discharge and swollen legs. He is extremely dehydrated and is taken to hospital.He has a high cANCA titre

ANSWERS

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 1. | 2. | 3. | 4. | 5. |

Clinical Chemistry Clinicopathological Conference

Prof Karim Meeran, Dr Paul Lewis & Dr Ann Sandison

**Case 1**

Mr. BB was born in 1939. He has never had a day’s illness in his life.

He first presents at the age of 52 with depression for no apparent reason. He has just been promoted at work, and his family seem supportive. However the depression becomes severe enough for him to see his GP about it.

The patient hoped he could see a councillor, but the waiting list for this is several months. His GP offered him “Prozac”, but he would prefer an alternative.

Q1. What alternative drugs are available for the treatment of depression?

A Szegedi, R Kohnen, A Dienel, M Kieser BR. Med. J. March 2005: 330: 503

He did “reasonably well” on this medication, but was unlucky enough to fall on the ice the following winter.

1b. Which of the following commonly causes clinical depression?

A. Hyperkalaemia

B. Hypokalaemia

C. Hypercalcaemia

D. Hypocalcaemia

E. Uraemia

Q2. What does this plain X-ray of the wrist show?

1. Normal
2. Colles fracture
3. Pott’s fracture
4. Osteoporosis
5. Osteomalacia
6. Smiths

Depression worsened. Stable for a few months but then admitted with severe abdominal pain.

Q3.What does this urine dipstick (on the right hand side) show?

[The left hand stick is a normal urine dipstick for comparison.]

1. Ketonuria
2. Glycosuria
3. Haematuria (large)
4. Non haemolysed trace of blood
5. Proteinuria

Q4. Suggest a cause.

1. Diabetic ketoacidosis
2. Glomerulonephritis
3. Acute rheumatic fever
4. Subacute bacterial endocarditis
5. Renal stones

Q5. What test would you like to do now?

1. arterial blood gases
2. renal biopsy
3. plain abdominal X-ray
4. abdominal ultrasound
5. echocardiogram

Q6. What does this investigation show?

1. Glomerulonephritis
2. Renal stones
3. Diabetic ketoacidosis
4. Aortic aneurysm
5. Pott’s disease

Q7. What investigation would you like to do now?

1. Arterial blood gases
2. Fasting glucose
3. Plasma calcium
4. Plasma PTH
5. Plasma vitamin D

Q8. Give three possible diagnoses:

a.

b.

c.

Q9. Which investigation will distinguish these?

1. PTH
2. Vitamin D
3. Whole body bone scan
4. Chest radiograph
5. CT thorax

Q10. Given the result, which is the correct diagnosis?

Q11. What is the urgent management for this patient?

Q12. What else needs to be done?

**Case 2**

Q13. 45-year-old Afrocarribean male presents with dyspnoea. What is the most helpful investigation?

1. Full blood count
2. Urea and electrolytes
3. Chest X-ray
4. ECG
5. echocardiogram

Q14. What does this investigation show?

Q15. The calcium is 2.82. What else do you want to measure, and what would be the expected results?

Q16. What treatment does this patient need?

For more information, see:

<http://www.granuloma.homestead.com/index.html>

The images on this website have been been collected over a period of more than 35 years and reflect a career- long interest in the pathological aspects of granulomatous diseases, particularly sarcoidosis.  These images may be copied and utilized for educational or other non- commercial purposes only.

Q17. What is the mechanism of the hypercalcaemia?

Acid-Base Handling

Dr Jaimini Cegla

##### Learning objectives

Understand how metabolic disturbances may arise and present

Know how respiratory disturbances affect acid-base status

Be able to recognise metabolic and respiratory acid-base disturbances from blood gas data

## METABOLISM - NORMAL HOMEOSTASIS

The end products of metabolism include the production of hydrogen ions (H+) and carbon dioxide (CO2) both of which affect acid-base status. To maintain hydrogen ion homeostasis in the short term the body can minimise changes by buffering. In the longer term the hydrogen ions need to be excreted by the kidneys and carbon dioxide via the lungs.

***BUFFERING***

Hydrogen ions can be buffered temporarily by intracellular and extracellular buffering systems.

The bicarbonate buffer system is the main buffer in the extracellular fluid.

H+ + HCO3- ⇔ H2CO3 ⇔ CO2 + H2O

Haemoglobin is important as an intracellular buffer.

Phosphate and ammonia act as urinary buffers.

## METABOLIC COMPONENT

Diet and metabolism result in the production of 50-100 mmol of H+ daily. This is buffered by the bicarbonate buffer system resulting in a reduction in bicarbonate. To maintain normal homeostasis the kidneys need to excrete hydrogen ions and regenerate bicarbonate.

Disturbances such as an increased production of H+ e.g. in diabetic ketoacidosis or the failure to excrete H+ e.g. as in impaired renal function affect acid base status – these are classified as non-repiratory or metabolic disturbances.

## RESPIRATORY COMPONENT

Diet and metabolism result in the production of 20,000-25,000 mmol of CO2 daily.

In health this is excreted through the lungs.

Any process which affects excretion of CO2  by the lungs affects acid base status – these are classified as respiratory disturbances.

CO2 + H2O ⇔ H2CO3 ⇔ H+ + HCO3-

***COMPENSATION***

Because Hydrogen ion concentration is affected by both metabolism and respiration, when there is a primary metabolic or respiratory acid base disturbance the body can compensate with an opposing acid base change in the other component.

***1. METABOLIC ACIDOSIS***

***Primary disturbance***

Increase in hydrogen ion and decrease in bicarbonate

Metabolic acidosis may be due to:

Increased H+ Production

e.g. Diabetic ketoacidosis

Lactic acidosis

Decreased H+ Excretion

e.g. Renal failure

Loss of Bicarbonate

e.g. Fistula

### *Respiratory Compensation*

In a metabolic acidosis the increase in hydrogen ion concentration rapidly leads to hyperventilation which reduces the hydrogen ion concentration and can partially correct the acidosis.

The blood gas results show a reduction in pCO2, which leads to a partial reduction in hydrogen ion (increase in pH). So hydrogen ion concentration returns towards normal but tends to remain elevated.

***2. RESPIRATORY ACIDOSIS***

***Primary disturbance***

### Retention of carbon dioxide will lead to raised pCO2, hydrogen ion and bicarbonate.

##### This may be due to: Poor Lung Perfusion

##### Impaired Gas Exchange

Decreased Ventilation

***Metabolic Compensation***

In respiratory acidosis increased excretion of hydrogen ion by the kidneys can compensate.

Over a period of days the kidneys will excrete more H+ (and generate bicarbonate) to compensate for the acidosis. This is the usual picture inchronic respiratory failure when renal compensation may be complete.

***3. METABOLIC ALKALOSIS***

***Primary disturbance***

Decrease in hydrogen ion and increase in bicarbonate.

This may be due to excess loss of H+ (e.g. pyloric stenosis)

or gain of bicarbonate (e.g. ingestion of bicarbonate)

Hypokalaemia also leads to renal loss of H+ and bicarbonate generation, producing a metabolic alkalosis with reduced hydrogen ion (high pH) and increased bicarbonate.

### *Respiratory Compensation*

In metabolic alkalosis hypoventilation can produce compensation, but this is usually limited by the increase in CO2 and reduction in O2 which stimulate the respiratory centre.

##### Blood gases will show an increase in pCO2 (which increases the hydrogen ion) and a further increase in bicarbonate.

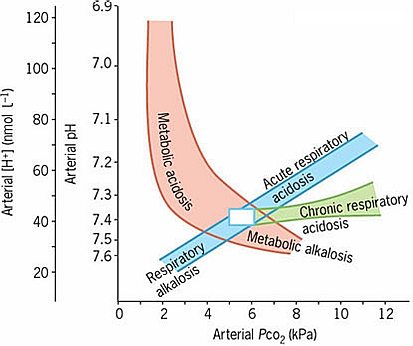
The pO2 also falls, so hypoxia is liable to limit the amount of compensation that can be achieved.

## 4. RESPIRATORY ALKALOSIS

## Primary disturbance

Hyperventilation will lead to reduced pCO2, hydrogen ion and some decrease in bicarbonate.

***ASSESSMENT***



H+/pH tells us whether there is an overt acidosis or alkalosis

pCO2 tells us whether there is a respiratory disturbance (primary or secondary)

pO2 does not directly affect acid-base status but may help in assessing respiratory function.

Bicarbonate is often used to assess the metabolic component; however changes in CO2 do have some effect on bicarbonate. Derived parameters such as base excess may be calculated to help assess the metabolic component.

***Example 1. \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_***

pH 6.9 (7.35-7.45) H+ 126 nmol/l (35-46)

pCO2 3.0 kPa (4.7-6.0)

pO2 24.0 kPa (10.0-13.3)

Bicarbonate 6 mmol/l (22-30)

***Example 2. \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_***

pH 7.55 (7.35-7.45) H+ 28 nmol/l (35-46)

pCO2 8.2 kPa (4.7-6.0)

pO2 10.0 kPa (10.0-13.3)

Bicarbonate 51 mmol/l (22-30)

#### *Example 3. \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_*

pH 7.55 (7.35-7.45) H+ 28 nmol/l (35-46)

pCO2 3.0 kPa (4.7-6.0)

pO2 14.4 kPa (10.0-13.3)

Bicarbonate 20 mmol/l (22-30)

***Example 4. \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_***

pH 7. 41 (7.35-7.45) H+ 39 nmol/l (35-46)

pCO2 10.4 kPa (4.7-6.0)

pO2 7.8 kPa (10.0-13.3)

Bicarbonate 47 mmol/l (22-30)

***Example 5. \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_***

pH 7. 46 (7.35-7.45) H+ 35 nmol/l (35-46)

pCO2 2.0 kPa (4.7-6.0)

pO2 17.8 kPa (10.0-13.3)

Bicarbonate 10 mmol/l (22-30)

***Example 6. \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_***

pH 6.93 (7.35-7.45) H+ 116 nmol/l (35-46)

pCO2 9.7 kPa (4.7-6.0)

pO2 65.8 kPa (10.0-13.3)

Bicarbonate 15 mmol/l (22-30)

Opportunistic Viral Infections

Dr Emilie Sanchez  
(handout courtesy of Dr David Muir

**OPPORTUNISTIC INFECTIONS OVERVIEW**

1. Basic principles
2. Types of conditions
3. Diagnosis
4. Mechanisms and manifestations of disease
5. Viral factors
6. Immunological factors
7. Organisms
8. HIV-patients
9. Antivirals and drug resistance
10. Prevention

**GI** = General Interest

**IMMUNOCOMPROMISED PATIENTS**

1. **Disease:**
2. **Primary immunodeficiency:** e.g. SCID
3. **Malignancy:** eg lymphoma
4. **Viral infections:** HIV/AIDS
5. **Iatrogenic immunosuppression (eg transplantation-related):** Steroids, chemotherapy, radiotherapy

**VIROLOGICAL DIAGNOSIS IN THE IMMUNOCOMPROMISED**

1. **Serology:**
2. Limited diagnostic value as impaired ability to produce an antibody response
3. **Virus detection:**
4. Preferred option
5. Virus isolation (culture), antigen detection, or nucleic acid detection (PCR etc…)
6. **Use of viral load (CMV, EBV, adenovirus):**
7. Guide to clinical significance of infection
8. Monitor response to Rx (e.g. CMV)

**WHAT IS PCR ANYWAY? GI**

1. Polymerase Chain Reaction
2. Method for amplifying specific RNA (RT-PCR) or DNA sequences
3. Cycle:

**1. Denature**

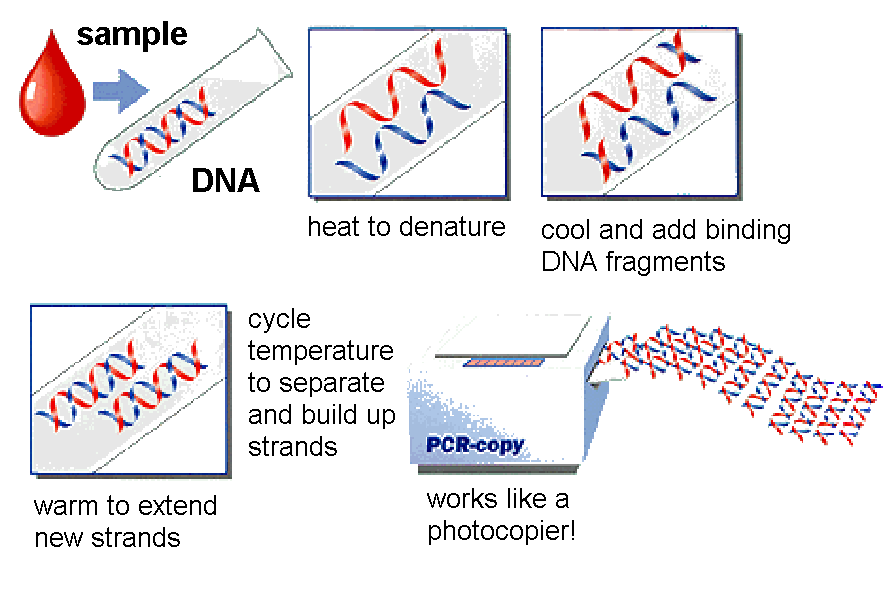
**2. Primer annealing**

**3. Chain elongation**

**dsDNA**

**GI**

**FEATURES OF OPPORTUNISTIC INFECTIONS**



1. Viruses also affect healthy individuals, but give rise to **greater morbidity** in the immunocompromised.
2. Often more **difficult to treat** (as lack of \* concomitant immune response)
3. Increased risk of antiviral **drug resistance**

**FEATURES OF OPPORTUNISTIC INFECTIONS**

1. **Reactivation** of latent endogenous infection

(e.g. herpesvirus family, polyomavirus, hepB, adenovirus)

1. Viruses **acquired from graft** (hepB, hepC, HIV, HTLV, CMV, EBV, adenovirus)
2. **Infection post-Tx**: (measles, parvovirus, VZV)
3. May primarily **involve the grafted organ**

**DISEASE MANIFESTATIONS**

1. Increased **severity** of disease
2. **Wider range** of systems involved.
3. **Multi-system** involvement / disseminated disease
4. **More varied** disease manifestation (eg retinitis, pneumonitis, colitis).
5. **Novel syndromes** (e.g. EBV-associated PTLD, CMV colitis, retinitis, adenoviral hepatitis).

**VIRAL FACTORS**

***Persistent / latent infections:***

1. Herpesviruses: lifelong latent infection (HSV & VZV within neurons, CMV & EBV within leucocytes), kept in check by the immune system\*, sporadic reactivation events may give rise to clinical manifestations (e.g. shingles with VZV)
2. HepB, hepC, HIV & HTLV: chronic carriers, risk of transmission through organ transplantation

**IMMUNOLOGICAL FACTORS**

1. **Humoral** immunity & complement
2. **Cell-mediated** immunity (CMI)
3. **Immunosurveillance**
4. Different patient groups are susceptible to different types of organisms
5. Each organism gives rise to different disease manifestations in different patient groups (eg CMV pneumonitis in BMT vs retinitis in AIDS)

**EBV/PTLD – ILLUSTRATION OF IMMUNOSURVEILLANCE BREAKDOWN**

1. **EBV infection in the normal host:**
2. **Acute**: Infectious mononucleosis
3. **Chronic**: Lifelong low-grade replication in B lymphocytes with polyclonal activation, kept in check by the cellular immune system (immunosurveillance)

**EBV/PTLD – ILLUSTRATION OF IMMUNOSURVEILLANCE BREAKDOWN**

1. **Post-transplant lymphoproliferative disease**
2. Associated with EBV infection
3. Breakdown of immunosurveillance
4. Latently infected B cells – **polyclonal activation**
5. Predispose to **lymphoma**
6. Diagnosis: EBV viral load (> 105 c/ml), biopsy
7. Management:
8. Reduce immunosuppression (regression in < 50%)
9. **Anti-CD20** monoclonal Ab therapy (B cell marker) *(“rituximab”)*

**MAIN OPPORTUNISTIC VIRUSES  
HERPESVIRUS FAMILY**

1. **Herpes simplex virus – HSV:** generalised infection, recurrent genital herpes
2. **Varicella Zoster virus – VZV:** multi-dermatomal zoster, disseminated infection
3. **Cytomegalovirus – CMV:** pneumonitis, retinitis, encephalitis, hepatitis
4. **Epstein Barr virus – EBV:** post-transplant lymphoproliferative disease – PTLD, lymphoma
5. **Human herpes virus 6 – HHV6:** graft failure, hepatitis
6. **Human herpes virus 8 – HHV8:** Kaposi’s sarcoma, Castleman’s disease (body cavity-associated lymphoma)

**HERPES SIMPLEX VIRUS**

1. Present:
2. Cold sores
3. Difficulty swallowing
4. Recurrent genital herpes (HIV+ particularly)
5. Disseminated infection (rare) including pneumonitis and hepatitis
6. Reactivation is common in the first month post-Tx
7. Diagnosis: Mainly clinical. Swab for culture

Blood PCR for disseminated infection

1. Treatment: Aciclovir, valaciclovir, famciclovir
2. Prevention: Aciclovir prophylaxis (started pre-Tx)

**VARICELLA ZOSTER VIRUS GI**

1. Primary infection: **Chickenpox**
2. Spread: **Respiratory** droplets
3. Diagnosis: DIF on **vesicle scraping**
4. Treatment: **Aciclovir** po (healthy adults)
5. Reactivation: **Zoster** (shingles)
6. Spread: **Direct contact**
7. Diagnosis (& treatment) as above

**VARICELLA ZOSTER VIRUS AND THE IMMUNOCOMPROMISED**

1. Increased risk of complications following primary (chickenpox) infection: 2o bacterial infection of rash, **pneumonitis**, encephalitis…
2. **Multidermatomal** or disseminated **zoster**
3. Rx**: iv aciclovir** if develop chickenpox or shingles
4. Prevention: Varicella zoster immunoglobulin (**VZIG**) prophylaxis within 10 days of a significant contact with a case of chickenpox (airborne) or shingles (direct contact).

**CMV AND SOLID ORGAN TRANSPLANTATION**

1. Increased risk of CMV disease with **seropositive** solid organ **donor** and **seronegative recipient**

**CMV AND SOLID ORGAN TRANSPLANTATION**

1. Renal Tx: **CMV prophylaxis:**
2. **Valganciclovir:**
3. Effective
4. Relatively toxic
5. Potential for emergence of resistance
6. **Valaciclovir:**
7. Fairly effective, safe

**(– CMV hyperimmunoglobulin:**

1. Expensive)

**CMV AND SOLID ORGAN TRANSPLANTATION**

1. Lung Tx – CMV:
2. Prophylaxis: iv GCV from day 7 to day 28 post-transplant, then VGCV (po) to day 90.

**CMV AND BONE MARROW TRANSPLANTATION (BMT)**

1. **Adoptive immunity** – risk of disease is greatest with seronegative donor and seropositive recipient (reactivation).
2. Greater risk of disease with mismatched / unrelated donors, as require more immunosuppression
3. High risk period: First 100 days post-Tx
4. Clinical presentation: Pneumonitis, oesophagitis hepatitis, colitis, retinitis, encephalitis, disseminated infection…

**CMV AND BMT**

**Diagnosis:**

1. PCR
2. **EDTA blood** (viral load), biopsy, CSF: High positive predictive value
3. BAL, urine: Less useful as coincidental finding due to asymptomatic shedding.

NB: Serology

1. Useful for pre-Tx screen, **but not for diagnosis** in the immunocompromised

**CMV AND BMT - MANAGEMENT: 3 OPTIONS**

1. Wait until develops disease and then **treat** – poor outcome in BMT
2. **Prophylaxis** (ganciclovir) during high risk period – marrow toxicity, emergence of resistant strains, late-onset CMV disease, increased mortality
3. **Pre-emptive therapy** – monitor CMV viral load in blood during high risk period. Treat (GCV) when rises above threshold (eg 1000 c/ml) – most favourable for BMT. Interval of several days between rise in viral load and disease onset.

**BMT – CMV DISEASE - TREATMENT**

1. Reduce immunosuppression
2. 1st line – **ganciclovir** (marrow toxicity!

🡪 G-CSF)

1. 2nd line – **foscarnet** (nephrotoxic), or…
2. **GCV + foscarnet** combination
3. 3rd line – **cidofovir** (nephrotoxic)
4. Continue Rx until CMV viral load in blood becomes undetectable – then maintenance Rx

**EPSTEIN BARR VIRUS (EBV)**

1. HIV patients:
2. Oral hairy leukoplakia
3. Lymphomas (primary brain lymphoma…)
4. Transplant recipients (mainly solid organ):
5. PTLD

**HUMAN HERPESVIRUS 6**

1. May cause graft rejection
2. In BMT patients, can cause pneumonitis, hepatitis, bone marrow suppression and encephalitis.
3. Diagnosis: PCR on blood
4. Treatment: Ganciclovir, foscarnet or cidofovir

**HUMAN HERPESVIRUS 8**

1. Particular problem in **AIDS patients** (pre-HAART era !)
2. Presentation:
3. **Kaposi’s sarcoma**
4. Body cavity-associated (primary effusion) lymphoma (**BCAL**)
5. **Multicentric Castleman’s disease**

**OTHER MAIN OPPORTUNISTIC VIRUSES**

1. **Adenovirus:** Pneumonitis, hepatitis, haemorrhagic cystitis, generalised infection
2. **BK virus (polyoma):** haemorrhagic cystitis (BMT) ureteric stenosis (renal Tx)
3. **JC virus (polyoma):** progressive multifocal leucoencephalopathy (PML)
4. **Respiratory viruses** (respiratory syncytial virus, parainfluenza virus, influenza virus): pneumonitis
5. **Hepatitis B:** reactivation of latent infection
6. **Measles** virus: pneumonia, encephalitis
7. **Parvovirus:** chronic anaemia

**ADENOVIRUS**

1. Particular problem **post-BMT**
2. Exogenous infection or reactivation of persistent endogenous infection.
3. More common with T cell-depleted grafts
4. Prognosis: **High mortality** with disseminated infection

**ADENOVIRUS - IMMUNOCOMPROMISED HOST**

Haemorrhagic cystitis

Necrotising pneumonitis

Hepatitis

Colitis

**ADENOVIRUS**

1. Diagnosis:
2. Adenovirus **PCR in blood** (weekly surveillance?)
3. Virus detection (eg culture) in two different sites (eg stool and BAL)
4. Management:
5. Reduce immunosuppression
6. **Ribavirin** or **cidofovir** (anecdotal evidence only!)

**HEPATITIS B MARKERS GI**

1. Acute infection :
2. Surface Ag +
3. **Core IgM +**
4. “e” Ag & HBV DNA +
5. Chronic infection / carrier status :
6. **Surface Ag +**
7. Core Ab + (IgM -)
8. “e” Ag/Ab +/- & HBV DNA +
9. Past infection (naturally immune) :
10. **Core Ab +**
11. Surface Ab +/-
12. “e” Ab +/-
13. (surface Ag, “e” Ag & BDNA -)

**HEPATITIS B MARKERS GI**

1. **Immunized :**
2. Surface Ab**+**
3. Core Ab**–**
4. **Surface antibody titres :**
5. < 10mIU/ml : **Non-responder** - ? cAb**+**
6. 10–100mIU/ml : Weak responder (boost)
7. > 100mIU/ml : **Protective** level

**HEPATITIS B IN THE IMMUNOCOMPROMISED**

1. Risk of reactivation in the immunocompromised.
2. sAg-/cAb+ can revert to sAg+

**LIVER TRANSPLANTATION – RECURRENCE OF HEPB**

1. Occurs in >80% patients
2. Prevent:
3. Immunoglobulin (**HBIG**): maintain serum levels at >100 mIU/ml (monthly administration)
4. **Lamivudine** (3TC) pre-transplant

**RESPIRATORY TRACT INFECTION IN POST-TRANSPLANT PATIENTS GI**

1. Diagnosis:
2. Specimens: **NPA** (paeds), **BAL**, throat swab
3. Investigations:
4. **DIF** for RSV, flu, paraflu, adenovirus, CMV, HSV
5. Cell culture (**virus isolation**)
6. **PCR**

**BMT - RESPIRATORY VIRUSES**

1. Increased risk of complications (**pneumonitis**) and high mortality associated with influenza, parainfluenza and RSV infection.
2. Treatment:
3. **Oseltamivir** for influenza
4. **Ribavirin** (aerosolised +/- iv) for RSV & parainfluenza (before progression to LRTI!)
5. Prevention:
6. Life-long seasonal **influenza vaccination** of recipient
7. Influenza vaccination for close contacts (e.g. family members and HCWs) prior to flu season.
8. **Oseltamivir prophylaxis** if significant contact with case of influenza.

**MEASLES**

1. **Fatal** disease in the immunocompromised (often in the absence of the typical rash)
2. Giant cell **pneumonia**
3. Subacute measles **encephalitis**
4. Immediate administration of **HNIG** (immunoglobulin) indicated in all immunocompromised measles contacts regardless of immune status!

**PARVOVIRUS**

1. Cause of **chronic anaemia** in the immunocompromised
2. Diagnosis:
3. Serology (IgM) not useful in the immunocompromised
4. **PCR on blood**
5. Treatment: **HNIG**. May require blood transfusion

**HIV PATIENTS**

1. Risk of developing specific opportunistic infections can be predicted from **CD4 count**.
2. E.g. CMV retinitis when CD4 <100 /ul.
3. Antiretroviral therapy initiated when CD4 count dips into 200-350 /ul range.

**HIV PATIENTS - VIRAL OPPORTUNISTIC INFECTIONS**

1. Retinitis (CMV, HSV, VZV)
2. Oral hairy leucoplakia (EBV)
3. Kaposi’s sarcoma (HHV8)
4. EBV-associated lymphomas
5. Recurrent/chronic genital HSV
6. Multidermatomal zoster
7. Molluscum contagiosum (poxvirus)
8. CMV or HSV oesophagitis
9. PML (JC virus)

**GANCICLOVIR (GCV) AND VALGANCICLOVIR (VGCV) GI**

1. Nucleoside analogues
2. First line treatment for CMV.
3. Also used for EBV and HHV-6 infections.
4. VGCV (po) is the prodrug of GCV (iv).
5. Toxicity: **Myelosuppression**!

**FOSCARNET GI**

1. Indications:
2. GCV-resistant CMV
3. Early BMT pre-emptive Rx

(1st 35 days post Tx)

1. **Nephrotoxic**

**CIDOFOVIR GI**

1. Indications: CMV (2nd line), adenovirus, PML
2. Very long intracellular half life
3. Dose:
4. Induction: 5mg/kg once a week X 2
5. Maintenance: 5mg/kg fortnightly
6. **Nephrotoxic**
7. **Infuse** over 1 hour
8. Maintain good **hydration** (saline infusion)
9. Co-administer **probenicid** (competes for uptake at the proximal renal tubules)

**IMMUNOTHERAPY**

1. **Donor lymphocyte infusion** / adoptive transfer of virus-specific cytotoxic T lymphocytes
2. Experimental
3. Considered for CMV, EBV and adenovirus infections in BMT recipients not responding to conventional antiviral therapy

**ANTIVIRAL DRUG RESISTANCE**

1. Emergence of drug resistance can occur as a result of prophylaxis
2. Inadequate dose allows low level viral replication in the presence of drug (partial suppression) 🡪 selection of mutant strains
3. e.g. ACV-resistant HSV, GCV-R CMV

**QUASISPECIES**

|  |  |  |
| --- | --- | --- |
|  | ► | ▼ |
|  |  |  |

**SELECTION PRESSURES**

- New host species

- Immune response

- Herd immunity

- Antivirals

**PREVENTION OF TX-ASSOCIATED INFECTIONS - PRE-TX SEROLOGY SCREEN**

**Donor**

1. HIV
2. HepB (sAg

+ cAb for liver Tx)

1. HepC
2. CMV
3. EBV
4. HTLV

**Recipient**

1. HIV
2. HepB sAg
3. HepC
4. CMV
5. HSV
6. VZV
7. EBV

**PREVENTION - INFECTION CONTROL**

1. **Nosocomial infections** (hospital-acquired) – common for adenovirus, respiratory viruses and VZV
2. Infection control measures:
3. Handwashing, protective clothing, limit visitors
4. **Isolate** immunocompromised patients (BMT)
5. **Positive pressure** cubicles
6. **Cohort nursing**
7. CMV antibody-negative blood (also filtered)

**PREVENTION OF TX-ASSOCIATED INFECTIONS   
VACCINATION IN TRANSPLANT RECIPIENTS**

1. Pre-Tx:
2. **Hep A** (for liver Tx)
3. **Hep B** (considered for all solid organ Tx)
4. **MMR** (unless immunocompromised, e.g. lymphoma!)
5. **VZV**
6. Post-Tx:

**Influenza** (yearly vaccination in October)

Haemolytic Anaemias

Dr Mark Layton

The normal life span of a red cell is 120 days. Haemolysis is defined by an increased rate of red cell destruction with reduction in red cell life span. Destruction of red cells may occur in the circulation, “intravascular haemolysis”, or there may be increased removal/destruction of red cells by the reticuloendothelial (RE) system, “extravascular haemolysis”.

Haemolysis may or may not be associated with anaemia. In the first instance the body attempts to compensate for the increased breakdown. The following may occur:

a) the rate of red cell production can increase

b) the bone marrow can expand

c) younger red cells (reticulocytes) are seen in the peripheral blood in increasing numbers

Patients with haemolysis are at particular risk of two complications. The first is of an associated folate deficiency due to the high turnover of red blood cells; this may lead to an acute exacerbation of anaemia as a result of megaloblastic erythropoiesis. The second is the risk of profound anaemia (an aplastic crisis) in association with parvovirus B19 infection. Parvovirus infects erythroblasts and temporarily halts red cell production. In normal individuals with a red cell life span of 120 days this has a negligible effect on the haemoglobin level. In situations where the red cell life span is shortened, however, halting red cell production, even transiently, leads to a fall in haemoglobin level.

**Causes of haemolysis**

There are several causes of haemolysis. These are usually classified in one of two ways.

1. Inherited versus acquired causes
2. Causes associated with predominantly intravascular versus extravascular haemolysis

Inherited and acquired causes of haemolysis are indicated on the diagram overpage.

CAUSES OF HAEMOLYTIC ANAEMIA

**INHERITED ACQUIRED**

Abnormal red cell membrane, Damage to red cell membrane,

e.g. hereditary spherocytosis e.g. by antibodies

(autoimmune haemolytic

anaemia) or toxins (snake bite)

Abnormal haemoglobin, Damage to whole red cell, e.g.

e.g. sickle cell in microangiopathic

anaemia haemolytic anaemia

Oxidant exposure –damage to

Defects in enzymes of haemoglobin and red cell

glycolytic pathways, membrane e.g. drugs such as

e.g. pyruvate kinase primaquine (an anti-malarial)

deficiency

Defects in enyzmes of

pentose shunt, e.g. Precipitation of episodic

glucose-6-phosphate haemolysis in individuals with

dehydrogenase (G6PD) deficiency an underlying enzyme deficiency

(*Courtesy Prof. Barbara Bain*)

**Causes of intravascular haemolysis are as follows:**

Plasmodium falciparum malaria (“Blackwater fever”)

ABO mismatched blood transfusion

Cold antibody haemolytic syndromes

Drug induced haemolytic anaemias

Microangiopathic haemolytic anaemias e.g. chronic disseminated

intravascular coagulation (DIC), haemolytic uraemic syndrome

Glucose-6-phosphate-dehydrogenase (G6PD) deficiency

Paroxysmal nocturnal haemoglobinuria

***Features of haemolysis***

1. **Clinical:** pallor, jaundice, splenomegaly (extravascular haemolysis), increased incidence of pigment gall stones.
2. **Laboratory:**

Haematology:

Polychromasia seen on blood film reflecting reticulocytosis

Reticulocyte count is high

Anaemia may be present

Biochemistry: red cell breakdown produces

Increased serum bilirubin

Increased urinary urobilinogen

Increased faecal stercobilinogen

Increased serum LDH

**If** **intravascular haemolysis** occurs, haemoglobin is released into the circulation and binds to plasma haptoglobins. The complex which forms is removed by reticuloendothelial (RE) cells. When plasma haemoglobin is present in excess of that

which can be bound by haptoglobin free haemoglobin enters the urine and is absorbed by renal tubular cells. Under these circumstances there are the following laboratory findings:

Haemoglobinaemia

Haemoglobinuria

Haptoglobins are low or absent

Haemosiderinuria

**INTRAVASCULAR HAEMOLYSIS**

**Anaemia**

**Red cell destroyed in circulation**

**Haemoglobin in plasma**

**Haemoglobin released from red cells**

**When all haptoglobin is saturated, free haemoglobin is filtered by the kidney**

**Haemoglobin binds to haptoglobin and the complex is cleared by liver**

**Haemoglobin and, later, haemosiderin in the urine**

**Low serum haptoglobin**

**EXTRAVASCULAR HAEMOLYSIS**

**Red cells phagocytosed by macrophages and destroyed**

Stimulation of bone marrow, **polychromasia** and **reticulocytosis**

**Anaemia**

**Red cell destruction leads to increased serum bilirubin and LDH and faecal and urinary bile pigments**

(Courtesy Prof Barbara Bain).

There are a wide variety of conditions associated with haemolysis. Hereditary spherocytosis and G6PD deficiency will now be discussed in more detail;

sickle cell disease and the thalassaemias are discussed in detail elsewhere.

***Hereditary spherocytosis***

This is an autosomal dominant condition characterised by spherocytic red blood cells on the blood film and splenomegaly. It is caused by genetic defects leading to abnormalities in the proteins which link the spectrin skeleton on the internal surface of the red cell membrane to the external phospholipid bilayer. As a result of this, membrane is progressively lost in the spleen as the red cells circulate and they become spherocytic.

**Clinical and laboratory features:**

In 75% cases there is a family history

Jaundice

Anaemia

General clinical and laboratory features of haemolysis (see above)

**Laboratory diagnosis:**

Spherocytes are more sensitive to osmotic lysis than normal red cells and this may be identified by the osmotic fragility test.

**Management:** Folate supplementation

Splenectomy corrects the anaemia but is associated with risk of infection with capsulated bacteria e.g. pneumococcus

***Glucose–6-phosphate dehydrogenase (G6PD) deficiency***

This enzyme is encoded on an X chromosome locus. Its normal function is to convert glucose-6-phosphate to 6-phosphogluconate the rate limiting step in the pentose phosphate pathway (PPP). In so doing, NADPH is generated which is required to maintain the level of glutathione to protect cells against oxidative stress.

In most cases of G6PD deficiency under normal circumstances there is sufficient residual activity to prevent haemolysis. However, NADPH generated will be insufficient to protect a cell from additional oxidative stress and haemolysis will occur. Three major types of trigger have been identified: fava beans (broad beans), infections and drugs. The following drugs should be avoided in patients with G6PD deficiency:

Antimalarials (primaquine, pamaquin)

Antibacterial agents (sulphonamides, ciprofloxacin and related

drugs)

Miscellaneous (dapsone, probenecid).

The above is not a comprehensive list, but gives some idea of the variety of drugs which have been implicated

**Clinical features:**

Deficiency is common around the Mediterranean, in areas of SE Asia and the Middle East and in those with African ancestry. In some parts of the world it affects up to 40% of the population.

Typically patients have episodes of acute haemolysis triggered by drugs, infection or fava beans. The severity of the haemolysis may vary from mild anaemia to life threatening anaemia requiring urgent transfusion. Between crises, the blood count is normal. Occasionally patients have a variant of the enzyme which leads to chronic intravascular haemolysis, but this is rare

**Management.**

Infection should be treated, and any relevant drugs stopped. A high urine output should be maintained and transfusion given if necessary.

**Theme: Haemolytic anaemia**

**OPTION LIST**

|  |  |  |  |
| --- | --- | --- | --- |
| A | α-thalassaemia | 3 | Malaria |
| B | Sickle cell disease | 4 | β-thalassaemia major |
| C | Autoimmune haemolytic anaemia | 5 | G6PD Deficiency |
| D | Hereditary elliptocytosis | 6 |  |
| E | β-thalassaemia intermedia | 7 |  |
| F | Paroxysmal nocturnal haemoglobinuria | 8 |  |
| 1 | Pyruvate kinase deficiency | 9 |  |
| 2 | Hereditary spherocytosis | 0 |  |

**For each scenario below, choose the most appropriate answer from the list above. Each option may be used once, more than once or not at all.**

1. A 25 year old man presents with jaundice. Physical examination reveals a palpable spleen. On investigation his red cells are found to exhibit increased lysis in hypotonic saline compared to a normal control.

2. Duniya presents aged 6 months old with a chest infection. Her mother reports this is her sixth infection since birth and that she seems to be smaller than other babies of the same age. On examination she is pale and icteric with protruding maxillae and frontal bones. Blood tests reveal a severe anaemia.

3. Substitution of the amino acid valine for glutamic acid at position 6 of the β chain of haemoglobin.

4. Coca-cola coloured urine after ingestion of fava beans.

5. A 45 year old woman visits her GP complaining of tiredness and yellow eyes. Investigation reveals anaemia and hyperbilirubinaemia (predominantly unconjugated).  
The direct antiglobulin (Coomb’s) test is positive. Spherocytes are seen on the blood film.

ANSWERS

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 1. | 2. | 3. | 4. | 5. |

Pancreatic Pathology

Dr James Carton

**Learning objectives**

* *In depth knowledge***:** diabetes, acute pancreatitis & pancreatic cancer.
* *Good knowledge***:** chronic pancreatitis & pancreatic endocrine neoplasms.
* *Passing knowledge***:** pancreatic malformations & pancreatic cystic tumours

**Pancreatic histology**

* Exocrine component composed of a branching ductal system lined by glandular epithelium terminating in pancreatic acini which produce digestive enzymes.
* Endocrine component composed of collections of endocrine cells (islets) which secrete insulin and glucagon to control blood glucose levels.

**Diabetes mellitus**

* A metabolic disorder characterised by chronic hyperglycaemia due to lack of insulin.
* Very common, affecting some 2% of people, and rising in incidence.
* Type 1 diabetes due to autoimmune destruction of insulin-producing beta cells.
* Type 2 diabetes strongly associated with obesity and insulin resistance.
* Insulin lack → mobilisation of energy stores in muscle, fat and liver → hyperglycaemia.
* Presents with polyuria (osmotic diuresis) and polydipsia (thirst centre stimulated).
* Type 1 diabetics may present in diabetic ketoacidosis.
* Fasting plasma glucose > 7 mmol/L or random plasma glucose > 11.1 mmol/L.
* Long term hyperglycaemia damages capillaries and accelerates atherosclerosis.
* **Important long term complications include: ischaemic heart disease, chronic kidney disease, blindness, peripheral vascular disease, foot ulceration.**

**Pancreatic malformations**

* Ectopic pancreas = pancreatic tissue located outside the pancreas. Most common sites duodenum, jejunum, ileum & Meckel’s diverticulum. Most are incidental findings.
* Pancreas divisum = failure of fusion of dorsal and ventral pancreatic buds. Duct of Santorini becomes dominant duct draining into the duodenum via the smaller minor papilla. Most cases asymptomatic and picked up incidentally on imaging. Some cases present in adulthood with pancreatitis.
* Annular pancreas = fusion of dorsal and ventral pancreatic buds around the duodenum. Presents about 1 year with vomiting & abdominal distension after meals.

**Acute pancreatitis**

* Acute inflammation of the pancreas and peripancreatic tissue.
* Gallstones and alcohol most common causes. Many cases are idiopathic.
* Injury to the pancreas releases activated enzymes which digest the pancreatic tissue.
* Presents with severe upper abdominal pain radiating to the back with nausea & vomiting.
* Macroscopically the pancreas is swollen & soft with flecks of peripancreatic fat necrosis.
* Histology shows acute inflammation and necrosis of the pancreas.
* **Severe cases can be life threatening requiring organ support on intensive care.**

Chronic pancreatitis

* A chronic inflammatory process of the pancreas leading to irreversible loss of function.
* Most cases are due to alcohol. A small proportion are now thought to be autoimmune.
* Presents with persistent upper abdominal pain and weight loss. Steatorrhoea and diabetes mellitus occur late.
* The pancreas becomes replaced by firm scar tissue with dilated ducts and calcification.
* Histology shows chronic inflammation, loss of exocrine tissue, and marked fibrosis.
* **Can closely mimic pancreatic cancer clinically, radiologically, and pathologically.**

**Pancreatic carcinoma**

* A malignant epithelial neoplasm arising in the pancreas.
* Usually presents in people aged over 60. More common in men.
* Smoking is the only recognised risk factor.
* Activation of KRAS and loss of function of TP53, P16 & DPC4 are common genetic alterations.
* Presents with persistent abdominal pain & weight loss.
* Tumours in the head of the pancreas may cause obstructive jaundice.
* Sudden onset of diabetes mellitus should always raise suspicion of pancreatic cancer.
* Macroscopically, there is a firm tumour mass in the pancreas. Most occur in the pancreatic head.
* Histologically most are well to moderately differentiated adenocarcinomas composed of infiltrating atypical epithelial cells forming glandular spaces set in a dense fibrotic stroma.
* Perineural invasion very common & may account for high rates of peripancreatic spread.
* **Prognosis very poor, with 5 year survival rates <5%.**

**Pancreatic endocrine neoplasms**

* A group of epithelial pancreatic neoplasms showing endocrine differentiation.
* About 15% associated with MEN-1.
* Functioning tumours present with features related to excess hormone production.
* Non-functioning tumours present incidentally on imaging or with symptoms related to local disease or metastasis.
* Macroscopically they are circumscribed pancreatic tumours measuring 1-5 cm in size.
* Histologically the neoplastic cells are arranged in nests or trabeculae. The cells have granular cytoplasm and finely granular chromatin.
* The endocrine phenotype can be demonstrated immunohistochemically by reactivity with CD56, chromogranin, and synaptophysin.
* **Behaviour is difficult to predict but all should be considered potentially malignant**.

**Pancreatic cystic neoplasms**

* Intraductal papillary mucinous neoplasm – a grossly visible mucin-producing tumour that grows in the pancreatic ductal system. Most arise in the head of the pancreas in men.
* Mucinous cystic neoplasms – a range of lesions, most of which are benign. Almost all occur in women. They are well circumscribed cystic tumours containing mucoid material. The cysts do not communicate with the pancreatic ductal system.
* Serous cystic neoplasms – a range of lesions, most of which are benign. Almost all occur in women. Most common type is the serous microcystic adenoma which is a well circumscribed pancreatic tumour containing many small cysts and a central scar.
* Solid pseudopapillary neoplasm – a peculiar pancreatic tumour which almost always arises in young women. Grossly appears as a pancreatic mass with cystic change and haemorrhage. Generally considered to behave as a low-grade malignancy.

Upper Gastrointestinal Disease

Dr Marjorie Walker

**Objectives:**

To understand the normal constituents of the upper gastrointestinal tract and how these may be affected as a result of inflammation, metabolic disturbance or neoplasia (specifically: oesophagitis, Barrett’s oesophagus and GORD, carcinoma of the oesophagus, varices, peptic ulcer, gastric cancer, lymphoma and to understand causes of malabsorption).

**OESOPHAGUS**

NORMAL

distal oesophagus

1.5-2cm situated below diaphragm, lined by columnar mucosa of gastric cardia-type

lower oesophageal sphinctre (LOS)

2-4cm segment just proximal to OGJ

oesophago-gastric junction (OGJ)

point where tubular oesophagus joins saccular stomach

squamo-columnar junction / Z-line

irregular serrated margin, usually at +/- 40cm (from incisors)

does not always coincide with OGJ’ may lie anywhere within distal 2cm

proximal extension of GOJ

hiatus hernia

Barrett’s oesophagus (BO)

**REFLUX OESOPHAGITIS/GORD**

Gastro-oesophageal reflux disease

commonest cause of oesophagitis - reflux of acidic gastric contents

pathogenesis

decreased LOS pressure

hiatus hernia

squamous lining – inflamed

exposure to refluxed acid (+ bile)

cell injury

accelerated desquamation

increased basal cell proliferation

**BARRETT’S OESOPHAGUS**

Re-epithelialization by metaplastic columnar epithelium with goblet cells  
Barrett’s / columnar lined oesophagus (CLO)   
Goblet cell / intestinal metaplasia

Histological diagnosis

classical 3cm or more of circumferential columnar metaplasia with goblet cells in distal oesophagus

SSB < 3cm columnar metaplasia with goblet cells in lower oesophagus

metaplastic glandular epithelium

dysplasia

adenocarcinoma

surveillance

- repeated endoscopy & biopsy to detect early neoplastic changes

Dysplasia

Malignant Epithelial Tumours

Squamous cell carcinoma

20% - upper 1/3

50% - middle 1/3

30% - lower 1/3

Adenocarcinoma

lower 1/3

Spread of cancer - metastases

**STOMACH**

Normal

Cardia

Body

Antrum

Pylorus

“Gastritis”

Acute gastritis

Infection

Chemicals

Chronic gastritis

Helicobacter pylori associated gastritis

biopsy antrum and body, pattern determines risk of ulcer and outcome

Chemical (reactive) gastritis

NSAIDs, Bile

Other gastritis Crohn’s

lymphocytic

heilmannii

(eosinophilic collagenous)

Autoimmune gastritis

< 10% cases

Antibodies to IF and gastric parietal cells

2-4% risk of developing carcinoma in the long term

Gastritis - ulcers

MALT – H pylori

B cell Lymphoma – 4% all tumours

**PEPTIC ULCER DISEASE**

Ulcer - breach in mucosa which extends through muscularis mucosa into submucosa or deeper.

usually chronic

solitary

<4cm diameter (size does not differentiate benign and malignant)

**SITES**

-duodenum 1st part, anterior wall

-stomach antrum, lesser curve

-G-O junction (reflux associated)

-within margins of gastrojejunostomy

-within or adjacent to Meckel’s diverticulum

-duodenum,stomach or jejunum in patients with - Zollinger Ellison syndrome

**EPIDEMIOLOGY**

Common - usually

middle age or older

M:F 3:1(duodenal) 1.5/2 :1(gastric)

**PATHOGENESIS**

gastric acid/pepsin pre-requisite

H.pylori - present in almost all patients with DU and in 70% with GU but only 10%-20% infected people develop DU

alcohol

smoking

NSAIDS

genetic/psychosocial factors

**GASTRIC ULCER**

macro - round to oval punched out lesion with rolled margins

micro - varies, active necrosis to healing and scarring

zonation from surface - necrosis - inflammation - granulation tissue

**COMPLICATIONS**

bleeding 15-20% patients 25% ulcer deaths

perforation 5% patients 60% ulcer deaths

obstruction 2%

malignant transformation unknown with DU and ++ rare in GU

pyloric stenosis

**Gastric Carcinoma sequence**

Consequence of gastric inflammation, not gastric ulcer

Atrophy and intestinal metaplasia

Dysplasia (low and high grade)

Adenocarcinoma - classification

(Lymphoma)

Duodenum

Ulcer

Endoscopy “itis”: 73.5% progressed to ulcer, mainly erosive duodenitis (biopsy - neutrophils)

The principal cause of duodenitis and duodenal ulcer is acid in the presence of gastric metaplasia

**Malabsorption**

suboptimal absorption of fats, fat-soluble and other vitamins, proteins, carbohydrates, electrolytes, minerals and water.

result of disturbed

-intraluminal digestion

-terminal digestion

-transepithelial transport

**Infection**

Acute infectious enteritis

Parasitic infestation

Tropical sprue

Whipple’s disease (Tropheryma whippelii)

**Gluten-sensitive enteropathy (Coeliac disease/sprue)**

prototype of noninfectious cause of malabsorption

sensitivity to gluten in cereals - wheat, oat, barley and rye

damages surface enterocytes

reduces absorptive capacity

reduction in small intestinal absorptive surface area

**Incidence**

1 in 2000 individuals in the UK

1 in 300 in West Ireland

rare in Asians

**Aetiology**

sensitivity to gluten

gliadin - water-insoluble protein component

toxic component shared by wheat, oat , barley and rye

**Pathogenesis**

Immune-mediated injury(cell-mediated immunity)

increased intraepithelial cytotoxic T cells

large numbers of lamina propria T helper cells sensitized to gliadin

cytokine release by T cells

damages the surface enterocytes

**Genetic susceptibility**

familial clustering

90-95% of patients express HLA-DQw2 histocompatibility antigen

80% express HLA-B8

associated with dermatitis herpetiformis

**Viral infection**

may trigger sensitivity to gliadin

gliadin cross-reactivity to type 12 adenovirus

Partial villous atrophy, Endoscopy - scalloping with a smooth shiny mucosa /normal , subtle early changes difficult on biopsy, Normal wide variation in villus height, Villus height: crypt depth ratio is 3:5, Surface enterocyte height 29-34um. Crypt hyperplasia

Intraepithelial lymphocytes

normal range 0-30/100 enterocytes

severity decreases from proximal to distal intestine

reverts to near normal upon withdrawal of dietary gluten

**Treatment**

Gluten-free diet

**Complications**

10-15% risk of gastrointestinal lymphoma

usually T-cell lymphoma

presents with haemorrhage, perforation, small bowel obstruction or systemic symptoms

higher incidence of other GIT cancers

ulceration of small intestine/chronic ulcerative enteritis

**FURTHER READING:**

CLINICAL REVIEWS IN BMJ from August 2001: ABC of the upper gastrointestinal tract

Skin Pathology

Dr Marjorie Walker

***OBJECTIVES***

* To understand pathology of common skin disease: dermatitis/ eczema, psoriasis, lichen planus
* To understand the basic pathology of bullous skin disease
* To know the differences between cutaneous squamous carcinoma, basal cell carcinoma and malignant melanoma
* To be able to define prognostic indicators of malignant melanoma

***SKIN PATHOLOGY***

The skin is the first line of defence against the environment and subject to external and internal injury and is an organ in its own right

**Structure**

Epidermis - squamous epithelium

- basal layer, maturation to granular layer and keratin

- melanocytes in basal layer produce melanin - donated to squamous basal cells

Dermis - connective tissue contains appendages - hair, sweat glands and blood vessels

Subcutaneous tissue - fat

***Eczema/ Dermatitis***

Clinical:

Erythema, Papules, Vesicles, Excoriation, Secondary infection

Contact dermatitis

Atopic dermatitis

Seborrhoeic dermatitis

Non specific dermatitis

All have same pathology:

spongiosis of epidermis, perivascular chronic inflammatory infiltrate in dermis.

chronic - acanthosis (epidermal thickening)

***Lichen Planus***

eruption of purple flat topped papules with mother of pearl sheen. Aetiology obscure.

characteristic pathology

hyperkeratosis with saw toothing of rete ridges and basal cell degeneration with a lichenoid chronic inflammatory infiltrate (band like)

***Psoriasis***

2% population affected in UK

Extensor aspects of limbs, nails, scalp, genitalia

Several forms

Psoriasis vulgaris - macules and papules covered with silvery scales, pinpoint bleeding

Arthritis

Pathology

Parakeratosis - scaling

loss of granular layer, clubbing of rete ridges, Munro's microabscesses

***Pityriasis rosea***

Salmon pink scaly eruption trunk, herald patch

?viral associated

non specific dermatitis pathology

Bullous disease

Vesicles - 0.5cm, Bullae - >0.5cm Site: subepidermal, intraepidermal, subcorneal

***Dermatitis Herpetiformis***

Itchy blistering eruption on buttocks, elbows

Association with gluten sensitivity and partial villous atrophy

Sub epidermal bulla - papillary microabscesses, neutrophils

***Pemphigoid***

Elderly, large tense bullae on flexor aspects of forearms, groin, axillae

Sub epidermal bulla with eosinophils

IgG binds to basement membrane

***Pemphigus***

Elderly, large bulla, mucous membranes

Intra epidermal bulla with acantholysis

IgG antibodies bind to desmosomes

***Erythema multiforme***

Pleomorphic skin eruption

macules, papules, urticarial weals, vesicles, bullae, petechiae

Sub epidermal bulla

Severest form Stevens Johnson syndrome

Food, drugs, infections

Epidermal and vascular sensitivity to antigens

***Lupus erythematosus***

Middle aged females

Chronic discoid LE - skin

Butterfly rash

Alopecia

Systemic LE - skin and internal involvement

***Tumours of skin***

Squamous tumours

Solar (actinic, senile) keratosis

irregular warty lesions in sun exposed areas

actinic skin damage

squamous carcinoma grade “half”

***Bowen's disease***

Carcinoma in situ

***Squamous carcinoma***

Predisposing conditions - solar keratosis, Bowen's, arsenical keratosis -may metastasise.

***Keratoacanthoma***

Rapidly growing dome shaped lesion, looks malignant but is benign

***Basal cell tumours***

Basal cell papilloma - Seborrhoeic wart. Elderly, common

***Basal cell carcinoma***

Rodent ulcer local destruction, metastasise very rarely

***Melanocytic tumours***

Lentigines (freckles)

Increased pigment only in basal layer

***Naevi***

Moles are common. Proliferation of melanocytes in basal layer, mature and nest into the dermis, hence junctional, compound and intradermal naevi. 5% of malignant melanomas arise in naevi.

***Malignant melanoma***

Classification:

Lentigo maligna - melanoma

Superficial spreading malignant melanoma

Nodular malignant melanoma

Acral Lentiginous melanoma

Lentigo maligna -Sun exposed areas of elderly caucasians

Flat, slowly growing black lesion

Proliferation of atypical melanocytes along basal layer with occasional nests. Proliferation down in hair follicle. MM can develop in LM, usually spindle celled, low aggression.

SSMM - Irregular borders, variation in colour. No special site

NM - All sites, younger age group.

ALM - Palms, soles, subungual areas.

***Stage and Tumour thickness***

Tumour thickness - BRESLOW

From top of granular layer with micrometer

98% 5 ysr <0.76mm

44-63% 5 ysr >1.5mm

**Clark's levels**

***Skin appendage tumours***

Hair follicle, sweat glands can produce specialised tumours of skin

***Vascular tumours***

Capillary haemangioma - strawberry mark

Flat haemangioma - Port wine stain

Kaposi's sarcoma

***Lymphoma***

Mycosis fungoides

***Infections***

Impetigo

Viral - warts, molluscum contagiosum

Fungi

TB

***Vasculitis***

Drugs. Aspirin, NSAIDs, penicillin

Infection, Hep B, Streptococcus.

Blood disorder, essential mixed cryoglobulinaemia.

Neoplastic, e.g. multiple myeloma, lymphoma.

***Sarcoid*** – Granulomatous disease

Non-Neoplastic Bone and Joint Infections

Dr Ann Sandison

***Fractures & Fracture Healing***

Fractures are classified according type and severity (simple;closed; comminuted; compound). Fracture repair should be considered in stages (organisation of the haematoma adverb fracture site; formation of fibro contrariety this callous; mineralisation of callous; remodelling). The factors influencing fracture healing include diffracted type, presence of infection or pre-existing systemic condition (neoplasm, metabolic disease, vitamin deficiency or drug therapy)

***Osteomyelitis***

Affected sites differ between adults (vertebra, jaw and toes) and children (long bones). Causative organisms also differ (adults mainly Staph. aureus; children Haemophilus influenzae and group B. strep).

Presenting symptoms non-specific. X-ray changes are delayed (usually after 10 days or so). Subperiosteal new bone formation called involucrum and later necrotic cortex may become detached (sequestrum).

Rare causes of osteomyelitis include TB (usually immunocompromised patients; can cause amyloidosis); and syphilis (congenital or acquired).

**JOINT DISEASE**

***Degenerative joint disease.***

*Osteoarthritis -* 1° - age related. 2° - any age, related to previously damaged or congenitally abnormal joint.

Main sites vertebrae, hips, knees +/- DIPJ, PIPJ, +/- carpometacarpal and metatarsophalangeal joints.

Aetiology uncertain. ? biomechanical factors, ? biochemical factors (inflammation).

Results in cartilage degeneration, fissuring, abnormal matrix calcification, and osteophytes.

**Inflammatory joint disease**

*Rheumatoid arthritis -* severe chronic relapsing synovitis.

Unpredictable course. Incidence 1% world population. 3F: 1M age of onset 30-40y.

Genetic predisposition. Increased incidence amongst first degree relatives.

Associated with HLA DR4. Sites- symmetrical, small joints, hands and feet (sparing distal IPJ), wrists elbows ankles and knees.

Aetiology - most likely autoimmune 80% patients rheumatoid factor (RF) positive. RF mostly IgM. RF forms immunocomplexes with IgG. These circulating immune complexes may underlie associated extra-articular disease.

Clinical - mild anaemia raised ESR, 80% rheumatoid factor positive. +/- rheumatoid nodules (25%). Can be multisystem disease. Characteristic deformities include radial deviation of wrist, ulnar deviation of fingers ‘swan neck’ and boutonniere deformities of fingers.

Histology - proliferative synovitis with thickening of synovial membrane. Hyperplasia of surface synoviocytes. Intense inflammatory cell infiltrate +/- lymphoid follicles in sub-surface layer. Fibrin deposition and necrosis. Pannus is the exhuberant inflamed synovium covering the articular surface.

***Infectious arthritis*** *–* acute suppurative - common pathogens gonococci, staph; strep; H.influenzae and gram negative rods. Salmonella in sickle cell patients. ‘Lyme arthritis’ associated with Borellia Burgdorfori.

***Gout*** - deposition of urate crystals (uric acid is end product of purine metabolism).

90% cases are primary, 10% secondary.

Characterised by acute arthritis, chronic tophaceous arthritis and tophi in soft tissue.

Affects any joint but great toe in 90%. Usually limited to lower extremities. Precipitate of needle shaped crystals into joint. Tophus is the pathognomonic lesion.

***Calcium crystal deposition disease*** - Calcium pyrophosphate (pseudogout) affects knees mainly. Calcium phosphates (hydroxyapatite) affects knees and shoulders.

Usual age > 50y.

Pseudogout distinct subsets –

a) hereditary (autosomal dominant)

b) metabolic

c) sporadic

d) traumatic.

Obstetric Haematology

Dr Carolyn Millar

**Learning Objectives**

* Understand the importance of the normal changes in blood parameters that occur during pregnancy and their role in complications of pregnancy.
* Be able to distinguish normal gestational changes from pathological changes
* Understand the role of maternal testing in preventing and anticipating fetal disorders.

**Why pay special attention to the haematological changes in pregnancy?**

1. it avoids misdiagnosis eg: ITP or protein S deficiency
2. it reminds you to anticipate problems eg: thrombosis and haemolytic disease of the newborn (HDN)
3. **Red and white cells in pregnancy**

A mild degree of ‘anaemia’ is common during pregnancy. Despite the rise in red cell mass during the second and third trimesters (up to 130% of non pregnant level), there is a greater rise in plasma volume (up to 150%). Iron deficiency is common due to the increase red cell mass and requirements of the fetus (total approx. 800mg). Folate requirements are also increased.

A slight ‘macrocytosis’ (rise of 5-10fl) is a normal feature of pregnancy in the absence of folate or B12 deficiency. A mild rise in neutrophils with some left shift may also be seen.

1. **Thrombocytopenia in pregnancy**

Gestational thrombocytopenia

A fall in platelet count is normal during pregnancy. A fall to >80 x109/l is regarded as normal ‘gestational thrombocytopenia’. The mechanism is partly dilutional and partly increased consumption and occurs mostly in the third trimester. It accounts for 75% of low platelet counts in pregnancy and is benign. It is not associated with thrombocytopenia in the infant.

Immune thrombocytopenic purpura (ITP)

ITP accounts for 5% of pregnancy associated thrombocytopenia. Indicated by preceding thrombocytopenia or early onset. Intervene for bleeding, high risk of bleeding eg platelets <20, or to achieve platelets >50 for delivery. Intravenous immunoglobulin, anti-D immunoglobulin or steroids are first line therapy. The child is unpredictably at risk of thrombocytopenia so check cord FBC at birth and for 5 days afterwards as the fall is often delayed. Risk of bleeding in child is very low (≤1%) and so plan for normal delivery. Neonatal thrombocytopenia usually responds to i/v immunoglobulin.

Preeclampsia

50% get thrombocytopenia in proportion to severity. Mechanism is thought to be accelerated clearance. Associated with subclinical coagulation activation.

Microangiopathic syndromes

HELLP (haemolysis, elevated liver enzyme tests, low platelets) has some overlap with Preeclampsia but there is higher fetal and maternal morbidity. Usually gets worse for 48hours after delivery.

TTP (thrombotic thrombocytopenic purpura) and HUS (haemolytic uraemic syndrome) are both more common in pregnancy. Features and treatment are as for those occurring outside pregnancy and are not aided by delivery.

1. **Coagulation in pregnancy**

Procoagulant factors tend to rise during pregnancy. The greatest rises are in factors VII, VIII, von Willebrand factor and Fibrinogen which all rise by roughly 3-5 fold. Factors II and V do not change and Factor XI may fall to about half the non-pregnant level.

Among the anticoagulant factors the most notable change is in protein S which falls rapidly to approximately half the non-pregnant level. Protein C and antithrombin do not change significantly.

Fibrinolysis is suppressed during pregnancy. This is because tissue plasminogen activator (tPA) falls and plasminogen activator inhibitor PAI-1 rises and PAI-2 is produced by the placenta.

The risk of thrombosis is further increased by the gravid uterus impairing venous return from the legs.

The changes in pregnancy result in a net prothrombotic state. This is partly manifest as an increase in activated protein C resistance (APCR) and an increase in measures of thrombin generation. Overall the risk of pregnancy associated thrombosis is 1 per 1000 <35 years and 2 per 1000>35 years. The risk is further increased by other factors such as: immobility, Body mass index>29, thrombophilic traits, previous thromboembolism, hyperemesis, Caesarean section.

Obstetric disasters such as amniotic fluid embolism and plancental abruption are potent causes of disseminated intravascular coagulation (DIC).

1. **Haemoglobinopathy screening in pregnancy**

All women have a FBC and haemoglobin electrophoretic analysis at booking.

HPLC - will identify Hb variants

FBC - MCH<27 pgused to identify possible beta thalassaemia trait

Hb A2>3.5**%** identifies beta thalassaemia trait

MCH<25 pg possible alpha thalassaemia trait.

Risk of alpha zero is assessed on basis of ethnic group (mostly Chinese, SE Asia, Greece & Turkey).

Abnormalities are followed up by testing partner and/or referral to haematologist. The aim is to avoid thalassaemia major/intermedia or Hb Barts hydrops fetalis, Sickle Cell disease, and compound heterozygous states causing symptomatic sickle syndromes such as compound heterozygosity for haemoglobins S and C (SC).

1. **Red cell antibody screening in pregnancy**

This is covered fully under blood transfusion.

1. **Thrombophilia and adverse pregnancy outcomes**

Traits associated with an increased risk of thrombosis (Factor V Leiden, lupus anticoagulant) may be associated with complications of pregnancy: fetal loss, growth restriction, abruption and severe PET. The mechanism in most cases seems to be thrombosis in the placental circulation; anticoagulation has been shown to improve pregnancy outcomes in patients with lupus anticoagulant, although this has not been shown for other traits.

Endocrine Disease

Prof Terry Cook

**PITUITARY**

Anterior pituitary – Composed of epithelial cells that secrete trophic hormones under the control of the hypothalamus – TSH, Prolactin, ACTH, GH, FSH, LH

Posterior pituitary – axonal processes extending from the hypothalamus – produces ADH and oxytocin

**Symptoms of pituitary disease**:

a. Hyperpituitarism – excess secretion of trophic hormones – most common cause is a functional adenoma

b. Hypopituitarism – Deficiency of trophic hormones arising from destructive processes including ischemia, surgery, inflammatory reactions or non-functioning adenomas

c. Local mass effects

**Pituitary adenomas**

10% of intracranial neoplasms that come to clinical attention. Adults. 4th – 6th decade.

20-30% secrete prolactin, 5% GH, 10-15% ACTH

**THYROID**

Composed of thyroglobulin-rich follicles and scattered parafollicular (C cells) that synthesize calcitonin

Hyperthyroidism – Graves disease, hyperfunctioning multinodular goitre, hyperfunctioning adenoma, TSH secreting pituitary adenoma, thyroiditis, struma ovarii, exogenous thyroxine intake

Hypothyroidism – Following surgery or radioiodine, Hashimoto thyroiditis, iodine deficiency, congenital biosynthetic defect, pituitary or hypothalamic failure

**Graves disease** – Autoimmune disorder with antibodies to TSH receptor. Thyrotoxicosis with enlargement of the thyroid, exophthalmos, pretibial myxoedema. Morphologically diffuse hypertrophy and hyperplasia – may be papillae

**Goitre** – enlargement of the thyroid – endemic most often due to iodine deficiency, sporadic, multinodular

**Thyroiditis** – Hashimoto thyroiditis – common cause of hypothyroidism – involves cellular and humoral autoimmune responses to the thyroid. Thyroid is enlarged and microscopically there is infiltration by mononuclear inflammatory cells. Follicles are lined by epithelial cells with abundant eosinophilic cytoplasm – oxyphil or Hurthle cells. F:M 20:1 commonly 45 – 65 years

Subacute granulomatous (De Quervain)

Riedel’s thyroiditis

**Neoplasms**

**Adenomas** – benign neoplasm derived from follicular epithelium

**Carcinomas**

Papillary – (80%) of cases. May occur at any age. Non-functional. Most behave in an indolent fashion. May have papillary architecture. Nuclei show optically clear appearance

Follicular – (15%). Peak incidence in middle age. Usually present as solitary nodules. Distinguished from adenoma by local invasion.

Medullary carcinoma – Neuroendocrine neoplasms derived from C cells. 80% sporadic, 20% familial in setting of MEN syndromes. Often multicentric. Amyloid often present. Calcitonin can be demonstrated by immunohistochemistry

Anaplastic- Occur primarily in the elderly. Very aggressive.

**PARATHYROID GLANDS**

Decreased levels of free calcium in the blood stimulate the synthesis of parathyroid hormone (PTH) which activates osteoclasts, increases renal tubular reabsorption of calcium, increases conversion of vitamin D to its active metabolite, increases urinary phosphate excretion and augments gastrointestinal calcium absorption.

**Hyperparathyroidism**

**Primary** – usually caused by parathyroid adenoma (1% carcinoma) or by primary hyperplasia (10-20%). May be associated with MEN syndrome. Most common cause of clinically silent hypercalcaemia. Traditionally associated with constellation of symptoms including “painful bones, renal stones, abdominal groans and psychic moans”. Morphologic changes in other organs include prominence of osteoclasts in bone which may give rise to osteitis fibrosa cystica and ‘brown tumours’. May be urinary tract stones and metastatic calcification

**Secondary** – Any condition with persistently low serum calcium leads to compensatory parathyroid over activity – renal failure is the most common cause – may become autonomous –‘tertiary hyperparathyroidism’

**Hypoparathyroidism**

Uncommon. Major causes are surgical ablation, congenital absence, autoimmune. Clinical consequences are related to hypocalcaemia

**ADRENAL CORTEX**

**Adrenal cortical hyperfunction**

Adrenal cortex synthesizes glucocorticoids (e.g. cortisol), mineralocorticoids (aldosterone) and androgens. Hyperfunction therefore produces three major groups of clinical syndromes – Cushing’s syndrome, hyperaldosteronism and virilising syndromes

**Cushing’s syndrome**. Most cases due to administration of glucocorticoids (adrenals show bilateral atrophy).

Other causes –

Primary hypothalamic-pituitary disease associated with increased ACTH (>50% of endogenous cases). Adrenals show bilateral hyperplasia

Primary adrenocortical hyperplasia or neoplasia (25 – 30%). Usually due to adenoma or carcinoma.

Secretion of ectopic ACTH by non-endocrine neoplasms (most commonly small cell carcinoma of the lung. carcinoid tumours, islet cell tumours of the pancreas). Adrenals show bilateral hypertrophy.

In cases associated with high levels of endogenous or exogenous glucocorticoids the pituitary shows Crooke’s hyaline change due to accumulation of cytokeratin filaments in ACTH-producing cells.

**Hyperaldosteronism**

Sodium retention and potassium excretion leading to hypertension and hypokalaemia.

Primary – 80% due to aldosterone secreting adenoma (Conn’s syndrome). Others due to primary adrenocortical hyperplasia.

**Adrenogenital syndromes**

Adrenal causes of androgen excess include neoplasms (more commonly carcinomas than adenomas) and an uncommon group of disorders collectively designated congenital adrenal hyperplasia due to hereditary defects in enzymes involved in cortisol biosynthesis

**Adrenal insufficiency**

Primary or secondary to reduced ACTH

Primary may be **acute** – associated with massive haemorrhage (anticoagulants, sepsis), sudden withdrawal of long-term corticosteroid therapy.

**Chronic**- autoimmune, infections (TB, fungi), metastatic neoplasms.

**ADRENAL MEDULLA**

**Phaeochromocytoma** – Neoplasm composed of cells that synthesize catecholamines. Important as they give rise to a surgically correctable form of hypertension. Rule of 10s

10% arise in association with a familial syndrome (MEN 2A and 2B, von Hippel-Lindau disease and Sturge-Weber disease). 10% are bilateral. 10% are malignant. 10% are extra-adrenal. Microscopically composed of small nests of neuroendocrine cells. Diagnosis of malignancy is difficult and depends ultimately on presence of metastases

**MULTIPLE ENDOCRINE NEOPLASIA SYNDROMES**

MEN 1 – autosomal dominant – parathyroid hyperplasia, endocrine tumours of the pancreas, pituitary adenomas

MEN 2A – Medullary carcinoma of the thyroid, adrenal phaeochromocytomas, parathyroid hyperplasia

MEN 2B - Similar to 2A but without hyperparathyroidism and with mucosal ganglioneuromas

Update on lipoprotein metabolism,   
cardiovascular disease & obesity

Prof. Gilbert Thompson

**Lipoprotein metabolism and dyslipidaemia**

The main physiological systems involved in the absorption, metabolism, and storage of cholesterol and triglyceride are the small intestine, liver, adipose tissue and peripheral cells. These lipids are transported within plasma by lipoproteins, which vary in size, composition and function. Dietary cholesterol and triglycerides are carried by chylomicrons and endogenously synthesised triglycerides by VLDL. Cholesterol is transported out to the periphery by LDL and returned thence to the liver by HDL. Most of the receptors, apolipoprotein ligands and enzymes involved in lipoprotein metabolism have now been identified. Non-genetic influences include age, hormonal changes, diet and exercise. Abnormal levels of plasma lipids are termed dyslipidaemia, which includes both hyperlipidaemia and hypolipidaemia: each can be primary, genetically-determined or secondary, acquired disorders. Primary hyperlipidaemias are subdivided into hypercholesterolaemia, hypertriglyceridaemia or mixed hyperlipidaemia, where both cholesterol and triglycerides are elevated.

Genetically-determined causes of primary hypercholesterolaemia are familial hypercholesterolaemia, due to mutations of the LDL receptor, apoB-100 or PCSK9 genes; cholesterol ester storage disease, due to mutations of lysosomal cholesterol ester hydrolase; phytosterolaemia, due to mutations of ATP-binding cassette (ABC) transporters G5 and G8; and cerebro-tendinous xanthomatosis, due to mutations of sterol 27α hydrolase. Genetically-determined primary hypertriglyceridaemias include familial deficiency of lipoprotein lipase, apoC-II and A-V, and familial hypertriglyceridaemia, the cause of which is unknown. Genetically-determined primary mixed hyperlipidaemias are type III hyperlipoproteinaemia, due to mutations of apoE, familial hepatic lipase deficiency, and familial combined hyperlipidaemia, which is probably polygenic.

Secondary hyperlipidaemia can be due to hormonal influences such as pregnancy, exogenous sex hormones or hypothyroidism; to metabolic disorders such as diabetes and obesity; to renal dysfunction or obstructive liver disease; to beverages, such as alcohol and coffee; and to iatrogenic causes, such as cyclosporin, amiodarone, retinoids and antiretroviral drugs.

Primary hypolipoproteinaemia (hypolipidaemia) is always of genetic origin and includes abetalipoproteinaemia, due to recessively inherited mutations of microsomal triglyceride transport protein (MTP); familial hypobetalipoproteinaemia, due to dominantly inherited mutations of the apoB gene; Tangier disease, due to homozygosity for mutations of ABCA1; and familial hypoalphalipoproteinaemia, due to heterozygous inheritance of mutations of either ABCA1 or of apoA-1.

**Lipids and cardiovascular disease**

A wealth of epidemiological evidence demonstrates a log-linear relationship between serum total and LDL cholesterol and coronary heart disease (CHD) whereas the latter’s relationship with HDL cholesterol is an inverse one. Serum triglyceride has a positive correlation with CHD but weaker than that of LDL. At the clinical level the best predictor of CHD risk is the total:HDL cholesterol ratio, which reflects the opposing influences of atherogenic VLDL and LDL versus anti-atherogenic HDL. Severe hypertriglyceridaemia (>10 mmol/l) can precipitate acute pancreatitis.

Deposition of LDL in the arterial wall results in its oxidation and subsequent uptake by scavenger receptors on monocyte-macrophages. Accumulation of cholesterol esters within macrophages leads to cell death and release of lysosomal enzymes, causing the build up of cholesterol-rich atheromatous plaques in coronary arteries - these have a propensity to fissure. Consequent thrombus formation leads to plaque progression, myocardial infarction or sudden death.

Lipid-lowering diets and drugs which lower LDL or raise HDL have been shown to arrest progression of atherosclerosis and reduce CHD morbidity and mortality. Meta–analyses of HMG CoA reductase inhibitor (statin) trials demonstrate that major vascular events including strokes are reduced by 25% for each 1 mmol/l decrease in LDL cholesterol. LDL-lowering drugs in the pipeline include MTP-inhibitors, anti-sense apoB oligonucleotides and anti-PCSK9 monoclonal antibodies. HDL-raising drugs include CETP inhibitors and apoA1 and HDL-mimetic compounds.

**Treatment of obesity**

Initial therapy consists of dietetic advice regarding an hypocaloric diet, increased exercise and pharmacologically-induced malabsorption using a pancreatic lipase inhibitor. Bariatric surgery i.e. gastric banding, Roux-en-Y gastric bypass and biliopancreatic diversion plays an increasingly important role in the management of morbidly obese subjects (BMI>40). A successful outcome is defined as a >50% loss in excess body weight (actual – ideal) and is accompanied by marked decreases in diabetes, serum triglycerides, fatty liver and hypertension. Post-operative mortality is 0.1 to 2%.



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Central nervous system infections & Meningitis

Dr Luke Moore

**ACUTE BACTERIAL MENINGITIS and related syndromes**

Acute meningitis can be caused by bacteria, viruses, parasites, and fungi. Of greatest concern is bacterial meningitis and/or septicaemia which can be rapidly fatal if treatment is delayed. The bacteria responsible vary with age and the immune status of the host. *Escherichia coli* and Streptococcus group B are the commonest pathogens in neonates, while *Neisseria meningitidis* and *Streptococcus pneumoniae* are the most common at all other ages. Other bacteria need to be considered in specific circumstances e.g. *Listeria* in the immunocompromised; *Leptospira* in association with sewage contact; Lyme disease in association with tick bites; and staphylococci in association with penetrating injuries and surgery. Bacteria gain access to the CNS either via systemic spread from a mucosal surface e.g. meningococci, or by local spread e.g. staphylococci following neurosurgery.

***Neisseria meningitidis***

The bacterium is a gram-negative diplococcus. Isolates from invasive disease possess a polysaccharide capsule - a major virulence factor. The organism can be subdivided into   
13 serogroups based on antigenic differences in the capsular polysaccharide- A,B,C,D,X,Y,Z,29E,W135,H,I,L,K.

A, B, and C are responsible for > 90% disease worldwide. Serogroup A causes periodic epidemics in sub-Saharan Africa and China some of which have spread throughout the world, but these have been rare in U.K since World War II. Group B causes endemic/sporadic disease world-wide and currently about 80% of the disease in   
U.K. Group C strains cause endemic-sporadic and outbreaks world-wide; there is now an effective vaccine available against serogroup C strains.

Attack rates are highest in children under 5 years, with a smaller peak in teenagers and early 20's. Disease is maximal in winter and spring.

Rare predisposing factors include splenectomy, hypogammaglobulinaemia, and complement deficiency, including C3 and properdin deficiency which predispose to fulminant disease, and C5, 6, 7, or 8- deficiency, which predispose to recurrent disease.

**Pathogenesis**

The human nasopharynx is the reservoir from whom the organism spreads. Overall carriage rates are about 10%, with low rates in the young, maximum rates in age 15-30, with subsequent decline with increasing age. Crowding, close contact, poverty, and coexistent viral infection facilitate transmission. If disease develops it does so shortly after exposure   
(1-5 days), with mucosal acquisition leading to blood stream invasion, and subsequent localisation to CNS and elsewhere e.g. joints.

**Clinical features**

Early symptoms are NON-SPECIFIC and include fever, sore throat, myalgia and arthralgia. These non-specific features are confused by patient, parent or GP as "flu". Septicaemia is manifest by increasing toxicity, and the hallmark of meningococcal disease, the RASH.   
Early in disease this may be macular/maculopapular, but can rapidly evolve to petechial, purpuric or ecchymotic. The haemorrhagic rash is characteristically non-blanching.   
The extent of the rash correlates with severity. Most patients who die from meningococcal disease die from septicaemia.

In those who develop meningitis, the early symptoms are followed by an increasingly severe headache, + / - vomiting, irritability and confusion which may lead to coma. Focal neurological signs are uncommon, but include fits, 3rd, 6th cranial nerve lesions or long tract signs Neck stiffness and a positive Kernig's sign are often present but their absence does not exclude meningeal involvement. Features in the young may be nondescript and in the elderly confused with cerebrovascular disease. Not only is the recognition of meningococcal disease of major clinical importance but the recognition of disease severity is fundamental to clinical management. A number of parameters associated with an adverse outcome have been described.

One of the most clinically useful systems for assessment is the   
**Glasgow Meningococcal Septicaemia Prognostic Score**:

Hypotension BP < 85 adults, < 75 children 3

Skin - rectal temp. difference > 3°C 3

Base deficit < 8 mmols / l 1

Coma score < 8 or deterioration > 3 in an hour 3

Lack of meningism 2

Parental opinion that worse in last hour 2

Widespread ecchymoses or lesions extending on review 1

**TOTAL 15**

All those with a score of 8 or more should be considered for ITU

***Streptococcus pneumoniae***

Are gram positive cocci, which can be subdivided into 90 serotypes based on antigenic differences in capsular polysaccharides. Opsonising anti-capsular antibodies are protective. Predisposing factors to disease include splenectomy, hypogamma-globulinaemia and C3‑deficiency (all rare), alcoholism, immunosuppression and previous head trauma with CSF leak. However attack rates are highest in those under 1 year, reflecting absent relevant antibody. Presenting features of pneumococcal meningitis are similar to those described above for meningococcal meningitis but without the rash. Important associated findings may include otitis media, sinusitis or pneumonia. There will be a vaccine that covers 7 serogroups introduced in the UK this year.

**DIAGNOSIS**

All patients with suspected meningococcal disease, or other forms of meningitis, should have blood cultures, acute serum for possible antigen detection and acute phase antibody, and EDTA blood sample for PCR for meningococci. A further serum should be obtained in convalescence for meningococcal serology, immunoglobulins and complement measurements. Non-microbiological investigations should include Hb, WBC, platelets, PT, APTT, Fibrinogen, dimers, urea, creatinine, Ca, + /- blood gases. Where there is a characteristic meningococcal rash further investigations should not impede immediate treatment (see below).

CSF examination is required if it is necessary to confirm the presence of meningitis, distinguish acute bacterial from other causes, and determine the bacterial aetiology. CSF examination is contraindicated in the presence of clinical or CT evidence of raised intracranial pressure, or fulminant sepsis, and is usually unnecessary in the presence of a typical meningococcal rash. If CSF is examined the important parameters are cell count and type and CSF / blood glucose ratio.

**Characteristic CSF findings**

**Condition Appearance cells protein glucose  
 g/l mmol/l**

Normal clear 0-5 lymph. 0.15-0.4 2.2-3.3

Bacterial turbid 10-5000 neutr. 0.3-3.0 0.0-2.2

Viral clear/slight turbidity 10-500 lymph. 0.5-1.0 normal

TB clear/slight turbidity 10-500 lymph. 1.0-6.0 0.0-2.2

Gram stain of centrifuged deposit may reveal organisms. Subsequent culture may yield growth when gram stain is negative, but the sensitivity of both is diminished when antibiotics have been given prior to LP. Occasionally polysaccharide antigen detection may provide additional information.

Increasingly CSF examination is not being performed, emphasising the importance of other diagnostic tests.

**TREATMENT**

Suspected meningitis or meningococcal disease cannot await laboratory confirmation and must be treated empirically. Suspected meningococcal disease should be treated by the first doctor involved. In general practice this will usually be benzyl penicillin. In hospital ceftriaxone should be used since it covers all common causes of community meningitis (except Listeria which is rare). Where Listeria is suspected (particularly the immunocompromised) ampicillin should be added. Treatment should be 5-7 days for meningococcal disease and 7-10 days for pneumococcal disease.

**PREVENTION**

**Chemoprophylaxis**

In meningococcal disease antibiotics are used to protect those who might be susceptible by eradicating the organism from the micropopulation in whom meningococcal transmission may be occurring, being given to family and close social and kissing contacts. Rifampicin 10 mg/kg 12 hourly for 4 doses, maximum 600 mg (5 mg/kg if under 3 months), and ceftriaxone 250 mgs in pregnancy.

Hospital staff should not receive chemoprophylaxis unless they are in close unprotected contact with respiratory secretions e.g. unprotected mouth to mouth resuscitation.

**Vaccination**

Antibodies to the capsular polysaccharides of meningococcal A and C, pneumococcal and Haemophilus influenzae b are protective but these purified polysaccharides are limited by a T cell independent response, which is short-lived, with no booster response, and a poor or negligible response in infancy.

Conjugation of polysaccharide to a protein carrier generates vaccines that are T-cell dependant and are immunogenic at a young age. Such an approach has virtually eliminated *Haemophilus influenzae* type b disease. Group C conjugate vaccine is now part of the primary vaccination schedule in infancy.

Group B meningococci pose a different problem. The polysaccharide is poorly immunogenic even in disease, and may not be the important antigen involved in protection.

**Questions**

1) The tumbler test is an effective for EXCLUDING meningococcal sepsis. T/F

2) Carriage of *N. meningitidis* is eradicated by treatment for meningitis with *β*-lactamases T/F

3) *Escherichia coli* is a common cause of meningitis in the elderly T/F

4) An immediate lumbar puncture is mandatory in patients with meningitis T/F

5) A high white cell count in the CSF indicates bacterial meningitis T/F

6) It is important to measure blood glucose to interpret CSF results T/F

7) Work contacts of patients with meningococcal infection need treatment T/F

8) Health care professionals need prophylaxis against meningococcal infection T/F

9) School contacts need prophylaxis against meningococcal infection T/F

**A.** Meningitis means inflammation of the meninges.   
Infection usually affects the ……….-…………… space.  
Spread to the meninges can occur by   
1)…………………………………, or   
2) …………………….. ………….

**B.** The organisms that cause meningitis depend on the age of the patient and the route of infection.

The commonest pathogens affecting neonates are  
1) ………………, and   
2) ………………

Immunocompromised hosts may be develop meningitis with other organisms such as …………………….. .

**C.** Have a high index of suspicion for diagnosing meningococcal sepsis.

**D.** Conjugate vaccines are routinely used in the UK against which serogroup(s) of  
 *N. meningitides* ?

Lymphoma

This session deals with lymphoproliferative disorders and provides a basic introduction to lymphomas followed by the histopathology and classification, the clinico-pathological aspects of lymphoma, Chronic Lymphocytic Leukaemia and other lymphoid disorders.

**Section 1 Lymphomas introduction.**Dr. Donald Macdonald

**Section 2 Histopathology and classification.**Dr. Alexandra Rice

**Section 3 Clinical aspect of Hodgkin Lymphoma and Non Hodgkin Lymphoma.**Dr. Donald Macdonald

**Section 4 Chronic Lymphocytic leukaemia and other lymphoproliferative disorders.** Dr Sasha Marks

**Section 1: Introduction** Dr. Donald Macdonald

**Learning Objectives**

1. To be able to define the term “lymphoma”
2. To understand the terms “Lymphoproliferative disorder” “Lymphoma” and Lymphoid Leukaemia”
3. To understand the importance of precise lymphoma classification, and the laboratory techniques used for classification.
4. To understand the different mechanisms whereby infectious agents contribute to lymphoma pathogenesis
5. To understand important molecular events which underlie the pathogenesis of lymphomas

To better understand the topic of lymphoma some simple underlying concepts are set out below;

* Lymphomas are a neoplastic proliferation of lymphoid cells. They are generally a monoclonal proliferation arising from a single transformed malignant cell.
* There are a wide variety of lymphoma sub-types (>40) and amongst lymphomas are examples of the fastest growing human malignancies e.g. Burkitt’s Lymphoma, whilst others are extremely indolent cancers and have a clinical course of response and relapse which may span 20-30 years.
* Precise Lymphoma classification is vital as it determines natural history, and optimal therapy.
* The ontogeny of normal lymphoid development is highly complex and allows maturation from a common lymphoid stem cell through different pathways to a range of mature lymphocytes, examples of which include NK cells, T helper cells, memory B-cells, etc.   
  A goal of modern lymphoma classification is to relate the malignant cells to a normal counterpart in both lineage and stage of differentiation. Consequently we endeavour to define lymphomas by lineage e.g. B cell or T cell and by stage of differentiation e.g. most immature such as a pre B cell malignancy Acute lymphoblastic leukaemia, or a mature effector cell malignancy such as NK cell lymphoma. This approach is not yet perfect but remains the basis of our current understanding and classification of lymphomas.
* Normal lymphoid cells are found throughout the body therefore malignant proliferation can occur in many sites. Most commonly occurring lymphoma sub-types tend to involve lymph nodes or other lymphoid organs such as gut-associated lymphoid tissue or spleen, these are termed lymphomas. Other sub-types which preferentially involve bone marrow and blood are generally termed lymphoid leukaemias. This is not an absolute distinction as the lymphoid leukaemias may involve nodal tissue and vice versa. Rarer disorders may preferentially involve skin and are termed cutaneous lymphomas. In practical usage the term lymphoproliferative disorder covers all malignant proliferations of lymphocytes.
* A final basic concept to understand is the major subdivision of lymphomas into two basic types 1) Hodgkin Lymphoma and 2) Non Hodgkin Lymphoma. The detail of this division is explained in the section pathology and classification.

**Aetiology and pathogenesis**

The aetiology of most cases of lymphoma is unknown. The molecular mechanisms of lymphomagenesis vary but it is important to understand some basic principles. In some sub-types there is a very clear link with infectious agents:

**Infectious agents and lymphoma:**

* ***Direct viral integration e.g. HTLV-1:*** This is a human retrovirus which can infect T-cells the virus integrates into cellular DNA and a carrier state is established. Infection is often by vertical transmission after many years (50-60) adult T-cell leukaemia/lymphoma syndrome (ATLL) may develop. ATLL is an aggressive syndrome of lymphoma/leukaemia often associated with malignant hypercalcaemia. Worldwide HTLV-1 infection is most common in Japan and the Carribean.
* ***Chronic antigenic stimulation (infectious or non infectious) e.g. H.Pylori:*** The commonest example is H.Pylori infection which may give rise to chronic antigenic stimulation of gastric mucosal associated lymphoid tissue (MALT.) In some cases this may lead to the emergence of a type of NHL termed marginal zone lymphoma. This would be an example of a MALT lymphoma (see NHL classification.) Other non infectious causes of chronic antigenic stimulation may give rise to lymphoma e.g. Auto immune thyroiditis and thyroid marginal zone lymphoma or Sjogren’s syndrome and parotid marginal zone lymphoma. This mechanism whereby chronic infection results in immune stimulation is entirely different from a direct viral infection of the lymphocyte which leads to disordered cell growth or survival.
* ***Ebstein Barr Virus:*** This virus has a complex and important relationship with the development lymphoproliferative disorders. The full detail is beyond the scope of this session. EBV infects B-cells and in-vitro can be used to immortalise B-cells for laboratory studies. In EBV infection after an acute illness which resolves, the infection persists but in a latent asymptomatic form. In the general population 90-95% of people are infected by EBV but very few develop a lymphoproliferative disorder. This is related to two factors; 1)The interaction of the virus with normal cellular genes. In rare cases the virus may breakdown normal cell cycle control or apoptotic pathways this can lead to B-cell proliferation in an immunocompetent healthy individual. The second factor in EBV infection is the normal T cell immune response to EBV infected B cells. Any condition which impairs this immune response will predispose to the development of lymphoma (see HIV infection)
* ***HIV :*** The relative risk for B cell lymphoma in HIV infected individuals is 60 times greater. Once again the interaction with EBV is critical though complex. In Diffuse Large B cell NHL (see lymphoma classification) the falling CD4 counts decrease the immune clearance of proliferating EBV infected B cells and permit the development of lymphoma. Other conditions which impair the T cell immune response also predispose to the development of EBV associated lymphomas. Examples include EBV associated tumours in primary immunodeficiency and post transplant lymphoproliferative disorders.

**Molecular lymphomagenesis:**

Two aspects of normal lymphocyte development are “high risk” in that errors in the normal pathway can lead to malignant transformation. Firstly normal lymphocytes undergo genetic recombination of the T cell receptor or Immunoglobulin genes, this enables each cell to develop a unique receptor. Secondly lymphocytes are capable of rapid proliferation and prolonged survival however a normal part of lymphocyte development is extensive cell death via apoptosis of those cells which either fail to successfully rearrange receptor genes or recognise self antigens. It is these processes that create the diversity and rapid response of the normal immune system a valuable protective mechanism for the organism. However there is a price to pay; genetic recombination i.e. the cutting and then rejoining of DNA molecules has scope for error (see chromosomal translocations.) and secondly any acquired mutation which inhibits apoptosis can have far reaching effects in the lymphoid system.

* **Chromosomal translocations:** Acquired translocations are a common finding in haematological malignancies. They can generally be divided into two sorts; those which create a novel fusion gene (see lecture on chronic myeloid leukaemia) or those which result in deregulation of an intact proto-oncogene, this type is most frequently but not exclusively seen in lymphoma. In normal B cells recombination results in the successful rearrangement of an immunoglobulin gene which lies downstream from an Ig promoter on chromosome 14. This promoter is highly active in B cells and results in high levels of antibody production. Chromosomal translocations arise as a result of an error in recombination and may place a proto-oncogene downstream of the Ig promoter.   
  This active promoter results in over expression of the translocated proto-oncogene.   
  The example shown is of a t(14;18) which is present in 70-95% of Follicular NHL cases. Bcl2 protein inhibits apoptosis and over expression confers a survival advantage in B-cells.

**Ig**

**promoterr**

**Ig promoter**

**Ig gene**

**Normal Chr14**

**Bcl2 gene**

**t(14;18)**

**Section 2: Histopathology and Classification**

Dr. Alexandra Rice

**Learning Objectives**

1. To understand the normal histology of the lymph node and basic lymphocyte morphology

2. To understand the principles of the WHO classification of lymphomas and pathological features of common lymphoma types.

3. To understand how lymphomas are diagnosed and the role of ancillary studies.

4. The outline of the lecture is mapped out on the next page

**Section 3: Clinical Aspects of Hodgkin and Non-Hodgkin Lymphoma**

Dr. Donald Macdonald

**Learning Objectives**

1. To state how lymphomas may spread to other parts of the body and to describe the staging of lymphoma
2. To state how lymphomas usually present, and the general symptoms that patients may have at diagnosis
3. To know what features at diagnosis of Hodgkin lymphoma and non-Hodgkin’s lymphoma (NHL) predict a less good outcome with therapy
4. To be able to describe, in outline, how patients with lymphoma may be treated and the major complications of therapy

The term ‘lymphoma’ means a neoplastic (malignant) tumour of lymphoid cells. Lymphomas usually arise in lymph nodes but may arise in other lymphoid organs such as the spleen or the gut-associated lymphoid tissue.

1. ***Classification:*** The lymphomas are classified into Hodgkin lymphoma (HL) and the non-Hodgkin’s lymphomas (NHL). NHL are further subdivided on the basis of cell of origin (B-lymphocyte or T-lymphocyte) and aggressiveness of disease i.e. indolent (also called low-grade), aggressive (or intermediate-grade) and very aggressive (or high-grade).
2. ***Incidence*** There are approximately 200 new cases per year for every million of the population (around 10,000 new cases a year in the UK). Of these 80% are NHL.

**Hodgkin lymphoma**

HL is more common in males than females. The peak incidence is in young adults (15-40 years). The aetiology of HL is unknown, but the Epstein-Barr virus (EBV) may be involved in some cases.

Usual presentation is with painless enlargement of lymph node/nodes. Constitutional symptoms such as fever, night sweats and pruritis may be present. (see ‘***Staging***’ ) A cyclical fever lasting 1-2 weeks and then subsiding for a similar period is classical but affects only a minority of patients (Pel-Ebstein fever).

The diagnosis is made by biopsy of an affected lymph node. The pathological ‘hallmark’ of HL is the ***Reed-Sternberg*** cell, a binucleate or multinucleate cell, set in a background of lymphocytes and other reactive cells.

***Staging:*** following pathological diagnosis of a lymph node biopsy patients are ‘staged’ as to the extent of their disease, since this has prognostic significance and also may determine the best approach for therapy. Lymphomas can spread to other parts of the body in 3 ways: via the lymphatic system, via blood vessels, or by local spread. The most useful staging procedure nowadays is a CT scan of thorax and abdomen/pelvis. This may be supplemented by bone marrow biopsy, liver biopsy, and other imaging investigations in selected patients. Characteristically HL spreads via the lymphatic system in a contiguous manner. NHL is more likely to be widespread at presentation.

The staging system (for both HL and NHL) is as follows:

* Stage I: one lymph node region or single extranodal organ / site.
* Stage II: involvement of two or more lymph node regions on the same side of the diaphragm.
* Stage III: involvement of lymph node regions on both sides of diaphragm
* Stage IV: diffuse or disseminated involvement of extranodal sites (e.g. liver or bone marrow), with or without lymph node involvement.

For the purposes of staging, the spleen is treated as a lymph node. The suffixes ‘A’ or ‘B’ are used to denote the absence or presence respectively of systemic symptoms i.e. fevers, night sweats, unexplained weight loss of at least 10% body weight in previous 6 months. The presence of any of these is denoted by ‘B’ e.g. Stage IIIB.

***Outline of therapy:*** therapy can include radiotherapy, chemotherapy, or both. Chemotherapy is often given as a combination of drugs that affect the malignant cells in different ways, and therefore hopefully have additive or synergistic effects. The most frequently used chemotherapy regimen is ABVD (adriamycin, bleomycin, vinblastine and dacarbazine.) Previously patients with limited disease (Stage IA or IIA) were treated with radiotherapy alone and had a good chance of cure, but nowadays a short course of chemotherapy is often given additionally to further improve outcome and the current trend is towards chemotherapy only (see complications of therapy). Treatment of more advanced disease is usually with longer courses of chemotherapy; radiotherapy may also be given to areas of bulk disease. Relapsed patients may benefit from very intensive therapy including autologous haematopoietic stem cell transplantation.

***Complications of therapy:*** most of the treatments available for HL and other lymphomas carry a risk of potentially serious complications. Patients with lymphoma have impaired immune systems and are therefore at risk of infection, including opportunistic infections. This tendency is exacerbated by the therapy of the disease i.e. chemotherapy and radiotherapy. Other complications include permanent damage to vital organs, infertility, and the causation of secondary cancers. The incidence of secondary cancers is greatest in patients who have combined modality (chemotherapy and radiotherapy) treatment. Some of these will reduce life expectancy in patients who are otherwise ‘cured’.

***Prognosis:*** this depends principally on stage. Cure rates ranges from 50-90%. Over 80% of patients with stage I or II disease are cured but only 50% of stage IV patients. Older patients generally do less well as do those with lymphocyte-depleted histology.

**Non-Hodgkin’s Lymphoma (NHL)**

***Incidence***: NHL accounts for approximately 5% of all cancers. The incidence increases with age.

***Clinical Presentation:*** as in HL, the usual presentation is with painless lymphadenopathy. Enlargement of liver and spleen and systemic symptoms may be present. Extra-nodal involvement, e.g. of the central nervous system or gastro-intestinal tract, is more common in NHL than HL.

***Pathological diagnosis:*** classifies NHL into a variety of types. Most of them arise from B cells. They are divided according to the histological appearance into indolent (also called low-grade), aggressive (or intermediate-grade) and very aggressive (or high-grade). In general, indolent tumours are characterised by small well-differentiated cells and aggressive tumours by larger less well-differentiated cells. The most common type of indolent lymphoma is ***follicular lymphoma;*** the most common type of aggressive lymphoma is ***diffuse large B-cell lymphoma.*** Paradoxically aggressive lymphomas are more easily cured than indolent lymphomas.

***Staging*** is carried out as in HL.

***Outline of Therapy:***

1. Indolent (low-grade): limited disease (Stage IA) is treated with radiotherapy and is curable. More advanced disease is not curable except with extremely intensive therapy in younger patients. Thus the majority of patients with more than limited disease need not be treated (‘watch and wait’ policy) until disabling symptoms or complications occur, at which time simple oral chemotherapy (e.g. chlorambucil) is used. Newer drugs (e.g. fludarabine, rituximab) and/or more intensive combination chemotherapy is reserved for relapsing/progressive disease.
2. Aggressive and very aggressive (intermediate-grade and high-grade) disease is often curable with intensive combination chemotherapy using a mixture of drugs usually including an anthracycline (e.g. doxorubicin). Some patients, particularly those who have relapsed after first-line therapy, benefit from high-dose therapy with autologous haematopoietic stem cell transplantation. A recent advance has been the addition of rituximab (anti-CD20) to the chemotherapy. The most common regimen in aggressive lymphoma is 6-8 cycles of R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine and prednisolone)
3. As with HL, treatment is associated with risks of infection and other complications.
4. ***Prognosis:*** the cure rate for aggressive NHL with therapy ranges from 25-75%, dependent on a number of prognostic factors these factors are brought together as the IPI score (International Prognostic Index.) :
5. age (adverse over 60y)
6. serum lactate dehydrogenase (adverse if raised above normal)
7. number of extranodal sites involved (adverse if more than one)
8. effect of disease on normal daily activity (performance status: adverse if significantly reduced)
9. stage of disease (adverse if Stage III or IV)

**Note: copies of the video on Hodgkin Lymphoma are available in the libraries at  
South Kensington, St Mary’s and Charing Cross and a version is also available as   
a webstream from**

<http://helix.imperial.ac.uk/ramgen/fom/int/Pathology/hodgkins.rm>

**Section 4:   
Chronic lymphocytic leukaemia and other lymphoproliferative disorders**

Dr Sasha Marks

***Learning Objectives***

• To be able to state the clinical features of CLL

• To be able to describe the typical peripheral blood picture

• To be able to state the major prognostic factors

• To be able to describe the natural history of CLL

• To understand the indications for treatment

**Introduction**

This is the commonest leukaemia in the western world. 67% of cases are in those over the age of 65. The male:female is 2:1. The cause of CLL is not known.

**Clinical and laboratory features**

CLL is commonly an incidental finding on a full blood count. Typically the white (lymphocyte) count is raised with normal haemoglobin and platelets.

The bone marrow is always involved and the pattern of involvement provides some prognostic information.

Serum immunoglobulins may be suppressed (immuneparesis), there may be a paraprotein and the direct Coombs test may be positive.

Prognostic factors include immunoglobulin gene mutational status (mutated=good prognosis and unmutated=bad) and cytogenetics (13q14 deletion is associated with good prognosis and 11q23 and/or 17p deletion are associated with bad prognosis).

More advanced cases are associated with lymphadenopathy, and/or hepatosplenomegaly and/or anaemia and/or thrombocytopenia.

Two clinical staging systems (Rai and Binet) based on these criteria are used to guide treatment.

Autoimmune disease, particularly autoimmune haemolytic anaemia, may be a feature at presentation or during the course of the disease.

Bacterial infections are common in advanced disease and may be related to immuneparesis.

**Natural history and treatment**

Most patients present with early stage disease (lymphocytosis only) and do not require treatment. The lymphocyte count may remain stable or may increase over a variable time that may extend over many years. If the lymphocyte count rises rapidly or major lymphadenopathy, hepatosplenomegaly, anaemia or thrombocytopenia develop treatment is instituted.

Conventional first line treatment is with an alkylating agent i.e. chlorambucil. On relapse or if the disease is refractory a purine analogue i.e. fludarabine is employed. The monoclonal antibody Campath has a role in the treatment of fludarabine refractory disease. The place of autologous stem cell transplantation is being determined in clinical trials.

**Prognosis**

Patients with mutated immunoglobulin genes have a median survival of 25 years and those with unmutated immunoglobulin genes have a median survival of 8 years.

Stem Cell Transplantation

Professor Jane Apperley

**Learning Objectives**

* Understand the nature of autologous and allogeneic stem cell transplantation.
* Understand the indications for stem cell transplantation
* Understand the pathogenesis of the complications of stem cell transplantation
* Be aware of the outcome of SCT for the more frequent indications

***What is stem cell transplantation?***

Allogeneic stem cell transplantation (allo-SCT) involves the replacement of the patient’s haemopoietic stem cells (HSC), normally found within the bone marrow, by a source of normal HSC, usually derived from an HLA-identical sibling or volunteer unrelated donor.   
Allo-SCT is indicated either when the patient’s own bone marrow has failed, in which case the goal of treatment prior to the transplant is to suppress the patient’s immune system, or where the marrow is affected by disease, e.g. leukaemia, where therapy pre-transplant must both eradicate the disease and suppress the immune system. Bone marrow failure syndromes include aplastic anaemia and some rare congenital disorders such as Fanconi anaemi and Dyskeratosis Congenita. Malignant indications for allo-SCT include the acute and chronic leukaemias, lymphoma, myeloma, myelodysplasia and some solid tumours.

Autologous stem cell transplantation (auto-SCT) refers to the use of the patient’s own HSC as the replacement tissue after high dose chemo- and/or radiotherapy. One of the first limiting toxicities of chemo- and radiotherapy is bone marrow failure. Higher doses can be given if the patient’s HSC are removed prior to the onset of treatment, cryopreserved and then thawed and re-infused after the administration of the high dose therapy. Auto-SCT is used in situations where either the bone marrow is not affected by the disease, e.g. some lymphomas, solid tumours, or can be rendered free of disease by prior therapy, e.g. acute leukaemia, or where allo-SCT is not possible because of the age of the patient or the lack of a suitable donor, e.g. myeloma, chronic lymphocytic leukaemia.

***Complications of stem cell transplantation***

**1. Toxicity of chemo-radiotherapy**

The combination of drugs and/or radiotherapy used to prepare the patient for the infusion of HSC is known as the ‘conditioning regimen’. In both auto- and allo-SCT the most frequently used cytotoxic drugs are the alkylating agents, eg, melphalan, busulphan and cyclophosphamide. These agents have well characterised side effects including alopecia, gastro-intestinal problems of nausea, vomiting, diarrhoea and mucositis, cardiotoxicity, pulmonary fibrosis, haemorrhagic cystitis, liver toxicity known as veno-occlusive disease and gonadal failure. Irradiation is more commonly used in allo-SCT and is administered as total body irradiation (TBI). TBI can also cause gastro-intestinal disturbance, pulmonary damage, pancreatitis, parotitis, gonadal failure and veno-occlusive disease. All these complications are more common in older patients and in those in whom organ damage is already present.

**2. Pancytopenia due to myeloablation**

The goals of the conditioning regimen are two-fold, first to eradicate the underlying disease and second, to immunosuppress the patient sufficiently to prevent rejection of the incoming donor tissue. Within a week of the therapy the haemoglobin (Hb), white cell and platelet counts will fall. This renders the patient susceptible to the consequences of anaemia, i.e. fatigue, lethargy, dyspnoea and heart failure, leucopenia, i.e. bacterial, viral and fungal infection, and thrombocytopenia, i.e. bleeding and bruising. At this time the patient will be nursed in a single room using a ‘reverse barrier’ system , to prevent the introduction of exogenous organisms into the room. Visitors will pay particular attention to hygiene, wearing plastic aprons and hand-washing. The patient will receive prophylactic antibiotics to try to prevent sepsis due to endogenous organisms. The immediate period of neutropenia is of the order of 7-28 days, depending on the conditioning regimen and the nature of the transplant, i.e. autologous or allogeneic. However, the effect on the immune system is prolonged and patients remain susceptible to viral and fungal infections for up to one year post transplant.

**3. Graft versus host disease**

In allo-SCT, the donor’s cells are immunocompetent and their T-lymphocytes are capable of recognising the patient as ‘foreign’. An inflammatory reaction, known as graft versus host disease (GvHD) occurs in most patients undergoing allo-SCT, but is variable in severity. Acute GvHD occurs within 100 days of transplant and can affect the skin, gastro-intestinal tract and liver. In its mildest form, it does not require treatment and is self-limiting. In its most severe form, affecting about 10% of recipients of sibling grafts and 20% of recipients of unrelated volunteer cells, it is uniformly fatal. The intermediate forms require treatment with additional immunosuppression which in turn increases the risk of infection. After day 100, on-going and de novo GvHD are referred to as chronic GvHD. This condition is similar to an auto-immune process with many of the features of scleroderma. If the condition is severe enough to require on-going immunosuppression, patients remain at risk of death from infection.

GVHD can be prevented by the removal of the donor’s T-lymphocytes prior to infusion.   
This is usually achieved by incubating the donor’s HSC with a T-cell specific monoclonal antibody, such as alemtuzamab (Campath) (ex vivo T-cell depletion), or by administering this antibody at the same time as the infusion of HSC (in vivo T-cell depletion). Although this strategy improves the outcome of transplant in the short-term, there is an increased risk of disease recurrence. This observation led to the concept of the ‘graft versus tumour’ effect, in which it was recognised that the mechanism of cure through transplant was due to both the intensity of the conditioning regimen and an on-going eradication of residual disease by immunocompetent donor cells. This was further confirmed by the ability of the infusion of additional donor lymphocytes (DLI) to restore remission in patients who had relapsed with their leukaemia after allo-SCT.

The combination of the risks associated with the conditioning regimen, prolonged immunosuppression and pancytopenia and GvHD, give a transplanted related mortality,   
i.e. risk of death due to the transplant as opposed to the disease, of approximately 5% in auto-SCT, 20-30% in sibling allo-SCT and 30-50% in unrelated allo-SCT. Unrelated allo-SCT is therefore one of the most dangerous elective procedures performed as a therapeutic strategy, and care must be taken to select only those patients most likely to survive the procedure and benefit long-term.

**4. Long term effects of SCT**  
Patients who have been treated by SCT require life-long follow-up, particularly those who received allo-SCT. Late sequelae of transplant include gonadal failure (premature menopause, permanent infertility), cataract formation (particularly after TBI), endocrine deficiencies (thyroid dysfunction, growth retardation and pubertal delay in children), pulmonary disease (fibrosis and bronchiectasis), cognitive impairment and psychological problems. The management of the transplant patient is complex and requires a highly effective multi-disciplinary team approach.

The Porphyrias

Dr Monica Nijher

(Handout by Dr Sara White)

**Porphyrias are important because…**

* Although largely asymptomatic, they can present at any age to a wide variety of specialists
* The diagnosis can be missed/delayed if not considered in your list of differentials as symptoms/signs overlap with other conditions
* Specific inheritance patterns means that a diagnosis in one family member may lead to a diagnosis in relatives
* Some precipitants of attacks are known and thus can be avoided
* They appear on exam questions more frequently than their prevalence in real life! Porphyria is rare (prevalence 0.5-10 per 100 000).

**Porphyrias: A group of seven disorders caused by deficiencies in the activities of the enzymes of the haem biosynthetic pathway, leading to overproduction of toxic haem precursors and acute neuro-visceral symptoms and/or cutaneous symptoms.**



Signs & symptoms (acute attack)

* Abdominal pain (>80%)
* Tachycardia (>80%)
* Dark urine
* Peripheral motor neuropathy
* Constipation
* Nausea, vomiting
* Mental changes
* Hypertension
* Absent reflexes
* Back pain
* Sensory neuropathy
* Postural hypotension
* Convulsions
* Chest pain

**What you need to know…**

* Definition
* Have some idea of the biochemical pathway involved
  + Haem synthesis with negative feedback control
  + Mitochondrial and cytosolic enzymes
  + Principle organs involved in heme synthesis: liver & erythroid bone marrow
* YOU DO NOT NEED TO REMEMBER EVERY STEP ALONG THE PATHWAY
* Clinical presentation & classification
  + Acute vs non-acute
  + Neurovisceral and/or cutaneous manifestations
  + Two porphyrias to know in more detail:
    - Acute intermittant porphyria (AIP)
    - Porphyria cutanea tarda

(Presentation, diagnosis, enzyme deficiency, inheritance, precipitating factors, treatment)

* Approach to diagnosis and treatment of a suspected porphyria.

Principles of management

*General*

Analgesia

Fluid balance

Carbohydrate support

Cardiovascular support

Motor neuropathy (respiratory support)

*Specific*

Intravenous haem

*Preventative*

See list of drugs to avoid [www.porphyria-europe.com](http://www.porphyria-europe.com)

|  |  |  |  |
| --- | --- | --- | --- |
| **Acute Porphyrias** | | | |
| *Neurovisceral manifestation only* | | | |
| Acute intermittent porphyria | AD | Porphobilinogen deaminase | Acute attacks |
| ALA dehydratase deficiency | AR | ALA dehydratase | Acute attacks or chronic neuropathy |
| *Neurovisceral and/or cutaneous manifestations* | | | |
| Variegate porphyria | AD | Protoporphyrinogen oxidase | Acute attacks & skin fragility |
| Hereditary coproporphyria | AD | Coproporphyrinogen oxidase | Acute attacks & skin fragility |
| **Non-acute porphyrias** | | | |
| *Cutaneous manifestations only* | | | |
| Congenital erythropoietic | AR | Uroporphyrinogen III synthase | Photosensitivity |
| Porphyria cutanea tarda | AD/Sp | Uroporphyrinogen decarboxylase | Skin fragility |
| Erythropoietic protoporphyria | AD | Ferrochelatase | Photosensitivity |

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**References:**

Kauppinen R, Lancet 2005;365:241-52 (overall review).

Anderson KE, Ann Intern Med 2005;142:439-450 (diagnosis and treatment).

[www.porphyria-europe.com](http://www.porphyria-europe.com) (very useful website: diagnosis, treatment etc.)

**Theme: Porphyrias**

OPTION LIST

|  |  |  |  |
| --- | --- | --- | --- |
| A | 5-aminolevulinic acid | I | Uroporphyrinogen III |
| B | Convulsions | J | Abdominal pain |
| C | Acute intermittent porphyria | K | King Henry VIII |
| D | Aminolaevulinic acid dehydratase deficiency | L | King George III |
| E | Aminolaevulinic acid synthase | M | King Edward I |
| F | Porphobilinogen deaminase | N |  |
| G | Porphyria cutanea tarda | O |  |
| H | Toxic porphyria | P |  |

For each scenario below, choose the most appropriate answer from the list above. Each option may be used once, more than once or not at all.

1. Autosomal dominantly inherited porphyria with neurovisceral manifestations only, resulting from porphobilinogen deaminase deficiency.

2. One of the commonest presenting features of acute porphyria

3. Autosomal dominantly inherited (or spontaneous mutation) porphyria with cutaneous manifestations only, resulting from uroporphyrinogen decarboxylase deficiency

4. Enzyme that catalyses the rate-limiting step of heme bio-synthesis

5. Porphyria has been suggested as a possible diagnosis in this king

ANSWERS

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 1. | 2. | 3. | 4. | 5. |

**Theme: Porphyrias**

OPTION LIST

|  |  |  |  |
| --- | --- | --- | --- |
| A | Alcohol | I |  |
| B | Urinary porphobilinogen | N |  |
| C | Low dose contraceptive | J |  |
| D | Phenytoin | L |  |
| E | Plasma porphyrin levels | M |  |
| F | Haem arginate | K |  |
| G | Sun exposure | P |  |
| H | Propanolol | O |  |

For each scenario below, choose the most appropriate answer from the list above. Each option may be used once, more than once or not at all.

1. Specific therapy used in the management of acute porphyrias

2. Anti-epileptic contraindicated in patients with porphyria

3. First line diagnostic test in suspected attack of acute porphyria

4. Useful in preventing cyclical attacks of porphyria in women

5. Causes excitation of porphyrin molecules and cutaneous symptoms

ANSWERS

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 1. | 2. | 3. | 4. | 5. |

Pyrexia of Unknown Origin & Endocarditis

Dr Claire Thomas

**Definition of PUO**

* Fever higher than 38.3ºC (101ºF) on several occasions, persisting without diagnosis for at least 3 weeks in spite of at least 1 week of intensive investigations (Petersdorf & Beeson 1961, Medicine 40:1-30)

**Classification**

* Classic PUO
* Nosocomial PUO
* Immune deficient PUO
* HIV-associated PUO

**History**

* Temperature pattern in absence of antibiotics
* Travel
* Occupation
* Contacts
* Pets
* Drugs
* Operations
* Familial disorders

**Physical Examination**

* May reveal focus in up to 60%
* Repeated examination usually necessary
* Temperature, CVS, RS, GIT, GUS, CNS, Skin rashes, Lymph nodes, Dental examination, Musculoskeletal, Fundoscopy

**Initial investigations**

* FBC, U&Es, LFTs, Bone, CRP, ESR
* 3 blood cultures w/o antibiotics
* Thick and thin blood films x 3 (if appropriate travel history)
* Urinalysis and culture
* Stool culture and occult blood
* CXR

**Further investigations** (depending on results above)

* Tuberculin skin test/Elispot
* HIV
* RhF, Autoantibodies
* LDH
* Serology for relevant infection, Serum save
* Ultrasound scan abdomen, Further imaging

**Even more…**

* Opthalmology, Dermatology or Haematology opinion.
* Biopsies: LN, liver, bone, gut
* Bone marrow (count & culture for TB)
* Bone scan
* Bronchoscopy and BAL
* Convalescent serology - titre rise

**Causes of PUO**

* Adults
  + Infections (34%)
  + Neoplasms (20%)
  + Connective tissue diseases (13%)
  + Miscellaneous(20%)
  + Undiagnosed (13%)
* Children
  + Infections (44%)
  + Auto-immune disorders (7.5%)
  + Neoplasms (3%)
  + Miscellaneous (3%)
  + Undiagnosed (42.5%).

**Infections**

* **Bacterial** 
  + Mycobacteria, Enteric fevers, Brucellosis, Psittacosis, Q-fever, Cat scratch disease, Borrelliosis, Leptospirosis, Kawasaki syndrome
  + Focal – Abscess, Cholecystitis, Osteomyelitis, Endocarditis
* **Viral** 
  + EBV, CMV, Hepatitis B or C, HIV
* **Parasitic** 
  + Malaria, Amoebic liver abscess, Schistosomiasis, Toxoplasmosis, Trypanosomiasis
* **Fungal** 
  + Cryptococcosis, Histoplasmosis, Pneumocystis

**Neoplastic Diseases**

* Hodgkin's Disease, Non Hodgkins Lymphoma, Colon carcinoma, Leukaemia, Renal cell carcinoma, Atrial myxoma, Hepatoma

**Autoimmune diseases**

* Still's disease, Systemic Lupus Erythematosus, Polymyalgia rheumatica, Erythema multiforme, Rheumatic Fever

**Granulomatous Diseases**

* Temporal arteritis, Granulomatous Hepatitis, Sarcoidosis, Crohn's disease

**Inherited Disorders**

* Familial Mediterranean Fever, Cyclic Neutropenia, Fabry's Disease

**Drugs**

* Septrin, vancomycin, penicillins, tetracycline, isoniazid
* Fever +/- rash, eosinophilia, neutrophilia, raised LFTs
* Rx - Stop drug, antihistamines +/- steroids

**Fever in returning traveler**

* Malaria (32-42%), RTI, Diarrhoeal illness, Hepatitis, UTI, Dengue fever, Enteric fever, Viral, Undiagnosed (25%)

**Nosocomial fever** (Hospital acquired infections, LHI, PHLS Colindale, 1997)

* UTI (1.6/100 admissions), LRTI (0.74/100 admissions), IV line infection (0.3/100 admissions), SSTI
* Septic screen (urinalysis, blood culture via line and peripheral, CXR)

**Fever in neutropaenic patient**

* Pyogenic bacteria **-** CVC infection**,** Pneumonia, Mucositis, UTI
* Pneumonitis (RSV, Influenza), Aspergillosis, CMV disease, Tumor related fever, Drug related

**Fever in HIV**

* Tuberculosis, MAC, visceral Leishmaniasis, PCP, NHL, Bacterial, CMV, Toxoplasma, Cryptococcus, HIV, Drugs, Other

**ENDOCARDITIS**

**Epidemiology**

* Incidence: 4 cases/100,000 persons/year
* Mortality: 30%

**Risk groups** (Clin. Pathol. 1992;45:945-948)

* Prosthetic valves 35%
* IVDU 22%
* Congenital heart defects 15%
* Rheumatic heart disease 6%
* Other 23%

**Aetiologic Agents**

* **Native valve** 
  + Viridans streptococci (30-40%)
  + Enterococci (5-18%)
  + Other streptococci (5-15%)
  + Staphylococcus aureus (10-20%)
  + CNS (1-3%)
  + HACEK (5%)
  + Other (gram negative orgs & fungi) 5%
  + Culture negative (5-20%)
* **Prosthetic valve: early onset** 
  + S. aureus (28%)
  + CNS (40%)
  + Gram negative bacilli (18%)
  + Diptheroids (8%)
  + Fungi 4%
  + Streptococci 3%
* **Prosthetic valve: late onset** 
  + Viridans streptococci (40%)
  + Enterococci (3%)
  + S. aureus (13%)
  + CNS (24%)
  + Gram negative bacilli (13%)
  + Fungi (3%)

**History**

* Fever, Non-specific symptoms (anorexia, weight loss, malaise, fatigue, chills and night sweats), Acute symptoms (Shortness of breath, chest tightness, Embolic complications),Dental history, Rheumatic fever, Congenital heart disease, Valve replacement, other cardiac surgery, IVDU

**Examination**

* Heart murmurs, Splinter haemorrhages, Finger clubbing, Petechiae, Janeway lesions, Osler nodes, Roth spots, Splenomegaly, Haematuria

**Investigations**

* Urinalysis, FBC, U&E, CRP, ESR
* Blood cultures x 3
* CXR
* Echocardiogram
* Further as directed – CT, USS

**Duke’s criteria for diagnosis of endocarditis**

* Definite diagnosis: 2 major criteria or 1 major plus 3 minor
* **Major**

1. Persistent bacteraemia (>2 +ve BCs)
2. Echocardiogram: vegetation
3. Positive serology for Bartonella, Coxiella or Brucella

* **Minor**

1. Predisposition (murmur, IVDU)
2. Inflammatory markers (fever , CRP high)
3. Immune complexes: splinters, RBCs in urine
4. Embolic phenomena: Janeway lesion, stroke
5. Atypical echocardiogram
6. Only 1 positive BC

**Therapy guidelines for endocarditis** (JAC 2004;54:971-981)

* Empirical
  + Acute – Flucloxacillin
  + Indolent – Penicillin + gentamicin
  + Prosthetic – Vancomycin + gentamicin + rifampicin
* For Viridans Streptococcus - Penicillin 1.2g 4hrly + gentamicin 80mg tds
* For S. aureus – Flucloxacillin 2g 4-6 hourly

**Complications**

* Cardiac
  + Destruction of valve, Valve ring / aortic root / myocardial abscesses, Myocardial Infarction, Cardiac failure, Arrythmias
* Systemic
  + Systemic embolisation (Kidney, Brain, Spleen, Lung, Skin, Eyes)
  + Glomerulonephritis

**Indications for surgery** (Heart 2004;90: 618-620)

* Heart failure
* Vegetations and high risk embolisation
* Peri-valvular infection
* Uncontrolled infection
* Valvular obstruction
* Prosthetic valve endocarditis

Zoonoses & Arthropod-borne Diseases

Dr Claire Thomas

***Learning Objectives:***

This lecture will introduce the definitions of zoonotic and arthropod-borne diseases and give an indication of the breadth of this important area for human infection.

As time is limited for this vast area, only selected examples of zoonotic agents and arthropod-borne diseases will be discussed in more depth. The two major zoonoses to be covered in more detail are rabies and brucellosis. Lyme borreliosis and plague will be used as examples of arthropod-borne diseases (it is probable that malaria will have been dealt with elsewhere during the course). Sources for further reading will be indicated.

***Learning outcomes:***

**After this session it is expected that students should have**

a clear understanding of what is meant by zoonotic or arthropod-borne disease.

Understanding of the scope and importance of these multi-host infections, coupled with knowledge of factors that influence the occurrence of zoonoses.

Diagnostic indicators of zoonoses/arthropod-borne disease.

In-depth examples of selected zoonoses and arthropod-borne diseases.

**Introduction to zoonoses**

Zoonoses are infections acquired from animals and include viruses, bacteria, parasites and fungi. Transmission can occur through direct contact, inhalation, food and milk products, saliva, faeces, urine, blood and live tissues. Greater detail using selected examples of viral and bacterial zoonoses will be given. For these agents, risk factors, routes of infection, clinical signs, laboratory diagnosis and patient management will be outlined.

***Rabies:*** This is an acute, progressive, incurable viral encephalitis.

The causative agents are “bullet-shaped” neurotropic RNA viruses belonging to the family Rhabdoviridae.

The greatest risk to man is through contact with rabid dogs with transmission usually through being bitten. Once infected, the virus migrates towards the central nervous system. Incubation is usually between 1-3 months, however this may vary depending on site of exposure.

Control is through prevention or intervention before clinical onset. This is achieved through use of vaccination and administration of immunoglobulin. Despite much progress in control of rabies, this disease is still a major public health concern.

***Brucellosis:*** This is a major worldwide zoonoses still causing significant clinical impact in many countries, particularly those where recent conflicts or poverty have distracted attention from disease control programmes.

Although the UK is “officially brucellosis free”, re-introduction is still a threat through movements of livestock. Infection is also acquired abroad, with clinical cases presenting as “pyrexia of unknown origin” or “undulant fever” upon their return.

Although rarely life-threatening, this is a severe and debilitating disease. Indeed, it was the first bacterial agent to be weaponised by the American military.

The causative organisms are facultative extracellular pathogens and usually one of   
*Brucella melitensis, B . abortus* or *B. suis.* This pathogen can infect multiple lymph nodes, organs, bone marrow and the central nervous system where it may cause meningoencephalitis or granulomatous lesions.

Treatment can be achieved through lengthy therapeutic regimes of doxycycline and streptomycin.

**Arthropod-borne diseases**

Arthropod-borne diseases are transmitted through arthropod vectors including sand flies, mosquitoes, lice and ticks. Greater depth will be given on two examples, one endemic in the UK, borreliosis and the other exotic, plague. Risk factors, clinical signs, diagnosis and patient management will again be discussed.

***Borreliosis:*** *Borrelia* can cause different clinical diseases. Lyme borreliosis results from infection with *Borrelia burgdorferi, B. garinii* or *B. afzelii* all of which are transmitted by *Ixodid* or “hard” tick vectors.

The disease has protean manifestations, but will frequently present with skin rashes known as erythema migrans. This may be followed by joint, neurological and occasionally chronic dermatological manifestations.

Diagnosis is usually achieved through serology and treatment usually with doxycyclines or penicillins. A “soft” Ornithodoros tick serves as the vector for other pathogenic Borrelia that cause tick-borne relapsing fever caused by Borrelia duttonii.

These spirochaetes are a major cause of death in children in endemic areas.

***Plague:*** *Yersinia pestis,* the bacillus responsible for bubonic plague, has caused major pandemics of “Black Death” throughout history. This disease should not just be considered as one in the history books, indeed, it is now considered to be a re-emerging disease in several areas.

The bacterium is transmitted by more than 30 species of flea, and has its reservoir in rodents (over 300 species, but especially rats and ground squirrels).

Human infection is usually through the bite of an infected flea, however transmission can also be through contact or via inhalation from a case of pneumonic plague.

Approximately 10,000 cases with 1000 deaths per decade still occur in places such as New Mexico, Arizona, Africa and India.

Treatment is usually with tetracyclines, aminoglycosides or chloramphenicol.

***Comment:***

Diagnosis is often delayed for these infections especially when history of exposure to animals or arthropod vectors is not given. This is in part through manifestation of protean clinical signs and failure to recall likely exposure routes for infection. Furthermore, although many of these infections are considered to be exotic, with global climatic changes, increased travel (people, livestock and pets), and indeed occasionally the vectors themselves doing the international travel, they should be remembered as possible infectious causes for clinical consideration. Changes of livestock management practices, environmental encroachment, fashion for owning exotic pets, petting zoos, or consumption of bush meat, are just some of the factors that can influence the incidence of zoonoses, or even emergence of new zoonoses through provision of opportunity to transfer between species.

**Further Reading:**

**(1-17)**

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Urological Pathology

Dr Rathi Ramakrishnan  
(handout courtesy of Dr Marjorie Walker)

**Learning objectives**

To know the histopathological features and clinicopathological significance of the main aspects of urologic pathology.

**BLADDER**

* Non neoplastic diseases – cystitis, malformations
* Transitional cell carcinoma

**PROSTATE**

* Non neoplastic diseases – prostatitis, prostatic hyperplasia
* Prostate cancer

**TESTES**

* Non neoplastic diseases – undescended testes, inflammation
* Seminoma, teratoma

**KIDNEY**

* Non neoplastic diseases – inflammation
* Renal cell carcinoma

**BLADDER**Normal bladder is lined by transitional epithelium, with an underlying smooth muscle layer

**Congenital abnormalities**

•Extrophy

•Vesico-ureteric reflux

**Inflammation/infection**

**Cystitis**

•Infections  
E coli, proteus, enterobacter, TB, candida

•Proximity of short female urethra to alimentary tract faecal flora, stasis of urine in bladder - prostatic outflow obstruction, bladder stones, urethral strictures

•Active inflammation - polymorphs

•Chronic inflammation - lymphoid follicles

•Cystitis cystica

•Follicular cystitis

•Interstitial cystitis

•Malakoplakia

**Tumours**

•Transitional cell carcinoma

•(Squamous, adenoca, lymphoma, sarcoma can also occur)

**Transitional cell carcinoma**

•Association with smoking, chemical exposure –

naphthylamine, benzidine, 4-diphenylaniline

•3:1 male:female preponderance

•Presentation:

•Haematuria, 'cystitis'

•GPs will see 1 new patient with TCC /3-4 years

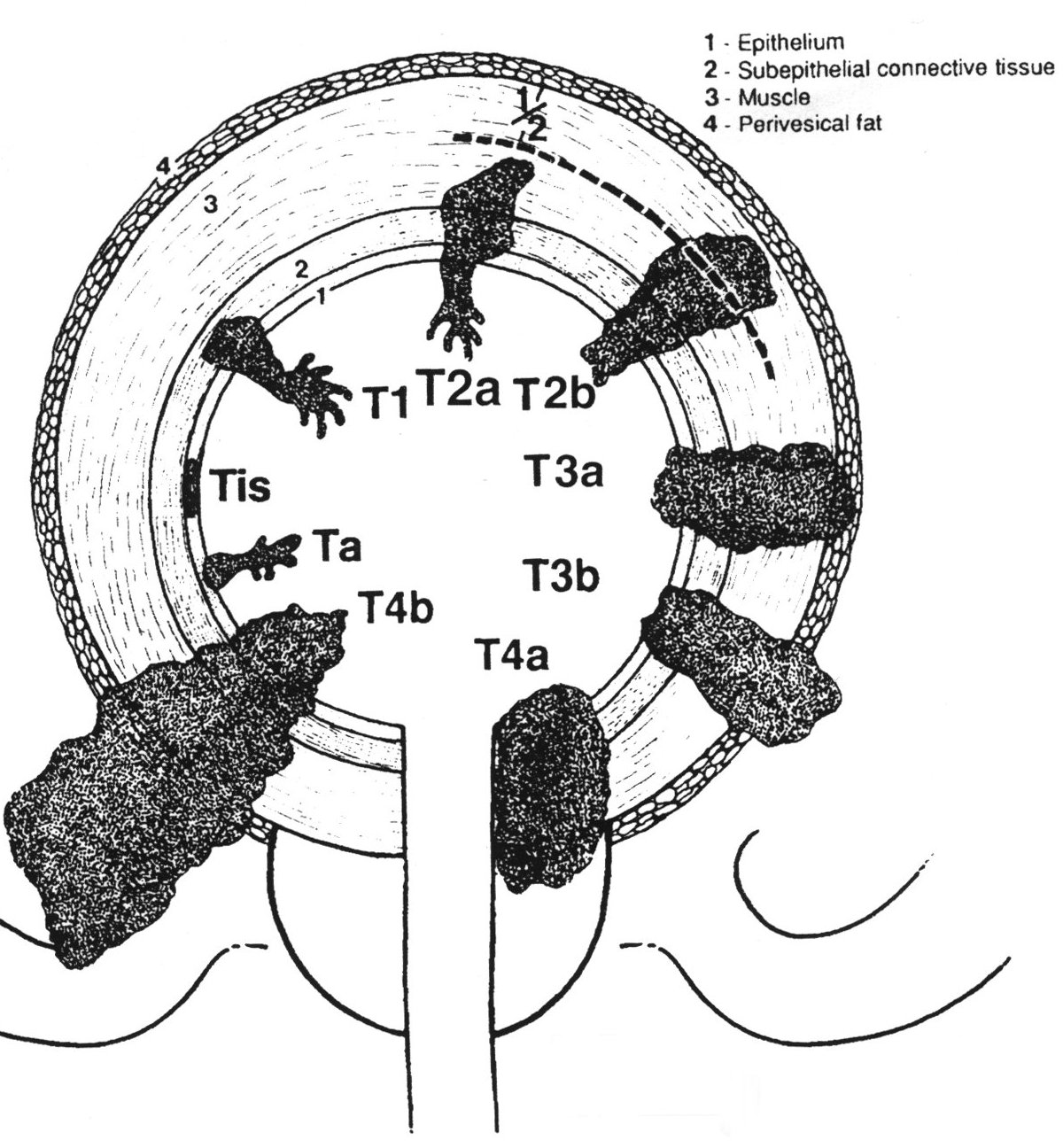
•One stop Haematuria clinic

•Prognosis depends on stage/grade

•TMN classification

**T = pT**

•At initial diagnosis, 70% of tumours are Tis, Ta, T1 i.e. superficial



**T = pT**

•T2 - invasion into muscle - death 3-5 yrs

•CIS - poor prognosis

•Grade 3 - poor prognosis

•Resection - papillary tumours

•Intravesical chemotherapy

•Intravesical BCG

•Radiotherapy

•Cystectomy

Squamous cell carcinoma

Adenocarcinoma

•Metaplasia of transitional epithelium to squamous in chronic damage

•Schistosomiasis

•Bladder apex - urachal remnants

•Secondary tumours

**Prostate**

Prostate situated at bladder neck, composed of gland acini interspersed by stromal smooth muscle and fibrous tissue, arranged in lobes, which are palpable by digital examination   
The glands produce ejaculatory fluid

•Inflammation

•Prostatitis

•Infective - gonococcus, e coli, staph

•Chronic - follows repeated infection

•Granulomatous - TB, following surgery

**BPH**

•Benign prostatic hyperplasia

•Benign nodular hyperplasia

•Common ++++

•Androgens oestrogens

•Central (periurethral) part of gland

•Nodular hyperplasia with gland and stromal hyperplasia, adenomyomatous hyperplasia Not premalignant

Bladder outflow obstruction

Sphincter involvement

Distortion of urethra

Symptoms: dribbling, poor stream, difficulty in micturition

•Acute retention

•Chronic retention - Stasis of urine, infection

•Hypertrophy of bladder muscle

•Hydroureter

•Hydronehrosis

•Pyelonephritis

Treatment

•TURP

•40,000 in 1993!

•5--reductase inhibitors?

•Laser?

•Microwave?

**Prostate adenocarcinoma**

•Cancer mortality in males 2nd to lung –1991 now rising++

•Increasing incidence - 11% of male cancer deaths in 1990

•Life time risk in USA 9-11%

•Loss of 9 years of life

•50-60% present with metastatic disease

•Foci of well diff ca in 30-40% in males 75+ at PM

Risk factors:

· Diet - high fat, green veg protects

· Genetic

· Cadmium, Radiation

· Sexual history

· Androgens

Diagnosis:

· Incidental

· Symptomatic

· DRE

· US

· PSA

Screening programmes?

40:1 ratio of fatal: non fatal cancers

need to recognise 'fatal' type

Arise in peripheral zone

Adenocarcinoma and PIN

Metastases:

· Bone - sclerotic lesions

· Lung, liver

· Lymph nodes

•Grade - Gleason system

**Treatment**

•Watch and wait

•Antiandrogen therapy - chemical

•Radiotherapy brachytherapy

•Radical prostatectomy

**TESTIS**  
•Testis composed of seminiferous tubules **-** germinal epithelium, spermatogenesis Tubules - 250 lobules, divided by fibrous septae, tunica albuginea The tubules converge to the rete testis to efferent ductules to the epididymis Tunica vaginalis surrounds testis

•**Hydrocoele** Forms in tunica vaginalis

•**Haematocoele** Trauma

•**Torsion** Pubertal males, pain +++

–anatomical abnormalities, maldescent, long spermatic cord - Infarction

•**Maldescent**/**Cryptorchidism**

•5% one or both testes undescended, majority 1st birthday

•Neoplasia risk **-** 10x more likely to develop tumour**,** 10% of tumours in cryptorchid testes

**Inflammation/infection**

•Mumps, Epididymo-orchitis - gc

•Syphilis

•Granulomatous orchitis

**Infertility**

•Endocrine,

•Testicular lesions, Vas obstruction

**Testicular neoplasms**

•Commonest cancer in men aged 20-34 in UK

•95% are germ cell tumours

•40% seminomas

•60% teratomas

•**Survival for early stage disease is high - 95-100%**

Much better treatment is available

**Seminoma**

•Presentation:

•Painless swelling

•Classical seminoma

•Spermatocytic seminoma - 3-5% older age group

**Teratoma**•presentation - as seminoma

•Endo,ecto and mesoderm

**Other testicular tumours**

•Leydig cell tumour - 2%

•Adenomatoid tumours

–Epididymis

–Mesothelial origin

**Kidney: Benign Neoplasms**

•**Oncocytoma**

•difficult to distinguish from RCC –

•central stellate area of fibrosis, little haemorrhage or necrosis

**Renal cysts**

**Common**

•**Angiomyolipoma**

•Tumour composed of variable amounts of mature fat, smooth muscle, and thick-walled blood vessels

•Tuberose sclerosis

• **Renal cell carcinoma (RCC)**

Common - 4 – 6/ 100,000 M:F ratio 2:1

•Genetic abnormalities

•Present with palpable mass, flank pain, haematuria

•Risk factors – smoking obesity, drugs industrial, stones

•Von Hippel-Lindau

•Renal tubules

•Classic RCC clear cell

•Chromophil RCC,papillary RCC,

•Chromophobe RCC –100 cases

•Fuhrman grading

•Polycystic kidney disease is possible risk

•Most cases –unknown

Fungal infections

Dr Michael A Petrou

The Fungal Kingdom includes a variety of ***eukaryotic*** organisms whose classification is based on their structural appearances and they can have both sexual and non-sexual methods of reproduction.

Broadly, the fungi of medical importance are divided into ***yeasts***, ***moulds***, and ***dimorphic*** fungi (possessing features of yeast during infection and mould in nature).

**Yeasts** are unicellular, possessing round, oval or elongated structures and reproduce mainly by budding. Examples are ***Candida albicans*** and ***Cryptococcus neoformans***.

**Moulds** consist of branching structures called ***hyphae*** which can form a ***mycelium***, and ***spores*** which are the reproductive structures.

There are about 1.5 million fungal species but only a handful regularly cause human diseases.

***Fungal infections:*** can be classified according to the part of the body that they affect. Generally most of the infections that arise in ‘normal’ hosts are ***superficial mycoses*** involving the skin, hair and the nails (the main example here is the ***Ringworm*** or ***dermatophyte*** fungi), or mucosal surfaces of the mouth or genital tract (e.g. ***vaginal candidiasis*** or ***thrush***).

The systemic or invasive mycoses arise when the infection breaches the skin or mucosal barrier, becomes disseminated via the bloodstream and involves a vital organ such as the brain, kidney, heart or liver. These infections more commonly arise in critical care or immunocompromised patients. The principal invasive mycoses are candidiasis and aspergillosis (primarily due to the mould ***Aspergillus fumigatus***).

Another category is the ***subcutaneous or deep seated mycoses***. These are found or acquired in tropical or sub-tropical counties and result from traumatic implantation of a fungus into the skin which then extends to deeper tissues including bone.

The ***Diagnosis*** of fungal infections is often difficult because they are slow growing organisms compared to bacteria and therefore may be masked by bacterial growth in cultures. Also invasive fungal infections are difficult to diagnose because of difficulties in obtaining biopsy material from affected organs. Serological and molecular techniques are limited to Aspergillus, Cryptococcus and Candida.

**Superficial mycoses:**

For **superficial mycoses** skin, hair or nail samples are taken, usually by general practitioners and Dermatologists, and are dispatched to Microbiology/Mycology laboratory for microscopy, looking for fungal elements, and culture. The principal fungal pathogens are the dermatophytes (those causing ringworm) of which there are 3 genera ***Trichophyton****,* ***Microsporum*** and ***Epidermophyton****.* They can be acquired from soil (geophilic), from animals including domestic pets (zoophilic) or humans (antropophilic). ***Tinea capitis*** (common in children) refers to ringworm infection involving the scalp and can involve both skin and hair, while **tinea pedis** (*athlete’s foot)* is another example. **Tinea unguium** and ***onychomycosis*** are terms used to describe the same thing, fungal infection of the fingernails or toenails. It is important to understand that dermatophytes have their preference for site of infection for example a dermatophyte causing scalp infection might not be capable of infecting nails and *vice versa*. Many moulds can also cause this type of infection particularly involving the nail and surrounding skin.

***Vaginal candidiasis*** is a common infection in women of child bearing age. It causes an itchy discharge which when examined in the lab by microscopy reveals many yeasts and pseudohyphae typical of *Candida albicans* which is the main pathogen. **Oral Candidiasis** can occur at the extremes of age, can complicate denture stomatitis, and can be a presenting feature of HIV infection. *Candida* can also cause infection of the skin and nails (***paronychia***).

***Pityriasis versicolor*** is a benign skin condition characterised by a scaly rash usually on the trunk which may cause hypo- or hyperpigmentation of the skin. It is due to a lipophylic fungus called *Pityrosporum* or *Malassezia furfur*.

**Invasive fungal infections**

These are most commonly due to *Candida* species, about 50% due to C. albicans, and arise in both critical care patients (usually seen in intensive care units) and in the immunocompromised such as patients with haematological malignancy. ***Candidaemia*** is an infection of the bloodstream with a mortality rate >40% and which is diagnosed by detecting the fungus in blood cultures. ***Invasive aspergillosis*** is a major opportunistic infection in immunocompromised patients especially bone marrow (or stem cell) and solid organ transplant recipients, with a mortality rate of upto 95%. It almost invariably presents as pneumonia and is very difficult to diagnose other than by suggestive CT imaging features and serum ELISA. Other invasive mould infections that occur less often are Mucormycosis (common in diabetic patients) and Fusariosis (particularly keratitis).

***Cryptococcosis*** is a systemic fungal infection due to the yeast *Cryptococcus neoformans* a fungus associated with pigeons, eucalyptus and other trees. It is the principal fungal infection of the central nervous system which presents as meningitis often with an insidious onset. It occurs mainly in AIDS patients but can be seen in other solid organ transplant and other immunocompromised hosts.

The principal endemic mycosis is ***Histoplasmosis*** due to the dimorphic fungus *Histoplasma capsulatum.* It is only found in distinct geographical locations examples being central parts of North America and caves with bats. It can cause a self-limiting respiratory infection resembling flu in normal hosts and a severe opportunistic infection in the immunocompromised patient, particularly those with HIV.

The most dangerous fungus is ***Coccidioides immitis*** and can be found between North and South America particularly theSan Joaquin Valley.

**Subcutaneous or deep seated mycoses:**

The main fungi causing this type of infections are the moulds. The most common belong to the Phaeohyphomyces group with Madurella mycetomatis the most important.

**Diagnosis:**

Diagnosis depends on the type of infection.

**Superficial mycoses:**

Microscopy and culture is the main tool for diagnosing superficial mycoses. It is very important to have the infective fungus identified for both epidemiological as well as treatment reasons. A few labs started applying PCR for screening specimens however there are more problems than benefits at present. The treatment for nails can vary from 3 to > 12 months therefore it is advisable to have the diagnosis prior to treatment as the choice of drug can be influenced depending to whether it is a dermatophyte or a mould.

**Invasive fungal infections**

The main tool as with the superficial mycoses is microscopy and culture however there are many commercial products for diagnosing different types of infection. Radiological investigations such as X-Rays, CT scan, MRI and PET scan are the first line of test used when an invasive fungal infection is suspected, particularly in the immunocompromised host; these tests and how to interpret them will be covered by the Radiology Department.

1. **Antigen**
   1. Latex- this is limited to *Cryptococcus* infections; this test detects capsule polysaccharides
   2. ELISA- Limited to Aspergillus infections; detects Galactomannan the main polysaccharide in Aspergillus species
   3. Β-Glucan- this is the main component of almost all the fungi and its detection indicates a fungal infection; however this is non-specific and some fungi such as the Mucorales and Cryptococcus produce very small amounts of β-glucan.
2. **Antibody**
   1. Precipitins for Aspergillus
   2. Endemic mycoses (also known as Category 3 fungi); a vatiety of tests
   3. Candida- useful for monitoring patients in ICU
3. **Molecular**
   1. PCR has been used successfully by some institutions and this resulted in considerable savings, however due to lack of standardisation this technique is not accepted as marker for invasive fungal infection at present

**Antifungal Drugs and Treatment Choices**

**Antifungal Drugs**

There are three distinct groups of antifungal agent the polyenes, the triazoles and the Echinocandins as well as several single drugs such as flucytosine, terbinafine, griseofulvin, and amorolfine. There are also many azoles world wide however with the exception of ketoconazole these are only used for topical treatment.

**Mode of action:**

**Polyenes-** cell membrane interaction resulting in pore formation

**Azoles and triazoles-** Cytochrome p450, inhibition of ergosterol biosynthesis

**Echinocandinds-** inhibition of cell wall synthesis

**Flucytosine-** metabolised to 5-fluorouracil causing errors in protein, RNA and DNA

**Terbinafine and Amorolfine-** inhibition of ergosterol biosynthesis

**Griseofulvin**- inhibition of mitosis thus nucleic acid synthesis

**Treatment** of fungal infections is limited by the fact that there are relatively few ***antifungal agents*** compared to antibacterial antibiotics as well as by the fact that unlike the prokaryotic bacteria the eukaryotic fungi have many similarities to the eukaryotic humans.

For dermatophyte infections ***terbinafine*** (an allylamine compound) and ***itraconazole***(a triazole) are the most effective agents. For mucosal or cutaneous candidiasis the triazole ***fluconazole*** is the agent of choice. For invasive fungal infections the polyene ***amphotericin B*** is often used as the agent of choice but it is nephrotoxic which often limits the duration of therapy thus its lipid formulations are preferred.

Apart from the triazoles (fluconazole, itraconazole, voriconazole and posaconazole) and polyenes (amphotericin B, Nystatin, AmBisome, Abelcet and Amphocil) a new class of antifungals called ***Echinocandins,*** (Caspofungin, Micafungin and Anidulafungin) offer a less toxic treatment choice for many fungi and in particular *Candida* sp.

Fortunately ***drug resistance*** is not a major problem with antifungal agents. An exception to this is *Candida albicans* infection in AIDS and other patients where the resistance to fluconazole results from prolonged exposure to the drug during prophylaxis. There is however a species shift when using triazoles from sensitive to resistant species.

***Further reading:***

Fungal Infection: Diagnosis and Management

MD Richardson & DW Warnock

Blackwell Science 3rd Ed. 2003.

Wound, Bone and Joint Infections

Dr Dunisha Samarasinghe

(handout courtesy of Dr Claire Thomas)

**Aims**

* Describe the context and type of wound bone and joint infections that affect humans with specific examples

**Objectives**

* List principle groups of bacteria involved in relation to the sites where they are relevant
* Describe the principle types of wound that occur and how they may be affected different bacteria
* Describe the pathogenesis of wound infection
* Describe examples of specific types of bone and joint infection

**Organisms you need to know about**

Staphylococcus aureus

Haemolytic streptococci

E.coli and coliforms

Bacteroides

Sporing anaerobes

**Risk factors for wound infection**

Pre-existing infection/skin disease

Foreign material (soil, clothing, debris, prosthesis, drain)

Immunosuppression

Hypoxia/hypothermia

Poor glucose regulation/diabetes

Devitalised tissue/poor oxygenation

**Microbiological Investigation of**

* **Wound infection.**

Pus

Swab

Tissue

* **Bone and joint infection**

Blood culture

Aspiration

Surgical debridement

**Interpretation**

* Results of wound swabs may be confounded because of normal flora or transient colonisation rather than true infection
  + Pyogenic cocci – Stapylococcus aureus, Haemolytic streptococci - treat
  + Intra-abdominal infection – treat according to laboratory results with micro/ID advice
    - Leg/pressure ulcers/burns
  + Staphylococcus aureus, Haemolytic streptococci and Pseudomonas aeruginosa – delay healing, may become invasive
  + Bone/Joint – normally sterile

**EMQ - Theme: Wound Infection**

**OPTION LIST**

|  |  |  |  |
| --- | --- | --- | --- |
| A | Airborne contamination | 3 | Implantation of a prosthetic hip |
| B | Oral administration of flucloxacillin | 4 | Haemophilus influenzae |
| C | Abdominal hysterectomy | 5 | I. V. injection of diazepam |
| D | Staphylococcal aureus | 6 | Drainage and evacuation of pus |
| E | I. V. injection of tetanus antitoxin | 7 | Escherichia coli |
| F | Oral administration of ampicillin | 8 | Removal of a breast carcinoma |
| 1 | Streptococcus pneumoniae | 9 | Oral administration of penicillin G |
| 2 | Heart valve replacement | 0 | I. V. injection of botulinum antitoxin |

**For each scenario below, choose the most appropriate answer from the list above. Each option may be used once, more than once or not at all.**

1. A 37 year old woman is complaining of pain a tenderness surrounding a recently sutured wound on her forehead. On examination you notice erythema and minimal serous discharge. Which pathogen is the most likely cause of this infection?

2. A 55 year old man comes into A&E complaining of a increasing difficulty in opening is mouth and that the muscles on his face occasionally spasm. On examination you observe that his eyes are partially closed and that the angles of his mouth are stretched outwards and slightly downwards. You also note that he has a very rigid abdomen. Which treatment option should be carried out first for this patient?

3. In which procedure is antibiotic prophylaxis not usually indicated

4. Postoperative inspection of a wound in the left axilla reveals the presence of an abscess. What is the appropriate treatment to resolve the abscess?

5. A man is recovering well from surgery but inspection of the wound suggests that it has become infected. A swab is taken and the laboratory results show Staphylococcal aureus infection. What is appropriate treatment for this man?

ANSWERS

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 1. | 2. | 3. | 4. | 5. |

EMQ Session – Enzymes, Chemsitry & Zoonoses

Prof Karim Meeran

**EMQ Theme: Enzymes**

OPTION LIST

|  |  |  |  |
| --- | --- | --- | --- |
| A | Acid phosphatase | 3 | Glucose |
| B | Alanine aminotransferase (ALT) | 4 | HBA1c |
| C | alkaline phosphatase | 5 | potassium |
| D | Aspartate amino transferase (AST) | 6 | sodium |
| E | Calcium | 7 | Triglyceride |
| F | Cholesterol | 8 | urea |
| 1 | Creatinine | 9 | vitamin D |
| 2 | Fructosamine | 0 |  |

**For each scenario below, choose the most appropriate answer from the list above. Each option may be used once, more than once or not at all.**

1. Which one of the above is increased in a patient with Paget's disease of the bone.

2. Which one of the above is increased in a patient with osteomalacia

3. Which one of the above is increased in a patient following an acute myocardial infarction.

4. Which one of the above is raised in Addison’s disease.

5. Which one of the above is most increased in a patient with jaundice caused by   
a gallstone

6. Which one of the above is most increased in a patient with jaundice caused by   
viral hepatitis

7. Which one of the above is most increased in a patient with jaundice caused by   
chronic alcoholic cirrhosis

8. Which one of the above is most increased in a patient with prostatic carcinoma.

9. Which one is raised in primary hyperparathyroidism

10 Which one is low in primary hyperparathyroidism

11. Which one rises most in acute renal failure where the cause is dehydration?

12. Which one rises most in chronic renal failure, caused by a fall in GFR?

13. Which one is a marker of glucose control over the last 3 months?

14. Which is a marker of glucose control over the last 3 weeks ?

ANSWERS

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 1. | 2. | 3. | 4. | 5. |

**EMQ Theme: Chemistry**

OPTION LIST

|  |  |  |  |
| --- | --- | --- | --- |
| A | Acute Gout | 3 | Primary hyperparathyroidism |
| B | Addison’s disease | 4 | Primary hypothyroidism |
| C | Cushing’s syndrome | 5 | Pseudogout |
| D | Diabetes insipidus | 6 | Rheumatoid arthritis |
| E | Diabetes Mellitus | 7 | Secondary hyperparathyroidism |
| F | Graves disease | 8 | Septic arthritis |
| 1 | Osteoarthritis | 9 |  |
| 2 | Pituitary failure | 0 |  |

For each scenario below, choose the most appropriate answer from the list above.   
Each option may be used once, more than once or not at all.

1. A 30-year-old man complains of polyuria and polydipsia. His fasting blood glucose is   
4.7 mmol/l. Biochemical investigations reveal Na 140mM, K 4.2mM, Ca 2.85mM, Phosphate 0.4mM, PTH 4.2 pM

2. A 50-year-old Asian woman complains of tingling in her hands and feet. When checking her blood pressure, her hands reveal carpal spasm. Her fasting blood glucose is 4.9 mmol/l. Biochemical investigations reveal Na 141mM, K 4.1mM, Ca 1.85mM, Phosphate 1.4mM, PTH 80 pM

3. A 51-year-old Asian woman complains of nocturia and dizziness.   
Her fasting blood glucose is 3.9 mmol/l. Biochemical investigations reveal   
Na 131 (135-145), K 6.1mM, Ca 2.75mM, Phosphate 1.0mM, PTH 1.3pM

4. A 60-year-old man complains of pain in his knee, and examination reveals an effusion. Withdrawal of fluid and microscopy reveals crystals, which on viewing under polarised light are positively birefringent.

5. Occurs in patients with Lesch-Nyhan syndrome.

6. Occurs in patients with osteomalacia

7. A 34-year-old man complains of polyuria and polydipsia. His fasting blood glucose is   
4.7 mmol/l. Biochemical investigations reveal Na 157mM, K 5.2mM, Ca 2.35mM, Phosphate 1.2 mM, PTH 4.2 pM

ANSWERS

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| --- | --- | --- | --- | --- |
| 1. | 2. | 3. | 4. | 5. |

**EMQ Theme: Zoonoses**

Normal ranges you should know

Na: 135 – 145 mM

K: 3.4 – 5.0 mM

Normal ranges that will be given to you in exams

Ca: 2.20 – 2.65 mM

Phosphate: 0.8 – 1.4 mM

PTH: 1.1 – 6.8 pM

OPTION LIST

|  |  |  |  |
| --- | --- | --- | --- |
| A | *Bacillus anthracis* | 3 | Rabies |
| B | *Borrelia burgdorferi* | 4 | *Rickettsia typhi* |
| C | *Brucella abortus* | 5 | *Yersina pestis* |
| D | *Brucella melitensis* | 6 |  |
| E | *Coxiella burnetii* | 7 |  |
| F | *Leishmania major.* | 8 |  |
| 1 | *Leptospira interrogans* | 9 |  |
| 2 | *Pasteurella multocida* | 0 |  |

For each scenario below, choose the most appropriate causative agent from the list above. Each option may be used once, more than once or not at all.

**1**. A 30 year man presented with jaundice and conjunctival haemorrhages. He had recently been canoeing in the US and had felt ‘run-down’ upon his return to the UK.

**2**. A 25 year old Maltese man presented to his GP with lethargy for a month and headaches and fever. On examination, he had a temperature of 39°C and one fingerbreadth splenomegaly. Small Gram-negative coccobacilli were seen on culture in Casteneda’s medium.

**3.** A 22 year old student presented to her GP upon return from a biology field trip, with a lesion on her leg which was 5cm in diameter and flat, with a red edge and dim centre. She also mentioned feeling tired and suffering from headaches. On examination, the GP noted a fever of 38.0°C and an irregular heartbeat

**4**. A tanner on holiday from India presented to hospital with an ulcerating papule on his hand. On inspection of the ulcer, the centre was black and necrotic. Gram-positive rods grew on blood agar culture and responded to treatment with large doses of penicillin.

**5**. A 49 year old man was admitted in A&E with a 3 day history of worsening right arm pain and a 1 day history of dysphagia, hypersalivation, agitation and generalised muscle twitching. Vital signs and blood tests were normal but he became confused.   
He developed renal failure and died 4 days later.

ANSWERS

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 1. | 2. | 3. | 4. | 5. |

Human Rights and Global Justice

(Ethics and law in pathology)

Dr Wing May Kong

**Mare Aleghan**

* 42 year old mother
* Late stage trachoma
* Unable to work through visual loss and pain
* Husband divorced her 10 years ago leaving her to bring up their 4 year old daughter alone
* Living on less than one dollar a day

**Trachoma – natural history**

Infection caused by *Chlamydia trachomatis*

Repeated infections cause scarring of the eyelids leading eyelashes to turn inwards and scar the cornea

Infection spread by direct contact and by Musca sorbens flies

Flies breed exclusively in human faeces

**Trachoma: an avoidable cause of blindness**

**S**

**A**

**F**

**E**

**Trachoma**

Eradicated from Europe and USA

However approx. 70 million sufferers worldwide, mainly in Africa and also Latin America and Asia

Cause of blindness in approx. 2 million

Women are 3 times more likely to have late stage, sight threatening disease

**Global Health inequalities**

The world is getting richer but…

**Are global health inequalities an ethical concern?**

Global health inequalities are a misfortune

The world would be better if global health inequalities could be reduced

However, life is full of misfortunes, some of which cause much suffering but not all of which we consider ethical concerns

**The libertarian position**

Individual liberty is the primary moral value

*The duty of the state is…*

*There is no moral duty to…*

**The libertarian rationale**

If I choose to work hard, it is right that I should reap the profits.

Provided my gains are honestly earned I have no moral obligation to help those less fortunate.

Any form of redistribution is unjust and equivalent to theft

**Libertarianism and bad luck**

That some people are born into poverty and extreme hardship is simply bad luck

**Libertarianism – an extreme view?**

Most people would like to pay less tax

Many believe that access to healthcare should be restricted when ill health is due to an individual’s personal choices

*How libertarian are you?*

**Libertarianism and global health**

Global health inequalities are unfortunate but are not an ethical concern

There is no moral obligation to help those less fortunate but, individuals are at liberty to help those in need through charity

**The benefits of charity**

Imagine a society where individuals only helped their friends and family because they were duty bound

*Charity fosters…*

**Charity and basic needs**

Some goods are optional luxuries that enrich our lives but are not essential for autonomous life

*However…*

**The problem with charity**

With charity recipients are dependent on the action of donors. They have no entitlement to such assistance

If individuals are dependent on charity to meet their basic needs, the donor-recipient relationship creates a power imbalance which undermines the autonomy of the recipient

**Global health and Utilitarianism**

*The morally right thing to do is that which brings about….*

All other things being equal, utilitarianism requires us take the actions which save more lives or reduce the most suffering

**Utilitarianism – on Acts and Omissions**

Under any consequentialist approach we are as morally responsible for our omissions as we are for our actions if the net result is the same

Therefore, if we fail to take a particular action to prevent suffering, we are as morally responsible as if we had directly caused that suffering

**Utilitarianism – too morally demanding?**

£10 would pay for a sight-saving operation for a trachoma sufferer

So if I pay for a download instead of donating the money to charity then I am as morally blameworthy as if I had given the sufferer poisoned eye drops which caused severe pain and blindness

*What do you think?*

**Utilitarianism and global health**

Therefore, rather than using our resources to improve our already comfortable lives, a utilitarian approach would require us to divert all our resources until all health inequalities had been removed

**Utilitarianism and individual rights**

Tom, Dick and Harry are extremely sick in hospital

Tom needs a bowel and liver transplant, Dick needs a heart transplant and Harry needs a liver transplant

Sally is a healthy 27 year old who happens to be visiting her sister in hospital and is an excellent tissue match for Tom, Dick and Harry

**So…**

The utilitarian transplant surgeon decides that the best solution will be to harvest the necessary organs from Sally (whether or not she is agreeable) and transplant them into Tom, Dick and Harry. Sally will die but three lives will be saved so overall net well-being is maximised

*Is this fair?*

**Justice and global health**

Libertarianism:

No moral obligation to help those in need

Assistance relies on charity

Utilitarianism :

Moral obligation to maximise well being

Do not recognise any individual right or entitlement to a decent level of health

**Justice**

Justice is concerned with the reciprocal relationship between individuals and society

It carries the fundamental notion that all humans are equally valued

Justice requires that equals are treated equally

**Justice and the State**

The just State must set up and maintain the social institutions needed to ensure justice is practised and upheld

A systematic failure to treat individuals fairly is unjust and implies that the State and its citizens consider such individuals of less value than others

**Is healthcare a matter for justice?**

Amartya Sen has argued that if we value all human lives equally then justice requires that we ensure that all individuals have an equal capability to flourish/pursue lives of value

Decent health and access to health care are necessary to achieve a minimally decent life

*Therefore, decent health access to healthcare is …..*

**Justice and Human Rights**

Rights are a special form of moral claim which impose obligations on others to ensure such claims are upheld

These rights apply to everyone whether or not the individuals are aware that the right exists

**The Human Rights Act 1998**

* The HRA 1998 incorporates the European Convention on Human Rights into English Law
* The Act is enforceable against public authorities **not** individuals or private bodies
* The Courts must interpret legislation consistently with Convention Rights

**The Human Rights Act and healthcare**

Public bodies such as the NHS must act in accordance with the HRA e.g.

Refusal of treatment

Medical confidentiality

Compulsory treatment and detention

Withdrawal of life sustaining treatment

Abortion

Assisted suicide

**The Human Rights Act and healthcare**

Article 2: Right to life

Article 3: Prohibition of torture

Article 5: Right to liberty

Article 8: Right to a private life

**Article 2 – Everyone’s life shall be protected by law**

The right is absolute with respect to intentional killing

Not all avoidable death counts as intentional killing

There is no absolute obligation to provided life saving treatment

Withdrawal of futile treatment will not breach article 2

The right does not extend to the fetus

**Article 3 – No one shall be subjected to torture or to inhuman or degrading treatment or punishment.**

This right is absolute

Non-consensual treatment of an incompetent individual may contravene article 3 if it is not therapeutically necessary

Excessive restraint may contravene article 3

Failure to legalise assisted suicide does not contravene article 3

**Article 5 – Everyone has the right to liberty and security of person**This right is not absolute

Detention is lawful if necessary for a mental illness

Individuals must have access to an effective and speedy means of challenging detention

* Appeal process under Mental Health Act
* Deprivation of Liberty Safeguards

**Article 8 – Everyone has the right for his private and family life**This right is not absolute

Protects a patient’s right to confidentiality

Protects the right to refuse medical treatment even if life saving

Article 8 will not be contravened if a breach is in accordance with the law AND is necessary in a democratic society

**Question 3**

B is a 61-year-old man who attends A+E with a history of fever and cough. He is a heavy smoker but denies any previous health problems. The on-call FY2 Dr R sustains a needlestick injury whilst taking an arterial blood gas. Dr R’s consultant is informed and asks B if he would be willing to have an HIV test. B refuses. Dr R does not want to take post exposure prophylaxis unless it is necessary. How would you advise Dr R?

1. The HIV test cannot be performed without consent
2. Dr R should go back and try to persuade B to consent to the test
3. Dr R should ask the lab to do an HIV test on a sample previously taken in A+E
4. B must consent to the test as otherwise it would be a breach of Dr R’s human rights under Article 3:
5. Dr R can do the HIV test on a sample previously taken provided she does not disclose the result to B
6. The hospital must perform the HIV test otherwise it will contravene Dr R’s right to life under Article 2:

**Question 5**

B made a good recovery with no evidence of neurological deficit. At discharge he was still refusing an HIV test. 3 years later B is brought into hospital with a headache and confusion. Dr R is now an ST3 in infectious diseases. B has a GCS of 10 (E3, M4, V3). A lumbar puncture is performed and confirms a diagnosis of cryptococcal meningitis. B’s HIV test comes back positive. The next day B’s conscious level is improved (E4, M6, V4) but he remains very confused.

His consultant says that there is a good chance that B will make a good neurological recovery.

B’s wife asks Dr R what is wrong with her husband. Should Dr R disclose B’s HIV status?

1. Disclose the diagnosis of HIV as his wife has a right to know under article 2 of the Human Rights Act
2. Disclose the diagnosis of HIV as B’s wife may have been exposed to HIV
3. Disclose the information if B’s wife has lasting power of attorney
4. Disclosure of B’s HIV status should wait until B is able to give consent
5. Dr R cannot disclose the diagnosis of HIV as B has an absolute right to confidentiality
6. The clinical team need to know B’s diagnosis of HIV so the information is no longer confidential and can be disclosed

**Is decent healthcare a human right?**

**The Universal Declaration of Human Rights 1948**

**Article 25**

Everyone has the right to a standard of living adequate for the health and well-being of himself and of his family, including food, clothing, housing and medical care and necessary social services…

**Healthcare - right or rhetoric?**

If healthcare is a human right, this imposes an obligation on others to ensure adequate healthcare is provided to all humans.

However, at a global level, who are these ‘others’ with whom the obligation rests?

Justice is a virtue of social institutions. Without the institutions to deliver these obligations, a right to decent healthcare is an empty entitlement and arguably no more than political rhetoric

**Global justice – moving forward**

The framework for global justice must be feasible and sustainable

The nation state must have primary responsibility for the healthcare of its citizens

There must be agreement between States and corporate institutions as to what constitutes global justice and how it is enforced

We need to build on and develop existing global institutions e.g. WHO, World Bank, IMF, WTO

**Global justice in practice: Access to HIV treatment in Brazil**

In the 1990s – 2nd highest no. of cases HIV/AIDS worldwide

World Bank advocated focus on investment in prevention programs rather than treatment of infected individuals

**Global justice in practice: Access to HIV treatment in Brazil**

A right to health is enshrined in the Brazilian constitution

In 1996 – statutory requirement for free universal access to anti-retroviral therapy

Government invested in national infrastructure for diagnosis and management of HIV/AIDS

However, high cost of anti-retrovirals threatened sustainability of the programme

Manufacture of antiretrovirals locally

**The global response**

Challenge to WTO TRIPS (Trade Related aspects of Intellectual Property Rights) agreement

Mobilisation of global political will to find fair solution

New interpretation of TRIPS in 2001 WTO Doha

Intellectual property rights could be waived in the face of a national public health emergency

*Allowed Brazil to manufacture generic antiretrovirals saving …*

HIV mortality reduced by 50%. Hospitalisation reduced by over 70%

**Summary**

* Global health inequalities are an ethical concern
* Health care is a matter for justice
* Healthcare decisions must take into account the Human Rights Act
* Humanitarian aid is morally valuable, but it is not a sufficient moral approach to global health inequalities
* An appeal to human rights is insufficient without a workable framework for global justice