School of Medicine

Year 5 2012/13

PATHOLOGY THEME GUIDE

Volume 4 – Week 4

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Theme leaders

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PATHOLOGY THEME

Year 5 (2012-13) – Study Guide – Week 4

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SOLE FEEDBACK – Week 4

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

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** |
| --- | --- | --- | --- |
| L**ecturer and Lecture Title** | Strongly Agree | Agree | Neutral | Disagree | Strongly Disagree | Strongly Agree | Agree | Neutral | Disagree | Strongly Disagree | Strongly Agree | Agree | Neutral | Disagree | Strongly Disagree |
| Prof Karim MeeranLiver Disease CPC |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Gemma PettsLiver Disease CPC |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Radha RamachandranEnzymes and Cardiac Markers |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Prof Barbara Bain Paediatric Haematology |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Prof Barbara Bain Haematology Quiz |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Stephen RobinsonThyroid |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Stephen RobinsonNutrition |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Amir SamElectrolyte Cases |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Marianne NolanNeonatal/childhood infections |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Donald MacdonaldChronic Lymphocytic Leukaemia & Lymphoproliferative disorder quiz |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Margaret HancockPaediatric Clinical Chemistry |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Mark AtkinsBacterial & Viral vaccines |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Eleni NastouliGI infections |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Dunisha SamarasingheWound, bone and joint infections |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Janice MainViral hepatitis |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr James CartonBreast Pathology |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Eimear BranniganHospital-acquired infections |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Prof Terry CookRenal disease |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Prof Karim MeeranDiabetes CPC |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Amir SamlDiabetes CPC |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Paul LewisDiabetes CPC |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Hugo DonaldsonInfection CPC |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Alex RiceInfection CPC |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Rathi RamakrishnanCerebrovascular disease |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Oliver CummingWhy Toilets are more important than doctors |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Anthony SolomonI’ve got you under my skin |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Gareth Tudor-WilliamsHIV in African children |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Jim BuckleyFever in the returning traveller |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

| **Lecturer and Lecture Title** | **Please use this box for additional constructive feedback.** |
| --- | --- |
| Prof Karim MeeranLiver Disease CPC |  |
| Dr Gemma PettsLiver Disease CPC |  |
| Dr Radha RamachandranEnzymes and Cardiac Markers |  |
| Prof Barbara Bain Paediatric Haematology |  |
| Prof Barbara Bain Haematology Quiz |  |
| Dr Stephen RobinsonThyroid |  |
| Dr Stephen RobinsonNutrition |  |
| Dr Amir SamElectrolyte Cases |  |
| Dr Marianne NolanNeonatal/childhood infections |  |
| Dr Donald MacdonaldChronic Lymphocytic Leukaemia & Lymphoproliferative disorder quiz |  |
| Dr Margaret HancockPaediatric Clinical Chemistry |  |
| Dr Mark AtkinsBacterial & Viral vaccines |  |
| Dr Eleni NastouliGI infections |  |
| Dr Dunisha SamarasingheWound, bone and joint infections |  |

| **Lecturer and Lecture Title** | **Please use this box for additional constructive feedback.** |
| --- | --- |
| Prof Karim MeeranDiabetes CPC |  |
| Dr Amir SamlDiabetes CPC |  |
| Dr Paul LewisDiabetes CPC |  |
| Dr Hugo DonaldsonInfection CPC |  |
| Dr Alex RiceInfection CPC |  |
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| Dr Oliver CummingWhy Toilets are more important than doctors |  |
| Dr Anthony SolomonI’ve got you under my skin |  |
| Dr Gareth Tudor-WilliamsHIV in African children |  |
| Dr Jim BuckleyFever in the returning traveller |  |

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| Timetable – week 4Monday 23rd July |
| 9.00-10.15 | CP | Liver Disease CPC (Prof Karim Meeran/Dr Gemma Petts) |
| 10.15 -11.00 | CP | Enzymes and Cardiac Markers (Dr Radha Ramachandran) |
| 11.00-11.15 |  | BREAK |
| 11.15-12.45 | Ha | Paediatric Haematology (Prof Barbara Bain) |
| 12.45-13.30 |  | LUNCH |
| 13.30-14.45 | Ha | Haematology Quiz (Prof Barbara Bain) |
| 14.45-15.00 |   | BREAK |
| 15.00-16.00 | CP | Thyroid (Dr Stephen Robinson) |
| 16.00-16..50 | CP | Nutrition (Dr Stephen Robinson) |
|  |  |  |
| Tuesday 24th July |
| 9.00-10.00 | CP | Electrolyte cases (Dr Amir Sam) |
| 10.00-11.00 | Mi | Neonatal and childhood infections (Dr Marianne Nolan) |
| 11.00-11.15 |   | BREAK |
| 11.15-12.15 | Ha | Chronic Lymphocytic Leukaemia & Lymphoproliferative disorder quiz (Dr D Macdonald) |
| 12.15-13.00 |   | LUNCH |
| 13.00-13.45 | CP | Paediatric Clinical Chemistry (Dr Margaret Hancock) |
| 13.45-14.45 | Mi | Bacterial and Viral vaccines (Dr Mark Atkins) |
| 14.45-15.00 |  | BREAK |
| 15.00-16.00 | Mi | GI infections (Dr Eleni Nastouli) |
|  |  |  |
| Wednesday 25th July |
| 9.00-10.00 | Mi | Wound, bone and joint infections (Dr Dunisha Samarasinghe) |
| 10.00-11.00 | Mi | Viral Hepatitis (Dr Janice Main) |
| 11.00-11.15 |   | BREAK |
| 11.15-12.15 | Hi | Breast Pathology (Dr James Carton) |
|  |  |  |
| Thursday 26th July |
| 9.00-10.00 | Mi | Hospital acquired infections (Dr Eimear Brannigan) |
| 10.00-11.00 | Hi | Renal disease (Prof Terry Cook) |
| 11.00-11.15 |   | BREAK |
| 11.15-12.30 | CP | Diabetes CPC (Prof Karim Meeran, Dr Amir Sam , Dr Paul Lewis) |
| 12.30-13.15 |   | LUNCH |
| 13.15-14.45 | Mi | Infection CPC (Dr Hugo Donaldson, Dr Alex Rice) |
| 14.45-15.00 |   | BREAK |
| 15.00-16.30 | Hi | Cerebrovascular disease and trauma (Dr Rathi Ramakrishnan) |
|  |  |  |
| Friday 27th July |
| 9.00-9.15 | Mi | Introduction to Tropical Day (Dr Gareth Tudor-Williams) |
| 9.15-10.00 | Mi | Why toilets are more important than doctors( Dr Oliver Cummings, LSHTM) |
| 10.00-10.45 | Mi | I’ve got you under my skin (Dr Anthony Solomon) |
| 10.45-11.15 |   | BREAK |
| 11.15-12.00 | Mi | HIV in African Children (Dr Gareth Tudor-Williams) |
| 12.00-12.45 | Mi | Fever in the returning traveller (Dr Jim Buckley) |
| 13.10-13.30 |   | Floor show and prizes for best Tropical Gear  |
| 13.30-14.30 |  | LUNCH |
| 14.30-16.00 |   | End-of-Course EMQ (Prof Karim Meeran and Dr Mike Barrett) |
| 16.00-16.30 |   | Quiz Answers & Clickers return (Prof Karim Meeran) |

CONTACT DETAILS

Theme leaders

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Course administration

Mrs Chandra Tambimuttu (c.tambimuttu@imperial.ac.uk)

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

HANDOUTS FOR INDIVIDUAL LECTURES

These handouts are in the anticipated order of presentation.

The page numbering follows from week 3 (volume 3).

Liver disease clinicopathological conference

Prof Karim Meeran and Dr Gemma Petts

Enzymes and Cardiac Markers

Dr. Radha Ramachandran

**Learning Objectives**

1. General understanding of enzymes and their roles in body metabolism
2. Know the patterns of enzyme changes associated with specific diseases especially pancreatic, bone and muscle disease
3. Knowledge of Biomarkers of myocardial injury.
4. Liver enzymes – dealt with in a previous lecture

**CLINICAL ENZYMOLOGY**

An enzyme is a protein which catalyses one or more specific biochemical reactions.

**Clinical Enzymology is the application of the science** **of enzymes to the diagnosis and treatment of disease**

Most enzymes are intracellular. Small amounts are present in plasma due to normal cell turnover. Physiological factors affecting enzyme levels include age, gender, pregnancy, exercise

Most enzymes are not tissue specific and widely distributed. Source of increased ezymes levels can be localised to specific tissues by

a) Measurement of more than one enzyme e.g. GGT can be used to localise ALP to liver

b) Separation and measurement of tissue- specific isoenzymes e.g. bone and liver ALP

Enzymes are usually measured by their activity, rather than mass, i.e. measuring changes in the concentrations of substrate or product under optimised analytical conditions.

Units for measuring enzyme activity – U/L

**One *International Unit* (U) of enzyme activity is defined as the quantity of enzyme that catalyses the reaction of one μmol of substrate per minute**

**Enzymes as marker of disease**

May be measured

1. in serum to detect injury to a tissue that makes the enzymes (increased levels)

2. in the tissue to identify abnormalities in enzymes, which may cause disease (usually decreased levels) – *dealt with in Inherited metabolic diseases lectures*

**Most useful when measured to confirm/exclude a working clinical diagnosis**

**Timing crucial when measuring enzymes - Ignoring optimal diagnostic time window can lead to misdiagnosis**

**AMYLASE**

Secreted by exocrine pancreas. High serum amylase activity is seen in acute pancreatitis. Usually levels > 10 times upper limit of normal. Remember salivary isoenzyme exists. Small increases may be seen in other acute abdomen states.

**CREATINE KINASE**

Most widely used marker of muscle damage**.** Three forms - dimers containing the M (muscle) and B (brain) subunits**.** CK-MM- skeletal muscles. CK-MM accounts for almost entire normal plasma activity. CK-MB (1 & 2) – cardiac muscles – was gold standard for detecting myocardial injury before troponin became widely available. Now not routinely used. CK- BB – brain – activity minimal even in severe brain damage

**Statin related myopathy:** Spectrum - myalgia to rhabdomyolysis. Risk Factors: 1. Polypharmacy (fibrates – gemfibrosil, cyclosporin, other drugs metabolised by the CYP 3A4 system) 2. High dose 3. Genetic predisposition 4. Previous history of myopathy with another statin

**Other Causes of raised plasma CK activity:** Muscle damage due to any cause; Myopthy e.g. Duchenne muscular dystrophy (>10xULN); Myocardial Infarction (>10xULN); Severe exercise (5xULN); Physiological – Afro-Caribbean (<5xULN)

**ALKALINE PHOSPHATASE**

Present in high concentration in liver, bone, intestine and placenta. Pathological increases most frequently due to liver or bone diseases. Increased in bone diseases associated with increased osteoblastic activity. Liver and bone ALP can be differentiated by - GGT measurement, electrophoretic separation of isoenzymes, bone specific ALP immunoassay (now available).

**Causes of Raised ALP:** Physiological: pregnancy (placental ALP) – 3rd trimester, childhood- especially during growth spurt. Pathological: > 5x Upper limit of normal in Bone ( Pagets, Osteomalacia) and Liver (cholestasis, cirrhosis) ; < 5 x Upper Limit Normal in Bone ( tumours, fractures, osteomyelitis) in Liver (infitrative disease,hepatitis)

**ALP not increased in osteoporosis unless complicated by fractures**

**BIOMARKERS OF MYOCARDIAL INJURY**

AST, LDH, CK, CK-MB – historical markers- obsolete.

**Current Biomaker: TROPONIN (not an enzyme)-** structural protein complex (troponin I, T and C) in the actin-myosin contractile apparatus of striated muscles. Cardiac specific Troponin I /T measured as myocardial injury biomarkers. Troponin I - many assays available- so diagnostic cut-offs are laboratory specific. Troponin T - only one assay available, so only 1 cut-off. Levels rise 4-6 hours post MI, peak at 12 -24 hours post MI and remain elevated for 3 -10 days**. Timing of measurement crucial** - 2 levels measured- at 6 hours and at least 12 hours after onset of symptoms. Sensitivitiy is 100% and specificity 98% at 12 -24 hours post MI. Troponin is sensitive enough to detect unstable angina. Different diagnostic cut-offs used for MI and unstable angina.

**MYOGLOBIN (not an enzyme):** rises with any muscle injury. First marker to rise in MI but specificity is very poor. Therefore not used in routine clinical practice.

**There are currently no biomarkers that rise quickly enough to be able to aid in decisions with regards to thrombolysis**

**BNP (not an enzyme):** Brain Natriuretic Peptide. Increasingly used as marker of Heart Failure.

**Diagnostic Criteria for acute, evolving or recent MI :
Role of Enzymes (& Laboratory)**

Either one of the following criteria satisfies the diagnosis for an acute, evolving or recent MI:

(1) Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:

(a) ischemic symptoms;

(b) development of pathologic Q waves on the ECG;

(c) ECG changes indicative of ischemia (ST segment elevation or depression); or

(d) coronary artery intervention (e.g., coronary angioplasty).

(2) Pathologic findings of an acute MI.

**Timing of release of various biomarkers following acute ischemic myocardial infarction.**

****

**peak A myoglobin;
peak B-cardiac troponin;
peak C- CK-MB;
peak D-cardiac troponin after unstable angina.**

**Data are plotted on a relative scale, where 1·0 is set at the AMI cutoff concentration.**

***Recommended text***

Clinical Chemistry Marshall, Fourth Edition, 2000

Lecture Notes on Clinical Biochemistry, A.F. Smith et al Blackwell Publishing

*Additional references/ links to other parts of the course*

1. Liver lectures

2. Inborn errors of Metabolism Lectures

3. **Cardiac biomarkers and acute coronary syndromes — The Euro Heart Survey of Acute Coronary Syndromes Experience**
Eur. Heart J., July 2003; 24: 1189 - 1194.

4. **Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: The Task Force on Acute Heart Failure of the European Society of Cardiology**
Eur. Heart J., February 2005; 26: 384 - 416.

5. [www.acbi.ie/cardiac.doc](http://www.acbi.ie/cardiac.doc) - good overview of AMI and its markers

6. <http://www.nacb.org/lmpg/biomark/card_biomarkers_chp1.pdf> - another brilliant overview

**Theme: Enzymology**

**OPTION LIST**

|  |  |  |  |
| --- | --- | --- | --- |
| A | Bone-specific Alkaline Phosphatase | 3 | Troponin  |
| B | Alanine aminotransferase (ALT) | 4 | Creatine kinase IsoEnzyme MB2 |
| C | Alkaline phosphatase | 5 | Myoglobin |
| D | Amylase | 6 | Creatine Kinase  |
| E | Aspartate aminotransferase (AST) |  |  |
| F | Creatine kinase IsoEnzyme MB1 |  |  |
| 1 | ã-Glutamyl transpeptidase (ã-GT) |  |  |
| 2 | Lactate dehydrogenase (LDH) |  |  |

**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 45 year old women with long standing history of high alcohol intake, presents to A&E with severe epigastric pain, which radiates to her back and associated with vomiting. Her pain is partially alleviated by sitting forward. Which enzyme measurement might be helpful with the diagnosis?

2. A 52 year old man presented to his GP with a history of exercise-induced central chest pain which radiated to his left arm and neck a week ago. As the pain lasted for half an hour, and subsided on rest he decided to not to go to his GP until today. He’s currently pain free, and his ECG at the GP surgery was normal. Which enzyme would be most sensitive to confirm a cardiac event?

3. An 82 year old women presented with bone pain, history of fractures and bowing of her tibia. Which enzyme is found to be raised on investigation?

4. A 64 year old man who smokes and has a family history of cardiovascular disease has recently been started on atorvastatin. Three weeks after commencing the tablet, he complains of generalised muscle pain. Which enzyme would be your investigation of choice?

5. A 39 year old woman with BMI of 43, presented with elevated alkaline phosphatase and RUQ pain. The local laboratory doesn’t offer ALP iso-enzyme measurement. What other enzyme would you measure to help for a differential diagnosis?

ANSWERS

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

Paediatric Haematology

Professor Barbara Bain

**Objectives**

The student will be able to

1. Explain how healthy children differ haematologically from adults
2. Explain how and why haematological conditions seen in children differ from those of adults
3. Describe haematological conditions seen in childhood that are either common, important to diagnose or both
4. Explain how healthy neonates differ haematologically from infants and older children
5. Explain why the range of haematological conditions seen in neonates differs from that in infants and older children
6. State the haematological conditions for which neonates are screened and explain why such screening is done

Children differ biologically from adults so that normal ranges for haematological and other variables differ from those of adults. They also differ between children of different ages. In addition, there is no gender difference in haematological variables, such as the haemoglobin concentration (Hb), in pre-pubertal children. Often what is ‘normal’ is not as well defined as there are practical and ethical difficulties in getting blood samples from healthy children in order to establish a normal range appropriate for each age group. Laboratories therefore often issue reports of laboratory tests in children with a reference range that is only appropriate for adults.

The range of haematological (and other) diseases seen in children differs from that seen in adults. This is partly because micro-organisms are often encountered for the first time in childhood and because children’s immune responses to micro-organisms and other antigenic stimuli differ from those of adults. The range of neoplastic diseases is very different so that the exposure to aetiological factors or the body’s response to such factors or both must differ. Some childhood diseases, even certain leukaemias, have their origin in intra-uterine life so that we also have to consider that the exposure and response of the fetus to potentially harmful intrauterine influences (e.g. maternal irradiation or intake of oncogenic substances by the mother) also influences the range of diseases seen in children.

Many inherited conditions first present and have to be recognized and managed in childhood. This is true of thalassaemia major, most cases of sickle cell anaemia and the more severe variants of inherited coagulation defects and inherited haemolytic anaemias. The interaction between the child and the environment may lead to the initial clinical presentation of an inherited condition. Thus an inherited bleeding disorder may first be diagnosed when a baby boy is circumcised or when he is learning to walk and starts falling over. Similarly, the first acute haemolytic crisis in a child (usually a boy) with glucose-6-phosphate dehydrogenase (G6PD) deficiency may occur as a result of infection, exposure to an oxidant drug or ingestion of fava beans; it may even occur in the neonate when the breast-feeding mother ingests fava beans or when the baby is dressed in christening robes newly removed from mothballs (containing naphthalene).

The same disease can have clinicopathological features in children that differ from those seen later in life. This applies both to inherited conditions, e.g. sickle cell anaemia, and acquired conditions, e.g. autoimmune thrombocytopenic purpura.

The child’s response to illness differs from that of an adult and children may also differ from adults as to how they metabolise drugs. In addition, there may be only limited information on drug safety in children. In children with serious illnesses, it is often necessary to use drugs that are not licensed for use in children. Growth retardation is a problem unique to children. It can result from the direct effects of prolonged severe illness on growth, from the damaging effects of therapy (e.g. irradiation of the spinal column) or from failure of puberty to occur (e.g. in iron-overloaded children with thalassaemia major who have gonadal failure). In treating children with serious conditions it is necessary to think of the very long-term effects of treatment, e.g. lifelong hyposplenism if the spleen has to be removed, gonadal failure and resultant infertility following chemotherapy, damage to the brain following cranial irradiation, second malignancies following chemotherapy or radiotherapy (such as therapy-related acute myeloid leukaemia and an increased incidence of brain tumours following cranial irradiation). However, it must be noted that a certain percentage of serious complications have to be accepted in the interests of curing a significant proportion of children with an otherwise fatal condition.

There are also social and legal factors that have to be considered when treating a child. It is the parent who gives consent to treatment and conflicts can arise if a parent refuses consent to life-saving treatment, e.g. blood transfusion. Parental beliefs have to be taken very seriously but the prime duty is to the child and recourse to the law is sometimes necessary. Compliance with unpleasant treatment can be difficult, particularly in adolescents. Treatment for a chronic condition must take account of the need of the child for schooling. It may be necessary, for example, for blood transfusions to be given during the late afternoon and night. A serious illness in a child has an effect on the whole family. If the condition is inherited, there may be additional factors to consider such as parental feelings of guilt and the need to consider antenatal diagnosis in any future pregnancy. The welfare of other children has to be considered, a factor that becomes critical if a sibling is the ideal donor for a child who would benefit from stem cell transplantation.

**Sickle cell disease**

Sickle cell disease is a generic term that covers all conditions leading to sickling of red blood cells with resultant clinicopathological effects. It therefore includes not only sickle cells anaemia (SS) but also compound heterozygous states such as sickle cell/haemoglobin C disease (SC), sickle cell/beta thalassaemia and other less common compound heterozygous conditions. Sickle cell trait (AS) is **NOT** classified as sickle cell disease. Precise diagnosis (by blood count and film, haemoglobin electrophoresis (or High Performance Liquid Chromatography—HPLC) and family studies) is essential, to permit genetic counselling. Because this is a beta globin chain defect it does not present at birth but can present during the first six months of life as haemoglobin F synthesis decreases and haemoglobin S synthesis increases. The initial presentation is often as a ‘hand-foot syndrome’. Another presentation almost confined to childhood is splenic sequestration. Parents or other carers need to be taught how to recognize this. Splenic atrophy/fibrosis develops in the first few years of life as a result of recurrent sickling and infarction in the spleen. This removes the risk of splenic sequestration but puts infants with sickle cell disease at high risk of fatal pneumococcal infection. Early vaccination and regular penicillin therapy are essential and for this reason it is important that sickle cell disease is diagnosed at birth rather than waiting for the first clinical features to develop. Acute red cell aplasia as a result of infection by parvovirus B19 is a complication of sickle cell disease that occurs mainly in children and adolescents. Once the primary infection has occurred and an immune response has been mounted the condition does not recur. In older children, manifestations of sickling are generally similar to those in adults. However stroke is a particularly important complication of sickle cell disease in children, although it is not confined to this age period.

**Beta thalassaemia major**

This condition is manifest in the first 6 months of life as haemoglobin F synthesis decreases but haemoglobin A synthesis does not occur or occurs at a greatly reduced rate. Precise diagnosis (by blood count and film, haemoglobin electrophoresis or equivalent, family studies and molecular analysis) is essential, to permit genetic counselling, Presentation is usually with pallor and failure to thrive. Treatment is by blood transfusion and, in the older child, when iron overload is developing, by iron chelation. This is usually by subcutaneous infusion of deferoxamine (previously known as desferrioxamine) on 5 or 6 nights a week.

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

G6PD deficiency should be suspected in cases of prolonged neonatal jaundice or when a baby, infant or child develops sudden pallor and jaundice and the blood count and film shows anaemia and the presence of irregularly contracted cells. G6PD deficiency is most frequently seen around the Mediterranean Sea (e.g. in Greece, Italy and the Middle East) and in those of African ancestry including Afro-Caribbeans. Diagnosis is by G6PD assay. However, it should be noted that, in the common variant found in Africans and Afro-Caribbeans, the level of G6PD is normal in reticulocytes and if there is a reticulocyte response to acute haemolysis the assay may be normal. The blood film is then critical in diagnosis and should lead to the assay being repeated when the acute haemolytic episode is over. Other family members, particularly male siblings, should be investigated and appropriate verbal and written information should be given to avoid, as far as possible, future haemolytic episodes.

**Other inherited haemolytic anaemias**

Hereditary spherocytosis can present in childhood with pallor and jaundice or with sudden onset of clinically apparent anaemia as a result of a parvovirus B19 infection. Diagnosis is by means of the blood count and film, reticulocyte count, bilirubin measurement and family studies. A direct antiglobulin (Coombs’) test is sometimes necessary to exclude autoimmune haemolytic anaemia, which is another cause of spherocytosis.

Other uncommon and rare causes of inherited haemolytic anaemia need to be recognized in this age range but diagnosis generally requires referral of children with unexplained anaemia, particularly if associated with jaundice, to a haematologist.

**Haemolytic uraemic syndrome**

The most common acquired haemolytic anaemia observed in childhood is the haemolytic uraemic syndrome (HUS). This is usually the result of infection by a pathogenic *Escherichia coli* that secretes verocytotoxin. This toxin damages endothelial cells leading to impaired renal function and a microangiopathic haemolytic anaemia. HUS is the most common cause of acute renal failure in children in the UK. Diagnosis is important so that the renal failure, which is usually temporary, can be appropriately managed. A blood count, blood film and reticulocyte count are very important in diagnosis.

**Inherited coagulation defects in children**

Children with severe inherited coagulation defects usually present with abnormal bleeding either shortly after birth or in the first few years of life. Haemarthroses and bleeding into deep tissues are particularly characteristic. The differential diagnosis includes non-accidental injury, other causes of swollen joints and acquired causes of a bleeding disorder (e.g. acute leukaemia or autoimmune thrombocytopenic purpura). A high index of suspicion should lead to consideration of ethnic origin, a family history and a coagulation screen and platelet count and then to further investigations, depending on the results of initial tests. Acquired coagulation defects, e.g. disseminated intravascular coagulation in meningococcal sepsis, do not usually enter into the differential diagnosis since the clinical presentation is very different.

**Autoimmune thrombocytopenic purpura**

Autoimmune thrombocytopenic purpura was previously known as idiopathic thrombocytopenic purpura and, although the condition is no longer ‘idiopathic’, it is still often referred to as ‘ITP’. In children it is usually an acute self-limiting condition whereas in adults it is much more likely to be chronic and relapsing. Presentation is with petechiae and bruises. Sometimes there are also ‘blood blisters’ in the mouth. The differential diagnosis includes non-accidental injury and other causes of thrombocytopenia, particularly acute leukaemia. A blood count and film are of critical importance. If the Hb and white cell count (WBC) are normal and if no blast cells are seen on a careful examination of the film, a diagnosis of acute leukaemia is highly unlikely. Often children are observed without treatment and in that case no bone marrow examination is necessary. If the haemorrhagic manifestations are sufficiently severe, treatment is indicated, either with corticosteroids or by infusion of high dose intravenous immunoglobulin. If corticosteroids are to be given, paediatricians often request a bone marrow examination, to exclude a diagnosis of leukaemia. Immune thrombocytopenic purpura in children may be triggered by infection. Apart from the clinical history, infection-related immune thrombocytopenic purpura does not differ much from autoimmune thrombocytopenic purpura and the management is the same. Because of the sudden clinical onset, ITP is not usually confused with inherited thrombocytopenias. However if the observation of a low platelet count does not result from presentation with bleeding but is incidental to investigation of another condition then both congenital and acquired causes require consideration.

**Inherited causes of thrombocytopenia or impaired platelet function**.

Congenital thrombocytopenia and congenital conditions with impaired platelet function are rare. Diagnosis requires family history, blood film and platelet count. The presence of bleeding typical of a defect of platelet function or number, e.g. petechiae, bruises and mucosal bleeding, in a child with a normal platelet count is an indication for platelet function tests and/or a bleeding time. Because these conditions are rare, heterogeneous and difficult to diagnose, referral to a haematologist is indicated when they are suspected.

**Acute leukaemia in children**

The leukaemia most typical of children is **acute lymphoblastic leukaemia** (ALL). Presentation is usually with pallor, bruising, lymphadenopathy and bone pain. In children with enlargement of the thymus there may also be respiratory distress. On examination, petechiae, hepatomegaly and splenomegaly may be found. The differential diagnosis includes other causes of bleeding and anaemia. A blood count and careful examination of a blood film are critical in diagnosis. Blast cells typical of acute leukaemia have to be distinguished from immature lymphocytes that often occur in children as a response to infection. A bone marrow examination is indicated in a child with unexplained anaemia and thrombocytopenia even if no blast cells are detected in the blood film. In approaching the parents of a child with suspected ALL, it is important to be aware that with current treatment more than three quarters of children can be cured. Current treatment is with complex protocols of oral, parenteral and intrathecal chemotherapy and with supportive care to mitigate the effects of anaemia, thrombocytopenia, neutropenia and impaired immune responses. Early referral to a haematologist is mandatory if this diagnosis is suspected.

In children under the age of two years the most common type of acute leukaemia is **acute myeloid leukaemia** (AML). AML also occurs in older children but over the age of 2 years it comprises a much lower proportion of total cases of acute leukaemia. Clinical features are similar to those of ALL—pallor, petechiae or bruising and fever. There may be hepatosplenomegaly. Lymphadenopathy can occur in AML as well as ALL but is less common whereas thymic enlargement does not occur. A blood count and blood film is usually adequate to confirm the diagnosis but occasionally only a bone marrow aspiration reveals the increased blast cells. Unexplained pancytopenia is an indication for a bone marrow aspirate. As for ALL, early referral of suspected cases to a haematologist is mandatory.

**Neonates**

Neonates are haematologically even more different from adults than are infants and older children. At birth the Hb is much higher, the WBC is higher and there may be nucleated red cells in the circulation. The mean cell volume (MCV) is much higher. In addition to haemoglobin A, there is still some haemoglobin F present and in premature babies this may be a high percentage of total haemoglobin. Haemoglobin production is greatly reduced immediately after birth so that Hb falls steadily to reach a lower level than is normal at any other time of life around the end of the first year.

**Haematological abnormalities in neonates**

All sorts of things can happen to a fetus that cannot happen outside the uterus. There may be transplacental passage of damaging alloantibodies (e.g. anti RhD or antiplatelet alloantibodies leading to alloimmune haemolytic anaemia or alloimmune thrombocytopenia purpura). Maternal autoantibodies can also cross the placenta and destroy fetal platelets. The fetus may bleed into the maternal circulation, leading to anaemia. If there are identical twins with a shared placenta there may be bleeding from one twin to another leading to anaemia in one and polycythaemia in the other. A fetus that is deprived of oxygen can also become polycythaemic. All these adverse events affect the fetus but the effects are still present in the neonate. In addition to the misadventures that may befall the fetus, the neonate may bleed during delivery, e.g. from damage to a cord blood vessel. Neonates are also susceptible to infection and have a limited neutrophil reserve, which impairs their response.

The coagulations system of the neonate is also immature so that the normal ranges differ from those at any other time of life. Neonates are also prone to vitamin K deficiency, which can lead to haemorrhagic disease of the newborn.

Prolonged jaundice in the neonate can have a haematological cause, e.g. haemolytic disease of the newborn or G6PD deficiency.

**Haematological screening of neonates**

Neonates are screened for various biochemical abnormalities such as congenital hypothyroidism and phenylketonuria. In the UK they are also now screened for sickle cell disease and thalassaemia major. The same ‘Guthrie card’ is used for all these purposes. This means that babies with sickle cell disease can be started on prophylactic penicillin and mothers can be alerted to the need to check for splenic sequestration. Babies with thalassaemia major can be started on regular blood transfusion once the haemoglobin falls significantly.

Haematology quiz and EMQ

Professor Barbara Bain

***AIMS***

The aims of this session are

* to show how a problem-solving approach can be applied to both clinical problems and laboratory results
* to offer revision of some of the haematological topics covered in the first three years of the course

***OBJECTIVES***

The student should be able to

* develop a differential diagnosis when given a clinical photograph or a clinical history and should be able to plan further relevant investigations
* recognize an abnormal laboratory result and be able to offer an interpretation and explain what should be done next

Students who wish to gain maximally from this exercise are advised to attend the lecture. They are unlikely to gain the same experience just by viewing a PowerPoint presentation away from the lecture.

Thyroid Disease

**THE USE OF CHEMICAL PATHOLOGY IN THEIR MANAGEMENT**

Dr Stephen Robinson

***Learning objectives***

•To review thyroid physiology

•To understand the use of chemical pathology in the management of thyrotoxicosis

•To understand the use of chemical pathology in the management hypothyroidism

•To understand the use of chemical pathology in the management thyroiditis

•To understand the use of chemical pathology in the management malignancy



**HYPOTHYROIDISM**

***Hypothyroidism aetiology***

* Hashimoto’s disease
* Atrophic
* Post Graves’ disease - RAI, surgery, natural history or thionamides.
	+ Thyroid agenesis or dysgenesis
	+ Iodide deficiency and dyshormonogenesis
	+ Secondary hypothyroidism
	+ Peripheral thyroid hormone resistance
	+ Post thyroiditis
	+ Drugs (amiodarone and lithium)

***MANAGEMENT***

MAKE DIAGNOSIS

* [TSH] 🡻 and [free T4] 🡹 and [free T3] 🡹

DIAGNOSE CAUSE

* Thyroid autoantibodies (thyroid microsomal)

OTHER CONDITIONS?

* other autoimmune disease

TREAT

* ?ECG heart disease

***TREATMENT***

•T4 (levothyroxine), 50-125-200mcg/day titrated to a normal TSH

•no EBM for excessive T4

•osteopaenia, atrial fibrillation

•use of T3??

**OTHER ISSUES**

Subclinical hypothyroidism

Pituitary disease

Radioactice iodine

Pregnancy

Neonatal hypothyroidism

**SICK EUTHYROID**

**THYROTOXICOSIS**

**AETIOLOGY**

•Graves’ disease 40-60%

•Toxic multinodular goitre 30-50%

•Single toxic adenoma 5%

•Subacute thyroiditis

•Postpartum thyroiditis

•Silent thyroiditis (immune and amiodarone)

•Factitious thyroiditis

•TSH induced

•Thyroid cancer induced

•Trophoblastic tumour and Struma ovarii

***MANAGEMENT***

MAKE DIAGNOSIS

* [TSH] 🡻 and [free T4] 🡹 and [free T3] 🡹

DIAGNOSE CAUSE

* Thyroid autoantibodies (thyroid microsomal)

OTHER CONDITIONS?

* other autoimmune disease

TREAT

* ?ECG
* ?Bone mineral density

***GRAVES’***

•Diffuse goitre

•Thyroid associated opthalmopathy

•Thyroid associated dermopathy

•Thyroid acropachy

•Other autoimmune disease (or FH)

***THYROIDITIS***

•Silent (painless) thyroiditis

•Subacute thyroiditis

•Post-partum thyroiditis

***THYROID MALIGNANCY***

THYROGLOBULIN

DIFFERENTIATED THYROID CANCER

•Papillary thyroid cancer

•Follicular thyroid cancer

•Surgery

•+/- RAI

•Thyroxine Rx at suppressive dose

***MEDULLARY THYOID CANCER***

•MTC sporadic/familial/part of MEN

•C cells of thyroid

•Calcitonin/carcinoembryonic antigen (CEA)

**EMQ**

**A. Consistent with clinical primary hypothyroidism**

**B. Consistent with euthyroid status in a patient complaining of tiredness.**

**C. Consistent with pituitary driven thyrotoxicosis**

**D. Consistent with secondary or pituitary hypothyroidism.**

**E. Consistent with sub-clinical hypothyroidism with risk of later clinical hypothyroidism.**

**F. Consistent with thyrotoxicosis.**

**G. To screen for medullary thyroid carcinoma**

**H. To screen for recurrence of differentiated thyroid carcinoma.**

Normal ranges TSH 0.33-4.5mU/L Free T3 3.2-6.5pmol/L Free T4 10.2-22.0pmol/L Thyroglobulin <5 ug/L

1. TSH < 0.01, Free T3 15.6, Free T4 38.0.

2. TSH 8.4, Free T4 11.7, Thyroid peroxidase (thyroid antibodies) positive

3. TSH 1.4, Free T4 12.1.

4. TSH 22. 4, Free T4 6.3.

5. Thyroglobulin 254

Nutrition

Dr Stephen Robinson

**Learning objectives**

1. Vitamins (D, folate, B12)
2. Minerals (Na, K, Ca, Fe)
3. Energy metabolism
4. Body composition and Clinical assessment
5. Amino acids, CHO, lipids (lipoprotein)
6. Malnutrition and obesity

***Fat Soluble Vitamins***

|  |  |  |  |
| --- | --- | --- | --- |
|  | ***Deficiency*** | ***Excess*** | ***Test*** |
| **A Retinol** | Colour Blindness | Exfoliation Hepatitis | Serum |
| **D Cholecalciferol** | Osteomalacia/rickets | Hyper-calcaemia | Serum |
| **E Tocopherol** | Anaemia/neuropathy?malignancy/IHD |  | Serum |
| **K Phytomenadione** | Defectiveclotting |  | PT |

***Water Soluble Vitamins***

|  |  |  |  |
| --- | --- | --- | --- |
|  | ***Deficiency*** | ***Excess*** | ***Test*** |
| **B1 Thiamin** | Beri-BeriNeuropathyWernicke Syndrome |  | RBCtransketolase |
| **B2 Riboflavin** | Glossitis |  | RBC glutathionereductase |
| **B6 Pyridoxine** | Dermatitis/Anaemia | Neuropathy | RBC ASTactivation |
| **B12 Cobalamin** | Perniciousanaemia |  | Serum B12 |
| **C ascorbate** | Scurvy | Renal stones | **Plasma** |
| **Folate** | MegaloblasticAnaemiaNeural tube defect |  | RBCfolate |
| **Niacin** | Pellagra |  |  |

***Trace Elements***

|  |  |  |  |
| --- | --- | --- | --- |
|  | ***Deficiency*** | ***Excess*** | ***Test*** |
| **Iron** | Hypochromic Anaemia | Haemochromatosis  | FBCFeFerritin |
| **Iodine** | Goitre Hypothyroid |  | TFT |
| **Zinc** | Dermatitis |  |  |
| **Copper** | Anaemia | Wilson’s  | CuCaeroplasmin |
| **Fluoride** | Dental caries | Fluorosis  |  |

**





***Body composition***

1. *Normal weight individual*

*• 98% O2, C, H, Na, Ca*

*• 60-70% H2O, 10-35% fat, 10-15% protein, 3-5% minerals*

1. *Variation body composition considerable, variation in LBM less*

**Definition of Obesity**

1. Weight
2. Body mass index

• weight/height2

• 25-30 kg/m2 overweight

• >30 kg/m2 obese

• >40 kg/m2 morbidly obese

1. Waist : hip ratio

**All cause mortality and obesity**



Age-adjusted 24yr follow up all cause mortality Framingham

**Waist circumference and CHD risk**

|  |  |  |
| --- | --- | --- |
|  | **Increased****risk** | **Major****risk** |
| **Men** | >94 | >102 |
| **Women** | >80 | >88 |

McKeigue 1991 Lancet 337:382

**Protein**

84gm men, 64gm women

1. Utility

– Indispensable (e.g. leucine)

– “conditionally” indispensable (e.g. Cysteine)

– Dispensable (e.g. alanine)

1. Protein synthesis/breakdown/oxidation
2. Assessment

– N excretion and balance

– Tracer techniques

**Lipid**

1. Polyunsaturated fatty acid (PUFA) include essential fatty acids (EFA)
2. Dietary fat determines LDL-C

 saturated fat  [chol]

 PUFA  [chol]

1. HDL associated reduced IHD risk

 (women, alcohol, obesity)



 

**Carbohydrate**

1. 40-80% total energy intake
2. Polymerisation into sugars, oligosaccharides and polysaccharides
3. 80 % complex 20 % simple
4. NSP - non-starch polysaccharides



**Nutrient gene interactions**

1. Cardiovascular disease
2. Obesity
3. Alcoholism
4. T2DM
5. Pregnancy
6. Most malignancy
7. Many GI conditions

**Treatment of obesity**

1. Exclude endocrine cause
2. Exclude complications of obesity
3. Educate
4. Diet
5. Medical therapy (Orlistat, sibutramine)
6. Surgical therapy (Gastroplasty)

**100Kg >> 10Kg weight loss**

|  |  |
| --- | --- |
| * Psychological benefit
* PCOS
* Oesophagitis
* CHD
* Osteoarthritis
* Liver function
* Pregnancy
 | * Mortality 20% ↓
* 0.9mm Hg per kg ↓
* HbAlc 1.5% ↓
* Risk of DM 4.0% ↓
* LDL 15% ↓
* HDL 8% ↓
 |
|  |  |
| **Protein energy malnutrition** |  |
| **Marasmus** | **Kwashiorkor** |
| * Shrivelled
* Growth retatrded
* Severe muscle wasting
* No s/c fat
 | * Oedematous
* Scaling/ulcerated
* Lethargic
* Lrage liver, s/c fat
* Protein deficient
 |

**Nutrition EMQ**

**OPTION LIST**

|  |  |
| --- | --- |
| A. Measurement of body mass index and waist circumference | 2 Oral vitamin K |
| B. Measurement of serum leptin concentration | 3. Parenteral thiamine (Pabrinex) |
| C. . Measurement of resting energy expenditure | 4. Reducing saturated fat and increasing mono or polyunsaturated fat in diet |
| D. Measurement serum polyunsaturated fat concentration | 5.  |
| E. Measurement of total plasma cholesterol and/or low density lipoprotein cholesterol concentration | 6.  |
| F. Oral ferrous sulphate | 7.  |
| 1. Oral Folic acid | 8.  |

For each Clinical scenario below, choose the SINGLE most likely,

1. To predict risk of myocardial infarction and decide of possible benefit of HMG-CoA reductase inhibition (statin therapy)

2. To assess the degree of obesity and resultant cardiovascular risk

3. To reduce risk of Wernicke’s encephalopathy in alcoholic patient admitted to hospital

4. To advise a patient on a method of reducing plasma cholesterol.

5. To reduce risk of neural tube defect in woman seeking advice before pregnancy, with a previous pregnancy complicated by spina bifida in the infant.

**ANSWERS**

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

Electrolyte Cases

Dr Amir H. Sam

Clinical Lecturer

**Learning objectives:**

* To interpret the clinical data in patients with serum electrolyte abnormalities.
* To plan the investigations and management of patients with serum electrolyte abnormalities.

**Case 1.** A 67-year-old man was started on bendroflumethiazide for hypertension 2 weeks ago. On examination he has dry mucous membranes and decreased skin turgor.
His past medical history is otherwise unremarkable.

Urea & electrolytes:

Na+: 129 mmol/L

K+: 3.5 mmol/L

Ur: 8.0 mmol/L

Cr: 100 μmol/L

**Case 2.** A 57-year-old woman is admitted with increasing breathlessness worse on lying flat. Her past medical history includes a Non-STEMI and hyperlipidaemia. She is on ramipril, bisoprolol, aspirin and simvastatin. On examination she has elevated JVP, bibasal crackles and bilateral leg oedema.

Urea & electrolytes:

Na+: 128 mmol/L

K+: 4.5 mmol/L

Ur: 8.0 mmol/L

Cr: 100 μmol/L

**Case 3.** A 55-year-old man presents with jaundice. He has a past history of excessive alcohol intake. On examination he has multiple spider naevi, shifting dullness and splenomegaly.

Urea & electrolytes:

Na+: 122 mmol/L

K+: 3.5 mmol/L

Ur: 2.0 mmol/L

Cr: 80 μmol/L

**Case 4.** A 40-year-old woman presents with fatigue, weight gain, dry skin and cold intolerance. On examination she looks pale.

Urea & electrolytes:

Na+: 130 mmol/L

K+: 4.2 mmol/L

Ur: 5.0 mmol/L

Cr: 65 μmol/L

**Case 5.** A 45-year-old woman presents with dizziness and nausea. On examination she looks tanned and has postural hypotension.

Urea & electrolytes:

Na+: 128 mmol/L

K+: 5.5 mmol/L

Ur: 9.0 mmol/L

Cr: 110 μmol/L

**Case 6**. A 62-year-old man presents with chest pain, cough and weight loss. On examination he looks cachectic. He has a 30 pack year smoking history.

Urea & electrolytes:

Na+: 125 mmol/L

K+: 3.5 mmol/L

Ur: 7.0 mmol/L

Cr: 85 μmol/L

**Case 7.** A 20-year-old man presents with polyuria and polydipsia. On examination he has bitemporal hemianopia.

Urea & electrolytes:

Na+: 150 mmol/L

K+: 4.0 mmol/L

Ur: 5.0 mmol/L

Cr: 70 μmol/L

**Case 8.** A 65-year-old man with type 2 diabetes mellitus and hypertension presents with malaise and drowsiness. He is on a basal bolus insulin regimen, ramipril, amlodipine, simvastatin and aspirin.

Urea & electrolytes:

Na+: 125 mmol/L

K+: 6.5 mmol/L

Ur: 18.0 mmol/L

Cr: 250 μmol/L

**Case 9**. A 50-year-old man is referred with hypertension that has been difficult to control despite maximum doses of amlodipine, ramipril and bisoprolol.

Urea & electrolytes:

Na+: 140.0 mmol/L

K+: 3.0 mmol/L

Ur: 4.0 mmol/L

Cr: 70 μmol/L

Neonatal and childhood infections

Dr Marianne Nolan

**Learning objectives:**

To familiarise the student with:

**NEONATAL INFECTIONS:**

* Reasons why neonates are at particular risk of infection.
* Congenital, early and late onset sepsis – organisms, presentation, treatment.
* NICU care and associated infections.

**CHILDHOOD INFECTIONS:**

* Common presentations: Rashes

Sore throat/URTI

Diarrhoea & vomiting

UTI

PUO

* Serious infections: Meningitis

Pneumonia

 Bone/joint infections

 Heart

* Immunocompromised patients.
* Importance of immunisation against vaccine preventable infections.

**NEONATAL INFECTION:**

Higher incidence of infection in this period than at other stage of life, even if preterm babies are excluded.

**Why?**

Immature immune system; Exposure to bacteria and viruses from the mother; Birth trauma; Thin skin and open areas e.g. umbilicus, become colonised with bacteria & can invade easily;
+/- overcrowding/understaffing on wards; invasive devices; antibiotic pressure etc.

**Types of neonatal sepsis:**

Congenital: Babies are born with congenital infections – i.e. transmitted vertically from mother to baby. Can occur at any time during pregnancy between first trimester and birth. Mostly viral infections, but includes toxoplasmosis and bacteria too.

Early-onset: Within the first 48 hours of life. e.g. Group B Streptococci; *Escherichia coli*; others (including *Listeria*).

Late onset: Onset after first 48 hours of life. Includes bacteria for early onset plus a large number of “opportunist” pathogens e.g. coagulase negative staphylococci; Enterococci; *Staphylococcus aureus*; coliforms, candida etc.

**Diagnosis:**

Clinical features often non-specific in neonates – therefore low threshold to culture and start antibiotics. Antibiotics can be stopped again if negative cultures at 48 hours.

Admission full septic screen: screening swabs including deep ear swab; blood cultures; +/- CSF; CXR, FBC and CRP will also be helpful.

Late onset: as above plus urine; ETS if ventilated; swabs from inflamed sites.

**Antibiotic Treatment:**

Benzylpenicillin & Gentamicin are the treatment for early onset sepsis.

Late onset in NICU: Flucloxacillin & gentamicin. (or vancomycin/tazocin if very unwell and long lines etc. in-situ).

Late onset from community: amoxicillin and cefotaxime. (to cover both *Listeria* and community meningitis pathogens)

NICU infections.

Neonates in NICU are at particular risk of infections related both to their premature status and also to the devices used – e.g. line related sepsis; ventilator associated pneumonia; necrotising enterocolitis (NEC) etc.

**CHILDHOOD INFECTIONS:**

* Age is important.
* Common viral and bacterial infections have a peak between 1-3 years of age. Viruses account for the majority of infections but bacteria (e.g. *Streptococcus pneumoniae,* Group A Streptococcus, *E. Coli)* are also important. Fever is common and may be the only feature of infection e.g. UTI, in this age group.
* **Meningitis**: Remains the most important bacterial cause of mortality and morbidity in children in developed countries.
* Diagnosis: clinical features and laboratory tests: LP for CSF, if possible. Full septic screen – Blood cultures; Throat swab; EDTA blood for PCR; Clotted serum for acute (and subsequent convalescent) serology.
* CSF in bacterial meningitis: Raised WCC – mostly polymorphs; Raised protein & mild-moderately low glucose on chemistry; +/- organisms seen on gram stain, if organism fails to grow then look for a positive antigen detection or PCR.
* Again aetiology varies with age. (neonates – see above)

|  |  |  |
| --- | --- | --- |
| **Age** | **Cause** | **Antibiotic treatment** |
| 1/12-3/12 | **Neisseria meningitidis****(Haemophilus influenzae b)****S. pneumoniae****Group B streptococcus****E. coli****Listeria monocytogenes** | Cefotaxime & amoxicillin |
| 3/12 - 5 years | **N. meningitides****(Haemophilus influenzae b)****S. pneumoniae** | Ceftriaxone |
| **≥ 6 years** | **N. meningitides****S. pneumoniae****Mycoplasma pneumoniae** | CeftriaxoneClarithromycin |

* **Respiratory tract infections** (RTI) account for about 1/3 of all childhood illnesses. Most of these are upper RTI and many of these are viral in origin. The aetiology of community-acquired pneumonia varies with age. Pneumococcus is an important cause in all ages. Mycoplasma tends to affect older children (> 4years). Respiratory viruses tend to affect younger children. Sputum is often difficult to obtain and many are treated empirically.
If cough fails to resolve quickly, consider pertussis (whooping cough), mycoplasma and TB.
* **Urinary Tract Infection**

Common. Up to 3% girls and 1% boys by age 11 years.

Diagnosis: symptomatic child (–may be difficult in young children); and >105 cfu bacteria/ml urine in pure culture, +/- pyuria (WBC in the urine). In reality these criteria may be difficult to fulfil but are important as proven UTI will require investigation and antibiotic prophylaxis in certain cases.

**Recurrent infections of any sort may be a sign of immunodeficiency and the child should be referred for specialist investigation.**

* Remember:
* Send cultures before antibiotics where possible
* Take blood cultures in as sterile a manner as possible. Contaminated blood cultures are a major problem in paediatrics and may necessitate repeat blood samples from children.

**Immunisation schedule (UK):**

|  |  |  |
| --- | --- | --- |
| **When to immunise** | **What vaccine** | **How it is given** |
| Two months old | DTaP/IPV/HibPneumococcal(PCV) | One injectionOne injection |
| Three months old | DTaP/IPV/HibMen C | One injectionOne injection |
| Four months old | DTaP/IPV/HibMen CPneumococcal (PCV) | One injectionOne injectionOne injection |
| Twelve months old | Hib/Men C | One injection |
| Thirteen months old | MMRPneumococcal (PCV) | One injectionOne injection |
| Between 3 and 5 years | DTaP/IPVMMR | One injectionOne injection |
| Between 13 & 18 years | Tetanus, Diphtheria and Polio | One injection |

Chronic Lymphocytic Leukaemia and
Lymphoproliferative Disorder Quiz

Dr Donald Macdonald

Paediatric Clinical Chemistry

Dr Maggie Hancock

**Topics to address:**

* + - * Sodium/water balance in the neonate and child
			* Hyperbilirubinaemia - neonatal
			* Ca/PO4 metabolism in the neonate and child

**Sodium/Water balance:**

Term Preterm (1kg)

Total body water 75% 85%

ECF 400 ml/kg 520 ml/kg

Fall in ECF during first week 40 ml/kg 100 ml/kg

1. Neonatal GFR is low giving a relatively reduced filtered load compared to the adult. The consequences of this are:
2. Proximal tubules are short and less convoluted than in the adult although:
3. The distal tubules are relatively unresponsive to aldosterone leading to:
4. The loops of Henle/distal collecting ducts are short and giving a:
5. Renal function does not fully mature until:

Disturbances:

Neonatal complications: Intraventricular haemorrhage

 Patent ductus arteriosus

 Central pontine myelinolysis

(Bronchopulmonary dysplasia and necrotising enterocolitis)

Causes: As for adults & in the neonate:

 high insensible loss

Inappropriate ADH

 Drugs (bicarb, antibiotics,methyl xanthines)

 Congenital adrenal hyperplasia (CAH)

 *[17OH-progesterone → →cortisol*

 *Commonly 21 hydroxylase def, OMIM +201910*

*Symptoms: ambiguous genitalia, salt wasting, hypoglycaemia]*

**Hyperbilirubinaemia:**

Transient unconjugated hyperbilirubinaemia presents with jaundice on about the second day of life and persists for up to 10 days (longer in preterm neonates) due to:

* Increased bilirubin synthesis
* Reduced transport into liver and reduced bile flow
* Slow excretion with enhanced enterohepatic circulation

1g/l albumin binds 10 μmol/l bilirubin. Kernicterus may develop if total bilirubin exceeds 340 μmol/l in the term neonate; this value is lower in the preterm neonate.

Causes of hyperbilirubinaemia:

* Unconjugated

 Haemolytic Haemolytic disease (ABO, rhesus etc)

 G-6-PD deficiency (OMIM 305900)

Non-haemolytic Feeding problems

Breast milk jaundice

 Prenatal infection/sepsis, hepatitis

 Hypothyroidism

 Crigler-Najjar type I (OMIM 218800)

* Conjugated (Conjugated/direct bilirubin above 20 μmol/L) is always pathological

 Biliary atresia

Choledocal cyst

TPN

Inherited metabolic diseases: Alpha-1-antitrypsin deficiency, Tyrosinaemia type I (OMIM 276700),Galactosaemias, Peroxisomal disorders

**Calcium/Phosphate:**

Neonatal: Calcium and phosphorus are actively transported across the placenta. High foetal ionised calcium concentration causes suppression of the foetal parathyroid. Transient post-natal hypocalcaemia is the norm, nadir day 3.

Reference intervals 0-4 weeks: Preterm Term (Adult)

Calcium 1.90 – 2.85 2.10 – 2.95 (2.15 – 2.65)

Phosphate 0.93 – 1.72 0.95 – 1.70 (0.80 – 1.40)

Osteopenia of prematurity usually presents 6th-12th postnatal week: due to:

 Inadequate substrates – phosphate and calcium

 Inadequate formation of calcitriol (1,25 hydroxy D)

Rickets may present with:

classical features - bowlegs/knock knees, frontal bossing, muscular hypotonia

tetany / hypocalcaemic seizure

 [note: beware transient hyperphosphatasemia of infancy]

Rickets may be due to:

 Vitamin D deficiency due to fat malabsorption, chronic hepatic/renal disease

 (*Low calcidiol (25 hydroxy D*)

Pseudo vitamin D deficiency I (OMIM #264700) due to defective renal hydroxylation, *(Normal calcidiol, low calcitriol (1,25 hydroxy D))*

Pseudo vitamin D deficiency II vitamin D resistance due to receptor defect *(Normal calcidiol and calcitriol)*

 Familial hypophosphataemias

*(Low Tmax phosphate, raised urine phosphoethanolamine)*

Bacterial and Viral vaccines

Principles of immunisation against infectious disease

Dr Mark Atkins

**Learning Objectives**.

(1) Understand the differences between active and passive immunity.

(2) Know the differences between live attenuated vaccines and inactivated/recombinant vaccines.

(3) Know when vaccines are given and what the main indications and contraindications are.

Detailed information and guidance is available in the Department of Health publication “Immunisation against Infectious Disease”. This is otherwise known as the Green Book.
A new edition is due out now and is available on the DoH website. The BNF also has a lot of useful information regarding vaccines and immunoglobulins.

Vaccination is one of the most important developments in the prevention of disease in man and animals. Smallpox was the first (and so far only) human disease to be eradicated and this was achieved by vaccination.

**Immunity** can be induced either **actively** (long term) or by **passive transfer** (short term) against a variety of bacterial and viral pathogens.

**Active immunity** is induced by using **live, attenuated** or **inactivated** organisms or their products (e.g. subunits, polysaccharide or recombinant proteins).

**Live attenuated vaccines** include;- Polio (oral), measles, mumps, rubella, Varicella-zoster, BCG and smallpox (vaccinia).

**Inactivated vaccines** include:- Polio (IPV), Rabies, hepatitis A, pertussis, wholecell typhoid, Tick-borne encephalitis, Japanese B encephalitis..

**Sub-unit / conjugate vaccines** include influenza, pneumococcal vaccine, meningococcal vaccine.

**Recombinant protein** vaccines include HBV.

**Conjugate vaccines**. The immunogenicity of some vaccine is improved by conjugating the bacterial polysaccharide to a carrier carrier protein such as tetanus toxoid or CRM197. This increases the immunogenicity, especially in young children. Examples of conjugate vaccines include hib, MenC and PCV

Vaccines in clinical development include HEV vaccine, DNA vaccines and new HBV proteins containing pre-S1 and pre-S2 regions.

Most vaccines are given prophylactically to prevent disease but a number of vaccines can also be given after exposure to prevent infection, these include HBV, Rabies, HAV, measles vaccines and smallpox.

HBV vaccine has proven very effective at preventing mother to baby transmission of HBV at birth. The subsequent reduction in chronic HBV infection has also resulted in a reduction in childhood liver cancer. This is the first example of a vaccine preventing cancer.

**Current Recommended Vaccination Schedule for Children in the UK**

**Vaccine Age Notes**

DTaP/IPV/Hib/pneumococcal (PCV) 2 months

DTaP/IPV/Hib/MenC 3 months

DTaP/IPV/Hib/pneumococcal (PCV)/MenC4 months

Hib/MenC 12 months

MMR (Measles, mumps rubella)/PCV 13 months

Booster DTaP/IPV/MMR 3-5 years

BCG during infancy for high risk groups

Booster Td/IPV 13-18 years Contains lower dose of diphtheria toxoid

***Adults should receive the following vaccines:***

Women seronegative for rubella rubella vaccine

Previously unimmunised DT and polio

High risk groups: HBV, HAV, rabies, influenza, pneumococcal vaccine (PPV in elderly)

**Key**

DTaP Diphtheria toxoid, tetanus toxoid and pertussis vaccine

IPV Inactivated polio vaccine

MenC Meningococcal vaccine

Hib Haemophilus influenzae type b

PCV pneumococcal conjugate vaccine

PPV pneumococcal polysaccharide vaccine

Gastrointestinal Infection

Dr Eleni Nastouli

**Definition of terms used in Gastro intestinal infection:**

Diarrhoea: Frequent passage of loose stools, ranging from mild to severe watery diarrhoea.

Dysentry: Frequent passage of blood and mucus in stools.

**Background:** Global problem, 1/3 the cause of death in children under the age of 5.

2.5 million death/yr. Poor hygiene, Low socio-economic condition,

Improper sewage disposal, use of untreated faeces as fertilisers. Infected animal feed

**Major organisms:**

**Bacteria:** Campylobacters, Salmonella, Shigella, E.coli( ETEC, EPEC,
Enteroadhesive, Vero toxin: E.coliO157) Cholera.

**Other bacterial causes:** Helicobacters\*( gastritis and peptic ulcer), V. parahaemolyticus, Pleisomonas, Aeromonas, Yersinenia , C. difficille.

**Protozoa:** Entamoeba histolytica, Giardia lamblia.

**Viruses:** Rota virus,Small round structured viruses (Norwalk, Norwalk-like)

 Hepatitis A

**Others:** Cryptosporidium.

**Pathology:**

* Production of Toxin: No invasion or damage to the epithelium e.g. Cholera (toxin mediated)
* Invasion of the epithelium:

 Damage to the epithelium e.g. Shigella, (Protein losing enteropathy), no bacteraemia.

* Invasion to submucosa e.g. Salmonella ,associated with bacteraemia.
* Adhesion to epithelium eg E.coli

**Toxins:**

Structure: A and B sub units

Mechanism of action: attatchment of B subunit to the mucosa, entry of A sub unit into epithelial cell, action due to excessive production of Cyclic AMP via adenylate cyclase .

 Labile toxins and Stable toxins of other enteric bacteria.

Identical LT, similar structure to cholera toxin present in different enteric bacteria.

 Labile toxin: “A” sub unit responsible for toxicity, not antigenic.

“B” sub unit, essential for attatchment to ganglioside receptors on intestinal epithelial surface and is antigenic , not toxic, identical structure of B subunit shared by Cholera toxin and Labile toxins produced by other bacteria. Therefore ideal for use in vaccines, and has been used in several vaccine trials.

**Other preformed toxins:**

**Verotoxin producing *E.coli*** producing Haemolytic uraemic syndrome **(HUS).**

**Travellers Diarrhoea:**  Due to different strains of E coli in a new environment.

**Antibiotic associated diarrhoea:** Superinfection withC.difficile, following broad spectrum antibiotics that suppress normal flora.

**Infective dose:** small e.g. Shigella: large e.g. Food poisoning

**Transmission:** Faecal oral, via infected food or water.Animal reservoirs→ food→ man,Man to man , Secondary cases , shigella, salmonella Environment to man (C. difficile) then man to manSea food to man

**Outbreaks:** Following contamination of cooked food by microbes that got chance to multiply in large numbers, usually associated with bulk cooking, or inadequate cooking or cooking previously and storing under unsatisfactory conditions. Usually associated with parties.

**Seasonal trends:** More in summer months.

**VACCINATION:**

**Several vaccines under different stages of trials e.g.:**

Live attenuated, genetically engineered, B subunit vaccines,

combined B subunit and killed/inactivated, Combination( S.typhi + O1 plasmid of V.cholerae ) some are promising.

**Control:** Socio-economic, to ensure safe water supply, and good standard of hygiene, along with vaccination and treatment.

**Treatment:** Prompt replacement of fluids and electrolytes.

Antibiotics are generally not recommended and used in systemic infections and in

**Vulnerable patients: neonates, elderly, immunosuppressed**

**Management:**

**Replacement of fluids and electrolytes, IV/ORS** oral rehydration soln.

**Isolation and barrier nursing**

**Notification to the MOEH**

**Food poisoning**

**Definition:** Diarrhoea and or vomiting following ingestion of food contaminated with bacteria and or their toxins.

**Causative organisms:** Salmonella, Campylobacters, V.parahaemolyticus,
Staphylococcus aureus, Clostridium perfringens, Bacillus cereus, Clostridium botulinum, E.coli.

**Mechanism of food poisoning:**

Factors influencing multiplication of bacteria (food passive vector)

 Cross contamination of cooked and uncooked food at all stages.

 Inadequate inactivation of bacteria, spores, and their toxins during preparation.

 Unsatisfactory storage conditions of food.

 Contamination of animal and poultry feed with bacteria

Conditions in which food poisoning occurs; i.e. bulk cooking, cooking previously and reheating inadequately, Adding infected additives to food. Cross contamination of raw food and cooked food.

**Prevention of Gastrointestinal infections:**

Good hygiene, Safe water

Safe food preparation and storage, Good practices of food handlers.

**Carriers**, and carriage of enteric pathogens. Long term carriage e.g. Salmonella

**Treatment:** Supportive usually (fluids and electrolytes), antibiotics not recommended except in systemic infections only.

Vulnerable patients: neonates, elderly, immunosuppressed.

**Isolation and barrier nursing**

**Notification:** Medical Officer of Environmental Health (MOEH) - to prevent outbreaks and identify source of infection.

**AGENTS WHICH CAUSE DIARRHOEA**

**1. Bacteria** \*Salmonella- gastroenteritis (food poisoning)

 Enteric fever, S.paratyphi A,B,C

 E.coli Enteropathogenic

 Enterotoxigenic

 Enterohaemorrhagic

 Enteroadhesive

 Verotoxin +ve

 O157

 Shigella

 \*Campylobacter \* associated with food- poisoning

 Vibrio cholera

 \*Clostridium perfringens

 Clostridium difficille

\*Staphylococcus aureus

Yersinia enterocolitica

\*Vibrio parahaemolyticus

\*Bacillus cereus

**2. Viruses** Rota virus- 30-40% cause of diarrhoea in children under 3 yrs

 Infective hepatitis (HepatitisA)

 Adeno virus

 Norwalk agent, astro, calici & echo virus

**3. Protozoa** Giardia lamblia

 Entamoeba histolytica

 Cryptosporidium

**4. Helminths** Strongyloides

 Ascaris

 Taenia

**5. Chemicals** Arsenic

 Muscarine Alkaloides

 Scrombrotoxins: Tryptophans Histamine

6**. Algae** Phytoplancton

**7. Fungi** mushroom

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.  |

Viral Hepatitis

Dr Janice Main

**LEARNING OBJECTIVES**

To be able to list the major causes of acute viral hepatitis

To be able to define “chronic” viral hepatitis

To be able to list the major causes of chronic viral hepatitis

To be able to list the medical complications of chronic viral hepatitis

To have sufficient knowledge to request diagnostic tests for viral hepatitis and to have a basic knowledge of the results

**INTRODUCTION**

Many viruses can cause hepatitis. Glandular fever (Epstein Barr virus infection), for example, can be complicated by acute hepatitis and it is not unusual to find deranged liver function tests in infection such as measles. This session concentrates on the key points of hepatitis A to G.

**HEPATITIS A VIRUS INFECTION (HAV**)

HAV is an enterally transmitted picornavirus (hepatovirus) with an RNA genome of 7.5kb.
It causes acute hepatitis which tends to be subclinical or mild in young children but can be especially severe in older people particularly in those with pre-existing liver disease. The incubation period is 2 to 6 weeks. Passive immunisation can be achieved with administration of human normal immunoglobulin (HNIG) and a safe and effective vaccine is available which is useful for travellers.

**HEPATITIS B VIRUS INFECTION (HBV)**

HBV is a small (3.2kb) DNA virus and a member of the hepadna group. Transmission is parenteral with risks of chronicity ranging from 5% in healthy adults to 95% in neonates.
The incubation period is 2 to 6 months. Chronic hepatitis B has risks of cirrhosis and hepatocellular carcinoma. Interferon alpha and oral nucleoside analogs ( entecavir, tenofovir etc) are used as therapy in selected cases. A safe and effective vaccine is available which, in the UK, is mainly targeted towards high-risk groups.

**HEPATITIS C VIRUS (HCV)**

HCV is an RNA virus and a member of the flavivirus group. Spread is mainly by blood and needles although mother to baby spread can also occur and there are reports of sexual transmission – mainly among gay men with HIV infection. Chronicity occurs in 60-80% of those infected with risks of chronic liver disease and hepatocellular carcinoma. Combination therapy with peginterferon alpha and ribavirin is successful in treating 40-50% of those with genotype 1 infection and 70-80% of those with genotype 2 and 3.

**HEPATITIS D VIRUS (HDV)**

HDV is an RNA virus and the smallest virus known to infect man. It requires the presence of HBV to replicate and effective HBV vaccination is therefore protective. Rapidly progressive liver disease can occur and only a modest response to interferon is reported.

**HEPATITIS E VIRUS (HEV)**

HEV is an RNA virus and enterally transmitted. It causes acute hepatitis which can be life threatening during pregnancy. Person to person spread is unusual and outbreaks have been reported related to contaminated water, consumption of wild boar or contact with pigs.

**HEPATITIS G VIRUS (HGV, GBV-C)**

Despite its name this virus appears to cause little liver damage. Recent reports in those with HIV/GBV-C infection suggest a more favourable outcome compared with nonGBV-C infected patients. The mechanism for this is unclear.

**BEGINNERS’ GUIDE TO LAB TESTS**

**HAV**

Anti-HAV IgM pos – recent ( i.e. acute infection or vaccine)

Anti-HAV IgG – previous exposure to virus or vaccine

**HBV**

Anti-HBc IgM pos - recent ( i.e. acute infection)

Anti-HBc IgG pos - previous infection

HBsAg pos, HBeAg pos, anti-IgG pos, anti-HBc IgM neg – ongoing infection ?chronic

Anti-HBs pos, anti-IgG neg - previous vaccination

**HCV**

Acute infection

HCV RNA pos, anti-HCV Ab pos/neg (can be negative for some months)

Chronic infection

anti-HCV Ab pos, HCV RNA pos

6 major genotypes ( 1-6)

**HDV**

Anti-HDV IgM – recent infection

Anti-HDV IgG pos, IgM neg – infection in past

**HEV**

Anti-HEV IgM pos– recent infection

Anti-HEV IgG pos – previous infection

BIOCHEMICAL TESTS

Generally significant increase in ALT

Monitor day to day severity with prothrombin time

Breast Pathology

Dr James Carton

**Learning Objectives**

* In depth knowledge: breast carcinoma and breast screening.
* Good knowledge: common benign breast diseases.
* Passing knowledge: normal breast histology & male breast diseases.

**Normal breast histology**

* Branching ducts ending in terminal-duct lobular units, the functional unit of the breast.
* Duct-lobular system lined by an inner glandular epithelium and an outer myoepithelium.

**Duct ectasia**

* Inflammation and dilation of large breast ducts. Presents with nipple discharge.
* Cytology of smears shows macrophages and proteinaceous material.
* Histology shows dilated ducts with periductal inflammation and filled with secretions.
* Benign condition with no increased risk of malignancy.

**Acute mastitis**

* Acute inflammation of the breast. Presents with painful red breast.
* Staphylococci the most common causative organism.
* FNA cytology shows abundant neutrophils.
* Histology shows acute inflammation +/- abscess formation.

**Fat necrosis**

* Inflammatory reaction to damaged adipose tissue in the breast.
* Associated with trauma, surgery, radiotherapy.
* Presents with a breast lump which may be firm.
* FNA cytology shows degenerate fat, foamy macrophages and giant cells.
* Histology shows degenerate adipocytes surrounded by foamy macrophages, giant cells, lymphocytes and plasma cells. Later changes include fibrosis and calcification.

**Fibrocystic change**

* A spectrum of changes which reflect normal, albeit exaggerated, hormonal responses.
* Very common, found in over one third of premenopausal women.
* Presents with breast lumpiness and nodularity which may be cyclical.
* Histological changes include cysts, apocrine metaplasia, adenosis, mild usual epithelial hyperplasia and stromal hyperplasia.
* No increased risk of malignancy.

**Fibroadenoma**

* A benign fibroepithelial tumour of the breast.
* Presents as a circumscribed mobile lump in young women aged 20-30.
* FNA cytology shows branching sheets of epithelium, bare bipolar nuclei and stroma.
* Histology shows a multinodular mass composed of expanded intralobular stroma and compressed slit-like ducts.

**Intraductal papilloma**

* Benign papillary tumour arising with the duct system of the breast.
* Presents with nipple discharge or a mass.
* Cytology of nipple discharge may demonstrate branching papillary groups of epithelium.
* Histology shows a papillary mass within a duct lined by epithelium and myoepithelium.

**Radial scar**

* Benign sclerosing lesion of the breast.
* Usually presents as a stellate mass on mammography, closely mimicking carcinoma.
* Histology shows a central elastotic nidus surrounded by a proliferative corona.

**Proliferative breast diseases**

* A diverse group of intraductal epithelial proliferations associated with an increased risk, of greatly varied magnitude, for subsequent development of invasive breast carcinoma.
* Picked up on mammography or incidentally in breast tissue excised for other reasons.
* Includes florid usual epithelial hyperplasia, flat epithelial atypia, in situ lobular neoplasia.

**Ductal carcinoma in situ (DCIS)**

* A neoplastic intraductal epithelial proliferation associated with an inherent, but not inevitable, risk of progression to invasive breast carcinoma.
* 85% present on screening mammography, 10% with symptoms, 5% incidentally.
* Histology shows ducts filled with atypical epithelial cells.
* Graded into low, intermediate or high grade according to degree of nuclear atypia.

**Invasive breast carcinomas**

* A group of malignant epithelial neoplasms which infiltrate within the breast and have the capacity to spread to distant sites.
* Most common cancer in women with lifetime risk of 1 in 9.
* Incidence increases with age. Risk factors include early menarche, late menopause, increased weight, high alcohol consumption, family history.
* About 5% show clear evidence of inheritance (e.g. BRCA 1 & 2).
* Present with a firm breast mass or on screening.
* FNA cytology shows many poorly cohesive atypical epithelial cells.
* Histology shows infiltrating atypical epithelial cells. Several histological types are recognised: ductal (80%), lobular (15%), tubular (5%), mucinous (5%).
* Low grade types tend to be ER, PR positive and Her2 non-amplified.
* High grade types tend to be ER, PR negative and Her2 amplified.
* Prognosis depends on axillary lymph node status, tumour type, tumour grade (grade 1 better, grade 3 worst), tumour size.

**NHS breast screening programme**

* Aims to detect DCIS or small invasive carcinomas.
* Women aged 50-70 are invited for screening every 3 years (extending to 47-73 by 2012).
* Screening test is a mammogram which looks for calcification or masses.
* About 5% are abnormal and require further investigation, often with core biopsy.
* Core biopsies are given a B code: B1 – normal, B2 – benign, B3 – uncertain malignant potential, B4 – suspicious of malignancy, B5 – malignant (B5a = DCIS, B5b = invasive).
* Published figures claim that screening saves some 1,250 lives each year in the UK.

**Gynaecomastia**

* Benign enlargement of the male breast. Usually seen around puberty and men over 50.
* Most cases are idiopathic or associated with drugs (therapeutic and recreational)

.

Healthcare-Associated infections

Dr Eimear Brannigan

**Implications**

* Morbidity
* Prolonged admission (average 2.5 times longer)
* ‘Blocking’ beds
* Repeat surgery
* Prolonged antibiotics
* Use of Isolation rooms
* Medical complications
* Death (7.1 times more likely to die)

**Incidence**

* 1 in 10 inpatients in the UK

**Cost**

* Enormous - social/clinical/economic
* £1 Billion a year

**Preventable**

* Probably about 15-30%

**Modes of Transmission**

* Direct contact
* Indirect contact
* Droplet
* Airborne
* Common source
* Endogenous

**Most common HAIs**

* Urinary tract infection
* Surgical site infection
* Hospital-acquired pneumonia
* *C. difficile* colitis
* Hospital-acquired bacteraemia

 8th leading cause of death in US

 Wenzel *EID ’*01

**Changing nature of HAI**

* Immuno-suppression
* Extremes of age
* New procedures
* Resistance
* Emerging organisms

**Increasingly vulnerable patients**

* Invasive procedures
* New surgical techniques and operations
* Prosthetic and implantable devices
* Immunosuppression
* Obesity
* Diabetes
* Extremes of age

**Increasingly resistant organisms**

* Widespread and prolonged use of antibiotics
* Broad spectrum antibiotics
* Increase in resistant organisms;
MRSA, VRE, ESBL,

 multi-resistant gram negatives eg Acinetobacter, E.coli Klebsiella, Pseudomonas

 *Enterobacter cloacae* ,etc .

**Increased Transmission**

* Increased invasive devices
* High bed occupancy
* Poor staffing ratios
* Poor infection control
* Poor hand hygiene
* Multiple bed moves
* Lack of isolation facilities

**Environmental issues**

* Importance of environmental hygiene e.g .C.diff, Norovirus, Acinetobacter outbreaks
* Environmental sources of outbreaks Legionella- cooling towers

 Aspergillus- building works

* Need for negative pressure isolation: TB, Chickenpox, RSV

**New infection challenges**

* Blood borne viruses
* CJD
* Rapid international travel
* Pandemic Flu
* SARS
* 2001- Bioterrorism
* Emerging resistance
* Community MRSA

**Surveillance: Why Track Infections?**

* To manage cases- a clinical ‘alert’ system
* To monitor and control the spread of transmissible diseases
* Early detection of outbreaks
* To benchmark and improve practice
* To audit clinical management/QA
* To monitor risk factors
* To target action and resources
* To understand their epidemiology
* Can reduce HAI by by 32%

 *Haley et al Am J Epi ‘85*

**Nosocomial Infection National surveillance Scheme (NINSS)UK 2000**

**HAB SSI**

1. *S.aureus* 1.*S.aureus*

 47% MRSA 61% MRSA

2. CNS 2. Coliforms

3. *E. coli* 3. CNS

4. Enterococci

 10% VRE

**How to reduce HAB ?**

* Hand Hygiene (*Pittet Lancet 2000; 356 )*
* Surveillance (*SENIC, NAO)*
* Line care (*UK Epic Guidelines 2006)*
* Reduce Antibiotic Usage

**Surgical Site Infection**

* Each SSI requires an extra 6.5 days and costs are doubled
* 3rd most common nosocomial infection in US
* 2.6% of ops complicated by SSI
* 2/3 confined to incision,1/3 deep space
* When patients with nosocomial SSI died- 77% related to infection

**NINSS UK: SSI Surveillance in English Hospitals 1997-99**

* Limb amputation and large bowel surgery most frequently
* Deep/organ space infection accounted for at least 23% of SSIs
* Incidence increases with risk factors
* 47% of micro-organisms were staph – 81% *S.aureus* (of these 61% were MRSA)

**Risks for SSI**

Complex interaction of factors

* Nature and no. of organisms contaminating surgical site
* Health of patient
* Skill and technique of surgeon

**Surgically important micro-organisms and sources of infection**

Intrinsic organisms

* Skin
* Site of surgery

Extrinsic organisms

* Health care workers
* Invasive devices
* Environment

**Patient risk factors**

* Age
* Nutritional status
* Diabetes
* Smoking
* Obesity
* Coexistent infections elsewhere
* Colonisation
* Altered immune response
* Length of pre-operative stay

**Operative factors**

* Glucose control
* Skin antisepsis
* Pre-op clipping (**never** shaving)
* Pre-op skin prep
* Instrument sterilisation
* Foreign material
* Surgical drains
* Surgical technique (i.e. poor haemostasis, failure to obliterate dead space, tissue trauma)
* Duration of op

**Post op factors**

* Hand hygiene
* Incision care
* Isolation, barrier precautions
* Cohorting elective patients
* Antibiotic control
* Antibiotic prophylaxis –timing, stopping and choice
* Surveillance of SSI

**Antibiotic Prophylaxis**

* **Which ops?**

Elective:

Clean contaminated– going through any hollow viscous

Clean- but infection would be catastrophic

* **Which antibiotics?**

Which bacteria are of concern?

What is the evidence base?

* **When to give?**

0-2 hours before incision

* **How long for?**

Not > 24 hours- no evidence longer is any use – and associated with greater rates of HAB etc

**Infection control strategy**

* Multidisciplinary
* Policies/Education/Training
* Audit and Surveillance
* Microbiology data
* High clinical profile, clinical management
* Purchasing, building, contracts etc
* Hospital epidemiology
* Decontamination
* Environmental and Technical expertise
* Bed management
* Outbreak prevention and management
* Antibiotic control
* Making it every HCWs responsibility

***Infection Control:* Our Key Strategies**

**Hand Hygiene**

One of the most effective methods of reducing HAI and the transmission of resistant organisms

Yet compliance still poor………

* Ignorance/Lack of awareness
* Lack of role model/example
* Lack of time/ staff ratios
* Lack of facilities
* Poor technique
* Doctors often the worst

**Improved Patient Outcomes associated with Proper Hand Hygiene**

* Semmelweis introduced antiseptic hand hygiene techniques.
* Noted post-partum women examined by medical students who did not wash their hands after performing autopsies had high mortality rates.
* He required students to clean their hands with chlorinated lime before examining patients
* Maternal mortality fell from 12% to <1%

Renal disease

Prof Terry Cook

The key is to correlate clinical syndromes with underlying pathological processes and to understand that similar pathological processes may have different aetiologies.

**Immune complexes and the kidney** – several glomerular diseases are associated with deposition of immune complexes in the kidney. Variations in the pattern of deposition underlie the complex classification of glomerular disease. It is important to understand that:

1. Complexes may be formed with endogenous (auto) antigens e.g. SLE, or exogenous antigens e.g. from infective organisms

2. Complexes may deposit at different sites in the glomerulus – mesangial, subendothelial and subepithelial – this affects the inflammatory response

3. Complexes may deposit at different rates – this affects the clinical presentation which can range from rapidly progressive renal failure to slow onset of renal impairment

**CONGENITAL**

Bilateral or unilateral agenesis. Ectopic kidney. Horseshoe kidney (1:500 to 1:1000)

**Cystic diseases**

Most important is *adult polystic kidney disease* – autosomal dominant (1:400-1:1000). 10% of end stage renal failure (ESRF). Cysts may arise from any portion of the nephron and growth of cysts compresses remaining parenchyma. Renal failure develops from 40-70 years. *PKD1* and *PKD2* genes have been identified

Cysts commonly arise in the kidneys of patients with ESRF after a prolonged period on dialysis (*acquired cystic disease*). Carcinoma may occur in these cysts (7% of patients at 10 years)

**SYNDROMES**

**Acute renal failure** – rapid loss of glomerular filtration and tubular function leading to abnormal water, electrolyte and solute balance. Reduced GFR manifests as increased creatinine and urea. May result in acidosis, hyperkalaemia and water overload

**Nephrotic syndrome** – break down of selectivity of glomerular filtration barrier leading to massive protein leak – Proteinuria >3.5g/day, hypoalbuminaemia, oedema, hyperlipidaemia

**Isolated urine abnormalities** – microscopic/macrocopic hamaturia and/or proteinuria (sub-nephrotic)

**Chronic kidney disease** – gradual decline in renal function that may eventually lead to end stage renal failure. 5 stages based on GFR

**ACUTE RENAL FAILURE**

May be pre-renal (hypoperfusion of kidneys), renal, or post-renal (obstructive)

**Acute tubular injury (acute tubular necrosis)**

Commonest cause of acute renal failure. Characterised by damage to renal tubular epithelial cells caused by ischaemia or toxins (e.g. drugs, myoglobin). Common in critically ill patients where there may be several aetiological factors. Drugs that inhibit vasodilatory prostaglandins e.g NSAIDS, COX-2 inhibitors predispose.

Morphologically, tubular epithelial cells show a range of changes from loss of brush border to detachment from the basement membrane with formation of intraluminal casts. Reduction in GFR is due to a combination of tubular obstruction, tubular leak and haemodymic changes. Tubules have excellent capacity to repair if the underlying insult is corrected.

**Acute glomerulonephritis**

Acute inflammation of glomeruli with reduction in glomerular filtration. Presents with oliguria with urine casts containing red and white blood cells. Glomerulonephritis sufficient to cause acute renal failure is almost always associated with glomerular crescents which form in response to holes in the GBM caused by macrophages and neutrophils. The causes of *crescentic glomerulonephritis* can be considered under three headings:

1. Immune complex disease, including SLE, IgA nephropathy and post-infectious glomerulonephritis. Immune complexes can be detected by immunohistochemistry and electron microscopy.

2. Anti-GBM disease. Rare disease associated with circulating and glomerular-bound antibodies against the GBM. Characterised by linear localisation of IgG on GBM by immunofluorescence. Antibodies also bind to alveolar basement membranes leading to lung haemorrhage.

3. Pauci-immune. Only scanty deposits of immunoglobulins and complement are present. Most will be associated with circulating anti-neutrophil cytoplasm antibodies (ANCA). Many patients will also have vasculitis in other systems e.g. skin, lung

**N.B.** Crescentic glomerulonephritis leads rapidly to irreversible renal damage but is often treatable. Therefore diagnosis and treatment are urgent.

**Thrombotic microangiopathy**

Damage to endothelium of glomeruli and vessels leading to thrombosis. Commonly associated with mechanical damage to red blood cells leading to haemolytic anaemia with red cell fragments on the blood film. Two forms:

1. Diarrhoea associated. Caused by bacterial (usually E.coli) infection of the gut that releases a toxin that targets renal endothelium

2. Atypical (non-diarrhoeal) – often associated with abnormalities of proteins that control activation of the alternative pathway of complement – may be familial.

**NEPHROTIC SYNDROME**

**Systemic diseases**

*Diabetes mellitus* – glomeruli show capillary wall thickening and mesangial increase with nodule formation. Arterioles show hyaline deposition

*Amyloidosis* – deposition of extracellular proteinaceous material that stains with Congo red to give green bifrefringence. May be derived from many precursor proteins – commonest in the kidney are:

AA – derived from serum amyloid A protein which is elevated in chronic inflammation e.g. rheumatoid arthritis, chronic infections

AL - derived from immunoglobulin light chains in patients with plasma cell dycrasias

*SLE*

**Primary glomerular disease**

*Minimal change disease* - primary disease of podocytes. Glomeruli look normal apart from effacement of podocyte foot processes on EM. Commonest in children. Generally responds to immunosuppression

*Focal and segmental glomerulosclerosis* - similar to minimal change disease but glomeruli develop segmental scars. Less likely to respond to immunosuppresssion

*Membranous glomerulonephritis* - associated with immune complex deposition on the outside of the GBM. May be primary (idiopathic) or secondary to SLE, infection, malignancy or drugs

**ISOLATED URINARY ABNORMALITIES**

**Microscopic haematuria -** usually due to thin basement membranes or IgA disease

**Asymptomatic proteinuria** - may be due to a wide range of glomerular structural abnormalities or immune complex deposition and final diagnosis may require renal biopsy

**CHRONIC KIDNEY DISEASE**

Most of the diseases above, together with hypertension, can cause chronic kidney damage. This is strongly associated with increased risk of cardiovascular disease. Some of these patients will progress to end-stage renal failure requiring renal replacement therapy - dialysis or transplantation. The commonest cause of end-stage renal failure in the UK is diabetes mellitus. Other common causes are glomerulonephritis, hypertension and polycystic kidney disease.

**SYSTEMIC LUPUS ERYTHEMATOSUS**

Autoimmune disease characterised by deposition of immune complexes in the kidney. 1:2500 M:F 1:9. Autoantibodies directed at a range of intracellular and extracellular antigens. Immune complexes commonly found in glomeruli and morphological changes depend on site of deposition: mesangial (mesangial proliferation); subepithelial (membranous glomerulonephritis); subendothelial (endocapillary proliferation + crescents). Clinical presentation may be isolated urinary abnormalities, nephrotic syndrome, acute renal failure or progressive chronic renal failure.

Diabetes clinicopathological conference

Professor Karim Meeran, Dr Amir Sam and Dr Paul Lewis

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Infection Clinicopathological Conference

Dr Hugo Donaldson & Dr Alex Rice

This page is blank for any notes you wish to make during the Infection clinicopathological conference.

Cerebrovascular Disease and Trauma

Dr Rathi Ramakrishnan
(Handout courtesy Dr Michael Osborn)

1. **Describe the major pathologies in Cerebrovascular disease:**
2. Infarction
3. Haemorrhage
4. Aneurism
5. **Infarction:**
6. An area of tissue death due to lack of oxygen
7. Caused by local interruption of blood flow
8. Most common form of cerebrovascular disease
9. 70-80% of strokes
10. Male > female
11. Most common in 60s
12. Cerebral atherosclerosis most common cause
13. Hence hypertension, diabetes, smoking are risks
14. Worst atherosclerosis in larger vessels
15. E.g. Internal carotids, middle cerebral, basilar arteries
16. Thrombosis of atherosclerotic segment is important cause
17. Often near carotid bifurcation or in basilar artery
18. Other cause is emboli
19. Usually from heart or atherosclerotic plaques
20. Except for basilar arterial system – Emboli are most common cause of intracranial occlusion
21. Embolic occlusion usually in middle cerebral artery branches
22. Location and distribution of infarct varies and depends on: Site of occlusion
Time to develop
Presence/absence of anastomoses
Systemic perfusion pressure
23. Collateral circulation less well developed distally
24. Hence distal arterial occlusion usually causes infarct
25. If atherosclerosis is severe can get infarct without complete occlusion if blood pressure drops significantly
26. Cell death occurs within minutes of arterial occlusion
27. Onset of symptoms usually sudden
28. Transient Ischaemic Attacks often precede main event
29. Last several minutes to 24hrs
30. Caused by self limiting vascular obstruction due to atheromatous emboli and/or platelet-fibrin aggregates
31. TIA important predictor of future infarct
32. 1/3 of those with TIA get significant infarct within 5 years
33. Most infarcts occur in areas supplied by branches of middle cerebral artery
34. Usually due to emboli
35. “Watershed” strokes are infarctions caused by hypoperfusion at the periphery of a blood supply. There does not have to be an occlusion.
36. **Intraparenchymal haemorrhage (non traumatic):**
37. Haemorrhage into the substance of the brain
38. Most commonly in middle to late adulthood
39. Usually due to the rupture of a small intraparenchymal vessel.
40. Hypertension is most common underlying cause
41. Hypertension accounts for 50% of clinically significant haemorrhages
42. Hypertension causes accelerated atherosclerosis in large vessels and hyaline arteriosclerosis in smaller vessels both cause weakening of the wall
43. May also cause “Charcot-Bouchard” microaneurisms less than 0.3mm –not Berry aneurisms
44. **Intraparenchymal haemorrhage (non traumatic):**
45. Other factors include clotting disorders, neoplasms, amyloid, vasculitis, vascular malformations
46. Haemorrhage most common in basal ganglia
47. Onset usually abrupt
48. Associated with evidence of raised intracranial pressure including severe headache, vomiting, rapid loss of consciousness
49. Localizing signs often hard to detect
50. **Subarachnoid Haemorrhage:**
51. Usually non traumatic and due to rupture of a Berry aneurism
52. Berry aneurisms present in 1% of general population
53. Higher incidence in people with polycystic kidney disease, coarctation of the aorta, fibromuscular dysplasia and AV malformations in the brain
54. 80% occur at arterial bifurcations of the internal carotid artery
55. 20% occur within the vertibrobasilar circulation
56. i.e they occur on the circle of Willis
57. **Subarachnoid haemorrhage (cont):**
58. Was thought they arose due to congenital weaknesses in the media
59. Unusual in children
60. Now felt more likely to be the result of an acquired degenerative lesion perhaps secondary to haemodynamic injury
61. Enlarge with time
62. Greatest risk of rupture when 6-10mm diameter
63. When greater than 25mm risk of rupture reduced but act as mass lesion
64. In 30% of patients they are multiple
65. **Subarachnoid haemorrhage (cont):**
66. Ruptured Berry aneurism less common than intracerebral haemorrhage
67. Women more than men
68. Usually before the age of 50
69. Onset sudden
70. Associated with severe headache, vomiting, loss of consciousness
71. 50% die within a few days
72. **Vascular Malformations:**
73. Important cause of intracranial haemorrhage
74. Most are developmental abnormalities
75. Vary in size
76. Four main types –

 Arteriovenous (AV) malformations

 Capillary telangectases

 Venous angiomas

 Cavernous angiomas

**CNS TRAUMA**

1. Describe the effects of head trauma
2. Head injury causes ¼ all accidental deaths
3. 20% of survivors have long term disability
4. 5% remain in permanent vegetative state
5. Three main patterns –

 Extradural haemorrhage

 Subdural haemorrhage

 Parenchymal injury

1. **Extradural Haemorrhage:**
2. Usually due to rupture of a meningeal artery
3. Usualy middle meningeal artery as it courses between the dura mater and the squamous portion of the temporal bone
4. Usually associated with a skull fracture
5. Many patients have a “lucid” interval followed by progressive loss of consciousness
6. Bleeding is arterial therefore pressure increases rapidly
7. **Subdural Haematoma:**
8. Blood between the internal surface of the dura mater and the arachnoid mater
9. Usually due to disruption of bridging veins that run from the brain surface to the dural sinuses
10. Anything causing rapid changes in head velocity can lead to tearing of these veins
11. Acute subdurals contain clotted blood
12. Usually a clear history of trauma
13. Cause raised intracranial pressure
14. Venous bleeding so slower to develop than extradural
15. Chronic subdural contains liquid blood
16. Less good history of trauma
17. Associated with brain atrophy
18. Often cause vague alteration in mental state rather than classical features of raised intracranial pressure
19. **Traumatic Parenchymal Injury:**
20. Concussion – transient loss of consciousness and paralysis sometimes with seizures with recovery over hours or days
21. Minimal morphological changes
22. May be due to temporary injury to reticular activating system
23. May be associated with some axonal injury
24. Diffuse Axonal Injury – Causes most post traumatic dementia and with hypoxic ischaemic injury is responsible for most cases of persistent vegetative state
25. Occurs due to sudden acceleration/deceleration sufficient to stretch or tear nerve cell processes in the cerebral white matter
26. Contusions – haemorrhages in the superficial brain parenchyma caused by trauma
27. Occur where brain comes in contact with skull or unyielding dura
28. May be associated with a skull fracture
29. “Coup” contusion where impact occurs
30. “Contracoup” contusion in areas away from impact
31. Impossible to tell coup and contracoup apart without information of mechanism
32. If associate with lacerations contusions are a major cause of traumatic subarachnoid haemorrhage
33. **Traumatic Parenchymal Injury (cont):**
34. Traumatic intracerebral haemorrhage – associate with contusions and deep within brain
35. If deep often associated with diffuse axonal injury
36. May occur deep and alone and be hard to tell from spontaneous intracerebral haemorrhage
37. Oedema of brain parenchyma
38. Can occur with any pathology
39. Vasogenic oedema – When integrity of blood brain barrier is disrupted, made worse due to lack of lymphatic drainage in brain, can be local or general
40. Cytotoxic oedema – Secondary to cellular injury eg due to general hypoxic-ischaemic injury
41. Often oedema is due to both processes

**Raised Intracranial Pressure 1**

1. Describe the effects of space occupying lesions and raised intracranial pressure
2. CNS is in an enclosed bony box
3. Pressure can increase because of localised (space occupying) lesions, or oedema or both
4. Other causes include hydrocephalus
5. Raised intracranial pressure poorly tolerated especially in adults
6. As pressure increases the brain is forced against unyielding structures
7. This leads to herniation
8. **Brain Herniation:**
9. Occurs due to raised intracranial pressure
10. Classical sites include –
11. Transtentorial (uncal gyral, mesial temporal) – medial temporal lobe compressed against the free margin of the tentoriium cerebelli
12. Subfalcine (cingulate gyrus) – cingulate gyrus displaced under the falx cerebri
13. Tonsillar – cerebellar tonsils through the foramen magnum, this causes brain stem compression and is life threatening and is often associated with secondary “Duret” haemorrhage

**Cerebral Infections**

1. List the major cerebral infections and describe the characteristic pathologies of these
2. Pathogens may enter CNS by several routes
3. Haematogenous
4. Direct implantation
5. Local extension
6. Invasion via nerves
7. Infection may be local or general
8. Pathogen may select certain part of CNS
9. Infection depends on interplay of hosts defences and pathogens virulence
10. **Epidural & Subdural infections**:
11. Rare
12. High mortality
13. In skull due to trauma or sinus infection
14. Epidural infections stay localised
15. Subdural generalised
16. Due to virulent organisms e.g. staphylococci
17. **Leptomeningitis (meningitis):**
18. Inflammation of the leptomeninges and subarachnoid space
19. Usually due to infection can be due to chemicals
20. Infection divided into acute purulent usually due to bacteria, acute lymphocytic usually due to viruses and chronic due to various agents
21. **Acute purulent meningitis:**
22. Major cause of morbidity and mortality in all ages
23. Usualy due to bacteria
24. Usualy reach CNS via bloodstream
25. In neonate usualy due to flora of maternal genital tract e.g. group B Streptococcus and E.coli
26. Children older than 6yrs Haemophilus influenzae was the major cause but now falling due to vaccine. Now Streptococcus pneumoiae causes most cases
27. Neisseria meningitidis is the major cause of epidemics and meningitis in older children, adolescents and young adults
28. In older adults Streptococcus pneumoniae and gram-negative bacilli are the major cause
29. Staphylococcus aureus and gram-negative rods are common causes in people with surgical shunts
30. Meninges appear congested
31. Purulent material in subarachnoid space
32. Infection of brain parenchyma rare
33. Clinical features include fever, headache, stiff neck, altered mental state
34. CSF is turbid and contains mostly neutrophils
35. Prognosis depends on speedy accurate treatment
36. **Acute lymphocytic (viral) meningitis:**
37. Cultures usually negative hence also called “aseptic” meningitis
38. Usually self limiting with much better prognosis
39. Echovirus, Coxsackie's virus, mumps virus, HIV are causative agents
40. Clinical features similar to bacterial meningitis but usualy less severe
41. CSF contains mostly lymphocytes
42. **Chronic meningitis:**
43. Often due to bacteria or fungi
44. Agents include Mycobacterium tuberculosis, Cryptococcus neoformans (especially in HIV), and less commonly Brucella sp, and Treponema palladium
45. Leptomeninges and sometimes dura are thickened
46. Exudate in subarachnoid space
47. Arachnoid adhesions may be present
48. Lymphocytes, plasma cells and epithelioid macrohages make up the infiltrate
49. Caseous necrosis and granulomatous inflammation may be present in TB
50. Clinical features may be similar to other meningitis or may be minimal
51. **Parenchymal infections:**
52. Encephalitis is generalised infection of the brain parenchyma
53. May be local or generalised
54. **Brain abscess:**
55. Due usually to bacteria eg Staph, Strep, anaerobes
56. Reach CNS by haematogenous, direct implantation or contiguous spread
57. Bacterial endocarditis, lung abscess, bronchiectasis all can lead to haematogenous spread
58. May occur anywhere but usually in cerebral hemispheres
59. Usually solitary but may be multiple particularly if due to haematogenous spread
60. Temporal and frontal lobes common sites due to spread from sinus or middle ear infections
61. Clinical features include, raised intracranial pressure, fever and focal neurological deficits
62. Complications include rupture and herniation
63. **Tuberculosis & Toxoplasmosis:**
64. Important causes of parenchymal infection
65. TB can involve parenchyma as well as meninges
66. Toxoplasmosis is usually associated with AIDS and causes multiple lesions usually in the grey matter
67. TB reaches the brain by haematogenous spread usually from the lung
68. It forms small nodules or large caseous lesions
69. **Viral Enchephalitis:**
70. Viruses are most common cause of encephalitis
71. May be localised or generalised
72. Usually associated with meningitis resulting in meningoencephalitis
73. Some viruses infect selective cell populations eg Rabies infects neurons
74. Eg Herpes Simplex Encephalitis – due to Herpes Simplex type 1, most common viral encephalitis in USA. Usually in healthy adults. Usually involves temporal lobes and frontal areas.
75. **Spongiform Encephalopathies:**
76. Uncommon, transmissible disorders
77. Include new-variant Creutzfeldt-Jakob disease (nvCJD)
78. Cause microscopic vacuolation in cell bodies of neurons and surrounding neuropil
79. Caused by “infectious” proteins - Prions
80. Prions are modified forms of structural proteins found in the mammalian nervous system
81. nvCJD occurs in younger adults than classical CJD
82. Clinically nvCJD causes rapidly progressive dementia
83. Death usually a year after onset
84. Linked to ingestion of cattle with BSE

**BRAIN TUMOURS**

List the major brain tumours and explain how to differentiate primary from secondary tumours in the brain

1. **Metastatic Neoplasms**:
2. Brain is the most common site for metastatic lesion
3. An intracranial tumour in an adult is most likely to be a metastasis from outside the CNS
4. Metastases occur most commonly in the elderly
5. Lymphoma and leukaemia may involve the CNS and can do so in the young
6. Metastases may involve the meninges as well as the parenchyma
7. Excluding haematopoietic malignancy the most common primary sites in descending order are – lung, breast, malignant melanoma
8. Metastases are usually well demarcated
9. May be solitary or multiple
10. Sharp interface exists between the metastasis and the surrounding parenchyma
11. Oedema often surrounds the lesion
12. Clinical features include neurological effects and raised intracranial pressure.
13. **Primary Brain Tumours**:
14. Originate in brain, spinal cord, or meninges
15. Effects depend on site as much as tumour type
16. A benign tumour in a bad place can be rapidly fatal
17. They rarely metastasise outside the CNS
18. Astrocytomas –

 Most common group of primary CNS tumours

 Heterogeneous group

 range from slow growing pilocytic astrocytoma to
 aggressive glioblastoma multiforme

1. Fibrillary or diffuse astrocytomas have an infiltrative growth pattern
2. Most common in adults but occur at any age
3. Usually in the cerebral hemispheres but can be anywhere
4. Subdivided into grades according to degree of differentiation
5. Histological grade is an important predictor of behaviour
6. Low grade well differentiated tumours have a tendency to become less well differentiated high grade tumours with time
7. Some high grade tumours arise denovo
8. Well differentiated astrocytomas – poorly defined, infiltrative, expand the parenchyma obliterating the grey/white interface
9. Anaplastic astrocytomas – Grossly indistinguishable from better differentiated counterparts but are of higher grade
10. Glioblastoma multiforme – Infiltrative irregular haemorrhagic necrotic tumour
11. Clinically infiltratative astrocytic lesions may present with evidence of raised intracranial pressure or with focal neurological signs
12. Prognosis depends on site, grade of tumour and age of patient
13. The elderly usually fair worse
14. Pilocytic astrocytomas

 More common in children but may occurr at any age

 Common sites include cerebellum or 3rd ventricle but can be anywhere

 Distinguished from fibrillary astrocytic neoplasm by more discrete nature and

indolent behaviour

Frank malignancy rare

Prognosis depends on site

1. Oligidendrogliomas –

 Most common in adulthood

 Usually in cerebral hemispheres

 Often have cytogenetic abnormalities

 Usually soft and gelatinous

 Better demarcated than infiltrating astrocytomas

 Calcification is common

 Prognosis less predictable than with astrocytomas and depends on

histological grade, site, patient age, cytogenetics and other factors

1. Ependymomas –

 Occur at any age

 Most occur in the ventricular cavities or within the canal of the spinal cord

 Intracranial lesions are most common in the first two decades of life, cord lesions in adults

Usually well demarcated

Clinical features depend on site but intracranial lesions may cause hydrocephalus or raised intracranial pressure

Anaplastic variants often disseminate throughout the subarachnoid space

1. Primitive Neuroepithelial Neoplasms –

Composed of embryonal (primitive) small cells

Usually in children

Undifferentiated lesions

EG – Medulloblastoma –
A lesion of the cerebellum
First 2 decades of life
Leads to raised intracranial pressure and cerebellar signs
Most survive 5 years or more with multimodality therapy

1. Primary CNS lymphoma has increased since AIDS
2. Meningiomas –

 Derived from meningothelial cells that invest the arachnoid mater
 Most occur outside the brain parenchyma

 Usually occur in adults

 May occur in cranial vault and cord

 Increased in people with neurofibromatosis type 2

 Usually lobulated firm lesions attached to the dura mater

 Sharp interface between tumour and parenchyma of brain or cord
 Overlying skull may be thickened or invaded by tumour

 Present with raised intracranial pressure sometimes with focal neurological signs

Histological grade and location alter prognosis

Introduction to Tropical Medicine

Dr Gareth Tudor-Williams

Why toilets are more important than doctors

Dr Oliver Cumming, LSHTM

I’ve got you under my skin

Dr Anthony Solomon

HIV in African Children

Dr Gareth Tudor-Williams

Fever in the Returning Traveller

Dr Jim Buckley