School of Medicine

Year 5 – 2012/13

PATHOLOGY THEME GUIDE

Volume 2 – Week 2

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**PATHOLOGY THEME**

Year 5 – Study Guide  
Week 2

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SOLE Feedback – Pathology Theme

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

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

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

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

|  |
| --- |
|  |

SOLE Feedback – Individual Lecturers – Week 2

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

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

|  | **The lecture(s) are well structured** | | | | | **The lecturer explains concepts clearly** | | | | | **The lecturer engages well with the students** | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Lecturer and Lecture Title** | Strongly Agree | Agree | Neutral | Disagree | Strongly Disagree | Strongly Agree | Agree | Neutral | Disagree | Strongly Disagree | Strongly Agree | Agree | Neutral | Disagree | Strongly Disagree |
| Dr Donald Macdonald  Leukaemia/CML |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Saad Abdalla  Myeloproliferative disorders |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Francis Matthey  Myelodysplastic syndromes |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Prof Barbara Bain  Acute Leukaemia |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Prof Barbara Bain  Leukaemia cases |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Prof Wendy Barclay  Pandemic Flu |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Nesrina Imami  Vaccination |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Mike Osborn  Lower GI disease |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Prof Karim Meeran  Pituitary |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Nesrina Imami  HIV infection |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Prof Margaret Callan  Immune therapies |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Graham Cooke  Mycobacterial disease |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Amin Rahemtulla  Plasma cell myeloma |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Prof Margaret Callan  Case studies |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Peter Kelleher  Case studies |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Nesrina Imami  Case studies |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Keith Gould  Case studies |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Robert Goldin  Liver disease |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Mary Thompson  Gynaecological pathology |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Prof Margaret Callan  Malabsorption |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Tim Orchard  Malabsorption |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Marjorie Walker  Malabsorption |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Prof Margaret Callan  Immunology quiz |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Peter Kelleher  Immunology quiz |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dr Hugo Donaldson  Urinary tract infections |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

| **Lecturer and  Lecture Title** | **Please use this box for additional constructive feedback.** |
| --- | --- |
| Dr Donald Macdonald  Leukaemia/CML |  |
| Dr Saad Abdalla  Myeloproliferative disorders |  |
| Dr Francis Matthey  Myelodysplastic syndromes |  |
| Prof Barbara Bain  Acute Leukaemia |  |
| Prof Barbara Bain  Leukaemia cases |  |
| Prof Wendy Barclay  Pandemic Flu |  |
| Dr Nesrina Imami  Vaccination |  |
| Dr Mike Osborn  Lower GI disease |  |
| Prof Karim Meeran  Pituitary |  |
| Dr Nesrina Imami  HIV infection |  |
| Prof Margaret Callan  Immune therapies |  |
| Dr Graham Cooke  Mycobacterial disease |  |
| Dr Amin Rahemtulla  Plasma cell myeloma |  |

| **Lecturer and  Lecture Title** | **Please use this box for additional constructive feedback.** |
| --- | --- |
| Prof Margaret Callan  Case studies |  |
| Dr Peter Kelleher  Case studies |  |
| Dr Nesrina Imami  Case studies |  |
| Dr Keith Gould  Case studies |  |
| Dr Robert Goldin  Liver disease |  |
| Dr Mary Thompson  Gynaecological pathology |  |
| Prof Margaret Callan  Malabsorption |  |
| Dr Tim Orchard  Malabsorption |  |
| Dr Marjorie Walker  Malabsorption |  |
| Prof Margaret Callan  Immunology quiz |  |
| Dr Peter Kelleher  Immunology quiz |  |
| Dr Hugo Donaldson  Urinary tract infections |  |

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| --- | --- | --- |
| Timetable Week 2 | | |
| All sessions are at the Charing Cross Campus | | |
| **Monday 9th July** | | |
| 9.00-10.00 | Ha | Introduction to leukaemia and CML (Dr. Donald Macdonald) |
| 10:00-11:00 | Ha | Myeloproliferative disorders (Dr Saad Abdalla) |
| 11.00-11.15 |  | BREAK |
| 11.15-12.15 | Ha | Myelodysplastic syndromes/Bone marrow failure (Dr Francis Matthey) |
| 12.15-13.15 |  | LUNCH |
| 13.15-14.15 | Ha | Acute leukaemia (Prof Barbara Bain) |
| 14.15-15.15 | Ha | Interactive leukaemia cases (Prof Barbara Bain) |
| 15.15-15.30 |  | BREAK |
| 15.30-16.15 | CP | Adrenal (Prof Karim Meeran) |
| 16.15-17.00 | CP | Forensics (Dr Sue Paterson) |
|  |  |  |
| **Tuesday 10th July** | | |
| 9.00-10.00 | Mi | Respiratory tract infections (Dr Rishi Dhillon) |
| 10.00-11.00 | Mi | Mycobacterial diseases (Dr Graham Cooke) |
| 11.00-11.15 |  | BREAK |
| 11.15-12.15 | Mi | Pandemic Flu (Prof Wendy Barclay) |
| 12.15-13.15 |  | LUNCH |
| 13.15-14.15 | Im | Vaccination (Dr Nesrina Imami) |
| 14.15-15.15 | Hi | Lower Gastrointestinal disease (Dr Mike Osborn) |
| 15.15-15.30 |  | BREAK |
| 15.30-16.30 | Ha | Haematology of systemic disease (Dr Donald Macdonald) |
|  |  |  |
| **Wednesday 11th July** | | |
| 9.00-10.00 | CP | Pituitary (Prof Karim Meeran) |
| 10.00-11.00 | Im | HIV Infection (Dr Nesrina Imami) |
| 11.00-11.15 |  | BREAK |
| 11.15-12.15 | Im | Immune therapies (Prof Margaret Callan) |
|  |  |  |
| **Thursday 12th July** | | |
| 9.00-10.00 | Mi | Antimicrobial agents I (Dr Annette Jepson) |
| 10.00-11.00 | Mi | Antimicrobial agents II (Dr Annette Jepson) |
| 11.00-11.15 |  | BREAK |
| 11.15-12.15 | Ha | Plasma Cell Myeloma & video (Dr Amin Rahemtulla) |
| 12.15-13.15 |  | LUNCH |
| 13.15-15.15 | Im | Case Studies in Immunology (Dr Keith Gould) |
| 15.15-15.30 |  | BREAK |
| 15.30-16.30 | Hi | Liver and biliary disease (Dr Robert Goldin ) |
|  |  |  |
| **Friday 13th July** | | |
| 9.00-10.00 | Mi | Viral Infections in Pregnancy (Dr Lila Paraskevopoulou/Dr H Donaldson) |
| 10.00-11.00 | Hi | Gynaecological pathology (Dr Mary Thompson) |
| 11.00-11.15 |  | BREAK |
| 11.15-12.45 | Im | Malabsorption CPC (Prof Margaret Callan, Dr Marjorie Walker, Dr Tim Orchard) |
| 12.45-13.45 |  | LUNCH |
| 13.45-15.00 | Im | Immunology Revision Quiz (Prof Margaret Callan) |
| 15.00-15.15 |  | BREAK |
| 15.15-16.15 | Mi | Urinary tract infections (Dr Hugo Donaldson) |

CONTACT DETAILS

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Course administration

Mrs Chandra Tambimuttu ([c.tambimuttu@imperial.ac.uk](mailto: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 are shown in the order of presentation as known at the time of going to press, and continues the page numbering from Week 1, Volume 1 of the Course Guide.

Introduction to LEukaemia

Dr Donald Macdonald

**Learning Objectives**

* To list the main cell types in peripheral blood cell and their precursor cells found in the bone marrow
* To describe in simple terms the basic principles of normal haematopoiesis and understand how haematopoiesis is disturbed in haematological cancers
* To describe the main types of genetic damage which gives rise to leukaemia or lymphoma and understand the distinction between the following:
  + chromosomal translocations creating a novel fusion gene
  + chromosomal translocation de-regulating a proto-oncogene
  + point mutations

**Introduction**

Throughout the pathology course you will have a series of lectures on haematological cancers; conditions such as multiple myeloma, acute myeloid leukaemia, chronic lymphocytic leukaemia, lymphoma, myelodysplasia, myeloproliferative disorders etc. In these lectures you will learn disease specific pathology and clinical features, however they will be better understood if you are aware of basic principles underlying the pathogenesis of all these diseases. Most importantly you should be clear about the following key features.

* These are clonal disorders, and the malignant cells seen in the bone marrow, blood, lymph-node or other sites are the progeny of a single transformed lympho-haemopoietic stem cell. Leukaemias and lymphomas are examples of cancer albeit often liquid tumours in contrast to solid tumours such as breast, lung or colon cancer. You should consider the bone marrow and blood as an example of a dispersed/liquid organ in contrast to solid organs such as brain liver and kidney.
* The stem cell is transformed due to acquired genetic damage (there may in rare cases be a background of inherited predisposition to cancer such as a defect in DNA repair enzymes)
* The cancer causing mutation(s) may affect one or more of the following processes; cell proliferation, cell differentiation (the process of developing from an immature lympho-haemopoietic stem cell to a mature end cell such as erythrocyte, neutrophil, or plasma cell) or apoptosis/cell survival (the process whereby cells undergo programmed cell death)
* Mutation(s) which block differentiation and increase proliferation/cell survival give rise to an excess of immature/precursor cells i.e. blasts. If the proportion of blasts in the bone marrow becomes greater than 20% then the diagnosis is acute leukaemia. If the block affects lymphoid differentiation or alternatively myeloid differentiation leading to an accumulation of lymphoblasts or myeloblasts then acute lymphoid or acute myeloid leukaemia is the diagnosis.
* Mutation(s) which permit differentiation but increase proliferation and or cell survival give rise to an excess of mature cells. Often the clonal population may predominately mature down one lineage pathway for example erythrocytes in Polycythaemia Vera (PV) or neutrophils/myelocytes in Chronic Myeloid Leukaemia. In such cases these cells although part of the malignant clone often retain some of the normal functions of end stage cells consequently these disorders generally have a longer natural history than the acute leukaemias.
* The malignant cells in chronic leukaemias or myeloproliferative disorders may acquire further DNA damage which blocks differentiation. Thus a variable proportion of CML, PV or myelodysplasia cases will ultimately evolve or transform into acute leukaemia.
* As the population of clonal malignant cells increase they may start to interfere with normal blood cell production, this can give rise to organ failure. The main clinical problems arising from bone marrow failure whatever the cause, are anaemia, infection and bleeding due to a lack of red cells, white cells and platelets respectively.

**What causes haematological cancers?**

In most individual cases we do not identify a cause for leukaemia. However overall we know that certain inherited genetic disorders predispose to developing leukaemia/lymphoma but individuals with these disorders do not inevitably develop haematological cancer. Genetic predispositions include Downs syndrome, Fanconi anaemia, Ataxia telangectasia.

The majority of patients do not have an inherited predisposition in these cases agents which damage DNA are most commonly implicated, either by 1) DNA mutagenesis as a result of chemotherapy, radiotherapy, 2) Viral integration into DNA or chronic latent infection by agents such as HTLV1 or EBV respectively, 3) Immuno-suppression either iatrogenic or HIV, impairing T lymphocyte function and resulting in increased incidence of lymphomas.

**What type of DNA damage/mutation(s) gives rise to haematological cancers?**

Acquired chromosome translocations and DNA point mutations are the most important and best understood mechanisms causing haematological cancers. You do not need to know a catalogue of these but you should understand the difference between the 3 following mechanisms.

Chromosome translocations

* Creation of a novel fusion gene: genes A and B on two separate chromosomes are split within introns. The translocation creates a new fusion gene containing 5’ exons derived from gene A and 3’exons from gene B. This novel gene has novel functions. The most important example of a fusion gene is the Philadelphia t(9;22) translocation creating a BCR-ABL fusion gene. Fusion genes are most commonly implicated in myeloid malignancies
* Deregulation of an oncogene: Expression of genes important in cell growth or apoptosis are normally tightly regulated and only expressed when required. In this scenario a translocation breaks DNA close to but outwith the coding sequence of an oncogene. The intact oncogene is translocated to a new chromosomal location and comes under the influence of an active DNA promoter. The most important example is the t(8;14) where cMYC comes under the influence of an Ig promoter, seen in Burkitt lymphoma. Deregulated oncogenes are most commonly seen in lymphoid malignancies.
* Point mutations: there are many described in haematological cancers and the significance of many of these is unknown. An important example is the JAK2 V617F mutation. Kinase genes transfer phosphate groups to downstream signalling proteins and are the mechanism for transmitting a growth signal from the cell surface to the nucleus. They are normally held tightly in an inactive form. JAK2 V617F is a single base substitution in a Tyrosine Kinase gene. The mutation abolishes an inhibitory domain causing constitutive activation of the gene Janus Kinase2. This results in a cell growth message this mutation is seen in approximately 98% of cases of Polycythemia Vera.

CHRONIC MYELOID LEUKAEMIA

**Learning Objectives**

**Chronic Myeloid Leukaemia**

• To state the clinical features of CML

• To describe the typical peripheral blood picture

• To state the diagnostic cytogenetic abnormality

• To describe the natural history of CML

• To know the average survival duration

**Introduction**

The chronic leukaemias are distinguished from acute leukaemias by the presence in the blood of mature cells and not primitive (blast) cells. In chronic myeloid leukaemia there are circulating cells of the neutrophil series.

***Chronic Myeloid Leukaemia***

CML is a disorder predominately of the middle aged (peak incidence 25-45 years). In CML there is a malignant population of white blood cells. The molecular basis of CML relates to the Philadelphia (Ph) chromosome. This is a chromosome 22 with a short long arm which results from a translocation of material between chromosomes 9 and 22. This translocation, t(9;22), is seen in 90-95% of all cases. It is an acquired translocation present only in the malignant cells. The translocation disrupts two separate genes BCR on chromosome 22 and ABL a Tyrosine Kinase on chromosome 9 to create a new BCR-ABL fusion gene. This new gene results in increased cell proliferation. In the chronic phase of CML the malignant cells proliferate excessively, however unlike AL they retain the ability to differentiate into mature cells which leads to different clinical and haematological features.

**Clinical and laboratory features**

Presenting symptoms may relate to hypermetabolism (weight loss, night sweats). Splenomegaly, which may be massive, is almost always seen.

The disorder may be diagnosed on a routine blood count. A FBC shows a high WCC 50-200x109/l. The film shows mature WCC such as neutrophils and myelocytes. Basophils may also be increased. The Hb and platelet count are usually normal.

The Ph chromosome is present in BM cells and molecular studies will reveal the novel BCR-ABL fusion gene. Serum urate may be increased.

**Natural history and treatment**

The disorder has a chronic phase (CP) of median 3-4 years duration, where the disease can be controlled by simple treatment. It then undergoes blastic transformation to AL, most commonly AML. Blast transformation to AL is generally poorly responsive to treatment, unlike the chronic phase and survival is short once transformation has occurred.

Treatment options during the chronic phase include:

1. oral hydroxyurea to suppress the WCC.
2. Interferon may also suppress the WCC and unlike hydroxyurea in some patients prolongs the duration of chronic phase. It has side effects and requires regular subcutaneous injections.
3. Imatinib mesylate is a novel oral drug which specifically inhibits ABL tyrosine kinase activity. The agent is extremely effective at controlling the proliferation of chronic phase cells in CML. New tyrosine kinase inhibitors (dasatinib, nilotinib) are also available for patients that fail or are intolerant to imatinib.
4. Allogeneic bone marrow transplantation in chronic phase is potentially curative, however this is only an option for patients <55, with an HLA donor. BMT does carry a morbidity and mortality.

**Prognosis**

The median survival is 3-5 years, with 20% of patients surviving 10 years or more.

Chronic Myeloproliferative Disorders

Dr Saad Abdalla

**Learning objectives**

1. To understand the distinguishing features of the chronic myeloproliferative syndromes from those of dysplastic and leukaemic disorders.
2. To be familiar with the major chronic myeloproliferative disorders:

a. Polycythemia vera (PV) (also called primary polycythaemia)

b. Essential thrombocythaemia (ET).

c. Idiopathic myelofibrosis (IMF).

d. Chronic myeloid leukaemia (CML) (discussed in a separate lecture)

1. For each of the listed conditions, to be familiar with

e. The clinical and natural history of these disorders

f. The haematological features and other tests used in diagnosis

g. The differential diagnosis

h. Principles of treatment.

**Characteristic features**

These are clonal disorders of haemopoietic stem cells. There is loss of the normal feedback control switch but maintenance of normal ability to terminal differentiation. The abnormal clone replaces the normal polyclonal cells resulting in an increase production of mature cells.

In the last year several groups have identified a mutation in a tyrosine kinase (JAK2) in most patients with polycythaemia and in approximately 50% of those with ET and MF. This is an important fundamental finding that has implications on the pathogenesis of this group of disorders and with potential implication for future therapy.

The diseases are associated with variable increase in reactive polyclonal bone marrow fibrosis which predominates in myelofibrosis. There is also an increase in the incidence of terminal acute leukaemic transformation in these disorders.

**Polycythaemia vera (PV)**

Literally a true increase in many cells in the blood. The predominant feature is the increased production in red cells leading to an increase in red cell volume, increased Hb and haematocrit. There is also an increase in the plasma volume. The increase in white cells, predominantly neutrophils is usually modest and of little clinical significance. The increase in platelet counts may play a role in the clinical picture of the disease.

Presentation: PV may present with features of increased blood viscosity such as headaches, visual disturbances, nose bleeds and in extreme cases cardiovascular or cerebrovascular thrombotic events. Patients may be plethoric with engorged fundal vessels and may also have splenomegaly. Patients may also be referred after an incidental finding on a routine blood test. Other presenting features are ‘aquagenic pruritus and gout.

Investigations: Full blood count, blood volume studies, exclude secondary causes. Bone marrow may be useful. Serum erythropietin level is usually low in contrast to secondary polycythaemia. In vitro erythroid colony growth is a useful test but not widely available.

Treatment: Aim to reduce HCT below 0.45 by venesection. Cytoreductive therapy (see below) may be needed especially if the platelet count is high.

**Essential Thrombocythaemia (ET)**

In ET the predominant cells affected are the megakaryocytes leading to a high platelet count. Common presentations are thrombosis (mainly arterial) but also paradoxically abnormal haemorrhagic tendency may also occur. The disease may also be diagnosed incidentally after a routine blood counts. Some patients may also present with headaches or TIAs. A persistent rise of platelets above 600 x109 is needed to make the diagnosis.

Clinical features: Predisposition to haemorrhage and thrombosis. Splenomegaly, usually modest. In most cases the white cell count and haemoglobin are normal.

Diagnostic tests: It is important to exclude causes of reactive thrombocytosis (haemorrhage, iron deficiency, infections and inflammation, acute and chronic and occult or overt neoplasia). Normal inflammatory markers (ESR and CRP) may help to exclude those. The bone marrow is diagnostic in many cases with an increase in megakaryocyes with some abnormal forms and with clustering. A small amount of fibrosis may be present but marked fibrosis may suggest the alternative diagnosis of myelofibrosis.

Treatment The aim of the therapy is to reduce the risk of thrombosis. Aspirin is used to try to reduce the likelihood of arterial thrombosis but may increase the risk of bleeding. Therefore risk stratification is needed for rationalisation of treatment. Recent studies have identified the need for cytoreductive therapy in the following groups:

1. Absolute platelet count >1500 x109/l.
2. Age >60 years
3. Presence of other prothrombotic risk factors
4. Presence of diabetes or hypertension

If treatment is started the aim is to keep the platelets between 200 and 400 x109/l.

**Idiopathic myelofibrosis:**

Is a disease in which there is a reactive fibrosis of the bone marrow secondary to a myeloproliferative process. There is a resultant myeloid metaplasia (haematopoiesis in extramedullary sites such as liver and spleen) with splenic enlargement. Presentation may be due to increased production of platelets mainly although granulocytic cells may also be increased, with varying degrees of anaemia and splenomegaly. Marrow aspiration may yield a blood tap or a dry tap, and diagnosis needs confirmation with a bone trephine. Characteristic peripheral blood changes include a tear drop poikilocytes, a leucerythroblastic blood film and increased platelets with some giant forms. In late stages, thrombocytopenia may also occur. Presentation can sometimes occur with the Budd-Chiari syndrome: portal vein thrombosis with portal hypertension. When needed treatment is by alleviating symptomatic anaemia with transfusions although this becomes difficult in later stages when the spleen can be massively enlarged. Splenectomy may relieve some of the symptoms and reduce the need for transfusions but may be hazardous and sometimes followed by transformation to acute leukaemia. Cytoreductive therapy may be needed if the platelet count is high. Recently treatment with thalidomide has shown promising result in a few patients, with an improvement in Hb and in thrombocytopenia. In patients below the age of 40, in whom the disease is rare, bone marrow transplantation is curative and could be considered.

**Appendix 1. Cytoreductive therapy in MPD:**

Hydroxycarbamide : a mild cytotoxic agent that reduces production of all cell lines, especially useful in patients with PV but also used in ET.

Anagrelide a non-cytotoxic agent that selectively suppresses platelet production, useful when other cells are normal or there is anaemia (e.g myelofibrosis).

Alpha interferon: useful in selected patients (pregnant women or others intolerant of other treatment).

Myelodysplastic Syndromes and Aplastic Anaemia

Dr Francis Matthey

Aims of Lecture

1 To provide an understanding of the definition, pathophysiology, clinical features and treatment of myelodysplasia.

2 To provide an understanding of the definition, pathophysiology, clinical features and treatment of aplastic anaemia.

1. The Myelodysplastic Syndromes (MDS)

These are a heterogeneous group of haemopoietic stem cell disorders characterized by:

i. Peripheral cytopenia

ii. Qualitative abnormalities of erythroid, myeloid and megakaryocyte maturation

iii. An increased risk to transform to acute leukaemia

The overall incidence of MDS is 3.8 per 100,000 with 75% of cases being over the age of 65 years.

The diagnosis of MDS is dependent on careful examination of the peripheral blood film, bone marrow (BM) and cytogenetics. MDS is biologically very heterogeneous; the precise pathophysiology in many cases remains unknown. The recent recognition of familial cases of MDS suggests that at least some types of MDS are likely to have a significant genetic component.

MDS is classified by the World Health Organisation (WHO) according to:

* Peripheral Blood findings
* Bone Marrow findings
* Cytogenetics

**Table 1: The current (WHO) classification of MDS**

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1. Refractory anaemia (RA)

with ringed sideroblasts (RARS)

without ringed sideroblasts

2. Refractory cytopenia with multilineage dysplasia (RCMD)

3. Refractory anaemia with excess of blasts (RAEB)

RAEB-I (BM blasts 5-10%)

RAEB-II (BM blasts 11-20%)

4. 5q- syndrome

5. Unclassified MDS (do not fit into the above group – e.g. fibrotic MDS)

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N.B. in the previous French-American-British (FAB) classification ,Chronic Myelomonocytic Leukaemia (CMML) was also included in the MDS classification.

Clinically MDS patients present with features of the cytopenia (infection, bleeding, fatigue) and their management will include supportive care (blood products, antimicrobials) and in some instances specific therapy.

The specific therapies include:

1. Biological modifiers (immunosuppressive therapy, azacytodine, lenalidomide)
2. Growth factors (e.g. erythropoietin, G-CSF)
3. Oral chemotherapy (e.g. hydroxycarbamide)
4. Low dose cytarabine
5. Intensive chemotherapy/stem cell transplantation (SCT)

Since MDS has been found to be very heterogeneous it has been useful to develop scoring systems to predict prognosis and decide on treatment for individual patients. One such scoring system is given below.

**Table 2: International Prognostic Scoring System (IPPS) for MDS**

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Risk category Score value Median survival (years) AML evolution (years)**

Low 0 5.7 9.4

Intermediate-1 0.5-1.0 3.5 3.3

Intermediate-2 1.5-2.0 1.2 1.1

High >2.5 0.4 0.2

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Calculation and interpretation** — To calculate the International Prognostic Scoring System (IPSS) for MDS, a score from 0 to up to 2 is determined for each of three variables:

* Bone marrow blast percentage — <5 (0 points), 5 to 10 (0.5 points), 11 to 20 (1.5 points), 21 to 30 (2 points)
* Karyotype — Good karyotype (0 points) includes normal karyotype, -Y, del (5q), or del (20q); Poor karyotype (1 point) includes complex karyotype (≥3 abnormalities) or abnormal chromosome 7; Intermediate karyotype (0.5 points) is assigned to all others
* Cytopenias — Defined as: haemoglobin <10 g/dL (100 g/L), absolute neutrophil count <1.8 x 10^9/l, platelet count <100 x 109/l. If 0 to 1 cytopenias (0 points), 2 to 3 cytopenias (0.5 points)

The IPSS score equals the sum of each of these three values, and defines four risk groups for both overall survival and AML evolution: low (0 points), intermediate-1 (0.5 to 1.0 points), intermediate-2 (1.5 to 2.0 points) and high (2.5 to 3.5 points).

Thus, the score value is based on the blast count, cytogenetics and the degree of cytopenia. In general the more intensive forms of specific therapy (including SCT) are reserved for patients with high risk MDS (high score) and who are relatively young.

1. **Aplastic anaemia** **(AA)**

Aplastic Anaemia (AA) is characterized by the inability of the bone marrow (BM) to produce an adequate number of circulating blood cells. It is associated with significant mortality and affects an estimated 2-5 people per million per year. AA can occur at any age, but there is a peak incidence between 15-24 yrs and after the age of 60 yrs. The vast majority (~75%) of these cases are classified as idiopathic, and the primary pathology remains unexplained. Occasionally (~15% of cases), a drug or infection can be identified that precipitates the aplasia, although it is not clear why only some individuals are susceptible. In approximately 10% of patients the disease is constitutional/inherited, where the disease is familial and/or presents with one or more other somatic abnormalities. AA thus represents a heterogeneous group of disorders (Table 3 below).

### Table 3: Classification of Aplastic Anaemia \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Idiopathic (~70%) Vast majority

Inherited (~10%) Dyskeratosis congenita

Fanconi anaemia

Shwachman-Diamond syndrome

Secondary (~10-15%) Radiation Predictable

Drugs Predictable Cytotoxic agents

Idiosyncratic Chloramphenicol

Non-steroidals

Viruses Idiosyncratic Hepatitis viruses

# Immune SLE

# \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

In all subtypes of AA the number of haemopoietic stem cells are reduced. In many patients with idiopathic AA it is possible to demonstrate that there is an immune attack on the haemopoietic system. There is a close link between AA, paroxysmal nocturnal haemoglobinuria (PNH) and leukaemia. The 10-year cumulative incidence rates for myelodysplastic syndrome (MDS) and leukaemia are ~ 10% and ~ 6%, respectively. Such observations suggest that AA can be regarded as a pre-leukaemic disorder.

The symptoms and signs of AA result from the reduced numbers of circulating blood cells: (i) anaemia leads to increasing fatigue and breathlessness

(ii) deficiency of leucocytes leads to an increased risk of infections, and

(iii) a tendency to bruise and bleed easily due to lack of platelets.

Typically patients present with easy bruising, gum bleeding or nose bleeding.

The diagnosis of AA is made on tests on the blood and BM. These tests also allow it to be classified into severe aplastic anaemia (SAA), very severe aplastic anaemia (VSAA) and non-severe aplastic anaemia (NSAA).

**Appearance of aplastic and normal bone marrow trephines:**

|  |  |  |  |
| --- | --- | --- | --- |
| |  |  |  | | --- | --- | --- | | |  |  | | --- | --- | | Bone marrow in aplastic anemia  image  Bone marrow biopsy in aplastic anemia. There are virtually no hematopoietic cells, and the marrow space consists of fat and stroma.  Courtesy of Stanley L Schrier, MD. | Normal bone marrow  image  Low power view of a normal bone marrow biopsy. The overall cellularity is between 30 and 70 percent, with the remainder of the space being occupied by fat and stroma. Courtesy of Stanley L Schrier, MD. | | |

**Severity of Aplastic Anaemia**

Patients with severe aplastic anaemia (SAA) have BM cellularity of <25% and 2 out of 3 of the following peripheral blood features:

1. reticulocytes <20 x 109/l
2. neutrophils <0.5 x 109/l
3. platelets <20 x 109/l.

Patients with very severe AA (vSAA) the same criteria as SAA but the neutrophils are <0.2 x 109/l. I.e.:

1. reticulocytes <20 x 109/l
2. neutrophil count of <0.2 x 109/l
3. platelets <20 x 109/l

A family history of AA, somatic abnormalities on clinical examination and the results of special investigations may point towards constitutional bone marrow failure.

**Treatment of Aplastic Anaemia**

Unless patients with SAA or vSAA are successfully treated, over 70 percent will be dead within one year. Treatment for patients with SAA can be divided into supportive care and specific therapy (e.g. immunosuppressive therapy and stem cell transplantation). One algorithm for the treatment of SAA or vSAA is shown below:



**Consititutional Aplastic Syndromes**

The two constitutional syndromes that are frequently associated with generalised BM failure/aplastic anaemia (AA) are Fanconi anaemia (FA) and dyskeratosis congenita (DC). These two syndromes are now also two of the best characterized and are providing important insights into normal haemopoiesis and how it might be disrupted in AA. In new patients presenting with AA it is important to recognise if they have an underlying genetic disorder (such as FA), as this will influence the precise management.

Acute Leukaemia

Prof Barbara Bain

**Objectives:**

At the end of this lecture and related personal study you should be able to:

* Explain what acute leukaemia is
* Recognise the typical clinical and laboratory features
* Outline the molecular mechanism of leukaemogenesis and the pathological basis of the clinical and laboratory abnormalities
* Explain the **principles** of treatment

Acute leukaemia is a neoplastic condition, i.e. a type of cancer of the blood and bone marrow. It is called ‘acute’ because the symptoms and signs develop fairly rapidly and, if effective treatment is not given, it leads to death in a few weeks or months. Like other types of cancer the leukaemic cells all originate from a single cell that has suffered a number of mutations. The leukaemic cells thus belong to a single clone. It is a feature of acute leukaemia that although the cells keep proliferating they fail to mature. These primitive cells are called blast cells. The leukaemic cells have a growth advantage over normal bone marrow cells so that they crowd out the bone marrow, leading to bone marrow failure. This manifests itself as neutropenia, thrombocytopenia and anaemia.

Acute leukaemia can be either lymphoid or myeloid, referred to as acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML) respectively. The word ‘myeloid’ in this context refers to granulocytes, monocytes, erythrocytes and megakaryocytes and their precursors. Neither ALL nor AML is a single disease. Each is a heterogeneous group of disorders that have features in common but also very striking differences. This matters when you come to treat them.



This diagram shows a simplified stem cell hierarchy, illustrating how all lymphoid and myeloid cells ultimately originate from a pluripotent lymphoid-myeloid stem cell. The cells that can suffer mutation and become leukaemic stem cells can be located at various points in this hierarchy. The solid arrows show types of cell that can mutate, giving rise to AML. The hollow arrows show the two types of cell that can mutate giving rise to ALL, either B-lineage ALL or T-lineage ALL.

**Acute myeloid leukaemia**

AML is more common in adults than children and in adult life the prevalence rises exponentially with age. Some causes are known (irradiation, certain drugs, benzene exposure) but in the great majority of patients the cause is unknown. There are some inherited genetic abnormalities that predispose to AML but usually you can reassure patients that their families are not at risk. In young infants Down’s syndrome is a risk factor. To develop AML it appears to be necessary to have at least two mutations, one that leads to a failure of cellular differentiation and apoptosis together with another that promotes cell proliferation and survival. Sometimes there are many more mutations.

The clinical effects of AML result from

* Growth of leukaemic cells (infiltration in various organs)
* Loss of normal bone marrow function (cytopenias)

The diagnosis requires

* Clinical history including past drug/irradiation exposure
* Physical examination
* Blood count and film
* Bone marrow aspiration (may be supplemented by cytochemistry)
* Cytogenetic/molecular analysis
* Immunophenotyping (if not obviously myeloid)

The principles of treatment are

* Supportive care to correct the effects of inadequate bone marrow function (red cells, platelets, antibiotics)
* Combination chemotherapy
* Possibly targeted molecular therapy (strongly indicated for acute promyelocytic leukaemia)
* Possibly immunotherapy
* Possibly haemopoietic stem cell transplantation (‘bone marrow transplantation’)

The prognosis is very dependent on

* The age and general fitness of the patient
* The molecular basis of the leukaemia
* Whether it occurs de novo (better) of follows a myelodysplastic syndrome

Or exposure to leukaemogenic drugs or irradiation

**Acute lymphoblastic leukaemia**

Acute lymphoblastic leukaemia is a heterogeneous group of disorders, commoner in children than adults.

Clinical features are as for AML but lymphadenopathy is much more common and in T-lineage disease here can be infiltration of the thymus. Infiltration of the CNS and the tests is much more common.

Diagnostic procedures are as for AML.

The principles of treatment are the same as for AML but the choice of drugs is different and it is necessary to give pre-emptive treatment for occult CNS disease. In about a quarter of adults there is a t(9;22) translocation and a *BCR-ABL1* fusion gene; these patients require imatinib.

Prognosis depends on

* The age of the patient (in children it is quite good but in adults it is much worse)

The molecular mechanism

To revise the Year 2 MCD leukaemia lecture (still relevant) see

<https://education.med.imperial.ac.uk/Years/2-1112/MCD/handouts/CA15-CAD-Leukaemia.docx> and <https://education.med.imperial.ac.uk/Years/2-1112/MCD/ppt/leuk.ppt>

Interactive Haematology Cases

Dr Donald Macdonald and Prof Barbara Bain

**Objectives**

At the end of this and related sessions and your own learning you should be able to

* Recognize the clinical or laboratory features that suggest that a patient might have leukaemia or a related condition
* Explain what laboratory or other investigations are needed
* Explain the **principles** of treating such patients
* Distinguish leukaemia and related conditions from unrelated conditions with which they might be confused

Here is an example of the type of case that could be dealt with

* A 5-year-old boy of Indian ethnic origin presented with lymphadenopathy and a mediastinal mass on chest radiology
* WBC 180 x 109/l
* Hb 9.3 g/dl
* Platelet count 43 x 109/l

Here is the chest radiograph of another patient with the same diagnosis



**The most likely diagnosis is**:

Thymoma

Acute myeloid leukaemia

Acute lymphoblastic leukaemia

Haemorrhage into the mediastinum

Pneumonia with a leukaemoid reaction

You do not have to ‘learn’ the individual cases. Their purpose is to help you think how to approach diagnostic and treatment problems.

The Adrenals

Prof Karim Meeran

***Learning Objectives***

1. To revise the histology and microanatomy of the adrenal and its zonation.

2. To interpret tests of adrenal function including synacthen tests.

3. To know the effects of deficiency and excess of the adrenal hormones

4. To know how to interpret chemical pathology data to determine whether a patient has adrenal failure or adrenal hyperfunction, and in the case of hyperfunction, to know which hormones are likely to be in excess.

The adrenal microanatomy can be revised on <http://library.med.utah.edu/WebPath/ENDOHTML/ENDO077.html>

For regions of the adrenal gland, see slide 42 of the adrenal section of webpath.

**Clinical Cases**

***Case 1***

A 31-year-old presents with acute and profound tiredness gets admitted vomiting.

Results

Na: 125, K=6.5 U=10 Glucose = 2.9 mM

FT4 <5pM TSH > 50 mU/l

What diagnosis does this TSH suggest:

A. A TSH producing pituitary adenoma

B. Graves disease

C. A toxic thyroid nodule

D. Primary hypothyroidism

E. de Quervain’s (viral) thyroiditis.

Give another diagnosis that could each explain his tiredness.

Explain the abnormal electrolytes.

Explain the low glucose.

What diagnosis can explain all the results?

What dynamic test will confirm the diagnosis?

A. Low dose dexamethasone suppression test

B. High dose dexamethasone suppression test

C. Synacthen test

D. Glucose tolerance test

E. TRH stimulation test

***Case 2***

A 32-year-old presents with hypertension and an adrenal mass.   
Write down the three possible differential diagnoses here.

1.

2.

3.

This patient has high levels of catecholamines. What is the diagnosis?

What are the possible treatments?

1.

2.

3.

***Case 3***

A 33-year-old hypertensive man presented with the following results:

Na 147, K 2.8, U 4.0, Gluc 4.0mM

Plasma aldosterone raised.

Plasma renin suppressed.

What is the diagnosis?

***Case 4***

A 34-year-old obese woman with type 2 diabetes, presented with hypertension, bruising and the following results.

Na: 146 mM, K 2.9, U 4.0, Gluc 14.0

Plasma aldosterone suppressed (<75)

Plasma renin: suppressed.

**True or False**: This excludes primary hyperaldosteronism and suggests another hormone is causing the hypertension.

What is the diagnosis?

Which ONE of the following (dynamic) investigations need be carried out to confirm the diagnosis?

A. Insulin tolerance (stress) test

B. Dexamethasone suppression test

C. Synacthen test

D. Glucose tolerance test

E. TRH stimulation test

**Case 5**

A 35 year old obese patient has the following results:

9am cortisol (Monday) 650 nM

Given 0.5 mg dexamethasone 6 hourly for 48 hours

9am cortisol (Wednesday) < 50 nM

What is the diagnosis?

A. Pituitary dependent Cushing’s disease

B. Adrenal tumour causing Cushing’s syndrome

C. Ectopic ACTH causing Cushing’s syndrome

D. Normal obese person

E. Cushing’s syndrome of indeterminate cause.

What should be done next?

A. Pituitary MRI

B. Adrenal CT scan

C. Chest X-ray to look for an ectopic source

D. Tell her she does not have any serious adrenal problem

E. High dose dexamethasone suppression test

**Case 6**

A 36 year old obese patient has the following results:

9am cortisol (Monday) 650 nM

Given 0.5 mg dexamethasone 6 hourly for 48 hours

9am cortisol (Wednesday) 500 nM

What is the diagnosis?

A. Pituitary dependent Cushing’s disease

B. Adrenal tumour causing Cushing’s syndrome

C. Ectopic ACTH causing Cushing’s syndrome

D. Normal obese person.

E. Cushing’s syndrome of indeterminate cause.

What should be done next?

A. Pituitary MRI

B. Adrenal CT scan

C. Chest X-ray to look for an ectopic source

D. Tell her she does not have any serious adrenal problem.

E. High dose dexamethasone suppression test

**Case 6b.**

She is given 2mg dexamethasone 6 hourly for 48 hours, starting on Wednesday morning, immediately after the low dose dexamethasone suppression test.

At 9am on Friday morning, her cortisol is 170 nM

What is the diagnosis?

A. Pituitary dependent Cushing’s disease

B. Adrenal tumour causing Cushing’s syndrome

C. Ectopic ACTH causing Cushing’s syndrome

D. Normal obese person.

E. Cushing’s syndrome of indeterminate cause.

What should be done now?

A. Pituitary MRI

B. Adrenal CT scan

C. Chest X-ray to look for an ectopic source

D. Tell her she does not have any serious adrenal problem.

E. High dose dexamethasone suppression test

For the Hammersmith bible of endocrine protocols, which includes dexamethasone suppression tests, see the endocrine specialist registrars handbook on <http://meeran.info>

(then click on “Endocrine Bible”).

Drugs & Forensic Toxicology

Dr Sue Paterson

**Learning Objectives**

* To be aware of the types of cases involving toxicology dealt with by HM Coroner and the types of drugs detected.
* To be aware of the major points of forensic toxicology concern for the most common drugs of abuse.
* To be aware of the problems with interpretation of analysis of post mortem samples.
* To be aware of why hair is used for analysis of drugs and its application.

**Major points of forensic toxicology concern for the most common drugs of abuse**

* **Ethanol**
  + OD
  + Accidents including RTAs
  + Additive effects other respiratory depressant drugs
* **Heroin (measured as morphine)**
  + iv injection, mix with tobacco, volatilised
  + Fatal OD with all routes of ingestion
  + Additive effects other respiratory depressant drugs
  + Few rapid deaths
  + Most respiratory depression or aspiration pnuemonitis
  + Tolerance
* **Cocaine**
  + Injected with heroin, “speedball”
  + Tolerance
  + Acute dangers : cardiac dysrythmias, acute heart failure, myocardial infarction
* Slowly developing damage to the myocardium, ventricular arrythmias, sudden death
* Lethal syndrome of excited delirium, occurs in regular users within 24 hrs of last dose
  + Body packers
  + Effects prolonged if used with ethanol, get cocaethylene formed
* **Amphetamine**
  + V. few deaths
* **Ecstasy (MDMA)**
  + Few deaths
  + Large OD causes direct toxic effect on heart
  + Can cause hyperthermia, leads to rhabdomyolysis, leads to muscle necrosis and renal failure
* **Mephedrone**
  + Any deaths?
* **Methadone**
  + Tolerance
  + After ingestion fatal amount takes 4-6 hours to die
  + Additive effects other respiratory depressant drugs
  + 5 mL can kill a child, 60 mL can kill healthy adult male
  + Maintenance dose can vary from 5 to 200 mL
* **Benzodiazepines (diazepam, temazepam)**
  + Additive effects other respiratory depressant drugs
  + Extremely rare to cause death alone
* **Cannabis**
  + Never fatal alone
  + Find in RTAs
  + Driving after alcohol + cannabis, lethal co**mbination**

**Types of cases analysed in Coroners’ toxicology**

This will be illustrate with slides

**Problems Re: Intepretation**

* Tolerance
* Site dependence
* PM redistribution of drugs

(NB PM blood concentration cannot be used to calculate the dose)

* Individual variation in response
* Stability of drugs

The problems will be illustrated by reference to cases

**Why use hair for analysis**

* Blood/serum, drugs typically can be detected for no more than 12 hours
* Urine, drugs typically detected for 2-3 days
* Hair is the only specimen can give information about long term drug use
* Drugs are incorporated into hair from the blood stream during the growth phase
* Hair growth approx 1cm/month – “tape-recording of drug use”

**Applications of hair analysis**

* Child custody cases
* Investigating spiked drinks defences
* Drug naïve deaths
* Monitoring drug use prior to return of driving license – Germany, Italy
* Investigation of drug use in exhumed/putrefied bodies
* Employment, pre-employment screening - USA

**Abbreviations used:**

OD Over dose

RTA Road traffic accident

IV Intravenous

MDMA MethyleneDioxyMethAmphetamine or ecstasy

PM Post mortem

AM Ante mortem

6-mam 6-monoacetylmorphine (a metabolite of heroin)

Conc concentration

**RESPIRATORY TRACT INFECTIONS**

**Dr Rhishi Dillon**

Mycobacterial Diseases

Dr Graham Cooke

(Handout by Dr Dan Agranoff)

**By the end of this lecture you should be able to:**

1. List the key mycobacteria of clinical importance and the diseases associated with them.
2. Outline the global impact of TB and the broad epidemiological trends in the UK.
3. Describe the natural history and main clinical manifestations of TB.
4. Describe both the conventional and newer laboratory tests for TB
5. List the key antibiotics used in treatment of TB and give an example of a treatment regimen.
6. Outline the UK policy for BCG vaccination
7. Describe the main manifestations of leprosy
8. Outline treatment for leprosy
9. List the main cutaneous diseases caused by mycobacteria

**MYCOBACTERIA**

1. Family *Mycobacteriacae*, order *Actinomycetales*
2. Gram-positive rods. Aerobic. Acid-fast. Non-branching
3. Thick, waxy cell wall (mycolic acids)
4. >40 species

**Clinically Important Mycobacteria**

***- M. tuberculosis complex***

Tuberculosis: ‘Consumption’, ‘Phthisis’, ‘White plague’

1. common in animals
2. human pathogen for 6-8000 years

***- M. leprae***

Leprosy ‘Hansen’s disease’

No animal reservoir

Human pathogen for ~ 2000 years

**- Others (non-tuberculous mycobacteria - ‘NTM’)**

*M. avium-intracellulare complex -* MAI

*M. ulcerans –* Buruli ulcer

*M. kansasii*

*M. xenopi*

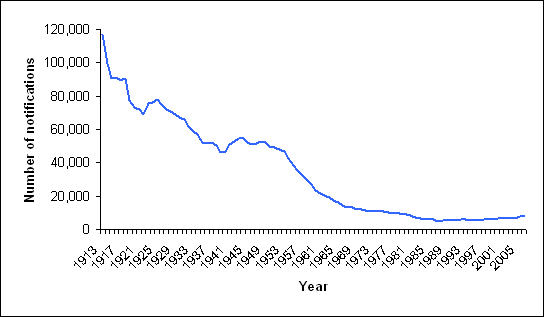
*M. marinum*

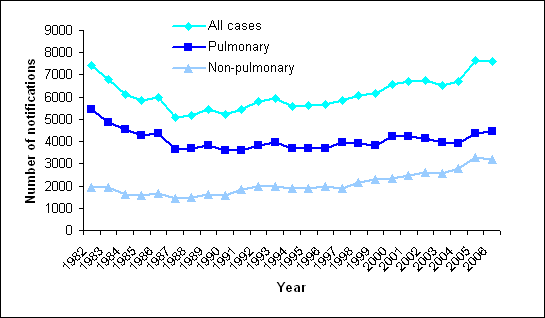
*M. chelonae*

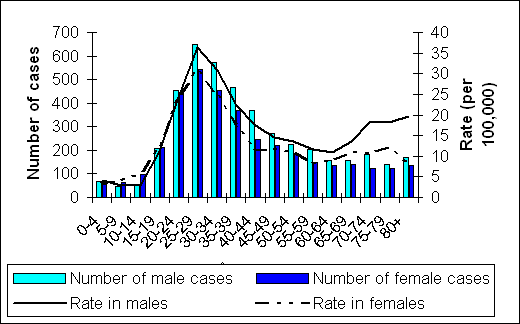
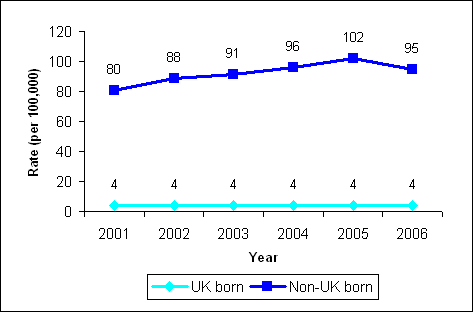
*M. fortuitum*

**TUBERCULOSIS**

1. Pulmonary
2. Extra-pulmonary
3. Lymphadenitis
4. Brain (TB meningitis/cerebral tuberculoma)
5. Bone (spinal TB – paraspinal abcess, osteomyelitis, discitis)
6. Pericarditis
7. Abdominal (peritonitis, ileitis)
8. Genito-urinary (renal, testicular)
9. Misc.: skin, liver etc.

**Notifications in the UK Rates increasing since ~1985**



**Highest rates in young adults and elderly Highest rates in non-UK born population**

**TB in the UK 2006**

1. 14.6/100,000 overall (8113 cases notified)
2. 448/100,000 in London (443 Mozambique, 940 S. Africa)
3. 278/100,000 in black Africans
4. 139/100,000 Indian subcontinent
5. 3/100,000 indigenous UK

**Sources:** HPA Annual report on tuberculosis surveillance and control in the UK 2007

WHO. Global Tuberculosis Control: Surveillance, Planning, Financing. WHO Report 2008

**Classification of TB disease**

1. ‘Primary’ vs ‘post-primary’ (traditional paradigm)
2. Reflection of age-related immune responsiveness
3. Site of disease

**Clinical tuberculosis**

1. **Pulmonary**
2. **Extra-pulmonary**
3. Lymphadenitis
4. Brain (TB meningitis/cerebral tuberculoma)
5. Bone (spinal TB – paraspinal abcess, osteomyelitis, discitis)
6. Pericarditis
7. Abdominal (peritonitis, ileitis)
8. Genito-urinary (renal, testicular)
9. Misc.: skin, liver etc.

**Childhood TB (‘primary’ TB)**

1. Organisms multiply at pleural surface (Ghon focus)

Macrophages take them to lymph nodes (primary complex)

Generalised lympho-haematogenous spread

1. Onset of CMI/DTH (3-8 weeks)

caseation of primary focus (+ nodes)

1. Rarely:

- tuberculoma

- ‘progressive primary’ TB; focus or node ulcerates into bronchus - pneumonia, cavity formation, bronchiectasis

The characteristic lesion is the granuloma

**Young adult tuberculosis (‘post-primary’)**

1. ? Re-activation
2. ? Re-infection
3. Usually affects upper lobes
4. Brisk hypersensitivity reaction
5. may progress rapidly to cavitation
6. miliary spread rare

**Summary of natural history**

**‘Primary TB’**

**10  complex**

**Lympho-haematogenous spread**

**Progressive 10**

**(~10%)**

**Healing (~90%)**

**Sterilisation**

**LATENCY**

**Childhood**

**Elderly**

**HIV**

**Re-activation**

**Re-infection**

**Naïve infection**

**‘Post primary’**

**Young adults**

**Diagnosis of TB**

1. History: cough, weight loss, fever, night sweats, etc
2. Chest X-ray
3. Skin tests (Mantoux/Heaf)
4. Sputum microscopy – ZN/auramine
5. Culture (sputum, urine, pus, biopsy, laryngeal swab, etc)
6. New tests: ã-interferon release assays/ PCR/line probe assays

**Vaccination: BCG – (bacille Calmette-Guerin)**

1. Attenuated strain of *M. bovis*
2. Introduced 1953 for 13yr olds in UK
3. Efficacy 0-80%
4. 2005 policy
5. Babies in areas with incidence >40/100,000
6. Babies with parents/grandparents born in a country with TB prevalence > 40/100,000
7. Previously unvaccinated new immigrants from high prevalence countries for TB.

**TB – antibiotic treatment**

**4 key drugs**

* Isoniazid
* Rifampicin
* Pyrazinamide
* Ethambutol

**Standard treatment for TB:**

1. INA + RIF + PYR + ETH for 2/12 *then* INA + RIF for 4/12 (8/12 for meningitis etc)
2. 90% of actively growing bacteria killed by INA in the first few days
3. RIF, PYR kill intermittently growing bacteria
4. **COMBINATION** therapy to kill bacteria at all growth phases and to prevent resistance

**Leprosy**

1. Hansen’s disease
2. Global prevalence ~220,000 (declining)
3. Chronic disease (life-long)
4. Incubation period ~ 5yrs
5. Inefficient transmission (nasal secretions)

– requires months/years of close proximity

1. Treatable with multi-drug therapy
2. Most disability secondary to nerve damage
3. Affects:
4. Skin: depigmentation, macules, plaques, nodules, trophic ulcers
5. Nerves: thickened nerves, loss of sensation
6. Eyes: keratitis, iridocyclitis
7. Bone (skull and limbs): periostitis, aseptic necrosis etc
8. Immunological/clinical spectrum

**BT**

**Tuberculoid (TT)**

**Lepromatous (LL)**

**Multibacillary**

**Paucibacillary**

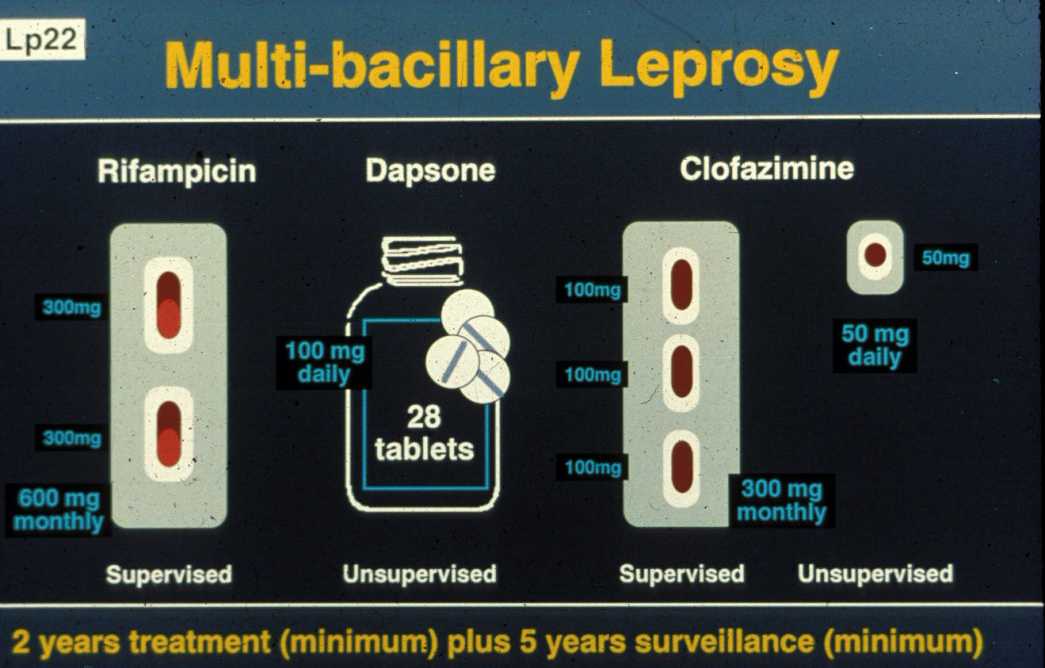
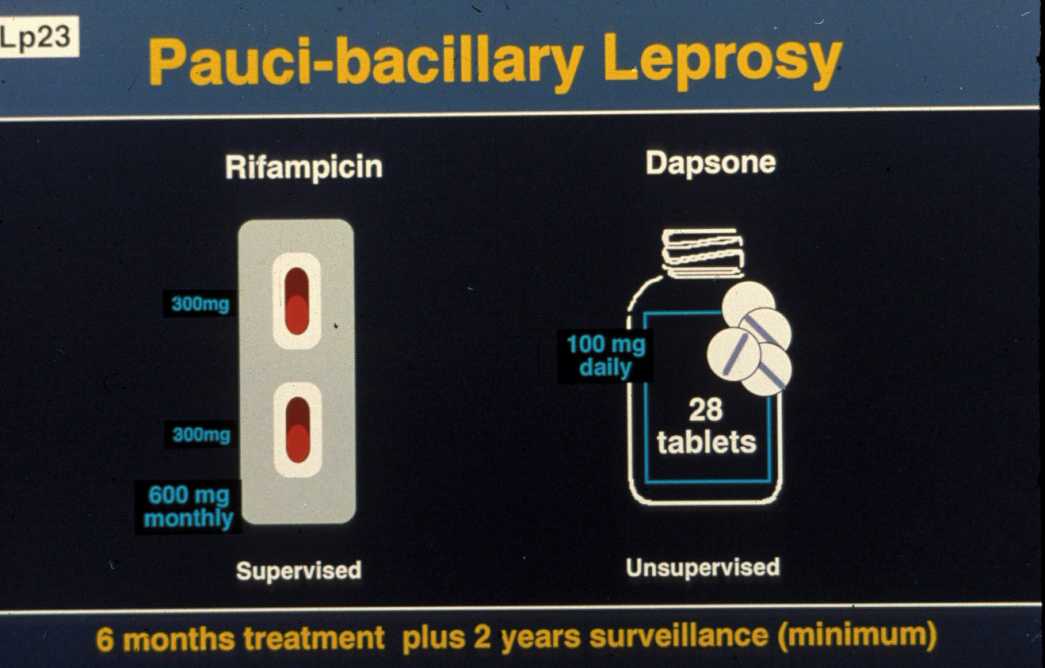
**Th1**

**BB**

**BL**

**Th2**

**Leprosy -Treatment**



***M. leprae***

1. *M. leprae* can replicate in the mouse foot pad and in the nine-banded armadillo
2. Acid fast bacilli are seen in the skin smears or biopsy materials
3. Acid fast bacilli are also present in the nasal secretions of patients with lepromatous leprosy.

***Mycobacterium avium-intracellulare***

1. **Children**
2. Pharyngeal/cervical adenitis
3. **Pulmonary**
4. Underlying lung disease (resembles TB)
5. **Disseminated**
6. Cytotoxics, lymphoma etc
7. **AIDS**
8. Disseminated multibacillary infection, mycobacteraemia

***Mycobacterial Skin Infections***

1. **Fish-tank granuloma (*M.marinum*)**
2. **Buruli ulcer (*M.ulcerans*)**
3. **Lupus vulgaris (*M.tuberculosis*)**
4. **Immune phenomena in TB:**
5. Erythema induratum
6. Erythema nodosum

**Buruli ulcer**

1. Common in tropics and Australia
2. Forms a nodule which breaks down into an ulcer
3. Produces a toxin (mycolactone) which causes skin necrosis
4. Transmission is likely to occur from infected insects
5. Diagnosis is by microscopy, culture and histology
6. Treatment is with rifampicin, streptomycin and surgery
7. *M.ulcerans* is thought to be derived from *M.marinum*

**The microbiological laboratory and mycobacteria**

The most commonly used stains to identify mycobacteria are the auramine and the Ziehl Neelsen stains. Both carbolfuschin and auramine bind to the mycolic acid of the cell wall. Auramine stained bacteria are bright yellow against a dark background. With the Ziehi Neelsen stain, mycobacteria stain red against a blue or green background. Media used for culture include non-selective culture media such as Lowenstin Jensen and Middlebrook, or selective media which contain antimicrobial agents to suppress bacterial and fungal contamination. The rate of recovery of mycobacteria and time to positivity have improved with the use of broth culture media.

*M. tuberculosis* can be identified using biochemical or molecular tests. Phenotypic characteristics of *M. tuberculosis* include 1) formation of non pigmented rough buff colonies 2) microcolonies form serpentine cords 3) accumulation of niacin 4) reduction of nitrated to nitrites . The optimum temperature for growth of *M. tuberculosis* is 37ºC. Each species of mycobacteria has an optimal temperature for growth and a range of time for recovery in culture. Nucleic acid probes can be used for identification of mycobacteria from culture. Probes are available for *M. tuberculosis complex, M. avium/ intracellulare complex, M. kansasii* and *M. gordonae.*

Some species of mycobacteria such as *M. ulcerans* and *M .marinum* have at optimum temperature of growth of 32ºC and 30ºC respectively. Hence it is important to inform the laboratory if infection with these species are suspected, so that specimens are incubated at the appropriate temperature. It has not been possible to culture *M. leprae* in vitro , but it can replicate in the mouse foot pad and in the nine-banded armadillo.

**New Assays**

There is a genomic segment in *M.tuberculosis* which is deleted from all strains of BCG and most environmental bacteria called *region of difference-1.*There are two proteins encoded by this region of DNA called early secretory antigenic target-6 (ESAT-6) and culture filtrate protein 10 (CFP-10). T cells from patients with current or past infection with *M.tuberculosis* become sensitised to ESAT-6 and CFP 10 in vivo. When T cells from such patients re-encounter these antigens , they release interferon- ã. Two assays have been developed based on this principle called the ELISPOT and Quantiferon . In the ELISPOT, the patients periphral blood mononuclear cells are incubated with ESAT-6 and CFP 10. If the patient has been infected with *M.tuberculosis,* interferon ã will be produced which will produce a spot as a result of a colorimetric reaction.The Quantiferon assay is a whole blood enzyme linked immunosorbent assay which measures the IFN ã concentration in the supernatant of a sample of diluted whole blood after 24 hrs of incubation with ESAT-6 and CFP 10. Neither assay can distinguish between past and present infection with *M.tuberculosis*, but they have the advantage that there is no antigenic cross-reactivity

with BCG vaccination.

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Pandemic influenza

Professor Wendy Barclay

* Three antigenic types/subtypes of influenza viruses currently circulate in humans and we use a trivalent vaccine in targeted populations to protect them against severe outcome.
* In wild birds at least 16 distinct antigenic subtypes of influenza A virus exist, but these viruses do not infect or replicate in humans.
* By a gene mixing process known as **reassortment**, the HA antigen of the avian viruses can be introduced into viruses that can infect humans.
* This is the known origin of pandemics in 1957 and 1968.
* Currently an avian influenza subtype H5N1 is widely distributed in wild birds.
* Unusually this virus has some propensity to infect mammalian species, including man.
* So far the H5N1 virus has not mutated nor reassorted to acquire the ability to efficiently transmit between people.
* For efficient transmission by the respiratory route, changes to the H5N1 virus would need to

1. adapt the virus for more efficient replication in the cooler temperatures of the human nose;
2. adapt the receptor binding preference of the viral HA protein for human receptors expressed in the upper respiratory tract.

* The number of mutations and the genes exchanged will determine the virulence of an H5N1 virus that emerges to have pandemic potential.
* The threat of an H5 or H7 pandemic is all the more worrisome because these two subtypes have HA proteins that can evolve to be cleaved by ubiquitous proteases for virus activation. This extends the tropism of H5 and H7 beyond the respiratory tract and is known in chickens to result in high mortality.
* In humans infected with H5N1, high viral load is associated with fatal outcome.
* High viral load and the genetic makeup of H5N1 triggers a higher than usual cytokine response.
* Some H5N1 viruses also appear to be resistant to the antiviral effects of the induced cytokines, which triggers a ‘cytokine storm’.
* Recently a new H1N1 influenza virus has emerged from pigs and is widely spread in humans causing a new human pandemic.
* This virus has no hallmarks as yet of high virulence and is currently susceptible to treatment with a widely available antiviral drug.
* Evolution of swine origin H1N1 may occur in the coming months and years.
* Management of patients with antiviral alone may control viral replication, but often patients die from the immunopathological effects of the inflammatory response.
* Antiviral drugs that inhibit the viral neuraminidase enzyme, such as zanamivir (Relenza) and oseltamivir (Tamiflu) have been stockpiled by governments.
* Resistant mutants of circulating H1N1 and H5N1 influenza viruses have emerged.
* Combinations of anti-viral with anti-inflammatory drugs may be a successful therapeutic strategy.
* Pandemic vaccines have been created and tested in humans.
* Higher doses are required to induce immune response than for annual flu vaccine.
* Adjuvants mean that lower doses can achieve effective immunization.

Ethical issues surround the administration of limited supplies of vaccine and drugs

Vaccination

Dr Nesrina Imami

**Objectives**

At the end of this lecture, you should:

* Know the principles of the generation of immunological memory, and how these principles apply in vaccine development
* Know the different types of vaccine and their advantages/disadvantages
* Understand recent developments in immunisation

Vaccine =”a biological substance which can be used to illicit an immune response in a host to provide subsequent protection”

Immunisation: provision of protective response, can be actively or passively acquired.

**Active Immunisation**

***Active immunity*** results from meeting the organism either naturally or through immunisation. Immunisation programmes use either live attenuated organisms (decreased virulence but still able to produce a protective immune response) or inactivated organisms or their altered products. Often the immune response is enhanced by inclusion of an adjuvant (see below).

**Generation of good immune response and memory induction**

*Dependant upon immunogenicity of the antigen*

Factors influencing Immunogenicity

|  |  |
| --- | --- |
| Composition | Proteins and glycoproteins best |
| Molecular complexity | more complex the greater the immunogenicity |
| Dose | a poor immunogen cannot be made better by giving bigger dose. |
| Route of administration | intravenous and intraperitoneal less antigenic than intramuscular |

Crucial to generate correct response (i.e Th1 or Th2) for protection

**B cell response,**

Protective responses are provided by plasma cells which secrete antibodies the most important are anti-toxins, opsonins, lysins, anti-adhesins, & neutralising antibodies.

Reactive memory responses are provided for by memory B cells which proliferate and differentiate to plasma cells in response to the later return of antigen.

**T cell responses**

Protective responses are provided by effector T cells which migrate to inflamed tissues

and demonstrate immediate effector function. Human effector memory T cells do not express CCR7, and are heterogeneous for CD62L expression. CD8 effectors carry large amounts of perforin. Both CD4 and CD8 effectors produce IFN-γ, IL-4, & IL-5 within hours following antigen stimulation.

Reactive memory responses are provided by central memory T cells which home to T cell areas of secondary lymphoid organs, have little or no effector function, but readily proliferate and differentiate to effector cells in response to antigenic stimulation.

Human central memory T cells express CD45R0 and also CCR7 and CD62L, Following TCR triggering, these cells produce mainly IL-2, but after proliferation they efficiently differentiate to effector cells and produce large amounts of IFN-γ or IL-4.

The relative proportions of effector and central memory T cells in blood vary in the CD4 and CD8 compartments, (more central memory in CD4 population, and more effector memory in CD8 subpopulaiton). Within the tissues, central memory cells are enriched in lymph nodes and tonsils, whereas lung, liver, and gut contain greater proportions of effector memory T cells.

**For a response to be protective it has to be above a certain level**

Measurement of effective response; (i) specific protective antibody titre (eg hemagglutination inhibition test); or (ii) DTH test in skin (e.g. Mantoux test); (iii) In vitro proliferation response.

To maintain responses above the protective level may require repeat exposure to vaccine depends on vaccine type.

**Passive Immunisation**

***Passive Immunity*** results from the transfer of immunoglobulins to individuals, providing protection for a limited period because the antibodies are catabolised (human IgG has a half life of about 3 weeks). Human normal immunoglobulin is prepared from pools of at least 1000 donations of human plasma. Replacement immunoglobulins are essential treatment for patients with primary antibody deficiency. Specific immunoglobulins = used to provide protection from specific infectious organisms or to prevent immunisation occurring e.g. passive immunity has been used for prevention of hepatitis A, both following exposure and prior to travel to an area of endemicinfection. Its use for these indications has decreasedsince the introduction of hepatitis A vaccines. When administered before or within 2 weeks after exposure, is 85 to 90% effective in preventing clinical hepatitis, butefficacy varies with the severity of exposure and the delay inadministeration (see Keller M & Stiehm Passive Immunity in the prevebntion and treatment of infectious disease, Clinical Microbiology Reviews, October 2000, p. 602-614, Vol. 13, No. 4)

**Different types of vaccine and advantages/disadvantages**

*Live attenuated vaccines*

Advantages Good response, often only single shot needed

Disadvantages Often poor stability and storage, reversion problems

*Inactivated vaccines*

Inactive whole organism or Component/Sub-unit vaccines

Advantages No reversion, relatively stable

Disadvantages Reduced immunogenicity requires boosting with adjuvant

**Adjuvants** “A compound which increases the immune response without altering its specificity”

*Action/function*

Facilitate antigen uptake /transport/presentation by APC’s

Act as a depot to allow persistence of antigen

Assist/provoke activation signals and provide addition induction signal.

Current clinically available adjuvant is Alum (= aluminium hydroxide) which has a depot effect.

Oils also used to enhance the persistence of antigen acting as a depot to slow the release of antigen. Vet use only because of problems in humans.

**New Developments**

*DNA vaccines*  Transfection of host cells by the DNA containing selected genes of choice.

*New Adjuvants*

CpG DNA **CpG sites** are regions of the DNA where a cytosine nucleotide is situated next to a guanine nucleotide. "CpG" stands for cytosine and guanine separated by a phosphate which links the two nucleotides together in DNA. Adjuvant activity is linked to DNA motifs that are rich in CpG dinucleotides which should be unmethylated

ISCOMS (Immunostimulatory complexes) consist of antigen assembled into multimeric form and the assembly has an accompanying adjuvant =saponin. ISCOMs induce a strong serum antibody response

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Lower Gastrointestinal Disease

Dr Mike Osborn

**Introduction:**

The lower gut generally refers to the colon, rectum and anus. The basic structure is identical to the upper gastrointestinal tract organised as mucosa – muscularis – submucosa – circular and longitudinal muscle, with a nerve plexus between these muscle coats and another in the submucosa. Unlike the small bowel the mucosa is flat and organised into crypts containing mucin secreting goblet cells, absorptive cells and some neuroendocrine cells.

The major disease categories are as elsewhere, inflammatory (of known and unknown aetiology) – functional – mechanical – vascular – neoplastic and iatrogenic. Here only the key major pathologies are considered, infective colitis, chronic inflammatory bowel disease (Crohn’s disease and ulcerative colitis), diverticular disease, polyps and cancer.

Large gut symptomatology is commonly manifest by obstruction (pain), altered bowel habit, diarrhoea, bleeding (anaemia) and for some conditions general systemic symptoms like skin and joint disease.

Investigation of the colon and rectum is via a wide range of imaging modalities that include plain X-rays showing gas shadows, barium studies, MRI scanning and colonoscopy with or without biopsy and recently “virtual” colonoscopy. The whole or any part of the colon and rectum can be surgically excised with appropriate anastomoses or “ostomies” and restorative surgery in the form of ileo-pouch anal anastomosis has considerably improved the patients lot.

**Inflammatory bowel disease**

This is usually divided into infectious colitis of known causes and “idiopathic” chronic inflammatory bowel disease that refers to Crohn’s disease or ulcerative colitis.

**Infection.** The commonest infectious colitides are bacterial in the Western world but world wide parasitic infestation by worms (e.g. hookworms, schistosoma) or protozoa, such as amoebae, is more common. In this country bacterial infection with campylobacter , salmonella or shigellae spp. are the most frequent Outbreaks of viral infection occur in children and cytomegalovirus or other opportunistic infections are problems in AIDS patients.

Normally the bacterial infections are treated by general practitioners with stool culture the mainstay of diagnosis. Characteristic biopsy features can be appreciated early on though the main bacteria cannot be distinguished each producing a similar picture in which neutrophil polymorphs predominate as the cellular infiltrate in the mucosa.

It is important to appreciate that antibiotics alter the normal bowel flora and this allows colonisation by Clostridium difficile, the cause of pseudomembranous colitis. This is amongst the commonest iatrogenic infections in a geriatric hospital ward and is best diagnosed by detecting the clostridial toxin in stool, though biopsy gives a characteristic picture.

Intestinal tuberculosis is becoming commoner in the West as the Asian population increase. Typically it results in stricturing in the ileo-caecal valve region making it difficult to distinguish from Crohn’s disease. Granulomas are a feature of both diseases but in tuberculosis they tend to be confluent, caseating and may contain acid-fast mycobacteria.

**“Idiopathic” chronic inflammatory bowel disease**

This term generally covers **Crohn’s disease and ulcerative colitis** which are the common inflammatory bowel diseases at the current time that are of unknown aetiology and play a large part in gastrointestinal practise. They have many features in common with each other, to the extent that some workers feel they may simply be different immunological expression of the same disease, akin to lepromatous and tuberculoid (granulomatous) leprosy. However a distinction is ultimately important as Crohn’s disease can recur at any site in the gut but ulcerative colitis is cured if colectomy is deemed inevitable. Moreover restorative pouch surgery is contra-indicated in Crohn’s disease.

**Crohn’s disease**. This is a transmural disease potentially of the whole gut but commonest in the terminal ileum and ileo-caecal junction - fistulae, fissures, anal disease, arthritis and skin disease are frequent accompaniments. The **Granuloma** is the diagnostic histological finding distinguishing it from U.C. in colonic disease, but it is seen in only approximately 60%. The patchy nature of the disease with skip areas of normal bowel between diseased segments is another characteristic. This too differentiates it from U.C if considering only colonic involvement. Although it is difficult to predict which segments of the bowel will be involved and over what time course, patients are never free from the possibility of a recrudescence somewhere in the GI tract.

**Ulcerative colitis**: This is solely a mucosal disease that is believed to commence in the rectum and spread proximally over a period of years in approximately half the patients and can involve the whole colon. It predominates on the left side and systemic illness is less common. In a small percentage it remains restricted to the rectum.

Both of the above diseases wax and wane in the long term and may be complicated by the development of a carcinoma after many years (>10yrs). In UC detecting dysplastic (premalignant) mucosa on biopsy (as with Barrett’s mucosa in the oesophagus) is thought to be a useful screening test with patients undergoing regular surveillance colonoscopic biopsy. The dysplasia in ulcerative colitis that precedes a cancer is a flat lesion, in contrast to the polypoid dysplasia (see below) in the non-colitic adenoma-carcinoma sequence.

The aetiology of both diseases is unknown though measles virus and atypical mycobacterium have been implicated in Crohn’s disease. It is likely the cause for both will be multifactorial with infection on an appropriate genetic background being the major determinant. Some genetic profiles in patients with Crohn’s disease are now beginning to emerge.

The pathologist plays a major role in the distinction between Crohn’s disease and ulcerative through colonoscopic biopsy characteristics and in the examination of surgical resections. In approximately 10% of cases of chronic inflammatory bowel disease a confident distinction cannot be made and the term **indeterminate colitis** is used.

**Tumours**

In the colon most cancers arise from polyps (adenomas with epithelial dysplasia). The **adenoma-carcinoma sequence** is an accepted pathway for colon cancer and several critical genes have been identified on route to cancer which accumulate over the years culminating in malignant transformation. As stated above the polyps-cancer sequence is different from that seen in ulcerative colitis where polyps are uncommon and the pre-malignant dysplastic changes occur in flat mucosa.

**Adenomas** (tubular or villous): An adenoma by definition has dysplastic epithelium as the basis. Dysplasia being the common term across the body for recognisable premalignant epithelial changes. If there is no invasive element or the stalk of the polyp is not involved polypectomy is adequate with regular follow-up. Invasion is defined by epithelial nests crossing the line of the muscularis mucosae.

There are also many non-adenomatous (non-dysplastic) types of colonic polyp (metaplastic, inflammatory, juvenile etc) and hereditary forms of multiple polyposis are recognised for each type, familial adenomatous polyposis being the commonest of the group**.** In the latter patients a carcinoma is an inevitable complication usually in the 3rd-4th decade.

**Carcinoma:** Colon and rectal adenocarcinomas are amongst the commonest cancers in the West. Prognosis depends on the depth of invasion and differentiation of the tumour. The Dukes classification is the classification most in use in Britain but several modifications exist to try to improve the accuracy of prognosis. Left sided tumours present earlier than those on the right, the latter masked by the capacious right colon. Change of bowel habit, bleeding, diarrhoea, passage of mucus and weight loss are common symptoms. Relatively recently hereditary non-polyposis forms of colon cancer have been appreciated and these tend to be right sided lesions with a better prognosis.

The approximate five year survival figure for Dukes A lesions (confined to bowel wall) is above 95%, for Dukes B lesions (through the wall but no lymph nodes involved) is around 80%, for Dukes C1 lesions (nodes involved but not the apical node) it is about 40% and for C2 lesions (apical node involvement) it is down to around 25%.

**Mechanical**

**Diverticular disease**: This is characterised by numerous outpouchings of the mucosa through the wall. The muscle coat is thickened. The sigmoid colon is the predominant site but they may be seen around the colon in a small number of cases. It is common in the West with >60% of folk >80yrs affected. It is rare in Asia and Africa. There is an inverse relation between dietary fibre and prevalence of diverticular disease. Recurrent bouts of abdominal pain, strictures, inflammation of diverticula, perforation and bleeding are common presentations Diet or surgery are the mainstays of therapy.

**PLEASE NOTE**: Appendicitis and Haemorrhoids are the commonest lower gut conditions seen in clinical medicine - they have not been considered here.

**Recommended Book: Pathologic Basis of Disease 7th ed. Robbins and Cotran or similar**

**HAEMATOLOGY OF SYSTEMIC DISEASE**

**Dr Donald Macdonald**

The Anterior Pituitary

Prof Karim Meeran

**Learning Objectives**

1. To remember the six anterior pituitary hormones and name the hypothalamic factors responsible for their control

2. To know that visual field defects are an important complication of pituitary tumours

3. To understand that stress tests are essential to test pituitary function and that static tests will not give you information about how the pituitary will perform under stress

4. To know how to carry out and interpret pituitary function tests.

5. To know the urgent treatment of pituitary failure.

The normal anterior pituitary secretes six hormones. List them in the right hand column of the table below. Then list the hypothalamic factors that control them in the left hand column of the table.

|  |  |
| --- | --- |
| ***Hypothalamic factor*** | ***Pituitary hormone*** |
|  |  |
|  |  |
|  |  |
|  |  |
|  |  |
|  |  |

***Testing for pituitary failure***

A 30-year-old woman complains of galactorrhoea and amenorrhoea. A CT scan of her pituitary shows a large (2cm) macroadenoma.

What complication of a large pituitary tumour should you examine for?

Her prolactin level comes back at 30,000 (normal <600). She has not had sexual intercourse.

What is the likely diagnosis?

A. Cushing’s disease

B. Acromegaly

C. Prolactinoma

D. Non-functioning pituitary adenoma

E. Conn’s syndrome

What investigations should be performed?

***Stress tests***

CPFT = Combined Pituitary Function Test

Administer insulin to cause hypoglycaemia. This will stimulate ACTH and hence cortisol release and GH release.

Administer LHRH to stimulate LH and FSH release.

Administer TRH to stimulate TSH and prolactin release.

***Method:***

Ensure patient safe for hypoglycaemia. ECG. History of ischaemic heart disease or epilepsy must be excluded.

Fast patient overnight

Ensure good IV access

Weigh patient. Calculate dose of insulin required (0.15 units / kg).   
For an average 70 kg woman, this will be 10.5 units.

Mix 200 mcg TRH with 100 mcg LHRH and then add the insulin in a 5 ml syringe.

Administer the mixture IV.   
Patient may vomit or have a warm flush.  
These symptoms disappear within 2 minutes.

Measure blood glucose regularly and ensure adequate hypoglycaemia.

Take blood every 30 minutes for the following and fill in the table below, which has the results from a normal individual.

This is a typical normal response:

Basal thyroxine 19 pmol/l (11-24)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| ***Time*** | ***Glucose*** | ***GH*** | ***Cortisol*** | ***LH*** | ***FSH*** | ***TSH*** | ***Prolactin*** |
| 0 | 4.7 | 0.5 | 340 | 2.3 | 2.5 | 1.2 | 300 |
| 30 | 1.8 | 1.6 | 450 | 12.6 | 10.9 | 11.7 | 800 |
| 60 | 2.3 | 12 | 630 | 8.7 | 7.6 | 8.9 | 1200 |
| 90 | 4.7 | 23 | 540 |  |  |  |  |
| 120 | 5.2 | 20 | 400 |  |  |  |  |
|  |  |  |  |  |  |  |  |

This is the response in the woman in question:

Basal thyroxine 5.5 pmol/l (11-24)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| ***Time*** | ***Glucose*** | ***GH*** | ***Cortisol*** | ***LH*** | ***FSH*** | ***TSH*** | ***Prolactin*** |
| 0 | 4.7 | 0.5 | 160 | 0.5 | 0.5 | 0.7 | 30000 |
| 30 | 1.8 | 0.5 | 170 | 0.7 | 0.8 | 0.8 | 30000 |
| 60 | 2.3 | 0.5 | 180 | 0.9 | 1.3 | 0.9 | 30000 |
| 90 | 4.7 | 0.5 | 160 |  |  |  |  |
| 120 | 5.2 | 0.5 | 150 |  |  |  |  |
|  |  |  |  |  |  |  |  |

Describe the abnormalities shown here.

What urgent treatment does this patient need?

What other medication will she need?

The next patient is a 27-year-old woman who also has a large (2cm) pituitary adenoma and a similar visual field defect. Investigations are given below.

Basal thyroxine 6.7 pmol/l (11-24)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| ***Time*** | ***Glucose*** | ***GH*** | ***Cortisol*** | ***LH*** | ***FSH*** | ***TSH*** | ***Prolactin*** |
| 0 | 4.7 | 0.5 | 160 | 0.5 | 0.5 | 0.7 | 2944 |
| 30 | 1.8 | 0.5 | 170 | 0.7 | 0.8 | 0.8 | 2865 |
| 60 | 2.3 | 0.5 | 180 | 0.9 | 1.3 | 0.9 | 2766 |
| 90 | 4.7 | 0.5 | 160 |  |  |  |  |
| 120 | 5.2 | 0.5 | 150 |  |  |  |  |
|  |  |  |  |  |  |  |  |

Describe the abnormalities.

What is the likely diagnosis?

A. Cushing’s disease

B. Acromegaly

C. Prolactinoma

D. Non-functioning pituitary adenoma

E. Conn’s syndrome

What urgent treatment does this patient need?

What other medication will she need?

The next patient is a 28-year-old woman who also has a large (2cm) pituitary adenoma and a similar visual field defect. Investigations are given below. What is the likely diagnosis?

Basal thyroxine 6.7 pmol/l (11-24)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| ***Time*** | ***Glucose*** | ***GH*** | ***Cortisol*** | ***LH*** | ***FSH*** | ***TSH*** | ***Prolactin*** |
| 0 | 4.7 | 30.5 | 160 | 0.5 | 0.5 | 0.7 | 1988 |
| 30 | 1.8 | 40.7 | 170 | 0.7 | 0.8 | 0.8 | 1744 |
| 60 | 2.3 | 60.2 | 180 | 0.9 | 1.3 | 0.9 | 2311 |
| 90 | 4.7 | 50.5 | 160 |  |  |  |  |
| 120 | 5.2 | 44.5 | 150 |  |  |  |  |
|  |  |  |  |  |  |  |  |

Describe the abnormalities.

What is the likely diagnosis?

A. Cushing’s disease

B. Acromegaly

C. Prolactinoma

D. Non-functioning pituitary adenoma

E. Conn’s syndrome

What dynamic test will confirm the diagnosis?

A. Low dose dexamethasone suppression test

B. High dose dexamethasone suppression test

C. Synacthen test

D. Glucose tolerance test

E. TRH stimulation test

Name one other test that will confirm the diagnosis.

What urgent treatment does this patient need?

What other treatment will she need?

For the Hammersmith bible of endocrine protocols, which includes combined pituitary function tests, see the endocrine specialist registrars handbook on <http://meeran.info>

(then click on “Endocrine Bible”).

Immunology of HIV infection

Dr Nesrina Imami

**Learning objectives**

* Understand the mechanisms of immune deficiency associated with HIV-1 infection
* Know the viral and host factors that affect the outcome of HIV-1 infection
* Understand the life cycle of HIV-1 and targets for current treatment
* Understand the use of laboratory tests in the diagnosis and monitoring of patients with HIV-1 infection
* Appreciate the role of antiretroviral drugs and success of HAART

#### The human toll of AIDS

1. >35 M people living with HIV/AIDS [www.unaids.org](http://www.unaids.org)
2. >25 M people have died of AIDS.
3. 7,200 persons infected per day - >10% of these are children.
4. Most infected people will die within 20 years, as most of them do not have access to antiretroviral drugs.

**HIV-1 is a retrovirus**

1. Genes composed of RNA molecules.
2. Replicates inside cells using an enzyme called Reverse Transcriptase (RT) to convert RNA into DNA which can be integrated into host cell’s genes.
3. Primarily infects immune system cells causing immunodeficiency and AIDS.

**HIV-1 targets the immune system**

1. Infects CD4+ cells of the immune system. Uses the cells to replicate and move cell to cell. In doing so changes the function of those cells.
2. Progressive decline in CD4+ helper/inducer T cell function & numbers: HIV-specific, Recall, Allo, and Mitogen (and even IL-2). Leading to severe immune deficiency, opportunistic infections and neoplasms.
3. One reason that the immune system fails to control HIV-1 infection is that the CD4+ T helper cells are the target of the virus. CD4+ T cells provide help for all other cells involved in a productive immune response.

**Protection** Effective immunity requires antibodies (B cells) to prevent infection, and neutralize virus and sufficient CD8+ T lymphocytes (CTL) to eliminate (kill) latently infected cells (both dependent on signals from CD4+ T cells). [www.iavi.org](http://www.iavi.org)

Receptor and Co-Receptor •CD4 molecule/Ag is the Receptor for HIV-1. •Most infecting strains of HIV-1 use co-receptor molecules (CCR5 and CXCR4) in addition to CD4 to enter target cells. •More appears to be necessary for entry: A chemokine receptor on the surface of MO and activated T helper CD4+ cells was targeted by researchers as co-receptor for HIV because of its known binding to three chemokines that block infection.

**Natural Immunity** •Mobilised within hours of infection and involves: Inflammation; Non-specific activation of macrophages; Non-specific activation of NK cells and complement; Release of cytokines and chemokines; Stimulation of pDC via toll-like receptors.

**Acquired immunity – antibody B cells** •Specific humoral responses where neutralising antibodies are produced; •Anti-gp120 and anti-gp41 (Nt) antibodies are thought to be important in protective immunity; •Non-neutralising anti-p24 gag IgG also produced.

**Acquired immunity - CD4+ T cells** •White blood cells that orchestrate the immune response, signalling other cells in the immune system to perform their special functions; •Recognise processed antigen - especially Gag p24 (peptides) - in the context of class II HLA molecules; •Also known as T helper (Th) cells, these cells are infected, killed or disabled during HIV infection; •Selective loss of CD4+ T cells.

**Acquired immunity - CD8+ T cells**

•White blood cells that kill cells infected with HIV or other viruses, or transformed by cancer (CTL). Also able to suppress viral replication; •Secrete soluble molecules (cytokines and chemokines such as MIP-1, MIP-1, and RANTES) which are able to prevent infection by blocking entry of virus into CD4+ T cells; •Recognise processed antigen - (peptides) - in the context of class I HLA molecules.

**Key points where HIV-1 can interfere with an immune response**

•Activated infected CD4+ helper T cells die and are lost; •Infected CD4+ T cells are also disabled (ANERGISED) by the virus; MO/DCs are not activated by the CD4+ T cells and can not prime naïve CD8+ CTL; CD8+ T cell and B cell responses are diminished without help; CD4+ T cell memory is lost; Infected MO/DC are killed by virus or CTL; Defect in antigen presentation; Failure to activate memory CTL.

**HIV-1 infection interferes at several key points of CD8+ T cell activation**



☸

**CD4+ T helper cell**

**CD4+ T helper cell**

**Naive**

**Memory**

**Effector CD8+ T cell**

**HIV**

**HIV**

**Antigen presenting cell**

**(MO/DC)**

**HIV**

**HIV**

**Lysis of infected cells**

1. **Perforin**
2. **Granzymes**
3. **Fas/FasL**

**Cytokines**

1. **IFN**
2. **TNF**

**Chemokines & CAF**

1. **MIP-1**
2. **MIP-1**
3. **RANTES**

**Variation and Mutation**

•Replication of the retroviral genome depends on 2 steps - Reverse Transcriptase lacks the proof reading mechanisms associated with cellular DNA polymerases and therefore genomes of retroviruses are copied into DNA with low fidelity. Transcription of DNA into RNA copies is also of low fidelity; •Therefore HIV can accumulate many mutations and numerous variants or quasispecies; •Escape from neutralising antibodies; •Escape from HIV-1-specific T cells; •Resistance and escape from antiretroviral drugs.

**Life cycle of HIV** •**Steps in Viral Replication** 1. Attachment/Entry; 2. Reverse Transcription and DNA Synthesis; 3. Integration; 4. Viral Transcription; 5. Viral Protein Synthesis; 6. Assembly of Virus & Release of Virus; 7. Maturation

**Therapies for HIV-1 infection/disease target the viral life-cycle**

Latest advances in the treatment of HIV: [www.bhiva.org](http://www.bhiva.org) BHIVA Guidelines;

[www.iasusa.org](http://www.iasusa.org) IAS-USA Guidelines; <http://aidsinfo.nih.gov/> US-DHHS Guidelines.

**Clinical course of disease**

•Median time from infection with HIV to development of AIDS is 8 - 10 years.

•Viral burden (set point) predicts disease progression.

•Rapid progressors (10%) in 2 - 3 years.

•Long-term non-progressors (LTNP; <5%) stable CD4 T-cell counts and no symptoms after 10 years.

•Exposed seronegative (ESN) individuals.

•Effect of HAART; dramatically changed the course of disease.

**Possible mechanisms of long-term nonprogression with HIV infection**

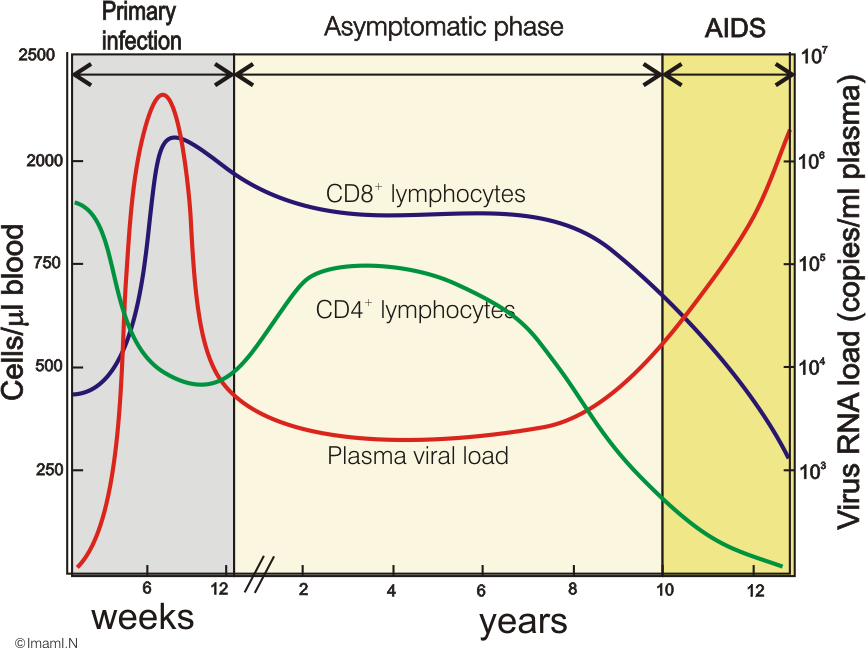
**Host genetic factors**

•Slow progressor HLA profile; •Heterozygosity for 32-bp deletion in chemokine receptor CCR5; •Mannose binding lectin alleles; •Tumor necrosis factor c2 microsatellite alleles; •Host immune response factors; •Effective CTL responses; •Secretion of CD8 antiviral factor; •Secretion of chemokines that block HIV entry co-receptors CCR5 (e.g., MIP-1, MIP-1, and RANTES) and CXCR4 (e.g., SDF-1); •Secretion of IL-16; •Effective humoral immune response; •Maintenance of functional lymphoid tissue architecture

**Virologic factors**

•Infection with attenuated strains of HIV; •Mutations or deletions within the HIV genes

**Patterns of HIV Disease Progression**



**HIV**

**Infection**

Long-term Non-progressors

Rapid Progressors

Typical Progressors

**<3 years**

**8-10 years**

**>10-15 yr**

85 %

10 %

<5 %

* Acute HIV-1 infection is associated with rapid and perhaps irreversible destruction of the CD4+ T-cell subset that resides in gut-associated lymphoid tissue
* Throughout the course of HIV-1 disease there is ongoing viral replication and progressive HIV-1-mediated loss of CD4+ T cells.
* Decline in VL after acute infection linked w. increased anti-HIV CD8 CTLs.

**Greater understanding of immunology** •HIV causes CD4 T-cell count to drop**;** •Treatment makes it go up**;** •Low CD4 T-cell count relates to risk of disease**;** •Raising it protects from disease**;** •HIV causes AIDS (CD4 T-cell count <200 cells/l)•Drug therapy works but immune therapy may be the long term answer (prevention and therapy).

**Detection of HIV-1**

**Human immunodeficiency virus (HIV)** is found in all cases of **AIDS**. •In the infected patient, it can be detected by the presence of anti-HIV antibodies or by the presence of the virus itself (viral load) using polymerase chain reaction (PCR). The latter is very sensitive and can show HIV in situations in which it is not detectable immunologically; •The HIV antibody ELISA is a screening test and the HIV antibody Western blot is a confirmatory test; •The initial baseline plasma viral load (that is when the patient is first monitored for virus number) is a good predictor of the time it will take for disease to appear.

CDC Recommendations HIV testing: [www.cdc.gov/hiv/topics/testing/healthcare/](http://www.cdc.gov/hiv/topics/testing/healthcare/)

HIV antibody tests: In UK we use 3 EIA tests; 3 different formats; Different manufacturers (different antigens). Test from primary clot and separated serum (Ask for repeat tests from all new positives to confirm result and identification).

**Assessment of CD4 T cell counts**

•The course of HIV-1 disease in the patient is followed by CD4+ T cell levels

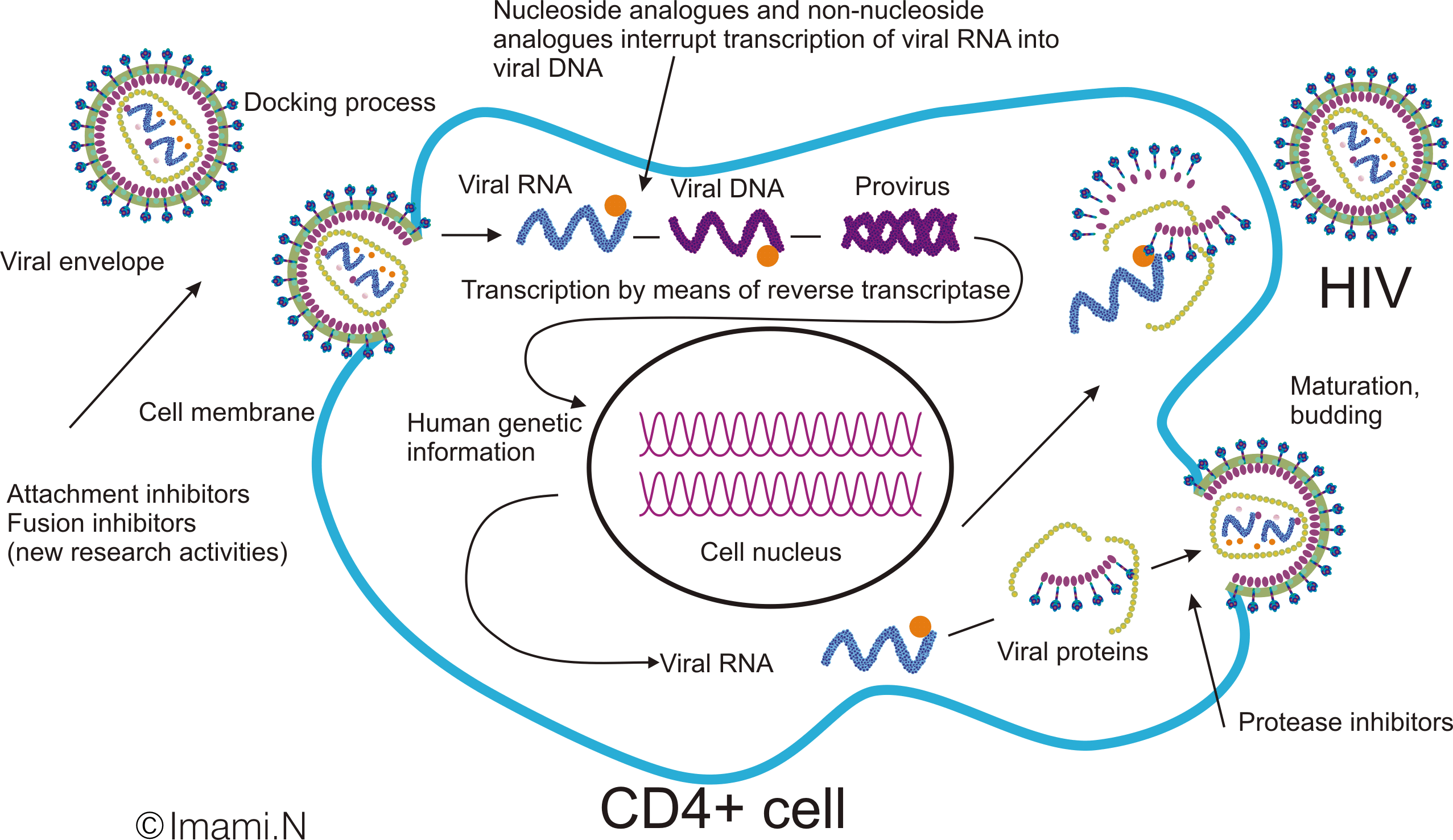
•The onset of AIDS correlates with the diminution of the number of CD4+ T cells but the major loss of T cells occurs late in infection

•Carried out by Flow cytometry: Whole blood analysis using cell surface markers

**Highly active antiretroviral therapy (HAART): Which HAART regimen?**

**When to initiate treatment?** [http://www.bhiva.org](http://www.bhiva.org/) BHIVA Guidelines

Drugs Used in the Treatment of HIV: <http://www.fda.gov/oashi/aids/virals.html>



AI

FI

RTI

INI

PI

HAART = 2NRTIs + PI (or NNRTI)

**Limitations & Complications of HAART regimens** •Effective HAART does not eradicate latent HIV-1 in the host**;** •Fails to restore HIV-specific T-cell responses**;** •Is dogged by the threat of drug resistance**;** •Significant Toxicities**;** •High pill burden**;** •Adherence problems; •Quality of life issues; •Cost (<10%).

= Rationale for immune-based therapies.

**References:**

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3. Walker BD. ‘HIV Controllers’. Immunity. 2007;27:406-16.
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Immune Modulation

Prof Margaret Callan

***Objectives***

Understand how the immune response may be manipulated in clinical practice

***Ways of Manipulating the immune response***

*Boosting the immune response*

Vaccination

Replacement of missing components

Augment existing responses with cytokines

*Suppressing the immune response*

Cortiosteroids

Anti-proliferative agents

Plasmapharesis

Inhibitors of cell signalling

Agents directed at cell surface molecules

Agents directed at cytokines

*Deviating the immune system*

Allergen desensitisation

***Boosting the immune response***

**Vaccination (see SPECIFIC lecture)**

**Replacement of missing components**

*Bone marrow transplantation*

*Antibody replacement: Human normal immunoglobulin*

Prepared from pools of >1000 donors

Contains preformed IgG antibody to a full range of unspecified organisms

Donors screened for Hep B, Hep C and HIV by antibody and PCR

Further treated to kill any live virus

*Antibody replacement: Specific immunoglobulin*

Passive immunisation

Hepatitis B, Tetanus, Rabies,Varicella Zoster

**Augmentation of existing responses**

*Recombinant cytokines*

Boost immune response to specific pathogens

Interferon alpha: Licensed for Hepatitis C, Hepatitis B, Kaposi’s sarcoma, Hairy cell leukaemia, chronic myelogenous leukaemia, malignant myeloma

Interferon beta: Effective in relapsing forms of multiple sclerosis (Mechanism unknown)

Interferon gamma: Licensed for chronic granulomatous disease: intrinsic defect in phagocyte killing

***Suppressing the immune response***

**CORTICOSTEROIDS**

**Phagocytes**

Decreased traffic of phagocytes to inflamed tissue and decreased release of proteolytic enzymes

**Lymphocytes**

Sequestration of lymphocytes in lymphoid tissue

Induction of apoptosis of lymphocytes at high dose

Inhibition of cytokine gene expression

Decreased antibody production

**ANTI-PROLIFERATIVE AGENTS**

**Cyclophosphamide**

Alkylates DNA, thereby preventing DNA replication

Affect B cells > T cells, but at high doses affects all cells with high turnover

Indicated for multisystem connective tissue disease with severe end-organ involvement eg Wegener’s granulomatosus, SLE

**Azathioprine**

Blocks de novo purine synthesis – prevents replication of DNA

Preferentially inhibits T cell activation & proliferation

Indicated in transplantation, autoimmune disease, inflammatory diseases, eg Crohn’s disease, ulcerative colitis

1:300 individuals are extremely susceptible to bone marrow suppression because of specific polymorphisms in Thiopurine methyltransferase (TPMT) gene. Check TPMT activity or gene variants before treatment if possible; always check full blood count after starting therapy

**Mycophenolate Mofetil**

Blocks nucleotide synthesis – prevents replication of DNA

Affect T cells > B cell

Indicated in transplantation, autoimmune disease especially where severe end-organ involvement occurs eg Wegener’s granulomatosus, SLE

**PLASMAPHERESIS**

Aim: removal of pathogenic antibody via cell separator; approx 50% plasma removed each time

Major problem: rebound antibody production limits efficacy, therefore usually given with anti-proliferative agent

Indication: severe antibody-mediated disease eg Goodpasture’s syndrome, severe acute myasthenia gravis

**INHIBITORS OF CELL SIGNALLING**

Ciclosporin and Tacrolimus

Block T cell signalling pathways

Both effective as immunosuppressants although side-effect profiles differ

Both are associated with significant nephrotoxicity

**AGENTS DIRECTED AT CELL SURFACE ANTIGENS**

**Anti-thymocyte globulin**

Antibodies directed at cell-surface molecules on T cells

Depletes and modulates function of T cellls

Indication: allograft rejection

**Anti-IL2 receptor antibody (CD25)**

Basiliximab

Expressed on surface of all activated cells

Used for rejection prophylaxis in transplantation

Well tolerated

**CTLA4-IG fusion protein**

Abatacept

Binds to ligands for CTLA4 and CD28 (CD80 and CD86)

Thereby prevents activation of T cells via CD28

Shown to be effective in rheumatoid arthritis

**TGN 1412**

Activating antibody directed against CD28

Induced cytokine storm in phase I clinical trials

**Anti-CD20 antibody**

Rituximab

Expressed on surface of all mature B cells but not plasma cells

Depleting antibody previously used to treat B cell lymphoma

Shown to be effective in rheumatoid arthritis and SLE

**Anti-4 integrin antibody**

Natalizumab

Blocks interaction between 41 and 47 ligands with VCAM1 and MadCam1

Prevents interaction between leukocytes and other cells

Thereby inhibits cell trafficking

Effective in multiple sclerosis and Crohn’s

Risk of PML (JC virus) in some patients – therefore only used in highly active relapsing and remitting multiple sclerosis

**Anti-CD11a (alpha subunit of LFA-1) antibody**

Efalizumab

Blocks interaction between LFA-1 and ICAM 1

Prevents interaction between leukocytes and other cells

Thereby inhibits cell trafficking

Effective in psoriasis (but not psoriatic arthritis)

Withdrawn due to development of PML (JC virus) in some patients

**Anti-IL6 receptor antibody**

Tocilizumab

Binds to membrane bound and soluble IL6R

Inhibits IL-6 driven activation of neutrophils, macrophages, T and B cells

Effective in rheumatoid arthritis and Castleman’s disease

**AGENTS DIRECTED AGAINST CYTOKINES**

**Anti-TNF alpha antibodies**

Infliximab, Adalimumab, Certolizumab, Golimumab

**Decoy soluble TNF receptors**

Etanercept

>1,000,000 people have now been treated with anti-TNF agents

Indications: Rheumatoid Arthritis, Crohn’s disease, Psoriatic arthritis, Ankylosing spondylitis

Dramatic improvement in short and long term disease outcome

Adverse events: Infection, particularly tuberculosis

**Anti-IL12 and IL-23 antibody**

Ustekinumab

Effective in psoriasis

**Anti-RANK ligand antibody**

Denosumab

Inhibits RANK ligand binding to RANK on osteoclasts

Thereby inhibits osteoclast differentiation and function

Effective in osteoporosis

***Major complications of long-term immune suppression***

**Infection**

*Risk of infection depends on*

Overall level of immunosuppression

Specific immune pathway targeted

*Protecting immunosuppressed individuals against infection*

Avoidance

High index of suspicion and low threshold for antibiotics

Vaccination

***Deviating the immune RESPONSE***

**Allergen desensitization (Immunotherapy)**

Supervised administration of an allergen

Effective at reducing clinical symptoms in monoallergic disorders, including bee or wasp venom, and grass pollen sensitivity

Risk of severe adverse reaction and death

Very costly

Mechanism of action unknown: ?change in regulation of immune response

Antimicrobial Chemotherapy (i)

Dr. Annette Jepson

**Objectives**

Lecture I

• to know the common drugs used to Rx bacterial infections

• to know of their sites of action (in broad terms)

• to be able to discuss mechanisms of resistance

The most important principle of antimicrobial chemotherapy is that of selective toxicity

Specific targets include the bacterial cell wall, ribosomes and biochemical or synthetic pathways

Inhibitors of cell wall (peptidoglycan) synthesis

e.g. β-lactams and glycopeptides

β-lactams

•Bind to PBPs (Penicillin binding proteins)

•Bactericidal

•Active against rapidly-dividing bacteria

•Ineffective against bacteria that lack peptidoglycan cell walls (e.g. Mycoplasma or Chlamydia)

The following are examples of β-lactams: penicillin, amoxycillin, piperacillin, the cephalosporins, the carbapenems (e.g. imipenem)

Glycopeptides

•Large molecules, unable to penetrate G –ve outer cell wall

•Active against G +ve organisms

•Inhibit cell wall synthesis

•Important for Rx serious MRSA infections

•Vancomycin and Teicoplanin are examples of glycopeptides

•Slowly bactericidal

•Nephrotoxic – hence important to monitor drug levels to prevent accumulation

**Inhibitors of bacterial protein synthesis**

aminoglycosides (e.g. gentamicin – must monitor levels because nephrotoxic and ototoxic); rapid, concentration – dependent bactericidal action. Especially useful in treating Gram –ve sepsis

tetracyclines – broad-spectrum agents with good bioavailability and active against intracellular pathogens; avoid in pregnant women and children

macrolides (e.g. erythromycin) / Lincosamides (clindamycin) / Streptogramins (Synercid) – the MSL group. Note minimal Gram –ve activity.

chloramphenicol (rarely used systemically because risk of aplastic anaemia)

Oxazolidinones (e.g. Linezolid) – highly active against Gram +ve bacteria, including MRSA & VRE. Not active against Gram –ve bacteria.

**Inhibitors of bacterial DNA synthesis**

Quinolones (e.g. ciprofloxacin, levofloxacin, moxifloxacin) – useful broad spectrum drugs with good bioavailability

Nitroimidazoles (e.g. Metronidazole) – rapidly bactericidal against anaerobic bacteria and protozoa

**Inhibitors of RNA synthesis**

Rifamycins (e.g. rifampicin) – bactericidal and particularly active against Mycobacteria. Must NOT use as a single agent on account of the rapid development of resistance

**Cell membrane toxins**

Daptomycin – activity limited to Gram +ve bacteria.

**Inhibitors of folate metabolism**

Sulphonamides and trimethoprim

**Mechanisms of antimicrobial resistance – BEAT**

**B**YPASS of targeted metabolic or synthetic pathway (e.g. MRSA)

**E**NZYME inactivation of the antimicrobial (e.g. beta lactamase enzymes)

**A**CCUMULATION impairment (drug can no longer enter cell, or may be pumped out) e.g., tetracycline resistance

**T**ARGET modification (of the antimicrobial target site) e.g. quinolone resistance

**Resistance may be:**

* intrinsic to the organism (e.g., cells that lack a peptidoglycan cell wall will be resistant to β-lactams)
* acquired by spontaneous mutation (mutants will then have a growth advantage in the presence of that antimicrobial)
* acquired via exchange or acquisition of genetic material, e.g. plasmid, transposon

If the use of broad-spectrum antimicrobial agents is excessive, the growth of increasingly resistant organisms will be encouraged. USE WITH CARE.

Antimicrobial Chemotherapy (ii)

Dr. Annette Jepson

**Objectives**

•To be able to discuss the factors that influence the choice of antimicrobial agent

•To be able to discuss the principal routes of administration

•To assess the need for antimicrobial therapy in the treatment of infection

Mis-use of antimicrobials is common, e.g. use in absence of current infection; inappropriate agent used; ianppropriate duration of therapy; expensive agent used when cheaper alternative available

Furthermore, approx 5% of patients receiving an antimicrobial may experience an adverse event

CHAOS – choice of the correct antimicrobial depends upon host factors; antimicrobial susceptibility of the infecting organism and the site of the infection

Choice of drug:

-Use a narrow spectum agent if possible

-Use bactericidal drugs if possible

-Ideally choice should be based upon a bacteriological diagnosis

-Consider patient characteristics (allergies, age, renal and hepatic function)

-Be guided by local sensitivity patterns

-Consider the cost

Choice of drug should also consider the following factors:

Pharmacokinetics (absorption, distribution and elimination)

Route of administration (i.v. for serious or deep-seated infections)

Dosage – depends upon age and renal/hepatic function. Also MUST monitor drugs (such as aminoglycosides or glycopeptides) that be toxic if accumulation occurs

Host factors

Known drug allergies/impaired renal or hepatic function/age/weight/genetics

Antimicrobial susceptibility

Some patterns may be predictable, some may not. Consider the most likely causative organisms if it is necessary to commence “blind” therapy before culture and sensitivity results are available

Organisms

Ideally cultures should be collected prior to starting antibiotics. If possible to submit a specimen (e.g. CSF or joint fluid) for an urgent Gram stain, this may further guide empirical Rx

Site of infection

The site of infection will define the route of antimicrobial administration; it will also influence the choice of antimicrobial, as CNS infections should be treated with antibiotics that are able to traverse the blood-brain barrier. Note, too, that deep abscess cavities may have a different pH from the surrounding tissues, which will also affect the pharmacokinetics.

Does the patient actually have an infection?

Consider the white cell response and differential count (? raised neutrophils, lymphocytes or eosinophils); other inflammatory markers (e.g. CRP or ESR); other “non-specific” markers.

Other factors to consider include – duration of symptoms; likely focus; previous antimicrobial Rx; underlying risk factors and exclusion of other pro-inflammatory medical disorders (e.g. vasculitides or malignancy)

Which route?

In general, i.v. for severe or deep-seated infection, or patient unable to absorb via the oral route. If admitted acutely unwell, but responds to initial i.v. Rx, it may be appropriate in certain circumstances, to switch to a suitable oral agent when stable (“i.v. to oral switch”)

Duration of Rx

Often needs to be guided by clinical response and inflammatory markers.

Norms for certain diseases, e.g. 3 days for simple UTI in women; 7 days for *N. meningitidis* meningitis; 4-6 weeks for bacterial endocarditis.

Yes, but – WHICH ONE?

- guidance for Rx suspected infections in SMH available on wall charts

anti-infective section in the BNF is also very comprehensive (chapter 5)

\*\* recommended

discuss cases with medical microbiologist/infectious diseases team

contact the antibiotic pharmacist

Remember, there are also situations that may require prophylactic antibiotics, e.g. to reduce risk of surgical infections;

following close contact with a patient who has *N. meningitidis* infection;

to prevent overwhelming sepsis post-splenectomy;

to reduce risk of bacterial endocarditis during dental procedures in “at risk” patients.

**Response to treatment**

Failure to respond to antibiotic treatment may be due to many causes:

* The choice of antibiotic was wrong
* Poor penetration into the site of infection, e.g abscess, osteomyelitis etc
* Adjuvant surgery needed (especially the drainage of pus from an abscess)
* Causative bacteria becoming resistant (RARE)
* Selection of resistant subpopulation of organisms
* Occasionally a non-infectious aetiology
* Poor compliance (oral therapy)

Plasma Cell Myeloma

**Dr Amin Rahemtulla**

***Summary***

1. a malignant disease of the plasma cells in the bone marrow.
2. Proliferation of one clone of plasma cells (monoclonal proliferation) results in production of a monoclonal immunoglobulin (Ig) molecule which can be detected in the serum or in the urine.
3. frequently associated with bone pain, anaemia, and renal failure.
4. accounts for about 1% of all cancers; 3,500 new cases of myeloma each year in UK.
5. incidence increases with age; most patients are over the age of 60 years
6. the cause is unknown in most patients; radiation exposure is known to increase the risk.
7. incurable in most patients, average survival 3-5 years.

***Monoclonal Immunoglobulins***

1. there are normally many different plasma cell clones, producing many different Ig molecules
2. In response to infection or inflammation, there is proliferation of a number of different plasma cell clones leading to an increased number of plasma cells in the marrow (a **reactive** increase) and a **polyclonal** increase in Igs, which appear as a broad band in the gamma region on serum electrophoresis.
3. in myeloma one clone overgrows and produces one particular immunoglobulin molecule - a **monoclonal** immunoglobulin, also termed a monoclonal protein (M-protein) or **paraprotein** - which appears as a dense narrow band on electrophoresis. There is a reduction in normal polyclonal Igs.
4. the abnormal plasma cells may also produce free light chains, which are small enough to pass

into the urine (**Bence-Jones protein** or BJP). Individual patients may have plasma cells which secrete a whole immunoglobulin alone, BJP alone, or both.

***The ESR in Myeloma***

1. a high level of Igs in the blood causes a raised ESR (erythrocyte sedimentation rate)
2. the ESR is therefore raised in most patients with myeloma, but is also raised in conditions where there is a polyclonal increase in Igs (infection and inflammation)
3. in patients with myeloma who produce only free light chains and no serum paraprotein, the ESR is normal

***Clinical Features of Myeloma***

1. **Bone pain**. This affects about 60% of patients. X-rays may show lytic lesions (punched out holes). Generalised osteoporosis (thinning of the bone texture) is also common and there may be compression fractures of the vertebrae, leading to back pain and occasionally to compression of the spinal cord and neurological symptoms
2. **Hypercalcaemia** - resulting from bone destruction. Causes dehydration, drowsiness, confusion, constipation and renal damage.
3. **Renal failure**. About 30% of patients have some degree of renal impairment and about 5% have severe renal failure. This is most commonly due to BJP, which damages the tubules. Other factors which can contribute include hypercalcaemia, infection, dehydration and drugs.
4. **Anaemia.** This is common in myeloma patients.
5. Increased susceptibility to **infection**, both bacterial and viral.
6. Amyloid. About 10% of patients with myeloma develop light chain amyloidosis (AL amyloid), in which the light chains are deposited in the tissues in the form of amyloid, causes enlargement and stiffness of the tissue. (Amyloid=starch-like) The kidney is usually affected, with glomerular damage leading to loss of albumen, low serum albumen level and consequent oedema (nephrotic syndrome)
7. Asymptomatic patients may be picked up by the finding of a raised ESR or abnormal protein electrophoresis.

***Diagnosis***

1. **Symptomatic plasma cell myeloma**
2. a **paraprotein** in serum or urine
3. **Clonal plasma cells** or **plasmacytoma**
4. Related **organ or tissue impairment (CRAB: hypercalcaemia, renal insufficiency, anaemia, bone lesions) or** myeloma related symptoms
5. **Asymptomatic (smouldering) myeloma**
6. **paraprotein** in serum at myeloma levels (>30g/l)

and/or

1. **10% or more clonal plasma cells** in bone marrow
2. **No related organ or tissue impairment or** myeloma related symptoms

***Treatment - General Aspects***

1. Renal failure: correct dehydration, treat hypercalcaemia, dialysis if required
2. Hypercalcaemia: rehydration, intravenous infusion of a bisphosphonate, e.g. pamidronate.
3. Bone disease: local radiotherapy for pain, long-term bisphosphonate.
4. Infection: treat promptly and vigorously, influenza vaccine annually.
5. Anaemia: usually improves when the disease responds. Blood transfusions may be needed

***Specific Treatment***

1. Chemotherapy is the mainstay of treatment in myeloma. Oral or intravenous drugs may be used, often combined with steroids. eg CTD (cyclophosphamide, thalidomide and dexamethasone), melphalan and prednisolone.
2. Bortezomib is used as second-line therapy and lenalidomide is used as third-line therapy.
3. Radiotherapy for local areas of disease, e.g. for pain or cord compression
4. High-dose therapy with stem cell support in younger patients (autologous or allogeneic)

***Outlook with Treatment***

1. The average survival of patients treated with conventional chemotherapy is around 3 years, although some patients may survive much longer
2. A number of factors predict prognosis, of which most important are the serum beta-2 microglobulin level and albumin at presentation..
3. Others include renal function, c-reactive protein, calcium and haemoglobin
4. High dose therapy prolongs survival to around 5 years but is not able to cure the disease.

Immunology Case Studies

#### Dr Keith Gould

***Learning objectives***

At the end of this case study session, you should:

Be able to recognise common immunological conditions

Be familiar with how immunological investigations can inform the diagnosis and management of a wide range of infectious, allergic and inflammatory disorders

Understand how immune based therapies can be used in clinical practice

***Case study 1***

A 40 year old man presents to A&E with sudden onset severe lip swelling

Over the next 20 minutes, he develops:

Itching of his hands and feet

Increasing breathlessness and chest tightness

When you assess him, his vital signs are

PEFR 200l/min

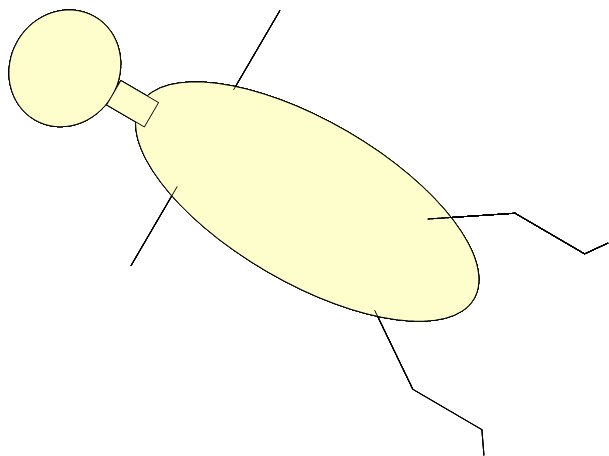
Blood pressure 80/30 mmHg

Oxygen saturations 88% on room air

**Questions**

What is the working diagnosis? ..................... ..................... ..................... ..................... ..................... ..................... ..................... .....................

What are the clinical features of anaphylaxis? ..................... ..................... ..................... ..................... ..................... ..................... ..................... .....................



What immediate treatment would you instigate and why? ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... .......................................... ..................... ..................... ..................... ...........

What questions would you ask once the patient is stabilised?..... ..................................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... .....................

Is the allergy to bananas a red herring? ..................... .......................................... ..................... ..................... .....................

How would you confirm the diagnosis? ..................... ..................... ..................... ..................... ..................... ..................... .....................

What long term management advice would you give? ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... .....................

Is desensitisation an option? ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... .....................

***Case study 2***

A 48 year old man is admitted to ITU with meningococcal septicaemia. He goes on to develop multiorgan failure requiring ventilation and dialysis. His wife tells you he has had two previous episodes of meningococcal meningitis.

What disorders are associated with recurrent meningococcal meningitis? ................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... .....................

What other questions would you ask him or his family?

..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... .....................

What immunological investigations would you request?

.................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... .....................

How would you manage him? .................... ..................... .....................

..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... .....................

***Case study 3***

A 21 year old student is referred with joint pain, a facial rash and swelling of her legs.

On direct questioning she admits to fevers, sweats and profound malaise

There is no past or family history of note

*Physical examination*

Tender joints without evidence of synovitis

Malar rash

Hypertension 165/95

Pedal oedema

|  |  |
| --- | --- |
| ***Investigation*** | ***Result*** |
|  |  |
| FBC | HB 9.5mg/dl: normocytic, normochromic; normal wcc, slightly elevated platelet count |
| U&E | Normal |
| CRP | 1 (Normal range <6mg/l) |
| RF  Anti-CCP Ab  ANA | Negative  Negative  1:1280 |

**Questions**

Which further immunological tests would you request to help make the diagnosis and to assess disease activity? ..................... ..................... ..................... ..................... ..................... ..................... ..................... .....................

Are you reassured by the normal urea or are there other tests that you would request? ..................... ..................... ..................... ..................... ..................... ..................... .....................

What is the predominant effector mechanism of disease in terms of the Gel and Coombs classification? ..................... ..................... ..................... ..................... ..................... ..................... ..................... .....................

Which of the following drugs might be useful in management?

Prednisolone / Pegylated IFN alpha / Azathioprine / Hydroxychloroquine / Allopurinol / Rituximab / IVIG / Mycophenolate / Adalimumab / Cyclophosphamide / Colchicine ..................... ..................... ..................... ..................... ..................... .....................

***Case study 4***

A 35 year old male is admitted with chest pain and breathlessness. Physical examination and CXR are consistent with left lower lobe pneumonia.

*Investigations on admission*

|  |  |
| --- | --- |
| ***Investigation*** | ***Result*** |
| CXR | Left lower lobe pneumonia |
| FBC | WCC 19.5x109/l, neutrophils 92% |
| ESR | 45 (Normal range <10mm/hr) |
| CRP | 60 (Normal range <6mg/l) |
| Urea/electrolytes | Normal |
| Creatinine | Normal |
| LFTs | Normal |
| Sputum culture | S. pneumoniae, sensitive to penicillin |

*Diagnosis*

Community acquired pneumonia. Treated with intravenous penicillin

*Subsequent course*

Symptomatically responds well to treatment. However, 3 days after admission, develops fever (temperature 39C), arthralgia of large joints, vasculitic skin rash, and deteriorating renal function. Over next 24 hours, becomes increasingly unwell and disoriented

*Investigations day 4 after admission*

|  |  |
| --- | --- |
| **Investigation** | **Result** |
| CXR | Left lower lobe pneumonia as previously |
| FBC | WCC 15.5x109/l |
| ESR | 65 (Normal range <10mm/hr) |
| CRP | 120 (Normal range <6mg/l) |
| Urea/electrolytes | Normal |
| Creatinine | 200 umol/l |
| LFTs | Raised ALT, AST |
| Sputum culture | Negative |
| Urine microscopy | ++ blood ++ protein |

**Questions**

What is the likely diagnosis?.........................................................................

What is the mechanism of the disease? ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... .....................

What further investigations would you do to confirm the diagnosis? ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... .....................

Explain the clinical manifestations of disease..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... .....................

How would you manage the patient? ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... .....................

..................... ..................... ..................... .....................

***Case study 5***

Jack’s mother is concerned because he has so many infections.

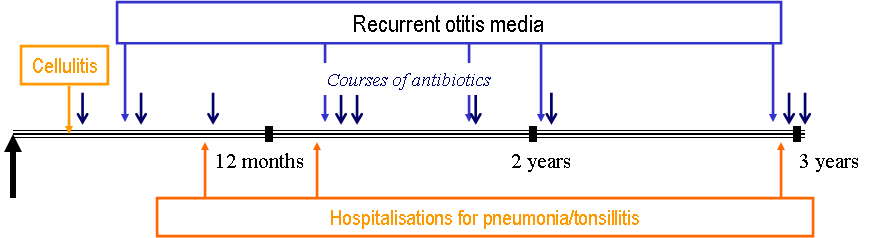
*Clinical history*

3 year old Caucasian male.

Full term, normal delivery; Normal pre and post natal screen

Not breast fed – parental choice; Normal immunisation schedule.

Weight and height dropping from 50th centile to 10th centile



First infection aged 3 months: cellulitis of gluteal region. Responded to antibiotics.

Recurrent ear infections: x5 episodes, all responding to antibiotics. ENT appointment pending - likely to require grommets. Age 15 months hospitalised for severe tonsillitis (quinsy). Tonsils removed

Recurrent chest infections: Age 8 months, 3 years hospitalised for bronchiolitis/ pneumonia, resolved after intravenous antibiotics. Most recently Haemophilus Influenza isolated. .

4th of 5 children, all under 10 years. 2 indoor cats, one indoor dog. Both parents smoke cigarettes. Family are frequent attenders to your GP practice

**Questions**

What are the features that suggest that Jack may have an immunodeficiency? ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... .....................

What other disorders would you consider? ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... .....................

How would you evaluate Jack for possible immunodeficiency? ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... .......................................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... .....................

Jack is subsequently diagnosed as having X-linked agammaglobulinaemia. What treatment would you recommend? ..................... .................... .................... .................... .................... .................... .................... .................... .................... .................... .................... .................... .................... ....................

***Case study 6***

A 64 year old lady is seen in A&E after injuring her right hip when getting out of the bath

*Other problems include:*

Persistent back pain and generalised lethargy for 12 months

Three episodes of pneumococcal pneumonia in last 2 years

Post-menopausal – on HRT

No other meds

*Physical examination*

Swollen, tender R hip with marked limitation of movement

Clinically anaemic

|  |  |
| --- | --- |
| ***Investigation*** | ***Result*** |
| X ray pelvis | Fracture of neck of R femur, through area of decreased bone density |
| FBC | HB 7.5mg/dl: normocytic, normochromic; normal wcc and platelet count |
| ESR | 100 (Normal range <10mm/hr) |
| CRP | <6 (Normal range <6mg/l) |
| LFTs | Normal |

**Questions**

What is your differential diagnosis? ..................... ..................... ..................... ..................... ..................... ..................... ..................... .....................

The patient is admitted to an orthopaedic ward. Further investigations include:

|  |  |
| --- | --- |
| ***Investigation*** | ***Result*** |
| Serum immunoglobulins | IgG 22.3g/l (NR 6.0-13.0g/l) |
|  | IgA 0.7g/l (NR 1.3–3.5g/l) |
|  | IgM 0.4g/l (NR 1.5-3.2g/l) |
| Serum protein electrophoresis | Monoclonal band in gamma region, shown to be IgG kappa |
| Urine electrophoresis | Free kappa light chains detected |
| Bone marrow biopsy | Increased number (30%) of abnormal plasma cells, containing IgG and kappa chains only. |
| Xray of spine and skull | Multiple punched out lytic lesions |

What is the diagnosis? ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... .....................

Why is Mrs Jones susceptible to pneumonia? ..................... ..................... ..................... ..................... ..................... ..................... .....................

Why is she anaemic? ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... .....................

Why is the ESR elevated if the CRP is normal? ..................... ..................... ..................... ..................... ..................... ..................... .....................

***Case study 7***

A 32 year old lady is referred with pain and stiffness affecting the small joints of her hands.

She has previously been well and denies rash, oral ulcers, hair loss, swelling of glands. Three episodes of pneumococcal pneumonia in last 2 years

She has recently given birth to a healthy baby girl. The pregnancy was uncomplicated

There is a family history of gout (older brother) and rheumatoid arthritis (aunt)

*Physical examination*

Swollen, tender MCP, PIP and wrist joints

Nil else abnormal

|  |  |
| --- | --- |
| ***Investigation*** | ***Result*** |
| X ray hands | Normal |
| FBC | HB 9.5mg/dl: normocytic, normochromic; normal wcc, slightly elevated platelet count |
| ESR | 40 (Normal range <10mm/hr) |
| CRP | 18 (Normal range <6mg/l |
| RF  Anti-CCP Ab  ANA | Negative  >300  Negative |

**Questions**

What is the diagnosis? ..................... ..................... ..................... ..................... ..................... ..................... ..................... .....................

Is the history of recent childbirth relevant? ..................... ..................... ..................... ..................... ..................... ..................... ..................... .....................

What are the RF and anti-CCP Ab tests and what are their approximate specificity and sensitivity for diagnosis of this condition? ..................... ..................... ..................... ..................... ..................... ..................... .....................

Give examples of genetic polymorphisms which predispose to this condition – what do these suggest about disease pathogenesis?. ..................... ..................... ..................... ..................... ..................... ..................... .....................

Which drugs would you want to prescribe for this patient in the first instance? ..................... ..................... ..................... ..................... ..................... ..................... ..................... ..................... .....................

If her disease remains active despite 6 months’ treatment which drugs would you consider using? .Are there any tests that you would do prior to prescribing these agents?.................... ..................... ..................... ..................... ..................... ..................... .....................

Liver and Biliary Disease Pathology

Dr Rob Goldin

**LEARNING OBJECTIVES**

* To be able to draw and label the normal liver lobule
* To list the cells found in the liver and their functions
* To define cirrhosis
* To be able to classify cirrhosis according to both nodule size and aetiology
* To list the causes of both acute and chronic hepatitis
* To describe the terms “spotty necrosis” and “interface hepatitis/piecemeal necrosis”
* To define the terms grade and stage as applied to chronic hepatitis
* To describe the 3 patterns of alcohol-induced liver disease, their pathogenesis and their prognostic significance.
* To name the 2 commonest causes of chronic biliary tract disease and their clinical associations
* To distinguish between the causes of haemochromatosis and haemosiderosis and their pathological consequences.
* For Wilson’s disease and alpha-1 antitrypsin, describe their pathogenesis and describe their pathological consequences
* To recognise the wide range of liver diseases caused by drugs
* To list the causes of granulomas in the liver
* To classify tumours of the liver according to their cell of origin
* To list the risk factors for developing liver cell cancer and cholangiocarcinoma
* To know the commonest primary sites of tumours metastasising to the liver

**LIVER PATHOLOGY**

**NORMAL STRUCTURE**

The liver lobuleis centred around a central vein

* the periportal hepatocytes receive blood rich in nutrients and oxygen,
* the perivenular hepatocytes are more metabolically active

**CIRRHOSIS**

May be reversible if underlying cause is treated

**Defining features:**

1) Whole liver involved,

2) Fibrosis,

3) nodules of regenerating hepatocytes,

**4) distortion of liver vascular architecture** (with intra- and extra-hepatic shunting of blood)

**classifications:**

a) according to nodule size:

(1) micronodular (< 3 mm) - most often alcohol,

(2) macronodular (> 3 mm) - most often viral and

(3) mixed

b) **according to aetiology** (approximately 15% are idiopathic)

*1) alcohol,*

*2) viral hepatitis,*

3) primary biliary cirrhosis,

4) autoimmune hepatitis,

5) haemochromatosis,

6) Wilson's disease,

7) other metabolic disorder, e.g. alpha-one antitrypsin deficiency,

8) drugs

**HEPATITIS**

**causes of acute hepatitis:**

1.viruses

2. drugs

**histology of acute hepatitis:** diffuse loular liver cell injury ("spotty" necrosis) and regeneration, reactive changes in Kupffer cells, portal inflammatory reaction

**causes of chronic hepatitis:**

1. viral hepatitis

2. drugs

3. auto-immune

**histology of chronic hepatitis:**

severity of inflammation = **grade**

(portal inflammation + interface hepatitis (piecemeal necrosis) +lobular inflammation)

severity of fibrosis = **stage**

**ALCOHOLIC LIVER DISEASE**

3 patterns which may co-exist:

**1) fatty liver** the liver is large and pale, there is large droplet fatty change centred around the central vein, caused by metabolic changes as a result of alcreversible

**2) alcoholic hepatitis** hepatocyte ballooning, neutrophilic infiltration, **Mallory** hyaline, pericellular fibrosis, may be irreversible

**3) cirrhosis**

**PRIMARY BILIARY CIRRHOSIS**

Inflammatory damage to bile ducts (may be granulomatous) leading to bile duct loss

antimitochondrial antibodies

**Primary sclerosing cholangitis**

periducatal bile duct fibrosis leading to bile duct loss, associated with UC

ERCP

**GENETIC HAEMOCHROMATOSIS** (bronzed diabetes)

organ damage secondary to parenchymal iron overload: liver, pancreas, heart, joints, skin etc., autosommal recessive, excessive iron absorption from the gut

**haemosiderosis** is characterised by the accumulation of iron in macrophages following multiple blood transfussions

**WILSON'S DISEASE** (hepato-lenticular degeneration)

accumulation of copper in liver, brain etc., autosommal recessive, failure of copper excretion

**AUTOIMMUNE HEPATITIS**

(lupoid hepatitis) prominent interface hepatitis with plasma cells

anti-nuclear antibodies

**ALPHA-ONE ANTITRYPSIN DEFICIENCY**

neonatal hepatitis, chronic hepatitis, genetic, intracytoplasmic inclusions due to accumulation of abnormal protein within hepatocytes

**DRUG RELATED INJURY**

“any kind of liver disease can be caused by a drug”

**HEPATIC GRANULOMAS**

1. TB
2. Sarcoid
3. PBC
4. Drugs etc.

**TUMOURS**

Classified according to the presumed cell of origin: hepatocytes, bile duct cells, endothelial cells etc.

**1. Benign**

1) liver cell adenoma,

2) bile duct adenoma,

3) haemangioma

**2. Malignant** (secondary tumours more common than primary), it is the most common site of metastases from the GIT

1) **hepatocellular carcinoma (not** hepatoma)

*risk factors:* cirrhosis, viral hepatitis, aflatoxin

*macroscopic*: unifocal / multifocal / diffuse, marked propensity for venous invasion

*microscopic:* resembles normal liver in its structure, capable of producing bile

2) **hepatoblastoma** primitive cells, may contain soft tissue elements

3) **cholangiocarcinoma**

*risk factors:* PSC , worms

adenocarcinoma

4) **haemangiosarcoma** malignant vascular tumour

Viral infections in pregnancy

#### Dr Lila Paraskevopoulou and Dr Hugo Donaldson

Gynaecological Pathology

**Dr Mary Thompson**

**Aims**

* Understand the link between infertility & pelvic inflammatory disease
* Know the pathology of cervical carcinoma & precursors (CIN)
* Know the pathology of vulval carcinoma & precursors (VIN)
* Define endometriosis and adenomyosis
* Define leiomyoma (fibroid)
* Know the major types of Endometrial adenocarcinorna and the outcome in this disease by grade and stage
* Know the major ovarian tumours and describe the prognosis of the different types

**Pelvic inflammatory disease (Salpingitis)**

1. Importance is relationship to infertility
2. Damage to fallopian tubes is the mechanism
3. Usually infective, acute and/or chronic
4. Usual organisms: Chlamydia trachomatis – increasing ++

Neisseria gonorrhoeae

1. In some parts of the world**: Tuberculosis Schistosomiasis**
2. **Sequence of events:**
3. Usually direct ascent from the vagina -> inflammation of epithelium +/- wall ->

resolution or scarring, depending on severity and treatment

1. **Scarring sequelae** Plical fusion, adhesions to ovary, tubo-ovarian abscess, peritonitis,

hydrosalpinx ?, infertility, ectopic pregnancy

**Endometriosis**

1. Presence of endometrial glands and stroma outside the uterus
2. Common – 10% of premenopausal women
3. **Origin** is disputed: 1 Metaplasia of pelvic peritoneum

2 Implantation of endometrium, retrograde menstruation

3 Induction of metaplasia by factors released from shed endometrium

**Sequelae**

Ectopic endometrial tissue is functional and bleeds at time of menstruation -> pain, scarring and infertility

Can -> hyperplasia, atypical hyperplasia, malignancy (usually endometrioid carcinoma)

**Adenomyosis**

1. Ectopic endometrial tissue deep within the myometrium
2. Cause of dysmenorrhoea

**CIN and Cervical Carcinoma**

Worldwide - second commonest female cancer

Important malignancy to know about:

1. Role of viruses in aetiology of cancer

2. Premalignant phase – CIN (Cervical intraepithelial neoplasia)

3. Role of screening

4. Intervention possible at preinvasive stage

5. Possibility of prevention by vaccination

**Aetiology**

1. HPV – >50 types
2. At least 9 infect the genital tract
3. Only 2 (types 16 and 18) cause CIN and cervical cancer
4. Vast majority of cervical carcinomas show DNA integration of HPV into DNA
5. Smoking ?co-factor
6. Immunosuppression
7. Outer cervix covered by squamous epithelium
8. Canal lined by glandular epithelium
9. **Squamocolumnar junction** is where they meet
10. This small area of cervix susceptible to malignant change - transformation zone
11. Young age at first intercourse increases risk because of the retraction of SCJ up the canal in late teens.

**Cervical intraepithelial neoplasia**

1. This is the histological term for **dysplasia** in this site
2. Epithelial cells have undergone some **phenotypic** and **genetic changes** which are **premalignant** and **preinvasive**
3. Basal membrane immediately deep to the surface epithelium is intact
4. Squamous epithelium is involved more often than glandular epithelium in the cervix

**1. CIN (Ectocervical squamous dysplasia)**

1. **Cytology smear** detects abnormal cells
2. Graded mild, moderate and severe **dysplasia on cytology**
3. A **colposcopic biopsy** is done to confirm cytological abnormalities
4. Graded **CIN 1, 2 or 3 on biopsy**
5. Grade 1 can regress
6. The higher the grade the more likely it is to become invasive
7. A **cone** biopsy can excise the lesion

**2. CGIN (Endocervical glandular dysplasia)**

1. Less common than CIN
2. More difficult to diagnose on cytology
3. More difficult to manage – high cone to excise all endocervix needed - compromises fertility
4. (Cf CIN where excision to just above SCJ needed)
5. 50% of CGIN also have CIN simultaneously
6. Can also become invasive

**Invasive cervical carcinoma**

1. Invasion through the basement membrane defines change from CIN -> carcinoma
2. **Microinvasive carcinoma**
3. <3mm deep x 7mm in width
4. Can be treated conservatively

**Invasive cervical carcinoma**

1. Usually squamous, also adenocarcinoma

**Prognosis**

Depends predominantly on stage

**1 Direct spread**

Occlusion of ureters late manifestation of direct spread to pelvic wall

**2 Lymphatic spread**

Wertheim’s hysterectomy involves extensive lymph node dissection

**3 Blood stream spread** is a very late phenomenon

Figo Stage I (90%) – IV (10%) 5 year survival

**Vulval Carcinoma**

1. 5% of gynae malignancies
2. Majority **squamous**
3. Association with HPV 16 infection
4. Preinvasive stage termed VIN (vulval intraepithelial neoplasia)
5. Only 5% VIN -> invasive (unlike CIN)
6. Prognosis of invasive disease depends on stage
7. **Paget’s disease of vulva** (adenocarcinoma-in-situ) rarely asociated with invasive adenocarcinoma (unlike breast)

**Leiomyoma**

1. Commonest uterine tumour
2. 20% of women >35yrs
3. Smooth muscle tumour of myometrium
4. Lay term is fibroid
5. Probably oestrogen stimulation is important:
6. Enlarge during pregnancy, regress post menopause, decrease in size when LHRH given
7. Usually multiple
8. May be very large
9. Circumscribed with a pseudocapsule of compressed myometrium -> can be shelled out
10. May be intramural, submucosal or subserosal

**Leiomyosarcoma**

1. Malignant counterpart of leiomyoma - is rare

**Endometrial carcinoma**

1. Usually postmenopausal women
2. **Risk factors:** nulliparity, obesity,diabetes meliitus, anovulatory cycles, exogenous oestrogen, oestrogen-secreting ovarian tumour, (tamoxifen)
3. ie excess oestrogen stimulation ->hyperplasia -> ////atypical hyperplasia -> ///// malignancy

**Classification**

**1Endometrioid**

1. **Grading:** 1 –3
2. Depends on:

**1. Pattern** (how much of tumour is acinar, how much solid sheets)

**2. Degree of cytological atypia -** Grading influences prognosis

**3. Serous papillary carcinoma** - Behaves more aggressively, stage for stage than low grade endometrioid variant

All regarded as Grade 3

**4. Clear cell carcinoma**

**5. Adenosquamous carcinoma** - 40% 5 year survival

**Staging (FIGO)**

1. Stage 1 – confined to uterus
2. Stage 2 – spread to cervix
3. Stage 3 – spread to adnexae, serosa, +ve peritoneal cytology, vagina or local lymph nodes (pelvic or para-aortic)
4. Stage 4 – pelvic organs or distant spread inc any other lymph node groups

**Prognosis**

**Stage 5yrs 10yrs**

I 80% 70%

II 70% 60%

III 40% 35%

**Reasons for staging and grading**

1. Prognosis for individual patient
2. Guide to management for individual patient
3. Comparisons of results between hospitals, countries
4. Stratification for entry to clinical trials
5. Interpretation of results of trials

**Ovarian Tumours**

1. 4000 deaths/year in UK
2. Difficult to diagnosis at an early stage
3. Associated with nulliparity, early menarche, late menopause
4. Decreased risk after pregnancy, oral contraceptive use
5. 1% cases have genetic basis

**Classification**

1. Can be primary or secondary
2. **Primary tumours**
3. Wide variety – 3 main sources of origin:
4. Surface epithelium
5. Sex cords
6. Germ cells

**Epithelial tumours**

1. Commonest type 65% of all ovarian tumours & 95% of malignant ovarian tumours (cf testis)
2. Usually post menopausal women
3. **Spectrum of behaviour:**
4. Benign
5. Borderline
6. Malignant
7. **Serous –** mimicking tubal epithelium
8. **Mucinous –** endocervical or intestinal
9. **Endometrioid –** mimicking endometrium

**Sex cord and stromal tumours**

Adult granulosa cell tumour

1. Theca cell
2. Fibromas
3. Sertoli-Leydig tumours

**Germ cell tumours**

1. 20% of ovarian tumours
2. 95% benign (cf testis, most of which are malignant)
3. All occur in first or second decade predominantly

Mature teratoma (Dermoid)

Immature teratoma

Germ cell tumours with no evidence of differentiation

1. Dysgeminoma
2. Yolk sac tumour
3. Choriocarcinoma

**Secondary ovarian tumours**

1. 2 yr survival <10%
2. **Endometrioid, serous, clear cell carcinomas –** can be difficult to know whether ovarian or uterine primary site when both involved
3. **Krukenberg tumours** **–** metastatic mucin-producing adenocarcinomas especially from stomach or breast
4. **Mucinous tumours associated with pseudomyxoma peritonei** **–** all thought to be secondary from appendix. These have a relatively indolent course because they are low grade tumours

Malabsorption Clinicopathological Conference

Prof. Margaret Callan, Dr Tim Orchard and Dr Marjorie Walker

Immunology Revision

Prof Margaret Callan and Dr Peter Kelleher

**Objectives**

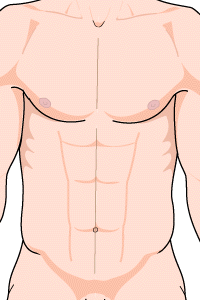
To review and integrate major areas in clinical immunology in the context of human disease

**Case study 1: traumatic rupture of spleen**

A 23 year old medical laboratory technician is involved in a road traffic accident and sustains a traumatic laceration of his spleen. He is admitted to the trauma ward for management of his injuries. He requires an emergency splenectomy for splenic laceration. Four days after his accident, he asks you what a spleen is, what it does, and whether it will matter to him that he no longer has one……..

*.*

Draw a picture of the spleen in its normal anatomical location



What are the functions of the spleen?

…………………………………………………………………………………………………

…………………………………………………………………………………………………

…………………………………………………………………………………………………

What are the implications of not having a spleen?

…………………………………………………………………………………………………

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What advice should you give this patient before he is discharged (at least 3 separate interventions)?

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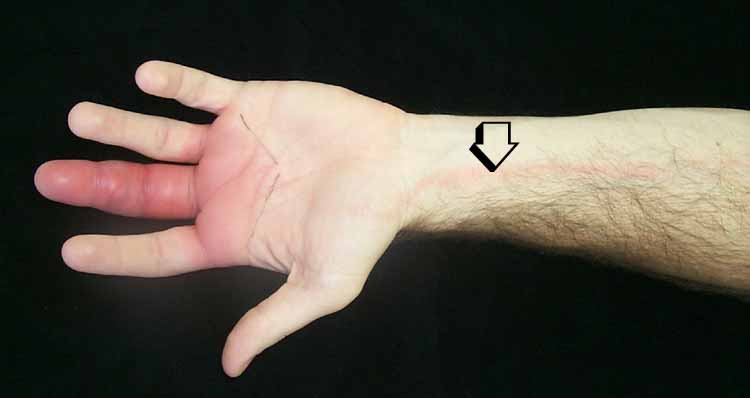
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What conditions are associated with functional hyposplenism?

……………………………………………………………………………………………………………………………………………………………………………………………………

**Case study 2: THe normal immune response to infection**

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*This man cut his finger with gardening knife three days previously. You are asked to see him in A&E.*

Describe and explain the clinical signs observed

…………………………………………………………………………………………………

…………………………………………………………………………………………………

…………………………………………………………………………………………………

What additional signs might you find on systemic examination

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…………………………………………………………………………………………………

How would you treat him?

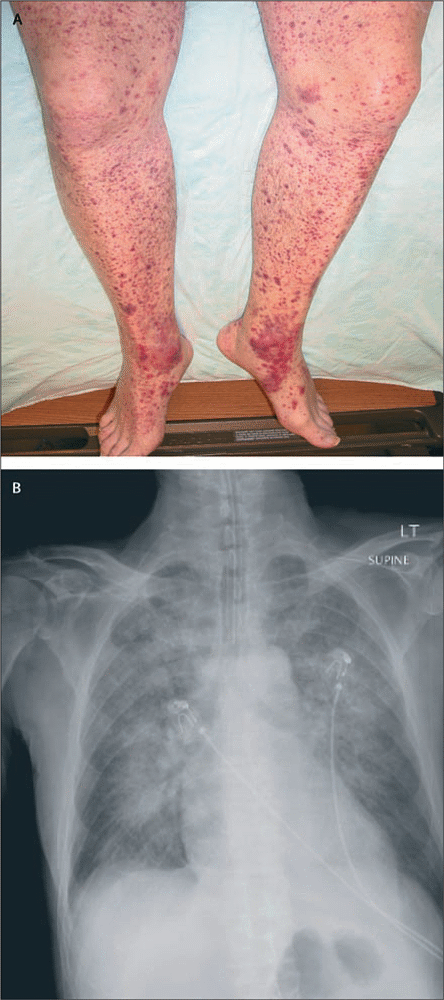
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**Case study 3: Infectious endocarditis**

*A 58-year-old man presents with fatigue and persistent fever over 2 months. He gives a history of profound fatigue, weight loss 9 kg, intermittent skin rash, and migratory joint pains, especially of large joints. On examination, he has a pansystolic murmur at left sternal border radiating to axillae, extensive palpable purpura and petechiae over torso and limbs and splinter haemorrhages.*



What causes the peripheral signs of infectious endocarditis, such as splinter haemorrhages, Osler’s nodes, Janeway lesions and petechiae?

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What is the pathophysiological basis of these signs and also of the systemic features of infectious endocarditis?

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…………………………………………………………………………………………………

**Revision QUestions:**

**Revision QUestions 1: immune deficiency**

*What are the clinical symptoms that should prompt you to consider immune deficiency in a differential diagnosis?*

|  |  |
| --- | --- |
| **Features of infection** | **Other features** |
|  |  |
|  |  |
|  |  |
|  |  |
|  |  |
|  |  |

**QUestion 2: Immune deficiency**

*Deficiencies of specific components of the immune system are associated with different types of infection. Complete the following table with two examples of each type of primary immune deficiency, and the infections that they may be associated with.*

|  |  |  |
| --- | --- | --- |
|  | **Example** | **Type of infection** |
| *B cell deficiency* |  |  |
|  |  |  |
| *T cell deficiency* |  |  |
|  |  |  |
| *Complement deficiency* |  |  |
|  |  |  |
| *Phagocyte deficiency* |  |  |
|  |  |  |

**Question 3: Hypersensitivity disorders**

*a) Give an example of an antibody-mediated (type II) autoimmune disease*

………….………………………….………………………….………………………….……

………….………………………….………………………….………………………….……

How can you test for this condition? ………….………………………….………………………….………………………….…………….………………………….………………………….………………………….…

How could you prove that the disease is mediated by autoantibodies? ………………………………………….………………………….………………………….………………………….………………………….………………………….…………

What are the principles of treatment of antibody mediated autoimmune diseases? ………………………….………………………….………………………….………………………….………………………….………………………….………………………….

*b) Give an example of an immune complex mediated (type III) autoimmune disease*

………….………………………….………………………….………………………….……

Is measurement of immune complexes useful in assessment of type III autoimmune diseases? ………………………….………………………….………………………….………………………….………………………….………………………….………………………….

Is quantitation of complement components useful in assessment of type III autoimmune diseases? …………………….………………………….………………………….………………………….………………………….………………………….………………………….……

*c) Give an example of cell-mediated (type IV) autoimmune disease*

………………………….………………………….………………………….………………………….………………………….………………………….………………………….

*Is quantitation of complement useful in assessment of type IV autoimmune diseases? …………………….………………………….………………………….………………………….………………………….………………………….………………………….……*

What are the major cell types involved in type IV diseases? …………………….………………………….………………………….………………………………………….………………………….………………………….………………

**Question 4: Autoimmune disease**

1. **From this list of immunological tests, which would you use to assist the *prognostic assessment* in a patient with newly diagnosed SLE who has skin rash, significant renal impairment and joint pain?**
2. **Which tests would you use to monitor disease activity in a patient with stable, established SLE?**

|  |  |  |
| --- | --- | --- |
|  | A) Initial diagnosis and prognostic assessment | B) Disease monitoring |
| Antibodies to extractable nuclear antigens |  |  |
| Anti-cardiolipin antibody |  |  |
| Anti-DNA antibody |  |  |
| Anti-mitochondrial antibody |  |  |
| Anti-neutrophil cytoplasmic antibody |  |  |
| Antinuclear antibody |  |  |
| Complement C3 and C4 |  |  |
| HLA typing |  |  |
| Kidney biopsy |  |  |
| Lupus anticoagulant |  |  |
| Rheumatoid factor |  |  |

**QUESTION 5: Autoimmune disease**

**A) Match the disease with the autoantibody. Each antibody can be used once, more than once, or not at all**

|  |  |
| --- | --- |
| **Disease** | **Autoantibody** |
| Congenital heart block in infants of mothers with SLE | Anti-DNA antibody |
| Lupus nephritis | Anti-RNP antibody |
| Mixed connective tissue disease | Anti-Sm antibody |
| Systemic sclerosis (limited cutaneous) | Anti-centromere antibody |
| Sjogren’s syndrome | Anti-Ro antibody |

**B) Match the autoantibody with the disease. Each disease can be used once, more than once, or not at all**

|  |  |
| --- | --- |
| **Autoantibody** | **Disease** |
| Antibody to gastric parietal cells | Autoimmune hepatitis |
| Anti-smooth muscle antibody | Coeliac disease |
| Anti-endomysial antibody | Pernicious anaemia |
| Anti-tissue transglutaminase antibody | Dermatitis herpetiformis |
| Anti-mitochondrial antibody | Primary biliary cirrhosis |
|  | |

**QUESTION 6: TRANSPLANTATION**

**A) Match the type of allograft rejection with the correct mechanism**

|  |  |
| --- | --- |
| **Mechanism** | **Rejection** |
| Mediated predominantly by antibodies which usually form after the transplantation | Hyperacute rejection |
| Both immunological and non-immunological mechanisms contribute | Acute cellular rejection |
| Due to presence of pre-formed antibodies | Acute vascular rejection |
| Mediated by activation of CD4 T cells which provide help for a CD8 T cell and B cell response and occurs within 1-4 weeks | Chronic allograft rejection |
|  |  |

**Question 7: Vaccination**

**A) Which of the following vaccines are contraindicated in patients on immunosuppressive therapy?**

|  |  |  |
| --- | --- | --- |
| Tetanus | BCG | Meningococcus |
| Measles | HIB | Diphtheria |
| Polio | Pneumococcus | Oral typhoid |
| Hepatitis B | Influenza | Hepatitis A |

**B) For those vaccines which are not contraindicated, what is a common problem associated with immunisation of individuals taking immunosuppressive therapy?**

……………………………………………………………………………………………………………………………………………………………………………………………………

**Question 8: immune based therapies**

**Please label this diagram with the side effects of long-term use of corticosteroids?**

**QUESTION 9: Immune based therapies**

1. **Please label the diagram with the site of action of the following immunosuppressive agents where possible. Which drugs do not act directly on this pathway?**

Azathioprine

Rituximab

Cyclosporin A

Adalimumab

Corticosteroids

Natalizumab

Mycophenolate mofetil

Abatacept



**B) The use of multiple immunosuppressive agents allows drug toxicity to be minimised. Select an appropriate combination of immunosuppressants for a 24 year old man undergoing kidney transplantation**

|  |  |  |  |
| --- | --- | --- | --- |
| **Combination 1** | **Combination 2** | **Combination 3** | **Combination 4** |
| Tacrolimus | Tacrolimus | Cyclophosphamide | Tacrolimus |
| Azathioprine | Mycophenolate | Cyclosporin | Mycopenolate |
| Cyclosporin | Azathioprine | Corticosteroids | Corticosteroids |

**PRactice EMQs**

**OPTION LIST**

1. Th17 cell
2. Macrophage
3. Epithelial cell
4. T reg cell
5. Dendritic cell
6. CD4+ T cell
7. Neutrophil
8. Th1 cell
9. Plasma cell
10. Tr1 cell
11. Megacaryocyte
12. Lymphocyte

*Match the most likely cell to the following descriptions:*

1. Expresses Foxp3 and CD25 and secretes IL-10. Deficient in the monogenic autoimmune disease known as IPEX,
2. In the immature form these cells are adapted for recognition and uptake of pathogens. Maturation is associated with expression of CCR7, migration to lymph nodes and enhanced capacity for antigen presentation.
3. These cells can be rapidly mobilised from bone marrow. They express pathogen recognition receptors and Fc receptors and are able to engage in oxidative and non-oxidative killing. They do not express HLA class II molecules and so do not activate CD4 T cells. They are the predominant cell type in synovial fluid taken from patients with gout,
4. These cells may be formed following a germinal centre reaction involving isotype switching and affinity maturation of receptors. They are long-lived and reside in bone marrow.
5. These cells express CD3 and secrete IL-17 and IL-22. They are thought to be important in some auto-immune conditions including rheumatoid arthritis.
6. These cells may be resident in peripheral tissues, express pathogen recognition receptors and Fc receptors and are able to engage in oxidative and non-oxidative killing. They are an important source of cytokines such as IL-1 and TNF-alpha and are thought to play an important role in some auto-inflammatory and auto-immune diseases.
7. The normal function of these cells is to express cytokines in response to recognition of specific peptides presented by HLA class II molecules. Depletion of these cells during HIV infection is an important factor in development of AIDS.

**OPTION LIST**

1. Gp120
2. Anti-metabolites
3. CCR5

D. Reverse transcriptase

E. Basophils

F. Gastric parietal cells

G. Protease inhibitors

H. CCR7

I. Macrophages

J. CD8 T cells

K. IL-8

*Match the most likely molecule/cell type to the following descriptions:*

1. Play a role in protective immunity against HIV infection by killing virus infected cells via perforin and FAS.
2. Acts as a co-receptor for HIV entry to cells
3. Serve to convert RNA to DNA which can be integrated into host cell genes
4. Directs homing of dendritic cells to lymph nodes
5. Are often infected by HIV if they express CD4

6. Antibodies against this target are partially protective against HIV infection

7. Are effective in management of HIV infection if used in combination with other drugs

**OPTION LIST**

1. anti-acetyl choline receptor antibody
2. anti-adrenal cortex antibody
3. antibody to double stranded DNA
4. anti-centromere antibody
5. anti-endomysial antibody
6. anti-intrinsic factor antibody
7. anti-mitochondrial antibody
8. anti-neutrophil cytoplasmic antibody
9. anti-RNP antibody
10. anti-smooth muscle antibody
11. anti-TSH receptor antibody
12. Rheumatoid factor

*Match the most likely positive autoantibody to the following clinical scenarios.*

1. A 58 year old pharmacist presents with a 3 month history of skin itching associated with lethargy and loss of energy. Physical examination is normal, but liver function tests reveal total bilirubin = 6umol/l (reference range 0-17umol/l), ALT = 28U/l (reference range 0-31U/l); Alkaline phosphatase 420U/l (reference range 30-130).
2. A 56 year old prison officer presents with a history of recurrent nose bleeds, haemoptysis and joint pain associated with profound lethargy. On examination, he has crackles in his upper left lung field, and a cavitating left lung lesion is demonstrated on chest radiography. Routine urine dipstick is positive for protein and blood.
3. A 22 year old woman presents with joint pain and fatigue. She has an intermittent, skin-sensitive rash, and also complains of mouth ulcers. Physical examination is otherwise normal. Urine dipstick is positive ++ protein and ++ blood. Full blood count shows a normocytic normochromic anaemia.
4. A 30 year old plumber attends his GP complaining of feeling tired all the time. He has type I diabetes, which is currently well controlled, and a history of irritable bowel syndrome. A full blood count shows a microcytic hypochromic anaemia, and iron studies confirm iron deficiency. Vitamin D levels are in the insufficient range.
5. A 44 year old builder presents with a history of fingers intermittently becoming very cold and white with recent development of a gangrenous tip of his finger. The skin over his fingers feels ‘tight’ and you note telangectasia on his hands.
6. A 19 year old student presents with a chronic, extremely itchy rash consisting of papules and vesicles which is distributed symmetrically over the extensor surfaces of her elbows, legs and buttocks. You suspect dermatitis herpetiformis.

Urinary Tract Infections

Dr Hugo Donaldson

(Handout courtesy of Dr Chris Chiu)

**Very common**

* Bimodal distribution
  + Young women (20-30% of women will have recurrent UTI at some stage)
  + Elderly

**Classification**

* Lower urinary tract
  + Urethritis
  + Cystitis
* Upper urinary tract
  + Pyelonephritis
* Uncomplicated
  + Young healthy sexually active women
* Complicated
  + Children
  + Men – possible prostatitis & should look for structural defects
  + Urological defect

**Predisposing factors**

* Old age
* Female sex
  + Short urethra
* Sexual intercourse
* Structural or neurological abnormalities of renal tract
  + Congenital abnormalities
  + Renal/ureteric calculi
  + Tumours
  + Diverticulae
* Instrumentation
* Surgery e.g. TURP

**Pathogens**

* Coliforms
  + Escherichia coli
  + Proteus
    - Associated with calculi
  + Klebsiella
  + Enterobacter, Serratia etc.
  + Pseudomonas
* Enterococcus
* Staphylococcus saprophyticus
  + Coagulase negative Staphylococcus
  + Most common in young women
* Candida
* Adenovirus (esp. type 11)
  + Haemorrhagic cystitis esp. young boys

**Pathogenesis**

* Host factors (see Risk Factors)
* Bacterial attributes
  + Adhesion to uro-epithelium (P fimbriae)
  + Capsular antigens (K antigen)
  + Haemolysins
  + Urease
* Physical factors
  + Ascending infection by bacteria colonising introitus
  + Catheterisation

**Symptoms & signs**

* Lower
  + Dysuria
  + Suprapubic pain/discomfort
  + Cloudy/smelly urine
  + Frequency
* Upper
  + Loin pain
  + Fever
  + Rigors
  + Unwell

**Investigations**

* Urine dipstick
  + Leucocytes
  + Nitrites
* Urine sample for microscopy & culture
  + Mid-stream urine
  + Clean catch
  + Bag urine
  + Catheter urine
  + Suprapubic urine
  + Ureteric urine
  + Nephrostomy urine
* Blood tests
* Ultrasound of renal tract

**Significant or not?**

* Type of specimen & likelihood of contamination
* Microscopy
  + White cells >50 cells/ml
* Culture
  + Organisms >10(5) cfu/ml
  + Mixed vs pure growth
  + Type of organism grown
* Sterile pyuria
  + Patient on antibiotics
  + Fastidious organism e.g. Mycobacterium tuberculosis
  + Other conditions e.g. STIs
* Asymptomatic bacteriuria
  + Elderly – treat or not?
* Catheters
  + Plastic rapidly colonised with bacterial biofilm
* Problem with sample e.g. Poor collection, long transit time, no refrigeration

**Treatment**

* Empirical therapy
  + Started before culture & sensitivities available
  + Best guess
  + Depends on your population
  + Knowledge of resistance patterns

**Community lower UTI**

* Amoxicillin 250-500mg tds
* Trimethoprim 200mg bd
* Nitrofurantoin 50mg qds
* Co-amoxiclav 375-625mg tds
* Cephalexin 500mg bd
* Ciprofloxacin 500mg bd

**Antibiotic resistance**

* Increasing resistance
  + Up to 30% Trimethoprim resistance
  + Up to 60% Amoxicillin resistance
* Mechanisms of resistance
  + Antibiotic altering enzymes e.g. Penicillinases (beta-lactamases)
  + Altered target site e.g. Cell wall & glycopeptides
  + Altered permeability e.g. Cell membrane & gentamicin
  + Efflux pumps e.g. Pseudomonas
* Intrinsic resistance
  + Klebsiella - Amoxicillin
  + Enterobacter/Serratia - penicillins & cephalosporins
  + Pseudomonas - multiple antibiotics
* Acquired resistance
  + Mobile genetic elements
  + Increasing incidence of beta-lactamases esp. Extended spectrum beta lactamases (ESBLs)

**Pyelonephritis**

* Infection of kidneys
* Commonly associated with sepsis & septicaemia
* Requires more aggressive treatment
* Treat with broader spectrum intravenous antibiotics
  + Co-amoxiclav 1.2g tds +/- Gentamicin 7mg/kg
  + Cefuroxime 1.5g tds +/- Gentamicin 7mg/kg
* Imaging
  + Structural cause
  + Renal calculi
* Complications

**Complications**

* Perinephric abscess
* Chronic pyelonephritis
  + Scarring
  + Chronic renal impairment
* Septic shock
* Acute papillary necrosis

**Prophylactic antibiotics for recurrent UTI**

* Controversial
* Likely to promote resistance
* Adverse effects
* Some clinicians will give e.g. Trimethoprim 100mg on
* Can try to break cycle with 3-6 month course initially
* Also non-antibiotic treatment
* Cotton underwear
* Hygiene
* Cranberry juice
* Showers *vs* baths