Lecture 1: Acute Leukaemia

- Leukaemia = cancer of white blood cells
- rapid, progressive if untreated then fatal
- 2 main types = lymphoblastic & myeloid

Signs & Symptoms

- Bone marrow failure = Anaemia - lethargy, tiredness, shortness of breath.
  Neutropenia - recurrent infections. Thrombocytopenia - nose bleeds, gum bleeding, skin bruising, petechial rash.
- High temperature, weight loss sweats.
- Bone and joint pain.
- Abdominal fullness or discomfort.
- Headaches, seizures, vomiting, blurred vision
- Swelling of the lymph glands

Gingival Hyperplasia

Leukaemia Cutis

Risk Factors

- Radiation
- Benzene and Smoking
- Blood disorders - MPN, MDS
- Genetic disorders - Downs
- Previous chemotherapy and radiotherapy
- Other unknown environmental factors.

Diagnosis

- Full blood count and blood film
- Bone marrow aspirate and trephine (> 20% blasts)
- Cytogenetics
- Molecular tests and PCR
- Lumbar puncture
- Radiology - CXR, CT scans – head, Chest

AML

- AML with recurrent cytogenic translocations
- AML with multi-lineage dysplasia
- AML and myelodysplasia, therapy related
- AML, not otherwise categorized

Cytogenetic Translocations
- t(8;21) -- some maturation of neutrophilic line; rare in older patients; AML1/ETO fusion protein; >90% FAB M2
- t(15;17) -- APL (granular and microgranular variants); retinoic acid receptor (RAR) leukemias; middle aged adults; DIC
- inv(16) or t(16;16) -- monocytic and granulocytic; abnormal eosinophilic component

**FAB Classifications**
- M0 -- Undifferentiated AML
- M1 -- AML without maturation
- M2 -- AML with maturation
- M3 -- Acute Promyelocytic Leukemia
- M4 -- Acute Meylomonocytic Leukemia
- M5 -- Acute Monocytic Leukemia
- M6 -- Erythroleukemia
- M7 -- Megakaryoblastic Leukemia
- L1: Small homogeneous blasts; mostly in children
- L2: Large heterogeneous blasts; mostly in adults
- L3: "Burkitt" large basophilic B-cell blasts with vacuoles

**Philadelphia Chromosome**
- 9 and 22 translocation almost specific to CML
- Karyotype to visualize Ph chromosome
- Produces BCR/c-abl fusion oncogene
- Gene product p190 is a hyperactive tyrosine kinase
- Ph chromosome seen in ALL produces p210 and chronic neutrophilic leukemia produces p230

![](Ph_chromosome_and_bcr-abl_gene.png)

**AML Cytogenetics & Prognosis**
- Favorable= t(8;21), t(15;17), inv(16) 91% CR, 65-75% 5 year survival
- Intermediate (Most patients)= normal, +8, +21, +22, del(7q), del(9q), 86% CR, 40-50% 5 year survival
- Adverse= -5, -7, del(5q), abnormal 3q, complex karyotype (> 3 -5 abnormalities), 63% CR, <15% 5 year survival
AML Mutations & Prognosis

- Flt 3 (ITD)= Adverse
- NPM-1 mutation & no Flt3 = Favourable

Treatment

- Age
- Performance status
- Organ dysfunction (heart, liver, kidneys)
- Goals of treatment
- Quality of life
- Cure vs control
- Treatment of underlying disease
- Treat the symptoms
- Treat the complications
- Radiotherapy
- Stem Cell transplantation – allogeneic=Full intensity, Reduced intensity
- Clinical trials

Intensive Chemotherapy

- Induction: Aim is to kill the leukemia and allow the normal bone marrow to regenerate to restore marrow function
- Consolidation: Aim is to prevent the leukemic relapse and to kill of any residual leukemic cells
- Maintainence: Prevent relapse

Chemotherapy

- Anthracyclines – Daunorubicin, Doxorubicin, Idarubicin= interfere with enzymes involved in DNA replication works in all cell phases
- Antimetabolites – Cytarabine= interfere with DNA and RNA synthesis by substituting the normal building blocks (nucleosides)
- Topoisomerase inhibitors – Mitoxantrone, etoposide= involved in separation of DNA separation, so that they can be copied
- Steroids
- Targeted therapy- tyrosine kinase inhibitors – Imatinib
- Immunotherapy= Rituximab (anti CD 20), Myelotarg (anti CD33)
- Differentiation agents – ATRA (All Trans-Retinoic Acid)

Side Effects

- Gastrointestinal
- Hair loss
- Bone marrow suppression/aplasia
- Organ toxicity – lungs, heart, kidneys, liver, brain
- Sterility – young patients
Risk of secondary cancer

Supportive Treatment

- Blood product support: Red cells and platelets
- Prevent infection: prophylactic antibacterial, antiviral and antifungal
- Symptoms control: pain, sickness
- Treat infection

Lecture 2: Clinical Management of Leukaemia
Lecture 3: Case Presentation Lymphoma

Symptoms

- LN enlargement
- Loss of appetite
- Loss of weight
- Night sweats

Signs

- LN enlargement
- Hepatosplenomegaly

Investigations

- Biopsy
- Blood tests
- Scans
- Bone marrow biopsy

Results

- MDT

Plan

- Next steps

Lump in Neck

Reactive LN

- Infective
- Bacterial
- Viral
- Other inc. TB
- Inflammatory

Malignant
Lymphoma
Metastatic
Primary Head and Neck

-Arising from underlying neck structures e.g. thyroid
-Embryologic remnant

**Lecture 4: Clinical Management of lymphoma**

Where does Lymphoma come from?

- malignant growth of white blood cells
- Predominantly in lymph nodes But also Blood, bone marrow Liver, spleen Anywhere
- Primary immunodeficiency= Ataxia telangiectasia, Wiscott-Aldrich syndrome, common variable immunodeficiency
- Secondary immunodeficiency= HIV, transplant recipients
- Infection= EBV, HTLV-I, Helicobacter pylori
- Autoimmune disorder
- impaired immunosurveillance of EBV infected cell
- infected B cells escape regulation and proliferate autonomously

Presentation

- Most commonly nodal disease
- Also extranodal disease
- Compression syndromes
- Systemic symptoms (‘B’ symptoms)

Diagnosis

- Blood film & bone marrow
- Lymph node biopsy
- Immunophenotyping
- Cytogenetics= Karyotype analysis, FISH
- Molecular techniques= PCR
- Diagnosis is complex
- Specimen sent to HODS (haematology oncology diagnostic service)

New Case Work-Up

- Staging= How bad is the lymphoma?
- Assessment of patient= How good is the patient?
- MDT= Facts & Planning
Staging
Investigations:

- Blood tests
- CT Scan chest/abdo/pelvis
- Bone marrow biopsy
- PET

Assessment of Patient

- History and examination
- Bloods= FBC, U/E’s, LFT’s, Viral serology (for HIV, Hep B, Hep C)
- CXR
- ECHO
- PFT’s
- Performance status

Performance Status

- 0 – Asymptomatic= activities without restriction
- 1 – Symptomatic= but completely ambulatory, Restricted strenuous activity but able to carry out work of a light nature.
- 2 – Symptomatic= <50% in bed during the day, Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours
- 3 – Symptomatic= >50% in bed, but not bedbound, Limited self-care, confined to bed or chair 50% or more of waking hours
- 4 – Bedbound= Cannot carry on any self-care. Totally confined to bed or chair
- 5 – Death

Lymphoma Subtypes

- Hodgkin’s
- NHL= Low grade e.g. Follicular Lymphoma, High grade e.g. Diffuse Large B Cell Lymphoma, Very high grade e.g. Burkitt’s Lymphoma
- Pathology crucial

Hodgkins Lymphoma

- ‘Lymphogranulomatosis maligna’
- On some morbid appearances of the absorbent glands and spleen
- Presentation= Painless lymphadenopathy, B symptoms (Sweats, weight loss)
- Diagnosis= Reed-Sternberg cell (4 histological subtypes)
Clinical Stages of Hodgkin’s

- 4 clinical stages: I, II, III, IV
- A = absence
- B = presence of ‘B’ symptoms

Hodgkin’s Treatment

- Depends on clinical stage
- Stage 1-2A = Short course combination chemotherapy followed by radiotherapy, 70-80% prolonged disease free survival
- Stage 2B-4 = Combination chemotherapy, 50-70% prolonged disease free survival
- ABVD = Adriamycin, Bleomycin, Vinblastine and Dacarbazine
- Relapse responds well to autologous bone marrow transplantation
- Good long term survival – therefore must minimise long term effects of treatment

Hodgkin’s Lymphoma Advances

- Current UK trial uses PET scanning to identify
  - Those who will respond well and therefore in whom treatment can be reduced
  - Those who will do badly who need escalation of treatment

Non-Hodgkin’s Lymphoma

- Presentation = More varied
- Subtypes = More categories
- Treatments used = Wide variety
- Outcomes = More varied

Indolent or Low Grade NHL
- e.g. Follicular Lymphoma
- Slow growing
- Usually advanced at presentation
- Incurable
- Median survival 9-11 years
- Wide range of treatments used
- ?optimal sequence of treatment
- ?maintenance treatment

**Indolent NHL - Treatment**

- Do nothing!
- Alkylating agents
- Combination chemotherapy
- Purine analogues
- Monoclonal antibodies
- Radio-immunoconjugates
- Radiotherapy
- Bone marrow transplant

**High Grade or Aggressive NHL**

- e.g. Diffuse Large B Cell Lymphoma
- Usually nodal presentation
- 1/3 cases have extranodal involvement
- Patient usually unwell
- Often short history

**Aggressive NHL Treatment**

- Early = Short course chemotherapy e.g. 3CHOP & IFRT
- Advanced = Combination chemotherapy + monoclonal antibodies e.g. 6 R-CHOP

**New Treatment Approaches**

- Increasing intensity of treatment
- Monoclonal antibodies
- Radioimmunoconjugates (e.g. Zevalin)

**Monoclonal Antibodies**

- Rituximab
- Monoclonal antibody
- Anti CD-20
• Targets CD20 expressed on cell surface of B-cells
• Chimeric mouse/human protein
• Minimal side-effects

Summary

• A wide range of lymphomas
• Increasingly complex diagnosis and risk assessment
• Range from very aggressive to indolent
• Variable prognosis
• Ever expanding range of treatments including designer drugs and transplantation
• Tailoring treatment to improve outcomes

**Lecture 5: Care of Terminally Ill Patients**

Challenges Defining End of Life Care

• definition of beginning of end of life care variable according to individual person & professional perspectives
• When does it begin? = At time of diagnosis of condition which usually carries poor prognosis. When deterioration in chronic illness occurs and becomes apparent likely prognosis is measured in months or possibly a year or two
• What does the GMC have to say?= If likely to die in the next 12 months

What is End of Life Care?

• Helps those w/t advanced, progressive, incurable illness to live as well as possible until they die
• Enables supportive & palliative care needs of both patient & family to be identified & met throughout last phase of life and into bereavement
• Includes management of pain and other symptoms & provision of psychological, social, spiritual and practical support.

Last days of life- dying

• profoundly weak
• bedbound
• semicomatose
• unable to swallow medications
• unable to take more than sips of fluid
• this all is relevant to = junior doctors, consultants, GPs, human beings

Care of Dying
• Approx 60% die in hospital
• Only one opportunity to get it right and then to create a positive lasting memory for relatives and carers

Relevance

• Variance in the quality of care
• 54% of complaints in acute hospitals relate to the care of the dying/bereavement care
• Few clinical specialties in Medicine or Surgery don’t deal with dying patients
• As a consultant or GP ultimately responsible for decision making

Care of Dying Patient

• Identify the dying patient
• Assess distress
• Indicate the importance of comfort
• Simplify medication
• Convert routes of administration if patient cannot swallow
• Pre-empt symptoms with as required treatment
• Explain condition and prognosis
• Review
• Listen to the nurses

How to Help Them?

• Pain
• Breathlessness
• Unable to drink or eat
• Nausea and vomiting
• Agitation/confusion
• Respiratory secretions (death rattle)
• Dry mouth
• Other discomforts

Algorithm’s for Pre-Emptive Prescribing

• Sometimes called anticipatory prescribing
• Prescription of drugs which may be needed for symptom management in dying phase
• Symptoms may not be present yet
• In hospital, done by using PRN section of the drug card

Other Factors?
• Psychosocial distress
• Fear, anger, sadness, regrets
• Previous problems with family, social circumstances
• Existential distress
• Spiritual issues
• Depression
• Family members distress

End of Life Care: What Matters to Patients

• Symptom management
• Choice & control
• Being treated as an individual – dignity
• Quality of life
• Preparation – practical & personal
• Carers support
• Co-ordination and continuity

Preparation

• Focus on the patient AND the family/care-givers
• Educate family on the last hours processes to reduce fear and increase involvement
• Ensure medications available to help manage symptoms (pre-emptive prescribing)
• Explore preferred place of care

Dying at Home

• What is available in hospital that isn’t standard at home?
• Nursing care
• Regular medical review
• Drugs
• Equipment (hospital bed, commode, wheelchair, hoist)

Liverpool Care Pathway (LCP 1997)

• Based on the hospice model of care of the dying
• Developed to reproduce the same quality of end of life care in all care settings
• STH version, ‘The End of Life Care Pathway for last hours/days of life’

Controversies in LCP

• Stopping food and drink
• Allow to starve
• Will bring about premature death
• Essential treatment stopped
• Use of sedation

Neuberger Report: Key Findings

• When applied correctly, the LCP does help patients have a dignified and pain free death
• Difficulty in diagnosing death
• Evidence of good & bad decision making
• Many cases where the LCP is used as a tick box exercise
• Too many serious cases of unacceptable care where the LCP incorrectly implemented
• Patients left without adequate nutrition, hydration and were inappropriately sedated
• Lack of/or poor communication with patients/relatives

Once Chance to get it Right Report 2014

• Improving people’s experience of care in the last few days and hours of life
• 5 Priorities for care of the dying person
• New focus for caring for people in last few days and hours of life
• Involve assessing and responding to holistic and changing needs of individual dying person and their families
  1. this possibility is recognised and communicated clearly, decisions made and actions taken in accordance with the person’s needs and wishes, and these are regularly reviewed and decisions revised accordingly
  2. Sensitive communication takes place between staff and the dying person, and those identified as important to them
  3. the dying person, and those identified as important to them, are involved in decisions about treatment and care to the extent that the dying person wants
  4. the needs of families and others identified as important to the dying person are actively explored, respected and met as far as possible
  5. an individual plan of care, which includes food and drink, symptom control and psychological, social and spiritual support, is agreed, co-ordinated and delivered with compassion.

What Happens During Recovery of Patient?

• Biochemical causes may become rectified
• Controlling the symptoms may allow reduction in sedative drugs – so patient wakes up
• The diagnosis of dying may have been wrong
After Death
The death must be verified:

- No heart sounds or carotid pulse for one minute
- No breath sounds or respiratory effort for one minute
- No response to painful stimuli
- Pupils are fixed and dilated

Death Certification

- Hospitals have a Bereavement Office
- The family must register the death officially with the Registrar for Births, Deaths and Marriages.
- To do this, they need a Medical Cause of Death Certificate
- Separate cremation form, completed by two doctors

**Lecture 6: Clinical Management of Myeloma**

Multiple Myeloma

Cancer of differentiated B lymphocytes, known as plasma cells, w/t osteolytic bone disease featuring:

- The accumulation of malignant plasma cells in the bone marrow leading to progressive bone marrow failure
- The production of a characteristic paraprotein
- Renal failure
- Destructive bone disease and hypercalcaemia
- Increase in bone resorption, decrease in bone formation & uncoupling of resorption & formation leading to bone loss, mechanisms on this poorly understood.

![Mechanisms of myeloma bone disease](image-url)
Multiple Myeloma Statistics

- 10% of all haematological cancers; overall, the second commonest haematological cancer after non-Hodgkins lymphoma
- Incidence 60-70 per million; approx 4,000 new cases of myeloma per annum in the UK
- Median age at diagnosis is 70 yrs (Bird et al 2010); 15% of patients are less than 60 yrs; and 2% of patients are less than 40 yrs (Smith et al 2006)
- Overall survival ranges from a few months to, in a small number of cases, over 20 yrs.
- Median overall survival of patients treated with intensive regimens plus autologous stem cell transplantation is 62 months ie 5 years, 2 months (Gulbrandsen et al. 2001).
- Median survival since introduction of thalidomide estimated at approx 7 years in the UK MRC MMIX trial (Morgan 2009).

Clinical Entities
- Monoclonal gammopathy of undetermined significance (MGUS) - <30g/dl, <10% plasma cells in BM, no ROTI, no evidence of amyloid or other LPD
- Asymptomatic myeloma (aMM) - >30g/l and/or >10% plasma cells in BM, no ROTI
- Symptomatic myeloma (sMM) – paraprotein**, clonal plasma cells in BM or Bx proven plasmacytoma, ROTI nb CRAB
- MGUS present in 3% people aged 50, 5% aged 70 – 1% risk per year of progression; majority of cases of MM present de novo but now recognised that most have had a preceding MGUS phase (Landgren et al 2009)
- aMM – 20% risk per year of progression in first year, then diminishes to about 5% per year after 5 years and then stabilises
- Only treat symptomatic myeloma – MGUS and asymptomatic myeloma watch and wait.

CRAB (Related Organ Tissue Involvement ROTI)
- C - ad Ca>0.25mmol/l above upper limit of normal or >2.75mmol/l
- R – renal impairment, creatinine>173mmol/l (40% pts at Δ have some degree of RF; 10% req dialysis Dimopolous et al, 2008, Leukaemia, 22, 1485-1493 Pathogenesis and treatment of renal failiure in multiple myeloma)
- A – anaemia 2g <NR or <10g/dl (75% at diagnosis; normochromic, normocytic, Kyle et al 2003)
- B – lytic lesions, osteoporosis c compression, spinal cord compression
- nb also hyperviscosity; recurrent infection ie >2 episodes in 12/12 , amyloid; raised ESR and globulin frequent signals
International Staging System

- **β2 mcg <3.5g/l, albumin >35g/l** (62m ie 5 years 2 months)
- **II. Neither I. or III.** (45m ie 3 years 11 months)
- **III. β2 mcg >5.5g/l** (29m ie 2 years 5 months)

Imaging in Myeloma

- skeletal survey using plain radiographs first line screen
- MRI, CT or PET/CT to clarify ambiguous lesions
- MRI to assess spinal cord compression

Immunoglobulin Product

- Myeloma cells usually produce both an intact immunoglobulin product - IgG (2/3), IgA (1/3) or rarely IgD (1.8%), IgM (0.4%) or IgE and monoclonal free light chains (FLC) (90% of cases); in a minority of cases, myeloma cells produce FLC only (15%) termed ‘free light chain myeloma’
- FLC designated κ or λ; a hallmark of clonality is therefore light chain restriction
- Designated IgG κ or IgG λ or IgA κ or IgA λ or IgM κ or IgM λ or κ FLC or λ FLC (IF)
- Rarely, myeloma can be ‘oligo-secretory’ ie secrete only small amounts of either intact Ig (measured in g/l) typically <10g/l or FLC
- Very rarely, myeloma may be completely non-secretory
- IgM monoclones are much more commonly seen in lymphoplasmacytic lymphoma formerly known as Waldenstrom’s macroglobulinaemia
- Remember other lymphoproliferative disorders can produce immunoglobulin products e.g. chronic lymphocytic leukaemia

Measuring the Monoclon
Electrophoresis of serum and urine is performed, followed by immunofixation to confirm and type any M-protein present.

Immunofixation repeats electrophoresis but adds anti sera to IgG, IgA, IgM and κ or λ ie will detect IgG κ or IgG λ or IgA κ or IgA λ or IgM κ or IgM λ or κ FLC or λ FLC.

A densitometry scan is then performed on the electrophoresis to quantify the paraprotein.

Serum Electrophoresis

- Separation by molecular electric charge
- Lots of differently charged molecules
- Lots of identically charged molecules
- Electroendosmosis (flows south) – counter flow of the buffer against the flow of the electrons between anode and cathode (flows north)
- IgG and IgM flow south with the electrendosmosis flow; due to it’s electrical charge, IgA migrates northwards localising with the β-proteins
- Lane 1 shows an IgG lambda M-protein of 7g/l
- Lane 2 shows an IgM lambda M-protein of 8g/l
- Lane 3 shows an IgA kappa M-protein of 28g/l
- Lane 4 shows normal polyclonal immunoglobulins

![Interpretation of banding patterns of normal serum](image)

Immunofixation

- Panel 1 is normal serum with polyclonal immunoglobulins
- Panel 2 is serum containing a high level of IgG lambda monoclonal immunoglobulin with monoclonal lambda FLC and little polyclonal immunoglobulin; the patient has myeloma with renal failure
- Panel 3 is serum containing a low concentration of IgA kappa M-protein
- Panel 4 is serum containing an IgM lambda M-protein
Measuring Monoclonal Conventionally

1. Electrophoresis - If a discrete additional band seen or bands fuzzy or suppressed, proceed to immunofixation
2. Immunofixation repeats the electrophoresis plus identifies monoclonal via the addition of specific antibodies. A second immunofixation is sometimes required if a rare band expected eg IgD or IgE; performed at diagnosis and at other key intervals eg relapse
3. Densitometry scan performed on 1. or 2. to quantify the monoclonal

Serum Free Light Chain Assay

- Useful for 3 groups 1. light chain only myeloma (15% of all myeloma; nb immunoparesis on EP is a clue) 2. non-secretory/low secretory disease, 3. AL amyloidosis
- Units quoted are mg/ml but in fact very poor correlation with densitometry
- Very high co-efficient of variance (25-50%)
- Nb also antigen excess may yield falsely low values ie interpret with caution
- In RF ½ life and [] may be increased 10 fold
- The presence of an abnormal κ to λ FLC ratio (RR 0.26-1.65; 0.37-3.1 in renal imp) suggestive of monoclonal FLC production can occur in the settings of both intact immunoglobulin MM and light chain only MM.
- Don’t have to have a large sMIG to develop light chain mediated cast nephropathy inducing AKI
- Useful disease marker in RF and entities where extent of sMIG may be discrepant with damage eg ‘non-secretory’ MM, amyloid

Treatment of Myeloma
• Explain remitting and relapsing nature of MM; period of remission is unpredictable and further treatment will be required at relapse.
• However, patients may progressively acquire resistance to treatments and eventually become refractory

Aims of Treatment

There are three overlapping aims of treatment:

1. To reduce myeloma burden
2. Prevent and treat bone and tissue damage and preserve organ function
3. Improve quality of life and survival

- Anti-myeloma treatment
- Combination chemotherapy e.g. CTD, MPT, HD-ASCT
- Prevention and treatment of bone and tissue damage Bisphosphonates, renal dialysis, MSCC treatment (radiotherapy, surgery), pain
- Improve quality of life and survival
- Infection prophylaxis and treatment, anaemia (EPO, transfusion)
1. Stem cell mobilisation
2. Stem cell collection
3. High-dose melaphlalan
4. Stem cell transplant

Treatment Options

- For non-transplant patients
- Treatment dependent of NICE Guidelines

Treatment at 1st Relapse

Velcade medication:

- Also known as bortezomib
- Is the first proteasome inhibitor to be used in myeloma
- Current NICE-approved 2nd line treatment
- Single agent (monotherapy) - 40% response rate
- Velcade + dexamethasone - 55% response rate
- Cyclophosphamide, Velcade + dex – 65% response rate
- Velcade, thalidomide + dex – 90% response rate
- Better responses if used early in disease course and in combination with other drugs
- Originally IV injection, moving more towards subcutaneous injection
- Once or twice weekly
- Generally combined with dexamethasone
- 21-day cycle (3rd week rest week)
- 4 – 8 cycles
- Potential side-effects:
  - Weakness, fatigue
  - Peripheral neuropathy
  - Low blood counts especially platelets
  - Nausea, diarrhoea or constipation
  - Postural hypotension

Other Options at First Stage

- Same treatment again if first remission
- lengthy
- Second transplant if first transplant remission >2yrs
- Enter a clinical study
Treatment at 2\textsuperscript{nd} Relapse

**Revlimid Medication:**

- Also known as lenalidomide
- Immunomodulatory drug (IMiD), similar to thalidomide but more potent and less toxic
- Current NICE approval at 3rd line and beyond, in combination with dexamethasone
- Revlimid monotherapy – 29% response rate
- Revlimid + dex – 65% response rate
- Revlimid, cyclophosphamide + dex – 75% response rate
- Oral capsule taken daily on days 1 - 21 of 28-day cycle
- Recommended starting dose of 25mg (lower for patients with kidney damage)
- Dose continued or modified, until disease progression
- Potential side-effects: Less constipation and neuropathy than thalidomide, Neutropenia and thrombocytopenia, Increased risk of blood clots, Fatigue, Muscle cramp

Treatments for Multiply Relapsed Myeloma
• Pomalidomide – alternative immuno-modulatory agent related to thalidomide
• Bendamustine – mixed purine analogue and alkylating agent
• Kyprolis (carfilzomib) – next generation proteasome inhibitor (cf bortezomib)
• MLN 9708 – oral proteasome inhibitor
• Elotuzumab – monoclonal antibody to CS1 antigen expressed by plasma cells
• Daratumumab – monoclonal antibody to CD38 antigen expressed by plasma cells
• Panobinostat – histone deacetylator inhibitor

Summary

• No standard best approach to treatment adapting to meet patients’ needs important
• identifying the best sequence of treatments is challenging
• Aims of treatment= Reduce myeloma burden, Prevent damage and preserve organ function, Improve quality of life and survival

Lecture 7: Nebulisers & Oxygen

Benefits of O2 Therapy

• O2 essential for cellular respiration
• Reduces organ failure, length of ICU stay & increases survival in critically ill patients
• Increased wound healing
• Relief of breathlessness/work of breathing
• Hyperoxaemia for CO poisoning

Oxygen in critically ill patients

- Give oxygen to all acutely ill hypoxic patients
  -15 l/ min
  - give first, document later

Critically Ill Patients
- High Conc Reservoir Mask (RM)
  - Flow 15 l/min
  - Delivers O2 conc of >60%
  - Short-term treatment

**High Conc Reservoir Mask**

- Prime reservoir by occluding valve
- Tight seal around face
- Non-rebreather

**Hypoxaemic Patients**

- Use pulse oximetry
- Normal range 96-98% for young & healthy
- Dips lower in sleep or high altitude
- Sustained fall <3% indicates acute illness
- Patients prescribed oxygen to achieve saturation 94-98%

**Oxygen Therapy**

- Record sats before starting
- Choose appropriate mask/cannula
- Start correct flow

**Nasal cannula**

- Recommended for most patients
- 2-4 (-6) l/min flow
- Approx. 24-50%
- Easily tolerated can eat
- No re-breathing

**Simple Face Mask**

- Type I resp failure
- O2 conc variable (35-60%)  
- Flow at least 5 l/min to avoid CO2 build-up
- Can be uncomfortable

**Venturi fixed performance mask**

- Constant O2 conc
- 24-40% accurate concs, 60%=50%
- Increased O2 flow for tachypnoeic patients
- Increasing flow does NOT increase concentration
Humified Oxygen

- Not routinely used
- Special circumstances: tracheostomy, CF, long-term high flow O2
- Flow meter = centre of ball indicates

Monitoring O2 therapy

- Start O2 & monitor saturations for 10mins
- Ensure target sats are met
- Monitor 4 hourly
- Mask escalator used
- No routine ABGs assessment needed when O2 has to be increased

Reducing O2 therapy

- Reduce O2 when sats higher than target
- Monitor for 10mins then record

Stopping O2 Therapy

- Stop when patient stable & sats within range on two consecutive readings
- Stop O2 & monitor for 10mins
- Remain off O2 if sats within range for 1hr on air
- Document after 1hr
- Cross of O2 chart

When O2 isn’t beneficial

- Adverse effects of O2
- Hypercapnia
- Formation of free radicals (cause ischemic damage/reperfusion injury)
- Coronary cerebral vasoconstriction aim for physiological oxygenation

Type II Respiratory Failure

- Hypoxaemic low PaO2
- Hypercapnic high PaCO2
- Acidotic low pH
- Inadequate alveolar ventilation: COPD, neuromuscular disease, chest wall deformities, obesity hyperventilation
- V/Q matching: hypoxic pulmonary vasoconstriction, respiratory drive (CO2, O2, pH

O2 in Type II Resp Failure Causes:

- Can increase V/Q mismatch
- Can decrease resp drive
- Increase hypercapnia leads to: acidosis nacrosis
- Target sats is 88-92%
- Avoid adverse effects of O2 therapy

O2 Therapy & Monitoring

- Venturi masks: 28% = 4l/min, 24% = 2l/min
- Initial ABG
- If not hypercapnic then target sats 94-98%
- Pulse oximetry
- Re-check ABG within 30-60mins

Patients with Previous Resp Acidosis

- Pre-specified target sats
- Oxygen alert card
- Patient notes
- Urgent ABG
- Don’t withhold oxygen to those who need it
- Only use O2 when necessary
- Careful with patients at risk of hypercapnia resp failure, monitoring is key

Asthma

- Target sats 94-98% or high conc if no sats
- Don’t withhold O2 in severe asthma for hypercapnia fears
- Nebulisers O2 driven 6 l/min

COPD

- Oxygen-driven nebuliser in COPD risks hypercapnic resp failure: air driven nebuliser used
- Taking O2 causes desaturation: nasal cannula should be in place
- Nasal cannula for O2 + mouthpiece for air-driven nebuliser

Acute Coronary Syndromes

- Only give O2 for hypoxaemic patients
- Monitor sats, target range 94-98%

Others

- Target sats might be adjusted e.g palliative patients
- Can be higher or lower
- Senior medical decision
Lecture 8: Anaemia

What is Anaemia?

- Reduced red cell mass = +/- reduced haemoglobin concentration
- Plasma volume
- Normal range: Male Hb = 13.1 – 16.6 g/dL, Female Hb = 11.0 – 14.7 g/dL

Consequences Anaemia

- Reduced O2 transport
- Tissue hypoxia
- Compensatory changes: Increase tissue perfusion, Increase O2 transfer to tissues, Increase red cell production

Pathological Consequences

- Myocardial fatty change
- Fatty change in liver
- Aggravate angina/claudication
- Skin and nail atrophic changes
- CNS cell death (Cortex and basal ganglia)
How to Clinically Approach Anaemia?

- Microcytic
- Normocytic
- Macrocytic
- Normal ranges: Males 81.8 – 96.3 fl, Females 80.0 – 98.1 fl

Microcytic Anaemia

- Iron deficiency
- Chronic disease
- Thalassaemia
- Rarely: Congenital sideroblastic anaemia, Lead poisoning

Investigating Iron Disease

- Tests of deficiency: Ferritin, Iron studies
- Tests of causes
- Treatment

Chronic Disease

- Clinical investigation
- Laboratory investigation
- Renal failure

Normocytic Anaemia

- Acute blood loss
- Anaemia of chronic disease
- Combined haematitic deficiency
Macrocytic Anaemia

- B12/folate deficiency
- Alcohol excess/liver disease
- Hypothyroid
- HAEMATOLOGICAL: Antimetabolite therapy, Haemolysis, Bone marrow failure, Bone marrow infiltration

Investigating B12 deficiency

- IF antibodies
- Schilling test
- Coeliac antibodies
- B12 replacement
- macrocytic anaemia needs haematology referral +/- bone marrow biopsy
- Combined haematic deficiency – malabsorption

What to do in Practice?

- Thorough history and examination
- FBC + film
- Reticulocyte count
- U/E’s, LFT’s, TSH
- B12, folate, ferritin

**Lecture 9: Red Cell Disorder**

**Heamoglobinopathies**

- Disorders of quality (abnormal molecule or variant haemoglobins) = Sickle cell disease
- Disorders of quantity (reduced production) = a or b thalassaemia
- Normal Hb 2xa, 2xb
- Foetal Hb 2xa, 2xg
- Haemoglobin S is variant haemoglobin arising because of a point mutation in the b globin gene.

**Sickle Cell Disorders**

- Carriers of HbS are symptom free
- Carriage offers protection against falciparum malaria
- Sickle cell diseases arise in the homozygous state (SS) or in combined heterozygotes (SC or Sb thalassaemia)
- Approx 15000 patients in UK
- Thiamine for adenine in 6th codon of b globin gene results in single amino acid change of valine for glutamine
Sickle cell: a multi-system disorder

<table>
<thead>
<tr>
<th>Table 2: Common Complications of Sickle Cell Disease</th>
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</thead>
<tbody>
<tr>
<td>• Occurring in Both Children and Adults</td>
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<tr>
<td>• Chronic hemolytic anemia</td>
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<tr>
<td>• Infections</td>
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<tr>
<td>• Painful crisis</td>
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<tr>
<td>• Splenic sequestration</td>
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<tr>
<td>• Acute chest syndrome</td>
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<tr>
<td>• Stroke (ischemic and hemorrhagic)</td>
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<tr>
<td>• Aplastic crisis</td>
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<tr>
<td>• More common or prevalent in adults</td>
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<tr>
<td>• Avascular necrosis</td>
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<tr>
<td>• Praptem</td>
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<tr>
<td>• Pulmonary arterial hypertension</td>
</tr>
<tr>
<td>• Sickle nephropathy</td>
</tr>
<tr>
<td>• Ocular disease</td>
</tr>
<tr>
<td>• Iron overload</td>
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<tr>
<td>• Leg ulcers</td>
</tr>
</tbody>
</table>

REDUCED LIFE EXPECTANCY ~ 50-60 YRS

Management of Sickle Cell

- Acute complications: Painful crisis, Sickle chest syndrome, Stroke
- Chronic complications: Renal impairment, Pulmonary hypertension, Joint damage
- Disease modifying treatment: Transfusion, Hydroxycarbamide, Stem cell transplant

Thalassemia

- Globin chain disorders resulting in diminished synthesis of one or more globin chains with consequent reduction in the haemoglobin
- Heterogeneous disorders of world-wide distribution
- Thalassaemia Major = Transfusion dependent
- Thalassaemia Intermedia = Less severe anaemia and can survive without regular blood transfusions
- Thalassaemia Carrier/heterozygote = Asymptomatic

b Thalassaemia Major

- Age at presentation: 6-12 months
- Clinical presentation with severe symptoms: failure to feed, listless, crying, pale
- Approx 1000 sufferers and ~220000 carriers
- Blood results: HB 40-70 g/l, MCV & MCH very low
- Blood film: large and small (irregular) very pale red cells, NRBC
- Hb F > 90% (neonatal sample)
- Ferritin normal
- Thalassemia major rare, genetic disease causes severe anaemia due to the inadequate production of hemoglobin.
- In absence of medical intervention, thalassemia results in death during childhood.
- Children who are afflicted with thalassemia major require lifelong blood transfusions if they are to grow and develop to adulthood.
- The unfortunate consequence of the transfusions is an inevitable progressive increase in body iron load. As there is no natural means for the body to eliminate the excessive iron, these patients inexorably develop a clinically worsening hemosiderosis.
- The excessive iron is deposited mainly in the liver and spleen, leading to liver fibrosis and cirrhosis.
- The excessive iron is also deposited in the endocrine glands and the heart, resulting in diabetes, heart failure and premature death. Death ultimately occurs, mainly due to cardiac hemosiderosis.

Management of Thalassaemia

- Treatment: Regular transfusion, Iron chelation, Endocrine supplementation (fertility), Bone health, Psychological support
- Monitoring: Ferritin, Cardiac and Liver MRI, Endocrine testing= (Gonadal function, Diabetes screening, Growth & puberty Vit D, Calcium, PTH, Thyroid), Dексa scanning

Alpha Thalassaemia

- Carriage very common
- Because of distribution of a0 thalassaemia significant a thal disease (HbH or Barts Hydrops) confined to Eastern Med and Far East

Membranopathies

- Autosomal dominant conditions
• Spherocytosis & elliptocytosis most common
• Deficiency of red cell membrane proteins caused by a variety of genetic lesions
• Neonatal jaundice
• Mild to moderate haemolytic anaemia with occasional exacerbations during infection
• Gallstones
• Folic acid and splenectomy in selected cases

Parovirus & Haemolytic Anaemias
• Common infection in children
• Occurs in epidemics
• “slapped cheek syndrome”
• Leads to decreased RBC production
• Dramatic Hb drop in patients who already have reduced red cell lifespan.

Enzymopathies
• Provides the fuel for the red cell
• Generates redox capacity to protect red cell
• Inherited enzyme deficiencies lead to shortened red cell lifespan from oxidative damage.
• G6PD deficiency and pyruvate kinase deficiency most common

Glucose 6 Phosphate Dehydrogenase Deficiency
• Caused by a wide variety of mutations within G6PD gene
• African, Middle Eastern, Mediterranean, S. Asian
• Most asymptomatic
• X linked but women may also be affected
• Diagnosed by screening test for NADPH
• Crises characterised by haemolysis, jaundice, anaemia.
• Precipitated by Broad beans, infection, drugs
• Usually self limiting
• Symptomatic patients rare.
• Important drug interactions: Primaquine, Sulphonamides, Nitrofurantoin, Quinolones, Dapsone

Summary
• Inherited abnormalities in structure/function of haemoglobin, red cell membrane and enzymatic pathways all lead to disease states.
• Carrier states may protect against malaria.
Sickle cell disease is the most common inherited disease in England (NHS Neonatal screening programme data) and remains a major worldwide public health issue.

**Lecture 10: Platelet Problems**

**Platelets**

- Anucleate cells = formed by fragmentation of megakaryocyte (MK) cytoplasm in bone marrow
- Important role in primary haemostasis
- Disc shape allows them to flow close to endothelium
- Life span 7-10 days
- Old platelets phagocytosed by splenic macrophages in red pulp

**Control of Platelet Production**

- Thrombopoietin (TPO): produced mainly by liver, Stimulates production of platelets by megakaryocytes, Binds to platelet and MK receptors, ↓ plts = less bound TPO = ↑ free TPO able to bind to MK = ↑ Plt prodn

**Platelet Physiology**

1. Following damage to endothelium:
   - Platelets adhere to endothelium via collagen and vWF
   - Binding of collagen stimulates cytoskeleton shape change and spreading
   - Activation causes = release of contents from platelet granules: ADP, fibrinogen, thrombin, Ca2+
   - Aggregation = cross-linking of activated platelets by fibrin
   - Activated platelets provide negatively charged phospholipid surface = allows coagulation factors to bind

![Platelet activation & role in primary haemostasis](image-url)
Specific Important Mechanisms

- Thromboxane A2 (TXA2) synthesized from Arachidonic acid in platelets: via cyclooxygenase (COX)-1, TXA2 induces platelet aggregation and vasoconstriction
- P2Y12 receptor: activated by ADP amplifies activation of platelets & helps activate Gp IIbIIIa integrin
- Gp IIbIIIa: receptor for fibrinogen and vWF aids platelet adherence and aggregation

Platelet Dysfunction Clinical Features

- Mucosal bleeding: Epistaxis, gum bleeding, menorrhagia
- Easy bruising
- Petechiae, purpura
- Traumatic haematomas (inc subdural)

Causes of Platelet Dysfunction

- Reduced platelet number: thrombocytopenia <150 x 10^9/l, Decreased production, increased consumption
- Normal numbers = (150-400 x 10^9/l) but reduced function, Medication (Aspirin, Clopidogrel, Tirofiban), Uraemia, von Willebrand disease, Congenital platelet dysfunction

Thrombocytopenia Decreased Production

- Congenital thrombocytopenia = Absent / reduced / malfunctioning megakaryocytes in BM
- Infiltration of bone marrow = Leukaemia, metastatic malignancy, lymphoma, myeloma, myelofibrosis
- Reduced production of TPO = Liver disease
1. Reduced platelet production by bone marrow:
   - Low B12 / folate
   - Reduced TPO
   - Medication: Methotrexate, chemotherapy
   - Toxins: e.g. ETOH
   - Infections: e.g. viral (e.g. HIV) TB
   - Aplastic anaemia

2. Dysfunctional production of platelets in BM
   - Myelodysplasia

Thrombocytopenia: Increased Destruction 1

   - Autoimmune: Primary immune thrombocytopenia (ITP), Secondary (e.g. CLL)
   - Hypersplenism: Portal hypertension, splenomegaly
   - Drug related immune destruction: E.g. Heparin induced thrombocytopenia

Thrombocytopenia: Increased Destruction 2

1. Consumption of platelets:
   - Disseminated intravascular coagulopathy (DIC)
   - Thrombotic thrombocytopenic purpura (TTP)
   - Haemolytic uraemic syndrome (HUS)
   - Haemolysis, elevated liver enzymes and low platelets (HELLP)
   - Major haemorrhage

Immune Thrombocytopenia

1. Primary:
   - May follow viral infection / immunisation esp in children
   - Antibodies (usually IgG) form to glycoproteins on platelets & MK
   - Antibodies opsonize platelets – increasing their removal by RES

2. Secondary:
   - Some malignancies, such as Chronic Lymphocytic Leukaemia (CLL)
   - Viruses e.g. HIV / Hep C

3. Investigations:
   - Any underlying cause?
   - Isolated thrombocytopenia (unless significant bleeding)

4. Treatment:
   - Immunosuppression e.g. steroids / IVIG
   - Rule out +/- treat underlying cause
   - If bleeding – give platelets - but will disappear quickly
   - Tranexamic acid good for mucosal bleeding
   - NOT if urinary tract bleeding (clot retention)
Disseminated Intravascular Coagulation

1. Investigations:
   - Underlying cause
   - Thrombocytopenia, prolonged PT and APTT, low fibrinogen, high d-dimers
   - +/- evidence of organ failure
2. Treatment:
   - Treat underlying cause
   - Supportive provision of platelets / FFP / Cryoprecipitate as needed

Thrombotic Thrombocytopenic Purpura

- Spontaneous platelet aggregation in microvasculature = Brain, kidney, heart
- Reduction in a protease enzyme – ADAMTS13 = Acquired TTP – due to antibodies against ADAMTS13, Failure to break down high molecular weight vWF multimers
- Consumption of platelets
- Microangiopathic haemolytic anaemia = Rbc fragments (schistocytes)
- Renal / CNS / cardiac impairment
- Fever
- Treatment: Urgent plasma exchange (replaces ADAMTS 13 and removes antibody), Immunosuppression (reduce antibody level), Do NOT give platelets –increases thrombosis

Heparin Induced Thrombocytopenia

- Development of an IgG antibody against complex formed between = Platelets (PF4) and Heparin
- IgG/PF4/heparin complexes bind to and activate platelets = Platelet consumption, Thrombosis (arterial or venous), skin necrosis
- Most at risk: After cardiac bypass surgery, Unfractionated heparin treatment
Usual presentation: Sharp fall in platelets 5-10 days after starting heparin treatment
- Life threatening – need to stop UFH / LMWH heparin immediately = Alternative anticoagulation (even if platelets low), Never re-expose patient to heparin

Platelet dysfunction without thrombocytopenia
- Antiplatelet medication
- Uraemia = Impaired platelet adhesion and aggregation
- von Willebrand disease = Impaired platelet adhesion and aggregation

Aspirin
- Irreversible inhibition of COX activity of prostaglandin H synthase-1
- TXA2 production: largely from platelet derived COX-1 therefore highly sensitive to aspirin

P2Y12 Receptor Inhibitors
1. Thienopyridines – irreversible P2Y12 antagonists
   - Clopidogrel: hepatic CYP2c19 conversion into active metabolite 2 step process
   - Prasugrel: single CYP step therefore faster transformation into active metabolite – more rapid onset of action. Greater risk of bleeding.
2. Non Thienopyridines
   - Ticagrelor: reversibly binding oral P2Y12 antagonist
   - Does not require metabolic conversion to an active form
   - Faster onset of action, relatively faster off set of anti-platelet effect (Bd dosing).

GP IIbIIIa inhibitors
- Tirofiban – non peptide tyrosine derivative, Rapid onset, rapid reversibility of antiplatelet effect

Summary
1. Platelets – highly active cells
   - Life cycle: BM - circulation – spleen
   - Production under influence of TPO
2. Dysfunction in platelet activity:
   - Too few around – thrombocytopenia
   - Decreased production
   - Increased consumption
3. Poor function
   - E.g. Medication

Lecture 11: Abnormal FBC

Practise result...

<table>
<thead>
<tr>
<th></th>
<th>Result</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>96</td>
<td>131-166</td>
</tr>
<tr>
<td>WBC</td>
<td>5.7</td>
<td>3.5-9.5</td>
</tr>
<tr>
<td>Plts</td>
<td>303</td>
<td>150-400</td>
</tr>
<tr>
<td>MCV</td>
<td>72.0</td>
<td>81.8-96.3</td>
</tr>
</tbody>
</table>

Not enough red blood cells that are too small

‘Microcytic anaemia’

Polycythaemia
- Too many red blood cells
- Causes: Reactive/Secondary, Smoking, Lung disease, Cyanotic heart disease, Altitude, Epo/Androgen excess
- Primary/Proliferative: Polycythaemia Rubra Vera (PRV)

PRV
- Myeloproliferative disorder
- ‘overactive bone marrow’
- Predominantly Red cells
- Also WBC’s and Plts
- JAK2 mutation 95%
- Clinical Presentation: Plethoric appearance, Thrombosis, Itching, Splenomegaly, Abnormal FBC
Treatment: Aspirin, Venesection, Bone marrow suppressive drugs (e.g. Hydroxycarbamide)

Neutrophilia
- Too many WBCs
- Causes: Reactive, Infection, Inflammation, Malignancy
- Primary: CML

Lymphocytosis
- Too many WBCs
- Causes: Reactive, Infection, Inflammation, Malignancy
- Primary: CLL

Thrombocytopenia
- Not enough platelets

Thrombocytosis
- Too many platelets
- Reactive, Infection, Inflammation, Malignancy
- Primary: Essential Trombocythaemia

Neutropenia
- Not enough neutrophils
- Normal 1.7 – 6.5
- Mild 1.0 – 1.7
- Moderate 0.5 – 1.0
- Severe <0.5
- Severe neutropaenia major infection risk
- Causes: Underproduction, Marrow failure, Marrow infiltration
- Marrow toxicity e.g. drugs
- Increased removal: Autoimmune, Felty’s syndrome, Cyclical

Lecture 12: Haematological Emergencies
What are Neutrophils?
- Most numerous white cell in the adult circulation (50-70%)
- Live around 5 days once made
- Are part of the innate immune system
- Part of the first line of defence of any pathogens which make it into your blood
- Can phagocytose foreign substances on site
Can release antimicrobial proteins out of their granules
- Release cytokines, start inflammatory response and attract other cells to site of infection
- First on the scene at site of infection
- Very motile, will migrate to site rapidly
- Will initiate a lot of the immune response to an infection
- Without them pathogens could have free reign
- Have an "if in doubt, eat it"
- Lymphocytes have to go away and have a think before fully acting (adaptive immune system).

Causes of Neutropenia?
- Neutropenia = count < 1.0
- Decreased production - bone marrow problem
- Acute leukaemia/Myelodysplastic syndrome
- Aplastic anaemia
- Marrow infiltration of any cause
- B12/folate deficiency
- Medictions = Methotrexate/carbimazole/clozapine
- Increased destruction: Autoimmune destruction
- Cytotoxics

Chemotherapy Induced Therapy
- Chemotherapy targets all cells in the body active in the cell cycle
- Does not discriminate between normal cells and cancer cells
- Bone marrow has a large number of cells in cell cycle—all stopped by chemotherapy: Anaemia, Thrombocytopenia, Neutropenia
- Mucosal barriers also all damaged which further inhibits the innate immune system

Features of Neutropenic Sepsis
- NICE: Neutrophil count < 1.0 + temperature > 38°C = neutropenic sepsis
- Not always straightforward
- Without neutrophils may not mount an inflammatory response
- May not get a temperature/rigors or typical features you would expect in infections
- Even though it can be not overt in its presentation immediate treatment is vital
- Can be rapidly fatal—even in the young and fit

Suspecting Neutropenic Sepsis & Steps to Take
• If anyone has had chemotherapy in the last 3 months
• Presents with a fever
• Feeling generally unwell/off
• Presents with isolated hypotension
• Patients on chemotherapy usually well educated and monitor their own temperature, will self refer if feeling unwell
  1. Cannula - from that take blood cultures, FBC, UE, LFT, CRP, Glucose, Lactate
  2. Broad spectrum antibiotic
  3. If any haemodynamic compromise, fluid challenge + senior review/HDU review

Early Management

• First dose of antibiotics is very important
• Don’t hang around, if in doubt then give antibiotics
• No one has died from a single unnecessary dose of Tazocin, lots have of neutropenic sepsis
• Take rest of history/examination once you have given the antibiotics
• Don’t wait for the FBC result. If not neutropenic, antibiotics can be changed later

Sickle Cell Disease

• Substitution of thymine for adenine in the 6th codon for Beta-chain gene
• Valine instead of Glutamate in Hb beta chain
• This is HbS
• Under deoxygenation becomes less soluble
• Gradual polymer formation each time the cell becomes deoxygenated
• Leads to sickling of the cell

Vaso-occlusive Crisis

• Much more complex than sickled cells getting lodged in microvascular system
• Complex interactions between sickle cells, vascular endothelium and white cells
• Occlusion of microvascular bed and tissue ischaemia
• Regional areas of hypoxaemia, acidosis which can occur in the bone
• Leads to increased intra-medullary pressure and necrosis in the bone which is agonising
Features

- Usually precipitated by either dehydration/cold weather/infection
- Gradual onset over 2-3 days of pain which patients often try to manage at home
- Eventually unbearable pain (10/10) = Arms/hands/legs, Back, Ribs/chest, Abdomen. Patients often have a typical site of pain

Worrying Symptoms

- Chest pain, could be chest crisis/PE/ACS
- Severe abdominal pain, can be difficult to distinguish from acute abdomen
- Any neurological symptoms, these patients are at high risk of stroke

Clinical Features

- Often Pyrexial-inflammatory process
- After several days can find swelling at joints-avascular necrosis
- Worrying clinical features: Hypoxia-chest crisis/PE, ECG changes, Neurological signs

Initial Investigations

- Bloods = FBC, UE, LFT, G+S (let blood bank know is sickle pt), blood cultures if pyrexial, Reticulocyte count (consider parvovirus if low)
- CXR if chest pain/desaturation
- Urinalysis for protein
- CT head if any neurological symptoms
- ECG if chest pain

Steps to Take

1. Priority 1 (after ABC):
PAIN CONTROL
- Paracetamol
- Ibuprofen/diclofenac
- Pregabalin
- Regular short acting opioids-oxynorm/fentanyl PO/SC/nasal
- Avoid IV opioids such as diamorphine
- Aim to get pain score <5/10

2. Priority 2-Slow process:
- IV fluids
- Keep warm
- Monitor for complications and for need for exchange transfusion

Acute Chest Syndrome
- Can arise a few days into an acute painful crisis
- Process is driven by a combination of events including bone marrow infarction and embolism to the lung
- This leads to lung infarction
- Sickling in the lung also can cause infarction
- Sometimes co-existing infection, this can be driven by hypoventilation due to pain/opiates

Features
- ACS defined by a combination of:
  1. ANY new pulmonary infiltrate on CxR
  2. New symptoms of SOB, fever, hypoxia, sputum production
- Be suspicious in any sickle patient in crisis who needs oxygen
- Can be rapidly fatal, need close monitoring and potential exchange transfusion

Steps to Take
- ABC approach
- Iv fluids
- Iv antibiotics as per LRTI
- Early HDU review if oxygen requirements are increasing
- If increasing O2 requirements, exchange transfusion
- Give blood bank plenty of warning, can be difficult to find suitable blood for sickle patients-G+S on admission

Multiple Myeloma
- Malignancy caused by uncontrolled expansion of plasma cells in the bone marrow
- Plasma cells normally make immunoglobulins
- In myeloma, they make one type of exactly the same useless immunoglobulin=monoclonal
- Malignant plasma cells also promote osteoclast activation leading to bone reabsorption, leading to lytic lesions

**Spinal Cord Compression**

- Can occur in any malignancy due to metastases and destabilisation of the spine
- Myeloma patients are particularly prone to this due to the nature of plasma cells
- Can also be caused by plasmacytomas (a lump of plasma cells outside the bone marrow) which can press on the spinal cord
- Rapid recognition and treatment is key to try preserve neurological function

**Features**

- Back pain—radiation to both legs
- Leg weakness/numbness
- Saddle anaesthesia
- Sphincter disturbance
- Suspicious in elderly patient “off legs” even in absence of back pain
- O/E—weak legs, decreased sensation, reflexes may be absent, unlikely to be brisk/traditional UMN signs

**Steps to Take**

- Keep the patient in bed
- Give high dose steroids
- Dexamethasone, 8mg BD With proton pump inhibitor such as omeprazole
- Organise urgent MRI—same day if possible, if any delay continue the steroids until the scan
- Make sure the patient doesn’t have other myeloma complications—check FBC, UE, Calcium

**Confirmed SCC**

1. Surgical vs medical management
2. Surgical:
   - Usually speak to the spinal surgeons first as surgery is quickest way to release compression
   - Usually reluctant unless single point compression or spinal instability
3. Medical:
• Once established not for surgery, discuss with oncologists for urgent radiotherapy
• Plasmacytomas are usually very radiosensitive
• Continue steroids-wean over a week
• Treat the myeloma with chemotherapy

Hyperviscosity Syndrome

• Malignant plasma cells can churn out a lot of immunoglobulin
• This protein will literally increase the thickness of your blood
• The bigger the immunoglobulin, the less you need to get the syndrome = IgM > IgA > IgG
• Leads to reduced blood flow through capillaries and organ congestion
• Also can rarely be seen in polycythaemia rubra vera and Waldenstroms Macroglobulinaemia

Symptoms

• Often non-specific symptoms
• Headaches
• Neurological symptoms—vertigo, hearing loss, ataxia, paraesthesia, seizures
• Blurred vision
• Fatigue
• Mucosal bleeding
• Confusion/altered mental state/decreased GCS
• Shortness of breath, hypoxia, evidence of heart failure

Examination

1. General:
   • Bruising
   • Epistaxis
2. Cardiovascular:
   • Pulmonary oedema
   • Evidence of fluid overload
3. Neurological:
   • Decreased GCS
   • Confusion
   • Ataxia
   • Nystagmus

Investigations

• FBC, UE, Calcium
• Immunoglobulins—result may take a while to come back
LFT-check globulin levels (or if not present take away albumin from total protein=Globulin gap)
- Plasma viscosity (>2)
- Don’t depend on the PV

Steps to Take

1. Hydrate the patient-decent access+IV fluids
2. Avoid giving blood transfusions
3. Treat the underlying cause-will be led by seniors however if the patient is known to have myeloma,a big dose of steroids (eg dexamethasone 20mg)may help-discuss with haematologist
4. May consider plasma exchange, though this is a holding measure while the underlying cause is treated

Summary

- Suspected neutropenic sepsis= ANTIBIOTICS IMMEDIATELY
- Acute sickle crisis= get the pain controlled and give IV fluids
- Chest Crisis= IV fluids, antibiotics, close monitor, think about HDU
- Spinal cord compression= Steroids, MRI, discuss with surgeons
- Hyperviscosity= IV fluids, avoid blood transfusion, discuss with haematologist

Formative Assessment: Haematology

1. What is the characteristic genetic abnormality in Chronic Myeloid Leukaemia?

   - t(15;17) ATRA gene
   - **t(9;22) Philadelphia chromosome**
   - t(8;21) AML/ETO gene
   - t(8;14) cMYC oncogene

Chronic Myeloid Leukaemia

- Usually 40-60yrs age
- Slow onset
- Sometimes incidental finding
- High WCC
- Splenomegaly
- Metabolic features
- Key diagnostic feature Philadelphia Chromosome
- t(9;22)
- Resulting in 210-kDa fusion protein –activated tyrosine kinase
- Imatinib (Glivec or STI571)= Blocks abnormal tyrosine kinase activity, Can result in molecular remission, BCR-ABL mutations may result in resistance
2. What class of drug best describes Rituximab?

Cytotoxic chemotherapy  
Disease-modifying therapy  
**Monoclonal antibody**  
Antibiotic

Rituximab

- Monoclonal antibody
- Targets CD20 expressed on cell surface of B-cells
- Chimeric mouse/human protein
- Infusional side-effects
- Widely used

3. Which age group is characteristically affected by Hodgkin’s lymphoma?

Children  
**Teenagers and young adults**

Middle aged (40-60 yrs)  
Older aged (>60 yrs)

4. How myeloma bone disease is usually assessed?

**Plain X-ray**

Clinical assessment  
Isotope bone scan  
PET scan

Myeloma

- Skeletal survey  
- Production of Osteoclast-activating factors  
- OAFs include RANKL, IL-3 and TNF-α

5. What is the correct mechanism of action for the anti-emetic drug Ondansetron?

Peripheral D2 antagonist  
Central D2 antagonist  
Anti-cholinergic  
**5HT3 antagonist**
Anti Emetics

- Select drug for Mechanism of action
- E.g. 5HT3 antagonist for chemo induced
- Pro-kinetics for gastostasis
- Centrally acting for drug induced

6. What is the commonest cause of microcytic anaemia?

B12 deficiency

**Iron deficiency**

Haematologic malignancy
Hereditary spherocytosis

Microcytic Anaemia

- Iron deficiency
- Chronic disease
- Thalassaemia
- Rarely= Congenital sideroblastic anaemia, Lead poisoning

Normocytic Anaemia

- Acute blood loss
- Anaemia of chronic disease
- Combined haematinic deficiency

Macrocytic Anaemia

- B12/folate deficiency
- Alcohol excess/liver disease
- Hypothyroid
- **HAEMATOLOGICAL**= Antimetabolite therapy, Haemolysis, Bone marrow failure, Bone marrow infiltration

7. In sickle cell anaemia what would you expect to see the reticulocyte count?

Absent
Low
Normal
**Raised**

SCA

- Chronic Haemolytic anaemia
• Reticulocyte response
• Film appearances
• Effect on MCV
• Marrow function

8. Bacterial infection usually causes?

Low lymphocyte count
Low neutrophil count
High lymphocyte count

**High neutrophil count**

9. Which best outlines the approach to the management of a patient with suspected febrile neutropaenia?

Encourage fluids and paracetamol
Perform cultures and wait for results before starting antibiotics
Perform cultures and start oral antibiotics

**Perform cultures and start broad spectrum iv antibiotics**

Febrile Neutropaenia

• Haematologic emergency
• ABC
• Perform cultures
• Broad spectrum iv Abs with 1 hour= E.g. Tazosin and Gentamicin

10. Malignant spinal cord compression usually presents with?

Back pain, ataxia and sensory neuropathy
**Back pain, spastic paresis and a sensory level**
Perianal numbness and urinary incontinence
Weak legs impaired joint position sense

Malignant SSC

• Emergency
• Urgent MRI
• Bed rest + pressure area care
• Steroids
• Analgesia
• Chemo or Radiotherapy

11. How does Aspirin exert its antiplatelet effect?
ADP receptor antagonist

**Inhibition of Cyclooxygenase enzyme**

Inhibition of Glycoprotein IIb-IIIa
Inhibition of PAR4 receptor