Learning Objectives

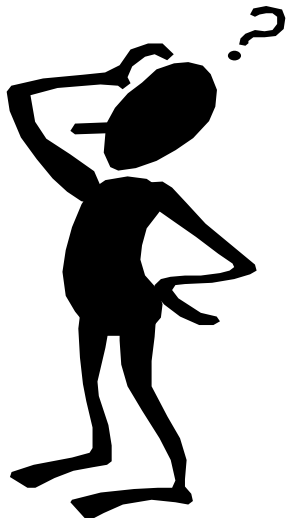
- At the end of this session participants are expected to be able to:
  - Describe sickle cell disease and types of sickle cell anaemia
  - Describe epidemiology, risk factors and pathogenesis of sickle cell disease
  - Recognize clinical presentation of sickle cell disease
  - Perform clinical and laboratory assessment of patients with sickle cell disease

Learning Objectives (2)

- Provide pharmacological and nonpharmacological treatment to patients with sickle cell disease
- Implement referral pathway for patients with sickle cell disease
- Conduct regular follow up monitoring to patients with sickle cell

Activity: Brainstorming

- What is Sickle Cell Disease?
- What are the types of sickle cell disease?



Definition of Sickle Cell Disease

- **Sickle cell anemia** is a genetic disorder whereby red blood cells are abnormally shaped, causing problems with the flow of blood through the body as well as transport of oxygen throughout the body
- SCD is one of the disorders in a broad group of hemoglobinopathies

Definition of Sickle Cell Disease (2)

- **Sickle cell anemia** is an inherited disorder of hemoglobin associated with abnormally shaped red blood cells, causing problems with the flow of blood through the body and the resulting transport of oxygen throughout the body

Hemoglobinopathie

- **Hemoglobinopathies**- inherited/genetic disorders that results into abnormal production of one of the globin chains that forms the hemoglobin
- In SCD, the beta chain is affected by a mutation that results into a formation of an abnormal hb called **HbS**
- NB: HbS formed by a point mutation, in which **glutamic acid** is substituted with **valine** at position 6 in the beta hb chain gene

Normal Human Hemoglobin

- Normally human have the following types of hb;-
  - HbA- 2alpha +2beta chains
  - HbA2- 2alpha + 2 delta chains
  - HbF- 2alpha + 2gamma chains

Normal Human Hemoglobin (2)

- HbF normally predominates in the first year of life
- After that HbA predominates (96%), with HbA2 making about 2-3%
- Simply presence of HbS makes the disorder so called Sickle Cell Disease

Types of Sickle Cell Disease

- The following are types of SCD:
- **Sickle Cell Anemia**
  - Homozygous form, in which both hemoglobin are HbS ie. (**HbS, HbS**)
  - Severest form

Types of Sickle Cell Disease (2)

The following are types of Sickle Cell Disease

- **Sickle Cell Trait**
  - Heterozygous with half of hb being normal and half being sickle hb ie. (**HbS, HbA**)
  - No symptoms unless under low oxygen tension

Types of Sickle Cell Disease (3)

- **Sickle cell beta thalathemias**
  - Heterozygous form but with the concentration normal hb being higher than sickle hb. Mild form

Types of Sickle Cell Disease (4)

- **Hemoglobin S-C** disease
  - There is no normal hemoglobin
  - Its form is **HbS, HbC**
  - Similar presentation to Sickle Cell Anemia except
  - mild and less frequent
  - **2nd most** common type SCD
  - Similar mutation forms HbC except **Glutamic acid** is substituted by **Lysine**

Epidemiology

- Sickle gene originates from **Africa** and **India**
- its now spreading worldwide (1 per 625 live births in America, Medscape)
- Highest incidence are found in Subsaharan Africa, India and Middle East
- Median age to acquire **renal failure** is **23.1** years and life expectancy is **27 years** regardless of dialysis (medscape) ie. SCA

Pathogenesis

- SCD is caused by a point mutation at position 6 of the beta haemoglobin gene in which a hydrophilic glutamic acid is replaced by valine
- The susceptible RBCs once subjected to an oxygen tension of **<40mmHg** for about **2-4 minutes** they become deoxygenated

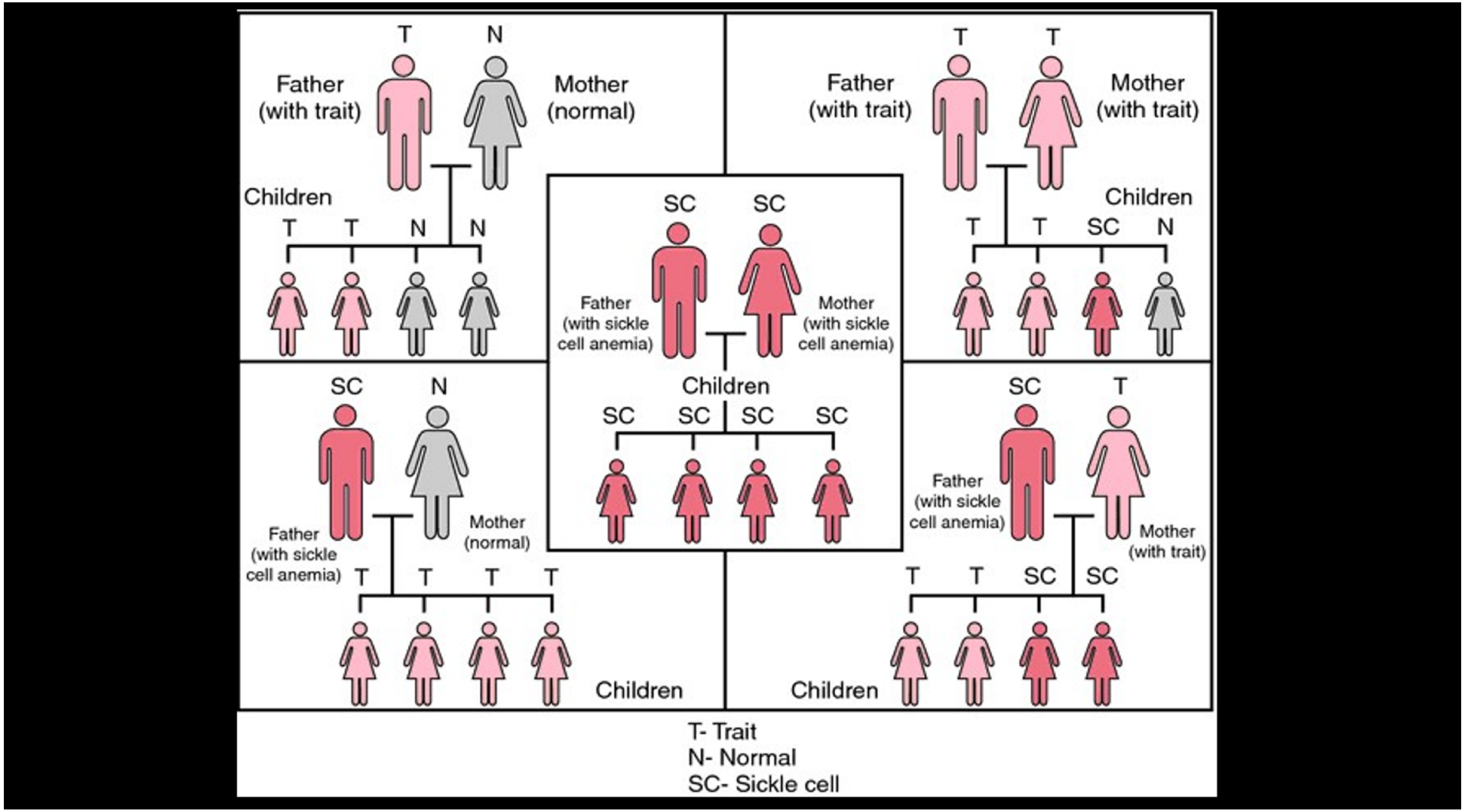
Pathogenesis (2)

- Deoxygenated haemoglobin undergoes **hydrophobic** interaction with adjacent sickle haemoglobin forming **large polymer** and thus RBC becomes less **deformable** and acquire **sickle shape**
- Rigid RBCs obstruct **microvasculature** causing tissue hypoxia which precipitates further sickling

Pathogenesis (3)

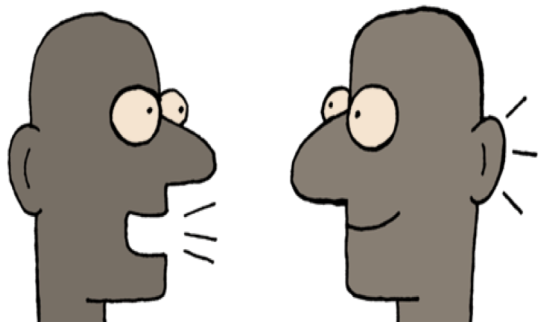
- Sickle cells rapidly haemolyze and have a life span of about **10- 20 days**
- The initiation of polymerization may be incomplete and reversible if **re-oxygenation** occurs early in the process
- Repetitive exposure to alternating deoxygenated and oxygenated states can lead to membrane distortion, oxidative damage and **irreversible sickling**

Sickle Cell Trait



Activity: Buzzing

What is the clinical presentation of sickle cell disease?



Clinical Manifestation of Sickle Cell Disease

- Chief cause for admission of patients is Sickle cell crises
- This includes the following:
  - Vaso-occlusive crisis
    - Pain Crisis
    - Splenic sequestration
    - Acute Chest Syndrome
    - Aplastic Crisis
    - Hemolytic Crisis

Clinical Manifestation of Sickle Cell Disease (2)

- The most common clinical manifestation is pain, which occurs unpredictably and is often excruciating
- Acute manifestations that may rapidly become life-threatening include bacterial sepsis or severe anaemia, acute chest syndrome, and stroke
- Other acute complications include aplastic crises and priapism

Factors that can Precipitate SC crises

- Infections
- Low oxygen tension
- Concomitant medical conditions (e.g., sarcoidosis, diabetes mellitus, herpes)
- Dehydration
- Acidosis
- Extreme physical exercise

Factors that can Precipitate SC crises (2)

- Physical or psychologic stress
- Alcohol
- Pregnancy
- Cold weather

Vaso-oclusive Crises

- Due to obstruction of microvasculature by rigid sickle cells
- **Painful crises**- can affect any part but is chiefly experienced in the **abdomen, bones, joints and soft tissues**

Vaso-oclusive Crises (2)

- Starts suddenly, very severe, and it may last for several hours
- Commonly **long bones** are affected, but in the 1st 18 months can involve metatarsals and metacarpals causing **dactylitis** (painfull swelling hands and feet)

Vaso-oclusive Crises (3)

- Splenic sequestration
  - When vasooclusion occurs in the spleen, the micro vessels blocked and blood accumulates in the spleen
  - Causes rapid enlargement and it's a life threatening medical condition
  - Common in the first five years of life and may cause splenic infarction (autosplenism) at the end of childhood

Vaso-oclusive Crises (3)

- **Splenic sequestration**
  - Sequestration causes worsening of baseline anemia and increase risk of infection by encapsulated organism
  - This includes **H. influenza, S. pneumoniae, S. typhi and N. meningitidis**

Vaso-oclusive Crises (4)

- **Acute chest syndrome**
  - Commonly characterized by **chest pain, fever, cough, tachypnea, pulmonary infiltrates, hypoxemia**
  - **Medical emergency** is commonly precipitated by chest infections in children

Aplastic Crisis

- Worsening of baseline anemia due to infection of **parvovirus B-19**
- This is **single stranded RNA virus** that is acquired by **respiratory droplets** and a special philia for erythrocytes progenitor
- Thus, switches off RBC production and causes drastic drop of reticulocyte counts

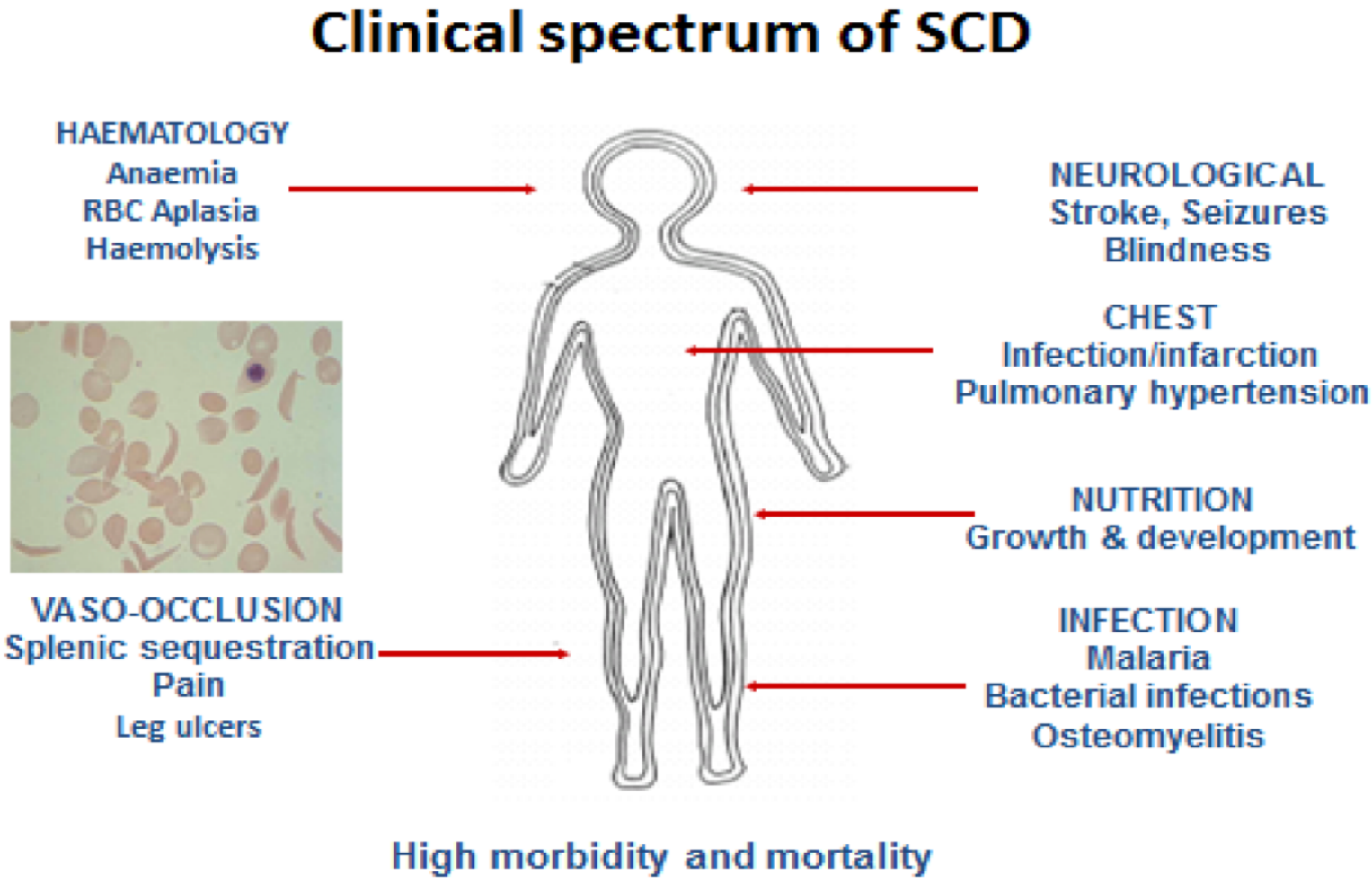
Hemolytic Crisis

- Accelerated breakdown of RBC that occurs with co-existence of **G6PD deficiency**
- **G6PD** is a **recessive X linked disorder** that results to deficiency of the enzyme reqiured for formation **glutathione** in **PP pathway**
- Glutathione is required for clearing **free radicals** to prevent **oxidative damage**

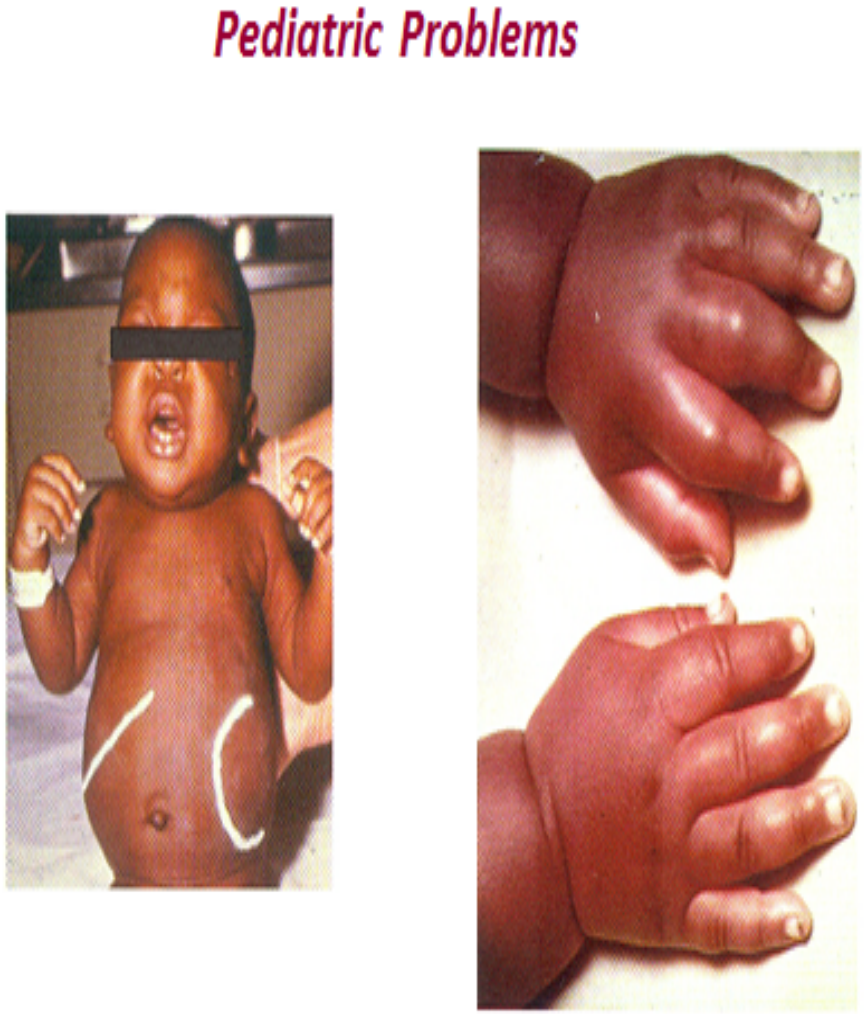
Chronic Manifestations

- Include anaemia, jaundice, splenomegaly, renal disease, Cholelithiasis and delayed growth and sexual maturation
- Avascular necrosis of the hip and shoulder and leg ulcers may cause chronic disability

Clinical Spectrum of SCD



Pediatric Problems



- All children presenting with unexplained acute illness
  - Including acute pain in any part of the body, anaemia, and acute neurological symptoms, loss of vision, collapse, respiratory symptoms, hepatosplenomegaly, jaundice, swollen limbs, family history of SCD and sepsis should be tested for SCD

Diagnosis

Screening Tests	Point of Care (POC) tests	Confirmatory tests
Sickling Test (non-diagnostic): All positive sickling test must be confirmed by the approved point of care tests.	• Sickle SCAN® • Hemotype SC™ • Gazelle	• Hemoglobin Electrophoresis • Iso-Electric Focusing (IEF) • High-Performance Liquid Chromatography (HPLC).

Clinical

- Attacks are diagnosed clinically, i.e. there is no gold standard diagnostic test
- Hemolysis (anemia and jaundice) is often present, although for painful crises the diagnosis depends essentially on how the patient describes the pain

Lab Investigation

- **For Screening, Diagnosis and Confirmation**
  - Sickling test (Hemoglobin S solubility test and sodium metabisulfite test), not for infants. Useful after 6 month from birth
  - Newborn Screening: HPLC fractionation (High performance liquid Chromatography) and thin Layer/Isoeletric focusing

Lab Investigation (2)

- Abnormal hemoglobin forms are detected on hemoglobin electrophoresis a form of gel electrophoresis on which the various types of hemoglobin move at varying speed
- Sickle cell hemoglobin (HbSS) and Hemoglobin C with sickling (HbSC) the two most common forms can be identified from there

Lab Investigation (3)

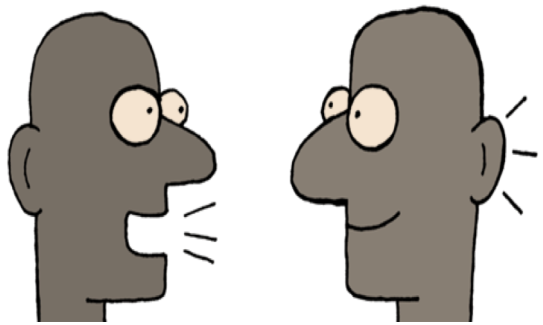
- DNA analysis
- Other tests that may be used to help evaluate someone who is suspected of having or who is known to have sickle cell trait or disease include:
- Complete blood Count (CBC)
  - Blood Smear
  - Iron Studies
  - LFT
  - RFT

Lab Investigation (4)

- Electrolytes
- Chest X-ray in Acute Chest Syndrome
- Trans-Cranial Doppler Ultrasound (TCD),MRI (with or without angiography) and Neuro-psychometric studies (NPM)

Activity: Buzzing

What is the treatment of sickle cell disease?



Pharmacological Treatment

- **Febrile illness**
  - Children with fever are screened for bacteraemia i.e. complete blood count, reticulocyte count and blood culture taken
  - Younger children (varies from center to center) are admitted for intravenous antibiotics while older children with reassuring white cell counts are managed at home with oral antibiotics
  - Children with previous bacteraemic episodes should be admitted

Pharmacological Treatment (2)

Painful (vaso-occlusive) crises

- Most patients with sickle cell disease have intensely painful episodes called vasoocclusive crises
- Painful crises are treated symptomatically with analgesics; pain management requires opioid administration at regular intervals until the crisis has settled

Pharmacological Treatment (3)

Painful (vaso-occlusive) crises

- For milder crises a subgroup of patients are managed by NSAIDs (such as diclofenac or naproxen)
- For more severe crises most patients require inpatient management for intravenous opioids; patient-controlled analgesia (PCA) “not applicable in our setting” devices are commonly used in this setting

Pharmacological Treatment (4)

Painful (vaso-occlusive) crises

- Diphenhydramine is effective for the itching associated with the opioid use
- NB: analgesia, Oxygen, hydration and warmth

Pharmacological Treatment (5)

Acute chest crises

- Management is similar to vaso-occlusive crises with the addition of antibiotics (usually a quinolone or macrolide)
- When the pulmonary infiltrates worsen or the oxygen requirement increases, simple blood transfusion or exchange transfusion is indicated

Pharmacological Treatment (6)

Acute chest crises

- Exchange transfusion involves the exchange of a significant portion of the patients red cell mass for normal red cells, which decreases the percent hemoglobin S in the patient's blood

Hydroxyurea

- The first approved drug for the causative treatment of sickle cell anemia

Pharmacological Treatment (7)

- Hydroxyurea had previously been used as a chemotherapy agent, and there is some concern that long-term use may be harmful
  - it is likely that the benefits outweigh the risk
- **Splenic Sequestration Crisis**
  - Treatment includes early intervention and maintenance of hemodynamic stability using isotonic fluid or blood transfusions.

Pharmacological Treatment (8)

- **Splenic Sequestration Crisis**
  - Careful blood transfusions with red blood cells are recommended to treat both the sequestration and the resultant anemia
  - Blood transfusion aborts the red blood cell sickling in the spleen and allows release of the patient's blood cells that have become sequestered, often raising the hemoglobin above baseline values

Pharmacological Treatment (9)

- Typically recommend only 5 mL/kg of red blood cells because the goal is to prevent hypovolemia
- Blood transfusion that results in hemoglobin levels above 10 g/dL may put the patient at risk for hyperviscosity syndrome because of the risk that that patient may release the blood within the spleen
- If there is recurrent episode Prophylactic splenectomy is the only choice for preventing future life threating episode.

Pharmacological Treatment (10)

Priapism

- The optimal treatment for acute priapism is unknown. Acutely, supportive therapy, such as a hot shower, short aerobic exercise, or pain medication, is commonly used by patients at home
- Urology consultation is required to initiate this procedure, with appropriate input from a hematologist

Pharmacological Treatment (11)

Priapism

- A prolonged episode lasting >4 hrs should be treated by aspiration of blood from the corpora cavernosa followed by irrigation with dilute epinephrine to produce immediate and sustained detumescence

Pharmacological Treatment (12)

- **Penicillin prophylaxis**
  - The most important intervention in the routine management of children with SCD is penicillin prophylaxis to prevent pneumococcal infection, which justifies newborn screening
  - Penicillin is given twice daily from as 2months of age

Pharmacological Treatment (13)

- Children with SCD-SS are given Penicillin VK: 125mg by mouth twice daily for those under 3yrs of age and 250mg twice daily for those 3 and older
- An alternative to oral penicillin is an injection IM of 1.2 million units of long acting Bicillin (Penicillin G Benzathine) every 3 weeks

Routine Medications for SCD

Drug	Dose: Adult	Dose: Child
Penicillin V	Not given	<1yr: 62.5mg BD 1-3yrs: 125mg BD >3yrs: 250mg > 5yrs: not usually given as prophylaxis
Folic acid	5mg or 1mg as available OD	<1yr: 1.25mg OD 1-3yrs: 2.5mg OD >3yrs: 5mg OD
Analgesia 2-week supply for PRN use	Paracetamol 1g QDS, Ibuprofen 400mg QDS	Paracetamol 15mg/kg QDS, Ibuprofen 5mg/kg TDS
Ferrous sulphate if MCH<25pg	200mg TDS	2mg/kg TDS for 6 weeks, then check Hb level and ferritin.
Mebendazole after every 3 months	200mg 400mg stat dose	1-2years 2years
Malaria prophylaxis	Low transmission Use insecticide treated nets Prompt diagnosis and treatment	

Pain Management

- Pain is the commonest acute complication in SCD
- Mild to Moderate Pain
- Use oral analgesics Paracetamol, Ibuprofen or diclofenac
- Encourage excessive oral fluids intake

Pain Management (2)

- DO NOT GIVE ANALGESICS PRN But rather regularly as recommended in treatment manual
- Severe Pain
- Use Morphine PO 0.2mg – 0.5mg/Kg every 4hrs
- Give IV fluids (ref Treatment manual)

Hydration

- **Hydration**
  - Patients with SCD are at risk of dehydration due to impaired renal concentrating power and poor fluid intake
  - **Encourage oral fluids first, it should be used whenever possible**
  - **Give IV fluids** if the patient is unable to drink well, has severe pain, abdominal symptoms, or is not settling

Hydration (2)

- **Hydration**
  - Hydrate with 150% of the normal daily fluid intake
  - Use fluids recommended in pediatrics IV therapy guidelines, usually 5% Dextrose + 0.45% saline (review need for added potassium)
  - **Stop IV fluids** when the patient is stable and pain is controlled
  - Maintain a strict input/output chart for every patient
  - For children, weigh them daily

Fluid Calculations

Body weight (kg)	Fluids (ml/kg/day)
<10 kg	150ml/kg/day
11 – 20kg	75ml/kg/day for every kilogram above 10kg ADDED TO 1500ml for the first 10kg of weight
> 20kg	30ml/kg for every kilogram above 20kg ADDED TO 225OML for the first 20kg of weight
Divide the total daily volume by 24 hours to obtain hourly fluid rate	

Prevention of Complications

- The following measures are recommended for prevention of acute complications
  - Early diagnosis and treatment
  - Provision of routine medications such as Folic acid, Penicillin V
  - Health diet
  - Routine deworming

Prevention of Complications (2)

- The following measures are recommended for prevention of acute complications
  - Adherence to routine methods of malaria prevention
  - Adequate hydration
  - Avoid extremes of temperatures
  - Avoid stressful environment

Prevention of Complications (3)

- The following measures are recommended for prevention of acute complications
  - Avoid demanding physical activity
  - Avoid emotional stress (or learn how to better cope with it)
  - Avoid tobacco and alcohol use
  - Attending routine SCD clinics

Non-Pharmacological Treatment

- **Counselling**
  - SCA counseling has two components education and decision-making
  - Reproductive Counselling:
    - Provide educational and health promotion counseling to all women and men of childbearing age to reduce reproductive risk and improve pregnancy outcomes

Non-Pharmacological Treatment (2)

- **Counselling**
  - If the partner of a man or woman with SCD has unknown SCD status refer the partner for SCD screening
  - After testing, refer couples who are at risk for having a potentially affected fetus and neonate for genetic counseling

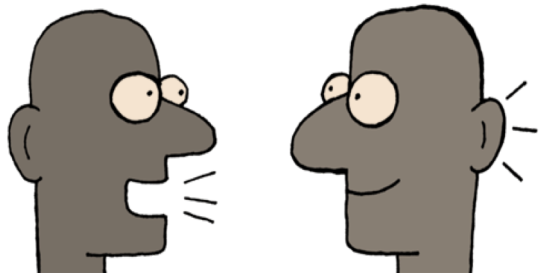
Non Pharmacological Treatment (3)

Counselling

- In women with SCD, regular use of contraception can decrease the health risks associated with unintended pregnancy

Buzzing

- How do you refer patient with sickle cell for further management?



Referral Pathway for Patients with Sickle Cell Disease

- Give first aid and immediately refer all patients with features suggestive of severe acute complications of SCD
- Advise all patients to do annual screening for chronic complications of SCD at district/regional hospital
- Give first aid

Referral Pathway for Patients with Sickle Cell Disease (2)

- Give first aid:
  - Analgesics
  - Fluid
  - Antibiotic

Referral Pathway for Patients with Sickle Cell Disease (3)

- Refer immediately : Delay may cause more harm
- Refer all patients with features suggestive of :
  - Severe anemia
  - Acute chest syndrome
  - Stroke
  - Priapism and septicemia

Brainstorming

How do you follow up and monitor a child with sickle cell disease?

Follow up Patients with Sickle Cell Disease

- Take history
- Full and thorough Examination
- Blood tests: at each visit (already said visits are yearly for older well children
- Provide / Organise / Prescribe / Check
- Follow-up appointment to be booked

Key Points

- **Sickle cell anemia** is a genetic disorder whereby red blood cells are abnormally shaped, causing problems with the flow of blood through the body as well as transport of oxygen throughout the body

Key Points (2)

- Clinical presentation of Sickle cell crises includes the following:
  - Vaso-occlusive crisis
  - Aplastic Crisis
  - Hemolytic Crisis

Key Points (3)

- Treatment include pharmacological and non-pharmacological interventions
- Follow up monitoring have to be done closely by doing complete assessment and treatment and counselling of parents

Session Evaluation

- What is sickle cell disease?
- How do you manage a patient with sickle cell diseases?