SICKLE CELL DISEASE (AND OTHER HEREDITARY HAEMOLYTIC ANAEMIAS)

HEREDITARY HAEMOLYTIC ANAEMIAS RESULT PRIMARILY FROM A DEFECT IN HAEMOGLOBIN PRODUCTION, RBC METABOLISM OR THE STRUCTURE OF THE RBC MEMBRANE

HAEMOLYSIS, PRIMARILY IN THE SPLEEN, IS A NORMAL PROCESS WHEREBY ABNORMAL, DAMAGED AND AGED RBCs ARE REMOVED FROM THE CIRCULATION

INHERITED HAEMOGLOBIN DISORDERS ARE DIVIDED INTO THOSE WITH ABNORMAL HB STRUCTURE (SICKLE CELL) AND DISORDERS OF ABNORMAL HB PRODUCTION (THALASSAEMIA)

SICKLE CELL DISEASE:

EPIDEMIOLOGY:

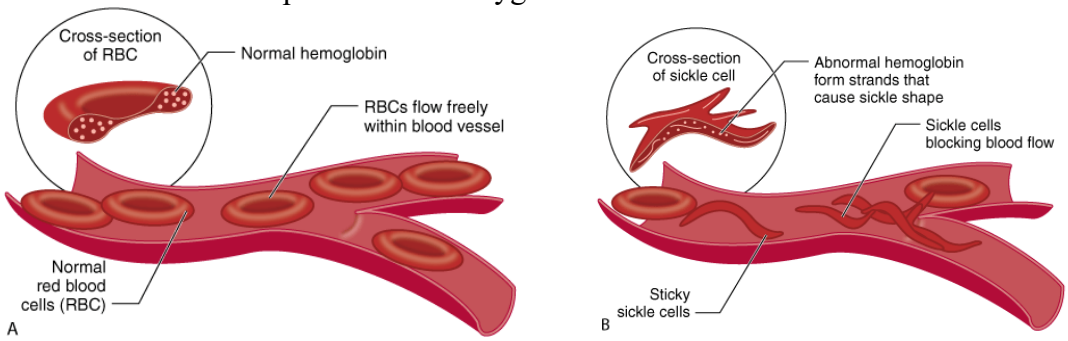
- An estimated 250 million people are carriers of the sickle cell gene and Sickle Cell Disease (SCD) accounts for ~70% of congenital Hb disorders
- Predominantly affects people of African Equatorial descent, but is also found in persons of Mediterranean, Indian and Middle Eastern origin
- During the last few decades, LIFE EXPECTANCY HAS IMPROVED DRAMATICALLY due to early diagnosis, parental education, close monitoring, prophylactic penicillin to prevent pneumococcal septicaemia and increased use of drugs like hydroxyurea

PATHOPHYSIOLOGY:

- Normal adult RBC contains three forms of Hb ➔ HbA, HbA2 and HBF (foetal Hb)
- Because of the 120 day RBC life span, HbF is the predominant Hb in the circulation for approximately the first four months of life

Table 231-1 Composition of Normal Human Hemoglobin and Hemoglobin Variants			
Syndrome	**Types of Hemoglobin (Hb) Present**	**Percent within the Red Blood Cell**	**Hemoglobin Tetramer Composition (globin chains)**
Normal adults	HbA	96–98	Two α-chains and two β-chains
	HbA_2	3.0–3.5	Two α-chains and two δ-chains
	HbF	0.5–0.8	Two α-chains and two γ-chains
Sickle cell trait (heterozygous)	HbA	60–65	Two α-chains and two β-chains
	HbAS	35–40	Two α-chains, one normal β-chain, and one sickle β-chain
	HbF	0.5–0.8	Two α-chains and two γ-chains
Sickle cell disease (homozygous)	HbS	80–90	Two α-chains and two sickle β-chains
	HbA_2	2–4	Two α-chains and two γ-chains
	HbF	2–20	Two α-chains and two γ-chains

- As a result of a genetic mutation, people with SCD, when under DEOXYGENATED CONDITIONS, their globin chains join together, HBS polymerises, deforming the RBC and producing the characteristic sickled appearance
    - This is inherited as AN AUTOSOMAL RECESSIVE TRAIT ➔ reveals itself when patient is homozygous

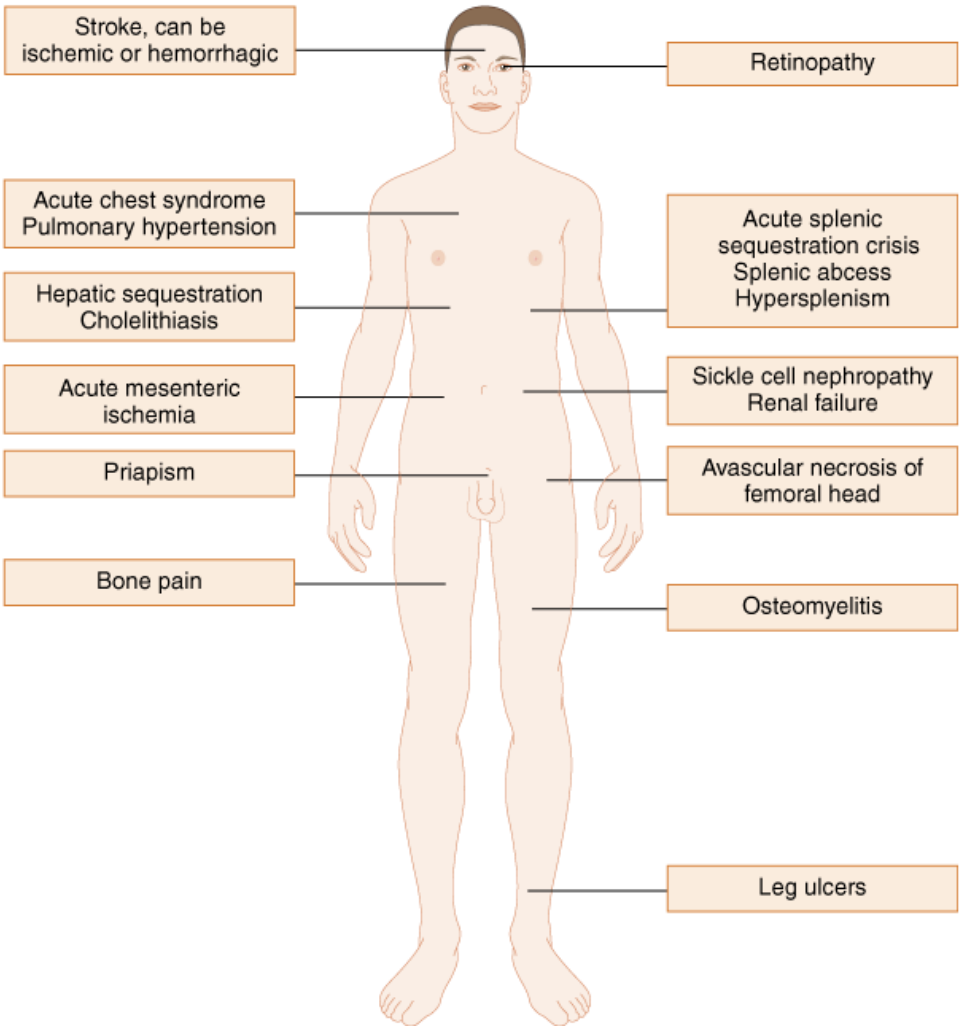


- The distorted sickle cell results in PREMATURE RBC DESTRUCTION (20 DAY LIFE SPAN COMPARED WITH 120 DAYS NORMALLY)
    - Also results in increased viscosity of blood, leading to obstruction within the microvasculature
    - Overall effect is chronic, ongoing haemolysis and episodic periods of VASCULAR OCCLUSION, RESULTING IN TISSUE ISCHAEMIC AFFECTING MANY ORGAN SYSTEMS
- People with sickle cell trait have a normal life span and usually are asymptomatic, but there is evidence that it is not benign:
    - Renal medullary carcinoma
    - Haematuria and renal papillary necrosis
    - Splenic infarcts
    - Exercise-related deaths

CLINICAL PRESENTATIONS AND TREATMENT:

- Majority of patients are diagnosed with newborn screening, hence presentations to ED will be those with known disease

- Majority of presentations will be VASO-OCCLUSIVE CRISIS ➔ the sickled RBC restrict the blood flow to various organs, thus causing ischaemic pain and organ damage
- Can also present with life-threatening complications ➔ stroke, aplastic crisis, acute chest syndrome and sepsis
- **VASO-OCCLUSIVE PAIN CRISIS:**
    - Acute painful sickle crisis is a common problment
    - Initiating event may not be identifiable, but common stressors are INFECTION, cold, dehydration and altitude
    - As a result of sickling ➔ small vessel occlusion lead to infarction of bone, viscera and soft tissue
    - Initial management involves AGGRESSIVE PAIN MANAGEMENT (beware that these patients are often opioid tolerant and require large doses) AND HYDRATION, AS WELL AS ASSESSMENT OF CAUSE OF THE CURRENT CRISIS
    - SEARCH FOR ADDITIONAL COMPLICATIONS



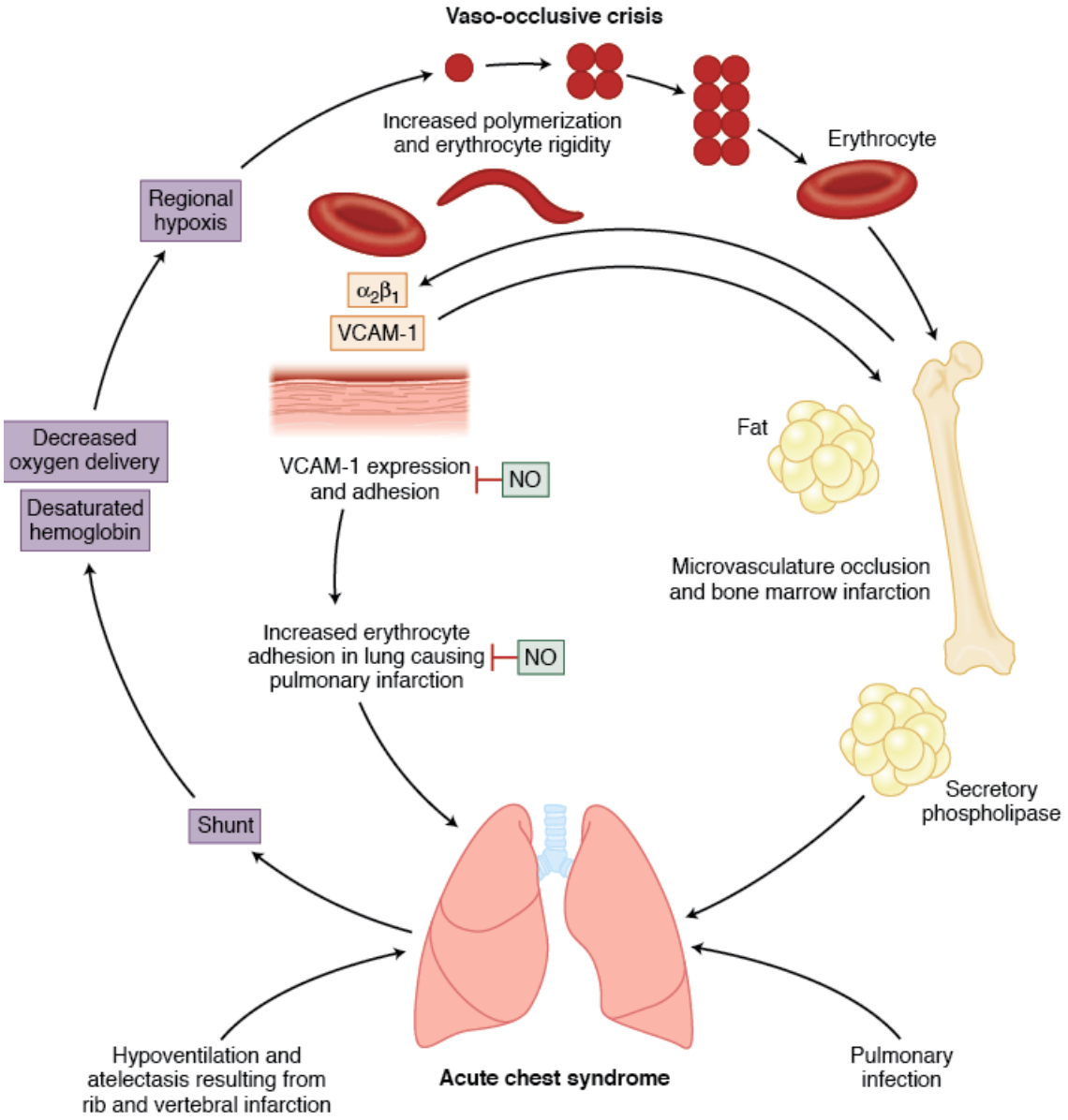
    - When needed, FBC and reticulocyte count assesses degree of anaemia and ensures marrow response is still producing red cells

        - An elevated WCC and low-grade fever is common in painful crises, but if WCC >20, consider sepsis
    - Chronic haemolysis leads to mild elevations in serum LDH and bilirubin
    - SUPPLEMENTAL OXYGEN IS USED COMMONLY ➔ however, unless the patient is systemically hypoxaemia, it HAS NOT BEEN PROVEN TO BE OF ROUTINE BENEFIT
    - SCD patients with painful crisis may have an absolute or relative hypovolaemia due to their disease (deficient renal concentrating ability) or crisis (anorexia, vomiting or fever) ➔ routine IV or PO hydration
    - TRANSFUSION → to reduce the concentration fo HbS-containing RBC has NOT BEEN SHOWN TO BE ADVANTAGEOUS for routine vas-occlusive crises ➔ indeed, can induce antibody formation that complicates future transfusions
        - Reserved for specific indications (APLASTIC CRISIS, PREGNANCY, STROKE, RESPIRATORY FAILURE, GENERAL SURGERY AND PRIAPISM)
    - HYDROXYUREA ➔ most successful drug therapy for SCD to reduce the frequency and severity of painful crises
        - Blocks synthesis of DNA and impairs cell division
        - Increases HbF production, protective against sickling
        - Indicated for those with more than 3 hospitalisations for vaso-occlusive crisis per year
    - PENICILLIN V AS PNEUMOCOCCAL PROPHYLAXIS → reduces incidence of infection

Table 231-2 Guidelines for the Assessment and Management of Acute Vaso-Occlusive Crisis	
History	Duration and location of pain
	History of fever
	History of focal swelling or redness
	Precipitation factors for acute episode
	Medications taken for pain relief
Physical examination	Assess degree of pain
	Inspect sites of pain, looking for swelling, warmth, redness
	General: respiratory distress, pallor, hydration, jaundice, rash
	Vital signs: especially temperature, pulse oximetry
	Respiratory: chest wall, lung sounds
	Heart: cardiomegaly and systolic murmur common with chronic anemia
	Abdomen: tenderness, organomegaly
Ancillary tests	If moderate to severe pain, focal pathology is present, or pain is atypical for acute episode
	Complete blood count, leukocyte differential, reticulocyte count, urinalysis
	Chest radiograph, if signs of lower respiratory tract pathology
	Blood cultures and additional blood tests: as indicated by clinical condition
General management	Bed rest, provide warmth, and a calm, relaxing atmosphere
	Distractions where appropriate—television, music, etc.
	Oral fluids: typically about 3 L per day
	IV fluids to correct dehydration or if reluctant to drink or vomiting is present
	Oxygen: not routinely required, unless hypoxemia is present
	Encourage deep breathing, incentive spirometry
Pain management	Use analgesics appropriate to degree of pain
	Acetaminophen for mild pain
	NSAID for mild to moderate pain (avoid if renal insufficiency is present)
	Opioids for moderate to severe pain, typical initial doses include:
	Morphine, 0.3 milligram/kg PO or 0.1–0.15 milligram/kg IV
	Hydromorphone, 0.06–0.08 milligram/kg PO or 0.015–0.020 milligram/kg IV
	Reassess response in 15–30 min, may repeat with one fourth to one half initial dose
Disposition and follow-up	Consider admission to the hospital if:
	Acute chest syndrome is suspected
	Sepsis, osteomyelitis, or other serious infection is suspected
	White blood cell count is >30,000/mm3
	Platelet count is <100,000/mm3
	Pain is not under control after two to three rounds of analgesics in the ED
	Consider discharge if:
	Pain is under control and patient can take oral fluids and medications
	Ensure appropriate oral analgesics are available
	Provide home care instructions
	Ensure resource for follow-up

- **BONE PAIN:**
  - Common during sickle cell crisis, usually localising to back and extremities
    - Usually no physical findings
  - The presence of redness, warmth or swelling suggests infection such as cellulitis or osteomyelitis
  - Complaint of localised hip pain with difficulty ambulating suggests the presence of aseptic necrosis of the femoral head ➔ 30% of patients will develop some degree of this by 30 years old
- **ACUTE CHEST SYNDROME:**

- DEFINITION ➔ a new infiltrate on CXR in association with one other new sign or symptom (FEVER >38.5C, COUGH, WHEEZING, TACHYPNOEA, CHEST PAINS)
- Occurs most commonly in 2-4 year old age-group and gradually declines in incidence with increasing age
- LEADING CAUSE OF DEATH and second most common cause of admission
- Can result in chronic lung disease after multiple attacks, but is most often single episode
- Multiple potential aetiologies, but is most commonly precipitated by:
    - PULMONARY INFECTION
    - FAT EMBOLISM
    - RIB INFARCTION
        - Aggressive hydration for painful crisis can lead to APO and chest syndrome
- One study (National Acute Chest Syndrome Study Group), found infectious pathogens in about half of patients admitted to hospital
    - CHLAMYDIA PNEUMONIAE AND MYCOPLASMA PNEUMONIAE most commonly
    - Pneumococcus now rare due to routine prophylaxis and immunisation
- Acute chest syndrome is the final result of several pathogenic processes that CREATE REGIONAL HYPOXIA, ACIDOSIS AND LUNG INJURY → cycle of injury involving inflammatory mediators, free radical species, vascular stasis and pulmonary infarction (see figure below)



- Hydroxyurea reduces the occurrence of acute chest syndrome by stimulating an increase in HbF
- Inhaled NO has shown benefite, perhaps by reducing RBC adhesion to endothelial cells by down-regulating VCAM-1

Table 231-3 Assessment and Treatment of Acute Chest Syndrome	
History	Major presenting symptom: dyspnea, fever, cough
	Accompanying chest, rib, bone, or joint pain
	Assess degree or severity of pain
	Recent or previous sepsis, infection, pneumonia, or hospitalization
	Prior history of acute chest syndrome, especially if required intubation and ventilatory support
	Potentially infectious contacts
	Current medications
	Immunization history: especially pneumococcal and *Haemophilus influenzae* type b
	Baseline hemoglobin level and arterial oxygenation saturation
Physical examination	General: respiratory distress, pallor, hydration, jaundice, rash
	Vital signs: especially temperature, pulse oximetry
	Respiratory: chest wall, lung sounds
	Heart: cardiomegaly and systolic murmur common with chronic anemia
	Abdomen: tenderness, organomegaly
Ancillary tests	Complete blood count, leukocyte differential, reticulocyte count, urinalysis
	Cross-match sample: if red blood cell transfusion is contemplated
	Arterial blood gas: if moderate to severe respiratory distress and/or hypoxemia on pulse oximetry
	Chest radiography
	Blood cultures
	Additional blood tests: as indicated by clinical condition
Treatment	Oxygen: adjust according to pulse oximetry
	Oral hydration: preferable
	IV hydration: use hypotonic fluids, use a rate and dose at approximately 1.5 of maintenance (over aggressive IV fluids can worsen acute chest syndrome)
	Analgesics: if needed, generally potent parenteral opioids are used, monitor for signs of respiratory suppression
	Antibiotics: empiric antibiotics recommended to treat community acquired pneumonia
	Bronchodilators: nebulized β_2-adrenergic agonists
	Chest physiotherapy
	Transfusion: use if severe acute anemia is present
Exchange transfusion	Consider when
	Severe acute chest syndrome on admission and past history of requiring ventilatory support: useful to prevent intubation
	Deterioration despite above management: useful to prevent intensive care unit admission
	Patient already intubated and on ventilatory support: useful to shorten duration of ventilatory need
	Suspected or confirmed fat or bone marrow embolism

- **ABDOMINAL CRISIS:**
  - Generalised and constant abdominal pain is a common complaint during an acute sickle cell crisis and makes assessment and differentiation between other focal abdominal problems difficult
    - PATIENTS WITH A TYPICAL VASO-OCCLUSIVE CRISIS **SHOULD NOT HAVE EVIDENCE OF PERITONITIS**
  - Hepatic infarction may produce jaundice and abdominal pain
  - BILIARY DISEASE IS COMMON ➔ due to pigment-related cholelithiasis seen in 30%-70% of SCD patients
- **GENITOURINARY SYSTEM:**
  - Vaso-occlusive crises involving the kidneys are common but often asymptomatic
  - Infarction in the renal medulla may cause flank pain and renal-colic type symptoms
  - PRIAPISM:
    - Occurs in up to 30% of males with SCD
    - Initial treatment is fluid hydration, pain control and transfusion
    - Early involvement of a urologist is advised
- **SPLENIC INFARCTION:**
  - Over time, microinfarctions result in a spleen that is essentially NONFUNCTIONAL
  - Rates of FUNCTIONAL ASPLENIA:
    - 14% by six months
    - 94% by age 5
  - This renders these patients at risk for SERIOUS INFECTION AND SEPSIS FROM **ENCAPSULATED ORGANISMS**
  - Immunisations and prophylactic penicillin use are mainstays
- **SPLENIC INFARCTION:**
  - IMPORTANT CAUSE OF SIGNIFICANT MORBIDITY AND OCCASIONAL MORTALITY IN SCD ➔ MORE COMMON IN CHILDREN THAN ADULTS
  - Manifests by sudden enlargement of the spleen with an acute fall in haemoglobin due to the SEQUESTRATION OF THE BLOOD VOLUME WITHIN THE SPLEEN
  - SYMPTOMS ➔ tachycardia, hypotension, pallor, lethargy and abdominal fullness
    - LUQ pain may or may not be present
    - Spleen is usually enlarged and firm
  - Platelets can also be sequestered
  - THERAPY ➔ volume resuscitation, simple transfusion or EXCHANGE TRANSFUSION
- **APLASTIC CRISIS:**
  - Generally the increased production of RBC by the bone marrow is able to compensate for the increased rate of destruction
  - APLASTIC CRISIS RESULTS WHEN PRODUCTION OF RBCs DECLINES SIGNIFICANTLY

    - Most common cause is INFECTION ➔ PARVOVIRUS specifically
    - Hb level will be UNUSUALLY LOW and NO RETICULOCYTES WILL BE PRESENT
    - Generally self-limiting, lasting <1 week, but transfusion may be required in the interim
- **NEUROLOGIC DISORDERS:**
    - Stroke (both ischaemic and haemorrhagic), SAH all occur in SCD
    - The risk of stroke in children with SCD is >200 times greater than those without
        - In most patients ➔ cause is cerebral infarction due to occlusion or narrowing of large cerebral vessels
        - ~10% patients with SCD will have a stroke by age 20
    - Acute stroke is treated with EXCHANGE TRANSFUSION
    - Unfortunately, children who suffer a stroke are at 70-90% risk of recurrence ➔ chronic transfusion therapy is indicated
- **INFECTIONS:**
    - Due to functional asplenia, patients are at high risk for infection from encapsulated organisms
    - Unexplained fevers above 38C should be evaluated for bacterial infection
    - Ensure influenza, pneumococcal and haemophilus immunisations remain up to date
- **CARDIAC COMPLICATIONS:**
    - Cardiomegaly is common
- **DERMATOLOGICAL ISSUES:**
    - Chronic, poorly healing ulcers around the malleoli are common

<u>THALASSAEMIA:</u>

- A diverse group of hereditary disorders caused by DEFECTIVE SYNTHESIS OF GLOBIN CHAINS, resulting in an inability to produce normal adult haemoglobin
- Most common in Mediterranean, Middle Eastern, African and SE Asian patients
- Categorised depending on the globin chain affected
    - Beta-thalassaemia have diminished production of the β-globin chain ➔ allows unmatched α-globin chains to accumulate as α tetramers, which are very insoluble and their precipitation damages the developing RBC precursor cells → early death. Thus the cells that are produced have decreased haemoglobin
    - Patients with alpha-thalassaemia develop an excess of β-globin chains that accumulate as tetramers (HbH) ➔ more soluble and stable so that in severe α-thalassaemia, ineffective erythropoiesis is less of a problem and increased destruction of the cells due to structural abnormality is more prominent
- The hypoxia associated with severe anaemia triggers compensatory mechanisms in an attempt to increase RBC volume ➔ enlargement of the reticuloendothelial organs and expansion of bone marrow ➔ osteopenia

ALPHA-THALASSAEMIA CARRIER AND TRAIT:

- Patients who are α-thalassaemia carriers and those with trait HAVE NO CLINICAL SYMPTOMS OR PHYSICAL FINDINGS ➔ detected b finding of microcytic RBCs and normal Hb

HAEMOGLOBIN H DISEASE:

- One α-globin gene is still functional ➔ usually presents in the neonatal period with severe hypochromic microcytic anaemia
    - Later in life ➔ anaemia plus jaundice and hepatosplenomegaly
- Conditions that increase oxidative stress result in haemolysis and may precipitate need for transfusion (as does infection)
- Avoid medications that precipitate haemolysis

Table 231-4 Drugs That Produce Oxidative Stress on Red Blood Cells	
Sulfonamides	Sulfacetamide
	Sulfamethoxazole
	Sulfanilamide
	Sulfapyridine
Antimalarials	Primaquine
	Chloroquine
	Pamaquine
	Pentaquine
Urinary agents	Nitrofurantoin
	Nalidixic acid
	Phenazopyridine
Miscellaneous antibiotics	Ciprofloxacin
	Norfloxacin
	Chloramphenicol
Mothballs	Naphthalene
Miscellaneous	Vitamin K analogues
	Methylene blue
	Acetanilid
	Doxorubicin
	Isobutyl nitrite
	Phenylhydrazine

β-THALASSAEMIA MINOR:

- Heterozygous for the β-globin mutation and have only mild anaemia
- May have splenomegaly
- Normally an incidental finding

β-THALASSAEMIA MAJOR:

- Both β-globin genes are defective and production of β-globin chains is severely impaired

- Newborns are usually well initially because of the predominance of HbF initially ➔ usually becomes apparent in second six months of life when HbF decreases
- These children develop hepatosplenomegaly, jaundice, expansion of bone marrow, osteoporosis, increased susceptibility to infection as well as severe hypochromic, microcytic anaemia
- ANAEMIA IS SEVERE AND REQUIRES LIFELONG TRANSFUSIONS
    - Eventually enhanced iron absorption leads to iron overload
    - Iron overload causes most of the morbidity and mortality associated with thalassaemia and if untreated ➔ HAEMOCHROMATOSIS with cardiac, hepatic and endocrine dysfunction

GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY:

- G6PD deficiency is the most common enzymopathy of RBCs in humans
- It is X-linked, hence rare in women
- The haemolysis relates to the exposure of older RBC to substances that have a high reduction-oxidation potential, hence G6PD-deficient RBC are SUSCEPTIBLE TO OXIDATIVE STRESS ➔ causes Hb to precipitate within the cell (forming HEINZ BODIES)
    - Affected RBCs are removed from the circulation by the spleen
- In most cases, haemolysis is self-limited and well tolerated
- Aside from FAVA BEANS and drug-induced cases, INFECTION is the most common cause of haemolysis in these patients
- A serious complication of G6PD deficiency is NEONATAL JAUNDICE leading to KERNICTERUS ➔ phototherapy indicated
- Main aim is to avoid oxidative stress (fava beans, implicated drugs)

HEREDITARY SPHEROCYTOSIS:

- The result of an erythrocyte membrane defect and is the most prevalent hereditary haemolytic anaemia among people of northern European descent
- Autosomal dominant inheritance
- Molecular abnomralities in the cytoskeleton of the cell membrane results in an abnormal shape of the RBC, that makes it less pliable and thus it cannot pass thorugh the spleen → INCREASED DESTRUCTION
- MAIN COMPLICATIONS ➔ aplastic or megaloblastic crisis, haemolytic crisis, cholecystitis or cholelithiasis, neonatal haemolysis with jaundice
- In severe cases, splenectomy generally reverses the anaemia, but spherocytes are still present
    - In moderate disease, modest splenomegaly is present with mild-moderate anaemia