Sickle Cell Disease- Case studies

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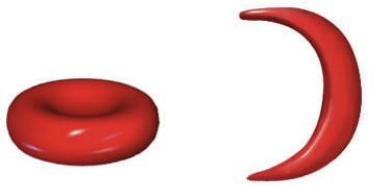
2017



Conditions requiring immediate admission

- Agonising pain (i.e. requiring opiate analgesia)
- Increased pallor, breathlessness, exhaustion
- Marked pyrexia (> 38 ^{o}C), tachycardia or tachypnoea, hypotension
- Chest pain; signs of lung consolidation
- Abdominal pain or distension, diarrhoea, vomiting
- Severe thoracic/back pain
- Headache, drowsiness, CVA, TIA or any abnormal CNS signs
- Priapism (> 4 hours)

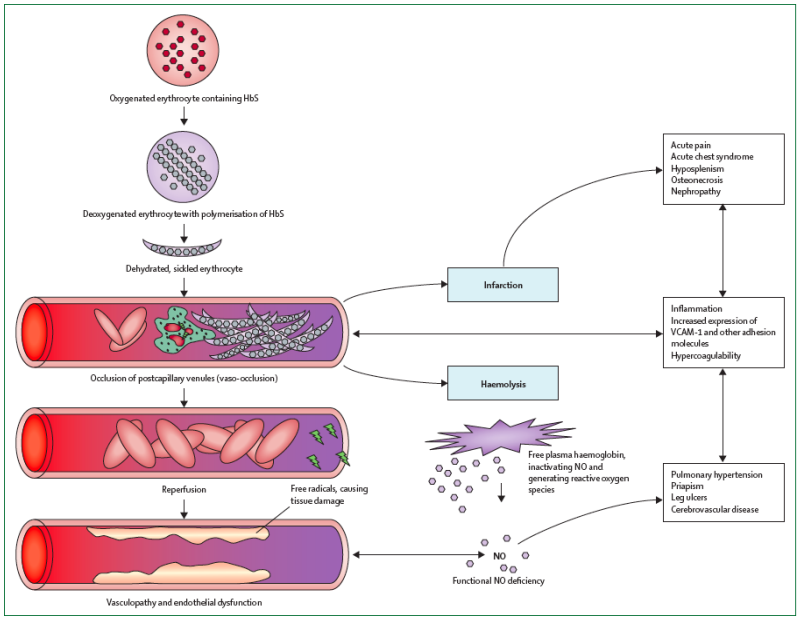
Haemoglobinopathy- global perspective

- 5% of the world's population carry a haemoglobinopathy mutation, either sickle cell or thalassaemia
- 300,000 children are born annually worldwide with a major haemoglobinopathy, including 200,00 in Africa with sickle cell anaemia
- Distribution of sickle carrier status varies according to geographical region
- Sickle cell disease is now the most common genetic disorder in the UK, affecting over 1 in 2000 live births and up to 1 in 300 births in some urban areas

WHO Provisional agenda item 11.4

Main types of Sickle Cell Disease

Name	Other names
• Sickle cell anaemia	HbSS (homozygous)
• SC disease	HbSC
• Sickleb^0thalassaemia	S-β^0thal
• Sickleb^+thalassaemia	S-β^+thal



Rees et al Lancet 2010; 376: 2018–31

Complications of SCD- acute

- Painful crisis
- Susceptibility to infection due to functional asplenia
- Dactylitis
- Sequestration crisis- hepatic/splenic
- Chest crisis
- Priapism
- Stroke

UK standards of treatment

- New born screening
- Penicillin prophylaxis
- Regular hospital clinic review
- Additional vaccination (Pneumovax, influenza)
- Transcranial doppler from age 2-16
- Parent and patient education
- Transition to adult
- Support of emergency admissions including analgesia within 30 minutes of presentation

Case 1

- 7 y/o girl, HbSS arrived at A&E department with severe left leg and left arm pain. Pain score 8.5/10
- Hb 80g/L MCV 68fl, Neutrophils 11 x10*9/L, Platelets 505 x10*9/L, Reticulocytes 276 x10*9/L, LDH 650IU/L
- Treated with oral morphine with some initial response. IV fluids started as mildly dehydrated, continued with usual penicillin prophylaxis as not febrile

Case 1a

- Needed 2 doses of morphine in A&E- admitted to the ward on regular morphine (300mcg/kg every 4 hours). IV fluids continue. Adjunct therapy with regular paracetamol and ibuprofen
- Morphine continued regularly for 48 hours, and then changed to PRN
- IV fluids discontinued on day 1 as patient drinking well
- Laxatives started with morphine, good response after 48 hours
- Discharged home on Day 3 (Repeat FBC on day 3- no change)

Case 1b

- No response to 2 doses of oramorph in A&E
- Intravenous morphine started on a PCA pump, along with optimum doses of paracetamol and ibuprofen
- IV morphine infusion complicated by nausea and itch- treated with naloxone and ondansetron
- Repeat FBC in 24 hours : Hb 65g/L MCV 68fl, Neutrophils 18 x10*9/L, Platelets 525 x10*9/L, Reticulocytes 450 x10*9/L CRP 118 mg/L

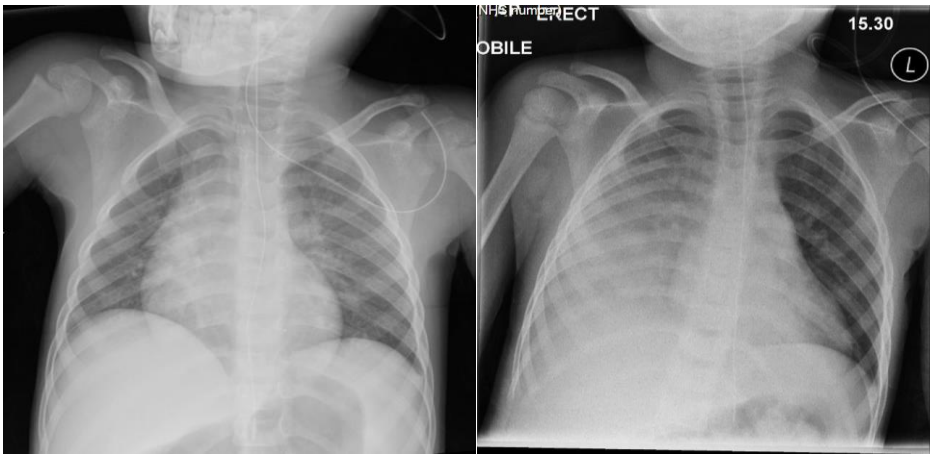
Case 1b

- IV fluids continued as reluctant to drink
- IV antibiotics (due to low grade fever and high CRP)
- 72 hours of IV morphine
- Changed to regular oral morphine and subsequently stopped
- Home on oral antibiotics and a supply of dihydrocodeine. Hb on discharge 72g/l

Case 1c

- No response to 2 doses of oramorph in A&E
- Intravenous morphine started on a PCA pump, along with optimum doses of paracetamol and ibuprofen. Low grade fever, CXR done
- Febrile, and noted to have increased work of breathing on Day 2. Started IV broad spectrum antibiotics and macrolide. Nasopharyngeal aspirate sent for respiratory viral screen
- Repeat FBC in 24 hours : Hb 65g/L MCV 68fl, Neutrophils 18 x10*9/L, Platelets 525 x10*9/L, Reticulocytes 450 x10*9/L CRP 118 mg/L

Case 1c



Day 1

Day 3

Case 1c continued

- Top up transfusion
- Optiflow
- Transfer to HDU for observation
- Good response to above measures
- Back on ward after 2 days in HDU
- Incentive spirometry
- Home on day 7 following morphine wean and completion of IV antibiotics

Case 2

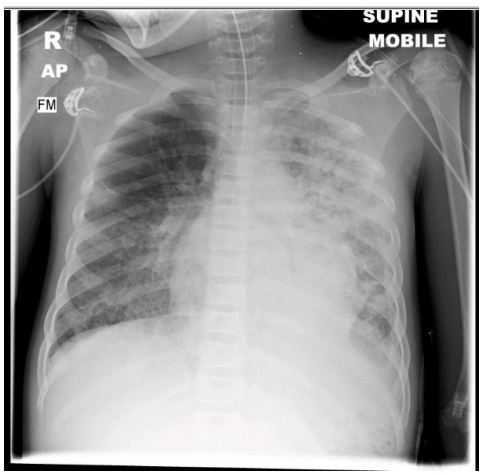
- 9 year old girl with HbSS
- PMH- Splenectomy age 7 for recurrent sequestration crisis, frequent vaso occlusive crises leading to school absenteeism
- Mum community nurse, had previously declined hydroxycarbamide

Case 2-presentation

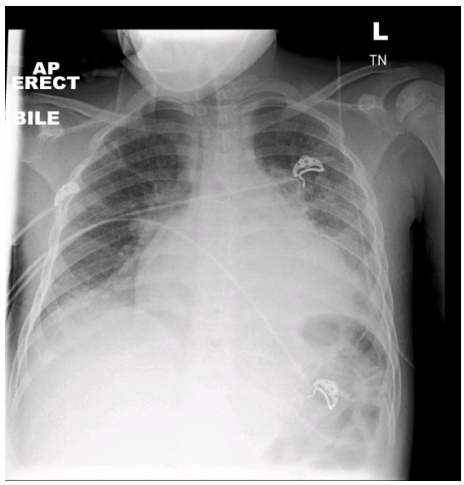
- Presented to local hospital with chest and arm pain following 7 days of fever and cough at home, CXR showed bilateral infiltrates
- Rapid deterioration in 72 hours with worsening respiratory symptoms and anaemia. R elbow swollen
- Day 4 of admission to local hospital- respiratory failure, intubated and ventilated locally by specialist transfer team

Case 1- progress

- PICU
- High ventilatory requirement
- High frequency oscillation and NO
- Triple inotropes, broad spectrum antibiotics
- Full volume red cell exchange transfusion
- R brachial vein thrombosis- LMWH for 12 weeks



Day 1 PICU



Day 2 PICU

Case 1- outcome

- Prolonged ventilation (10 days)
- Successful ventilatory wean
- No renal failure
- Discussions with local hospital regarding early warning scores in chest crisis and early referral for respiratory support and exchange transfusion

ACS

- High index of suspicion
- Oxygen saturation in air: if <95% and no past history of hypoxia: CXR
- If Oxygen saturation in air: <95%-, increased respiratory effort, new infiltrates on CXR, chest pain- may need ventilatory support and red cell exchange transfusion
- Severe respiratory failure in about 2-5% (? Delayed diagnosis)- invasive ventilation

Treatment of recurrent chest crisis

- Hydroxycarbamide
- Chemotherapy agent licensed for many cancers- has been used in SCD for 15 years, even in very young children
- Usually started at a lower dose, and then increased to maximum of 25mg/kg/d
- Among other beneficial effects, it increases Fetal haemoglobin levels, which is protective
- Reduced incidence of painful crises, chest crises, duration of admission with painful crises,

Sepsis

- Universal prophylaxis with Penicillin V, Pneumovax/HiB/MenC/Prevenar,
- Double up PenV when unwell at home
- Seek medical help if high fever, cough, pallor, lethargy
- Prompt assessment for sepsis : Vital signs
- Septic screen: Clinical and laboratory including blood and urine cultures, Xray
- Prompt institution of antibiotics as indicated

Sepsis

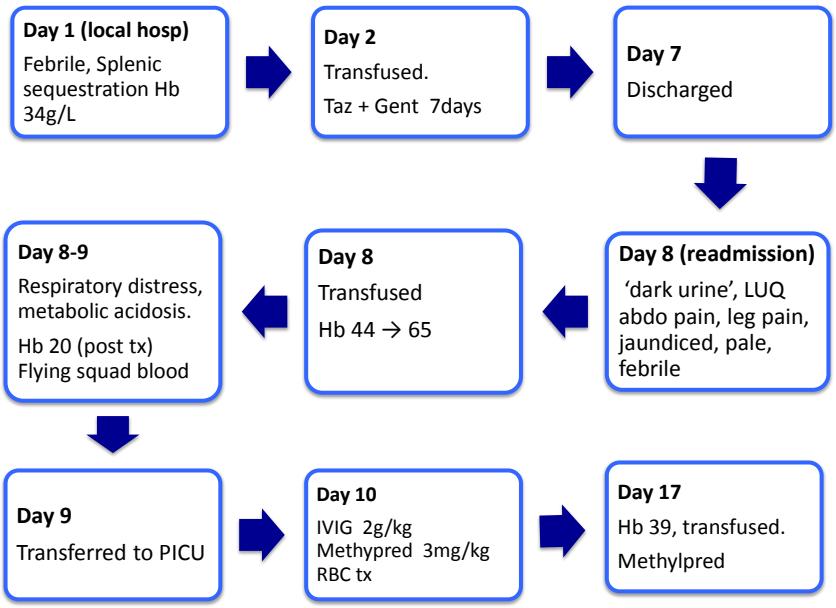
- Osteomyelitis/septic arthritis: may present with localised pain and fever- relatively rare in UK, often mimics VOE
- X ray of bone usually unhelpful- MRI is investigation of choice, but can still be non-diagnostic
- Gold standard- positive blood cultures. Septic joints need evacuation
- Prolonged course of antibiotics– upto 8 weeks – IV or oral, depending on pathogen
- Most cases of presumed OM are likely VOE

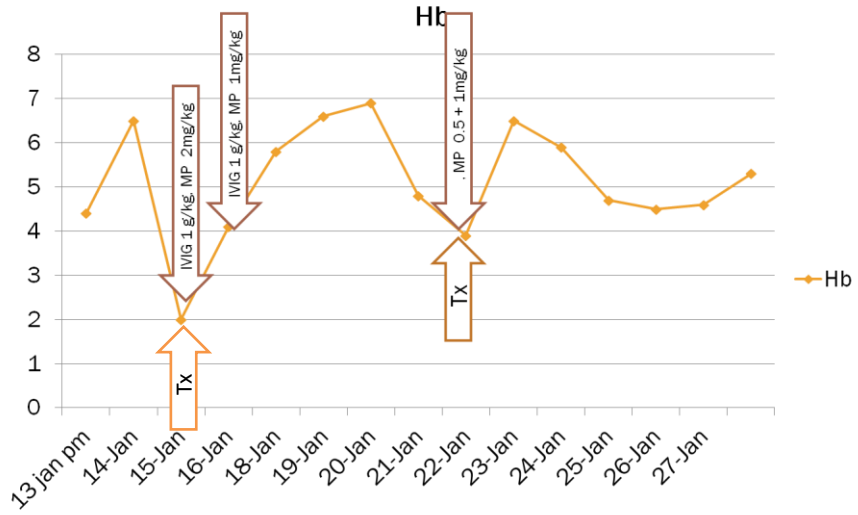
Sepsis- malaria

- High index of suspicion in febrile children returning from holiday from endemic areas
- Blood film for malaria parasite
- Beware of G6PD deficiency

Case 3

- 3 year old girl (Hb SS)
- PMH
  - 2 vaso-occlusive crises requiring hospital admission
  - Recurrent splenic sequestration
  - Anti-S allo antibody
  - Needlephobia





Complexity of Case 2

- Manifestations of an acute or delayed haemolytic transfusion reaction.
- Antibodies
  - Anti S (known for 1 year; Emergency O neg blood was S positive)
  - Anti C developed subsequent to recent admission
- Marked reticulocytopenia
- Development of a more severe anaemia after transfusion
- Subsequent transfusions may further exacerbate the anaemia and therefore required significant immunosuppression

Case 3: Outcome

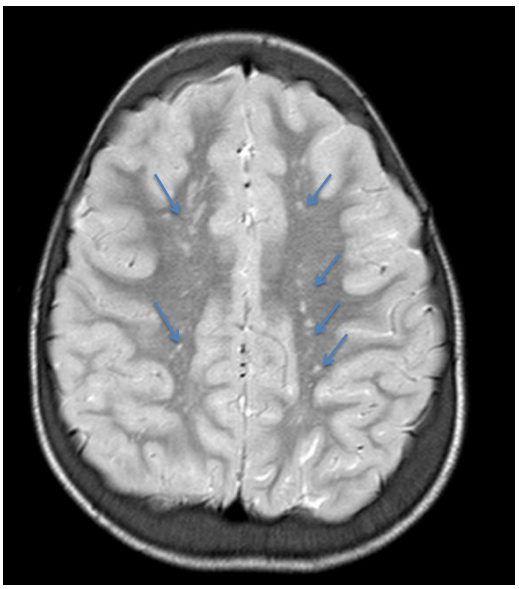
- Recovered well despite needing further transfusion and immunosuppression on day 17
- Needs splenectomy to prevent recurrent sequestration crisis- life threatening in an untransfusable child
- Baseline Hb 6 g/dl- but untransfusable
- Therefore erythropoietin and hydroxycarbamide given to increase pre op Hb-surgery

Case 4

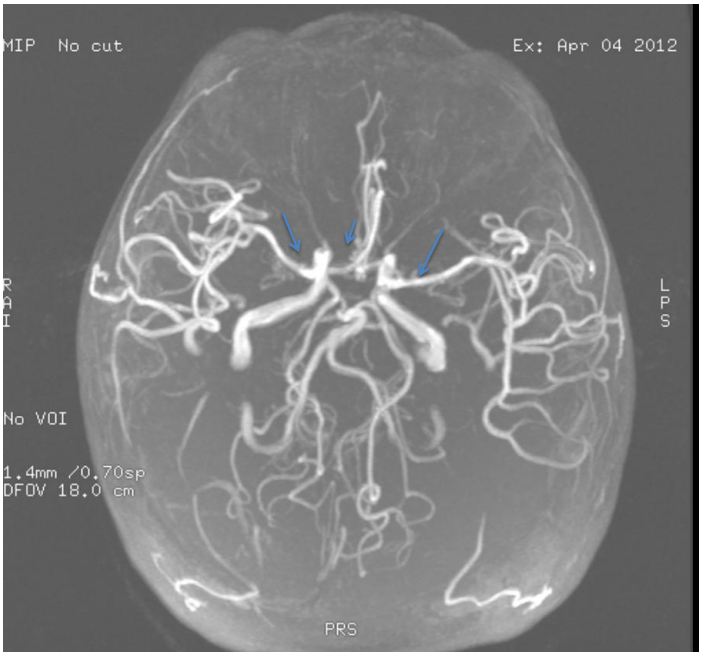
- 6 year old girl (HbSS)
- Recurrent infections – previous UTI, pneumonia, and recurrent vaso- occlusive episodes
- Persistent raised transcranial doppler velocity for 12 months, parents not agreed to start transfusion
- Adenotonsillectomy
- Hydroxycarbamide started 2 months earlier

Case 4- clinical progress

- Fever + cough for 4 days at home
- Unresponsiveness + hypertonic episode at home- admitted to local hospital
- Hb 45g/l- top up transfusion, transfer to PICU.
- MRI : New watershed infarcts (normal MRI/MRA 12 months ago). No neurological deficit- hence defined as silent cerebral infarction (SCI)
- MRA : MCA stenosis and collateral vessel formation
- Parvovirus IgM positive- Aplastic crisis and silent cerebral infarct



MRI scan of brain showing new infarct



MRA

Case 4- outcome

- No neurological deficit
- Neuropsychometry shows significant abnormalities in processing, memory and FSIQ
- Chronic transfusion therapy for SCI and primary stroke prevention
- Brother HLA match- underwent successful bone marrow transplant with normalisation of TCD velocities and SCI.

Cerebral vasculopathy in sickle cell disease

- 11% of patients with sickle cell anaemia have a stroke by age 20 yrs (Ohene-Frempong, 1998)- 75% ischaemic, 25% haemorrhagic
- Most frequent cause of ischaemic stroke is blockage of intracranial ICA or MCA
- 24% of patients by age 45 yrs (Ohene-Frempong)
- Highest risk in first decade of life: 1% per year
  - 2-5 years 1.02 per 100 patient years
  - 6-9 years 0.79
  - 10-19 0.41
- Strokes recur in 2/3 of patients, mostly within 2-3 years of the initial event (Powars, 1978)
- Children with SCD are at 300 times higher risk of developing strokes compared to their normal counterparts

Risk factors for stroke in SCD

- High blood flow velocity on transcranial Doppler (TCD),
- low hemoglobin
- high white cell count
- Hypertension
- silent brain infarction
- history of chest crisis
- Familial predisposition
- Nocturnal hypoxaemia
- Exchange transfusion

Transfusion therapy to prevent recurrent strokes

- If left untreated, about 90% of children with a stroke will have a recurrence
- Transfusion therapy to keep S% to <30% causes reduction of this recurrence to <10%
  - Russell et al, Blood, 1984- This study also demonstrated for the first time that pathophysiology of stokes was due to arterial stenosis in the Circle of Willis rather than distal capillary or venular occlusion

Emergency management of stroke in sickle cell disease

- High index of suspicion
- Thorough physical examination
- Often coexists with chest syndrome
- May known to be at risk
- Urgent imaging
- Involve neurologists early
- Exchange transfusion

Role of transfusion

- Raised cerebral blood-flow velocities related to
  - severe anemia,
  - vessel stenosis,
  - cerebral vasodilatation caused by tissue hypoxia.
- Transfusion reduces cerebral blood flow velocities by correcting these abnormalities to some degree, and may explain the reduction in stroke risk

Detection of at-risk children

- Transcranial doppler
  - Adams et al NEJM 1992-
  - TCD can identify the children with sickle cell disease who are at highest risk for cerebral infarction.
  - 190 children with SCD (3-18) were followed up for average of 29 months- children with abnormal TCDs were at a significantly higher risk of developing strokes ($p<.000001$)
  - Longer term follow up (up to 4 years of 315 children) showed similar rates of pick up

Transcranial doppler screening

- Risk of overt stroke in 3 years

TAMMV

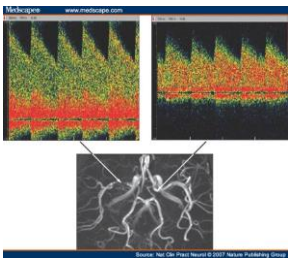
Abnormal 40%

Conditional 7%

Normal 2%

>200 cm/s

170 -199 cm/s



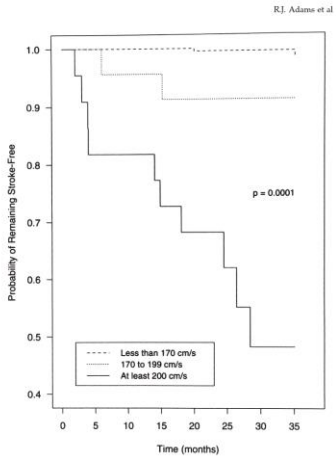
Source: Nat Clin Pract neurol 2007

- Annual screening
- SS/Sβ0
- 2-16 y

http://www.bilocharitiesphoc.com/trans-cranial-doppler-ultrasound.php

Adams NEJM 1992 Annals neurol 1997

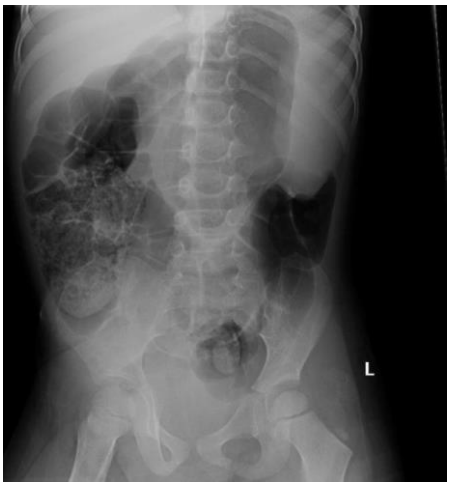
Stroke-free survival vs TCD velocities



Adams NEJM 1992

Case 5

- 8 y/o boy HbSS
- Severe abdo pain and distension
- BNO for 4 days
- Admitted with IV fluids and



Other complications of SCD

- Aplastic (severe anaemia, reticulocytopaenia), Parvovirus IgM/ PCR positive
- Priapism-past h/o stuttering priapism
- Sequestration syndrome-hepatosplenomegaly
- Girdle Syndrome-ileus
- Hyperahaemolysis-severe pallor, jaundice, reticlocytosis
- Delayed transfusion reaction, jaundice and pallor

- Avascular necrosis
- Nocturnal enuresis
- Chronic pain
- School absenteeism for health reasons
- Socially deprived backgrounds- problems with housing, cross infection, learning difficulty
- Lack of self esteem, bullying, poverty, unemployment, lack of understanding of own disease

Hydroxycarbamide

- Only agent to have shown significant efficacy in RCT
- Reduction in number and duration of painful crises
- Reduction in chest crises
- Increase in well being, Hb, HbF
- Prolongation of life expectancy
- Reduction of long term organ damage

Blood transfusion in SCD

- Children may present with severe haemolysis and anaemia during a painful crisis and may require a top-up transfusion
- Sequestration and aplastic crises need to be urgently treated with blood transfusion and can be life –saving
- Acute chest crisis, stroke and sever painful crises also need transfusion- usually exchange transfusion- aim is to reduce HbS% to<20%

Blood transfusion in Sickle

- Acute exchange transfusions are critical procedures and can precipitate stroke
- Best done in ITU in children
- Routine exchanges are performed in children with strokes or increased risk of stroke- this is to reduce HbS% as well as minimise the risk of transfusional iron overload- this can be done as OPD
- Automated red cell exchanges can reduce further the risk of iron overload

SCD in adolescents

- Chronic disease
- Quality of life issues
- Chronic pain
- Substance abuse
- Relationships
- Moving from paediatric to adult services
- Exams, university, jobs