

University Hospitals of Southampton Paediatric Sickle Cell Disease Guidelines

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Based upon St. Marys Hospital, (London) Paediatric Sickle Cell Guidelines 2010

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Conditions requiring immediate admission

- Agonising pain (i.e. requiring opiate analgesia)
- Increased pallor, breathlessness, exhaustion
- Marked pyrexia (> 38 °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)

Admission procedure for UHS

- Children are seen either on PAU or Piam Brown ward by the oncology SHO or paediatric on call SHO out of hours
- Patients should be clerked within one hour of arriving in hospital – **NB Analgesia should precede the taking of a detailed history and should be administered within half an hour of admission to hospital**
- Inform the Haemoglobinopathy CNS (Ext 4567) and Paediatric Haematology SpR as soon as possible. Out of hours the paediatric SpR on call should be informed
- All local children with sickle cell disease should have open access to PAU

Clinical Assessment

A full history and examination must be carried out, paying particular attention to symptoms/signs of complications including acute chest syndrome, splenic sequestration, aplastic crisis, or septicaemia – **these are life threatening complications of sickle cell disease**

The following should be recorded in the notes:

- The site and intensity of the pain
- Any analgesia already taken
- Any focus of infection (including the urinary tract)
- Chest symptoms and signs, including respiratory rate
- Liver and spleen size (cm)
- Degree of pallor, blood pressure.

Discharge from PAU or ward:

If there are no other indications for admission, following discussion with the Paediatric Haem SpR (out of hours

on call SpR) or CNS, a child can be discharged with:

- A supply of oral analgesia

- Instructions to drink one and a half times maintenance whilst unwell
- A follow-up appointment for review within a week with either the Haemoglobinopathy CNS or Paediatric Haem SpR
- Ensure they have enough supply of Folic acid and prophylactic Penicillin V
- Antibiotics if there is any evidence of infection (refer to hospital antibiotic policy). If not, may suggest increasing the normal penicillin prophylaxis to the treatment dose whilst unwell.

Inform the haemoglobinopathy CNS (ext 4567) about patients attending PAU, if out of hours this can be done the following day

Sickle Cell Crisis: Investigations

ROUTINE INVESTIGATIONS (All cases)

Blood Tests

- FBC, retics + Film
- Group, screen and save
- Renal function
- LFTs, LDH
- CRP
- Blood culture

Microbiological screen

Consider

- Urine dipstick & MSU culture
- Viral & atypical pneumonia serology 'to store'
- Throat/ wound swabs

Other tests

- Pulse oximetry (SaO₂) on air
- CXR if signs/ symptoms indicate

ADDITIONAL INVESTIGATIONS

Consider the following:

Abdominal pain:

- Abdominal USS
- Serum Amylase
- Stool MC+S including Yersinia, Yersinia serum antibodies (this applies only to patients on iron chelation with diarrhea in which case consider stopping desferrioxamine)

Chest signs/ symptoms:

- CXR
- Blood gas
- Mycoplasma/ Chlamydia serology
- ECG

Low Hb with low reticulocyte count:

- Parvovirus B19 IgM serology

HbS level only helpful if patient on regular transfusions and ACS/ Stroke is being considered

Focal neurology:

- CT/MRI brain (see stroke and other CNS complications section)

X-rays:

- Generally not helpful in painful crisis unless acute trauma. Can be helpful in chronic/intermittent pain for confirming AVN. MRI most helpful for investigating osteomyelitis

Investigation of patients new to the hospital with known Sickle Cell disease:

Routine investigations as above plus

- Hb HPLC, including %HbF
- Full red cell phenotype - Rh, Kell, MNS+U, Fya+b, Jka+b
- G6PD
- Ferritin
- Hepatitis B serology (may need to consider hepatitis C depending on which country the patient has been transfused in)
- CMV IgG
- Parvovirus B19 serology
- *Consider HIV serology*

Painful Sickle Cell crisis management:

During working hours, the Paediatric Haem SpR and CNS should be informed of any admission. Any queries should also be discussed with the Paediatric Haematology SpR or on call Haematology SpR, and all overnight admissions must be notified to the Paediatric Haematology SpR/ Consultant on call by 9am the next day.

Management is supportive unless there are indications for exchange transfusion, which should first be discussed with a senior member of staff. The aim of treatment is to break the vicious cycle of: sickling → hypoxia + acidosis → more sickling → all exacerbated by dehydration.

1. Analgesia:

- Pain should be assessed on an age appropriate pain scoring system and analgesia administered if required within 30 minutes of arrival in hospital
- Baseline observations including BP, sats, RR and HR should also be recorded at this time
- For analgesia dosing please see BNFc

- Mild-moderate pain: paracetamol/ ibuprofen/ diclofenac
- Severe pain: bolus of opioid orally

- Reassess + record the efficacy of the analgesia offered 30 minutes after administration, using the age appropriate pain rating scale
- If additional analgesia is required, continue to reassess every 30 minutes until pain is well controlled

- Continue to reassess and record observations (RR, HR, BP, sats, temp, pain rating) every 4 hours

- Patients receiving strong opioid analgesia should have their observations recorded every hour for the first 6 hours and every four hours subsequently if stable

- Examples of age appropriate pain rating scales can be found in the Appendix

2. Fluids:

Dehydration occurs readily in children with sickle cell disease due to impairment of renal concentrating power (hyposthenuria) and dehydration can worsen the acidotic picture and therefore sickling cycle

- If taking oral fluids well, hydration may be maintained via the oral/ NG route
- Most patients will require an IV line sited for parenteral opiates/ antibiotics/ IV fluids

- Hyperhydration (150% maintenance) should be initiated if clinical signs of dehydration

- An accurate input/ output chart and daily weights should be kept to ensure adequate hydration is achieved
- Knowledge of the child's baseline Hb and Hct can be useful in the assessment of dehydration
- Check U+Es daily – a raised Urea is particularly significant as most children with HbSS disease will usually have a low urea
- Add KCl as required
- Beware of the risk of SIADH, especially in chest crisis
- Rarely IV diuretics may be required, but this should be in an HDU/PICU environment with specialist paediatric haematology input only

:

3. OXYGEN

- Administer oxygen if sats <95%
- Continuous measurement of sats if chest crisis/ on O2
- Minimum four hourly sats if in air

4. ANTIBIOTICS

Infection is a common precipitating factor of painful and all other types of crisis.

Children with sickle cell disease are at particular risk from encapsulated organisms (pneumococcus, H. Influenza, Salmonella) as a consequence of their functional hyposplenia/ asplenia

For patients admitted with uncomplicated painful crisis without specific evidence of infection commence oral Amoxicillin or increase prophylactic Pen V from BD to QDS (i.e. treatment dose).

Stop prophylactic Pen V if commencing additional more specific antibiotics

Always consult the Infectious Diseases and Haematology teams if you are unsure about which antibiotics are most appropriate or if the patient is not responding to antibiotics

Always take BC, urine culture, throat swab and line swab (if relevant) prior to commencing any antibiotics

Basic guide according to source of infection:

- Chest: IV Cefuroxime + Clarithromycin
- Abdominal girdle syndrome: IV Cefuroxime + Metronidazole
- Focal infection EG UTI/ tonsillitis: consult hospital antibiotic policy
- Osteomyelitis: IV Ceftriaxone + Clindamycin
- Diarrhoea in a patient on Desferrioxamine: commence Ciprofloxacin immediately. Ensure, however, they are not GPD deficient – Cefotaxime/ Ceftriaxone are alternatives if the patient is GPD deficient. Cipro can be stopped once you know the diarrhoea is not caused by Yersinia

5. OTHER DRUGS: dosing as per BNFC

- Analgesia: as above
- Folic acid: 1 month – 3years: 2.5mg OD, >3 years: 5mg OD
- Antiemetic: Ondansetron 1st line. Dose as per BNFC
- Laxatives: always prescribe laxatives alongside opioid analgesia. Lactulose/ Movicol/ Senna depending on patient preference and age.
- Antipyretics if itching associated with opioid analgesia: Chlorphenamine 1st line
- Naloxone: always have written on PRN side of chart if patient on opioid analgesia: Naloxone as per BNFC

6. PAIN AT PARTICULAR SITES

- Limb/Joint pain: This is usually due to vaso-occlusive crisis but the possibility of osteomyelitis/septic arthritis must be considered. Management depends on index of suspicion and should be discussed with senior colleagues if in doubt.

The diagnosis of osteomyelitis in the context of sickle cell disease is often difficult, and relies on factors such as positive blood cultures, persistent local inflammation, unusual swelling and/or pain and fever.

Ultrasound and MRI may be helpful, note that X-ray changes do not appear until about 10 days after the onset of infection.

Involve senior colleagues, ID team and orthopaedics early where there is clinical concern.

Organisms:

- Salmonella: most common
- Staphylococcus
- Strep pneumonia

Abx: see above. Decisions on duration of Rx are based on certainty of diagnosis and clinical course. Always consult trust paediatric antibiotic protocol and/or discuss with paediatric infectious diseases team/ microbiology.

- Chest/ Abdominal girdle: see individual sections

Management of Specific Sickling Problems

1. ABDOMINAL CRISIS & GIRDLE SYNDROME

Abdominal crisis can be difficult to diagnosis as abdominal pain is a frequent and often non specific paediatric presentation. Constipation often coexists.

Signs/ symptoms indicating abdominal crisis:

- Generalised abdominal pain
- Anorexia
- Abdominal distension
- Diminished bowel sounds

Girdle syndrome: this is an established ileus and is often associated with ACS (acute chest syndrome)

Signs/ symptoms girdle syndrome:

- Vomiting
- Silent distended abdomen
- Generalised abdominal pain
- Distended bowel loops and fluid levels on AXR
- Hepatic enlargement is common

Differential Diagnosis

- Acute appendicitis
- Pancreatitis
- Cholecystitis
- Splenic abscess
- Ischaemic colitis
- Peptic ulceration

Investigations

- All baseline invx as per page 2
- AXR/ Abdominal USS
- Amylase

Management

In addition to analgesia and fluids, as outlined before:

- NBM and NGT if vomiting, distension, absent bowel sounds
- Monitor abdominal girth approx. 4hourly
- Consider IV abx: Cefuroxime and Metronidazole
- Girdle syndrome may be an indication for [exchange transfusion](#)
- If surgical intervention is contemplated, exchange transfusion should be performed prior to laparotomy

2. ACUTE CHEST SYNDROME (ACS)

Acute sickle chest syndrome is likely to be multifactorial in origin with infection, thrombosis of pulmonary arteries and fat embolism all resulting in potentially similar clinical patterns.

Warnings:

- Cough may be a late symptom
- Dyspnoea and pleuritic chest pain are good indicators
- Physical signs often precede CXR changes
- Pneumonia and ACS can be clinically and radiologically indistinguishable

Signs:

- Bronchial breathing
- Fever, tachycardia and tachypnoea
- Signs of lung consolidation – usually bi-basally initially

Differential diagnosis

- Pneumonia: upper/middle lobe changes without basal involvement can be more indicative of a LRTI than ACS
- Pleuritic pain can also be due to spinal/rib/sternal infarction or sub-diaphragmatic inflammation

Investigations

- Arterial blood gases (ABG) if SaO₂ < 90%
- Chest x-ray
- Blood, throat & sputum cultures and respiratory infection serology (Mycoplasma, Legionella, viral)
- Group & Save, make sure phenotyped red cells are available for transfusion; if diagnosis of ACS clear, blood should be x-matched for exchange transfusion.

Management

- **Transfer all unstable patients to HDU**
- **Oxygenation** – Low threshold for early CPAP if chest signs and sats <90% in air.

A worsening chest x-ray, rapid fall in O₂ saturations or persistent fever may all be indications for exchange transfusion.

- **Intravenous fluids with hyperhydration**, as for painful sickle crisis (maintain strict fluid balance to detect fluid overload)
- **Antibiotics**. IV cefuroxime and oral clarithromycin bd. (Stop prophylactic penicillin V)
- **Incentive spirometry + early physiotherapy intervention**

- **Diuretics:** Be **CAUTIOUS:** must only be used after consultation with a senior paediatric haematologist
- **Bronchodilators:** may be useful for those patients with known airways disease but should not be used routinely

3. APLASTIC CRISIS

Transient red cell aplasia caused by Parvovirus B19 can be lead to a sudden deterioration in anaemia. It is often precipitated by a prodromal illness, the classical 'slapped cheek syndrome' is uncommon. Parvo B19 can affect multiple family members consecutively or concurrently, but secondary infection is uncommon

Diagnosis

- Hb >2 g/dl below steady state level or rapidly falling Hb.
- Reticulocytopenia, absence of polychromasia and nucleated red blood cells on blood film despite low Hb.
- Parvovirus IgM present

Management

- Urgent red cell transfusion is often necessary (if Hb <5 g/dl and/or symptomatic)
- Symptomatic management: O₂, analgesia, fluids as above
- Spontaneous recovery is heralded by return of nucleated RBCs and reticulocytes to peripheral blood

Stroke and other CNS Manifestations

1. STROKE

Stroke is a potentially devastating complication which is often under recognised by those less familiar with managing patients with sickle cell disease.

It occurs most commonly in those with homozygous disease, due to vaso-occlusion of the cerebral vessels.

Risk factors:

- Trans-cranial Doppler (TCD) velocities of >200cm/sec
- Hypertension
- Low HbF
- Anaemia
- ACS
- Previous TIAs

Investigations

- MRI/CT scan of brain should be performed to look for CVA and to exclude haemorrhage (infarcts may not be apparent on CT in the very early stages).
- MR angiography should be performed later (see below).
- Stroke is an indication for exchange transfusion. The following bloods must be taken prior to transfusion if not already performed: ferritin, LFTs, red cell phenotyping, serology for HIV, CMV, and Hepatitis B & C infection

Management

- Rehydrate immediately
- Urgent neurological assessment, and regular monitoring of neurological status
- Seizures may occur and require anticonvulsant therapy

- If clinically unstable, exchange transfusion must be carried out urgently; this is usually performed in 2 or 3 stages with an interval of 4-8 hours between each exchange; the aim is to achieve a HbS level below 20% within 2 days

- If clinically stable exchange transfusion should also be carried out urgently whenever possible; the decision about the timing of exchange transfusion will need to be made for each individual patient depending upon past history and ease of venous access; these cases should be discussed with the Paediatric Haematology consultant on call.

- **Transient Ischaemic Attack:** It is not usually necessary to exchange transfuse urgently 'out of hours'; the decision for exchange transfusion should be taken only where there is evidence that there is a new infarct or bleed and/or the child is clinically unstable. Discuss need for exchange transfusion with Paediatric Haem Consultant on call.

Non-urgent management:

- MR angiography (to assess the pathogenesis, risk of recurrence and need for revascularisation) - the risk of recurrent neurological events is greatest in those with abnormal cerebral vasculature.
- Trans-cranial Doppler studies
- Establish a monthly transfusion programme to maintain the HbS level below 30%.

2. SUBARACHNOID HAEMORRHAGE

Uncommon in children, and often associated with multiple intracranial aneurysms.

Investigation

- CT scan without contrast
- Consider MR angiography later

Management

- Exchange transfusion should be arranged urgently as re-bleeds may occur and surgery may be required.
- Refer to neurosurgeons.

3. CONVULSIONS

Febrile convulsions may occur with high fevers including after vaccination. It is important to distinguish from convulsions due to cerebral sickling. Convulsions may also occur following a stroke

Investigations

- EEG
- CT/ MRI
- Consider MR angiography
- Blood cultures & other infection screen, as clinically indicated

Management

Immediate

- Anticonvulsants as per APLS guidelines
- Antipyretic
- CT brain – unless likely febrile convulsion or known epileptic
- Discuss need for exchange transfusion with Paediatric Haem Consultant on call. Unless the child is clinically unstable, it is not usually necessary to exchange transfuse urgently 'out of hours'; the decision for exchange transfusion should be taken only where there is evidence that the seizures are associated with a new infarct or bleed and/or the child is clinically unstable.

Definitive

- If no abnormality on EEG and CT/MRI, and no recurrence, watch and wait
- If EEG abnormal, but CT/MRI and MR angiography are both normal, consider anticonvulsants.

- If infarction on scanning, or vessel stenosis/occlusion on angiogram, exchange transfuse and consider hyper transfusion regime

Sequestration Syndromes

1. SPLENIC SEQUESTRATION

Splenic sequestration is more common in those under the age of three years and may be recurrent. This is why parents are taught to palpate their child's spleen.

Symptoms

- Abdominal pain
- Abdominal distension
- Sudden collapse

Signs

- Rapidly enlarging spleen (may or may not be painful)
- Pallor, shock (tachycardia, hypotension, tachypnoea)
- +/- Fever due to associated sepsis

Investigations

- FBC & retics (raised in sequestration, absent in aplastic crisis)
- Blood cultures & other infection screen, as clinically indicated
- Parvovirus B19 serology (differential diagnosis is aplastic crisis)
- Cross match and order half the patient's estimated blood volume immediately

Management

- Fluid resuscitation (0.9% NaCl)
- Emergency top-up transfusion, if necessary with O Rh -ve ('flying squad') blood
- Broad spectrum antibiotics – cefuroxime
- Consider a hypertransfusion regime
- **Consider splenectomy if recurrent (> 1 episode)**

Indications for splenectomy: recurrent splenic sequestration (>1 episode), chronic splenic sequestration after trial of monthly transfusion (usually 6-12 months), symptomatic splenomegaly, hypersplenism causing significant pancytopenia

2. HEPATIC SEQUESTRATION

Symptoms

- Right hypochondrial pain
- Abdominal distension
- +/- Fever due to associated sepsis

Signs

- Enlarging tender liver, increasing jaundice
- Collapse/shock is less common than with splenic sequestration

Investigations

- LFTs: Bilirubin often very high
- USS – exclude gallstones/ cholestasis
- Blood cultures & other infection screen, as clinically indicated

Management

- May need urgent top-up transfusion
- IV Cephalosporin, Cefuroxime.
- If the patient becomes tachypnoeic, or develops chest signs, then check arterial blood gases and treat for sickle chest syndrome

Transfer to PICU/HDU

Children requiring CPAP, emergency exchange transfusion or who are unstable in any other way require transfer to HDU/PICU where they will be jointly managed by the Paediatric Haematology and HDU/PICU teams

It is important to discuss any patient likely to require HDU/ PICU admission as early as possible with the PICU team. Patients will be considered for admission to PICU for invasive monitoring and therapy of the following:

- Airway compromise
- Respiratory failure
- Hypotension requiring inotropic support
- Sepsis requiring intensive fluid resuscitation/ inotropic support
- Renal failure likely to require dialysis/haemofiltration
- May need transfer for insertion of adequate access for exchange transfusion

Transfusion

Exchange Transfusion

Purpose of exchange transfusion:

- Rapidly reduce % of sickled RBCs when life threatening complication/ organ failure develops

Patients considered for exchange transfusion:

- ACS causing respiratory failure
- Girdle syndrome
- Stroke
- Multi-organ failure
- Fulminant and resistant priapism (>4hours)

Exchange transfusion requires careful planning and experienced personnel – the transfusion laboratory should be notified as soon as possible, and make it clear the blood is for an exchange transfusion. The RBCs will need to be specially grouped – HbS negative, ABO compatible, Rh negative, Kell compatible

Aims of exchange transfusion:

- a) To reduce the HbS level to < 20% over 2 - 3 days unless acutely unwell
- b) To keep Hb \leq 10g/dl throughout
- c) To maintain a steady state blood volume and Hb throughout

- Do not use diuretics unless discussed with senior haematologist
- Continue to administer IV fluids at the standard rate between transfusions.

Critically ill patients may require exchanges to be more frequent than daily and may require the sickled cell percentage to be reduced at a faster rate than above.

Aim to leave a 4-8 hour break in between exchanges, but this may need to be a continuous process in the very unwell patient.

Particular attention should be paid to PaO₂, coagulation, CVP, acid-base balance, blood pressure, citrate load, calcium, renal function and temperature.

Preliminary investigations

- FBC
- HbS level (or S+C level if HbSC disease)
- Extended RBC phenotype (if not already known), x-match.
- U & Es, Ca²⁺
- Arterial blood gases - in those with symptoms suggestive of acute chest or girdle

Syndrome

- Serology for Hepatitis B & C, if not done recently.

Volumes required

- The number and volume of exchange transfusions performed in a child with sickle cell disease will

depend on the severity of the clinical problem and the haemodynamic stability of the child

- A 'total' exchange is 1.5 - 2 times the child's blood volume and this is usually performed in 3 or 4 exchange procedures

Volume (ml) of blood removed *for each procedure* should be:

$30 \times \text{weight (in kg)} = \text{volume in ml}$

Procedure preparation:

- Patients must be well hydrated prior to starting an exchange transfusion.
- Adequate explanation of the purpose, risks and benefits of the exchange transfusion should be discussed with the parents +/- patient and documented
- Two ports of venous access – one for venesection, the other for administration of blood/crystalloid
- Essential that blood is readily available from blood bank before starting the procedure

Procedure

The aim is an isovolaemic procedure with monitoring of blood pressure, heart rate and oxygen saturations every 15 minutes, and 1hourly temperature monitoring.

- Exchanges are done in 'aliquots' of approximately 1/10 of the total to be exchanged (never greater than 5% of the blood volume) – remember transfused blood has a higher Hct than the venesectioned blood
- Ensure the child is well hydrated between exchanges
- Hb should be kept $\leq 10\text{g/dl}$ at all times
- **For the first procedure**, venesect 30% of the above volume (i.e. approx. 10 ml/kg) in aliquots of 10 - 50 ml using a large syringe.
 - Normal saline should be concurrently infused at the same rate to maintain isovolaemia.
 - If the child has haemoglobin of less than 6 g/dl replacement with blood rather than normal saline will be needed.
 - The venesectioned blood can be discarded into a venesection bag via a 3-way tap.
- Continue venesectioning the remaining 70% of the volume (approx. 20 ml/kg) replacing with blood at a rate of 7.5ml per kg per hour (red cells in SAG-M) instead of normal saline. This process should take about 160 min, depending on the rate of flow of blood and the clinical condition of the patient.
- Where possible leave at least 4-6 hours between each exchange procedure. In critically ill patient's exchanges may need to be continuous.
- Check FBC, HbS %, U&E including calcium, and coagulation, at the end of each procedure. Ensure that the Hb $\leq 10\text{g/dl}$ to reduce the risk of hyperviscosity.
- Continue with 3 to 4 exchange procedures until the Hb S $\leq 20\%$.

- **NB** for the second and subsequent exchange procedures, it may be necessary to use a ratio of 50% saline:50% blood (rather than 30:70) in order to prevent the Hb from rising too high. This should be discussed with the paediatric haematology SpR or consultant when planning the procedure.
- A top-up transfusion can be given at the end of the final exchange procedure to give a final Hb of 10 -12 g/dl.

Possible immediate complications

- Anaphylactoid reactions due to HLA antibodies. Treat with antihistamine and/or Corticosteroid
- Metabolic disturbances are rare, occurring usually in small children
- Convulsions are very rare. They are usually a sign of cerebral sludging, often in patients with previous CNS problems. Give O₂, ensure hyperhydration and that the Hb is not >11g/dl, antiepileptic as necessary
- Hypertension is occasionally seen in patients with circulatory overload. If diastolic BP increases by > 20 mmHg, slow down exchange, check Hb not >11 g/dl or Hct not > 0.4. If diastolic BP is > 100 mmHg stop the exchange, venesect, and consider antihypertensives.

Elective Transfusions

Indications:

- Stroke, & other CNS complications
- Chronic organ damage e.g. Chronic Renal Failure or chronic lung disease
- Failure to thrive (when causes other than sickle cell disease has been excluded)
- Intractable or very frequent painful crises

The objective is to keep the HbS level below 25%. This can be achieved by regular top-up transfusions keeping the Hb between 10 and 14 g/dl,

Regular exchange transfusions may also be undertaken in some circumstances, which are equally as effective in reducing complications and cause less iron accumulation. However, they are associated with higher donor exposure and require better venous access and are more complex to undertake.

Ensure patient has been vaccinated against Hepatitis B.

Investigations:

1-2 days prior to planned transfusion

- FBC
- HbS level
- Antibody screen & cross match
- U&Es, LFTs
- Ferritin

Prior to undertaking regular transfusions:

- HBsAg, level of anti-HBs Ab (revaccinate if < 100 iu/ml) annually. Remember to state on the virology request form that the patient has been vaccinated.
- HCV Ab and save serum annually

For top-up transfusions the volume of blood required (ml) is:

$(Hb_{desired} - Hb_{current}) \times \text{weight (kg)} \times 4$

Do not attempt to raise the haemoglobin by more than 4 g/dl at any one transfusion.

The usual rate of transfusion is **5ml/kg/hour** and for elective transfusion should **never exceed a maximum rate of 150 ml/kg/hour**.

Post-transfusion, check FBC and HbS level.

Top up transfusions are generally performed monthly; if the pre-transfusion Hb is < 10 g/dl, more frequent transfusions are required. If the post-transfusion Hb is < 13 g/dl, insufficient blood is being given. In some cases, failure to get an adequate increment may be due to hypersplenism.

Transfusion Reactions

Intravascular haemolysis: usually presents within minutes of starting the transfusion and may be an indication of blood group incompatibility.

- Discontinue the transfusion immediately
- Check ABO of blood against patient's blood group
- Ensure adequate hydration
- Inform the haematology SpR and Blood Transfusion Laboratory.
- Monitor for renal dysfunction and haemoglobinuria by urine dipstick and measuring the urine output.

Non-haemolytic, febrile reactions: occurring an hour or more after commencing the transfusion, often indicate sensitisation to plasma proteins or white cells.

Initially slowing the rate of transfusion and administer chlorphenamine +/- hydrocortisone. If pyrexia persists or the patient is clinically unwell discontinue the transfusion.

Pyrexia associated with rigors (but not hypotension) occurring more than one hour after starting the transfusion usually indicates alloimmunisation - antibodies to Rhesus or other blood group antigens, the transfusion should be discontinued. Paracetamol and/or chlorphenamine should be given.

Discuss with haematology SpR and Blood Transfusion Laboratory and investigate appropriately following discussion.

Iron Overload

Iron overload arises from recurrent transfusions. DESFERRIOXAMINE is the iron chelator of choice

Chelation therapy should usually commence after a child has received 15 transfusions or when the ferritin reaches 1000 mcg/l. Ferritin will need to be checked on more than one occasion when the child is well, since it is an acute phase reactant.

Treatment should not be commenced until after the age of 2 years and only when needed (see above) since it has a detrimental effect on skeletal growth. It can also cause local and allergic reactions.

Desferrioxamine (DFO) is usually given as an overnight subcutaneous infusion. **The standard dose of DFO is 25 - 50 mg/kg/day up to 7 nights per week.**

Vitamin C at a dose of 100 – 200 mg/day) should be given on the days when the patient receives DFO. This should not be commenced until the patient has been on DFO for one month. It should not be given to patients with cardiac dysfunction.

Investigations

- Annual ophthalmology (including baseline)
- Annual audiology reviews (including baseline)
- Glu, HbA1C, cortisol,

- TSH/T4, FSH/LH/oestradiol or testosterone
 - ECG & ECHO or MUGA-scan
 - Monitor growth including sitting and standing heights (see also growth and endocrine section)
 - MRI for estimate of liver/cardiac iron overload at intervals depending on compliance
- DFO must be stopped and the patient admitted for investigation and treatment if they develop abdominal pain & diarrhoea as this may be due to Yersinia infection.

Oral chelators

Deferasirox and deferiprone, both oral iron chelators, are used for selected patients who are unable to tolerate or comply sufficiently well with desferrioxamine. Both oral chelators require very close monitoring both of full blood counts (particularly for deferiprone which may cause agranulocytosis) and renal function (particularly for deferasirox).

Priapism

Priapism may occur in childhood and is often under reported. You should ask about it specifically when taking a medical history from a male with sickle cell disease. It often starts at night, associated with a full bladder and left untreated it can cause cumulative damage and potentially impotence.

Types of presentation

- Acute, fulminant (> 4 hours).
- Stuttering (repeated painful erections lasting more than 30 minutes)

Management of acute/fulminant priapism

- Rehydrate
- Opiate analgesia, +/- sedation
- Catheterisation, if necessary, to empty bladder
- Urgent Paediatric urology opinion
- Where a Consultant Paediatric Urologist is available and priapism persists he/she may decide to administer an intracavernous alpha-agonist, e.g. phenylephrine 0.5 mg. [1 ml of 1% (i.e. 10 mg/ml) phenylephrine is added to 39 ml of normal saline to produce a solution of 0.25 mg/ml; 0.5 mg is injected (i.e. 2 ml) directly into one corpus cavernosum via a 27-gauge needle; injection can be repeated every 15 minutes to a maximum of 6 injections; monitor BP regularly.] NB Where a GA is required the 'low/intermediate risk' surgery transfusion guidelines should be followed.

- **Where a Consultant Paediatric Urologist is unavailable and priapism persists exchange transfusion is likely to be required but should be first discussed with the Paediatric Haematology Consultant.**

- If detumescence has not begun within 24 hours, penile aspiration or the Winter procedure (a spongiosum-cavernosum shunt) should be considered (patients will require exchange transfusion first).

Management of stuttering priapism

- Increased oral fluids, with frequent emptying of bladder
- Oral analgesia
- Drug treatments such as Anti-androgens (cyproterone), alpha-agonists (etilefrine) or oestrogens (diethyl stilbestrol) can be used in the short to medium term (on the advice of the Paediatric Urologists) to prevent spontaneous erections.

The patient should seek medical attention if an episode lasts > 3 hours.

Renal Problems

1. HAEMATURIA

Microscopic haematuria is common in sickle cell disease; macroscopic haematuria may be due to urinary infection or papillary necrosis. Passing of renal papillae may cause renal colic and ureteric blockage. Haematuria can also occur in patients with sickle trait.

Investigation

- MSU for culture to exclude infection
- Ultrasound scan
- Hydrated intravenous urography may be necessary to establish the diagnosis, discuss with registrar or consultant first.

2. NOCTURIA AND ENURESIS

Nocturia and enuresis are common in part due to obligatory high fluid intake, coupled with reduced urinary concentrating capacity.

Reassurance and measures such as reward systems, bell and pad training, etc. may be required. Referral to a local Enuresis Clinic. Always exclude UTI first.

3. URINARY TRACT INFECTIONS

Investigate and manage as per RCPCH/ NICE guidelines as for any child with a UTI
Remember it may be precipitated by haematuria, secondary to papillary necrosis.

4. CHRONIC RENAL FAILURE

Uncommon in children. Predictors include increasingly severe anaemia, hypertension, proteinuria, the nephrotic syndrome, and microscopic haematuria.

Investigations

- Urea and electrolytes, calcium, phosphate, bicarbonate; immuno-globulins and autoantibodies.
- FBC and reticulocytes
- MSU for M, C & S; 24-hour urine collections for protein and creatinine clearance
- Ultrasound of kidneys and urinary tract

Management

- Refer to paediatric nephrologists
- Consider erythropoietin and/or hypertransfusion regime

Eye Problems

Ocular complications are uncommon in children. Retinal vessel occlusion may occur in adolescence particularly in Hb SC disease. Children and their parents should report any change in vision and be referred for an urgent ophthalmological opinion. Annual ophthalmology review is required for all children receiving iron chelation therapy

Vitreous haemorrhage and retinal detachment can also occur.

The Biliary Tract

1. GALLSTONES

Haemolysis increases the risk of pigmented gallstones. This can cause:

Pigmented gallstones due to ongoing haemolysis is common in sickle cell disease, occurring in at least 30% of children. It is often asymptomatic but can precipitate painful abdominal crises

. It can also cause:

- Girdle syndrome
- Acute/ chronic cholecystitis
- Biliary colic
- Acute pancreatitis
- CBD obstruction

Investigations

- Plain abdominal x-ray (as many as 50% of stones may be radio-opaque)
- Abdominal ultrasound

Always consider the possibility RUQ pain may represent a chest crisis or hepatic sequestration

Management

- Analgesia
- Hydration
- Antibiotics
- Surgical review
- Recurrent episodes of cholecystitis is an indication for cholecystectomy

2. INTRAHEPATIC CHOLESTASIS

Some patients experience episodes of severe hyperbilirubinaemia (conjugated + unconjugated) with raised alkaline phosphatase, associated with fever and hepatic pain in the absence of demonstrable stones. These episodes are thought to be due to severe intrahepatic sickling.

Management

- Analgesia (care as most opiates are metabolised in the liver)
- Hydration
- Antibiotics; e.g. cefuroxime
- Monitor liver function tests, and as for girdle syndrome/hepatic sequestration
- Hyperhaemolysis +/- sequestration may supervene, requiring frequent transfusion.

In severe cases, exchange transfusion may be needed

Avascular Necrosis

AVN occurs most commonly in the hips and shoulders and causes chronic pain, joint damage and significant limitation to movement

Presentation

- Pain: hip/ groin/ knee/ shoulder. Initially just pain on movement but later there is pain at rest, also.
- Limitation of movement; particularly abduction and external rotation of the hip, external rotation of the shoulder.

Differential diagnosis

- Osteomyelitis
- Septic arthritis
- These are suggested by swinging pyrexia, severe systemic disorder, positive blood cultures and neutrophilia

Investigations

- X-ray (late changes only) – helpful initially to exclude fracture/ dislocation
- MRI (This will usually show changes earlier than x-ray)

Management

- Analgesia with non-steroidal anti-inflammatory agents
- Rest and the avoidance of weight bearing (v. difficult to implement).
- Transfusion cannot reverse the process but may prevent progression to the contralateral joint; it is performed pre-operatively and for 3 months post-operatively to maximise bone healing.
- Refer for orthopaedic assessment

Osteotomy and/or decompression surgery may be considered.

Major joint surgery may be necessary if pain is continuous (> 2 years) or very severe, or if the patient's mobility is seriously affected.

Different types of prosthesis, hip fusion, or bone grafting are used depending on the individual case.

Growth, Puberty and Fertility

1. DELAYED PUBERTY

Common particularly in boys. Related to chronic disease and lower Body Mass for age. Very rarely hypothalamic / hypophyseal infarcts are responsible.

Refer to paediatric endocrinologist if there are no signs of puberty by 13 years in a girl or 14 years in a boy, it may be appropriate to refer earlier if there is poor growth
Height and weight should be recorded at clinic review

Management

Optimise nutrition, refer to dietitian
Consider regular transfusions for 6-12 months

2. FERTILITY

Most girls are fertile. Many boys, however, have reduced sperm motility +/- reduced sperm counts. Recurrent priapism can also result in erectile impotence.

3. CHILDREN ON REGULAR TRANSFUSIONS (+/- DESFERRIOXAMINE)

Should have regular endocrine monitoring because of the risk of iron overload
Desferrioxamine can cause bone abnormalities and reduced spinal growth.

Measurements

Height at least yearly to 10 years of age, and then every 6 months.
Sitting height at each visit.

Puberty

Puberty may be delayed or fail to occur. The commonest pituitary abnormality related to iron deposition is gonadotropin deficiency. Pubertal development should be monitored and referral made to paediatric endocrinologist.

Blood tests

Once yearly after age 7:

- Thyroid function
- Calcium and bone profile
- Random or fasting glucose
- Electrolytes
- LFTs
- LH/FSH
- Estradiol or testosterone

Once yearly after age 10:

- Oral Glucose Tolerance Test: *if there are clinical concerns about adrenal function*

Surgery and Anaesthesia

Pre-operative sickle screening

- Children from the following ethnic groups should be screened:
African, Afro-Caribbean, Mediterranean and Middle Eastern.
- Screening at risk groups must include an FBC and haemoglobinopathy screen, stating the ethnic group of the child on the request form
-
- A sickle solubility test will only be performed when necessary
-
- Cases that have to be done as emergencies will all need a sickle solubility test (urgently) and HPLC (to follow), which will be costlier and will not provide a full diagnosis immediately.
- The admitting clinician must ensure that consent (verbal) is obtained for testing and that an appropriate explanation is given to parents.
- All children with newly identified sickle cell disease (SS, SC, SD-Punjab, S_ thalassaemia) should be referred to the Paediatric Haematology clinic. Sickle cell trait does not require referral.

Peri-operative management plan

All patients with sickle cell disease are at risk of sickle complications at the time of surgery, however, certain patients with sickle disease are at greater risk of peri-operative complications. They include patients with:

- o severe sickle related problems such as chest crisis, CNS disease and frequent, painful crises
- o severe obstructive sleep apnoea
- o major surgery

It is essential that the paediatric haematology team be informed well in advance so that they formulate an appropriate management plan.

Pre-op clinic

- o Ensure that the red cell phenotype is known by the blood transfusion laboratory. In all cases except the most minor surgery, there must be phenotyped blood cross-matched before surgery. In all cases, there must be at least a group and save in the laboratory before theatre.
- o Ensure that there is a plan from the paediatric haematology team for the peri-operative

management of the patient.

- Ensure that any special support. e.g. PICU/HDU bed for CPAP has been organised.
-
- Ensure the anaesthetist is aware prior to the date of surgery

Pre-op transfusion

Appropriate peri-operative management is essential, optimising oxygenation, peripheral blood flow and analgesia.

1. Top up transfusion

Most patients with sickle cell anaemia are relatively asymptomatic with an Hb down to 6.5 g/dl. This chronic anaemia is not in itself an indication for transfusion regardless of the sickle ratio.

a) Low/intermediate risk surgery

Top-up transfusions where the Hb is less than 6.5 g/dl should be considered for children with no special risk factors who are currently well and having minor (e.g. grommet insertion) or intermediate risk (e.g. umbilical hernia repair) surgery. Aim for Hb > 8 g/dl post transfusion, and in all cases Hb should not exceed 10 g/dl.

b) Laparoscopic cholecystectomy and laparoscopic splenectomy

In cases where there are no special risk factors, it is reasonable to use top-up transfusions where the Hb is less than 6.5 g/dl. Aim for Hb > 8 g/dl post transfusion, and in all cases Hb should not exceed 10 g/dl.

c) Tonsils/adenoids hypertrophy +/- obstructive sleep apnoea

Top-up transfusions should be given pre-operatively where the Hb is less than 6.5 g/dl

2. Exchange Transfusion

Exchange transfusion is likely to be required if the patient has serious chronic complications e.g. chest crises, stroke or frequent painful crisis. Exchange transfusion should be considered for major surgery, especially when conditions may predispose to sickling.

It is mandatory in preparation for:

- major abdominal surgery
- hip/knee replacement
- eye surgery
- organ transplantation
- surgery involving hypothermia or tourniquets (e.g. cardio-thoracic, some orthopaedic)

Procedure for surgery:

- Admit the patient to the paediatric ward, not the day care unit, and warn the parents and child that at least one overnight stay is required.
- Start iv fluids when oral fluids are stopped and continue until the patient is able to take oral fluids freely.
- Monitor SpO2 for 24 hours after surgery.
- Give prophylactic antibiotics (antibiotic choice depends on type of surgery).
- Keep the patient normothermic throughout the perioperative period.
- Use appropriate analgesia and minimise sympathomimetic effects of the pain response.
- Intraoperative transfusion will depend on blood loss and the risk of post-operative complications. For thoracic surgery and some abdominal and pelvic surgery, including splenectomy, CPAP on HDU or PICU for a minimum of 24 hours after surgery is recommended. Prophylactic post-operative chest physiotherapy, including incentive spirometry, should be instituted.

Patients with sickle cell trait:

These patients are also at risk in situations where there is a risk of hypotension, hypoxia or prolonged application of a tourniquet. They should be well hydrated, oxygenated and kept warm in the perioperative period as for patients with sickle cell disease. If the need for prolonged tourniquet application is likely, this should be discussed with the paediatric haematologists in advance.

Outpatient Management of Patients with a Sickle Cell disorder

The Aims of the Clinic are to:

- Monitor progress of the children: medical, educational and psychosocial.
- Establish baseline observations for comparison in acute illness.
- Educate parents and children in the management of sickle- related problems.
- Genetic counselling.

New Patients

Infants are usually referred following neonatal cord-blood screening. The aim to review them by three months of age.

- Confirm diagnosis with quantitative Hb HPLC: HbS, A2, F and other abnormal HbS, e.g. HbC. Check FBC, retics, U + Es, LFTs and LDH. This should be repeated at 1 year of age when the blood group, red cell phenotype and G6PD level should also be checked.
- Take full personal and family history including names and ages of parents and siblings. Parents and all siblings should have a full blood count, and quantitative Hb electrophoresis, if this has not already been performed. Also plans for future children can be discussed.
- Explain to parents the probable diagnosis and its implications, including genetic counselling.
- Weigh, measure height and examine the child.
- Check immunisations.
- Discuss acute complications in infancy including dactylitis, acute splenic sequestration
- Prescribe Penicillin and folic acid if appropriate and give follow-up appointment
- Ensure that a haemoglobinopathy card has been issued, and that the patient and family have contact details for the hospital, the CNS, the consultant's secretary and PAU
- Check that the child is known to the Health visitor, GP and sickle cell counsellor.
- Issue a splenectomy/hyposplenism card
- Discuss analgesia to ensure analgesics available and being used appropriately at home

Routine Medication

Folic acid

From to Dose

1month - 3 years 2.5 mg

3 years onwards 5 mg od

Penicillin V

From to Dose

birth 1 year 62.5mg bd

1 year 5 years 125 mg bd

5 years onwards 250 mg bd

Regular Patients

- Weight and height; pulse oximetry; BP if aged >10 years. Each patient should have a growth chart.
- Document any sickle-related or other disease since last visit, immunisation up to date, school progress and attendance's and holiday plans. Ask about bed-wetting, priapism and symptoms of upper airways obstruction.
- Examination: check especially for jaundice, heart for size and murmurs, liver and spleen size (measure).
- Any questions from parents, involve children as appropriate, any letters to be written.
- Prescribe Penicillin (check being taken), folic acid. General Practitioner prescribes anti-malarials if required.
- Annual review - All patients should have FBC, retics, film, LDH, liver function tests, electrolytes, urea and creatinine, ferritin, blood group and antibody, Hepatitis Bs-Ab to check immune status, vit D level.
- Transcranial Doppler (TCD) from the age of 2 years
- Discuss analgesia to ensure analgesics available and being used appropriately at home.
- Offer support from psychologist if indicated.

Prophylaxis against pneumococcal infection

There is now very good evidence that penicillin prophylaxis protects against pneumococcal septicaemia / meningitis PROVIDED IT IS TAKEN REGULARLY.

It is essential that all children with sickle cell disease take penicillin twice daily continuously, starting by the age of 3 months.







In addition, all children with sickle cell disease should receive Routine vaccinations, which includes Prevenar.

Pneumovax is given to children over the age of two years at 5 yearly intervals but does not give complete protection and is not an alternative to penicillin.

Appendices:

Examples of age appropriate pain charts:

Initial morphine boluses should be given orally. IV morphine should be set up as an infusion.

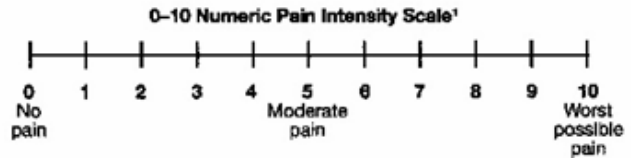
							Patient Details			
Admission Checklist for Acute Painful Crisis in Sickle Cell Disease (Younger Children)										
Date and Time presented:										
<input type="checkbox"/>	Initial observations (including O2 saturations) recorded									
- Are O2 saturations >95%? If not, supplemental oxygen required										
				<input type="text"/>						
					0 No Pain	1-2 Mild Pain	3-4 Moderate Pain	5-6 Severe Pain	7-8 Very Severe Pain	9-10 Worst Possible Pain
<input type="checkbox"/>	Pain Score on admission:		/10							
<input type="checkbox"/>	Recent analgesia (within last 24-48hrs):									
<input type="checkbox"/>	Analgesia offered within 30 minutes - Morphine bolus of 100mcg/kg required? Y/N									
- if severe pain, or moderate pain with previous analgesia, give strong opioid										
- if moderate pain with no previous analgesia, give weak opioid										
Record pain score every 30 minutes until satisfactory pain relief, and then every 4 hrs										
- if patient on strong opioid, record observations (including sedation score) every hour for 6 hours, then every 4 hours										
<input type="checkbox"/>	Re-assessment of pain by 1 hour									
- Morphine bolus of 100mcg/kg required? Y/N										
- If repeated (>2) boluses are required, IV infusion should be started early										

Patient Details

Admission Checklist for Acute Painful Crisis in Sickle Cell Disease (Older Children)

Date and Time presented:

- Initial observations (including O2 saturations) recorded
- Are O2 saturations >95%? If not, supplemental oxygen required



Pain Score on admission: /10
Recent analgesia (within last 24-48hrs):

- Analgesia offered within 30 minutes - **Morphine bolus of 100mcg/kg required? Y/N**
- if severe pain, or moderate pain with previous analgesia, give strong opioid
- if moderate pain with no previous analgesia, give weak opioid
- Record pain score every 30 minutes until satisfactory pain relief, and then every 4 hrs**
- **if patient on strong opioid, record observations (including sedation score) every hour for 6 hours, then every 4 hours**
- Re-assessment of pain by 1 hour
- **Morphine bolus of 100mcg/kg required? Y/N**
- **If repeated (>2) boluses are required, IV infusion should be started early**

Hydroxycarbamide

- Hydroxycarbamide reduces the frequency of painful crisis, chest syndrome and transfusion requirements in both adults and children with severe sickle cell disease.
- It also appears to improve growth and possibly prevent hyposplenism in children. It has not been proven to prevent stroke or avascular necrosis in joints.
- Caution is advised, however as its long-term profile in terms of toxicity, mutagenicity, teratogenicity and leukaemogenic potential is unknown. Careful discussion of these issues with the parents prior to commencing hydroxyurea is essential, and parental consent should be recorded in the patient's notes.
- **The decision to start hydroxycarbamide must only be made after discussion with a Paediatric Haematology Consultant.**

Patient Exclusion criteria

- Age < 2 years
- Regular transfusion regime
- Abnormal liver function tests (AST or ALT > x2 upper limit of normal)
- Inability to attend clinic regularly for follow-up

Patient Eligibility

Patients (HbSS or S β -thalassaemia, *not* HbSC) with a severe clinical course *may be offered* hydroxycarbamide i.e. with

either: 3 admissions with painful crisis within one year
or Frequent days of pain at home, leading to a lot of time off school
or Recurrent acute chest syndrome

The following predict a more severe clinical course and are additional reasons *to consider offering* hydroxycarbamide if a child also has severe clinical symptoms:

- Steady state values: Hb <7 g/dl
- WBC >15 x10⁹/l
- HbF <6%
- Renal insufficiency due to sickle cell disease

Dose & Monitoring

- Start at 15 mg/kg/day (if old enough to swallow tablets then round up to the nearest tablet dose. If no or poor response increase dose by increments of 5 mg/kg/day every 8-12 weeks (max: 35 mg/kg/day)
- Monitor FBC, HbF level and retics, every 1 - 2 weeks initially, then 4 - 6 weekly when on a stable dose
- Monitor biochemistry profile (hydroxycarbamide has renal excretion & hepatic toxicity)
- Assess clinical response after 9 - 12 months. If being treated for painful crises, if there is no improvement at this time, consider stopping - discuss with Consultant.

Stop treatment if any of the following occur:

- Neutrophils < 1.5 x10⁹/l
- Platelets < 80 x10⁹/l
- Retics < 80 x10⁹/l
- Hb < 5.5 g/dl

Hb drops by more than 20% from baseline, or $> 2\text{g/dl}$

☒☐ If treatment is interrupted, check FBC weekly and restart after counts recover, at a dose lower than the patient was on at the time toxicity developed

☒☐ Aim to give the maximum tolerated dose (MTD), but if haematological and clinical responses are achieved at a lower dose consider using this dose.

☒☐ Hydroxycarbamide may need to be stopped during an acute admission when sepsis is known or suspected.