NHS
West London
Haemoglobinopathy
Coordinating Centre

GUIDELINES FOR THE MANAGEMENT OF SICKLE CELL DISEASE IN PAEDIATRICS

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Name of originator/author:	
Name of responsible committee/individual:	Dr Kirstin Lund, Consultant Paediatric Haematologist, Imperial College Healthcare NHS Trust Dr Rubina Malik, Consultant Paediatric Haematologist, St George's University Hospitals NHS Foundation Trust Dr Indu Thakur, Consultant Paediatric Haematologist, Cardiff and Vale University Health Board Dr Alison Thomas, Consultant Paediatric Haematologist, St George's University Hospitals NHS Foundation Trust Dr Sheana Wijemanne , Consultant Paediatric Haematologist, London North West University Hospitals NHS Trust
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Contents

INTRODUCTION

This guideline covers the management of clinically significant sickle cell disorders in children and is directed at all clinical staff involved in the care of children with sickle cell disease (SCD).

This guideline is divided into 4 sections A/ acute and B/ chronic presentations which are explored by organ system. C/ explores general elements of the management of sickle cell disease and D/ covers therapeutic approaches.

DEFINITIONS

A&E	Accident and Emergency (Emergency Department)
ACS	Acute chest syndrome
APLS	Advanced Paediatric Life Support
CMV	Cytomegalovirus
CNEP	Continuous negative extrathoracic pressure
CNS	Clinical Nurse Specialist
CNS	Central Nervous System
CPAP	Continuous positive airways pressure
CRP	C-reactive protein
CT	Computerised tomography
CVA	Cerebrovascular Accident
CVS	Cardiovascular System
DFO	Desferrioxamine
DFP	Deferiprone
DFX	Deferasirox
ED	Emergency Department
FBC	Full Blood Count
HCC	Haemoglobinopathy Coordinating care Centre
HIV	Human immunodeficiency virus
IV	Intravenous
LDH	Lactate dehydrogenase
LFT	Liver Function Test
LHT	Local Haemoglobinopathy Team
MRI	Magnetic resonance imaging
MSU	Mid-stream urine
NCA	Nurse controlled analgesia
NHR	National Haemoglobinopathy registry
PA	Personal Assistant
PCA	Patient controlled analgesia
PED	Paediatric Emergency Department
PRN	As and when needed
SAE	Serious Adverse Effect
SAGM	Saline, adenine, glucose mannitol (additive solution in blood)
SCD	Sickle Cell Disease
SHO	Senior House Officer
SHOT	Serious Hazards of Transfusion
SHT	Specialist Haemoglobinopathy Team
SpR	Specialist Registrar
TCD	Transcranial Doppler

TCDi	Transcranial Doppler Imaging
U&E	Urea and electrolytes
UTI	Urinary Tract Infection

SCOPE

This guideline is directed at all clinical staff within the West London Haemoglobinopathy Coordinating Care (HCC) network involved in the care of children with sickle cell disease (SCD). It applies to all patients known to have or who are diagnosed with SCD. SCD includes sickle cell anaemia (HbSS) as well as those compound heterozygous states (HbSC, HbSD, HbSO-Arab and sickle ß-thalassaemia) and other less common conditions that give rise to a clinically significant sickling disorder.

The guideline describes the clinical management of SCD. It should be read in conjunction with:

Sickle Cell Disease in Childhood: Standards and Recommendations for Clinical Care
https://www.sicklecellsociety.org/wp-content/uploads/2019/11/SCD-in-Childhood_Final-version-1.pdf

NICE Guidance on the management of sickle cell acute painful episodes
http://guidance.nice.org.uk/CG143

BCSH Guideline on the management of Acute Chest Syndrome in Sickle Cell Disease 2015
http://onlinelibrary.wiley.com/doi/10.1111/bjh.13348/epdf

BCSH guidelines for the use of Hydroxycarbamide in children and adults with sickle cell disease
https://b-s-h.org.uk/guidelines/guidelines/guidelines-for-the-use-of-hydroxycarbamide-in-children-and-adults-with-sickle-cell-disease

BCSH guidelines for red cell transfusion in sickle cell disease
https://b-s-h.org.uk/guidelines/guidelines/red-cell-transfusion-in-sickle-cell-disease-part-I
https://b-s-h.org.uk/guidelines/guidelines/red-cell-transfusion-in-sickle-cell-disease-part-ii

CONTACTS

Specialist Haemoglobinopathy Team switchboard phone numbers –

Paediatric Haematologist on call

North West London	St Mary's Northwick Park Hospital	Switchboard: 020 3312 6666 Switchboard: 020 8864 3232
South West London	St George's	Switchboard: 020 8672 1255
UHB-Cardiff and Vale	Children's Hospital for Wales	Switch board 02920 747747

Specialist Haemoglobinopathy Team – Consultant Contact Details

Dr Kirstin Lund	Consultant Paediatric Haematologist, Imperial College Healthcare NHS Trust	Email: kirstin.lund@nhs.net
Dr Alison Thomas	Consultant Paediatric Haematologist, St George's University Hospitals NHS Foundation Trust	Email: alison.thomas6@nhs.net
Dr Sheana Wijemanne	Consultant Paediatric Haematologist, London North West University Hospitals NHS Trust	Email: sheana.wijemanne@nhs.net
Dr Indu Thakur	Consultant Paediatric Haematologist, Cardiff and Vale University Health Board	Email: Indu.Thakur@wales.nhs.uk
Dr Susan Baird	Consultant Paediatric Haematologist,	Email: Baird, Susan Susan.Baird@nhslothian.scot.nhs.uk

LIST of Local Haemoglobinopathy Teams

Paediatric Haematology service	Lead consultant	Email
Chelsea and Westminster Hospital NHS Foundation Trust	Dr Anne Davies	annedavies@nhs.net
West Hertfordshire Teaching Hospitals NHS Trust	Dr Jeremy Roskin	jeremyroskin@nhs.net
Luton and Dunstable University Hospital NHS Foundation Trust	Dr Toyin Lythe	toyin.lythe@nhs.net
Bedford Hospital NHS Trust	Dr Swati Pradhan	swatipradhan@nhs.net
Epsom and St Helier University	Dr Arun Kundu	arunavakundu@nhs.net

Hospitals NHS Trust		
Ashford and St. Peter's Hospitals NHS Foundation Trust	Dr Claire Mitchell	claire.mitchell15@nhs.net
Kingston Hospital NHS Foundation Trust	Dr Rowan Heath	rowan.heath@nhs.net
Surrey and Sussex Healthcare NHS Trust	Dr Kamal Khoobarry	Kamal.khoobarry@nhs.net
Royal Surrey NHS Foundation Trust	Dr Juliet Oliver	Juliet.oliver@nhs.net

Sickle Cell Society
Address:
54 Station Rd,
Harlesden,
NW10 4UA
(020 8961 7795/4006)
Website: www.sicklecellsociety.org e-mail: sicklecellsoc@btinternet.com

A/ ACUTE COMPLICATIONS

A 1/ ASSESSMENT OF THE SICK SICKLE PATIENT

Sickle cell disease is a multi-system disorder which can manifest both acutely and chronically with a variety of symptoms, some of which may be easily overlooked by healthcare professionals not used to managing patients with sickle cell disease. It is not uncommon for multiple symptoms to present simultaneously. The triggers which warrant a high degree of suspicion in this patient group are as follows:

- Severe pain
- Pallor or jaundice
- Dyspnoea, tachypnoea, chest pain
- Marked pyrexia (>38 ^{o}C), tachycardia, hypotension
- Abdominal pain or distension, diarrhoea, vomiting
- Headache, seizure, focal neurological disturbance
- Priapism (> 4 hours)

Local guidelines should be followed regarding patient admission pathways as they differ between centres. Initial assessment should be undertaken in an acute care setting. The relevant paediatric junior doctor should see the patient as soon as possible. If the patient is clearly in a painful crisis, analgesia should be administered **as soon as possible,** UK Sickle guidelines state that the patient should be treated within 30 minutes of arrival. Analgesia may precede the taking of a more detailed history. The senior paediatric team (and if deemed necessary the Haematology team) should be informed of all children admitted.

A full history and examination must be carried out, the following should be assessed and recorded in the notes:

- The site and intensity of the pain
- Any focus of infection (including the urinary tract)
- Observations: pulse, blood pressure, oxygen saturation on air, respiratory rate, temperature.
- Chest symptoms and signs
- Liver and spleen size (cm)

Baseline Investigations

- FBC & reticulocytes
- Haemoglobin electrophoresis (HPLC)
- Group & screen
- Biochemistry (Renal profile, LFTS, LDH, CRP)
- Microbiology screen

Additional tests should be undertaken if indicated:

Test	Indication
Venous gas	Respiratory symptoms
Chest x-ray if indicated (i.e. symptoms/ signs)	Respiratory symptoms
ECG	Cardiac symptoms/signs
Serum amylase Abdominal Ultrasound	Abdominal symptoms/signs Symptoms suggestive of Cholecystitis
Throat, nose, sputum, stool, CSF cultures	As clinically indicated
Stool MC&S for *Yersinia* and *Klebsiella*	Patients on chelation with diarrhoea/abdominal pain
Yersinia serology	
Legionella Ag/ Mycoplasma and Chlamydia serology	Chest symptoms/signs
Parvovirus, B19, IgM and IgG serology, and PCR	Fall in Haemoglobin with low reticulocytes
CT/ MRI scan of head	See stroke and other CNS complications
XR/ MRI of affected joints/ limbs	Suspected osteomyelitis

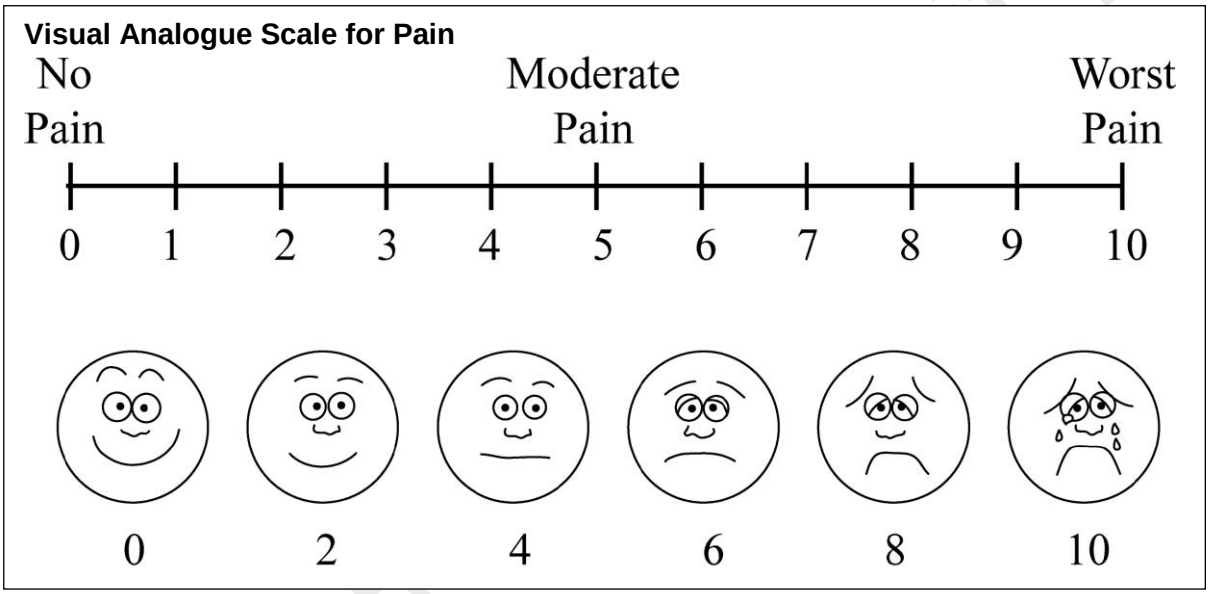
A 2/ ACUTE SICKLE PAIN - ASSESSMENT & MANAGEMENT

Acute painful sickle cell episodes are caused by blockage of the small blood vessels by sickled red cells. Pain can fluctuate in both intensity and duration, and may be excruciating. The majority of painful episodes are managed at home, with patients usually seeking hospital care only if the pain is uncontrolled or they have no access to analgesia.

Treat an acute painful sickle cell episode as an acute medical emergency.

Offer analgesia within 30 minutes of presentation to all patients presenting to hospital with an acute painful sickle cell episode

Pain Scoring:
The use of pain scoring is an important means of observing response to analgesia and, alongside clinical assessment, should be used to titrate pain control. It should be assessed and documented by doctors and nursing staff in the clinical notes.
In children the visual analogue score (VAS) is used most widely but different pain scoring systems are available.



Analgesia
Local analgesia guidelines should be followed as availability of certain analgesic presentations differ between Trusts.
When offering analgesia for an acute painful sickle cell episode, ask about and take into account any analgesia taken by the patient for the current episode before and refer to patients' previous experience with different medications

An analgesic ladder is used according to the severity of pain:

Dosing tables below provide a guide, but refer to BNFc dosing where this differs with local practice

α) Mild/Moderate Pain

Paracetamol, **oral** (over 1 month of age)

From	To	Dose
> 1 month of age	<50 kg	18 mg/kg/dose 6 hourly or 10-15mg/kg/dose (**maximum 75 mg/kg/day in 4 to 6 divided doses, up to a maximum of 4g in 24 hours)**
≥50 kg		1 g 4-6 hourly (maximum of 4 g in 24 hours)

Paracetamol, IV

From	To	Dose
Term age	<10 kg	10 mg/kg 8 hourly, regularly **(maximum 30mg/kg/day)**
10 kg	<50 kg	15 mg/kg 6 hourly, regularly **(maximum 60 mg/kg/day in 4 divided doses)**
≥50 kg		1 g 6 hourly **(maximum of 4g in 24 hours)**

Ibuprofen, oral

From	To	Dose
1 month	11 years	7.5-10 mg/kg/dose 6-8 hourly. Or BNFC (maximum 30mg/kg/day)
≥12 years		7.5-10 mg/kg/dose 6-8 hourly (maximum 600 mg 6 hourly)

Naproxen, oral

Note: round doses to 250mg or 500mg where possible, liquid is available as 250mg/5ml suspension but may not be stocked routinely, consider ibuprofen if not available.

From	To	Dose
6 months	18 years	5 mg/kg twice daily (maximum 1g/day)

Note: Dispersible diclofenac is no longer available.

Please note that codeine is no longer used in children <12 year, codeine should only be used in children over 12 years of age who have had it before.

β) Moderate/Severe Pain

First-line analgesia for severe pain is **a combination of intranasal fentanyl or diamorphine (if available) and oral morphine.** All children admitted must have analgesia prescribed at regular intervals; a PRN basis is not recommended.

Ensure all patients requiring strong opiates also have regular ibuprofen/naproxen and paracetamol prescribed.

Intranasal Fentanyl

Age	Dose

All ages	1.5 microgram/kg

A second dose of 0.75 – 1.5micrograms/kg may be administered 10 minutes after the first dose if needed.

Intranasal diamorphine

Age	Dose
All ages	0.1 mg/kg (maximum dose 6 mg)

Oral Morphine

From	To	Dose
1 month	2 months	50 – 100 microgram/kg max. 4 hourly
3 months	5 months	100 – 150 microgram/kg max. 4 hourly
6 months	11 months	200 microgram/kg max. 4 hourly
1 year old		200 – 300 microgram/kg max. 4 hourly
2 years	11 years	200 – 300 microgram/kg (max. 10mg) max. 4 hourly
12 years	18 years	5-10 mg max. 4 hourly

Dihydrocodeine

From	To	Dose
1 year	3 years	0.5mg/kg 4 to 6 hourly
4 years	11 years	0.5 - 1mg/kg (max 30 mg) 4 to 6 hourly
over 12 years		30 mg, 4 to 6 hourly

Stat IV bolus of morphine (if required) - once access established. This will take 5 - 20 mins to take effect. If necessary, repeat opiate (50 - 100% of initial dose after 20 mins.) Only to be given by doctors or anaesthetists or nurses trained in IV opioid pain relief.

From	To	Dose
1 month	11years	100 micrograms/kg/dose (max. 5mg)
12 years		5 mg

Patient/Nurse controlled analgesia (PCA/NCA)

Consider patient-controlled analgesia if repeated bolus doses of a strong opioid are needed within 2 hours. Ensure that patient/nurse controlled analgesia (Appendix 1) is used in accordance with locally agreed protocols for managing acute painful sickle cell episodes and/or acute medical emergencies.
UK National Institute for Health Care Excellence guidelines recommend monitoring (including sedation score) every 1 hour for the first 6 hours and at least every 4 hours thereafter.

Adjunctive non-pharmacologic approaches include heat pads, acupuncture, massage, and psychological techniques such as relaxation techniques/distraction with music and art therapy can also be useful.

Ongoing pain assessment

Assess the effectiveness of pain relief:

- every 30 minutes until satisfactory pain relief has been achieved, and at least every 4 hours thereafter
- using and documenting the outcomes of a pain scoring tool

Analgesic de-escalation

De-escalation of parenteral opioids should be considered when the patient hasn't needed boluses for 10 -12 hours. The baseline dose of opioid in PCA/NCA should be decreased gradually with stringent pain assessment concurrently by roughly 2 mcg/kg/hour every 6 – 8 hours. Once the rate is down to 10 mcg/kg/hr and the patient hasn't needed boluses, the infusion could be temporarily stopped (preferably overnight) and

then completely if no breakthrough dose is needed. Oral opioids should be prescribed on a regular basis (rather than PRN) before stopping the parenteral opioids. Once the patient is off PCA/NCA and pain free on regular PO opioids for about 24 hours, consideration should be given to making the oral opioids PRN. Whilst de-escalation of opioids is going on, it is extremely important to have Paracetamol & NSAID's prescribed on a regular basis.

Hydration status and fluid management

Dehydration occurs readily in children with sickle cell disease due to impairment of renal concentrating capacity (hyposthenuria). Diarrhoea and vomiting are thus of particular concern.

The ill child should be assessed for the degree of dehydration by the history; the duration of the illness; by clinical examination; and (if known) weight loss. Haemoglobin and haematocrit may be elevated as compared with the child's steady state values.

A fluid chart should be started and kept carefully, both input and output and daily weights should be recorded.

The volume of fluid resuscitation required in an acute crisis should be assessed on a case by case basis. In a simple painful vaso-occlusive crisis, a short period of hyperhydation (150%) could be considered but this should be reviewed early with a review to reducing to 100% maintenance.

In the majority of cases 100% maintenance is satisfactory when a patient's own oral intake is taken into account.

Caution should be taken in over hydrating patients where there is concern of cardio-respiratory pathology such as chest crisis or pneumonia (where there may be inappropriate ADH secretion) as such patients are at risk of fluid overload.

An IV line should be inserted whenever parenteral opiates are given or if the patient has a poor oral intake.

The total maintenance fluid should be commenced on admission; **this must be reviewed regularly. Caution if concomitant pneumonia as there may be inappropriate ADH secretion and hence normal maintenance could be more appropriate. This can be given IV or oral, depending on the child's ability to drink.**

Electrolytes should be reviewed, remembering that a slightly raised urea will often be significant as these children normally have a low blood urea due to renal hyperfiltration.

Fluid type to prescribe should be either sodium chloride 0.9% with glucose 5% or Plasmalyte with glucose 5%. Check U&Es at least daily and use sodium chloride 0.9% with glucose 5% + potassium containing bags (10-20mmol/500mL) as required.

In less severely affected patients who have a good fluid intake, hydration can be given orally. Alternatively consider nasogastric fluid if the patient is able to tolerate.

Oxygen

This is of doubtful use if the patient has only limb pain, but may be given if requested by the patient. The patient's oxygen saturation (SaO_2) should be monitored by pulse oximetry with regular readings in air (minimum 4 hourly)

- If SaO_2 < 95% in air, give O_2 by face mask.
- Refer to patient's baseline oxygen saturations from clinic letters
- Monitor SaO_2 while patient is on supplementary O_2, aiming to keep SaO_2 > 98%.
- Check SaO_2 after a few minutes off O_2 on a daily basis, if clinically possible.
- If SaO_2 remains <95% in a child with normal baseline SaO_2, exclude emerging acute chest syndrome (ACS), see below.

Incentive spirometry

Incentive spirometry should introduced for all children early for all children presenting with sickle cell crisis. This patient-led exercise should be encouraged every 1-2hrs as a means of increase lung expansion and prevent atelectasis. This may help reverse or reduce the chance of chest crisis.
In younger patients or those unable to perform incentive spirometry, chest physiotherapy in other forms should be sought.

Adjunctive Medications

Folic acid:

From	To	Dose
1 month	2 years	2.5 mg once daily
≥3 years		5 mg once daily

Anti-emetic: e.g. ondansetron or cyclizine (if receiving opiate analgesia)

From	Ondansetron dose (IV/tabs/orodispersible films/liquid)
All ages	100 micrograms/kg (max. 8mg) three times a day

Note – "orodispersible films" dissolve in the mouth and require no water for administration, they are an excellent alternative to IV during supply problems.

From	To	Cyclizine dose
1 month	5 years	0.5 - 1 mg/kg bolus dose oral/iv (maximum 25 mg three times a day)
6 years	11 years	25 mg three times a day po/iv Can be given as an infusion
12 years	17 years	50mg three times a day po/iv

Laxatives, if receiving opiate analgesia (unless there are abdominal signs)

Macrogols sachets (e.g. Movicol / Movicol paediatric / Laxido / Cosmocol – brands stocked vary, prescribe generically)

From	To	Dose
Use macrogol paediatric sachets:		
1 month	11 months	Half to one sachet daily – eg *Movicol Paediatric*
1 year	5 years	1 sachet daily (adjusted to produce soft stools, max. 4 sachets/day) – eg *Movicol Paediatric*
6 years	11 years	2 sachets daily (adjusted to produce soft stools, max. 4 sachets/day) – eg *Movicol Paediatric*
Use macrogol "adult" sachets:		
12 years	18 years	1-2 sachets daily - eg *Movicol (Adult) / Laxido*

Lactulose (NB do not prescribe macrogols AND lactulose concomitantly as both osmotic laxatives)

From	To	Dose
1 month	11 months	2.5 mL/kg/dose twice a day
1 year	4 years	2.5 - 10 mL twice a day
5 years	18 years	5 - 20 mL twice a day

Senna liquid (5 mL = 7.5 mg)

From	To	Dose (starting from)
1 month	3 year	3.75-15 mg once daily, dose adjusted according to response
4 year	5 years	3.75-30 mg once daily, dose adjusted according to response
6 years	17 years	7.5-30 mg once daily, dose adjusted according to response

Naloxone - Partial reversal of opioid-induced respiratory depression (see BNFC for full reversal dosing)

From	To	Dose
All ages		4micrograms/kg IV (max. 400mcg) as required

Naloxone - Anti-pruritic (if receiving opiate analgesia)

From	To	Dose
All ages		0.5 micrograms/kg IV, repeat as necessary

Chlorphenamine (oral)

From	To	Dose (starting from)
1 month	1 year	1 mg 12 hourly
2 years	5 years	1 - 2 mg 4-6 hourly (maximum 6 mg in 24 hrs)
6 years	11 years	2 mg 4-6 hourly (maximum 12 mg in 24 hrs)
12 years	18 years	4 mg 4-6 hourly (maximum 24 mg in 24 hrs)

Hydroxyzine

From	To	Dose
6 months	5 years	5 - 15 mg initial daily dose at night increased if necessary to 50mg/day in 3 - 4 divided doses Max 2mg/kg/day
6 years	17 years & <40kg	15 - 25 mg initial daily dose at night increased if necessary to max 2mg/kg/day
6 years	18 years & ≥40kg	Initially 15-25mg daily dose at night, increased if necessary to 50-100mg daily in divided doses

Venous thromboembolism prophylaxis

Increased hyperviscosity and the endothelial, platelet and leucocyte activation associated with sickle cell disease make the condition a risk factor for venous thromboembolism (VTE) although overall the risk of clot formation in children is low.

All children should be assessed based on their individual risk factors. Compression stockings should be considered where appropriate in at-risk patients who are long-term immobile/critically unwell

The addition of low molecular weight heparin is generally recommended in adolescent sickle cell disease patients (12+ years). Risk factors for bleeding should be considered and the use of prophylaxis weighed up on a case by case basis. Trust specific guidelines should used to determine the choice of which anticoagulant and what dose to use.

A 3/ INFECTION

Infection is a common precipitating factor of painful or other types of sickle crises. Children with sickle cell disease are immunocompromised;

1. Functional asplenia or hyposplenia occurs, irrespective of spleen size, in all ages resulting in an increased susceptibility to infection, in particular with capsulated organisms such as Pneumococae. *Haemophilus influenzae* and Salmonellae. – all of which can cause life-threatening sepsis.
2. Neutrophil function is inadequate.

There is a low threshold to increasing antibiotic cover from standard Penicillin V prophylaxis when patients are admitted with sickle cell complications. The recommendations made below should be considered but local antibiotic guidance should be followed as deemed necessary.

The antibiotics referred to below are the commonly recommended choices used at specialist centres for the management of sickle complications. Local teams may refer to this guidance or use Local antibiotic guidelines. See BNFc for age appropriate dosing.

Uncomplicated VOC and no specific evidence of infection not requiring admission	Increase prophylactic penicillin V to four times a day until symptoms settled
Uncomplicated VOC without specific evidence of infection	Azithromycin 10 mg/kg (maximum 500 mg) once daily orally for three days or Clarithromycin* [Consider high-dose Co-amoxiclav* if there is an allergy or intolerance] *Check BNF for age/weight tailored doses
Chest signs or abnormal CXR	Ceftriaxone 50-100 mg/kg IV (dose dependent of severity- maximum 4 g) once a day and oral azithromycin 10 mg/kg (maximum 500 mg) once a day for three days. Ceftriaxone can be changed to high dose co-amoxiclav orally to complete a minimum of 14 days treatment once there is significant clinical and laboratory improvement.
Abdominal pain or girdle syndrome	Ceftriaxone 80-100 mg/kg IV (maximum 4 g) once a day and metronidazole 7.5 mg/kg every 8 hours (maximum 500 mg) IV until resolution (minimum five days).
Suspected osteomyelitis	Ceftriaxone 80-100 mg/kg IV (maximum 4 g) once a day and oral clindamycin 6-10 mg/kg (maximum 450 mg) every 6 hours.
Symptoms/signs of focal infection (e.g. tonsillitis, UTI)	Consult the hospital antibiotic policy for drug of choice (discuss with ID team if necessary)
Second line antibiotic	Meropenem 20 mg/kg (maximum 2 g) IV every 8 hours Complete course of azithromycin in any case

Patients on desferrioxamine (DFO) who have diarrhoea should be started on ciprofloxacin immediately (after checking they are not G6PD deficient) and the DFO stopped. Ciprofloxacin (20 mg/kg twice daily (max. per dose 750 mg) can be stopped if Yersinia infection has been excluded. Use cefotaxime or ceftriaxone if patient is G6PD deficient.

Osteomyelitis

Limb/Joint pain is usually due to vaso-occlusive crisis but the possibility of osteomyelitis/septic arthritis needs to be considered.

The diagnosis of osteomyelitis in the context of sickle cell disease is often difficult, and relies on factors such positive blood cultures, persistent local inflammation, unusual swelling and/or pain. Fevers may not be persistent. A high CRP may be helpful, but together with most of these features may also occur in uncomplicated vaso-occlusive crisis.

X-ray changes often do not appear until about 10 days after the onset of infection but are still a useful baseline investigation.

MRI scan of affected bone or joint can be helpful to distinguish ischaemic from infective changes

Joint aspiration/wash-out may be useful in order to try to identify organisms in potential cases of septic arthritis. Discussion with the specialist haemoglobinopathy team (SHT) Paediatric Haematologist and early input from the orthopaedic team is valuable. Note that the fluid can be quite purulent even in patients with sterile infarcts.

Salmonella is the commonest organism in osteomyelitis in sickle cell patients, but *Staphylococcus* and *S. pneumoniae* are also common. If the decision is taken to treat for osteomyelitis antibiotics should be chosen to cover these organisms. Input from Microbiology/Infectious diseases colleagues is useful in determining appropriate antibiotic cover and duration.

A 4/ ACUTE ABDOMINAL PRESENTATIONS

There can be a variety of conditions resulting in abdominal pain and these can be difficult to differentiate.

Constipation – this is a very common cause of abdominal pain in children with SCD, particularly if opiates have been used for analgesia, and may co-exist with other conditions.

Abdominal crisis – this often starts insidiously with non-specific abdominal pain, anorexia and abdominal distension. Bowel sounds are diminished and there is often generalised abdominal pain but no rebound tenderness. The abdomen is not rigid and moves on respiration. Vomiting and diarrhoea are not usually prominent features.

Girdle (or mesenteric) syndrome – this is often a diagnosis of exclusion. It characteristically results in an established ileus with vomiting, a silent, distended abdomen and distended bowel loops with fluid levels on AXR. Some hepatic enlargement is common and the syndrome is often associated with bilateral basal lung consolidation (chest syndrome) – respiratory symptoms may be concurrently evident.

Surgical causes – can occur concurrently with sickle crisis or be an alternative cause of symptoms. Differential diagnoses to be excluded include acute appendicitis, pancreatitis, cholecystitis, biliary colic, splenic abscess, ischaemic colitis, peptic ulcer. Well localised or rebound tenderness and/or board-like rigidity or lack of movement on respiration are suggestive of these diagnoses.

Examination/Investigations:
Monitor abdominal girth (at umbilicus), bowel sounds, spleen/liver size and monitor chest (SaO2 in air)

- Routine haemolysis screen (reticulocytes, bilirubin – total & conjugated, LDH), HbS%, G&S, CRP, lactate, amylase, serum lipase +/- culture for infection if clinically indicated
- Abdominal imaging – plain abdominal XR/ abdominal ultrasound/ MRI abdomen

To identify concurrent chest crisis: CXR (may need to be repeated every 1-2 days)

Management:

- Supportive care: Intravenous fluids, analgesia (consider need for NCA/PCA), anti-emetics, laxatives,
- Consider limiting oral intake +/- naso-gastric suction if vomiting, abdominal distension or absent bowel sounds.
- Broad spectrum antibiotics: if patient is pyrexial and/or unwell (As per local Trust protocol e.g. ceftriaxone and metronidazole)Consider need for transfusion: Girdle syndrome is an indication for exchange blood transfusion. If top up transfusion given and if large volumes of blood required – do not exceed 20ml/kg in a single transfusion – transfuse slowly at 5 ml/kg/hr (maximum 150ml/hr) to avoid overload
- Paediatric surgical review if not improving
- Supportive chest care: Incentive spirometry, physiotherapy

A 5/ SEQUESTRATION SYNDROMES

These potentially life-threatening syndromes occur when excessive blood is trapped in the spleen or liver resulting in rapid enlargement of the organ and a sudden drop in circulating blood volume which may result in clinical shock. This may accompany an infection or simple painful crisis.

Differential diagnoses:

Aplastic crisis is a differential diagnosis as another cause of sudden onset anaemia in sickle cell disease. Vaso-occlusive pain crisis or any cause of acute abdomen should also be considered.

Splenic sequestration

Splenic sequestration is more common in infants and young children (from 6 months to the age of 5) after which time the spleen becomes autoinfarcted. The majority of cases appear before the age of 2yrs. This condition may present later in patients with milder forms of sickle cell disease (HbS/C or HbS/beta thalassaemia where splenic function may be better preserved. It may be recurrent particularly in patients who have their first presentation before the age of 1year.

Parents/carers of infants with sickle cell disease should be taught to recognise symptoms and to palpate for the spleen to enable detection of an increase in spleen size.

Hypersplenism is a chronic condition which can occur after an acute sequestration leading to chronic splenomegaly with anaemia, leucopenia and thrombocytopenia.

Symptoms:

- Abdominal pain
- Abdominal distension
- Sudden collapse

Signs:

- Rapidly enlarging spleen
- Abrupt onset pallor, weakness, tachycardia, hypotension+/- tachypnoea
- Fever (in cases of associated sepsis)

Investigations:

- FBC, reticulocytes (raised in sequestration crisis, absent in aplastic crisis)
- Screen for infection as clinically indicated
- Parvovirus B19 PCR (if reticulocytopenia)
- Emergency crossmatch half the patient's blood volume

Management:

- Fluid hydration as appropriate (avoid overhydration if degree of anaemia is too severe)
- Emergency top-up transfusion - target Hb ~ 70 g/L (avoid over-transfusion to avoid complications of hyperviscositiy syndrome).
- Broad spectrum antibiotics

In recurrent sequestration:

- Commence a hypertransfusion regimen to reduce spleen size + proceed to splenectomy

Hepatic sequestration

This rare syndrome is caused by obstruction of sinusoidal flow by red cells, trapping further cells within the liver and compressing the biliary tree. Other acute sickle related liver pathology which should be considered includes self-limiting hepatic crisis and potentially lethal intrahepatic cholestasis.

Symptoms

- Right hypochondrial pain, abdominal distension
- Fever (in cases of associated sepsis)

Signs

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

Investigations

- Hyperbilirubinaemia
- Transaminitis
- US abdomen to exclude gallstones/cholestasis
- Screen for infection as clinically indicated

Management

- Fluid resuscitation (avoid if degree of anaemia is too severe)
- Emergency crossmatch
- Broad spectrum antibiotics

A 6/ ACUTE CHEST SYNDROME (ACS)

Acute chest syndrome (ACS) is defined as an acute illness characterised by fever and/or respiratory symptoms accompanied by a new pulmonary infiltrate on CXR in a child with sickle cell disease.

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.

Children with SCD frequently develop simple pneumonia. Generally, these children have unilateral chest signs, are only mildly unwell, have normal SaO2 and have no chest pain. Care should be taken with opiate analgesia in any type of crisis, as over sedation can result in hypoventilation, atelectasis and worsening hypoxia precipitating a chest crisis. Oxygen saturations on air must be recorded in all patients with sickle cell disease.

Any child with SCD in hospital has the potential to develop a chest crisis regardless of their presentation – it is a life-threatening complication.

Symptoms and signs of ACS: (physical symptoms often precede CXR changes):

Symptoms	**Signs**
Chest and more generalised pain (**that may be absent** particularly in younger children)	Fever
Cough (may be productive)	Tachypnoea
Breathlessness	Tachycardia
Wheeze	Wheeze, crackles
Fever/rigors	Bronchial breathing
	Cyanosis

Investigations

- Venous blood gas to exclude acidosis
- Chest x-ray- clinical signs may precede x-ray changes
- NPA, throat and sputum cultures
- Blood tests (FBC, reticulocytes, LFT, LDH, U&E, CRP, 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

Differential diagnosis

Infection- Sickle lung and pneumonia can be clinically and radiologically indistinguishable. However, consolidation in the upper and/or middle lobes, without basal changes, is suggestive of chest infection rather than sickle chest syndrome. Bilateral disease is most likely due to sickling, but atypical pneumonia should be considered.

Pleuritic pain may also be due to spinal/rib/sternal infarction, or from subdiaphragmatic inflammation.

Management

- All children with suspected ACS must be discussed with the attending/on call general paediatrician/paediatric haematology consultant and Specialist Haemoglobinopathy Team (SHT).

- Discuss all unstable patients with the PICU team/ STRS/ CATS team if in DGH

- Oxygenation - maintain saturations 98-100%. Options include face mask oxygen, CPAP, Optiflow, ventilation, and the use of exchange transfusion. Have a low threshold for using CPAP, Optiflow if there are chest symptoms and O2 saturations <95%. A worsening chest x-ray, rapid fall in O2 saturations or persistent fever are all be indications for discussion with the specialist haemoglobinopathy team (SHT) and potential need for transfer for further respiratory support and exchange transfusion may be required.

- Intravenous fluids- maintenance fluids. Maintain strict fluid balance aiming for even balance.

- Antibiotics: IV Ceftriaxone and Clarithromycin or Azithromycin. (Stop prophylactic penicillin V).

- Analgesia: Ensure good pain control according to analgesia guidelines. Avoid over-sedation as this causes hypoventilation and atelectasis.

- Incentive spirometry device in conjunction with the physiotherapist (refer to Appendix 4 for further details)

- Monitor oximetry on air & blood gases as indicated, pulse & respiratory rate.

Diuretics are contraindicated even though chest x-ray and/or signs may mimic pulmonary oedema.

Bronchodilators: may be useful for those patients with known airways disease but should not be used routinely. (Cochrane Database Syst Rev. CD 003733, 2012: insufficient evidence for routine use).

Transfusion therapy: red cell transfusion should be considered in all patients with acute chest syndrome. Exchange transfusion is the treatment of choice, however top up transfusion may be given in the interim whilst waiting to transfer the patient to HDU/PICU. Please see table below for transfusion thresholds.

Patients haemoglobin levels	**Volume of transfusion**
< 80 g/L *	Consider increasing Hb to 100g/L
80-100 g/L *	Consider 5ml/ kg top up
>100g/L	Consider exchange transfusion

- Further exchange transfusion should be considered.

Steroids: Consider corticosteroids in children with severe ACS +/- asthma; Dexamethasone**:** 0.3mg/kg IV every 12 hours for a total of 4 doses may be helpful in rapidly deteriorating patients. They should be weaned on to prednisolone.

Disease modifying therapy:

- If not already on hydroxycarbamide: this should be strongly considered and the family given written information prior to discharge
- Already on hydroxycarbamide: should be dose escalated to maximum tolerated dose
- On hydroxycarbamide at maximum tolerated dose: consider switching to chronic transfusion program.
- Ensure immunisations up to date.
- Patients to be informed they must not fly until they have been reviewed in clinic to ensure recovery from this episode of acute chest crisis.

A 7/ APLASTIC CRISIS

Aplastic crisis is characterised by a rapid fall in haemoglobin associated with a low/absent reticulocytes reflecting a failure of bone marrow erythropoiesis. Parvovirus B19 infection of (and less frequently other viral or bacterial infections) can suppress bone marrow function.
The cellular receptor for Parvovirus is the blood group P antigen, explaining the targeting of red cells and the virus triggers apoptosis leading to an absence of the erythroid precursors.
A viral prodromal illness may occur, but classic 'slapped cheek syndrome' is uncommon. Recurrent infection with Parvovirus is extremely rare as once immunity is conferred it is life-long.
Bone marrow recovery generally occurs after 7-10 days and is indicated by return of nucleated RBCs and reticulocytes to the peripheral blood.

Diagnosis

- Hb >20 g/L 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 <50 g/L and/or symptomatic)
- Spontaneous recovery is heralded by return of nucleated RBCs and reticulocytes to peripheral blood

A 8/ STROKE AND OTHER CNS MANIFESTATIONS

This section comprises the following complications:

- Infarctive stroke
- Haemorrhagic stroke
- TIA
- Sinovenous thrombosis
- Epilepsy
- Headache

Stroke is a potentially devastating complication of sickle cell disease, most commonly occurring in individuals with homozygous disease (HbSS) or HbS beta 0 thalassaemia. Stroke occurs in any age group but is most common in children under 10 years.
According to the Cooperative Study of SCD, the prevalence of abnormalities such as infarction, silent ischaemia and atrophy in children under 10 years is around 22%.
Aneurysms are multiple in the majority (57%) of patients with SCD and more often originate from the posterior circulation (30%).

Predictive factors for stroke include:
1- History of transient ischaemic attacks
2- Acute chest syndrome in the previous 2 weeks or recurrent episodes of ACS
3- Hypertension
4- Low Hb F and/or a low total haemoglobin.
5. Nocturnal hypoxaemia
6. SCD sibling who had a stroke

The Stroke Prevention Trial (STOP) showed that children with trans-cranial Doppler (TCD) velocities of >200 cm/s are also at significant risk. (Adams et al, New ENgl J Med. 1998; 339: 5-11)

Precipitating factors for stroke can be fever and dehydration.

Alpha thalassaemia (of any degree) is protective from stroke through its positive effect on steady state haemoglobin.

Infarctive stroke
It is more common than haemorrhagic stroke in children.
Vaso-occlusion or stenosis of the cerebral vessels commonly involving distal ICA and or proximal MCA leads to infarction, and untreated the majority will have a recurrence.
Smaller infarcts may be due to distal emboli or local stasis/thrombosis.

Haemorrhagic stroke
It is uncommon in children but beware of teenagers, and often associated with multiple intracranial aneurysms. It happens due to the rupture of an aneurysm or small friable collateral vessels. Bleeding may be parenchymal due to haemorrhagic transformation of ischaemic brain or occur in the subarachnoid or intraventricular compartments. Intraventricular haemorrhage is usually encountered in older patients with Moya Moya vasculopathy

Visual manifestations
If there are visual symptoms (reduced acuity, blurring, loss of vision, flashing lights) due to vaso occlusive event, it is difficult to discern whether the symptom is related locally to the eye, or to cerebrovascular disease. The child should be referred for an urgent ophthalmic opinion and requires further neurological

investigation. Detectable retinal disease is rare in childhood, occurring commonly between 15-30yrs in patients with HbSC and HbS/βthal rather than in Hb SS.

Initial Management in the Emergency Department

The ED consultant, paediatric consultant and paediatric haematology consultant should be involved in the management of all children with suspected sickle stroke.

- Manage Airway, breathing, monitor SpO2 and maintain oxygen saturations >96%
- Secure IV access and take urgent blood samples (see below)
- Rehydrate according to the hydration status- avoid fluid overload
- Manage hypoglycaemia
- Control seizures
- Assess GCS
- **Arrange URGENT imaging within 1 hour of arrival in A&E : non-contrast CT head**
- **Call SHT and paramedic retrieval team to plan URGENT transfer to PICU**
- **Plan urgent top up transfusion if Hb < 80 g/L & thereafter an emergency red blood cell exchange transfusion** (see detail below)
- **The use of thrombolysis/aspirin does not form an essential part of the management of a sickle stroke**
- Consider other diagnoses in assessment like meningitis - depending on clinical presentation it may be necessary to add broad spectrum antibiotics with CNS penetration, with IV Acyclovir to cover for possible intracranial infection and consider LP

Urgent blood tests

Haematology

- FBC, reticulocytes, blood film, HbS% and HbF%
- PT/APTT and Fibrinogen
- Blood Group (ABO RhD and Kell & antibody screen – extended red cell phenotype if not previously documented) and urgent cross match (request sickle negative blood)

Biochemistry

- Blood glucose
- Blood gas analysis - Venous (arterial if arterial line available)
- CRP, Urea and Electrolytes, Calcium, Magnesium
- Liver Function tests, ALT and LDH

Infection screen

- Blood culture, urine, throat swab and ASO titres
- Viral serology: HSV, CMV, Varicella ZV, Parvovirus, Hepatitis ABC serology (HepBsAg, HbsAb, HCV) and HIV.
- Malaria screen if foreign travel

Immunology

- Autoantibody screen with ds DNA antibodies,
- Anti-cardiolipin antibodies, Beta 2 glycoprotein antibodies

Other

- Consider urine/serum drug screen if altered mental status with no explanation
- Check – most recent TCD result (all children with HbSS /HbS B^0thal should have TCD scans annually from age 2-16 years)

Further investigations

- Arrange MRI MRA (head and carotid/vertebral arteries) with diffusion weighted imaging –to assess the pathogenesis, risk of recurrence and need for revascularisation. For children <7 years this may require GA and should only be done after exchange and when the patient is stable. The risk of recurrent neurological events is greatest in those with abnormal cerebral vasculature.
- Consider MRV if possible cerebral venous sinus thrombosis
- Transcranial Doppler including with extra cranial vessels
- Cardiac Echo – to exclude embolic cause for CVA

On-going management following admission

Exchange Transfusion: Patients with suspected or confirmed stroke require an exchange blood transfusion aiming for target HbS<30% (ideally below 20%) and Hb ≤110g/L.

Replacement of sickle cells by normal cells can help prevent further vaso-occlusion, although pre-existing vaso-occlusion may not be reversed.

If clinically unstable, exchange transfusion must be carried out urgently; this should be done preferably by automated erythrocytapheresis or if unavailable, by manual exchange transfusion performed in 2 or 3 stages with an interval of 4-8 hours between each exchange. The aim is to achieve HbS level below 30%.

If clinically stable exchange transfusion should also be carried out urgently whenever possible and children should be transfused to 100 g/L until such time; the decision about the timing of exchange transfusion will need to be made for each individual patient depending upon all considerations including past history and ease of venous access; such cases should all be discussed with the Paediatric Haematology consultant on call.

Seizures may occur and require anticonvulsant therapy

Transient Ischaemic Attacks: 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 there is a new infarct or bleed and/or the child is clinically unstable. Discuss need for exchange transfusion with the tertiary paediatric haematology team.If there are evolving symptoms an exchange transfusion is required.

Children with haemorrhagic stroke: exchange transfusion should be arranged urgently as re-bleeds may occur and/or surgery be advised. Keep platelets more than 100 x 10^9/l. Refer to neurosurgeons urgently.

Paediatric neurology/stroke team input

- Inform Paediatric neurology team and arrange review within 24 hours of admission
- Physiotherapy, Speech & Language Therapy, Occupational Therapy referrals

Prior to discharge

- Children require on-going transfusion therapy to maintain HbS <30%. The date for the next transfusion should be booked prior to discharge. Venous access should be discussed in young children.
  - Establish a monthly transfusion programme to maintain the HbS level <30% for first event and <20% for subsequent events or evidence of progressive vasculopathy.
- Ensure an outpatient clinic appointment is booked for 6 weeks post discharge

Outpatient management includes:

- Neurocognitive assessment and liaising with school SENCO
- Regular MRI/MRA to assess for progressive vasculopathy. Imaging to be reviewed in neuroradiology MDT
- 6 monthly TCD imaging unless uninformative
- Management of iron overload

Discussion regarding bone marrow transplantation:

- Child and any full siblings should be HLA-typed
- The possibility of bone marrow transplantation should be discussed with the family.

Progressive neurovascular disease

- Review in neuroradiology MDT and haemoglobinopathy (HCC) MDT
- Consider intensifying transfusions to achieve HbS <20%
- Addition of hydroxycarbamide
- Referral to Revascularisation clinic for discussion regarding revascularisation surgery.

Convulsions

Febrile convulsions may occur with high fevers, including after vaccination, however it is important to distinguish these from convulsions due to cerebral sickling. Convulsions are not uncommon following stroke, and may occur following administration of intravenous pethidine.

Investigations

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

Management

Immediate

Refer to APLS guideline – "Management of the convulsing child"

- Anticonvulsant, usually IV lorazepam, buccal midazolam, or rectal diazepam,
- Antipyretic, such as paracetamol
- Unless likely to be a febrile convulsion or the child is known to be epileptic, an urgent CT scan should be performed
- Discuss need for exchange transfusion with paediatric haematology 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 regimen.

Silent Infarct or silent cerebral ischaemia (SCI)

It is common to see 'silent infarcts' on MRI in children with sickle cell disease. TCD is normal in 75% of these cases.

Silent infarcts typically occur at the ("watershed") border zones of vascular territories, which are supplied by smaller end arterial branches and therefore vulnerable to ischaemia.

The ischaemia may be caused by a proximal stenosis or by generalized reduction in cerebral perfusion, e.g. in systemic hypotension.

Ischaemia can present as impaired cognitive function or subtle neuropsychological deterioration. There are no overt signs and symptoms like limb weakness. There should be a low threshold for performing MRI if there is poor school performance indicative of poor cognitive function.

Silent infarcts should prompt a detailed neurocognitive assessment when detected in children.
Silent infarcts must prompt the initiation of preventative treatment in order to reduce the risk of subsequent stroke and regular blood transfusion should be discussed with the parents.

Moya Moya disease
Sickle cell vasculopathy can involve both large and small vessels, although typically the terminal internal carotid artery (ICA), proximal anterior cerebral artery (ACA) and middle cerebral artery (MCA) are affected leading to stenosis. Over time and with progressive occlusion of the main intracranial arteries, a so called "Moya Moya" (Japanese: puff of smoke) appearance is seen, which is characterized by the formation of numerous tiny collaterals.

Posterior reversible encephalopathy syndrome (PRES)
PRES is not commonly seen in SCD. PRES typically manifests as vasogenic oedema with a predilection for parieto-occipital white matter. PRES in SCD has been reported in association with acute chest crisis, steroid use and over-transfusion.

Headache
Acute – if there is a sudden severe headache or sudden change in the type of the usual headache, investigate for haemorrhage or thrombosis.
Chronic- can be due to migraine, tension headache, idiopathic intracranial hypertension or sleep apnoea. If there are no neurological features, then these patients should be referred to general paediatric team.

Stroke Prevention

Transcranial Doppler imaging (TCDi) or TCD

TCD ultrasound imaging assessment (TCDi) is a non-invasive method of identifying children at risk of ischaemic stroke. Annual assessments are recommended in children with SCD and SB0 thalassemia from the age of 2 until at least 16 years. In children with other genotypes (SB+ thalassemia and HbSC), TCD is not recommended as a standard of care and should be reviewed on a case by case basis.

Stroke risk is currently based on the time-averaged maximum mean velocity from the; MCA, TICA & ACA. Although a bilateral scan is performed, the single highest TAMMV determines the STOP classification.

Normal – All TAMMV less than 170 cm/sec- Re-scan annually up to the age of 16, then discharge to adult programme

Conditional – A TAMMV of at least 170 cm/sec but less than 200 cm/sec in one or more of the three designated vessels.
Re-scan within 1 month for children under 10 years and children with velocities at upper limit of conditional (185-199cm/s) and re-scan in 3 months for children aged 10 years and over.
MRI/MRA head scanning should be considered.

Abnormal – TAMMV of at least 200 cm/sec in any one of the MCA, ACA or TICA.
If initial TAMMV is ≥220cm/s – patient to be reviewed immediately by a specialist clinician (consideration for transfusion or alternative treatment) and urgent MRI/MRA head performed
If initial TAMMV is 200-219cm/s repeat scan within 1-2 weeks.
If values remain in abnormal range on second scan – patient will be reviewed by Clinician immediately (consideration for transfusion or alternative treatment). and urgent MRI/MRA head performed

Low Velocities – TAMMV <70cm/s in one or more of the three designated vessels is indicative of possible occlusion. If noted repeat TCD within 2-3 weeks and if persistent proceed to MRI/MRA for confirmation of pathology.

Non-Diagnostic – Velocity not measurable due to patient compliance or poor imaging window. Repeat scan if poor compliance.

Inadequate – A study that does not provide readings from right and left MCA/ICA/ACA would be classified as inadequate however, if one vessel is clearly abnormal this scan should be classified as INADEQUATE but ABNORMAL

Consider alternative imaging for non-diagnostic scans. In this context a repeat scan should be attempted or an alternative scanning method, such as MRI/MRA head should be considered.

Changes in velocity may be affected by other factors:

Velocity will be decreased:
Following transfusion which decreases velocity for several days' post transfusion - perform TCD assessment at least 2 weeks after transfusion

Hyperventilation decreases pCO2 levels and reduces velocity - wait until the child is calm

Velocity will be increased by; Fever, Sleep, Crying, Sickle chest syndrome, Hypoxia worsening anaemia, significant hypoglycaemia

Results obtained under these conditions will be unreliable. It is advisable to avoid scanning when they are present however, any result obtained can be reviewed by the clinician and the decision for a repeat scan made at this time.

Primary stroke prevention

The risk of stroke can be reduced by 90 % in those with elevated TCD velocities, by regular blood transfusions.

In the children without severe vasculopathy (multiple stenoses, moyamoya) who had been on regular transfusions for more than a year, can be considered for switching to hydroxycarbamide. This was found to be equivalent to transfusion in the TWiTCH study. Regular transfusions were continued until the maximum tolerated dose of hydroxycarbamide was established.

Secondary stroke prevention

Regular blood transfusion can reduce the risk of recurrent stroke from 50–75% to about 13%. The aim of the transfusion regimen is to maintain the HbS level below 30%. Although it is recommended to continue transfusions throughout childhood, transfusions can be relaxed after 3 years to maintain HbS below 50% in some patients. The hydroxycarbamide was less effective at secondary stroke prevention as compared to the transfusions as shown in SWiTCH study. This switch can be considered only if there are contraindications for transfusions like presence of antibodies, Jehovah's witnesses or uncontrolled iron overload.

MRI/MRA head scanning

Abnormal scans should be discussed in a specialist neuroradiology meeting at the HCC. In some cases referral to neurosurgery for a neovascularisation procedure may be warranted.

A 9/ PRIAPISM

Priapism: Unwanted painful penile erection persisting >1hr

- **Prolonged or fulminant priapism:** priapism lasting >3 hours. Penis fully erect (both corpus cavernosa and spongiosa involved)
- **Stuttering priapism:** repeated painful erections lasting more than 30 minutes but less than 3 hours, occurring several times a week. Penis may not be fully erect (corpus spongiosa [glans] not involved)
- **Minor priapism:** isolated or infrequent episodes of <3 hours

Precipitating factors: such as trauma, infections, or the use of drugs e.g., alcohol, psychotropic agents, sildenafil, testosterone, cocaine.

Prolonged priapism is an emergency and requires urgent assessment and treatment. Urgently discuss with the Specialist Centre (Specialist Haemoglobinopathy Team).

Fulminant priapism is often preceded by episodes of stuttering priapism. It can occur in childhood although it goes unreported. Bicorporal priapism occurs in 3–5% of pre-pubertal boys and has a better prognosis for normal erectile function than tricorporal priapism in post-pubertal boys.

It often starts at night in relation to a full bladder. If it is left untreated it can cause cumulative damage and may result in impotence. It is important that patients and families are educated about priapism at routine clinic visits and given advice about how to manage it. Many patients are not aware this is a complication of sickle cell disease or are reluctant or embarrassed to discuss it. Parents and children should be informed about this and enquiries made as outpatients. Emphasise that it is vital to attend for treatment as early as possible, if simple measures fail to achieve detumescence. Delay may increase the risk of cavernosal fibrosis and impotence.

Measures that can be tried at home

- Emptying the bladder, exercise (jogging on the spot), brisk walk, climbing stairs and a warm shower or bath can be helpful
- Analgesia and hydration
- The patient should seek medical attention of an episode lasts > 2 hours, if severe pain or unable to pass urine

Management of stuttering priapism (Under Specialist Haemoglobinopathy Team (SHT) guidance)

- Increased oral fluids with frequent bladder emptying
- Oral analgesia
- A short course of pseudoephedrine can be used in the short term to prevent spontaneous erections – seek the opinion of the paediatric urology team
- Consider exchange transfusion followed by a period of hypertransfusion
- Drug treatments such as Anti-androgens (cyproterone), α-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.

Management of acute/fulminant priapism in emergency department

- IV hydration and analgesia
- Opiate analgesia, +/- sedation
- Catheterisation, if unable to urinate, to empty bladder

- **Urgent Paediatric urology opinion is the first priority**
- **Paediatric Haematology team to plan emergency red cell exchange transfusion in parallel**

- If not already given at home oral pseudoephedrine:
  - 6-12 years 30mg 6 hourly
  - 12-18 years 60mg 6 hourly

Urological management

- If priapism does not terminate after 4 hours of conservative measures including maximum analgesia and pseudoephedrine:
  - Then mobilise theatres and inform the anaesthetic consultant and the urology consultant (if not informed earlier) to prepare for penile aspiration and irrigation.
  - If this fails to terminate the priapism, further management should be as directed by the paediatric urology consultant on call.

Things that might be needed in the theatre

- Scalp veins – different sizes 22G, 20G, 18G,16 G
- Send blood gas, bloods if not sent already
- Warm saline
- Drugs – Ketamine during GA, Phenylephrine / Etilefrine for intracorporeal injection
- Minor Instrument Set
- Trucut Biopsy needle

Discharge criteria

- Able to urinate
- Penis more flaccid
- Pain controllable on oral medications
- Management on discharge: patients should be discharged with a 3-5 day course of pseudoephedrine.

- **Follow up post discharge**
- Patients should be followed up in the paediatric urology clinic.
- Measures for all patients:
  - Patient and family education
  - Keeping pseudoephedrine at home for use to help with early termination of further episodes
- If recurrent, treatment considerations to be discussed at an HCC MDT meeting:
  - Etilefrine 0.25mg/kg/dose BD orally
  - Leuprorelin Acetate GnRH analog 3.75mg s/c every 4 weeks
  - Disease modifying therapy for sickle cell disease

Etilefrine prescribing guidance

Treatment and prophylaxis with Etilefrine 0.5mg/kg at night OR 0.25mg/kg bd (depending on when onset of symptoms is more common eg. night only or throughout the day and night)

Continue for a total of 4 weeks and then stop / wean depending on recurrences

Monitor blood pressure (follow up at 1 week and then monthly)

Monitoring during therapy, patients should be seen weekly on day care ward, for assessment of response and of side effects.

Blood pressure should be checked and treatment stopped if blood pressure >150 systolic and > 90 diastolic or experiencing increased headaches or any symptoms suggestive of TIA

A 10/ TRANSFUSION REACTIONS

Delayed transfusion reactions (DHTR) present from 24 hours up to three weeks post-transfusion. Typical DTR process results from the formation of new alloantibodies to red cell antigens. Around 30% of sickle cell patients develop red cell antibodies. The higher alloimmunization is observed in sickle cell disease (SCD) due to the higher prevalence of C, E, Fy^a, JK^b and S group antigens polymorphism in blood donors than in patients of African descent, the high cumulative transfusion burden in SCD, and the inflammatory nature of the condition.
The diagnosis of DTHR can be made when the Hb level drops by more than 50%, and/or that post-transfusion Hb is > 30% lower than the pre-transfusion level .

Hyperhaemolysis

Hyperhaemolysis (HH) is a less common form of delayed haemolytic transfusion reaction which is characterised by a haemoglobin level fall below the pre-transfusion level, indicating the destruction of transfused as well as the recipient red cells. The condition recurs/ worsens with subsequent transfusion, hence future transfusion should be avoided

There are a spectrum of abnormalities at presentation: Classical DHTR is characterised by extravascular haemolysis associated with anaemia, raised reticulocyte count, unconjugated hyperbilirubinemia raised LDH, and positive DAT with new red cell alloantibody formation. Hyperhaemolysis, is associated with intravascular haemolysis, lower haemoglobin and reticulocytopenia. DAT is often negative and no alloantibody is detected. Hyperhaemolysis is mostly seen in transfused sickle cell patients but has been reported in thalassaemia and some haematological malignancies. An incidence of 3—5 % has been reported. Hyperhaemolysis may occur in all age groups, nonetheless, a small study suggested that it may be more common in children.

Pathophysiology

The pathophysiology of hyperhaemolysis is not fully understood but proposed mechanisms include: red cell allo-antibody mediation, red cell damage from osmotic shock, oxidative stress or ATP depletion, damage-induced exposure of inner cellular membrane leading to red cell lysis and macrophage attraction and activation. There is some anecdotal evidence that alternative (low C3 normal C4) or terminal complement (low sC5b9) activation occurs in hyperhaemolysis. Genetic predisposition, infection and previous transfusion are potential precipitating factors.

Clinical presentation

Hyperhaemolysis should be suspected with the recurrence or appearance of a vaso-occlusive event following a recent transfusion, dark urine (coca cola coloured), worsening jaundice, onset or worsening of anaemia, and increased LDH. Free haemoglobin delocalizes to tissues once haptoglobin and haemopixin are exhausted, and initiates tissue damage by free-radical reactions and by NO depletion. This can cause vasoconstriction, ischaemia, and cardiac failure. In addition, disruption of endothelial NO signalling by cell-free Hb in cerebral arteries may cause vasospasms and may facilitate microthrombosis by disinhibiting platelet adhesion and aggregation.

There may be a reduction in seizure threshold and an increased risk of cerebrovascular events. If not recognised early and treated promptly, the patient therefore may progress to multiorgan failure and death.

Investigations:

- FBC: worsening anaemia – Hb may fall to below the pre-transfusion level.
- Reticulocytes: may be raised or decreased, due to suppression of red cell production.
- Haemolysis markers:
  - Raised unconjugated bilirubin
  - Raised LDH
  - Absent haptoglobin
  - Urine haemoglobinuria
- Blood film
- Haematinics: serum B12 and red cell folate
- Direct Antiglobulin Test (DAT) & Group and screen: Reference lab investigations are advised if no new alloantibodes are detected & a DHTR is suspected (2 extra crossmatch samples)
- Haemoglobin electrophoresis/HPLC: to quantify how much, if any, HbA (transfused blood) remains. Consider serial urine electrophoresis. HbS in the urine supports the diagnosis of HH. The disappearance of HbS from serial urine samples may herald the resolution of the HH
- Red cell genotyping; if extended serological red cell phenotyping is not possible to obtain e.g. transfusion in the last three months.
- Venous blood glucose
- Septic screen
- Parvovirus serology
- Serum ferritin – to identify macrophage activation
- Hepatitis B surface Antigen (HepB sAg), Hepatitis C antibody, HIV antibody

Treatment and management

Supportive management:

- Prompt recognition and discussion with the specialist haemoglobinopathy team (SHT)with a view to transfer of care is essential. Regular updates are advised if patient is managed at the local Haemoglobinopathy centre (LHT) as the clinical picture can quickly change.

- Low threshold for escalation of care in the context of:
  - Severe anaemia on presentation
  - Haemodynamic instability
  - Worsening haemolytic markers

Acute management:

- Secure IV access; liaise with PICU to arrange for a central line if difficulties are encountered with cannulation.
- Pain relief as per standard sickle-cell guidelines
- Stop hydroxycarbamide until haemoglobin and reticulocytopenia recover to the steady state level.
- If there is fever and/or high CRP, start broad spectrum antibiotics (as per local protocol)
- Initiate 100% maintenance hydration and monitor urine output to maintain an output of 0.5-1 ml/kg/hour
- Maintain SaO2>94% and proceed as appropriate if SaO2 drop <94% or ≥ 3% from baseline
- *Minimise blood sampling*.

First line disease modifying therapies:
These treatments are commissioned by NHS England but should be guided by the Haemoglobinopathy specialist centre.
IVIg: 1g/Kg for 2 days (total dose 2g/kg. NB dose based on ideal body weight)
Methylprednisolone: 10 mg/Kg IV for 2 days (Max 500 mg)

Transfusion:

- *Avoid further blood transfusion* (where possible**)** as it will exacerbate this phenomenon and delay its resolution. However, if the patient is unstable or has very low haemoglobin, blood transfusion should be considered after discussion with consultant haematologist.
- A rescue transfusion is indicated if life threatening anaemia ensues (i.e. shock or hyperlactatemia)
- If indicated transfuse small volumes of blood to keep patient stable whilst minimising exacerbation of haemolysis
- Extended cross match for RH CcDEe and Kell and negative for antigens the patient is allo-immunised against is the standard of care.

Supportive care

- Consider prophylactic anticoagulation in children >13 year of age. Patients with more than 2 risk factors should be considered for pharmacological thromboprophylaxis (as per local guidelines).
- Recombinant erythropoeitin (rHuEPO) e.g. Neorecormon at a dose of 100 to 300 units/Kg daily, SC or IV for 5 days then 300 units/Kg three times a week until Haemoglobin reaches the steady state level and reticulocytes count increases. Care should be taken to prevent exceeding the steady state haemoglobin level if unknown or haemoglobin 100-110 g/l.
- Folic acid 5 mg/d PO daily. If serum B12 < 200 pg/ml; prescribe vitamin B12 (hydroxocobalamin) at 1 mg/day IM for 5 doses.
- Iron replacement is recommended if baseline ferritin < 100 ug/l or transferrin saturation is less than 20%. Ferric Carboxymaltose (Ferinject®) is recommended with rHuEPO therapy. Patients < 35kg: 15-20mg/kg/week as an IV infusion over 15-30 minutes (up to 1000mg/week. This will usually have to be given in divided doses a week apart (round doses down to nearest 100mg vial to minimise waste) Can be administered neat or diluted with sodium chloride 0.9% to a final concentration of 4mg/ml. Patients ≥ 35kg and Hb <10g/dL: 1500 mg course in divided doses.

Second line disease modifying therapies
Indicated if there is ongoing rapid haemolysis with symptomatic anaemia or compromise of another organ (respiratory, neurology or cardiac or renal failure despite first line therapies.
All cases will be required to seek approval (ideally before administering treatment) at the local Haemoglobinopathy Co-ordinating Centre (HCC) MDT.

1/ Eculizumab (IV)

- Eculizumab dosing in paediatric patients is based on body weight: patients <10kg = 300mg, 10-40kg = 600mg; >40kg adult dose of 900mg dose.
- A second dose after 7 days should be considered: if there is evidence of efficacy of treatment but ongoing haemolysis; maximum of two doses are commissioned. Further doses may be considered is there is evidence of ongoing terminal complement activation and ongoing haemolysis.
- Patients receiving eculizumab should be vaccinated with a tetravalent Meningitis ACWY (Menveo (Novartis) or Nimenrix (GSK)) conjugated vaccine and multicomponent serogroup Meningitis B vaccine (Bexsero® Novartis) as soon as possible after Eculizumab.
- Ciprofloxacin prophylaxis is recommended for 2 weeks post Eculizumab dose (to be determined at clinician's discretion)
- Long term prophylactic penicillin V or erythromycin if penicillin allergic.

2/ Rituximab (IV)
2 doses of 375 mg/m^2 up to 4 weekly doses, should be considered if there is ongoing blood transfusion dependence. Rituximab is more likely to be effective if in DTHR where RBC antibody is detected.

Other therapies

- **Acute**:
- Tocilizumab (IL6 antagonist)
- Plasma exchange

- **Long term:**
- Hydroxcarbamide/novel sickle cell therapies (such as Voxeletor) to minimise need for transfusion
- Stem cell transplant:
- Hyperhaemolysis cases should be reported to SHOT

B/ CHRONIC COMPLICATIONS

B1/ CHRONIC PAI

Chronic pain or acute on chronic pain is prevalent mostly in adolescent and adult patients with sickle cell disease (SCD). It has a profound effect on the quality of life. It is defined as an ongoing pain present on most days over the past 6 months in either a single location or multiple locations. Other causes of pain such as avascular necrosis (see below) and non-sickle musculoskeletal or rheumatological causes of pain should also be considered.

This form of chronic pain is usually due to vaso-occlusion induced tissue damage. Many patients can have widespread pain, or lack an anatomic correlate for their pain, and exhibit hyperalgesia and/or allodynia, signs of peripheral and central sensitization. It has been hypothesized that factors inherent to SCD, such as tissue damage, persistent pain input, and inflammation, cause maladaptive changes in the central nervous system (CNS), promote and sustain the perception of pain and contribute to the pathogenesis of a chronic pain syndrome. There is also some evidence that painful episodes that are not treated promptly may lead to a higher incidence of chronic pain owing to repeated inflammation.

Recurrent painful episodes have a negative psychological impact and the experience of poorly managed episodes in hospital, together with perceived negative attitudes of some staff, are often reported. These attitudes make it more difficult to develop effective long-term pain-coping strategies and may lead to problematic behaviour on the ward. The psychological needs of the child and family regarding coping with pain and avoiding painful sickle cell episodes should be addressed during the admission and a referral to psychological services to support a child or family should be considered.

The management of chronic pain involves multidisciplinary team which includes haematologist, clinical psychologist, pain nurse/physician, physiotherapist, and if available, art or music therapists.
Treatment may involve multiple modalities, including alternative cognitive, behavioural, or pharmacologic therapies such as neuropathic analgesia) with the aim of avoiding resorting to long-term opiates. If the disease modifying therapies fail to control the pain, a trial of blood transfusion to reduce the sickle percentage to <30% may be considered.

All patients with sickle cell should have access to psychological therapies as part of holistic care. The experience of chronic pain is not a purely biological sensation and can be complex. Research has shown that a biopsychosocial approach to managing pain can be helpful and psychological treatments are an important part of pain management. Understanding and managing the thoughts, emotions and behaviours that accompany pain and discomfort can help young people to cope more effectively with pain and can, in part, reduce the intensity of pain. Therapies such as Acceptance and Commitment Therapy (ACT) and Cognitive Behavioural Therapy (CBT) are recommended for children with health conditions and can support pain management.

As part of supporting a child/young person to manage their pain reasonable adjustments may need to be made at school. Multiagency outreach to schools will assist in supporting a young person to continue to access their education.

B 2/ AVASCULAR NECROSIS

Avascular necrosis (AVN - also known as aseptic necrosis or osteonecrosis) is bone death due to a compromised blood supply It occurs when capillaries are blocked by sickled red cells at distal portions of the bone near a joint where there is hypoxia and inadequate collateral circulation. It most commonly occurs in the femoral and humeral heads. Many patients have

bilateral disease at the time of diagnosis.

This complication occurs in approximately 15% of all patients. Although it is more common in SC and Sβ^0, it may occur in all types of SCD and children with high HbF levels are not protected. The normal age of onset is adolescence and after, but *de novo* it is uncommon after the age of 30 years. The shoulder joint is more likely to be affected in older age groups. It often gives rise to chronic pain and limitation of movement due to joint damage, rather than on-going vaso-occlusion Although weight-bearing makes femoral head necrosis more likely to cause severe joint destruction, healing with minimal destruction may be the outcome if it occurs before closure of the femoral epiphysis.

Risk factors

- Low haemoglobin level
- Hyperviscosity
- Sickle genotype (HbSC > HbSS)
- Alpha gene deletion
- Frequency of vaso-occlusive crises

Presentation

- Pain in the hip, leg, groin, knee or shoulder on movement; later at rest. Repeated or prolonged pain (> 8 weeks) should be investigated for avascular necrosis.
- Limitation of movement; particularly abduction and external rotation of the hip, external rotation of the shoulder.

Differential diagnosis

- Osteomyelitis
- Septic arthritis
- Slipped upper femoral epiphysis

Swinging pyrexia, severe systemic disorder, positive blood cultures and toxic granulation of the neutrophils on blood film can be the clues.
Fevers may not be persistent. A high CRP / ESR may be non-specific.
The diagnosis of osteomyelitis in the context of SCD is often difficult and relies on factors like persistent signs of inflammation around site, unusual swelling and / or pain.

Investigations

- X rays of the affected area (and contralateral area)
- MRI (This will usually show changes earlier than x-ray, X-ray changes in osteomyelitis do not appear until at least 10 days after the onset.).

Consider also imaging other regions which might be affected by AVN

Radiological staging is used to evaluate the development and progression of the disease. It is essential to have specialist radiology review of these cases and depending on area of involvement , input from orthopaedics/ spinal team.

Management

Patients with avascular necrosis should be managed in conjunction with the paediatric orthopaedic team

- Analgesia
- Rest and the avoidance of weight bearing (v. difficult to implement).
- Hydroxycarbamide or transfusion cannot reverse the process but may prevent progression to the contralateral joint. Transfusion is the a preferable choice in the paediatric population – with consideration of a switch to Hydroxycarbamide at a later stage based on imaging/orthopaedic review

- Pre-operative transfusion prior to tenotomy or osteotomy and for 3 months post-operatively to maximise bone healing.
- Treat Vitamin D deficiency

Children should be referred for:
1-Orthopaedic assessment which will likely involve surgery or prosthesis
2-Physiotherapy, including consideration of hydrotherapy
3-Orthotics if there is a leg length discrepancy

Child and adolescent patients with avascular necrosis secondary to sickle cell disease generally have good symptomatic improvement with intensive physiotherapy. Surgical intervention should only be considered in exceptional cases where physiotherapy and hydrotherapy have not resulted in an improvement.

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. Cemented prostheses are best avoided. Loosening of the prosthesis is quite common. Infection is not uncommon.

The possibility of failure, the likelihood of some residual pain, the potential life of the prosthesis, and the limitations imposed must always be discussed with the patient pre-operatively.

The life expectancy of prosthesis is 10 years so delay as long as possible.

B 3/ CARDIO-RESPIRATORY DISORDERS

Pulmonary Hypertension

Cardiopulmonary complications are rare in younger children. Symptoms may be non-specific and include fatigue, poor exercise tolerance, chest pain, pre-syncope and syncope. It is associated with increased morbidity and mortality and is a potential cause of sudden death.

Children at higher risk are those with higher rate of steady state haemolysis, lower oxygen saturations, if or with a history of acute chest syndrome, stroke.

Cardiac investigations should be sought to exclude it in sickle cell patients presenting with risk factors suggesting the development of vasculopathy such as dyspnoea, hypoxaemia, signs of right heart failures or evidence of high level haemolysis or urine proteinuria.

As patients get older the chronic impact of sustained haemolytic anaemia and episodic vaso-occlusive episodes leads to progressive end organ complications. A baseline cardiac echo with estimation of tricuspid valve regurgitant jet velocity (TRV) and NT-pro BNP should be undertaken in all adolescent patients prior to transition to the adult service. Echocardiography is recommended every 3 years if TRV < 2.5 m/s and annually if TRV >2.5m/s.,

Sleep Disorders

Sleep disordered breathing comprises a group of conditions characterised by cessation of normal respiration during sleep and is relatively common in sickle cell disease. It can be associated nocturnal hypoxaemia and/or obstructive sleep apnoea and is linked to an increased risk of vaso-occlusive crises,

cerebrovascular complications and priapism. It may be caused by rhinitis or tonsillar/adenoid enlargement. Parents should be asked to monitor for disturbed sleep (grunting, snoring, stuttered breathing or apnoiec episodes), excessive daytime fatigue, early morning headaches and if present , or if daytime saturations are <95%, children should be referred for sleep studies and to see a respiratory specialist/ENT surgeon.

Asthma

Chronic obstructive respiratory disorders such as asthma contribute to the morbidity of sickle related respiratory complications. Patients with these concurrent conditions should be monitored to ensure asthma management is optimal.

Routine pulmonary function testing is not recommended in asymptomatic patients.

Chronic Sickle Lung Disease

This is an interstitial lung parenchymal disorder resulting from chronic sickling which results in slowly progressive onset of symptoms and signs (cough, exertional breathlessness, chest pain, hypoxia, and pulmonary hypertension). It may be associated with recurrent acute chest syndrome but is not limited to this patient group. It is also rare in children. The clinical picture overlaps with isolated pulmonary hypertension and chronic pulmonary thromboembolic disease.

Lung function tests reveal a restrictive pattern with reduced vital capacity (VC), total lung capacity (TLC) and reduction in gas transfer (TLCO and KCO) and would necessitate referral to a respiratory specialist for further investigation.

B 4/ RENAL CONDITIONS

Sickle cell nephropathy encompasses a large spectrum of renal abnormalities such as hyposthenuria, defects of urinary acidification and potassium excretion, glomerular abnormalities, haematuria, papillary necrosis, and at times, renal medullary carcinoma. If not adequately controlled, it may even progress to end-stage renal disease.

Specialist input should be sought early for these conditions from the Paediatric Nephrology team

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, although specialised CT scans can be equally reliable in making the diagnosis; discuss imaging and modality with a specialist at a Specialist Haematology Team (SHT)

Albuminuria and Proteinuria

Albuminuria and proteinuria are not uncommon in children with sickle cell disease and may reflect underlying renal damage due to Sickle Cell Disease.

It is very important to undertake dipstick urinalysis in children **over 6 years** at every clinic visit and to quantify urine protein: creatinine ratio (PCR) in children with 1+ or higher protein on urinalysis.

Ensure urinary tract infection (UTI) is excluded by requesting a MSU for MC&S.

Persistent proteinuria **on two early morning samples** requires further investigation, such as requesting urine microalbumin (albumin: creatinine ratio = ACR) or retinol binding protein: creatinine ratio (RBPCR).

Proteinuria in the nephrotic range (UACR >250mg/mmol, or PCR >300mg/mmol) requires urgent referral to a nephrologist.

Even lower ranges of proteinuria (UACR > 30mg/mmol, and PCR >50mg/mmol) in the presence of hypertension and/or CKD should be discussed with the consultant and referral to the nephrologist should be considered.

Nephrocalcinosis

Nephrocalcinosis (NC) is described in a variety of conditions including sickle cell disease.
It is caused by diseases that cause hypercalcemia, hyperphosphatemia, hypercalciuria, hyperphosphaturia, and hyperoxaluria. Distal Renal Tubular Acidosis is the most common cause of nephrocalcinosis due to hypercalciuria without hypercalcemia.
It is characterised by the deposition of calcium salts in the tubules, tubular epithelium and/or the interstitial tissue of the kidney.
It is usually detected incidentally as diffuse renal calcifications on ultrasound for another indication without evidence of kidney dysfunction.
Rarely, the disease may be severe enough to result in metabolic dysfunction and end-stage renal

disease.

Investigation:
Serum electrolytes, calcium, phosphate should be measured.
Measurement of urine pH should help determine the presence of distal renal tubular acidosis.
Ultrasound and CT are the most sensitive tests for the detection of NC whereas MRI is not ideal for visualising calcification.

Treatment:
To optimise management of sickle cell disease
To increase fluid intake to aim to produce at least 2 litres of urine a day.
Discuss with paediatric nephrology re excluding other causes and the need to adopt strategies to reduce the urinary concentration of calcium, phosphate, or oxalate (may include restrict animal protein intake, reduce dietary sodium, increase potassium and potential use of thiazide diuretic)

Urinary Tract Infections

Not uncommon in sickle cell disease, in both sexes. It should be vigorously investigated and treated to prevent serious renal pathology. Haematuria, secondary to papillary necrosis, can precipitate UTI, but other factors must be excluded. Any child with a UTI should be treated and then investigated according to RCPCH guidelines/ICHC guidelines (intranet).

Chronic Renal Failure

This is uncommon in children. Predictors include increasingly severe anaemia, polyuria and polydipsia, hypertension, proteinuria, nephrotic syndrome, and microscopic haematuria, rising creatinine/fall in estimated GFR (40xheight (cm)/creatinine in micromol/l.

Every child with proteinuria or evidence of chronic kidney disease should have their blood pressure checked manually, and if above the 90th centile this should be repeated after 30min and at the next clinic visit, unless in “urgency” or “emergency” range.

Investigations

- Urea and electrolytes, creatinine, chloride, calcium, phosphate, bicarbonate (all under “paediatric renal profile”), PTH, Vitamin D; immunoglobulins 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
- Consider formal GFR (CrEDTA GFR, nuclear medicine)

Management

- Refer to Paediatric Renal Consultant
- Consider erythropoietin and/or hyper-transfusion regime

B 5/ BILIARY TRACT DISORDERS

Gallstones

Pigmented gallstones due to on-going haemolysis are common in sickle cell disease, occurring in at least 30% of children. It occurs in about 50% of children above the age of 10 years. It is often asymptomatic but can precipitate painful abdominal crises and the girdle syndrome. It can also cause:

- Acute cholecystitis
- Chronic cholecystitis
- Biliary colic
- Obstruction of the common bile duct
- Acute pancreatitis

Investigations

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

Differential diagnosis of Right Upper Quadrant (RUQ) abdominal pain

- Biliary colic;
- Cholecystitis;
- Hepatitis (viral);
- Peptic ulcer;
- Vaso-occlusive episodes;
- Hepatic sequestration;
- Chest syndrome

Management

Acute episode of cholecystitis

- Analgesia
- Hydration
- Antibiotics

Recurrent episodes of cholecystitis

- Indication for cholecystectomy

Common bile duct obstruction (Acute)

- Endoscopic retrograde cholangiopancreatography (ERCP) *or* emergency surgery.

Common bile duct obstruction (Sub-acute)

After one attack, refer for surgical opinion regarding elective cholecystectomy; generally undertaken laparoscopically.

Intrahepatic Cholestasis

Some patients experience episodes of severe hyperbilirubinaemia (conjugated + unconjugated) with moderately 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; i.e. ceftriaxone, metronidazole (discuss with the liver team)
- Monitor liver function tests, and as for girdle syndrome/hepatic sequestration
- Hyper haemolysis +/- sequestration may supervene, requiring frequent transfusion.
- In severe cases, exchange transfusion may be needed

- Annual steady-state liver function tests should be carried out; children with evidence of progressive hepatopathy (increasing bilirubin, persistently high ALT) should be referred to a paediatric hepatology service with experience of SCD.
- Recurrent episodes of abdominal pain should be investigated with an ultrasound of the liver and biliary tree.
- Elective cholecystectomy should be carried out in symptomatic biliary disease

B 6/ OPHTHALMOLOGICAL COMPLICATIONS

Causes
1-Sickle retinopathy
2-Iron chelation related retinopathy

Sickle retinopathy
Vaso-occlusive events affecting vascular bed in the eye may have serious and permanent visual consequences. The ocular complications due to sickle cell disease are uncommon in children; however retinal vessel occlusion may begin in adolescence, commonly between the age of 15-30 years. Patients with HbSC and HbS/β thalassaemia are more likely than those with HbSS to have serious ocular problems.

Proliferative sickle retinopathy refers to changes in the retina due to vascular damage caused by SCD, which are grouped into non-proliferative and proliferative. Infarction of the peripheral retina results in the proliferation of fragile, thin-walled blood vessels 'sea fans' at high risk of bleeding, neovascularization.

The clinical manifestations are grouped according to whether there is neovascularisation or not. In non-neovascular or 'non-proliferative' cases, there are rarely any visual consequences. In contrast, revascularisation and proliferation may proceed to vitreous haemorrhage and retinal detachment. However, there is a high rate of spontaneous regression or non-progression and the indications for treatment are not clear.

Thus these children require annual ophthalmological assessment from puberty onwards.

Iron chelation related retinopathy
Also children on regular transfusion regimens receiving desferrioxamine or deferasirox require annual ophthalmological assessment.

Ocular findings of desferrioxamine toxicity include the so called desferrioxamine retinopathy.

Complications are mainly associated with high doses of DFO in young patients and low ferritin levels. Ocular toxicity usually presents as night-blindness, blurred vision, decreased visual acuity, colour vision impairment, or cataract formation. Retinal and optic nerve disturbances sometimes associated with pigmentary retinal changes, were originally described at very high doses of desferrioxamine

Deferasirox related retinopathy is a recognised clinical entity. Ocular side-effects include cataracts, retro bulbar optic neuritis, pigmentary retinopathy, bull's eye maculopathy and vitelli form maculopathy. The pigmentary retinopathy is classically macular or peripheral but can rarely present in the Para macular, papillomacular or peripapillary pattern. It is still unclear whether ocular toxicity is dose-dependent or not; however, existing literature shows that those with lower iron loads and Deferasirox dosage higher than 30 mg/kg/day are at increased risk for developing systemic toxicity.

Any change in vision or a significant visual symptom including sudden or gradual diminution of vision, flashes of light, or floaters should be referred to ophthalmologist urgently.

These symptoms may reflect the development of macular ischemia, retinal tears, retinal detachment, or vitreous haemorrhage.

Management

- Refer to the Paediatric Ophthalmology Consultant
- Laser therapy is the treatment of choice for proliferative sickle retinopathy
- Surgical treatment should not be undertaken without prior exchange transfusion
- Surgical treatment should Urgent review of on-going chelation therapy

B 7/ ENDOCRINOLOGICAL ASSESSMENT

Growth

Height and weight should be reviewed at every clinic
Referral to dietician is necessary in the event of poor growth
(Exceptionally, infarcts in the hypophysis and hypothalamus are responsible, if suspected an urgent endocrine review is indicated)

Delayed Puberty

Common, particularly in boys.

Related to lower body mass for age in children with sickle cell disease.

Reassure, as most will progress to puberty and achieve normal height despite the delay.
Gonadotrophin status, oestradiol and testosterone may need rechecking at the end of growth if treatment to induce puberty, to check if long-term sex steroid replacement is needed.

Management

a. In the very thin patient, attempt to improve the appetite and quality of nutrition in order to increase the body weight.
b. If an endocrine review is appropriate, or replacement therapy needed then refer to Paediatric Endocrinologist
c. Consider the role of transfusion in parallel with endocrine referral

Fertility

Girls are normally fertile, whereas many boys with HbSS and beta thalassaemia have reduced sperm counts and reduced sperm motility - some may have erectile impotence because of past priapism.

For information about pregnancy, contraception and termination of pregnancy discuss with the Paediatric Haematology Consultant and refer to adult guidelines.

Non-transfused patients

Measurements

Height should be measured and plotted at least yearly including the height velocity. Parental heights should be measured and plotted on the chart with the target centile range. Sitting height measurements should be recorded if the child is likely to start regular transfusions, if there are spinal crises in sickle cell anaemia, or there is concern about low bone density.

Puberty

There is an increased risk of pubertal delay in patients with sickle cell disease. Pubertal development should be monitored using the Tanner score. Seek endocrine review if there are 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 evidence of psychological distress related to pubertal onset delay).

Blood tests

Regular Vitamin D monitoring

If the height velocity is reduced or the child is below the parental target centile range, check thyroid function, coeliac screen, IGF1 and karyotype in girls.

Bone age and scans
Radiological assessment of bone age is indicated if the height velocity is poor or if the child's height is below the parental target centile range. Pelvic ultrasound for uterine volume, endometrial thickness and ovarian volumes is useful as a baseline in girls with pubertal delay and in monitoring the progress of treatment.

Bone Mass Densitometry (BMD)
There is an increased risk of low BMD in this group. Consider at age 10 if there are concerns & all should have Bone Mass Densitometry (BMD) at the end of pubertal growth.

Children on Regular Transfusions
Should have regular endocrine monitoring because of the risk of problems related to transfusions, particularly if Desferrioxamine is used for iron chelation as it can cause bone abnormalities and reduced spinal growth.

Measurements
Height should be plotted on a growth chart annually up to 10 years of age, and then every 6 months.
If there are growth concerns for children on desferrioxamine, measure their sitting height.

Puberty
Pubertal onset may be delayed or fail to occur at all. The commonest pituitary abnormality related to iron deposition is gonadotrophin deficiency which may not reverse even after the iron levels improve. Treatment should be considered if endocrine testing indicates that pubertal onset is unlikely to occur spontaneously.

Blood tests
Once yearly after age 7:
Thyroid function
Calcium and bone profile
Random or fasting glucose
Electrolytes
LFTs

If there are concerns about growth rate:
IGF1

Once yearly after age 10:
HbA1c
LH/FSH
Oestradiol or Testosterone

Consider a Synacthen test to look at adrenal function if there is clinical suspicion:
Tiredness with no other cause
Hyponatremia
Low random cortisol levels
Other endocrine problems related to iron deposition

Bone age and scans
Bone age XR- after age 4: Every 2-3 years if there are concerns about growth and if patient is starting desferrioxamine.

Spinal x-rays should be considered if growth is disproportionate in patients on desferrioxamine.
Pelvic ultrasound is useful as a baseline in girls with pubertal delay and in monitoring the progress of treatment.

Bone Mineral Density (BMD)
BMD measurement should be taken at 10 years and at the end of puberty.
Check annually if the BMD is abnormal (i.e. in the osteopaenic or osteoporotic range).

Further investigations
GH testing is needed if growth velocity is poor over a reasonable period of time (at least a year).
GnRH test may help in defining gonadotrophin status but does not always predict progress in puberty.

B 8/ MENTAL HEALTH

Wellbeing

The impact of the diagnosis of sickle cell disease undoubtedly has a significant impact on the mental health of a proportion of young patients. Psychological input is an essential aspect of sickle cell care. There is not a significant correlation between disease severity and psychological adaption to the condition, therefore psychological support should be accessible for all individuals with sickle cell to promote wellbeing and adjustment to living with a lifelong health condition.

Psychoeducation for families of children and young people with sickle cell has shown improvements in understanding of sickle cell which has lead to improved overall management and medication adherence. It is important for educational establishments to have an understanding of a child's health condition so that they can support the child in actively managing their health when they are at school.

Psychological interventions can be valuable in supporting children and families and research tells us that there is a link between emotional wellbeing and the experience of pain. Psychological therapies have been shown to be effective in reducing pain and therefore, hospital admission for children and young people.
A referral to local health psychology services should be made to support children/young people with the following:

- Procedural difficulties (i.e. fear of needles, blood tests, difficulties with having transfusions, fear of attending hospital appointment)
- Difficulties with medical adherence
- Frustration surrounding living with a health condition
- Worry and anxiety surrounding upcoming procedures
- Fluctuations with mood which may affect physical health and experience of pain
- Pica
- Multiple hospital admissions or a difficult hospital admission

Referrals to general Child and Adolescent Mental Health (CAMH) Services should also be facilitated for young people who are experiencing more generalised mental health concerns. Family can be encouraged to access these referrals via GPs or schools in between clinic appointments.

Pica

Pica is eating or craving non-food items which have no nutritional value beyond an expected developmentally appropriate age and when the behaviour is not part of a culturally supported or socially normative practice. The onset is most common in childhood and there is a higher prevalence in children

who have sickle cell disease, more specifically HbSS. Research has shown that the prevalence of pica is correlated with lower Hb levels and it is associated with iron and/or zinc deficiency. There is also a link between pica and low body weight.

Pica can cause damage to health and impair functioning. There can be several physical health implications; poisoning, weight loss, intestinal and colonic obstruction, gastrointestinal problems and abdominal pain depending on the substances ingested.

Children with pica are often aware that they 'shouldn't' be eating non-food items, and it is important for parents/carers ad children to be aware that they can access support surrounding this. To support children and parents in understanding and managing pica the following should be considered:

- Parents/carers of young people with sickle cell disease should be provided with information about pica to support early detection.
- Pica should be discussed in annual wellbeing reviews and referrals made to local psychology teams, if families consent for support.
- Blood tests to be taken if a child has pica to further understand a child's iron and zinc levels and dependant on the result appropriate treatment should be given.
- Referrals to dietician should be considered if a child has a low body weight to support holistic care and address a nutritional effect.

B 9/ TRANSFUSION RELATED IRON OVERLOAD

Iron overload is a complication which ultimately results in sickle cell patients on long-term top-up or partial manual exchange transfusion programmes. Patients on automated red cell exchange less prone to iron loading but still require monitoring for iron overload

If untreated iron toxicity causes significant morbidity (hepatic fibrosis, pituitary damage affecting growth hormone/gonadotrophin/thyroid function, glucose intolerance & diabetes mellitus and hypoparathyroidism). There is also a potential risk of cardiac arrhythmias and cardiac failure although this occurs rarely in sickle cell patients.
Iron overload generally becomes of concern once patients have received in excess of 10-15 transfusions (and/or when serum ferritin levels exceed 1000ug/L).
Ferritin should be checked monthly in transfused patients and on at least two occasions when the patient is in steady state prior to decision to start chelation therapy. All transfused patients with serum ferritin persistently raised >1000 µg/l should have quantitative monitoring of liver iron concentration using magnetic resonance imaging (MRI).

Ferriscan - An MRI-based liver scan which provides an accurate measurement of liver iron concentration (LIC). High LIC levels have a strong correlation with liver fibrosis and cardiac disease. Iron chelation is recommended in patients who have a liver iron concentration of > 7mg/g dry weight with the aim of targeting an LIC of around 3mg/g dw.

MRI T2* (Hepatic & Cardiac) - These scans quantifying both T2* liver and cardiac iron levels (expressed in m/s) and generally correlate well with Ferriscan results. A myocardial T2* of <20m/s and hepatic T2* of <5m/s are abnormal .

Both of these scans need to be performed at specialist centres. They rely on patients being able to lie still enough for sufficient time to capture adequate images and may require play specialist input or oral sedation. In circumstances when oral sedation is not effective the scans may need to be performed under general anaesthetic.

Liver biopsy - Percutaneous biopsy enables direct measurement of liver iron (mg/g dry weight) and assessment of hepatic fibrosis (Ishak stage). This invasive technique requires general anaesthesia and as iron deposition can be patchy.
This test is recommended in patients with significant iron overload via imaging, those who are difficult to chelate and patients for planned bone marrow transplant.

See **Section D 4** for iron chelation treatment

C/ GENERAL MANAGEMENT

C 1/ ADMISSION AND DISCHARGE PATHWAYS

Each LHT (Local Haemoglobinopathy Team) and SHT (Specialist Haemoglobinopathy Team) will have its own pathways for admitting patients for in-patient care. Patients should be given advice regarding the local routes for admission to ensure they are assessed as quickly as possible.
All patients should be reviewed expediently by a senior member of the Paediatric team (and discussed with the Haematology consultant if deemed necessary).

Once a patient is fit for discharge (or if a patient does not require admission following acute assessment), the regular medical team (Consultant & CNS) should be informed to ensure appropriate follow-up is arranged. Electronic discharge summaries should be forwarded where possible.

Transfer to PICU
Children with progressive organ failure or requiring an emergency exchange transfusion should be considered for admission to high dependency care.
Each HCC Network will have its own escalation pathway for sickle patients requiring high dependency care. This may involve transfer to a centre with Specialist Haematology and ICU care. Discussions about the need to transfer a patient should be considered and discussed early with both the Paediatric Haematology and PICU teams.

C 2/ OUT-PATIENT CARE

Clinics are multi-disciplinary and run on a regular basis. In addition to the consultant and CNS, the sickle cell counsellors, the paediatric dietician, psychologist and social worker are often available.

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 screening. We aim to review them by three months of age. Older patients may be referred after moving into the area or for discussion of more complex problems, e.g. the role of hydroxycarbamide (hydroxyurea) or consideration of bone marrow transplantation

- Full personal and family history including names and ages of parents and siblings.
- Explain the diagnosis and its implications
- Weight & height measurements, observations and physical examination Immunisation history & advise on need for additional vaccines in the future
- Discuss acute problems arising in infancy including dactylitis, sudden onset anaemic episodes (splenic sequestration) and infective complications
- Check that Penicillin and Folic acid have been prescribed and encourage adherence to treatment.
- Ensure that the family have contact details for the hospital, the CNS, the consultant's secretary and GP
- Verify the family understand the pathway for an acute admission via Accident and Emergency.

New patient Investigations

- Hb, reticulocytes, blood film
- HPLC
- Alpha and beta globin genotyping & Xmn1 polymorphism
- Red cell genotype (or phenotype)
- Group and Save X2
- G6PD
- U&E, LFTs, bone profile, LDH
- Vitamin D
- Ferritin
- Hepatitis B,C & HIV serology
- Parvovirus B19 serology

Routine Medication

Penicillin V

There is 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 at the latest.

From	To	Dose
Birth	1 year	62.5 mg twice a day
1 year	4 years	125 mg twice a day
5 years	onwards	250 mg twice a day

For patients who are allergic to Penicillin, a macrolide (e.g. erythromycin) is recommended but hyposplenic cover is less optimal with this approach and patients should be counselled to have a low threshold for review in the event of an infection

Folic acid

From	To	Dose
Birth	1 year	1mg once daily
1 year	5 years	2.5 mg once daily
5 years	onwards	5 mg once daily

Regular Patients

- Weight and height; pulse oximetry; BP if aged >10 years. Each patient should have a growth chart.
- Monitor general health, growth and good nutrition.
- Document any sickle-related or other disease since last visit, immunisation up to date, school progress and attendance and holiday plans.
- Continue education on the recognition of signs and symptoms to ensure early access to medical care when appropriate
- Discussion around patients' mental health & determine need for referral to psychological services
- Examination: check for jaundice, cardiac murmurs, liver and spleen size, tonsillar enlargement
- Ensure adherence to treatment with Hydroxycarbamide, penicillin and folic acid.

Annual review:

- All patients should have FBC, reticulocytes, HPLC, U&Es, LFTs. Vitamin D, Hepatitis B surface antibody levels at least once per year
- Patients long term management plan should be discussed (including review of Hydroxycarbamide use/transfusion/chelation and discussion regarding bone marrow transplant if appropriate.
- Trans cranial Doppler ultrasound should be performed once a year in patients >/= 2 years.
- Mental health
- School progress
- Inheritance and genetic counselling (Discuss pre-natal planning for future children)

Follow-up Appointment

Ensure a follow-up clinic appointment is made, ideally before the patient leaves the clinic and that patient and GP contact details are up to date.

Children with Sickle cell anaemia are seen 3 monthly until 2 years of age and six-monthly thereafter for patients on Hydroxycarbamide, recommendation is to see every 3 months, unless there are medical, educational or psychosocial concerns in which case they should be seen more frequently. Older patients with a mild phenotype sickle cell disease may be seen less frequently as determined by the Consultant.

Adolescent transition Clinics

Discussion about transition should start once children are around 14 years of age. Transition to Adult clinic will take place between 16-19yrs (individual hospitals vary with regards to when this occurs) . Young people should be seen in a joint transition clinic where they are co-reviewed by the paediatric and adult teams. (See separate Haemoglobinopathy Adolescent Transition guideline)

Social /Psychological support

The community specialist nurse/social worker are often present at the clinic to help support the child and their family with needs at school and home. Patients can also be referred to the haemoglobinopathy specialist psychologist where indicated.

C 3/ VACCINATION SCHEDULE

Routine childhood vaccinations

Routine childhood vaccinations are recommended for all children with sickle cell disease.
The most important vaccines in this schedule from a sickle cell perspective are those which protect again organisms which protect vs hyposplenic organisms
Please check Government Guidelines for up to date recommendations (1/ Complete routine immunisation schedule 2/ Department of Health Green Book -(www.gov.uk))

Pneumococcal vaccine

Pneumovax® (23-valent pneumococcal polysaccharide vaccine) is given to children every 5 years over the age of two, in addition to the Pneumococcal Conjugate Vaccine received as part of the universal immunisation programme. Pneumovax does not give complete protection and is not an alternative to penicillin.

Influenza vaccine

Annual influenza vaccine should be given from age 6 months each Autumn. Children on Hydroxycarbamide should be offered the inactivated vaccine if this is available, but this is not mandated and the live vaccine is not contraindicated in these patients.

Meningitis ACWY vaccine
The standard UK vaccine guidance recommends this additional meningitis vaccine in all young people around the age of 16yrs, In sickle cell disease it is advised that children should be offered the vaccine around the age of 12 months due to their increased hyposplenic risk. This should be given 1 month after Meningitis C conjugate vaccine.

Hepatitis B Vaccine
This is recommended for all children with HbSS and HbSβ thalassemia, and is imperative that children requiring blood transfusions, whether as an elective or emergency procedure are appropriately protected
Children born in the UK since Autumn 2017 will routinely receive the Hepatitis B vaccine as part of the universal paediatric vaccination programme. Children born in the UK prior to this time or overseas may not have received the vaccine – perform serological testing for Hepatitis B surface antibody – if the patient is non-immune, arrange vaccination via the GP as per the schedule outlined;
Engerix B dosing stated below (**alternative brands also available - be aware that dosing may vary**), see BNF-C for specific dosing information

Injection	Dose
1st dose	0.5 mL IM
2nd, 1 month after the first dose	0.5 mL IM
3rd, 6 months after the first dose	0.5 mL IM

Hepatitis B antibody levels should be checked 2 - 4 months after 3rd dose to ensure an adequate response (>100 iu/mL). Thereafter, antibody levels should be checked every year and a booster given if levels are sub-optimal.

COVID vaccine
Children with sickle cell disease and no other risk factors have not been deemed at increased risk of severe COVID infection. Government guidance will be updated seasonally and should be sought with regards to the recommendation of COVID vaccines for children.

BCG is recommended, preferably at birth. If this is not administered at birth, follow the national/RCPCH guidelines.

Malaria Prophylaxis

- The formulation advised depends on area to be visited. Consult at a Travel clinic (based in GP practice or community pharmacy)
- Check G6PD status as certain preparations are contraindicated in deficient patients.
- Patients going to live in malarial areas should be advised to stay on prophylaxis lifelong if possible.
- General advice re preventing bites – mosquito nets, clothing, and repellents should be given.

C 4/ SURGERY AND ANAESTHESIA

Peri-operative management plan
Children with SCD are at high risk of complications and serious adverse events related to their underlying condition during the peri-operative period, regardless of the operative risk of the procedure itself. The peri-operative planning requires good communication between surgeons, anaesthetists, haematologists, paediatricians and nursing staff. It is critical that the paediatric haematology team at the Specialist

Haemoglobinopathy Team (SHT) is informed well in advance of the planned date of surgery so that an appropriate management plan can be formulated (≥ 2 weeks in order to allow for time to arrange an exchange transfusion if required). Decision making regarding the safest location for the operation will be taken according to level of surgical risk. Children undergoing splenectomy should have their vaccination record checked to ensure they have had the appropriate pre-operative immunisations (see www.gov.uk. The Green Book, Chapter7).

Pre-op clinic visit

- Ensure that the extended red cell phenotype is known by the transfusion laboratory and that phenotyped blood is cross-matched prior to surgery
- Ensure that there is a peri-operative plan in place from the paediatric haematology team. If the patient is referred from another centre, there must be good communication between centres to ensure that relevant past medical history is known and a joint plan can be devised
- Ensure that the surgeons and anaesthetists are aware of the plan
- Ensure that appropriate post-operative management is communicated e.g. the need for an HDU/PICU bed
- In order to ensure good peri-operative and post-operative care, surgery should be avoided immediately prior to a weekend

Pre-op transfusion

The TAPS study (Lancet 2013) examined the benefit of pre-operative transfusion in low-intermediate risk surgeries and found that the incidence of serious adverse events (mainly acute chest syndrome) was significantly higher in the non-transfused group – the trial was closed early and the investigators concluded that pre-operative transfusions could be beneficial for patients undergoing low or intermediate risk surgery.

The guidance below applies to HbSS and HbSbeta zero patients.

Patients with HbSC disease usually have higher steady state Hb (>90g/l) and top up is likely to cause hyper-viscosity and complications.

Certain patients are at greater risk of perioperative complications due to certain risk factors. The patient related risk factors include:

- those with a history of severe sickle-related problems, such as acute chest syndrome, cerebrovascular disease requiring PICU admission
- those with frequent painful episodes
- those with severe obstructive sleep apnoea.

Low/intermediate risk surgery

Low risk procedures e.g. grommet insertion, simple tooth extraction

Intermediate risk procedures- tonsillectomy, adenoidectomy with OSA, splenectomy, cholecystectomy, portacath insertion, hernia repair, orchidopexy

1-No patient related risk factors and low risk surgery

Top-up transfusion only if Hb <60g/l to Hb 90-110g/l irrespective of HbS level, e.g. for grommet insertion or a simple tooth extraction

Top-up transfusions should be considered for children undergoing other low risk surgery where the baseline Hb is < 90 g/L. Aim for a post transfusion Hb of ~ 100 g/L (avoid an Hb > 110 g/L).

2- Patient related risk factors and low risk surgery

Top-up transfusions should be considered for children undergoing surgery where the baseline Hb is < 90

g/L. Aim for a post transfusion Hb of ~ 100 g/L (avoid an Hb > 110 g/L).

3-Patient related risk factors and intermediate risk surgery
Top-up transfusions should be considered for children undergoing surgery where the baseline Hb is < 90 g/L. Aim for a post transfusion Hb of ~ 100 g/L (avoid an Hb > 110 g/L).
Consider exchange transfusion in children with an Hb > 90 g/L but < 100 g/L, aiming for a pre-operative HbS < 30%.

High risk surgery and high risk patient
High risk surgical procedures e.g. cardiothoracic, major abdominal surgery, neurosurgery, posterior chamber ophthalmic surgery, joint replacement, complex orthopaedic surgery, organ transplantation

High Risk Patient: previous life-threatening sickle-related complications, e.g., severe ACS, CVA or PICU admissions
• Red cell exchange transfusion aiming for HbS <30% or HbS + C < 30% and pre-op Hb 100g/l:either a manual or automated exchange procedure within a week of planned surgery, depending on patient's size, availability of apheresis etc.

Surgical Admission Pathway at the Specialist Haemoglobinopathy Team (SHT)

- Ensure that the multidisciplinary team are aware of date and time of procedure. Pre-emptive discussion with PICU team to determine whether high dependency bed is warranted.
- Admit the patient to the paediatric ward and advise the parents and child that they will need to remain in hospital for at least one night following surgery
- Start iv fluids when oral hydration stops; continue until the patient can take fluids orally
- Monitor oxygen saturations for 24 hours post-surgery
- Give prophylactic antibiotics (choice depends on type of surgery)
- Keep the patient normothermic throughout the peri-operative period
- Use appropriate analgesia and minimise the sympathomimetic effects of the pain response
- Intraoperative transfusion will depend on the intra-operative blood loss and the risk of post-operative complications
- For thoracic surgery and some abdominal and pelvic surgery (including splenectomy), CPAP is recommended for a period of at least 24 hours post operatively.
- Prophylactic post-op physiotherapy including incentive spirometry should be instituted.

Venous thromboembolism prophylaxis
See guidance on p15 re consideration of venous thromboembolism prophylaxis management.

Pre-operative sickle screening in children

Children from the following ethnic groups should be screened if they were not screened as part of newborn screening (e.g. over 10 years of age, born overseas):

- African
- Afro-Caribbean
- Mediterranean (including North Africa, Greece, Turkey, Cyprus and Italy)
- Middle Eastern

An FBC and haemoglobinopathy screen should be requested – the ethnic group should always be given

on the request form.
If SCD needs to be urgently excluded prior to surgery, a sickle solubility test should be performed, followed by an HPLC.
All children with newly identified SCD (HbSS, HbSC, HbSD-Punjab, HbS/thalassaemia) should be referred to the paediatric haematology team. Those with sickle cell trait do not require referral.

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, well oxygenated and kept warm in the peri-operative period as for patients with SCD. If the need for prolonged tourniquet application is likely, this should be discussed with the paediatric haematologists at the Specialist Haemoglobinopathy Team (SHT) at the SHT in advance.

D/ THERAPIES

D 1/ HYDROXYCARBAMIDE

Hydroxycarbamide is the first drug shown to ameliorate the clinical severity of SCD. It decreases vaso-occlusive pain and acute chest crisis, reduces the need for hospitalisation and blood transfusion requirement.

Evidence indicates that it improves survival in SCD, and potentially modifies the onset or progression of end organ damage. The mechanism of action is to reduce HbS polymerisation by increasing fetal haemoglobin (HbF), improving red cell hydration, and reducing leucocytosis and thrombocytosis.

Patient eligibility:

First line indications:

All patients with sickle cell anaemia (HbSS) and sickle beta zero thalassaemia (HbSB0) over 9 months of age should be offered hydroxycarbamide regardless of presence or absence of symptoms.

Hydroxycarbamide therapy should be offered in genotypes other than HbSS and $S\beta^0$ thalassaemia who have recurrent acute pain, acute chest syndrome or episodes of hospitalisation

Hydroxycarbamide therapy should be considered in children with SCD with genotypes other than SS and $S\beta^0$ thalassaemia for other indications on a case-by-case basis

Children with TCD velocities in the range 170–200cm/s (conditional risk category) should be treated with hydroxycarbamide to help prevent progression from conditional to abnormal TCD velocity

Switch from transfusions

Children who have started regular blood transfusions for abnormal range TCD can be switched to hydroxycarbamide if they have received at least 1 year of regular transfusions and have no magnetic resonance angiography-defined severe vasculopathy. (Transfusion should be continued in parallel until they have reached maximum tolerated dose of hydroxycarbamide)

Dosing & Monitoring: Starting dose 20mg/kg orally– dose increments of 5mg/kg (see flow chart below)
FBC/biochemistry testing at 2 weeks following use or after any dose modification and every 2 months
Aim to increment to a maximum tolerated dose (not exceeding 35mg/kg/day)

Side Effects: transient, dose dependent marrow suppression (neutropenia, thrombocytopenia and rarely anaemia), mild gastrointestinal upset, renal & hepatic dysfunction, hyperpigmentation of skin, and nails and hair thinning. Skin ulcers have been reported but do not seem to be any more frequent than in those not on hydroxycarbamide.

Long term concerns

Parents should be reassured that there is no evidence for increased of leukaemogenesis in children.

Growth and development is not adversely impaired.

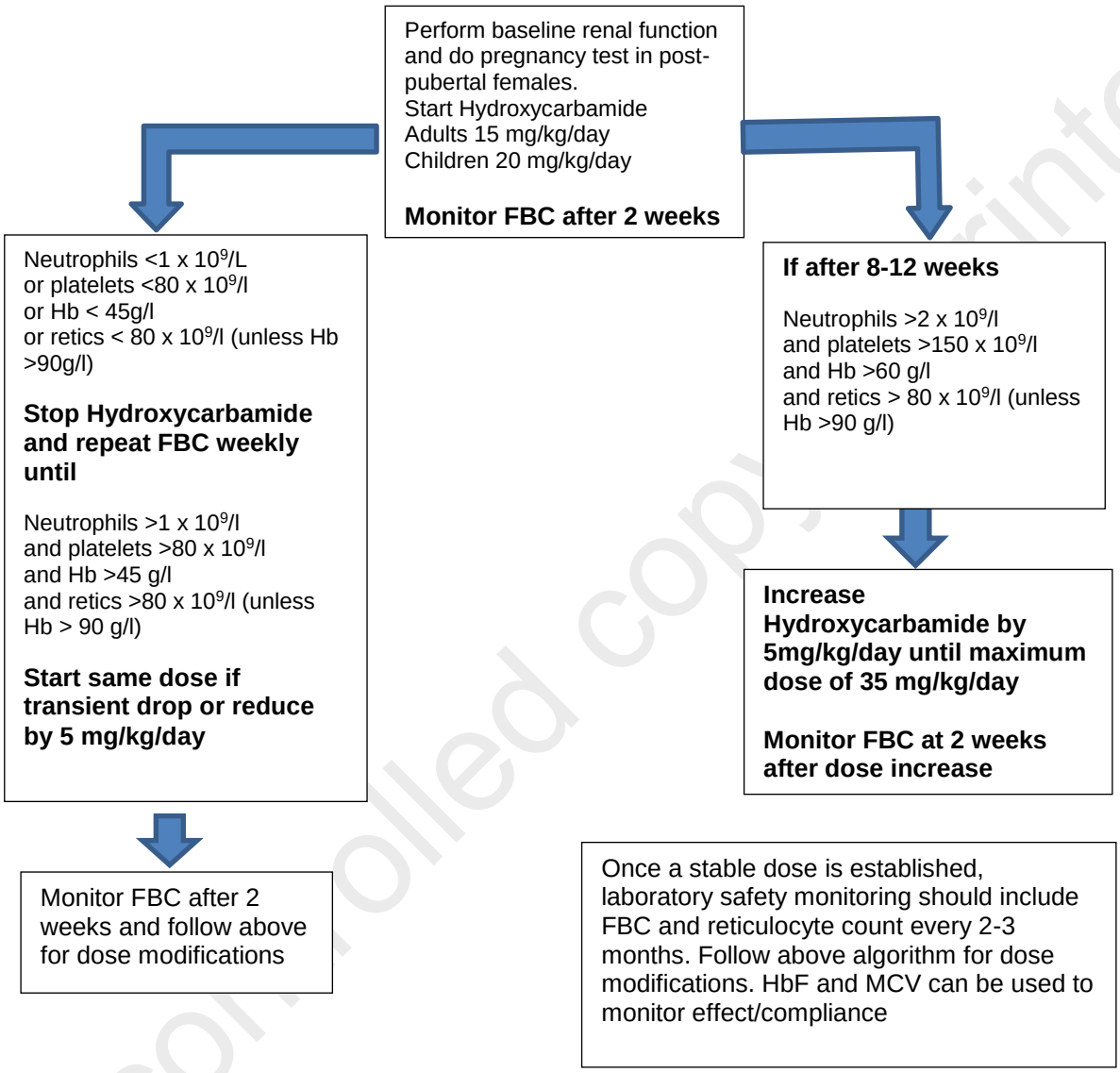
Fertility

There is no available evidence in females or males that hydroxycarbamide has a long term effect on fertility Hydroxycarbamide can cause reversible azoozspermia in older patients but the impact on male spermatogenesis and fertility when the drug is started in pre-pubertal children is unknown. The option of offering sperm banking prior to starting this medication can be considered.

Teratogenicity
Contraception is advised for sexually active patients taking hydroxycarbamide

Patient Exclusion criteria

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



Full explanation of indications, side effects and dosing/monitoring strategy should be given to patient/parents at the outset. Taking written consent for Hydroxycarbamide treatment is recommended.

D 2/ OTHER DISEASE MODIFYING THERAPY

In order to prescribe these novel sickle disease therapies, patients must be assessed by a member of the specialist Haematology team and individual cases must be reviewed by the regional HCC multi-disciplinary team meeting. Eligibility for these treatments should be in line with published NICE guidance or NHSE commissioning criteria.

Voxeletor (Oxbryta®)

Voxelotor is an oral haemoglobin oxygen-affinity modulator. It binds reversibly to haemoglobin, stabilising the oxygenated haemoglobin state and preventing HbS polymerisation by increasing haemoglobin's affinity for oxygen. It is indicated in patients with clinical symptoms and biochemical markers of haemolysis as it has been shown to have disease-modifying potential by raising Hb and reducing the resultant end organ damage. It may be used in isolation or in combination with Hydroxycarbamide. It is licenced in paediatric patients >12years.

Dosing: Voxeletor is prescribed at a standard dose of 1500mg once daily orally (500mg tablet strength). The drug can be taken with other medications (but co-administration with CYP3A4 inducers (e.g. phenytoin, rifampicin, steroids) should be avoided if possible. No dose modification is required in the context of mild/moderate renal or liver impairment.

Common side effects: headache, diarrhoea, abdominal pain, nausea, fatigue, rash and pyrexia

Crizanlizumab (Adakveo)
Crizanlizumab is a humanized anti-P-selectin monoclonal antibody which binds to P-selectin on the surface of platelets and endothelium in the blood vessels and prevents these cells interacting with red blood cells and leucocytes, and prevents these cells from being able to bind to P-selectin. P-selectin is one of the major drivers of the vaso-occlusive process.

It is indicated in patients who have had two or more confirmed sickle vaso-occlusive crises in the previous twelve months (defined an acute painful episode that requires pain relief medication to manage at home or in hospital). It is licensed in patients over the age of 16 years.

Dosing: Crizanlizumab is delivered on an out-patient basis by monthly IV infusion (5 mg/kg administered over a period of 30 minutes at week 0, week 2, and thereafter every 4 weeks). It can be given in isolation or in combination with Hydroxycarbamide.

Common side effects: joint pain, nausea, back pain, fever and abdominal pain.

Less common side effects include nausea, diarrhoea, vomiting, pruritus, chest pain, muscle pain and tiredness.

Patients may suffer an allergic response or infusion site reaction post infusion and very occasionally anaphylaxis. In this subgroup pre-medication can be given.

D 3/ TRANSFUSION

Indications for transfusion:

In the context of sickle cell disease, transfusion is undertaken to reduce the percentage of sickle cells in the circulation or to increase the circulating blood volume. This may need to occur acutely on a one-off basis when a patient develops a life-threatening complication of the disease or as a regular process for patients with severe complications. Transfusion should not to be undertaken without careful consideration, as there is a risk complications may occur.

Mode of Delivery

Transfusions can be delivered either in the form of RBC exchange (erythrocytapheresis – either via automated or manual method) or as a top-up.
It is accepted that where practical a RBC exchange is preferable, in both acute and regularly transfused patients, as this has a more significant impact in reducing the sickle cell % in the acute setting and reduces the iron burden in the long term. RBC exchanges can be associated with their own complications and result in higher donor exposure and require better venous access.
Automated exchanges allow for safer, euvolemic and full-volume exchanges in a much quicker timescale compared to manual exchanges. However, manual exchanges, may need to be undertaken out of hours, when trained staff are not available or if suitable IV access is not secured.

The exception to this is in sequestration or aplastic crisis where the severe drop in Hb makes top-up transfusion necessary as an increase in total blood volume is required. It is also sometimes necessary to undertake a top-up transfusion as an interim measure if an exchange cannot immediately/safely be performed.

Acute (Emergency) transfusion

Indications:

- Severe chest syndrome or girdle syndrome
- A new stroke
- Intractable/widespread acute painful crisis (if substantial drop in Hb from baseline, haemodynamic compromise or impending critical organ complications)
- Fulminant priapism - unresponsive to aspiration/ intercavernosal sympathomimetic injection (initial urological intervention should not be delayed while a transfusion is arranged)
- Splenic/hepatic sequestration
- Aplastic crisis
- Acute sickle-mediated organ failure, e.g. renal, liver, systemic fat embolism
- In anticipation of surgery

Transfusion targets

The aims of an urgent RBC exchange are:

- To reduce the HbS level to <30% (<20% in the case of recurrent neurological event) as quickly/safely as possible
- To keep Hb $\leq$100 g/L by the end of the procedure (or at steady state level in those with higher baseline Hb, e.g. HbSC patients 110-120 g/L).
- To maintain a steady state blood volume and Hb throughout the exchange

The aims of an urgent top-up transfusion are:

- To reduce the HbS level by as much as is safely possible within the limits of the volume of blood which can safely be transfused.
- The maximum volume that can be given in one transfusion should not exceed 20ml/kg to avoid circulatory overload and cerebral hyperviscosity.

Pre-transfusion practical advice

RBC exchange

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. An exchange may replace 50-100% of a child's blood volume and this is usually performed in one automated procedure (or potentially 2 manual exchanges).
The exact volume is calculated dependent on height, weight and haematocrit of the patient and should be discussed with the member of staff due to perform the RBC exchange.

Estimated volume of blood (mL) for one full automated RBC exchange
70 x weight (in kg) = volume in mL

Estimated volume of blood (mL) for one manual RBC exchange procedure
30 x weight in kg (<50kg) or 40 x weight in kg (>50kg) = volume in mL

Patients must be well hydrated prior to starting an exchange transfusion. Two ports of venous access are required; one for venesection, the other for administering blood and crystalloid; in certain circumstances, an arterial line may be used for venesection.

Top-up transfusion

Estimated volume of blood (mL) for a top-up transfusion:
(Target Hb in g/L – baseline Hb in g/L) x weight (kg) x 4

The usual rate of top-up transfusion is 5mL/kg/hour and should never exceed a maximum rate of 150 mLhour. Maximum volume for a single episode of transfusion: 20ml/kg.

Investigations
Preliminary investigations prior to acute transfusion

- FBC
- HPLC
- Cross-match (2 samples in patient never previously transfused)
- U&E, bone profile (particularly calcium)
- Venous blood gases

It is important that the blood bank is fully informed when a sickle cell patient requires transfusion so appropriate blood can be sourced in a timely fashion.

- SAG-M blood, which is the freshest available (to prolong its life in the patient).
- Blood should at the least be Rh/kell antigen matched & HbS negative. Further extended crossmatching will be undertaken if the patient has any allo-antibodies
- Blood does not need to be irradiated (unless the patient is due to undergo bone marrow transplant imminently or has been transplanted in the past- or if other specific indications deem it necessary)

Chronic (Regular transfusion programme)

Indications:

- Secondary stroke prevention & other CNS complications
- Chronic organ damage such as chronic lung, renal or liver disease or sickle retinopathy
- Intractable or frequent painful crises (where alternative medical management has failed or is contraindicated)
- Avascular necrosis

Transfusion targets

The frequency of regular elective transfusions is determined by the rate of haemolysis/HbS regeneration. Patients are generally initiated on 4 weekly transfusions, this may be extended to 6-8 weekly in occasionally patients who can sustain satisfactory blood counts for longer intervals.

The aims of a regular RBC exchange programme are:

- To reduce the post-transfusion HbS level to around 10% - this may require a couple of RBC exchanges in a previously transfusion patient over 2 - 3 days unless acutely ill, when more rapid exchange may be appropriate
- To maintain a pre-transfusion HbS% of <30% (<20% in the case of recurrent neurological event)
- To keep Hb <100 g/L by the end of the procedure (or at steady state level in those with higher baseline Hb, e.g. HbSC patients 110-120 g/L).

The aims of a regular top-up transfusion are:

- To maintain a pre-transfusion HbS < 30%. Achieving this may require a couple of top-up transfusions depending on the starting HbS%.
- The maximum volume that can be given in one transfusion should not exceed 20ml/kg.

Baseline investigations prior to starting regular transfusions

- RBC phenotype/genotype (depending on availability) –
- HBsAg, anti-HBs Ab*
- HCV Ab
- HIV Ab

*Ensure patient has been or is being vaccinated against hepatitis B. Recheck annually and (revaccinate if anti anti-HBs Ab<100 μ/mL)

Regular Investigations required immediately prior to every elective transfusion

- FBC
- Hb electrophoresis
- Antibody screen & cross-match
- U&Es, LFTs
- Ferritin

Post-transfusion investigations (to monitor response)

- FBC
- Hb electrophoresis

MANUAL EXCHANGE

If automated red cell exchange is not available, an emergency manual exchange may be required, occasionally manual exchanges are undertaken electively.
The procedure is quite involved and requires dedicated staff to be present at the patient's bedside. In an unwell patient this procedure should be undertaken in a high dependency unit (**see Appendix 2 for full manual exchange protocol).**

D 4/ IRON CHELATION

Deferasirox (DFX) film coated tablets (Deferasirox FCT) is the chelator of choice in children > 2 years of age on regular transfusions who have evidence of organ iron overload. Chelation therapy should usually commence after a child has received 10-15 transfusions or when the ferritin reaches 1000 µg/l. However as ferritin is an acute phase reactant which rises with acute infection or inflammation, it is important that the ferritin is checked at least on 2 occasions when the patient is well, prior to starting chelation therapy. The decision to start chelation therapy must be discussed with a Paediatric Haematology Consultant.

Deferasirox may cause hepatic or renal dysfunction. Ensure renal and liver function are normal prior to commencement of therapy. Baseline ophthalmology and audiology monitoring is recommended in parallel to starting treatment and yearly thereafter. Monitor serum biochemistry, urine protein; creatinine ratio and full blood count fortnightly for 1 month when starting treatment and at every dose escalation, and then monthly for the duration of therapy.

The dose of deferasirox FCT can be quite broad depending on the clinical context however generally it is started at a dose of 14mg/kg/day orally, rounded up to nearest available tablet sizing; 90mg, 180mg and 360mg tablets are available. These are film coated tablets. They may be crushed and administered by sprinkling the whole dose onto soft food such as yoghurt or apple sauce. Increase doses every 3-6 months at 3.5-7mg/kg steps according to the response, aiming to reach a dose of 21mg/kg if necessary. Ensure that compliance is adequate before dose increases to >21mg/kg. Never exceed a dose of 28mg/kg as higher doses are significantly associated with hepatic and renal dysfunction. Discuss with the patient's named consultant prior to increasing chelation doses.

Desferrioxamine (DFO) may also be used in children who are intolerant to DFX. Desferrioxamine has a detrimental effect on skeletal growth and treatment should be deferred until the age of 2 years unless iron overload is particularly severe. For those on regular top-up transfusions with a rising ferritin, DFO is usually given as an overnight subcutaneous infusion. The standard dose of DFO is 25 - 40 mg/kg/day up to 7 nights per week. Local reactions and severe allergy may occur at DFO infusion site. Vitamin C at a dose of 2 mg/kg/day (maximum 100 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.

Deferiprone (DFP) is another oral iron chelator which is particularly efficient in removing cardiac iron. It is used as a single agent in patients who cannot tolerate deferrioxamine and deferasirox or as part of dual therapy in difficult to treat patients. It is not licenced for use in sickle cell disease. DFP is usually taken in doses of 75 mg/kg/day, in 3 divided doses and should not exceed 100mg/kg/day. Adverse effects include agranulocytosis and arthropathy, gastrointestinal disturbance, transaminitis and zinc deficiency. Children will require weekly FBC check to monitor neutrophil count.

Iron chelation 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.

Investigations prior to starting and on Chelation

- Monitor growth including sitting and standing heights (see also growth and endocrine section)
- Monitor liver and renal function, urinalysis for proteinuria. FBC for neutropenia with DFP.
- MRI for estimate of liver/cardiac iron overload at intervals depending on compliance.
- Annual ophthalmology review (including baseline)
- Annual audiology review (including baseline)

D 5/ VITAMIN D

(Normal range 50-150 nmol/L)

There is a high prevalence of vitamin D deficiency in patients with sickle cell disease and overlap between symptoms of pain in both conditions. Furthermore, vitamin D deficiency is associated with poor bone mineralisation and increased bone fragility, problems also seen in SCD.
Treatment of hypovitaminosis D may help to improve pain symptoms as well as bone health.

All patients with SCD should have vitamin D levels checked regularly (at least 6 monthly) and if deficient should be replaced.
Guidance schedule for Colecalciferol are supplied below (each hospital team should follow its own local guidance to adopt appropriate brands):

Maintenance therapy (for levels 40-69nmol/L)
InVita D3 25,000 units in 1ml oral liquid <1yr 1ml once every 8 weeks, >1yr 1ml once every 6 weeks
Fultium 20,000 unit capsules (licensed from 12 years of age) 1 capsule every 6 weeks
Other products or multivitamin supplements – 400units per day 400 / 600 / 800 units per day depending on formulation

Treatment dose (for levels <40nmol/L)
InVita D3 25,000 units in 1ml oral liquid 1ml once every 2 weeks for 6 weeks
Fultium 20,000 unit capsules 1 capsule once every 2 weeks for 6 weeks

D 6/ BONE MARROW TRANSPLANT

Any potential candidate for consideration of bone marrow transplant should be referred to the specialist clinic at St Mary's (c/o Dr Leena Karnik or Dr Adam Gassas). Current UK practice permits NHS funding for transplant of young patients up to the age of 19years. Studies are open to enable transplant of older patients in the context of a clinical trial.

The consideration of donor options is an important part of this process and if a patient has full siblings both the patient and sibling will be HLA typed to establish if they are compatible. This generally occurs at the BMT clinic itself but in some circumstances it is helpful for this to be undertaken before the initial clinic review (this should be discussed with the relevant consultant and samples should be sent to Histocompatiblity & Immunogenetics (H&I) lab at Hammersmith hospital).

Any case for consideration of bone marrow transplant would be welcome for discussion at the HCC MDT meeting (particularly if the patient does not entirely fulfil transplant criteria or if donor options are limited).

The standard criteria necessary to justify bone marrow transplant in the context of sickle cell disease are well established (see UK Paediatric BMT Group HSCT Indications, 2015)

1. Veno-occlusive crisis (VOC) despite hydroxycarbamide: four or more episodes a year requiring hospitalisation or impacting in schooling despite hydroxycarbamide treatment.
2. Recurrence of acute chest syndrome despite hydroxycarbamide.
3. CNS disease:
   a. Stroke
   b. Abnormal Transcranial Dopplers (TCD) with either i/ silent infarct ii/ abnormal psychometric tests or formally assessed poor school performance iii/ generation of red cell alloantibodies precluding transfusion support
   c. Silent infarct with associated cognitive deficiency
   d. Significant abnormalities on MR angiogram despite transfusion support
   e. CNS disease requiring transfusions leading to significant iron overload despite best attempt at adequate chelation management
4. Suboptimal availability of standard medical care for sickle cell disease

Bone marrow transplant registry data clearly show a correlation between age at transplantation and outcomes in haemoglobinopathies (Baronciani, BMT 2016; Li, Blood Advances 2019; Capellin, Haematologica 2019; Eapen, Lancet Haematology 2019) with minimal mortality risk in patients receiving a sibling BMT <5 years and best outcomes up to the age of 15 years of age. Hence, transplantation as an option needs to be incorporated in the management plan and discussion with the parents for each patient from an early age, The NHS approval for transplantation in sickle cell disease for patients <5 years of age who have a HLA matched sibling, independent of clinical manifestations is under evaluation at the present time but a final decision is yet to be reached. Until such point, the same criteria as for other age groups applies.

Gene therapy

The option to consider entry into a gene therapy clinical trial as an alternative curative option for sickle cell disease in patients who do not have a fully matched donor is under scrutiny.

D 7/ PRENATAL TESTING/CORD BANKING/PGD-IVF

Parents of a child with sickle cell disease should be counselled about the potential for future affected pregnancies. The option of pre-natal diagnostic testing of future offspring may be considered and should be discussed at booking appointment.

There is also the potential to identify if a potential sibling might be an HLA match for an affected sibling whilst in utero by performing fetomaternal blood sampling If there is an HLA match, the parents may pursue the option of cord blood banking & storage at the time of delivery. These cells could potentially contribute to a future bone marrow transplant donation and facilitate bone marrow transplant being an option at an earlier stage. This is arranged with support from the obstetric team and would need to be privately funded.

Some families might be keen to purse pre-implantation genetic diagnosis/IVF treatment (PGD-IVF) for future pregnancies where an IVF process is employed to create and select embryos which are not affected by sickle cell disease. Families should be referred to uclh.haemoglobinopathygenetics@nhs.net (c/o Dr Marie Petrou, Consultant Geneticist). Criteria for NHS funding for this process are strict and this may require private funding.

IMPLEMENTATION

Training required for staff	✓Yes ☐No
If yes, who will provide training:	Self-reading
Date for implementation of guideline:	Immediate

MONITORING / AUDIT

When will this guideline be audited?	N/A
Who will be responsible for auditing this guideline?	N/A
Are there any other specific recommendations for audit?	No

REVIEW

Frequency of review	**Please indicate frequency of review:** Every 3 years **Person and post responsible for the review:** SHT and LHT Paediatrics, Pharmacy, Surgery, ENT, PICU

6 REFERENCES

References are included within the main body of the document.

GUIDELINE DETAIL

Start Date:	**Oct 2023**
Approval Dates	Name of Group: HCC Steering Group Date of ratification: 11.10.23
Has all relevant legislation, recommendations, alerts and	Sickle Cell Disease in Childhood. Standards and Guidelines for Clinical Care. 2nd edition. (October 2010) Sickle cell disease: managing acute painful episodes in hospital. NICE guideline (CG143) (June 2012) Sickle cell disease. NICE guidelines [QS58] (April 2014) BCSH guidelines on management of acute chest syndrome in sickle cell disease (March 2015) BCSH guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease (May 2018) Thalassaemia in the UK revised version 2008: UK BCSH guidelines on transfusion for fetuses, neonates and older children.(Nov 2016) West Midlands Quality Review Service Quality Standards. Health services for people with Haemoglobin disorders. 2018
Have all relevant stakeholders been included in the development of this guideline?	Dr Kirstin Lund: Lead Consultant for Paediatric Haemoglobinopathy Service, Imperial College Healthcare NHS Trust Dr Rubina Malik, Consultant Paediatric Haematologist, St George's University Hospitals NHS Foundation Trust Dr Indu Thakur, Consultant Paediatric Haematologist, Cardiff and Vale University Health Board Dr Alison Thomas, Consultant Paediatric Haematologist, St George's University Hospitals NHS Foundation Trust Dr Sheana Wijemanne , Consultant Paediatric Haematologist, London North West University Hospitals NHS Trust

	Dr Toyin Lythe, Consultant Paediatric Haematologist, Luton and Dunstable University Hospital Dr Toni Petterson: Deputy Lead Consultant for Haemoglobinopathy Service Prof Josu De La Fuente: Paediatric Blood and Marrow Transplant Programme Director Dr Leena Karnik: Lead Consultant for Paediatric Haematology Dr Adam Gassas: Clinical Lead of Women & Children Service, Paediatric Haematology/Oncology Consultant Becky Armstrong: Specialist Psychologist for Haemoglobinopathy Service Becky Easton: Specialist Psychologist for Haemoglobinopathy Service Neil Tickner/Poonam Lumb / Penny Fletcher Paediatric pharmacists

Who will you be notifying of the existence of this guidance?	**Please give names/depts:** SHTs and LHTs of the West London HCC and associated networks
Author/further information	**Name:** Kirstin Lund **Title:** Consultant Paediatric Haematologist **Trust:** Imperial College Healthcare NHS Trust **Telephone/Bleep:** 02032127682 **Trust email address:** kirstin.lund@nhs.net
Document review history	**Next review due:** October 2026

7 INTRANET HOUSEKEEPING

Key words	Exjade, Desferal, PCA, cyclizine, senna, naloxone, chlorphenamine, hydroxyzine, pain, sickle, girdle syndrome, exchange transfusion, sickle crisis, priapism, phenylephrine, Prevenar, Pneumovax, hepatitis B vaccine, hydroxycarbamide, hydroxyurea, spirometry deferasirox, deferiprone Paracetamol, Ibuprofen, diclofenac, naproxen, codeine, tramadol, morphine, Oramorph, lactulose, Movicol, Movicol paediatric, Laxido, Cosmocol, folic acid, penicillin, desferrioxamine, meningitis B, dihydrocodeine

8 EQUALITY IMPACT OF GUIDELINE

Is this guideline anticipated to have any significant equality-related impact on patients, carers or staff?
No ✓

Appendix 1 – Intravenous opiate infusions

An opiate infusion may be given as long as frequent monitoring of respiratory rate, oxygen saturations and conscious level will be assiduously carried out. A nursing ratio of 1:2 is recommended for all children on intravenous morphine infusions. This is best delivered by Patient or Nurse Controlled Analgesia (PCA/NCA). PCA/NCA must only be set up by staff who have been trained and authorised to programme the infusion pump. See local paediatric PCA/NCA Guidelines.

Dosing tables for morphine & fentanyl PCA/NCA are provided as a guide below – but advise to use in combination with local guidelines where variations may apply.

MORPHINE PCA/ NCA

Stop opiate infusion and inform doctor.

	Children <50kg		**Children ≥ 50kg**	
	NCA	**PCA**	**NCA**	**PCA**
Morphine sulphate	1mg/kg in 50mL sodium chloride 0.9% syringe		50mg in 50mL sodium chloride 0.9% syringe	
Loading dose	2.5 – 5mL (50 – 100micrograms/kg)		1 – 5mL (1 – 5mg)	
Bolus doses	0.5 – 1mL (10 – 20 micrograms/kg)	0.5 – 1mL (10 – 20 micrograms/kg)	0.5 – 1mL (0.5 – 1mg)	0.5 – 2mL (0.5 – 2mg)
Lockout	20 – 30 minutes	5 – 10 minutes	20 – 30 minutes	5 – 10 minutes
Background infusion	0, 0.2, 0.5 or 1mL/hr (0, 4, 10 or 20 micrograms/kg/hr)	0 or 0.2mL/hr (0 or 4 micrograms/kg/hr)	0, 0.2, 0.5 or 1mL/hr (0, 0.2, 0.5 or 1mg/hr)	0 or 0.2mL/hr (0 or 0.2mg/hr)

FENTANYL PCA/NCA

	Children <50kg		**Children ≥ 50kg**	
	NCA	**PCA**	**NCA**	**PCA**
Fentanyl	25 micrograms/kg in 50mL sodium chloride 0.9% syringe		1250 micrograms in 50mL sodium chloride 0.9% syringe	
Loading dose	0.5 – 2mL (0.25 – 1microgram/kg)		0.5 – 2mL (12.5 – 50 micrograms)	
Bolus doses	0.5 – 1mL (0.25 – 0.5 micrograms/kg)	0.5 – 2mL (0.25 – 1 micrograms/kg)	0.5 – 1mL (12.5 – 25 micrograms)	0.5 – 2mL (12.5 – 50 micrograms)
Lockout	20 – 30 minutes	5 – 10 minutes	20 – 30 minutes	5 – 10 minutes
Background infusion	0, 0.2, 0.5 or 1mL/hr (0, 0.1, 0.25 or 0.5 micrograms/kg/hr)	0 or 0.2mL/hr (0 or 0.1 micrograms/kg/hr)	0, 0.2, 0.5 or 1mL/hr (0, 5, 12.5 or 25 micrograms/hr)	0 or 0.2mL/hr (0 or 5 micrograms/hr)

Links to prescription documents:

Morphine PCA / NCA Proforma < 50Kg https://intranet.imperial.nhs.uk/Interact/Pages/Content/Document.aspx?id=2753

Morphine PCA / NCA Proforma > 50Kg https://intranet.imperial.nhs.uk/Interact/Pages/Content/Document.aspx?id=2756

Fentanyl PCA / NCA Proforma < 50Kg https://intranet.imperial.nhs.uk/Interact/Pages/Content/Document.aspx?id=2754

Fentanyl PCA / NCA Proforma > 50Kg https://intranet.imperial.nhs.uk/Interact/Pages/Content/Document.aspx?id=2751

Note on withdrawal from opiates

It is advised that patients who have required a PCA/infusion should remain in hospital for at least 24 hours after discontinuation of the PCA/infusion to ensure that he/she does not suffer from recurrent pain or opiate withdrawal.

Appendix 2- Manual Exchange Transfusion protocol:

Pre-exchange: Bloods should be taken for FBC, Hb electrophoresis, U&E, bone profile and group and save. If the patients starting haemoglobin level is < 60g/L, they should be topped up to 80g/L before starting the procedure. It is essential to ensure that blood is ready and easily available from Blood Bank before commencing. The volume of blood for manual exchange depends on the weight of the child. Children <50 kg will have a 30ml/kg exchange and > 50 kg will have a 40 ml/kg exchange transfusion.

The aim is that this should be an isovolaemic procedure with monitoring of blood pressure, heart rate and oxygen saturations every 15 minutes, and 1 hourly 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). Note that the haematocrit of transfused packed cells (approximately 0.5-0.7) is higher than that of the venesected blood.

It is important to ensure that the child is well hydrated between successive exchanges and that the haemoglobin is regularly monitored and kept at or below 100 g/L at all times.

Equipment :
2x cannulae
Giving sets
10/ 20 ml syringes
Pump for blood/ saline infusion
X2 three way taps
Waste bag for collection of blood
0.9% Saline for line flushes
Packed red cells and 0.9% saline for infusion s

Method
Set up with two cannulas on either arm. One is used to withdraw blood and the other is used to infuse blood or saline.

First procedure: start by venesecting one third (30%) of the total volume (ie approx 10 mL/kg) in aliquots of 10 - 50 mL every 15 minutes using a large syringe. Sodium chloride 0.9% should be concurrently infused at the same rate to maintain isovolaemia. If the starting haemoglobin is low then replacement with blood rather than sodium chloride 0.9% should be considered. The venesected blood can be discarded into a venesection bag via a 3-way tap.

Continue venesecting the remaining two thirds (70%) of the volume (20 mL/kg) in aliquots of 10 - 50 mL (approximately 1/10 of total exchange) every 15 minutes replacing with blood at the same rate (approximately 12 mL/kg/h, red cells in SAG-M). This process should take no more than 120 min, depending on the rate of flow of blood and the clinical condition of the patient.

Check FBC, Hb electrophoresis, U&E, LFT, bone profile and clotting, at the end of each 10 mL/kg. Ensure that the Hb $\leq$100 g/L to reduce the risk of hyperviscosity.

Post-procedure:
Once the procedure has been completed, FBC, Hb electrophoresis, U&E, LFT should be repeated

If the patients' haematocrit is > 0.35, there should be further discussion with consultant paediatric haematologist regarding need for venesection or treatment with IV fluids, to avoid hyperviscosity. If the final Hb is low a top up transfusion could be given to bring the Hb up to 100g/L.

Second/further exchange procedures
Further manual exchange procedures may be required to achieve the target HbS. Where possible leave at least 4-6 hours between each exchange procedure.
In critically ill patients exchanges may need to be continuous.
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.

Worked example:
30kg child requiring manual exchange transfusion:

Total volume of blood removed from patient: 30 x 30 = 900 ml
Volume of blood removed per hour: 900/4 = 225 ml
Volume of blood removed every 15 min: 56 ml

Total volume of 0.9% saline to be replaced 900/3 x1 (one third of total) = 300 ml
Total volume of blood to be replaced 900/3 x 2 (two thirds of total) = 600ml

Appendix 3 – The Annual Review

Annual Review NHR Template – 2022/23

Patient Name:
Hospital Number:
NHS Number:

Period and Centre
Period: *
Centre completing review: *
Centre Designation: *

Resource Utilisation
Number of emergency department attendances: *
Number of unscheduled inpatient admissions: *
Number of bed days in hospital: *
Number of planned daycase attendances: *

Support Services
Patient required access to psychology services to support their care:
Yes No Unknown

Patient received psychology support:
Yes No Unknown

Patient required other mental health support services:
Yes No Unknown

Patient accessed haemoglobinopathy community services:
Yes No Unknown

Patient discussed at National MDT panel:
Yes No Unknown

Disease Modifying Therapy

Patient eligible for hydroxycarbamide:
Yes No Unknown

Patient offered for hydroxycarbamide:
Yes No Unknown

Patient declined hydroxycarbamide:
Yes No Unknown

Patient currently receiving hydroxycarbamide:
Yes No Unknown

Reproduction
Fathered a child this year?
Yes No Unknown

Appendix 4 – Incentive Spirometry Guidelines

Patient Selection

All patients of 3 years and older with sickle cell disease who fulfil one or more of the following criteria:

- Acute chest, back or abdominal pain
- Receiving opiate analgesia and prolonged immobility e.g. post fracture, limb pain
- Pre-op and post-op abdominal surgery
- Consultant or Clinical nurse specialist specifically requests

Initiation of Incentive Spirometry Programme

The doctor on the ward or specialist nurse should: -

- Inform the nurse in charge of that shift
- Refer all participants to the physiotherapist in order that the physio may monitor their chest and teach the family how to use the device

The nurse in charge of the shift has responsibility for ensuring that the programme is commenced

Incentive Spirometry Programme

- 10 maximal inspirations for a 3 second hold using the incentive spirometer every 2 hours from 08.00 to 22.00 and while awake at night
- Documentation will include measurement of pain scale and SaO_2 prior to incentive spirometry and recording of maximum inspiratory capacity achieved following incentive spirometry
- Incentive spirometry to be carried out with the patient sitting in an upright position
- Patients requiring > 35% oxygen should continue oxygen therapy via nasal specs during breaths or via oxygen tubing attached to device

Discontinuation of Programme

Medical staff or physiotherapist will be responsible for deciding when to discontinue the incentive spirometry programme. Patients should fulfil all of the following:

- Chest, abdominal and/or back pain subsided
- Opiate analgesia discontinued/ mobilising independently
- No clinical signs of a respiratory infection

OR

- Medical staff consider patient unfit to continue for medical reasons

Appendix 5 – Preparation of Child with Sickle Cell Disease for Surgery

To be completed prior to surgery using peri-operative guidelines

Patient Name: Dob: MRN: Ward: Consultant Surgeon: Consultant Haematologist: Planned Procedure:	FIX PATIENT LABEL HERE		
Documentation			
		Initial & date	
Procedure booked			
Special instructions:			
Consent Complete			
Have Anaesthetists been informed			
PICU / HDU booked?			
CPAP?			
	Yes	**No**	**Not applicable**
PRE-OP BLOODS			
Red Cell Phenotype (if not known), Group and save, FBC, Biochemistry with CRP, Clotting Screen with Fibrinogen, S%			
Ensure Cross match done within 72 hours of surgery			
Bloods checked and results satisfactory and documented			
Blood ordered for 07.30am on day of procedure			
X ray/ scans/ ECG/Sleep study			
PRE-OP TRANSFUSION			
Haemoglobin Platelets			
PT APTT			
Fibrinogen			
S%			
Surgery			
	Yes	**No**	**Not applicable**
IV fluids from nil by mouth until drinking freely			
Oxygen rich environment until fully awake. Monitor oxygen saturations for 24 hours post-surgery			
Prophylactic antibiotics			
Pain management Plan			
Discuss pain management			