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A Clinical Guideline on the Management of Adult Patients with Sickle Cell Anaemia (guidance from the North Middlesex Specialist Haemoglobinopathy Team)

For Use in:	Clinical areas where adult patients with sickle cell anaemia are treated
By:	Clinical staff caring for adult patients with sickle cell anaemia
For:	Adult patients with sickle cell anaemia
Division responsible for document:	Medical
Key words:	Sickle Cell Disease, veno-occlusive crisis, acute chest syndrome, exchange blood transfusion, pain management, Haematology, Transfusion, Iron Chelation, Perioperative management
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Assessed and approved by the:	Regional guideline – NNUH is allowed only to put a front sheet on the document. NNUH follow the standards set by North Middlesex.
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Norfolk & Norwich Hospital is part of a Regional Haemoglobinopathy Network in which the North Middlesex Hospital is our Haemoglobinopathy Specialist Team centre. The North Middlesex Hospital provides Outreach clinics and specialist advice when required for haemoglobinopathy patients across the East of England regional hospital network. These clinical guidelines are provided by the North Middlesex Hospital to be used across their haemoglobinopathy network.

It should be noted that clinicians at Norfolk & Norwich Hospital who need advice about patients with sickle cell anaemia should contact the NNUH Haematology Registrar or Consultant directly for any advice, or to refer a patient with sickle cell anaemia.

- Patients presenting with problems that primarily relate to their haemoglobinopathy (including, but not limited to, painful crisis, chest crisis, infections, and transfusion reactions) should be triaged to Haematology.

- Patients presenting with other problems that require urgent management by another team (e.g. stroke, myocardial infarction, emergency surgery) may be triaged appropriately, but should be discussed with a Haematologist.

- The NNUH Haematology Consultant will liaise with the Regional Haemoglobinopathy Consultant at North Middlesex Hospital if necessary.

Contact numbers for Haematologists at NNUH:

Haematology SpR on call:	DECT ext. 2919
Haematology Consultant on call:	DECT ext. 6744 Out of hours: mobile via Switchboard

Version and document control:

Version number	Date of issue	Author	Status	Change Description*
8.0	19/02/2020	Arne de Kreuk NMUH	Definitive	Major review following publication of the National Standards for the Clinical Care of Adults with Sickle Cell Disorder in the UK 2018

This is a Controlled Document

This is a Controlled Document. Staff must refer to the Intranet version of this document to confirm the most up to date version of this guideline. If older versions are in circulation, they must be either returned to the author above or destroyed.

Clinical Guideline Approval Sheet

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Approved in departmental/divisional meeting NMUH Adult Haemoglobinopathy Services (Local Business Meeting) TBA		
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Guidance Notes

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Summary

This clinical guideline covers the management of adult patients with sickle cell disease according to the national standards. It includes policies for both management of acute complications, including emergency exchange blood transfusion, as well as long term management.

This guideline has the aim to provide the users with a concise overview for safe and effective clinical care for adult patients with sickle cell disorder (SCD). The guideline should guarantee that all SCD patients within the network receive the same level of care and the contents should form the framework for all individual Trusts. Section 1 contains the actual clinical standards. Section 2 contains the local / regional contact details and referral pathways and should be amended by each individual Trust using this guideline.

This guideline applies to all staff involved in the management of adults with sickle cell disease trustwide.

Introduction:

Sickle cell disease is now the commonest inherited single gene disorder in the UK. With over 300 new patients being born annually. There are estimated to be 14,000 people with sickle cell disease in England, with a large proportion of these living in London. Sickle cell disease may be caused by the coinheritance of the sickle cell disease with another sickle cell gene i.e. HbSS; with another abnormal haemoglobin e.g. HbSC, HbSOArab, HbSD; or with a thalassaemia gene i.e. HbSbeta thalassaemia. Patients with sickle cell disease may suffer a variety of complications, some acute and some longer term. These conditions are complicated and difficult to manage and may lead to rapid clinical deterioration. It is therefore essential that these patients are managed with reference to these guidelines and the involvement of the Red Cell Team in a timely and efficient manner.

<u>Pathophysiology:</u>
Sickle cell disorders are inherited disorder of haemoglobin, the oxygen carrying pigment in the red blood cells. When exposed to low oxygen conditions, the red cells become stiff, misshapen ("sickled") and sticky, and cannot squeeze through the smallest blood vessels in the circulation. This vaso-occlusion, or blood vessel blockage, causes damage to the tissues beyond, and severe pain in the affected area - the "painful crisis". Bones are most commonly involved but other tissues can be affected; the dangerous sickle "chest syndrome" can occur in the lungs, or a stroke can result when the brain is affected.

The high rate of haemolysis as a result of increased destruction of red cells is linked to inflammation and endothelial dysfunction and is a separate risk factor linked to stroke, thrombo-embolism, ulcers and CKD.

Precipitants, which can trigger a vaso-occlusive crisis, include infection (fever), exposure to cold, dehydration, strenuous exercise, menstruation, pregnancy and emotional stress. Less frequently, problems can result from profound anaemia +/- hypovolaemic shock due to the

bone marrow switching off resulting in an aplastic crisis, or from "sequestration" of a significant part of the blood volume in the spleen, and sometimes the liver.

A person with a sickle cell disorder is also prone to various infections, particularly with pneumococcus, that can become life threatening. Overwhelming pneumococcal sepsis remains a preventable cause of death, especially in infants; penicillin prophylaxis and pneumococcal vaccinations reduce the risk.

A person with a sickle cell disorder can experience recurrent, acute painful 'crises' or chronic pain due to a number of complications such as ankle ulceration or avascular necrosis of a joint. They can experience acute, life-threatening complications such as stroke, acute chest syndrome, or overwhelming sepsis. They can also develop chronic complications such as pulmonary hypertension, chronic kidney disease or retinopathy. Finally in certain circumstances such as pregnancy or surgery, expert multidisciplinary input is required.

This guideline aims to detail the initial Accident and Emergency assessment, inpatient and outpatient management and monitoring of adult patients with sickle cell disorders.

Definitions

Sickle cell disease (SCD) is defined as the coinheritance of a sickle cell gene with another abnormal haemoglobin (HbS, HbC, HbD, HbOArab or other) or thalassaemia gene that is known to cause the clinical phenotype of sickle cell disease.
Sickle cell trait is defined as HbS co-inherited with a normal haemoglobin (HbA) and is not covered by this document.

Glossary and Acronyms

Hb	Haemoglobin
SCD	Sickle Cell Disease
ED	Emergency Department
ACS	Acute Chest Syndrome
Venous thromboembolism	VTE
Deep Vein Thrombosis	DVT
Pulmonary Hypertension	PHT
Chelators	Medications that remove iron from the blood e.g. desferrioxamine (desferal), deferiprone (L1) and Deferasirox (exjade)

Duties within the organisation

Responsible Officer: The Medical Director has executive ownership of this guideline.
Service Managers and Clinical Managers: Managers with responsibility for areas caring for patients with sickle cell disease are responsible for ensuring staff are aware of this policy and have access to appropriate training in order to provide the most appropriate and best quality of care to patients with sickle cell disease.

Medical Staff: Medical staff are responsible for the delivery of care and medical advice to patients with sickle cell disease in line with this policy.
Ward based registered practitioners, for example nurses: are responsible for following the guidance of care to patients with sickle cell disease as outlined within this policy within the boundaries of their registration and competencies.
Other staff: Other staff should be aware of this policy and that there is specific guidance for the care of patients with sickle cell disease.

Clinical guideline

This document, in line with national recommendations and guidance, outlines the policy for safe and effective chronic and acute treatment of patients with sickle cell disease. The guidance within has been written by the specialist inherited red cell disorder team based at North Middlesex Hospital NHS Trust for the use of all staff involved with the care of patients with sickle cell disease both at the North Middlesex Hospital and across the North East London and East Anglia networked hospitals.

North Middlesex Hospital would like to acknowledge University College London Hospitals and the South Thames Sickle Cell and Thalassaemia Network for kindly providing documents partly used in this guideline.

Dissemination and implementation

This guideline replaces the previous clinical guideline for the care and treatment of patients with sickle cell disease. The guidance has been completely rewritten, following publication of the 2018 Standards for Clinical Care of Sickle Cell, in order to provide a document that is suitable for use across the network as well as within North Middlesex University Hospital NHS Trust. The guidance will be made available via the NMUH and network trusts intranet to ensure that all staff working with these patients have access to the same standard and guidance ensuring appropriate care. All staff (in particular nursing and medical staff) should be signposted to the guideline on starting within the specialist service. Ward based staff responsible for the care of patients with sickle cell disease should be made aware of the policy via trust communication and signposting by managers.

Process for monitoring compliance and effectiveness

The Specialist Haemoglobinopathy Teams as part of the North London and East Anglia Network, supported by the UCLH Haemoglobinopathy Coordinating Centre, participate in regular audit and surveillance in order to ensure that the service provision and standards of care are met. Results of the monitoring and audits can be obtained from the specialist team and policy authors. The required standards and audits to be performed are outlined within the standards for clinical care in patients with sickle cell and the requirements of the WMQ peer review requirements. The local and network MDTs discuss errors, incidents and concerns with the process ensuring overview that standards are being met and that failures to process are being reviewed and appropriate actions implemented

References and Associated Documents

For a full and comprehensive overview, please refer to the Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK 2018 and other references given in the relevant section.

SECTION 1: CLINICAL STANDARDS

1. MANAGEMENT OF THE ACUTE PATIENT WITH SCD

1.1. Acute Presentation and Assessment:

Patients with Sickle cell disease complications should be treated on their merit and not on the underlying genotype. The majority of patients will present with acute pain, but other acute symptoms may also be present. It is important to realise that patient with SCD can RAPIDLY DETERIORATE AND DEVELOP LIFE-THREATENING COMPLICATIONS so early detection of critical warnings signs is paramount and these observations should never be omitted during any presentation.

The initial assessment should include:

- Consult the patient's specific care plan. Known sickle patients should have a Care Plan [see Section 2 for where to find this] that contains up to date information about pain management and key medical complications. Patient may also have a record on NHS Coordinate My Care.
- History of presenting complaint
- Site & severity of pain if applicable
- Shortness of Breath
- Fever
- Precipitating event – e.g. Diarrhoea & vomiting upper respiratory tract infection, Stress
- Review of systems
- Recent analgesia use
- How typical is this compared to their usual crises
- Observations: Pulse, Respiratory rate, Blood pressure, Saturations ALWAYS TO BE MEASURED ON AIR.
- Are there any critical warning signs

Critical Warning Signs include:

- Feeling very unwell
- Sepsis or fever >38c
- Cardiovascularly unstable
- Chest signs: O2 saturations (ON AIR) < 94% or < 4% from baseline, chest pain
- Neurological signs - altered GCS, meningism, focal neurology, a new asymmetrical weakness, severe headache
- Symptomatic anaemia, or Hb<20g/L from baseline
- Abdominal complications: Abdominal distension, absent bowel sounds (rebound and guarding usually absent), dilated loops on AXR
- Large liver or spleen
- Uncontrolled pain

These warning signs could be indicative of a (SCD-specific) underlying critical complication requiring IMMEDIATE TREATMENT, including:

- Sepsis
- Acute chest syndrome (O2 saturations (ON AIR) < 94% or < 4% from baseline
- Organ Dysfunction e.g. Acute renal failure
- Stroke
- Severe acute anaemia e.g. aplastic crisis, hyperhaemolysis, transfusion reaction
- Priapism
- Osteomyelitis
- Pregnancy
- Abdominal crisis, Girdle Syndrome: Abdominal distension, absent bowel sounds, rebound and guarding usually absent, dilated loops on AXR
- Sequestration (hypovolaemia and shock secondary to large numbers of red cells trapped in the spleen or liver – usually in children but can occur in adults.)

1.1.1. Minimal Set of Observations and Investigations

All patients with an acute presentation should have a minimal set of observations and investigations as specified below:

Observations:

- Pulse
- Respiratory rate
- Blood pressure
- Saturations ALWAYS TO BE MEASURED ON AIR

Examination:

- Soft tissue swelling over site of pain
- Signs of complications: e.g. large liver for hepatic sequestration, respiratory compromise in acute chest syndrome.

Urgent Initial Investigations:

- FBC + reticulocytes
- U&Es
- LFT
- Bone profile
- LDH
- Haemoglobinopathy screen (Haemoglobin S Level) if patient transfused in last 3 months or no historical record on system
- Coagulation profile
- Blood transfusion specimens: group and antibody screen *Label for sickle cell patient*
- If transfused elsewhere or not known to locally, please inform blood transfusion where the patient usually attends so that they can contact the local hospital laboratory for further information. This is crucial as antibodies are not always detectable. Furthermore, **blood transfusion will only know if the patient has sickle if you tell them**.
- If previous antibodies send 3x6mL EDTA to blood transfusion.
- If If not known to NMUH or another specialist centre, send 3 x 6ml EDTA specimens for group, antibody screen and full red cell phenotype / genotype, stipulating clearly that “one sample to go to Colindale RCI for full red cell phenotype/genotype”. Consider including – if not known to NMUH get transfusion history – when and where last transfused.

Further investigations:

- G6PD screen if not done previously
- CXR - If chest, abdominal or spinal signs.
- ABG - If O2 saturations on room air are <92% or 4% less than baseline, abnormal CXR or respiratory symptoms/signs.
- Malaria if recent foreign trave (SCD does NOT prevent Malaria)
- Samples for microbiology as indicated by signs and symptoms, for example stool, sputum etc.
- Amylase – if abdominal signs.

1.2. General Care for the Acutely Unwell Patient

1.2.1 Monitoring:

- This is a minimum requirement for all patients throughout their admission. Escalation will be necessary if the patient becomes more unwell.
- Observations: Pain score, observations Heart Rate, Respirations, Blood Pressure, Oxygen Saturation (ON AIR), Temperature and GCS, every 30 minutes until pain relieved, then 4 hourly.
- If on strong opiates - hourly for at least 6 hours.
- If on PCA, then PCA policy must be followed.
- Fluid balance, and height & weight on admission
- Frequency of further monitoring as per Trust policy (NEWS). As a rough guidance, please see table below. PLEASE NOTE that even in the absence of abnormal parameters, a minimum of 4-hourly frequency should be maintained at all times!
- All oxygen saturations to be monitored on air
- Fluid balance

	30mins– 1hourly	**2-4 hourly**	**4 hourly**
Sedation	≥2		0-1
Respiratory rate	<12		12-24
Pain Score		≥4	≤3
O2 saturations on AIR	≤94%		≥95%

1.2.2 Criteria for Escalation:

- All patients sick enough to require a red cell exchange
- As per trust protocol for the pathway of the deteriorating patient
- Any patient who has a history of deteriorating quickly **even if currently well**
- Any deteriorating patient
- Pa O2 <8.5pa
- The attending / on call Haematology Consultant and/or SpR should be informed directly (24x7) when escalation criteria are met.

1.2.3. Management – non pharmacological

Fluid Replacement:

- The treatment most likely to influence the resolution of a crisis is hydration. Patients become dehydrated because they cannot concentrate urine. Increased blood viscosity exacerbates sickling.
- Try oral route, however, if the patient is unwell, intravenous fluids maybe usually needed.
- Care should be taken not to fluid overload as some patients have compromised cardiac reserve or abnormal renal function. Gentle fluid resuscitation is preferred over aggressive fluid replacement. Do not exceed 4litres/24hrs intravenously unless severely dehydrated.
- Patients need a total (by all routes) of 70-90 mL/kg body weight per 24 hours. (Approximately 3 litres in 24h for most adults).
- In the absence of any oral intake, give 1 litre of sodium chloride 0.9% over 3 hours. Thereafter give alternate infusions of sodium chloride 0.9% then Glucose 5% with potassium chloride 20mmol/l. Infuse at 3 mL/kg/hr (corresponding to 70mLs/kg/day).
- Start a fluid balance chart.
- Check U&E for hypokalaemia and change of creatinine from baseline.
- Avoid central lines unless absolutely necessary and even then they should stay in for a maximum of 48 hours (due to the high risk of thrombus formation and infection) unless discussed with consultant.
-

Oxygen:

- This is of no proven benefit unless there is hypoxia.
- Monitor pulse oximetry OFF oxygen.
- If saturations are <94% on air or there is a fall in oxygenation of 4% or more from baseline steady state an ABG on air should be performed and follow the management for acute chest syndrome.

NB. Excess opioid analgesia can cause respiratory depression. If respiratory rate falls below 12 per minute or saturations decrease significantly patients should be assessed immediately. Avoid naloxone if possible (though isn't always). Injudicious use of naloxone can cause recurrence of severe pain that may be difficult to control. Most patients will "sleep off" the effects of opioids but must be watched very closely during this period. Opioids must be stopped and the patient should be closely monitored if the respiratory rate drops <12 per minute. NB. Some patients will have low baseline oxygen saturations due to underlying chronic sickle lung disease. If the baseline is known, then any changes in the oxygen saturation needs to be correctly interpreted and acted upon. In general, a fall in oxygen saturation of 4 percentage points or more from baseline should be interpreted as a significant drop. Do not assume chronic hypoxia unless clearly documented in the patient's clinical records.

Respiratory Management:

- Incentive spirometry.
  This should be prescribed on the regular side of the drug chart in any patient at risk of chest syndrome (See relevant section). The intention is for 5 inspirations per hour while the patient is awake.
- CPAP / Optiflow
  See Section on Acute Chest Syndrome.

- Chest Physiotherapy
  See Section on Acute Chest Syndrome.

1.2.4. Management – Medication

Adjuvant Medication should always be offered when patients are on opioids or present with a painful crisis (NICE, 2012).

1.2.4.1. Anti-emetics:

- Not required routinely, but some patients may develop significant nausea from opioid use
- Do not prescribe cyclizine by intravenous or intramuscular injection – some patients become dependent on parenteral cyclizine.
- A selective 5-HT3 receptor antagonist such as ondansetrone should be the first choice because of minimal CNS effects.

1.2.4.2. Laxatives:

- Opioids are very constipating as is the sickle crisis itself.
- Prescribe before onset of constipation usually on admission.
- One or more laxatives are usually required.
- Common laxatives include senna, sodium docusate, lactulose, macrogol. It is often preferable to use a bulk-forming agent in combination with a motility agent. Patients will often know what works for them.
- In case of intractable opioid-induced constipation, methylnaltrexone by subcutaneous injection or naloxegol per os may be an effective treatment.

1.2.4.3. Anti-pruritics:

Some patients develop severe pruritus when taking morphine or diamorphine. Clorphenamine is often effective. Cyclizine is not to be given intravenously or intramuscularly.

1.2.4.4. VTE Prophylaxis:

Patients with sickle cell disease are allocated as medium risk of VTE and require routine prophylaxis when admitted/immobilised UNLESS they have had previous VTE in which case the patient should be discussed for consideration of more aggressive VTE prophylaxis (if no longer on treatment).

All patients with a central venous catheter in situ for longer than 24-48 hours should be considered for VTE prophylaxis, including PICC lines and port-a-caths.

1.2.4.5. Antimicrobials:

- Patients should be on prophylactic dose penicillin 250mg p.o. b.d. as they are functionally hyposplenic. If penicillin allergic prescribe erythromycin 500mg mg p.o. b.d.
- Pneumococcal septicaemia is common and life threatening. It can be fulminating because of absent splenic function and fatal within a few hours. Mortality is highest in first 3 years of life. Pneumococcal infection presents as septicaemia with shock or meningitis, peritonitis, pneumonia or osteomyelitis. It may be associated with sequestration.

- Haemophilus influenzae may present in the same way.
- Salmonella osteomyelitis may affect all age groups.
- Other infections such as staphylococcal osteomyelitis and mycoplasma pneumonia, E Coli UTI, may be seen.
- Parvovirus infection is the usual cause of an 'aplastic crisis'
- Full septic screen (no LP unless clinically indicated) if suggestion of sepsis prior to starting antibiotics.
- There should be a low threshold for starting antibiotics.
- If mildly unwell, but source of infection unclear, commence antibiotics – refer to the individual Trust's Guidelines. For a summary in SCD, see below
- If patients on Desferrioxamine (DFO) have diarrhoea and/or abdominal pain, the DFO should be stopped and Ciprofloxacin started immediately but stopped if diagnosis of Yersinia has been excluded.
- The three most common organisms implicated in chest crisis are chlamydia, mycoplasma and RSV.
- All patients with chest symptoms need cover for atypical bacteria and a nasal swab.
- Treat all positive cultures or suggestions of sepsis even if symptoms are initially mild.

  <u>Antibiotics: (please check against individual Trust's policies:</u>

  Sepsis of unknown origin First line
  - Adult: Ceftriaxone 2g IV od
  - Ceftriaxone 40 mg/kg if under 50 kg, [> 50 kg give adult dose]

  IV-oral switch
  - co-amoxiclav 625mg po tds

  Severe Penicillin allergy (anaphylaxis)
  - Adult: Teicoplanin 400mg (6 mg/kg if > 70kg) IV BD for 3 doses then IV OD
    AND
    Gentamicin* 5mg / kg
    IV- oral switch
  - According to source or speak with Microbiology

  <u>Additional Notes:</u>

  In the adult patient presenting with NO high or med-to-high risk factors for sepsis then:
  - Oral doxycycline 200mg loading, followed by 100mg bd is an alternative agent (requires safety netting). Review need at 48-72 hours. Maximum course 5 days.

  Consider the additional need for atypical cover if severe chest sepsis suspected
  - Doxycycline 200mg loading, followed by 100mg bd po / clarithromycin 500mg bd IV

  In severe sepsis i.e. NEWS2> 5 in adults
  - ADD gentamicin* 5mg / kg (Max 450mg) until haemodynamically stable (Max 5 days)
  - Consider increasing Ceftriaxone to a max of 4g / day in divided doses

*Use actual body weight or corrected body weight if >120% ideal body weight. Requires therapeutic drug monitoring and dose adjustment in renal impairment. See MicroGuide app or gentamicin guidelines.

Add Metronidazole if abdominal source likely (not required if patient is on co-amoxiclav

- Adult: Metronidazole 500 mg IV tds

If Yersinia enterocolitis suspected

- Adult: Levofloxacin 500 mg bd IV /po

For suspected community acquired pneumonia or urinary sepsis treat as per clinical guidelines or see MicroGuide app.

1.2.4.6. Naloxone for reversal of opioid-related respiratory depression:

Excess opioid analgesia can cause respiratory depression. If respiratory rate falls below 12 per minute or saturations decrease significantly patients should be assessed immediately. Avoid naloxone if possible (though isn't always). Injudicious use of naloxone can cause recurrence of severe pain that may be difficult to control. Most patients will "sleep off" the effects of opioids but must be watched very closely during this period.

<u>If Naloxone needs to be given:</u>

- Naloxone (Narcan) 100-200 mcg (1.5-3mcg/kg) by slow i.v.i
- Can also be given sc or im if necessary
- If response inadequate repeat doses 100 mcg every 2 minutes, to a maximum dose of 10 mg.
- Relatively short acting, monitoring of patient following administration required as further doses or infusion may be necessary, and maintaining pain relief is also required.
- Hypertension, cardiac arrhythmias, pulmonary oedema and cardiac arrest can result from inappropriate dosing of naloxone.
- Administer maximal inhaled oxygen by face mask

<u>1.2.5. Discharge form ED or ward.</u>

- Patients should be supplied with oral analgesia as TTAs as suggested by the Red Cell team.
- If patient attends ED and is fit for discharge, small supplies of analgesia can be issued for 2-3 days if medically prudent. Please inform Red Cell CNS / haematology team if patient attended ED and was well enough to be discharged.
- Patients must remain for 2 hours for observation within ED or Haematology Day Unit prior to discharge if given injections of opioids.
- If you feel a sickle cell patient requires home follow up by the specialist nursing community team please contact the Sickle Cell Counsellors in their area.
- Patients should be encouraged to make their own arrangements for transport home. Patients should be advised not to drive home whilst on opioid therapy.
- Discharge letter should be completed <two working days from discharge and sent to GP and copied to other departments/hospitals under whom they have regular care. This includes the local data manager.

- All patients should receive a follow up OPA, please discuss with haematology as to when but ideally within 2-3 weeks.
- If behind with aspects of routine care, e.g. annual cardiology/ophthalmology assessments, please refer for these also.
- Before discharge, provide the patient (and/or their carer) with information on how to continue to manage the current episode, including (NICE, 2012):
    - How to obtain specialist support
    - How to obtain additional medication
    - How to manage any potential side effects of the treatment they have received in hospital.
- Serious adverse events as well as other key fields of the National Haemoglobinopathy Registry (NHR) should be recorded on the database by the Data Manager.

1.3. Uncomplicated Painful Crisis

The acute painful episode, or crisis, is the characteristic presentation of sickle cell disease (SCD). These episodes can occur unpredictably, often without clear precipitating factors. Pain can fluctuate in intensity and duration, ranging from mild to severe and debilitating. The acute painful episode is the most frequent cause of hospitalisation, accounting for more than 90% of hospital episodes but the majority of acute painful episodes are managed within the community.

Please bear in mind that there is no specific test that confirms whether the patient is in a sickle cell crisis or not - regard the patient (and/or their carer) as an expert in their condition.

Patients who present with a painful crisis (also referred to as veno-occlusive crisis or VOC) should be treated as an acute medical emergency and adequate analgesia should be offered within 30 minutes from presentation (NICE, 2012) like is applicable to all other causes of acute severe pain.

This implies that an SCD patient presenting with an acute **painful crisis should always be triaged as 'orange' = urgent.**

1.3.1. Management of the patient with an uncomplicated pain crisis (NICE, 2012):

2. Orange triage

3. Initial assessment as described under
1.1. Acute Presentation and Assessment.

4. See Section below
1.3.2. Analgesia for acute painful episode

5. As described under 1.2.1 Monitoring: and
1.2.4. Management – Medication

6. As described under section acute presentation
and management - complications

7. As described under
1.2.3. Management – non pharmacological

8. See section below
1.3.3. step down pharmacological treatment

9. As described under section
1.2.5. Discharge form ED or ward

1.3.2. Analgesia for acute pain crisis

First of all, check the **patient's care plan** or NHS Coordinate My Care for recommendations on treatment for acute pain and any contra-indications.

Not all patients need (strong) opioids for their analgesia. Patients who have moderate pain and not yet had analgesia can be offered a weak opioid initially. All patients should be offered regular paracetamol and NSAIDs (non-steroidal anti-inflammatory drugs) by a suitable administration route, in addition to an opioid, unless contraindicated.

Do not offer Pethidine. Pethidine is short acting and the metabolite of pethidine, nor-pethidinic acid (long T1/2) may cause seizures.

Entonox It can be used for pain control in the ambulance but should not be used frequently or for more than 60 min (BCSH guidelines 2003). It causes metabolic inhibition of B12 causing bone marrow and neurological toxicity. There are also issues with dependency.

Route of administration:

Oral analgesia is preferred. However, parenteral (or intranasal if available) administration has a more rapid onset of action and may be preferred at least initially. Iv injection has a very rapid effect but has the drawback of requiring venous access. Most opioid drugs are as effective given by subcutaneous injection as by intramuscular but im administration has a swifter onset of action. However, repeated intramuscular injections can result in muscle necrosis that results in variable drug absorption and can also lead to the formation of chronic, painful abscesses. NB Oxynorm should only be administered orally or subcutaneously; not intramuscularly.

Choice of opioids:

Each of the morphine derivatives has its own pros and cons. Morphine is a good choice for both oral and parenteral treatment. Diamorphine (Heroin) is essentially a pro-drug of morphine and as such there are no significant differences in the pharmacodynamics of diamorphine when compared to morphine when used for acute pain. However, diamorphine has the advantage that it can be dissolved in a smaller volume of diluent (less than morphine) and has a better lipid-solubility allowing s.c. infusion, which is particularly useful in patients with poor IV access. However, there are concerns that diamorphine gives the highest level of euphoria of all opioids and contributes to dependency and difficulties with weaning. The UK is the only country in the world where the production of diamorphine is not illegal. At the time of writing of this guidance, there are significant supply issues and for this reason and the concerns mentioned above, diamorphine is not first choice.

Oxycodon is available as a second line opioid available for patients unable to tolerate oral or subcutaneous morphine.

Cautions:

- **Immediate release, modified release and injection preparations have similar-ish names. Take care when prescribing, dispensing or administering morphine or oxycodon.**
- Liver impairment - reduced clearance.
  Avoid in patients with moderate to severe liver impairment.
- Renal impairment - reduced excretion.
  Titrate slowly and monitor carefully in mild to moderate renal impairment. Avoid in chronic kidney disease stages 4-5 (eGFR <30ml/min).
- Take into account the equivalent doses of the various opioid drugs. A quick reference is given below.

OPIOID DRUG	EQUIVALENT DOSE
ORAL MORPHINE	30 mg
SUBCUTANEOUS MORPHINE	15 mg
SUBCUTANEOUS DIAMORPHINE	10 mg
ORAL OXYCODONE	15 mg
SUBCUTANEOUS OXYCODONE	7.5 mg

Suggested analgesia for patients who have **never taken opiates before or in mild pain**:

- Co-codamol 30/500 x2 QDS
- NSAIDS (Ibuprofen 400mg)
  Not if urine dip +ve for protein/ low eGFR/pregnant

If insufficient effect, add

- Immediate release morphine sulphate (Oramorph or Sevredol) 10-15 mg PRN
- Max 3 doses in 4 hours

if >40-60mg in 24 hrs change to:

- sustained release morphine (MST, Zomorph) 20-30 mg BD
- and immediate release morphine sulphate 10mg PRN 4 hourly
  OR
- Oxycontin 10mg BD
- and Oxynorm 5mg PRN 4 hourly
- Always prescribe adjuvant medication 1.2.4. Management – Medication

Suggested analgesia for patients who **have already taken weak opioids or in moderate pain:**

The oral drug of choice is immediate release morphine sulphate (oramorph liquid or sevredol tablets).

If weight < 50 kg:

- Morphine Sulphate immediate release: 20 mg at presentation (time 0h)
- 20 mg 1 h after first dose (time 1h)
- 20 mg 3 hours after first dose(time 3h)

- Then 20 mg every 3 hours.

If weight ≥50 kg:
- Morphine Sulphate immediate release: 25 mg at presentation (time 0h)
- 25 mg 1 h after first dose (time 1h)
- 25 mg 3 hours after first dose(time 3h)
- Then 25 mg every 3 hours.

- If regular Morphine Sulphate immediate release required, add morphine sustained release (MST) at a dose of 1mg/kg up to a maximum of 60mg BD

- Always prescribe paracetamol and NSAIDs if urine dip and eGFR normal.
- Always prescribe adjuvant medication 1.2.4. Management – Medication

Suggested analgesia for **opioid tolerant patients or in severe pain:**

Always check if the patient has a personal care plan before prescribing analgesia for this category because individual doses may vary significantly based on day-to-day opioid exposure.

If the patient does not have a care plan, the schedule below can be used:

	MORPHINE	OXYCODON
1st loading dose (A&E)	0.15 mg/kg to a max of 15 mg sc or slow iv bolus	5-10 mg sc or slow iv bolus. Max 15 mg
	In practice usually 10-15 mg for all	
Continue with	3-4 hourly injections 10-15 mg	3-4 hourly injections 5-10 mg
'stat' doses*	2x 10-15 mg PRN/ 24 h for 2 days	2x 5-10 mg PRN/ 24 h for 2 days

* 'stat' doses are only intended as an escape for those patients who do not achieve adequate analgesia during the acute painful episode. These extra doses are given not less than an hour after the usual injection; the following injection can be given at the normal interval.

Administration of morphine or oxycodone via a patient-controlled analgesia (PCA) device is a preferred method if available. PCA avoids the high peak doses involved in bolus injections (which in turn contribute to euphoria and dependency) and more importantly, restores the patient's control over their analgesia. See separate guideline on Patient-Controlled Analgesia (PCA) in Sickle Cell Disease (Guideline under development).
- Always prescribe paracetamol and NSAIDs if urine dip and eGFR normal.
- Always prescribe adjuvant medication 1.2.4. Management – Medication

1.3.3. Step down pharmacological treatment

There is no agreed evidence-based guideline on the weaning of analgesia in patients with SCD. A typical painful episode lasts between 3 and 7 days, but especially in older patients can take longer to settle. The analgesic requirements may vary from individual to individual and a

common-sense approach is required to achieve a successful transition from the hospital setting to ambulatory care with adequate pain relief. Long-term opioids should be avoided as much as possible in order to reduce the risks of tolerance and dependence.

General principles include:
- Do not reduce opioids during the first 24 hours unless there is respiratory depression or increased lethargy
- Reduce the DOSE rather than the FREQUENCY. Patients often request to discontinue parenteral morphine at once but this approach is more likely to cause rebound or withdrawal symptoms with a risk of readmission.
- Typically, reduce the dose by 10-20% at the time (regardless of way of administration).
- Avoid reducing the opioid dose during the night when pain assessment is suboptimal
- Convert to oral medication in a dose equivalent to the parenteral dose as soon as possible.

1.3.4. Barriers to effective pain management in sickle cell disease

Despite the NICE Guidance and NICE Pathway (NICE, 2012) as summarised above, patients with SCD often still receive suboptimal treatment of an acute painful episode. Ongoing audit shows that the time to analgesia is often significantly longer than 30 minutes. Dosing is variable and often insufficient leaving the patient in severe pain. Lastly, the re-assessment is often overlooked leaving patients waiting for a next dose for several hours. Whilst factors like staffing levels and ED capacity play a role, several studies have identified specific barriers to the treatment of the acute painful episode in SCD. A summary is given below. It is important to take these factors into account during the assessment and treatment of a patient with SCD.

1. Patient-related factors: Manifestation of vaso-occlusive pain
    - Vaso-occlusive pain is complex and multifactorial.
      Primary etiology of acute episodic crises: vaso-occlusion of postcapillary venules.
      Most frequently boney areas where marrow is present.
    - Children: hands, feet often swollen (‘visible crises’)
    - In adolescents and adults: many other etiologies; the crises is not ‘visible’ and there is no diagnostic test that confirms sickle cell pain.
        - Avascular necrosis
        - Regional pain syndromes
        - Neuropathic pain
        - Opioid-induced hyperalgesia
        - Depression

2. Negative provider attitudes. A series of reports have published survey results indicating that providers have misperceptions that interfere with the assessment, including:
    - SCD patients exaggerate their pain
    - SCD patients are dishonest and manipulative
    - SCD patients are uncooperative and frustrating to manage
    - People with SCD are addicted to opioids. Whilst about 2-5% of the SCD population truly has an opioid dependency problem, a large survey revealed that 46% of ED providers believe >10% of SCD individuals are addicted.

However, the small proportion of SCD patients that truly have an opioid dependency problem are more likely to attend ED frequently and contribute to the biased view of ED providers that the majority of SCD patients have an addiction problem. See also section below on frequent attenders.

3. Disrupted therapeutic relationship between patient and provider:
   As a result of the above, SCD patients have often developed a SCD patients mistrust of their health care providers. This in turn can lead to more stress, which is associated with more pain. SCD patients often take an opposing position if they feel not listened to or if they don't receive adequate analgesia, which in turn reinforces already existing negative provider attitudes.

1.3.5. Frequent attendance

Frequent attendance with acute painful episodes needs to be taken seriously and is often indicative of either one or more of the following:

- Severe phenotype with suboptimal disease-modifying treatment
- Suboptimal ambulatory care
- Social issues
- Suboptimal chronic pain management
- Opioid dependency.

Frequent attendance puts patients seriously at risk of receiving suboptimal care in the acute and inpatient setting because of the repetitive nature and possible provider misperception about the underlying causes. It is paramount that patients who attend ED frequently remain at risk of SCD-related complications and should always be assessed as outlined in paragraph 1.1.

The responsible haemoglobinopathy team can under certain circumstances put restrictions in place for individual patients. This should be summarised in the patient's care plan and ideally also in NHS Coordinate My Care, especially if there are concerns about multi-site attendance. A Trust-specific policy can be found in Section 2.

1.4. Acute Chest Syndrome

Definitions:

- Acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on chest X-ray (Charache et al, 1979; Ballas et al, 2010)
- May have a severe clinical course and can progress rapidly from mild hypoxia to respiratory failure and death. Hypoxia is a useful predictor of severity and outcome (Vichinsky et al, 1997, 200)
- Note: patients often describe an uncomplicated painful episode with chest pain as a 'chest crisis'. Please be aware that this is very different from the definition of acute chest syndrome (ACS).

1 in 2 patients with SCD will have an episode of acute chest syndrome during their life (based on the CSSD study in the US). 78% of ACS episodes are associated with a vaso-occlusive pain crisis (in other words, 22% of patients DO NOT HAVE A PRECEEDING PAINFUL EPISODE. The highest incidence is found in HbSS and HbS/βo thal Vs HbS/C or HbS/β+ thal. Important to realise that is that the mortality rate in adults per episode was found to be 4.3 %. **Early recognition and prompt treatment is critical.**

Typically, the onset of ACS is within 48 to 72 hours after hospital admission for pain underlining the importance of the ongoing monitoring of SCD patients as described in section 1.2.1.

Diagnosis:

New onset hypoxia is an early indicator, defined as any patient with an oxygen saturation < 94% or a fall of 4% or more from baseline. Any patient with SCD and new onset hypoxia should have a full review and ACS should be considered. **Simply providing the patient with oxygen in order to improve the O2 saturation without further assessment is a critical error** and may result in lack of escalation of care. For more details on monitoring and escalation, see section 1.2.

The differential diagnosis of hypoxia in SCD includes:

1. Chest infection. Clinically, ACS may be indistinguishable from a purely infective episode. If in doubt, treat for both. All patients with ACS should receive intravenous antibiotics as part of their management.
2. Pulmonary embolism. Typically presents with pleuritic chest pain, hypoxia and a normal chest X-ray, D-dimers are not helpful in SCD, as they tend to be elevated. On clinical suspicion, diagnostic imaging with Ventilation perfusion scan (VQ scan), CT Spect OR CT pulmonary angiogram (CTPA) should be performed and treatment dose low molecular weight heparin initiated pending CT report. ACS may be complicated by pulmonary embolism or may occur secondary to pulmonary embolism. In such cases ,treatment will be required for both conditions simultaneously.
3. Over-narcosis (Opiate toxicity) Careful monitoring should avoid this untoward effect of opiates. Regular monitoring of respiratory rate, sedation and pain scores should be in place. Opiate narcosis is associated with a **falling respiratory rate**. Opiate dose

modification or discontinuation may be necessary. Naloxone (1.2.4.6) may be required to reverse significant opiate toxicity. Opiate narcosis may trigger or worsen ACS.

4. Hypoventilation due to pain. Effective analgesia is necessary to prevent hypoxia and hypercapnia developing due to a restrictive ventilatory defect as a consequence of ongoing chest pain. This may contribute to the development of ACS
5. Fluid overload. Fluid replacement is an integral part of the management of ACS. However, overhydration may lead to pulmonary vascular congestion and pulmonary oedema, especially in patients with decreased cardiac function. Close attention should be paid to fluid balance and a fluid balance chart must be maintained. Acute deterioration in a patient after blood transfusion should prompt consideration of fluid overload or transfusion-related acute lung injury (TRALI)

Assessment and Investigations:

- **All** observations and investigations as described under section 1: acute presentation.
- In addition, request:
    - Nose and throat swab for respiratory viruses in patients with coryzal symptoms
    - Consider urine for pneumococcal and Legionella antigen
    - Consider nasopharyngeal aspirate for chain reaction (PCR) for viruses
- A chest X-ray is required in any patient with hypoxia, chest pain, respiratory symptoms or fever **but must not delay the institution of urgent clinical management** if the patient is very unwell or has rapidly progressive respiratory deterioration.
- Specifically, liaise with high dependency /intensive care unit even in mild cases, as clinical deterioration is often rapid and unexpected. Early warning track and trigger systems should be in place.
- Involve Consultant Haematologist/Haematology SpR as soon as ACS is suspected.
- In low prevalence areas consider HDU management from outset and transfer to a specialist sickle centre before clinical deterioration. (see Section 2 for referral pathways)

Management:

The immediate aim of treatment in ACS is to prevent or reverse acute respiratory failure. In addition to the specific items listed below, all patients should receive the (1.2) General Care for the acutely unwell sickle cell patient and adequate analgesia according to the guidance for acute pain in SCD (1.3.2).

- Oxygen therapy:
  Maintain SpO2 ≥ 95% or within 3% of the patient's baseline.
  Bronchodilator therapy may help, and NIV (CPAP or Optiflow) may be required. Discuss with Critical Care Team.

- Chest physiotherapy and Incentive spirometry.
  Coupled with effective pain relief, incentive spirometry has been shown to be beneficial in children and young adults by reducing chest splinting and is likely to be a useful adjunct to other forms of therapy. The Sickle adult standard recommends it for all patients at risk of ACS. See Appendix 1 for further guidance.

- Antimicrobials: It is prudent to treat all patients empirically for severe community acquired pneumonia, unless there are clinical data to suggest an alternative infection. Choice of

antimicrobial will be guided by local policy. Close liaison with microbiology is helpful. Specific guidance is required for pandemic flu.

- Transfusion:
  Not all patients with ACS will require a blood transfusion and the decision to transfuse may be difficult. A senior decision maker should be involved. While there are no randomised controlled trials, there is observational and case control evidence for the efficacy of transfusion in ACS and it can be lifesaving in severe cases. The degree of hypoxia and respiratory compromise partly governs the need for and mode of blood transfusion. **Prompt transfusion often results in a fairly rapid response as rapid reduction in HbS and improvement in overall haemoglobin is more important than a specific target haemoglobin S%.** Simple top up transfusion may suffice early in the course of ACS and may also be used if Hb is <70g/l, aiming for a post transfusion haemoglobin no greater than 100g/l. When indicated, exchange transfusion should be carried out, manually if automated red cell exchange is not readily available.
  Please see the section on Transfusion for specific details.

  As a rule of thumb:
  - PaO2 on air 9.0 K Pa or above:
    Give high percentage inhaled oxygen and monitor patient carefully.
    Consider top-up transfusion - depending on haemoglobin level and taking into account any previous transfusion reactions / alloantibodies.

  - PaO2 on air between 8.0 K Pa and 9.0 K Pa:
    Monitor patient, repeat blood gases on air at 2 - 4 hrs and continue maximum inhaled oxygen in the meantime. Strongly consider top-up transfusion.
    If Hb > 90, perform (mini) exchange instead.
    Proceed to full urgent exchange transfusion if deterioration despite initial top-up or mini exchange.

  - PaO2 on air 8.0 K Pa or below:
    Monitor patient, repeat blood gases on air at 2 - 4 hrs and continue maximum inhaled oxygen in the meantime.
    Arrange urgent exchange transfusion. If Hb < 90, a top up transfusion can be initiated whilst awaiting preparations for the exchange transfusion, but should not replace or delay the exchange.

  - Pa02 not being maintained above 8.5 K Pa on maximum inhaled oxygen or if there are **signs of significant respiratory distress**: Arrange urgent exchange transfusion. If Hb < 90, a top up transfusion can be initiated whilst awaiting preparations for the exchange transfusion, but should not replace or delay the exchange.

1.5. Stroke and other neurological complications

Stroke is another severe/life-threatening complication in sickle cell patients. It may be ischaemic due to occlusion of cerebral arteries or haemorrhagic due to aneurysmal rupture or bleeding from MoyaMoya vessels.

Symptoms and signs of stroke:
Characteristically patients present with hemiparesis, but other neurological symptoms such as severe headache, seizures, decreased consciousness and/or behavioural change may occur. Transient ischaemic attacks can predict stroke.

Differential Diagnosis:
The differential diagnosis to either ischaemic or haemorrhagic stroke includes:

- Hemiplegic migraine: migraines, particularly hemiplegic migraine headaches should be part of the differential diagnosis of a patient with SCD who presents with a focal neurologic deficit. Recurrent headaches and migraines are common and undertreated in SCD.
- Seizures: the prevalence of seizures in children with SCD is 10 times that of the general population. In case studies, those with seizures had increased perfusion and electroencephalographic abnormalities, suggesting that vasculopathy and focal hypoperfusion may be factors in the development of SCD-associated seizures.
- Posterior reversible encephalopathy syndrome (PRES): PRES was initially defined as a reversible clinical–radiologic syndrome, with patients presenting with a constellation of symptoms, including headache, seizure, visual disorders, and altered mental status, and supported by imaging findings that show parietal and occipital involvement of the brain, likely resulting from vasogenic oedema. PRES can be associated with ACS and has been linked sporadically to blood transfusion. Evidence exists that not all cases of PRES are reversible, nor do they always involve the posterior brain.
- Cavernous Sinus Venous Thrombosis (CSVT) is a less common neurologic complication in SCD when compared with ischemic strokes. Despite the low frequency, detecting the presence of CSVT is important because its presence may alter the treatment strategy. Children and adults with SCD and CSVT can present with symptoms that mimic a stroke, such as seizures, coma, cranial nerve palsies, headaches, nausea, and vomiting. An evaluation with a MRV is the preferred initial imaging study because the imaging sequence only adds a maximum of 7 minutes to the initial MRI to detect an ischemic or haemorrhagic cerebral infarct.

Acute management of stroke:
Patients presenting within 4 hours of the onset of symptoms should be transferred directly to the Hyperacute Stroke Unit (HASU) for consideration of thrombolysis. The red cell team at the tertiary unit will need to arrange an urgent red cell exchange while the patient is there. Please refer to Section 2 for referral pathways. Those presenting with symptoms of longer duration should also be discussed with HASU. If transfer to HASU is not deemed appropriate, ensure patient is stable and organise urgent CT scan of the brain. If the CT is performed within 24 hours of the onset of symptoms, there may be no evidence of ischaemia or changes may be subtle.

Urgent discussion with and referral to a neurosurgical unit (see section 2 for referral pathways) is required if there is evidence of cerebral or subarachnoid haemorrhage.

Urgent red exchange transfusion is required unless this will delay transfer to a neurosurgical unit. If there will be a delay in obtaining the volume of blood required for the exchange transfusion, consider initial top-up transfusion to 100 g/l.

Headache:
Headache is a common symptom and requires evaluation including measurement of vital signs: blood pressure and heart rate, neuroimaging of the brain and cerebral vessels, and referral to a neurologist if the symptoms persist.

1.6. Priapism

Priapism is a persistent, painful erection and is generally under-reported.
Priapism may be stuttering, lasting several minutes up to 3 hours and is often recurrent.
Fulminant priapism is a urological emergency; if it lasts for more than 4 hours, there is a significant risk of cavernosal fibrosis and impotence.

Management of fulminant priapism:
Hydration, analgesia and anxiolytic, such as lorazepam PO.
Urgent discussion with the urologists to perform penile aspiration and irrigation +/- instillation of phenylephrine under local anaesthesia (See Appendix II)

Note: some patients can perform aspiration on themselves and should be provided with the necessary equipment ie antiseptic, syringe and needles.

If these measures fail to relieve priapism, the patient requires urgent transfer to a specialist centre for further management such as shunt surgery. (See section 2 for referral pathways).
Exchange transfusion may be performed if there is a delay in transfer, it may fail to relieve priapism but may be required if GA surgical intervention is planned.

Management of stuttering priapism:
Symptomatic relief may be achieved by emptying the bladder, hydration, oral analgesia, a warm bath and/or exercise such as jogging. Ephedrine 15-30mg OD nocte (unlicensed for this indication) or Etilefrine 25-50mg OD nocte (unlicensed) may be given, often giving marked reduction in episodes. As only the short acting forms are now available, some patients take a dose before bed-time and a second dose in the early hours of the morning if episodes are still happening after a single, pre-sleep dose.

1.7. Abdominal pain and jaundice

Patients with sickle cell disorders may experience abdominal pain due to a number of causes. Careful examination and investigation will help to determine the cause and allow appropriate

management. Abdominal pain can lead to hypoventilation due to pain and thus increases the risk of developing acute chest syndrome.

- Mesenteric syndrome is caused by sickling / slow flow or obstruction within the mesenteric vessels leading to pain, abdominal distension and quiet bowel sounds. An abdominal Xray may show dilated bowel loops. This may mimic an acute, surgical abdomen, but requires conservative management with analgesia, intravenous fluids, nil-by-mouth +/- nasogastric tube +/- oxygen therapy. If there is no improvement with conservative measures, exchange transfusion should be considered.

- Gallstones are common due to haemolysis, resulting in pigment gallstones and/or biliary sludge. If asymptomatic, they do not require intervention. However acute cholecystitis characterised by right upper quadrant abdominal pain, fever, nausea and vomiting or ascending cholangitis can result, requiring intravenous antibiotic therapy, in addition to intravenous fluids and analgesia. Referral for consideration of cholecystectomy is usually offered after such presentations.

- Splenic sequestration occurs when blood pools within the spleen, resulting in tender splenomegaly, rapidly worsening anaemia which can progress to hypovolaemic shock. This occurs most commonly in infancy but can rarely occur in adulthood. Top-up transfusion is required.

- Hepatic sequestration occurs when blood pools within the liver, resulting in tender hepatomegaly, worsening anaemia and jaundice. It is often associated with infection and thus requires intravenous fluids, analgesia, consideration of blood transfusion and antimicrobial therapy.

- Patients with sickle cell disorders may also present with abdominal pain unrelated to sickle cell, such as acute appendicitis.

- Viral hepatitis due to any of the hepatitis viruses can occur, and follows a similar course as in those without sickle cell, with raised transaminases and bilirubin. Potentially HBV and HCV may be transmitted by blood transfusion and so HBV immunisation and hepatitis serology is recommended in those receiving blood transfusions; HBV can be transmitted vertically so a viral screen (HBsAg, HBsAb, HBcAb) is undertaken in outpatients.
  Acute viral hepatitis requires referral to a local hepatologist. Fulminant hepatitis or liver failure requires discussion and transfer to a specialist liver unit with availability of red cell services on site. See section 2 for referral pathways.

Jaundice in sickle cell disorders, is often due to an unconjugated hyperbilirubinaemia secondary to haemolysis and is painless. Hydration is recommended. Unconjugated hyperbilirubinaemia can also be caused by G6PD deficiency which is particularly relevant in SCD patients because of the risk of severe anaemia as a result of haemolysis, and by Gilbert's syndrome, which is a conjugation disorder and virtually harmless apart from the increased risk of gallstones.

However jaundice may be an indicator of hepatic or biliary disease, as above.

Acute intrahepatic cholestasis is a rare but severe form of sickle hepatopathy, caused by sickling within hepatic sinusoids, leading to vascular stasis, hypoxic damage and can lead to acute hepatic failure. There is tender hepatomegaly, hyperbilirubinaemia [predominantly conjugated] without evidence of extrahepatic biliary obstruction, coagulopathy and thrombocytopenia. Transaminitis, if present is mild or moderate. This syndrome has a high fatality rate; early exchange blood transfusion may be helpful.
Additional investigations that may be helpful:

- Liver function tests including conjugated and unconjugated bilirubin, AST, ALT, γGT, alkaline phosphatase
- Abdominal x-ray to be undertaken if abdominal symptoms or signs including pain, distension, abnormal or reduced bowel sounds. It may also show constipation.
- Abdominal ultrasound to evaluate liver +/- Dopplers. It may also show gallstones.
- Viral serology and/or viral PCR including HAV, HBsAg, HBcAb, HCV, HEV
- Clotting studies

1.8. Acute kidney problems

Haematuria

Painless, macroscopic haematuria is most commonly due to renal papillary necrosis due to sloughing of the renal papilla. A high fluid intake is required, blood transfusion may be necessary, and a urology opinion sought. Ultrasound of the kidneys should be requested, plus further imaging if there are any atypical features. Urine microscopy and culture should also be undertaken as urinary tract infections are also common in both men and women, and urine cytology should be sent in case of malignancy: people with sickle cell disease [and trait] can develop an otherwise very uncommon medullary renal carcinoma.

Acute renal failure

Patients with sickle cell disorders often have a degree of renal impairment, initially resulting in hyposthenuria – an inability to concentrate the urine. This makes them susceptible to nocturnal enuresis and dehydration, so maintenance of adequate hydration is important. They also usually have low serum creatinine levels, due to hyperfiltration, so it is important to know their baseline value. A creatinine of ~80 umol / l is NOT normal in people with HbSS / S beta zero thalassaemia.

Many patients have a degree of chronic kidney disease manifest by proteinuria, for which they should be fully evaluated and considered for treatment with an angiotensin converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) if the urine protein:creatinine ratio is persistently raised >50mg/mmol, having excluded infection. They are at risk of acute kidney injury due to dehydration, sepsis or as part of multi-organ failure. Aggressive fluid replacement and, where indicated, blood transfusion are indicated with strict fluid balance monitoring. Urinary tract infection should be sought and treated, and NSAIDs discontinued and subsequently avoided.

Patients with acute kidney injury (AKI) as defined by a 1.5x rise in creatinine or oliguria (<0.5ml/kg/hour for >6 hours) will follow the North Central London AKI guideline and pathway, and be managed with early involvement of the Renal Team.

1.9. Acute Visual Loss

Sickling within the vascular bed of the eye can lead to sickle retinopathy, which is subdivided into proliferative - with new vessel formation, or non-proliferative retinopathy. In non-proliferative retinopathy a number of characteristic findings are seen on ophthalmoscopy, but they are not associated with visual impairment. In contrast, progression of proliferative retinopathy can lead to vitreous haemorrhage (Stage IV) or retinal detachment (Stage V) with visual impairment.

Patients with sudden visual deterioration should be seen within hours in Eye Casualty, including out of hours. Please see section 2 for referral pathways.

Central retinal artery occlusion and central retinal vein occlusion can also result in sudden visual loss and requires emergency ophthalmological intervention. Acute trauma to the eye also mandates emergency ophthalmological review.

Ischaemic and haemorrhagic stroke can also lead to acute visual loss.

Endophthalmitis is a rare septic disorder than can cause acute visual loss and requires urgent antibiotic treatment for sepsis.

1.10. Marrow Fat Embolism Syndrome

(text adapted from Clin Case Rep. 2017 Jan; 5(1): 39–43.)
Fat embolism syndrome (FES) resulting from extensive bone marrow necrosis (BMN) is a rare but potentially underdiagnosed and probably the most devastating acute complication of sickle-cell disease (SCD). It is characterized by acute respiratory failure, neurological manifestations, thrombocytopenia, and involvement of various other organs and systems / multi-organ failure. The mortality rate is very high. The peripheral blood smear shows a leukoerythroblastic picture with a striking number of circulating nucleated red blood cells (NRBCs), whereas biochemical analysis shows extremely high levels of serum ferritin (SF) and lactic dehydrogenase (LDH).
It is mostly associated with nonhomozygous SCD and disease of a previously milder clinical phenotype.
FES is potentially underdiagnosed: Its association with milder forms of SCD may lead to late diagnosis or under-recognition. Several reports have previously identified rates of unexplained or “sudden” death as high as 40% occurring in relatively healthy patients during a painful crisis while an autopsy study showed that pulmonary fat emboli were present in one-third of cases of “sudden death” in SCD 8. Moreover, some cases of “multiorgan failure syndrome” a well-recognized but poorly understood in its pathophysiology entity also affecting previously well

patients presenting with a seemingly uncomplicated painful crisis and deteriorating rapidly may indeed represent cases of FES.

Given the respiratory and neurological manifestations, the syndrome can be mistaken for isolated ACS or stroke whereas the combination of fever, neurological manifestations, and thrombocytopenia may suggest a diagnosis of thrombotic thrombocytopaenic purpura or even acute leukemia if the cytopaenias are severe. Examination of the peripheral blood smear is essential.

Management of Marrow Fat Embolism Syndrome:

Treatment should be in ITU with full support and treatment for sepsis. In case of liver failure, early transportation to a tertiary liver unit (with on-site red cell services) should be considered.

The mainstay of specific treatment is rapid red cell exchange transfusion, preferably automated. There is limited evidence that an additional plasma exchange (1 volume) may be of possible benefit in reversing the multi-organ failure.

2. BLOOD TRANSFUSION

This section addresses blood transfusion issues specifically related to SCD. Please refer to the Trust's Blood Transfusion Policy for general principles and haemovigilance.
There are 2 main purposes for blood transfusion in SCD:

- To correct anaemia and so improve the oxygen-carrying capacity of blood: use simple top up transfusion
- To treat or prevent the occurrence of painful/vaso-occlusive or sequestration complications by lowering %HbS relative to HbA: Use exchange transfusion

2.1. General principles of transfusion in SCD patients:

- For cardiovascular stable patients requiring top up transfusions, do not exceed the maximum infusion rate of 5 mL/kg/hr.
- Do not use diuretics routinely.
- Extended phenotype matched (Rh DCEce, and K), sickle negative blood should be used, less than 7 days old (automated exchange blood transfusion) or less than 14 days old (all other indications).
- Label the transfusion form: Sickle Cell disease. This should ensure that the patient receives the correct phenotyped blood i.e.: Sickle negative ABO compatible, Rh compatible and K compatible cells that is negative for any alloantibodies they may have (or crossmatch compatible in the presence of certain allo-antibodies as per BCSH guidelines)
- The patient should have a full red cell phenotype recorded on the computer system. If not, send an additional sample to the transfusion laboratory labelled as per blood transfusion guidelines. Mark form for "full red cell phenotype FAO Colindale RCI". The Rh and K phenotype can be done quickly by the hospital transfusion department if not already known.
- Inform Blood Bank if the patient is known to another hospital and in particular if transfused there
- In the emergency setting CALL blood bank immediately and discuss the decision to transfuse with a BMS (Biomedical Scientist). INFORM THE BMS THAT THE BLOOD IS REQUIRED FOR A SICKLE CELL PATIENT. They will order blood in for you. They will then crossmatch the units against the sample you send them. Doing this will expedite the availability of blood, as it frequently has to come from Colindale, as appropriate units are not always available from on-site stock.
- PLEASE NOTE: The decision to use / transfuse the units is different to requesting that blood transfusion get units ready / on site.

- Exchange transfusions can be carried out using the Optia apheresis machine (automated exchange), or by a manual exchange.
- An automated exchange has advantages in that it is more effective in lowering the percentage of haemoglobin S in the blood and thus increases the intervals between procedures. It is also iron neutral and therefore does not lead to transfusional iron overload unless there are particular requirements to run the Hb much higher than the baseline Hb.

- The disadvantages of automated exchange are that the need for excellent venous access and larger volumes of blood required may delay a procedure and this can be life threatening.
- If patients present acutely unwell then they should have a manual exchange unless an automated exchange does not delay the procedure.
- Junior medical staff should be trained in the manual procedure so that they can do it if needed.
- **If the patient is in a local hospital and needs an urgent top-up or exchange procedure, this should be commenced before the patient is transported to a specialist centre. This is a vital part of stabilising the patient prior to transportation and transfusion treatment should not be deferred until the patient arrives at the specialist centre.**
- No unscheduled exchange transfusion should be initiated without consultation with the Consultant Haematologist on call.

- **NOTE: in acutely unwell or bleeding patients, the rules should be reconsidered**. If life-saving, timing is more important than perfectly matched, age, volume, HbS negative or even antigen negative units. This decision should be discussed with Consultant and Hospital Transfusion Team.

2.2. Indications for Blood Transfusion

The main indications for (exchange) blood transfusion are summarised in the table below.

Please note that the following are NOT indications for transfusion:

- Asymptomatic anaemia, especially if there is plentiful polychromasia, and a good reticulocyte response. Transfusion is not usually necessary unless Hb < 50g/l, depending on age and clinical state of patient.
- Uncomplicated painful episode. Transfusion does not reduce the pain or duration of opioid treatment.
- Uncomplicated pregnancy, especially if mild sickle cell phenotype.

(Relative) contra-indications include:

- History of hyperhaemolysis (see separate section)
- Multiple allo-antibodies
- Rare blood group phenotype (eg U-negative)

	Top Up	Emergency Exchange	Long term exchange transfusion programme	Short term or one off exchange
Indications	Symptomatic or worsening acute on chronic anaemia e.g. sequestration, aplastic crisis.	Acute stroke Acute chest syndrome Severe sepsis Acute hepatic sequestration Acute multiorgan failure Progressive intrahepatic cholestasis Fulminant priapism if no response to urology intervention	Primary stroke prevention (children) Secondary stroke prevention	(Elective) Surgery (discuss each case with haematology team) – see also section on peri-operative management

		Other life threatening complication		
Possible Indications	Can be used in incipient chest syndrome if there is sufficient "space" i.e. a top up to raise the Hb to ≤110g/L	Persistent priapism despite medical therapy	Repeated severe painful crises or acute chest syndrome , and no response to hydroxyurea Pulmonary hypertension Progressive organ compromise (ie progressive renal failure)	Pregnancy Leg ulcers
Aim	To raise Hb to patient's baseline haemoglobin, this generally should not exceed Hb of 110g/L	To reduce the % of Hb S to < 30% (in some patients on long term transfusion this may be lower). To maintain a steady blood volume in the patient throughout the procedure		

2.3. Manual Exchange Blood Transfusion

The guidance on exchange blood transfusion assumes an untransfused patient with a baseline HbS% of 80-90% aiming at a post-exchange level of < 30% (Note: for HbSC patients, take the total of HbS and HbC together instead of looking at HbS only; if HbC is not available, multiply the HbS percentage by 2 for HbSC patients)

Please consider the setting during which the manual exchange needs to take place:

- Emergency setting.
    - Adequate venous access? If not, please see Trust's policy on obtaining urgent venous access (under development)
    - Is critical care aware (patient may deteriorate or even become hypotensive as a result of the exchange procedure)
    - Is emergency trolley readily accessible
    - Discuss urgent samples of FBC and HbS% with haematology lab
    - Use simplified protocol for the emergency setting for clarity and avoiding mistakes.

- (Semi) Elective setting.
    - Consider staffing levels if out of hours
    - Preference for weight-based protocol (more accurate results)
    - The typical post-exchange HbS% that can be achieved after a manual exchange is 30-40%, whereas with a single automated exchange this can be lowered to as little as 10% if required. Consider if the manual exchange can wait if not urgently required.

Please note that under all circumstances and for each individual unit of blood used, **the blood must be checked by two trained people, and the hospital Transfusion Policy must be followed**. Ensure that the details on the compatibility label (tag) on the blood bag match those on patient's wristband and prescription chart.

Step 1: preparation:

Equipment Required
Gloves
Assorted venflons
An assortment of syringes from 5 ml – 50 ml
Venesection packs
Three-way tap
Heparinised saline
Sodium chloride 0.9% and appropriate administration set.
Blood pressure monitor
Saturation monitor
Emergency trolley readily accessible.
Observation chart, blood prescription chart and fluid balance charts
Sharps Bin

Calculate the amount to be exchanged, depending on starting haemoglobin, as follows:
- Hb >80g/l: 5-8 units
- Hb 60-79g/l: 4-6 units
- Hb <60 g/l: up to 4 units

Discuss with blood transfusion, see general principles.

Step 2: monitoring
Observations including BP, HR, temperature & oxygen saturation are mandatory!
- Prior to, and post removal of unit of blood;
- Before, and 15 minutes into the transfusion of a unit of blood.
- As clinically indicated

2.3.1. Simplified Protocol for Emergency Manual Exchange

This protocol is adapted from the South Thames Sickle Cell and Thalassaemia Network (STSTN) guideline. Whereas the weight-based protocol below gives a more accurate end result, the STSTN guideline is easier to work with, especially for those who perform emergency manual exchanges only incidentally and if the work conditions are stressful.

1. Set up a normal saline infusion 1l and run 500mls over 15 to 30 minutes to ensure pre-hydration before the procedure.
2. Ensure that the blood to be transfused is set up before venesecting the patient, to avoid hypotensive emergencies and to ensure a degree of warming of the blood prior to transfusion.
3. Note that procedure should be performed more slowly than described in patients with significant renal or cardiac abnormalities, or if acutely cardiovascularly unstable.
4. Note that the patient should be kept in overall fluid balance throughout the procedure. This may require the infusion of additional saline if small units of blood are provided.
5. To venesect: remove 450-500ml of blood over approximately 15-30 min. Blood can be aspirated from the line using 20-60ml syringes, which can either be discarded in a freshsharps bin – and easily counted if necessary – or using a 3-way tap expel the contents into an attached venesection bag.
6. A repeat Hb is required on completion of the procedure and **should not exceed 10g/dl if Hb S% more than 30%. Haematocrit should not exceed 0.33.** If this is the case, consider further venesection.

Procedure

Hb > 80 g/l	Venesect 1st unit	WHILST	Replacing with 500 mls of normal saline stat
	Venesect 2nd unit	THEN	Transfuse 1st unit over 30-40 minutes. *
	Venesect 3rd unit	THEN	Transfuse 2nd unit over 1 hour
	Venesect 4th unit	THEN	Transfuse 3rd unit over 2 hours
	Check FBC and HbS	If Hb<90g/l:	Transfuse 4th and consider 5th units (over 3 hours each)
		If Hb>90g/l:	Restart from "venesect 1st unit" if HbS% unsatisfactory
	NB This method involves removing 2 units of blood before transfusing the 1st replacement unit, and results in a more efficient lowering of HbS%. However if the patient is cardiovascularly unstable, or becomes hypotensive during the venesection, the replacement transfusion should be started sooner, ie after the venesection of the 1st unit.		
Hb 60 – 79g/l	Venesect 1st unit	THEN	Transfuse 1st unit over 30-40 minutes. *
	Venesect 2nd unit	THEN	Transfuse 2nd unit over 1 hour Transfuse 3rd unit over 2 hours Transfuse 4th unit

			over 2-3 hours
	Check FBC and HbS	If Hb<90g/l:	Transfuse 5th and consider 6th units (over 3 hours each)
		If Hb>90g/l:	If HbS% or clinical improvement unsatisfactory, follow 'venesect 1st unit' for Hb > 80 g/l
Hb < 60 g/l	-	-	Transfuse 1st unit over 30-40 minutes. *
	-	-	Transfuse 2nd unit over 1 hour Transfuse 3rd unit over 2 hours
	Check FBC and HbS	If Hb<90g/l:	Transfuse 4th and consider 5th units (over 3 hours each)
		If Hb>90g/l:	If HbS% or clinical improvement unsatisfactory, follow 'venesect 1st unit' for Hb > 80 g/l

2.3.2. Weight-based Protocol for Manual Exchange Transfusion

Ensure the patient is fully hydrated with crystalloid before starting to venesect.

In adults usually 500 ml aliquots but if acutely ill/hypoxic adult, use aliquots of not more than 5ml/kg

For total volumes, according to patients weight in Kg and starting Hb g/l; see table below.

- If starting Hb is >80 g/l in an ill patient, or >70 g/l in a well patient, if only one line is available give an iv bolus of 500mls of saline then venesect 2 units; if 2 lines are available, venesect 2 units and infuse 500mls of saline via the other line at the same time.

- In those with Hb SC and Hb Sβthal, the starting Hb may be as high as 130-140 g/l, venesection of up to 30ml/kg may be necessary, preceding every unit venesected with an equal volume of saline infused to maintain isovolaemia.

- If starting Hb is lower than these levels **but above 60 g/dl**, and only a single line is available, following an iv saline bolus, it is permissible to venesect a single unit as long as a replacement unit of red cells is standing by and transfused rapidly once the venesection is complete.

- If 2 lines are available, begin to venesect one unit and transfuse at the same time. However if the Hb is <60g, the exchange will commence with transfusion.

NB Try at all times to maintain fluid balance in/out so that fluid is replaced at the same rate it is removed. This is to achieve an isovolaemic exchange, minimising fluid shifts and the likelihood of hypotension.

- One or two units may be given by straight transfusion after the formal exchange. If, for example, the starting Hb is 75g and you have removed 4 units replacing them with 4 units simultaneously, you can expect the final Hb to be 70-80g but now there will be approximately 50% HbA and approximately 50% HbS. Check the Hb level at this point. It will often be safe to transfuse a further 2 units of blood which will dilute the remaining HbS and increase the HbA% further.

- Upon completion of the procedure, take FBC sample and request Hb and HbA level. A further exchange may be needed the following day. Aim to achieve a Hb of 100-110g/l and an HbA of >70%. In those with Hb SC and HbSβThal disease a final Hb of 120g/l may be acceptable.

Procedure for exchange transfusion in individuals with sickle cell disease

Stage 1:	**starting Hb**		
<60g/l	<70g/l	70-90g/l	>90g/l
	5ml/kg saline IN	10ml/kg saline IN	15ml/kg saline IN
	5ml/kg blood OUT	10ml/kg blood OUT	15ml/kg blood OUT
5ml/kg blood IN	5ml/kg blood IN	5ml/kg blood IN	5ml/kg blood IN
5ml/kg blood OUT	10ml/kg blood OUT	10ml/kg blood OUT	15ml/kg blood OUT
5ml/kg blood IN	5ml/kg blood IN	5ml/kg blood IN	5ml/kg blood IN
total	**total**	**total**	**total**
5ml/kg out 10ml/kg in	**15ml/kg out 10ml/kg in**	**20ml/kg out 10ml/kg in**	**30ml/kg out 10ml/kg in**
	then check Hb		
Stage 2:	**if:**		
<70g/l	70-80g/l	80-90g/l	>90g/l
10ml/kg saline IN	15ml/kg saline IN	15ml/kg saline IN	20ml/kg saline IN
5ml/kg blood OUT	10ml/kg blood OUT	15ml/kg blood OUT	15ml/kg blood OUT
5ml/kg blood IN	5ml/kg blood IN	5ml/kg blood IN	5ml/kg blood IN
10ml/kg blood OUT	10ml/kg blood OUT	10ml/kg blood OUT	15ml/kg blood OUT
total	**total**	**total**	**total**
15ml/kg out 5ml/kg in	**20ml/kg out 5ml/kg in**	**25ml/kg out 5ml/kg in**	**30ml/kg out 5ml/kg in**
	TOTAL VOLUMES		
20ml/kg out 15ml/kg in	**60ml/kg out 15 in**	**35ml/kg out 15ml/kg in**	**45ml/kg out 15ml/kg in**

Stage 3: **Check FBC for Hb urgently, request HbA% for next "in hours" run.**
If Hb <70g/l transfuse 2 units; if Hb >130g/l venesect 2 units
The aim is to achieve a Hb of 100-110g/l and a HbA level of 70% or more.
If HbA level >50% transfuse up to Hb 110g/l;
If HbA level <50% discuss as further exchange - stage 2 - may be required.

Notes:

"saline" = sodium chloride 0.9%; blood = red blood cells

2.4. Automated Exchange Blood Transfusion

This guideline does not address the actual operation of the apheresis machine – please refer to the Trust's SOP for technical details.

The Optia apheresis machine gives a very reliable result in terms of target HbS% and Haematocrit post-procedure. The target parameters can be programmed into the machine prior to running the red cell apheresis cycle. However, blood products will need to be ordered in advance and it is recommended to simulate an exchange using the Calculation Tool for an accurate estimate of the required number of units: https://www.terumobct.com/therapeutic-apheresis/protocols/rbcx/calc-tool

The machine can run two programmes for the purpose of red cell apheresis:

- Red Cell Exchange. This is an iso-volaemic exchange of red blood cells
- Depletion / Exchange cycle. The procedure starts with an iso-volaemic haemodilution by replacing patient red cells with a saline (or albumin) solution, followed by the exchange programma.

It is the clinician's decision whether to perform a depletion cycle or not. Benefits of depletion include the fact that fewer units of blood can be used to achieve the same result (although dependent on the patient's pre-exchange haemoglobin) and that there is a net negative balance, which can positively influence iron overload. A drawback is that not all patients tolerate a depletion cycle very well; the efficacy is reduced if safer margins (ie, a lower depletion volume) are selected.

Venous access:

- The patient will need two points of venous access (inlet and outlet). This can be achieved by the placement of two peripheral cannulas, or by a double lumen central venous catheter. NOTE: a PICC line is not suitable for the apheresis machine, at least not for the machine inlet. Other (long-term) options are an A/V fistula or Dual-Lumen Port-a-Cath.
- Please refer to the Trust's policy on obtaining venous access for red cell apheresis for further details.

Investigations and preparation:

- Medical assessment, including patient's recent height and weight
- Obtain written consent
- Blood test including FBC, Sickle cell percentage, biochemistry including Calcium and Magnesium, and antibody screen for 6-12 units (see simulation and blood ordering below).
- Nurse consultation including assessing patient's peripheral access.
- Stimulate patient to drink well before the procedure to prevent vasovagal collapse and help improve venous access.
- Withhold therapeutic anticoagulants if a central venous catheter or PICC line is inserted. Anticoagulation can be continued for connecting to a porth a cath or for insertion of peripheral cannulas; for midlines discuss with CNS or interventional radiology.
- Consider withholding ACE inhibitors to prevent vasovagal collapse.

- AFTER the procedure: repeat FBC, Sickle cell percentage, biochemistry including Calcium and Magnesium. Replenish any deficiencies. If the post-exchange Hct is unexpectedly high as a result of more densely packed RBC than average, it may be necessary to venesect the patient especially if the HbS% is still high.

Simulation of the procedure:

1. Enter the patient data:
   - Sex
   - Height (in cm)
   - Weight (in kg)
   - Patient Hct prior to exchange (in %)
   - Volume in blood warmer (not required)

   The Calculation Tool will now give the patient's Total Blood Volume in mL
2. Choose the exchange type (Exchange or Depletion/Exchange)
3. Enter the exchange fluid Hct.
   NOTE: A standard red cell component in additive solution contains red cells (Hct 0.50 - 0.70 and Hb content > 40 g/unit), in a total volume of 220 - 340mL. It is safest to enter an average Hct of 60%. Other red cell components (washed RBC) may have a higher Hct! For calculating the number of units required, take an average of 300 mL per RBC.
4. Enter the Run Targets.
   - If Exchange:
     - Set the desired target Hct post-exchange (generally < 33%)
     - Set the desired FCR (Fraction of patient's Remaining Cells). For example, if the baseline HbS% is 90%, and the desired post-exchange target is 30%, the FCR is 33%.
     - The Calculation Tool will now give the Replaced Exchange Volume in mL.
     - Divide the Replaced Exchange Volume by 280 mL to estimate the number of RBC units to perform the procedure (the volume per RBC unit varies between 220 and 320 mL)
     - If the Calculation Tool gives an error, the Run Targets can't be achieved. Try a different target Hct or FCR.
   - If Depletion/Exchange:
     - Set the minimum Hct desired for the procedure. The lowest the machine can go is 20% but it is important to avoid depleting a very large volume. The amount of depletion depends on the patient's pre-exchange Hct and the minimum Hct set for the procedure. For example, if the patient's Hct is 25% and the minimum Hct for the procedure is 23%, the depletion volume will only be 80-100 mL for the average sized patient. However, if the patients Hct is 32% and the minimum Hct for the procedure is 20%, the depletion volume will be 550-650 mL for the average sized patient.
     - Set the desired target Hct post-exchange (generally < 33%)
     - Set the desired FCR (Fraction of patient's Remaining Cells). For example, if the baseline HbS% is 90%, and the desired post-exchange target is 30%, the FCR is 33%.

- The Calculation Tool will now give the Replaced Exchange Volume in mL, and also the replaced depletion volume (=net loss)
- Divide the Replaced Exchange Volume by 300 mL to estimate the number of RBC units to perform the procedure.
- If the Calculation Tool gives an error, the Run Targets can't be achieved. Try a different target Hct or FCR.

Complications and specific problems:

- Venous access problems.
  Complications and problems linked to venous access are addressed in the relevant guidelines.
- Operational problems
  For all technical aspects including trouble shooting please refer to the Trust's SOP.
- Vasovagal syncope.
  - Stop any ACE inhibitors 24-72 hrs before the procedure.
  - Make sure the patient is well hydrated prior to the procedure
  - Iv fluids as required.
- Citrate related hypocalcaemia: tingling sensation, nausea and vomiting, hypotension.
  - Prophylactic Oral /IV Calcium given to all patients with a (borderline) low Calcium.
  - Reduce the speed of the procedure.
- Allergic reaction:
  - Check patient medical history.
  - Stop transfusion
  - Administer antihistamines, hydrocortisone
  - Manage anaphylaxis as per hospital policy.
- Anxiety
- Fatigue
- Boredom
- Apheresis induced thrombocytopenia
  - Rarely < 100 unless pre-existing low counts. Refer to haematologist.

2.5. Complications Related to Blood Transfusion

Complications related to blood transfusion include Transfusion Reactions (Haemolytic, Delayed Haemolytic, non-haemolytic febrile, anaphylactic, etc), Transfusion Related Cardiac Overload and transfusion-related infections. For further management of these complciations, please refer to the Trust's Transfusion Policy.

The management of transfusional iron overload is discussed in paragraph 6.3.

2.5.1. Hyperhaemolysis

Background:

Hyperhaemolysis is a well-recognized but rare complication of blood transfusion in patients with sickle cell disease (SCD). It is characterised by rapid haemolysis following a blood transfusion, and the post-transfusion haemoglobin(Hb) will often be lower than the pre-transfusion Hb, implying the **destruction of recipient as well as donor red cells**. It may be associated with a fever and with pain typical of sickle cell disease. It may be associated with a delayed haemolytic transfusion reaction and the development of a new red cell allo-antibody but may occur with no evidence of new red cell allo-antibody formation. **In this situation the direct antiglobulin test (DAT) is usually negative and there may be a reticulocytopenia**. **Additional transfusion has been associated with increasing haemolysis and worsening anaemia, and should be avoided if possible**. The haemolysis can be treated with intravenous immunoglobulins (IVIg) and IV (Methyl)prednisolone. In cases where there is very rapid haemolysis and critical anaemia, additional transfusion will be required and this should be preceded by IVIg and IV Methylprednisolone. Potentially other agents such as **Eculizumab and Rituximab** may be necessary.

Erythropoetin, iron replacement, B12 and folate replacement should also be considered. Hyperhaemolysis can recur following blood transfusions several months or years after the initial episode, and patients should be retreated with IVIg and (Methyl)prednisolone prior to future transfusion. The Department of Health immunoglobulin guidelines have changed this indication from grey to blue.

Diagnosis:

Hyperhaemolysis should be considered in any patient with SCD who presents with increasing haemolysis after a blood transfusion. Patients typically present at 7-14 days post transfusion, but may develop symptoms sooner if they are re-challenged with transfusion. Clinical features: Increasing jaundice, dark urine ('coca-cola' coloured), anaemia. They may also have a fever, back leg or abdominal pain, hepatomegaly or hepatic discomfort. It is often associated with severe bone pain, typical of sickle crisis.

Investigations:

- FBC: increasing anaemia – Hb may often fall to below the pre-transfusion level
- Haemolysis: raised bilirubin, raised LDH
- Reticulocytes: may be raised (in keeping with haemolysis) or decreased, due to suppression of red cell production
- Direct Antiglobulin Test (DAT): may be positive if hyperhaemolysis is associated with a new allo-antibody, but may be negative.
- Group and Antibody Screen: Hyperhaemolysis often occurs without evidence of new red cell allo-antibody formation but regular group and screens should be performed as red cell allo-antibodies may become apparent up to 3-4 months after the haemolytic episode.
- Haemoglobin electrophoresis: A rapid increase in HbS% indicates haemolysis of the transfused blood
- Ferritin, folate and B12 levels: This may aid in decisions about replacement.

- Differential diagnosis is a delayed haemolytic transfusion reaction due to new allo-antibodies and blood must be sent to the transfusion laboratory for the investigation of new allo-antibodies.
- Urine haemoglobin electrophoresis: presence of HbA

Treatment:

- Discuss with Haematology Consultant (Contact the on-call Consultant if out-of-hours)
- Prescribe Folic acid 5mg.
- Primary treatment is with immunosuppression: IV Methylprednisolone and IVIg
- Consider treatment with erythropoietin and IV iron replacement
- Consider B12 replacement.
- When a case of hyperhaemolysis is suspected and having discussed with the haematology consultant it is important to communicate the suspected diagnosis to the transfusion biomedical scientist **who will add a comment to the patient record**. Blood transfusion should only be given after discussion with the Haematology Consultant.
- If further transfusion necessary, phenotyped blood should be given (Rh and K matched) as outlined in Section 1.2. Consideration should be given to genotyping the patient and obtaining genotypically matched / or best matched units.
- CHECK FBC and Haemolysis parameters regularly after treatment, at least until 7-14 days afterwards.

- Dosage:
    - Intravenous immunoglobulin (IVIg):
      Use 1g/kg for brisk haemolysis but consider lower doses (0.5g/kg) for pre-treatment
      Adult and paediatric dose (unlicensed indication) Up to 1g/kg once daily for 2 days (total dose = 2g/kg) Administration and choice of preparation as per Trust guidance)

    - Methylprednisolone Adults: 500mg IV for 2 days Paediatrics 10mg/kg IV for 2 days (maximum dose 500mg)
      Review dose after 2 days.
      Consider continuing prednisolone 30 mg OD per os for 5-7 days + taper over 3 days, especially if previous evidence of late onset hyperhaemolysis.

    - Erythropoietin NeoRecormon® 300units/kg subcutaneously once daily for 5 days, followed by 300units/kg once daily on alternate days (i.e. 3 times per week

3. PERIOPERATIVE MANAGEMENT

There are over 12,500 patients with sickle cell disease in the UK. Administration of **general anaesthesia** to these patients carries an increased risk of perioperative complications. The TAPS trial (Howard J et al, The Lancet, 2013) showed that preoperative transfusion was associated with decreased perioperative complications in patients with sickle-cell disease.

Sickle complications are less likely with **spinal or epidural anaesthesia** than with general anaesthesia and unless patients have very severe phenotypes or are very anaemic, this group is unlikely to need pre-operative transfusion.

Tourniquet surgery is considered to be a very high risk procedure, even in asymptomatic carriers (HbAS) and should be avoided where possible.

The following protocol, adapted from the STSTN (South of Thames Sickle Cell and Thalassaemia Network) relevant protocol, aims to provide guidance on the perioperative management of patients with sickle cell disease in order to minimise complications.

3.1. Accountabilities and Responsibilities

- The surgical team/preoperative assessment nurse should inform the Haemoglobinopathies team as soon as possible when a patient with sickle cell disease is scheduled for a surgical intervention. The Haemoglobinopathies team will arrange for the patient to be assessed regarding phenotype and will finalise a treatment plan for perioperative and postoperative management. **PLEASE SEE SECTION 2 : LOCAL PATHWAYS FOR THE TRUST'S AGREEMENTS ON HOW TO REFER**
- The preoperative investigations should include an FBC, Group and Screen and extended red cell phenotype (if not done previously), Hb electrophoresis (if not done previously) and renal function.
- It is important to inform the patient in advance that final approval and date for the procedure will only be confirmed after agreement on the full perioperative management plan.
- The Haemoglobinopathies team will assess the following clinical information of the patient: Sickle genotype, sickle-related complications, evidence for end-organ damage (renal dysfunction, pulmonary hypertension, cardiomegaly, transfusion history, baseline Hb level) and agree a preoperative management plan.
- The Haemoglobinopathies team will communicate the plan to the surgical team via e-mail or clinical letter and document it on the patient's electronic file. It will also arrange for any required preoperative transfusion.
- Postoperatively, the Haematology team will provide input and clinical review of the patients to ensure absence of or early intervention for any sickle-related complications.
- Postoperative care for at least 24 hours in HDU or ITU/ICU is desirable
- Because of the complexity of the perioperative management, especially when an exchange blood transfusion is involved, it is important that elective surgery DOES NOT GET CANCELLED OR MOVED AT THE LAST MOMENT.

- Communication is paramount. Both the surgical team and the haemoglobinopathies team share the responsibility of informing each other about the patient with SCD in theatre / on the ward.

3.2. Perioperative Measures

- Ensure **good hydration**. Patients will normally be fasted from midnight on the day before operation. Commence iv hydration from nil by mouth to prevent dehydration that can precipitate sickling. Unless there are problems, e.g. of fluid overload, give 1 litre of alternating 0.9%sodium chloride / 5% dextrose 6-hourly
- Ensure good patient **oxygenation**. (supplemental oxygen as indicated, aim at SO2>95%). Use of incentive spirometry is encouraged. Monitor SO2 on air. Notify Haematology team immediately if patient becomes hypoxic. (O2 saturations (ON AIR) < 94% or < 4% from baseline)
- Ensure patient is kept **warm**, **also in theatre**
- **Do not use ice packs for swelling**
- **Effective analgesia** (take into account pain score and patient opiate tolerance, which would dictate use of higher doses of opioids for adequate pain control)
- **Antibiotic prophylaxis** as per sickle or surgical guidelines, as indicated
  Individuals with sickle cell disorders are also more prone to infection than others.
  If the operation carries an infection risk (e.g. gall bladder, ERCP , gynae, bowel operations) give prophylactic antibiotics even if the surgical guideline states that this is not required, such as Co-amoxiclav (Augmentin®) first dose 1.2g i.v. with the pre-med, continue 8-hourly for at least 24 - 48 hours, converting to oral 625 mg tds as soon as the patient can drink.
  For penicillin-allergic patients, Clarithromycin 500mg iv with the pre-med, continue 12-hourly for at least 24 – 48 hours converting to oral 500mg bd as soon as the patient can drink
- **Continue other regular medications** (such as folic acid and Hydroxycarbamide)
- **Use thromboprophyaxis** according to Trust guidelines. See also section 1.2.4.4.

3.3 Elective Surgery

3.4. Emergency Surgery

4. MANAGEMENT DURING PREGNANCY

Most maternal and fetal complications of pregnancy are more common in women with sickle cell disorders [especially in HbSS] such as pre-eclampsia, placental abruption, premature labour, intrauterine growth retardation and miscarriage. Pregnant women with sickle cell disorders often experience an increase in frequency and/or severity of painful crises. They are also more prone to infection, such as urinary tract infections and to thrombo-embolic problems, so pregnant women require close monitoring throughout pregnancy and prompt treatment of complications.

Please also see the separate full guideline '**Management of pregnancy, contraception and fertility issues in women with Sickle Cell disease**'

Ensure partner has been screened for haemoglobinopathies, and the couple have been referred for consideration of pre-natal diagnosis if they are at risk of having a baby with a major haemoglobin disorder.

4.1. Methods and timing of delivery:

This is an important part of the management plan. This will not be finally decided upon until the patient has been evaluated in the maternal medicine clinic for a haematological review. However it is helpful to discuss with the patient that a planned delivery date or route of delivery, rather than full vaginal term delivery, may be the most appropriate approach depending on the risks of vaso-occlusive crisis and other complications during prolonged labour. The risk of this will vary from patient to patient and the previous history of sickle related or other complications as well as the obstetric history will need to be considered.

4.2. Management Plan and Medication

- **Four weekly haematology out-patient appointments during pregnancy are usual; obstetric appointments** are usually every 4 weeks until 28 weeks, then every 2 weeks until 36 weeks, then weekly to term.
- **Monitor Hb and ferritin**; prescribe iron IF necessary [but please be sure that anyone who has a high iron level is not given iron by the antenatal clinic staff, because of anaemia].
- **Stop any chelation therapy -** desferrioxamine, deferiprone or deferasirox. Patients should ideally not be receiving either deferiprone or deferasirox chelation therapy within 12 weeks of conception. If the pregnancy is planned, chelation should therefore either be stopped or switched to desferrioxamine during this time.
- **Stop hydroxycarbamide therapy 3 months before planned conception, or immediately pregnancy identified if not already stopped.**
- **Stop ACE inhibitors**
- Continued **routine pneumococcal prophylaxis** with penicillin V 250 mg b.d. or erythromycin 250mg bd if penicillin allergic is encouraged.
- It is important to avoid infection during pregnancy so: the Pneumovax, HiB and Meningococcal ACWY, hepatitis B vaccination status should be checked and updated as necessary. Influenza vaccine as per current National Guidance. Meningococcal B is available and recommended for this patient group
- **Folic acid**, 5 mg daily, should be taken pre-conception, but if not, start it as soon as the pregnancy is confirmed. NOTE: the dose in SCD patients is higher than the recommended dose of 400 mcg in pregnancy for other individuals.

- Pregnant SCD women should be considered for **low-dose aspirin 75 mg** once a day from the time pregnancy is confirmed, to reduce the risk of pre-eclampsia.
- **Avoid NSAIDs, especially in the first trimester and after 32 weeks gestation.**
- Ensure recent ophthalmology assessment and ECHO for pulmonary hypertension screening and arrange these investigations as necessary**.**
- Thrombotic Risk in Pregnancy: There is a significantly increased risk of thrombosis. This should be discussed and explained to the patient at this stage, and documented by the haematology consultant in the high risk pregnancy clinic team.
- There is no clear evidence for routine antenatal thromboprophylaxis in ambulatory care in women without additional risk factors. However, the UK Standards of the Clinical Care of Adults with Sickle Cell Disease rates women with SCD as intermediate risk for thrombosis and recommends that thromboprophylaxis with low molecular weight heparin (LMWH) is considered from 28 weeks gestation.
- Antenatal thromboprophylaxis in patients with previous thrombotic episodes or other VTE risk factors: please refer to the maternal medicine clinic for assessment by the consultant haematologist early in pregnancy for individualised assessment and plan for antenatal and peri and post-partum thromboprophylaxis.
- Following delivery patients should be included in the high risk group for thromboprophylaxis. (see below under delivery)

4.3 Blood Transfusion in Pregnancy

There is an increased risk of sickle related complications during pregnancy. The risks of vaso-occlusive episodes can be decreased by transfusion or exchange transfusion. The pros and cons of transfusion need to be considered and discussed on a case by case basis. The decision whether this is desirable / necessary is made in early pregnancy with the woman +/- partner, and often with input from the Obstetrician - according to clinical severity of sickle cell, previous obstetric history, any red cell antibodies present, and the patients personal or religious beliefs. Sometimes the decision to start transfusions is made 'acutely', during an admission for pain or other complications during the pregnancy. Blood transfusions have been shown to reduce the incidence of painful crises in the mother but do not improve foetal outcome. In patients at high risk of vaso-occlusive- painful crises or of chest syndrome or of serious complications, exchange transfusion may be offered, typically from approximately 20 weeks of pregnancy.

It is important that blood transfusion is aware that the patient is pregnant, as in addition to special blood requirements for sickle patients, CMV negative units should be obtained. Where allo-antibodies are known, HDFN needs to be considered.

- In such cases, a target HbA >50% and Hb 10-11g/dl at time of delivery should be aimed for
- Indications for prophylactic transfusions may include:
    - Previous sickle problem requiring regular transfusion. e.g. recent stroke.
    - Pre-existing transfusion regimen
    - History of acute chest syndromes
    - History of severe sickle cell disease related complications

- Women who have previously been on hydroxycarbamide for recurrent pain crises / chest syndrome may be transfusion from earlier, soon after they stop the hydroxycarbamide [3 months before conception].
- Hb regularly less 75 g/d with evidence of foetal intrauterine growth retardation.
- Anaemia with respiratory or cardiovascular compromise
- Twin pregnancies

4.4. Admission in crisis during pregnancy

a) The woman may come to the Labour Ward or otherwise be admitted through the Obstetric team. Please inform the Haematology team of the admission and they will review promptly.

b) Management of painful sickle cell crises in pregnancy is essentially as per the general protocol for painful sickle cell crises, with meticulous monitoring of oxygen saturations, respiratory rate, pulse, temperature, blood pressure, pain and sedation scores should be monitored at least 4 hrly. FBC, U+Es, LFTs should be checked daily and urinalysis performed regularly. Foetal monitoring should also be performed.

c) Give prophylactic tinzaparin 4,500 units daily unless this is contra-indicated.

d) If febrile or patient becomes febrile during the admission give antibiotics parenterally as in the general protocol - Co-amoxiclav (Augmentin®) is suitable initially, having sent cultures of blood, urine and any other potential infective site.

e) If the crisis is severe, and/or recurrent, transfusion should be discussed with her. Exchange transfusion from early on in the admission will often effect rapid improvement and can be continued as an Out-patient after discharge to prevent further crises.

f) Any decision regarding delivery should be made on the usual obstetric or foetal grounds**. If at all possible delivery should be postponed until after a crisis is resolved.**

4.5. Delivery

a) When she arrives in labour, an **i.v. infusion** should be sited and fluids (eg 0.9% sodium chloride alternating with 5 % dextrose) given at a rate of 3-4 litres/24 hrs continuously from the time of arrival until 24 hrs after delivery.

b) Epidural analgesia can be used.

c) Consider **antibiotics**, especially if febrile, in the immediate post-partum period, continuing for 5 days; Co-amoxiclav (Augmentin®) is suitable.

Caesarean section

Caesarean section may be needed for obstetric reasons as in any other individual. For a planned Caesarian section, see guidance for perioperative management in patients with sickle cell disorders even if the procedure will be carried out under epidural. For an emergency procedure, see protocol for Emergency Operations in patients with sickle cell disorders.

RhD negative women

As with other RhD negative women who are not known to be sensitised with anti-D, they require routine antenatal anti-D prophylaxis as per Trust guidelines.

Post-partum

Women with sickle cell disorders, especially HbSC disease, are at risk of post-partum pulmonary emboli, and in all women with sickle cell disorders daily prophylactic low molecular weight heparin should be given for 10 days. If there are additional risk factors for VTE including operative delivery, obesity, smoking, poor ambulation, a previous clot, or if antenatal prophylaxis was given, six weeks of post-partum thromboprophylaxis is recommended. The patient will need to be taught to self-administer it or a District Nurse can be arranged.

One must be particularly watchful in the early post-partum days, especially if delivery was by Caesarian Section, as sickling can give rise to clinical problems including 'acute chest syndrome'. Patients should remain in hospital for at least 48 hours even if well, in order that they can be closely observed.

Reinstate iron chelation if appropriate and not breast feeding.

Please send neonatal capillary blood sample for haemoglobinopathy screen to the Special Haematology Laboratory on all infants potentially at risk of having a sickle cell disorder – ie when both are parents carriers, or mother a carrier and father not tested.

4.6. Termination of pregnancy in sickle cell disorder.

Please ensure the Haematology Department is contacted as soon as possible in all cases!

Medical termination is generally undertaken if the pregnancy is under 9 weeks gestation, thereafter surgical termination is performed.

Termination may be undertaken under local anaesthetic (LA) such as spinal or general anaesthetic (GA). If under LA, transfusion preparation will not usually be necessary. If under GA, the need for preparatory blood transfusion should be considered as detailed in the paragraph 'perioperative management'.

Admission

The patient should remain in hospital at least overnight after the procedure.

Hydration

Patients will normally be fasted from midnight on the day before operation. Put up an I.V.I. from the time of arrival in the hospital to prevent dehydration that can precipitate sickling. Unless there are problems, e.g. of fluid overload, plan to give 1 litre of alternating 0.9% sodium chloride / 5% dextrose 6-hourly.

Thromboprophylaxis

As per Trust Guideline. See also paragraph 1.2.4.4.

Antibiotics

Co-amoxiclav (Augmentin®) i.v. would be appropriate (first dose1.2 g with pre-med and continue iv or oral for 24 - 48 hrs). Also screen for chlamydia pre-op (endocervical swab) as usual and treat with oral erythromycin or tetracycline pre-op if positive.

RhD negative women

As with other RhD negative women who are not known to be sensitised with anti-D, they require 250iu of prophylactic anti-D immunoglobulin if the pregnancy is less than 20 weeks gestation, and 500iu of anti-D immunoglobulin if the pregnancy is over 20 weeks gestation.

Discharge

The Haematology Team will assess the following day for fitness to discharge.

4.7 Contraception

Women with sickle cell disorders have normal fertility. Maternal and foetal complications are more common during pregnancy. There are no absolute contraindications to the use of the combined contraceptive pill, progesterone only

preparations or intrauterine devices in women with sickle cell disorders per se and these methods should be discussed. Contraceptives of choice would be progesterone only contraceptives as evidence suggests they reduces sickling. Progesterone-only contraceptives such as the progesterone only pill 'mini pill' are also safe in breastfeeding. Alternatives also include the Depo provera IM or Mirena coil (from 6 weeks post-partum).

The following recommendations are taken from the Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK (2018):

- Progestogen-only contraceptives (pills, injections and implants), progestogen-releasing intrauterine systems and barrier methods have no restrictions for use in women with SCD.
- The advantages of using low-dose combined hormonal contraceptives (pills, patches and rings) and intrauterine devices generally outweigh the theoretical or proven risks in women with SCD.
- Women should be informed that in the general population the risk of venous thromboembolism with use of combined hormonal contraception is approximately doubled compared to non-users, but that the absolute risk remains low**. There is lack of evidence on whether this risk increases further due to their sickle cell disease.**
- When assessing safety of contraceptive methods in women with SCD, any co-existing medical conditions that may contra-indicate use of the method must be taken into consideration.
- Use of long acting reversible contraceptive (LARC) methods such as injectables, implants and intrauterine devices are more effective in preventing pregnancies than user-dependant methods such as oral contraceptive pills and barrier methods.
- There is limited evidence that the use of depot medroxyprogesterone acetate (DMPA) reduces the frequency of acute painful episodes.
- Due to the significant health risk during pregnancy in women with SCD, women should be advised to consider LARC methods, which are highly reliable and effective. The sole use of barrier methods and user-dependent methods of contraception (e.g. oral contraception) may not be the most appropriate choice for these women given their relatively higher typical use failure rates.
- Due to the potential teratogenic effects of hydroxycarbamide, sexually active couples should use contraception if one person is using hydroxycarbamide. Hydroxycarbamide should be stopped prior to conception.
- Health care professionals should have access to specialist advice about appropriate contraception for people with SCD when required.

5. MANAGEMENT OF CHRONIC COMPLICATIONS

The sickle cell disorders are multisystem conditions. Care of adult patients involves surveillance to detect the emergence of chronic complications and appropriate management of these. Regular outpatient reviews are required, and every patient has a detailed annual review during which these complications are systematically reviewed.

Outlined below are the general recommendations for monitoring, investigations and treatment, based on the Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK (2018).
Section 2 of this policy contains Trust-specific information on referral pathways and on how to arrange investigations.

5.1. Chronic Pain

The Pain in Sickle Cell Epidemiology Study (PiSCES) concluded that pain in SCD was far more prevalent and severe than previously thought with most patients managing their pain at home. Adult patients in this American single site study reported experiencing pain on 54.5% of the surveyed days; with 29% of patients experiencing pain on more than 95% of the days. Whilst this study did not distinguish between acute and chronic pain it does suggest that a large number of patients experience pain on most days. Another American study of adult patients with SCD reported 92% of patients experienced pain lasting from 6 months to 2 years with 90% taking pain medication on a daily basis for a period of 6 months.
There is little robust evidence about the management of SCD chronic pain, so most of the following is derived from general guidance on the management of chronic pain, and prescribing in non-cancer chronic pain. Alongside medication-directed management, there is increasing support and recommendation for working within a multidisciplinary team(MDT) in managing chronic pain, including therapeutic interventions such as psychology and specialist pain physiotherapy, rather than depending on pharmacological therapy alone. Through engagement with the MDT, people living with SCD can be supported in acquiring and developing skills in pain management, including managing unhelpful or difficult thoughts, managing difficult emotions including anxiety, stress and worry, pacing activities, moving and exercising in the presence of SCD and mindfulness and relaxation strategies.

Characteristics of Chronic Pain:

- On the background of ongoing vaso-occlusion.
- exacerbating/remitting course with periods of high and low pain.

- Mechanisms different from vaso-occlusion:
- Secondary to avascular necrosis, leg ulcers, or other sequelae from vaso-occlusion,
- Often no anatomic correlate to explain the pain
- nerve damage and chronic inflammation
- Opioid use (hyperalgesia)

Problems related to long-term use of opioids:

SCD patients with chronic pain are often dependent on regular use of opioid analgesia. Whilst the analgetic effect is often adequate, there are some serious problems with the long-term use of (strong and highly dosed) opioids:

- Higher doses and larger quantities of oral opioids often do not help.
  Old principle: 'there is no ceiling to the analgesic effect of opioids'
  However, in actuality:
  There is little evidence that long-term high-dose opioids (typically defined as 90 mg of morphine equivalents per day) improve pain or function but plenty of evidence that they cause harm:
  Opioids can trigger:
    - Mast cell degranulation, causing pain and pruritus
    - Increased NO secretion, resulting in vasodilation
    - Interaction with PDGF / VEGF receptors, particularly in long term subcutaneous injection, can lead to delayed wound healing, retinopathy and vascular permeability, as well as mesangial proliferation and kidney injury.
- chronic pain in adults follows an exacerbating/remitting course, with large fluctuations in daily pain, and long-acting and long-term opioids (especially in high doses) could necessitate that the patient take the dose on "good" days simply to prevent withdrawal.
- Analgesia in situations of acute-on-chronic pain in patients on long-term opioids is challenging because of high levels of tolerance.
- High-dose opioid use can lead to paradoxical hyperalgesia

Guidance on Management of Chronic Pain in SCD:

1. Focus on underlying other factors contributing to frequent attendance in adults with high rates of utilization for pain
2. Treat any underlying causes of pain, including SCD, aggressively. This includes disease-modifying treatment (HU, transfusion) and local treatment of eg AVN.
3. Apply principles of chronic pain management with focus on opioid reduction and alternatives:
    - Patients with neuropathic pain should be offered appropriate analgesic medication.
    - Individual care plans should be considered for patients with complex care needs.
    - Long-term opioid use should be regularly reviewed. A care plan should be devised to avoid an escalating regime of opioids. Clear prescribing guidance should be developed in conjunction with the chronic pain team and GPs to ensure a single prescriber.
    - All health care professionals involved in caring for the patient, including primary care, should be aware of prescribing plans for opioids and who the key prescriber is.
    - Self-management techniques such as pain management programmes and complementary therapies like CBT need further evaluation in patients with SCD.

5.2 Neurological Complications

Central nervous system (CNS) complications in adults with sickle cell disease (SCD) cause significant morbidity and mortality. Acute presentations can include headache, seizures, focal neurological signs, visual impairment, altered consciousness and acute deterioration in cognition; aetiologies include stroke and infection. Early recognition of acute neurological complications is vital, alongside rapid diagnosis and appropriate management. Please refer to paragraph 1.5 for the management of acute neurological complications.

Stroke:

Adults with SCD are at risk of both acute ischaemic and haemorrhagic stroke with the risk of acute ischaemic stroke increasing with older age. Strokes have long-term effects including neurocognitive and neuropsychological dysfunction. There is very little evidence or commentary focused on the assessment and management of these conditions in adults. Most guidance and treatment strategies are extrapolated from paediatric data and expert consensus. Consequently, there are key questions that remain unanswered.

Recommendations:

In adults with SCD presenting with acute stroke, causes of stroke seen in adults without SCD should also be considered (such as thrombophilia, CNS infection, illicit drug use, arterial dissection and congenital heart disease.

- Standard investigations:
    - MRI brain and MR angiography
    - Echocardiogram to determine if a patent foramen ovale is present
    - ECG to determine if atrial fibrillation (AF) or other arrhythmia is present
    - 24 hour blood pressure monitoring
    - Lipid screen
    - Limited thrombophilia screen (protein C, protein S and antithrombin levels)
- Standard management**:**
    - Management of modifiable risk factors such as systemic hypertension, hyperlipidaemia, or atrial fibrillation
    - Advice on smoking cessation
    - Refer to appropriate specialist and consider anti-platelet therapy as per national stroke guidelines.
- Stroke prevention in SCD patients:
    - Adult patients who experience an acute ischaemic stroke attributed to sickle cell disease should be offered long term transfusion therapy.
    - Patients who have been started on chronic transfusion therapy for **primary prevention** during childhood should be assessed by an expert in SCD at transition to adult care to discuss the risks and benefits of ongoing transfusion. They should be offered continuation of transfusion therapy or hydroxycarbamide if they have had a previous abnormal transcranial Doppler (TCD) that has normalised and there is no evidence of vasculopathy.
    - Patients who have been started on chronic transfusion therapy for **secondary stroke prevention** during childhood should be offered continuation of transfusion therapy.

- Patients who have been started on hydroxycarbamide for primary stroke prevention during childhood should be offered ongoing hydroxycarbamide therapy after transition to the adult service.
- There is inadequate evidence to recommend routine screening by TCD or MRI to predict stroke risk in adults.
- Hydroxycarbamide should be considered for prevention of recurrent stroke where transfusion is not possible or acceptable.

Intracranial aneurysms and moyamoya disease:

Some patients with SCD develop a cerebral vasculopathy, including stenosis of the supraclinoid carotid arteries causing a moyamoya syndrome. Intracranial aneurysms are more common in SCD, especially in HbSS (prevalence up to 10%; Stroke. 2016;47:1710–1713). In this paper, there was also a trend towards a higher occurrence of aneurysmal subarachnoid haemorrhage, with women aged 30-39 particularly at risk. There was no correlation between intracranial aneurysms and moyamoya vasculopathy, suggesting that moyamoya syndrome and intracranial aneurysms may be the result of 2 different pathobiological processes. The management of small asymptomatic aneurysms is as of yet unclear.

At present, the data does not justify routine screening for aneurysms and/or moyamoya disease. However, all SCD patients with a new onset (especially if acute) should have further investigations on aneurysmal SAH.

Headache:

Recurrent headaches and migraines are common and undertreated in SCD. Headache is a common symptom and requires evaluation including measurement of vital signs: blood pressure and heart rate, neuroimaging of the brain and cerebral vessels, and referral to a neurologist if the symptoms persist.

5.3. Chronic Lung Disease

Chronic lung disease can result from recurrent acute chest syndromes, or thromboembolic disease, but can also arise in the absence of previous clinical episodes. It may manifest with low baseline oxygen saturations or worsening dyspnoea on exertion.

Investigations:

- Assess all patients for respiratory symptoms and with respiratory examination at each annual review.
- Monitor oxygen saturation SpO2 [on air] at least annually
- Routine Pulmonary Function tests in asymptomatic adult patients are not recommended.
- Patients with respiratory symptoms or chronic hypoxia should be investigated with:
  - Spirometry with transfer factor
  - High resolution computerised tomography (CT) of the lung
- A sleep study should be recommended in all patients with:
  - self-reports of disturbed sleep
  - excessive daytime sleepiness (Epworth sleep score >10)
  - oxygen saturations awake <95%

    - a history of snoring, priapism or early morning headaches.
- Patients with suspected chronic lung disease or abnormal sleep studies should be referred to a respiratory physician for review and consideration of therapy. (see Section 2 for Trust-specific referral pathways)

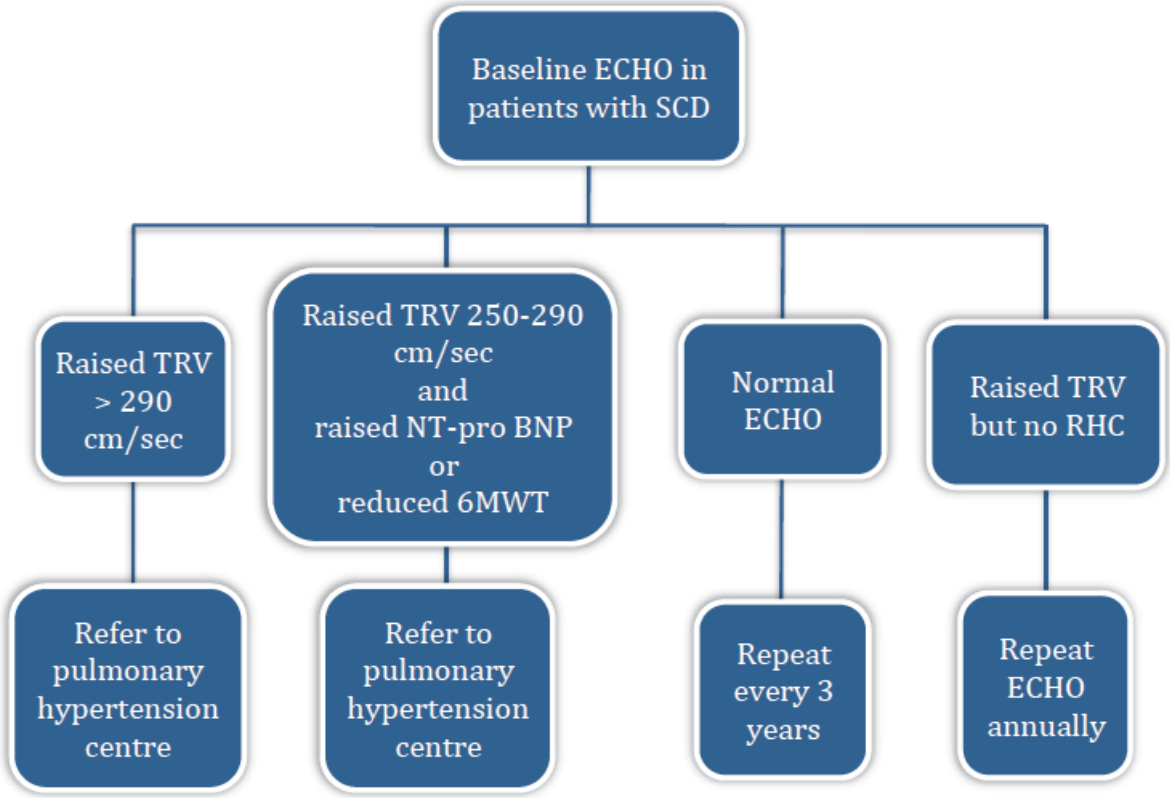
Management:

- Prompt treatment of chest infections
- Advice on smoking cessation
- Home oxygen therapy when appropriate

5.4. Pulmonary Hypertension

Pulmonary hypertension (PH) has been reported in 6-11% of adult patients with SCD. The causes are multifactorial and include chronic intravascular haemolysis leading to reduced nitric oxide scavenging, left sided heart disease, chronic lung disease, chronic thromboembolic disease, pulmonary vascular disease, hypoxaemia, oxidant stress and asplenia.
PH in SCD is associated with increased age, poor functional capacity, prior history of cutaneous leg ulceration, anaemia, higher N-terminal pro–brain natriuretic peptide (NT-proBNP) levels, renal insufficiency and markers of haemolysis.

Investigations:
The mainstay of pulmonary hypertension screening is Doppler echocardiography.
A useful algorithm for a screening strategy is given below:



ECHO = echocardiography
TRV = tricuspid regurgitant jet velocity
NT pro-BNP = N-terminal pro-brain natriuretic peptide
6MWT = 6 minute walk test
RHC = right heart catheterisation

Management:

- Referral to pulmonary hypertension centre: See section 2 for Trust-specific referral pathways.
- Patients with PH should be evaluated for thromboembolic disease, chronic lung disease, hypoxaemia, sleep-disordered breathing,HIV infection and autoimmune disease.

- Consider disease modifying treatment, aiming at improved anaemia and reduced haemolytic rate.

5.5. Renal and Urological Complications

Sickle Cell Nephropathy:
Renal complications (sickle cell nephropathy, SCN) occur in approximately 60% of patients with the more severe forms of SCD (sickle cell anaemia and S/β0thalassaemia) at some point during their lives, although these figures are halved in individuals with HbSC. In most cases, SCN develops slowly and insidiously over time, starting in the very young with glomerular hyperfiltration and leading to microalbuminuria in late childhood or early adulthood. The majority of patients do not progress further, but a number will gradually develop unselective proteinuria and slowly progressive chronic kidney disease (CKD) leading to decreased renal reserve. The mechanisms of disease and the impact of treatment options are poorly characterised but an increase in glomerular blood flow (profound anaemia!), reduction in medullary blood flow from ischemia, papillary necrosis, and use of non-steroidal anti-inflammatory drugs are all recognised contributors to sickle nephropathy.

Hyposthenuria:
Hyposthenuria (the inability to concentrate urine >450 mOsm/kg under water-deprived conditions) is a universal finding in patients with SCD. This is not the same as sickle cell nephropathy. In children, hyposthenuria is usually reversible by blood transfusion, but with age, the condition becomes irreversible and it becomes a permanent. This may manifest as nocturnal enuresis and predisposes patients to dehydration when unwell. All patients with SCD should be encouraged to have a minimum fluid intake of at least 3-4 litres/day.

Haematuria:
Renal papillary necrosis , caused by vaso-occlusion of the vasa recta, manifests as haematuria in patients with SCD and sickle trait. The clinical manifestations depend on the degree of infarction and range from asymptomatic to frank haematuria. In rare cases, the haematuria is severe with the passage of clots and severe pain (renal colic). Renal ultrasonography (US) can be used to show the renal abnormalities but computed tomography (CT) urography may be needed to confirm the diagnosis. The treatment of haematuria is conservative with maintenance of a high urinary flow with intravenous saline and when necessary, blood transfusion support if blood loss is significant. Urologists should be involved at an early stage to offer advice on bladder irrigation. Radiological or surgical intervention may be required in severe cases with prolonged haemorrhage.
Patients with **renal medullary carcinoma** may also present with haematuria, sometimes with additional abdominal or back pain and weight loss. This rare and aggressive cancer is virtually restricted to those with the sickle gene, particularly sickle trait, sicklecell/haemoglobin C disease and occasionally sickle cell anaemia.

Recommendations
- Annual monitoring of urine protein:creatinine ratio (UPCR) and more frequently if UPCR is rising.

- Commence ACE inhibitor when UPCR >50 mg/mmol and increase as tolerated to control proteinuria – usually perindopril 2 mg initially, increasing if the proteinuria is not controlled, and blood pressure allows.
- Patients with a UPCR > 50 mg/mmol should be considered for hydroxycarbamide therapy
- If UPCR >100 mg/mmol and / or there is any derangement of renal function, refer to nephrology.
- Patients with SCD who develop acute renal failure should have close monitoring of their renal function. These patients should have adequate hydration and fluid balance; nephrotoxic drugs should be avoided.
- All patients with SCD should be encouraged to have a minimum fluid intake of at least 3 l/day.
- NSAIDs should be avoided in patients with stage 3-5 CKD not on renal replacement therapy (eGFR <60 ml/min).
- Patients with hypertension and ACR <3.5 mg/mmol (or UPCR < 20 mg/mmol) should be treated with a BP target of <140/90 mmHg. Patients with hypertension and ACR >3.5 g/mmol (or UPCR > 20 mg/mmol) should be treated with a target of <130/80 mmHg. An ACE inhibitor would be the drug of first choice in either instance.
- New-onset haematuria should be investigated, regardless of age, to exclude malignancy. Isolated microscopic haematuria in the absence of proteinuria should also be investigated.

5.6. Orthopaedic Complications

The two most common orthopaedic complications of SCD include avascular necrosis (AVN) and osteomyelitis. Both conditions can cause chronic pain with the resulting consequences. Osteomyelitis can also mimic veno-occlusion and if in doubt, imaging should be requested.

<u>Osteomyelitis:</u>
Salmonella, Staphylococcus Aureus and other gram-negative enteric bacilli are the most common causes of osteomyelitis, perhaps due to bowel micro-infarcts facilitating the egress of these organisms. Tuberculosis has also been reported to cause osteomyelitis in SCD. Osteomyelitis can arise as a result of septic emboli, but it is also likely that pre-existing AVN predispose to osteomyelitis as a result of the reduced clearance of micro-organisms and debris from dead space.
NOTE: Chronic osteomyelitis, especially when low-pathogenic micro-organisms are involved, causes pain but may not necessarily present with systemic symptoms and/or a raised CRP.

Treatment:

- Blood cultures should be taken in patients with ongoing bone pain and/or fever where a clinical diagnosis of osteomyelitis is suspected. In selected cases radiological examination or bone biopsy/aspiration should be considered to confirm the diagnosis.
- Treatment of osteomyelitis should be with a prolonged course of an antibiotic appropriate to cover the organism isolated.

- If a large AVN is involved, a multidisciplinary approach is desirable exploring if surgical options (debridement, dead space control, local antibiotics) may be indicated.

Avascular Necrosis (AVN):

Avascular necrosis may affect up to 50% of patients with sickle cell disorder and most commonly affects the femoral head and the humeral head, although it has also been reported to affect multiple other joints including the knees, feet and back. It commonly affects multiple joints. AVN may be asymptomatic in the early stages but the majority of patients present with intermittent, progressive or acute pain. Patients with hip AVN commonly present with groin pain, but may also present with pain in the buttock, knee or with diffuse lower limb pain.

Treatment:

The treatment for AVN is dependent on the grade of joint involvement. Management approaches useful in patients with early stage disease include: physiotherapy; pain management approaches, including injection of local anaesthetic into the joint; activity modification; and walking aids. Although helpful, conservative treatment of AVN alone does not provide prolonged symptomatic relief and does not prevent disease progression. Disease-modifying treatment (hydroxycarbamide, transfusion) does not prevent disease progression but may stop new AVN from developing and may improve healing of the bone after surgical decompression, although there is no available evidence.

- AVN in SCD patients should be managed using a multidisciplinary team (MDT) approach involving the haematologist and a specialist orthopaedic surgeon
- AVN should be considered in SCD patients presenting with either sudden onset or progressive joint pain especially in the hip or shoulder joints and initial investigation should begin with plain X-ray, MRI should considered if the plain X-ray is normal.
- Analgesia and physiotherapy should be offered in the early stages of AVN
- The anaesthetic and pain management team should be involved in preoperative management of patients with SCD prior to joint replacement surgery.
- Core decompression can be considered in selected cases of non-collapsed femoral head and early stage shoulder AVN in the young patient. The theory is that decompression will promote revascularisation and healing of the dead core. However, long-term results appear disappointing with the majority of patients eventually progressing.
- Total hip replacement is indicated in patients with persistent, intractable hip pain and disability affecting daily activities who have failed non-operative management.
- There are fewer studies reported for shoulder surgery in sickle patients. However good outcomes have been reported with regard to both arthroplasty and resurfacing surgery in sickle patients.
- The use of cementless prosthetic devices is preferred for hip replacement surgery in SCD.
- Post-operative infection prophylaxis and thromboprophylaxis are recommended unless contra-indicated
- Major joint arthroplasty surgery should be carried out in centres experienced in managing patients with SCD

5.7. Hepatobiliary Complications

Abdominal pain is common in sickle cell disease (SCD) and may be due to complications of SCD or to other causes of abdominal pain, as in other patients. The differential diagnosis of abdominal pain includes sequestration syndromes, mesenteric syndrome, constipation, gall stone complications, infective aetiologies (e.g.pyelonephritis, intra-abdominal abscesses and diverticulitis) and dysmenorrhoea. Hepatobiliary complications in SCD are common and have a multifactorial aetiology.

Depending on the nature of the problem, referral to a specialist centre with expertise in sickle hepatopathy may be appropriate. In progressive liver disease, treatment may include an exchange transfusion programme and liver transplantation can be considered for highly selected patients with end stage liver disease.

Diagnoses to consider:

- Splenic sequestration (rare in adults)
- Mesenteric Syndrome
- Obstructive Jaundice (gall stone complications)
- Hepatic sequestration
- Acute intrahepatic cholestasis
- Chronic sickle cell hepatopathy
- Viral hepatitis
- Iron overload

Investigations:

- LFTs including conjugated bilirubin, ALT, γGT
- Clotting studies
- LDH
- Iron, ferritin, transferrin saturation
- Abdominal ultrasound with Dopplers
- MRCP
- Abdominal CT
- R2* MRI scan of liver (or T2*)

Management:

- Symptomatic gallbladder stones should be treated with laparoscopic cholecystectomy because of the shorter hospital stay and fewer immediate surgical complications.
- Exchange transfusion should be considered early in the presentation of patients with intrahepatic cholestasis.
- Simple transfusion to baseline haemoglobin can be considered for patients with acute hepatic sequestration associated with anaemia.
- Liver biopsy should only be considered in cases of genuine diagnostic dilemma and should be done via the trans-jugular route to minimise bleeding risk.

- Patients with sickle-related liver disease should be managed by a multi-disciplinary team including haematologists and specialist hepatologists.
- Patients with liver dysfunction should be investigated for other causes of liver disease including autoantibody screen, viral hepatitis serology and hepatobiliary imaging
- The investigation and management of patients with acute complications of gallstones should follow general treatment guidelines for these conditions.
- Patients with progressive liver disease should be considered for exchange transfusion programmes under the supervision of a specialist sickle/liver service.
- Patients with chronic cholestasis may be treated with ursodeoxycholic acid.
- Liver transplantation in SCD should be considered in highly selected patients, and in specialist centres with dual expertise in sickle cell disease and hepatology.

5.8. Endocrinopathies

From childhood, delayed growth and puberty is a common finding in both males and females (see paediatric guidelines). In adult males, hypogonadism can occur and semen analysis may show decreased total sperm counts (oligospermia), reduced motility, and reduced indices of semen quality. Osteopenia and osteoporosis can also occur and is often multifactorial. Transfusional iron overload can also lead to endocrinopathies but these occur infrequently in patients with sickle cell disorders compared to those with the thalassaemia syndromes.

Investigations:

- LH, FSH, testosterone / oestradiol
- R2 MRI scan of liver
- Bone mineral density scan (DEXA)

Management:

- Referral to endocrinology
- Chelation for transfusional iron overload
- Bisphosphonate therapy and lifestyle modification for bone thinning

5.9 Ophthalmological Complications

The most important ophthalmic complication of sickle cell disease (SCD) is sickle retinopathy, which can cause significant visual impairment. Patients with sickle cell/haemoglobin C compound heterozygosity have a higher risk of sickle retinopathy than patients with sickle cell anaemia. Another potential cause of visual loss in SCD is drug-induced retinopathy due to iron chelating agents (such as desferrioxamine).

Laser photocoagulation therapy for eyes with proliferative sickle cell retinopathy (PSR) may prevent visual loss and vitreous haemorrhage and should be considered as a therapeutic intervention for patients with PSR. However, there is insufficient evidence to suggest that laser photocoagulation therapy will prevent the development of new proliferative lesions. As such, the role and frequency of regular ophthalmic screening is uncertain and there may be a benefit of targeted screening for those patients who are most likely to develop visual loss

(sickle cell/haemoglobin C disease and patients with previous episodes of visual loss or vitreous haemorrhage).

Another frequent finding in SCD is temporal thinning of the retina by Optical Coherence Tomography (OCT), likely representing ischemic retinal atrophy from occlusions of the retinal circulation.

There is currently no evidence that disease modifying treatment can reverse or prevent either proliferative sickle cell retinopathy or ischaemic retinal atrophy.

Recommendations:

- Patients with SCD should be treated by ophthalmologists with sub-specialty expertise in retinal disorders and SCD.
- Patients on desferrioxamine or deferasirox should also be monitored for visual problems due to the development of drug-induced retinopathy.
- Laser photocoagulation therapy should be considered for patients with proliferative sickle retinopathy
- Screening recommendations (local consensus may differ!)
    - All patients with SCD should have a baseline retinopathy screening.
    - Follow up screening:
        - HbSS stage 0 or 1 retinopathy: every 5 years
        - HbSC stage 0 or 1 retinopathy every 2 years
        - Asymptomatic temporal thinning by OCT: yearly
        - HbSC or HbSS stage 2, 3, 4 or 5 - review planned on individual basis.

5.10. Leg Ulceration

Leg ulceration is a frequent and disabling complication of sickle cell disease (SCD). Once they occur they may persist for months or years and are associated with severe chronic pain; recurrence is frequent. There is little evidence about best management but a multidisciplinary approach is necessary and treatment may include both local wound care and systemic treatments. Leg ulceration is possibly linked to haemolysis/endothelial dysfunction rather than veno-occlusion. In addition, mechanical obstruction, high blood viscosity, venous incompetence, hypercoagulability and thrombosis may also play a role in the development of ulcers. These factors place patients at higher risk of developing ischaemia and once tissue damage occurs the cycle repeats leading to further tissue damage with fluid retention and inflammation encouraging ulcer formation and limiting healing. Zinc deficiency has also been suggested.

Whereas there is limited evidence that topical morphine may help healing of leg ulcers, care must be taken that long-term (parenteral) morphine is associated with capillary leak, oedema and impaired wound healing as a result.

Hydroxycarbamide has been shown to be associated with leg ulceration in patients with myeloproliferative neoplasms, but this association has not been seen in multicentre studies in SCD. There is insufficient evidence to interrupt hydroxycarbamide treatment in patients with

SCD and leg ulceration. In fact, a good response to hydroxycarbamide may be beneficial to ulcer healing.

Recommendations:

- Patients with leg ulceration should be treated by a multidisciplinary team which includes wound care experts.
- Patients with sickle-related leg ulcers should be assessed for venous insufficiency with venous reflux studies
- Multi-component compression bandaging should be offered, particularly in patients with evidence of venous insufficiency.
- Dressings directed at inhibiting/modulating MMPs (eg, UrgoStart® is a protease inhibitor dressing combining a soft-adherent technology lipido-colloid nano-oligosaccharide factor or TLC-NOSF layer) can reduce healing times in a variety of chronic wounds and therefore improve patient outcomes.
- Zinc levels should be measured in patients with leg ulcers and supplements should be offered to those with deficiency.
- Patient education is a vital part of ulcer management and advice should include:
    - Eating a nutritious and well balanced diet;
    - Avoiding injury, especially to feet, ankles and legs;
    - Avoiding dry skin by using local moisturisers ;
    - Wearing socks and well-fitting shoes;
    - Using insect repellents and protection against insect bites;
    - Treating minor trauma around the ankles quickly
    - **Avoiding blood tests or intravenous line insertion in the lower limbs**;
    - Considering wearing compression stockings to reduce oedema.
- Patients with SCD-related leg ulcers should be offered appropriate analgesia and may require support from a specialist pain team. Regional nerve blocks may be of benefit.
- Hydroxycarbamide should not be withheld from patient with leg ulceration.
- A trial of blood transfusion therapy should be considered in patients with intractable leg ulcers.

6. SPECIFIC TREATMENTS

6.1. Disease-Modifying Treatment

6.1.1. Hydroxycarbamide (hydroxyurea)

(Adapted from the BSH Guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease, British Journal of Haematology, 2018, 181, 460–475)

6.1.1.1. Background:

Hydroxycarbamide (also known as hydroxyurea) is currently the only medication licensed in the UK for the prevention of recurrent painful crisis in patients with SCD. The randomised controlled Multicentre Study of Hydroxyurea (MSH) study showed definitively that treatment with hydroxycarbamide could decrease episodes of pain and acute chest syndrome (ACS) and reduce the need for transfusion. Since then, multiple trials have confirmed its efficacy in

disease modification in children and in the prevention of additional disease complications, and have shown an improved survival in patients taking hydroxycarbamide.
Adults entered into the randomised controlled MSH study were subsequently entered into a non-randomised observational study. At 9 years of follow-up use of hydroxycarbamide was associated with a **40% reduction in mortality**. After a 17.7-year follow-up period the analysis of mortality in 3-month intervals according to hydroxycarbamide usage in the interval, showed that death rates were reduced by 40% during 3-month intervals when patients were taking hydroxycarbamide. Twenty-four percent of deaths were due to pulmonary complications and **87.1% of these occurred in patients who never took hydroxycarbamide or took it for <5 years**. In the same cohort, the reduction of painful VOC was reduced by 44% and the incidence of ACS by 51%. The clinical benefits of hydroxycarbamide have been correlated with a rise in Hb, HbF and MCV.

Mechanism of action:
Hydroxycarbamide is an inhibitor of ribonucleotide reductase and has been used as an oral anti-proliferative drug for several decades. Its mode of action in SCD is based on both its ability to increase HbF levels and its ability to reduce intercellular adhesion and hence improve blood flow and reduce vaso-occlusion .

- Increase in Foetal Hb (HbF): Hydroxycarbamide has the ability to increase the number of 'F-cells' (red blood cells with the ability to contain HbF) as well as increase the actual content of HbF within the individual F-cell. It is thought that the induction of mild intermittent bone marrow suppression, which results in a state of stressed erythropoiesis, where production of HbF is increased relative to steady state. This is not an immediate effect and it may take several months (6-12) of dose escalation to achieve an optimal rise in HbF levels.
- Reduction of intercellular adhesion: In part, this is due to decreased expression of integrins and other adhesion molecules on red cells, white blood cells (WBCs) and vascular endothelium. The interactions between these cells are involved in neutrophil migration and red blood cell flow and reduction of adhesion leads to decreased vaso-occlusion. Nitric oxide (NO) levels are decreased in patients with SCD and stimulation of NO production by hydroxycarbamide may result in local vasodilation, which will improve blood flow and reduce vaso-occlusion.

Laboratory effects of hydroxycarbamide:
In addition to the increase in HbF%, the laboratory effects of hydroxycarbamide also include:

- raised haemoglobin concentration (Hb) levels
- increased mean cell volume (MCV)
- reduction in absolute reticulocyte count (ARC)
- reduction in WBC count

Rationale for hydroxycarbamide:
Strong evidence:

- Reduction in mortality
- Reduction in acute pain complications and ACS
- Reduction in hospitalisation and pain in the community

Weak evidence:

- (Primary and) secondary stroke prevention

- End organ damage
- Improvement of symptomatic anaemia

6.1.1.2. Concerns of Hydroxycarbamide:

Despite the clear benefits of hydroxycarbamide, it remains under-utilized due to reluctance in both clinicians and patients to use it. This is partly due to concerns about its side effects, which include myelosuppression, with a need for regular blood monitoring, and uncertainties about its effect on spermatogenesis and misconceptions about possible teratogenicity and leukaemogenesis.

- Short term complications and side effects:
    - Fatigue
    - Mild gastrointestinal symptoms
    - hyperpigmentation of the skin and darkening of nails, which is not dose-dependent
    - Hair thinning
    - Marrow suppression
- Medium and long term concerns:
    - NO RISK of leukaemogenesis
    - No concerns about normal growth and development
    - No evidence that hydroxycarbamide affects fertility.
        - Females: no concerns
        - Males: the effect on spermatogenesis remains unclear.
            - Baseline sperm abnormalities already exist in men with sickle cell disease in up to 90%.
            - One study showed that pre-treatment 18% of men were oligospermic and 4% were azoospermic at baseline. During treatment, a further 20% developed oligospermia and 10% developed azoospermia. The parameters reverted to normal after stoppage of hydroxycarbamide for 3 months in 73% of patients.
            - The association of abnormal sperm parameters and fertility is not clear as men with low sperm number and abnormal morphology can still be fertile.
            - The effect of hydroxycarbamide on male spermatogenesis and fertility when the drug is started in pre-pubertal children are unknown.
            - In view of these uncertainties it has been suggested that it is reasonable to offer post –pubertal male patients sperm analysis and cryopreservation prior to starting treatment with hydroxycarbamide.

6.1.1.3. Recommendations for treatment:

Recommendations vary from a strong indication for treatment, to an open discussion on possible benefits. Please offer all patients the information leaflet (Appendix III) prior to start of treatment and obtain full informed consent according to Good Clinical Practice principles. The patient's ongoing consent should be obtained yearly, based on the treatment goals and side effects.

In the list below, the use of hydroxycarbamide for the various situations is listed as treat, offer treatment, recommend, consider or discuss, based on the available level of evidence.

- The benefits of hydroxycarbamide should be **discussed with ALL adolescents and adults** with **SS/Sb0** to enable informed joint decision-making. Hydroxycarbamide therapy should be considered in adults and children with SCD with **genotypes other than SS and Sb0 thalassaemia on a case-by-case basis**. There should be on-going discussion between provider and patient.
- In adolescents and adults with SS/Sb0, **offer treatment** with hydroxycarbamide in view of the impact on reduction of mortality.
- In adults with SS/Sb0 who have **3 or more sickle cell-associated moderate to severe pain crisis in a 12-month** period, **treat with hydroxycarbamide**. Consider treatment in other genotypes who have 3 or more sickle cell-associated moderate to severe pain crisis in a 12-month period.
- In adults with SS/Sb0 who have sickle cell **pain that interferes with daily activities and quality of life**, **treat with hydroxycarbamide.** Consider treatment in other genotypes who have sickle cell pain that interferes with daily activities and quality of life.
- In adults with SS/Sb0 and a history of **severe and/or recurrent ACS treat with hydroxycarbamide.** Consider treatment in other genotypes and a history of severe and/or recurrent ACS
- In adults with a previous history of acute ischaemic stroke or infarcts, hydroxycarbamide should be **recommended** as second line therapy for **secondary stroke prevention** when transfusions are contraindicated or unavailable.
- There is insufficient data to advise commencing hydroxycarbamide therapy for primary stroke prevention in adults
- The potential benefits of hydroxycarbamide in **preventing end organ damage** (renal/splenic and retinopathy) should be **discussed** with all patients with SS and Sb0
- In patients with **sickle nephropathy with persisting proteinuria** despite angiotensin-converting-enzyme inhibitor/ angiotensin receptor blocker therapy, **consider** the addition of hydroxycarbamide therapy.
- There is insufficient evidence to treat patients with SS/Sb0 with **pulmonary hypertension and avascular necrosis** with hydroxycarbamide but it should be **considered** on a case-by-case basis.
- In adults with **chronic hypoxia, recommend** treatment with hydroxycarbamide.
- Patients should be counselled that hydroxycarbamide may prevent **priapism. Consider** treatment.
- In adults with SS/Sb0 and **symptomatic chronic anaemia** that interferes with daily activities or quality of life, **recommend** treatment with hydroxycarbamide.

Other treatment-related recommendations:

- Post-pubertal male patients should be considered for sperm analysis and cryopreservation prior to starting treatment with hydroxycarbamide.
- Consider stopping hydroxycarbamide pre-conception in male and female patients and in pregnant women if the patient is not at high risk of serious complications relating to sickle cell disease.

- Prenatally and during pregnancy, consider a transfusion programme if there is a severe clinical phenotype as an alternative to hydroxycarbamide treatment.
- Contraception is advised for patients on hydroxycarbamide

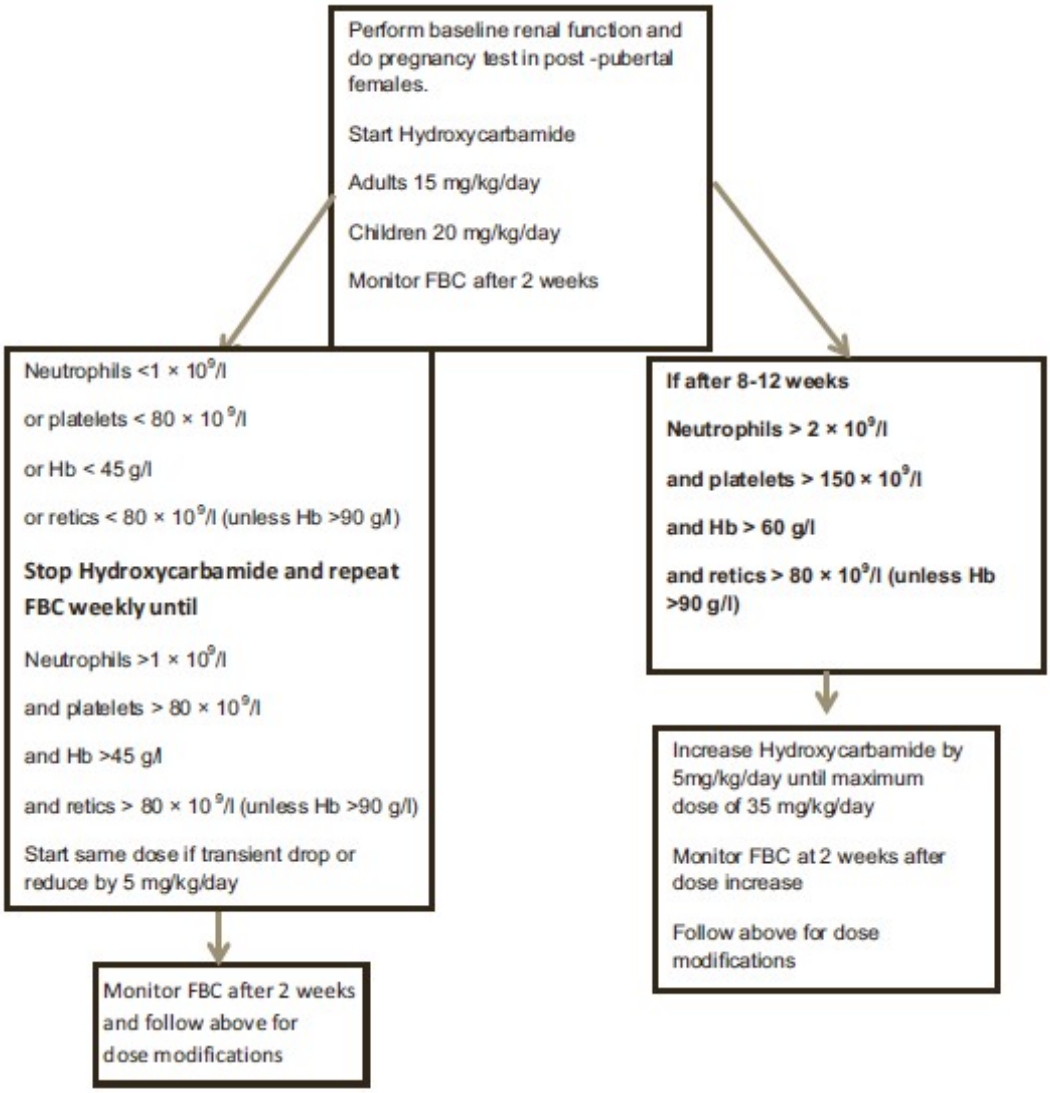
6.1.1.4. Dosing and Monitoring

The main aim of therapy is to optimise HbF% without causing excess bone marrow suppression. Patients with the highest HbF% are more likely to benefit in terms of clinical effect and survival. A high HbF% is correlated with the highest hydroxycarbamide doses. In other words, individual patients should be titrated to their maximum tolerated dose (MTD). Aiming for the lowest possible dose is therefore not a sensible approach!

Baseline elevation of HbF should not affect the decision to initiate hydroxycarbamide therapy (except for HbS/Hereditary Persistence of Foetal Haemoglobin)

- Dosing should start at 15 mg/kg/day for adults (rounded up to the nearest 500 mg).
- Use 5–10 mg/ kg/day as the starting dose if the patient has chronic kidney disease (estimated glomerular filtration rate [eGFR] < 60 ml/ min/1.73 m2) and hydroxycarbamide should be avoided if eGFR < 30 ml/min/1.73 m2.
- The dose can be escalated by 5 mg/kg every 8–12 weeks, aiming for a neutrophil count of 2–3 x 10e9/l and stopping if neutrophils fall below 1 x 10e9/l or if there is other haematological toxicity. This is the maximum tolerated dose.
- The maximum dose should not exceed 35 mg/kg/day.
- Hydroxycarbamide therapy should be continued during hospitalisations or illness **unless due to febrile neutropenia or bleeding with thrombocytopenia**.
- Avoid use with didanosine, stavudine and clozapine.
- Caution with yellow fever vaccine (although risks and benefits should be considered).
- Review treatment if cutaneous vasculitic ulcerations develop.
- Patients should be informed to present to hospital if unwell with high fevers and infection and inform hospital staff to perform a FBC in case of neutropenia.

Please refer to the dosing and monitoring algorithm below:



- Once a stable dose is established, laboratory safety monitoring should include FBC and reticulocyte count every 2-3 months. Follow above algorithm for dose modifications. HbF and MCV can be used to monitor effect/compliance

6.1.2. Crizanlizumab

Crizanlizumab has been FDA-approved in November 2019 for preventing sickle cell crises in sickle cell disease. NICE appraisal report is expected in September 2020.

6.1.3. Voxelotor

Voxelotor has been FDA-approved in November 2019 for treatment of anaemia in sickle cell disorder. NICE review has not been scheduled yet.

6.1.4. (Exchange) Blood Transfusion

Please see section 2: Blood transfusion

6.2. Allogeneic Stem Cell Transplantation

Allogenic haematopoietic stem cell transplantation (allo-HSCT) is the only currently available therapy that can cure sickle cell disease. It is currently offered to children, but not adults. In September 2019, NHS England launched a consultation on a policy for the use of haematopoietic stem cell transplantation for sickle cell disease for adults. After review of the evidence, the proposal is that allo-HSCT with a fully matched (HLA-identical) sibling should be further considered for routine commissioning. However, there was not enough evidence to make allo-HSCT available for patients with severe sickle cell disease using a matched unrelated donor, or a related donor (this may be sibling, parent, child) that is half-matched to the recipient (haplo-identical).

Indications for HSCT:
The results of sibling-HSCT in adults show survival rates of 81-100%. For adults with severe SCD, including those with additional co-morbidities e.g. stroke, pulmonary hypertension, severe disease, the mortality rate is 25% over a 10-year period. Therefore, survival with HSCT is better than survival with current standard care and HSCT should be offered to this sub-group of adults with predicted worse outcomes.
This includes patients with a:

- History of >= 3 severe pain crises or other acute complications per year despite institution of supportive care measures (optimal treatment with hydroxycarbamide (HC) or transfusion therapy). Other acute complications would include acute hepatopathy or splenic sequestration or acute priapism
- Recurrence of acute chest syndrome despite optimum treatment with hydroxycarbamide (HC) or transfusion therapy.
- Clinically significant neurologic vascular event or deficit lasting over 24 hours and confirmed radiologically (i.e.stroke) or progressive cerebral vasculopathy
- Administration of regular transfusion therapy, either by simple transfusion or exchange transfusion with the aim to prevent severe sickle complications by maintaining a low HbS%. Severe sickle complications include a history of >= 2 chest syndromes, >= 3 painful crises or severe recurrent priapism

- Patients assessed as requiring transfusion but with red cell allo-antibodies/very rare blood type/history of hyperhaemolysis, rendering it difficult to continue/commence chronic transfusion
- Patients requiring hydroxycarbamide/transfusion for treatment of SCD complications who cannot tolerate either therapy due to significant adverse reactions
- Establishedend organ damage relating to SCD including but not limited to progressive sickle vasculopathy and hepatopathy.
- The patient should not meet any of the standard exclusion criteria for HSCT
- Case discussed at the National Haemoglobinopathy Panel before referral for HSCT to obtain constant and equitable referral patterns. This will ensure national review of all referrals for HSCTs.

Exclusion Criteria for HSCT:

- DLCO(diffusing capacity of lung for carbon monoxide) <45% predicted
- LVEF(left ventricularejection fraction) <40% estimated by ECHO
- Uncontrolled bacterial, fungal or viral infections within one month of HSCT
- Active lower limb ulcers
- Active hepatitis B or C orhuman immunodeficiency virus (HIV) infection
- Liver cirrhosis or organ failure incompatible with survival following HSCT
- Major ABO mismatch if high titre antibodies present
- Failure to comply with adequate iron chelation pre-HSCT
- Pregnant or lactating
- Where haplo-identical donor is the only option available, presence of anti-bodies to donor HLA antigens.

6.3. Iron Chelation

6.3.1. Background

Anyone receiving frequent or long term top-up transfusions will come to need **iron chelation treatment**, in order to control total body iron load and try to minimise related organ damage.

This usually needs to start after about 1 year of regular transfusion or when the ferritin level is climbing to ~ 1,000 ng/ml. However, serum ferritin can be notoriously unreliable in SCD and could be significantly elevated in the absence of iron overload and transfusion. Time is needed to explain the benefits and possible adverse effects of each option. The decision process should be recorded in the patient's records. Patients and carers should be supported in adhering to chelation therapy using a multi-disciplinary team approach which includes medical and nursing staff, clinical psychology, pharmacy, allied health professionals, and – in children - play therapy.

Adherence should be monitored regularly, and problems carefully identified and addressed. Use of a treatment diary may assist with monitoring.

Patients should be carefully monitored for side effects of iron chelation, and treatment interrupted or reduced promptly to avoid serious toxicity. All professionals managing these

patients and checking their monitoring investigation results need to be familiar with the issues, and aware of what to watch out for / escalate for discussion with the Consultant.

The aim of therapy with all chelation regimes is to attain and maintain annual average serum ferritin below 1500 ng/ml [ideally < 1000 ng/ml], liver iron below 7 mg/g dry weight [ideally below 5 mg/g dry weight], and cardiac T2* >20 ms.

The oversight of iron chelation therapy is a responsibility of specialist haemoglobinopathy teams (SHT); this includes decisions about starting, monitoring, changing and stopping therapy. Provision of chelation may be provided at either the SHT or an accredited local haemoglobinopathy team (A-LHT) as part of network arrangements and agreed by the local commissioner. Initiation and modification of chelation regimes should be undertaken by a SHT or A-LHT; however, chelation drug dispensing and prescription can and should occur at the centre where the patient normally is transfused.

Indications for starting:
Chelation should be started after~ 10 transfusions, or when then serum ferritin is, on repeat, nearing 1,000 ng/ml. Recent expert opinion suggests starting chelation as early as possible after regular transfusion commences, even before there is evidence of substantial iron loading.

6.3.2. Individual Chelators and Specific Considerations

There are three licensed chelator drugs, desferrioxamine ['Desferal', DFO], deferiprone ['Ferriprox', DFP], and deferasirox ['Exjade', DFX]. Desferrioxamine has to be given parenterally over long periods to be effective: typically sub-cut for 12 hours overnight on 5 nights per week in a fully transfused patient. The other two are taken by mouth.

Desferrioxamine by subcutaneous infusion has been the standard starting chelator and remains the only one currently licensed for first line use in children under 6 years.

The dose for adults is 20 - 50 mg/kg/day if given on 7 days per week, over 10 - 12 hours, but for those on high transfusion volumes, doses in excess of 50 mg /kg/day x 5 days a week may be required.

Where there are serious concerns about iron overload and organ damage, it can be given continuously, intravenously through a Port device or, more usually, subcutaneously, 24/7, sometimes in combination with deferiprone especially if there is evidence of severe cardiac iron loading or failure [see 'combination chelation treatment' below].

Some patients are allergic to desferrioxamine, and many find the route of administration difficult. Disposable desferrioxamine infusers and fine 'thumb-tack' type sub-cutaneous needles ['Thalaset'] aid adherence. It is also not ideal as a chelator because it is only effective at the time it is running so for at least 12 hours a day, in normal use, there is no active chelation going on. If a local reaction is problematic, consider adding hydrocortisone to the desferrioxamine.

At high doses it can cause audiological, ophthalmological and/or skeletal abnormalities in growing bones and thus monitoring for these side effects is required. Once the iron overload has been reduced satisfactorily (eg ferritin <1000 ng/ml in those with transfusion dependent thalassaemia / major, also taking into account the results of MR tissue iron quantitation results) the dose of desferrioxamine should be decreased.

It is important that a therapeutic index of < 0.025 is maintained at all times. Significant side effects as mentioned above are unlikely to occur when the mean daily dose (mg/kg) /current serum ferritin (microg/L) remains below 0.025.

If a patient receiving desferrioxamine develops abdominal pain, diarrhoea or unexplained sepsis, desferrioxamine must be stopped and stool samples taken as desferrioxamine increases susceptibility to **Yersinia enterocolytica** infection.

Iron excretion is reduced if there is ascorbic acid (vitamin C) deficiency, and supplementation should be commenced one month after commencing desferrioxamine in patients with normal cardiac function; dose 50 mg if under 20 kg, 100 mg if 20 - 50 kg, 200 mg if > 50 kg body weight, taken orally just on the days the 'pump' is used.

Deferiprone has particular cardio-protective effects, and it is used singly or in combination with desferrioxamine where there are concerns about heart iron levels. The usual dose is 25mg/kg TDS ie 75 mg/kg/day, up to a maximum of 100mg/kg daily in adults with significant heart iron loading. Side effects include nausea and vomiting, abdominal pain, arthralgia and neutropenia. Zinc deficiency has been reported. In those found to be deficient, zinc supplements should be supplemented.
The most serious adverse effect of deferiprone is **agranulocytosis** and thus weekly monitoring of the full blood count with a white cell differential is recommended for the duration of therapy**.** Many do not attend for such frequent testing in practice, and **the most important safety message is that if the person has fever of 38 C or above, or other signs of infection, they must stop the medication and attend the hospital quickly for a blood count to exclude a significantly reduced neutrophil count.**

Deferiprone is available in 500mg tablets and 100mg/ml suspension.

Table 1

Body weight (kg)	Total daily Dose (mg)	Dose (mg) 3 times/day	Number of tablets 3 times/day
20	1500	500	1.0
30	2250	750	1.5
40	3000	1000	2.0
50	3750	1250	2.5
60	4500	1500	3.0
70	5250	1750	3.5
80	6000	2000	4.0

90	6750	2250	4.5

Deferasirox starting at 7mg/kg/day then adjusted in steps of 3.5–7 mg/kg every 3–6 months to a maximum dose of 28 mg/kg/day (usual maximum dose 21 mg/kg) can be used in children <6 yrs of age if desferrioxamine is 'contraindicated or inadequate', and can be used as first line chelation in children age >6 yrs and adults. Because of ease of administration, some patients greatly prefer it.

It is available in 90, 180 and 360 mg film coated tablets, which can be crushed for paediatric use; the usual starting dose is 14 mg/kg/day. Side effects include gastrointestinal symptoms, including severe indigestion and on occasion upper GI bleeding, skin rash, deranged liver and renal function. To minimise the risk of intolerance, a gradual step up to 14 mg/kg by weekly dose increases is recommended.
Serum creatinine and liver function, and urine for protein/creatinine ratio must be measured on 2 separate occasions before initiating therapy, and weekly for 4 weeks after starting or increasing dosage.
It is contraindicated in those whose creatinine clearance is <60ml/min.
Once established on treatment, checks on U&E, LFT and urine PCR are required <u>every month.</u>
Do not administer NSAIDs to patients on deferasirox because of the added risk of upper GI irritation.

All three chelators are contraindicated in pregnancy. Please see section 4.2 management during pregnancy.

Patients who are / or appear to be having problems with adherence - for example who cancel or delay home deliveries, do not request repeat prescriptions, whose iron levels continue to rise despite high / appropriate dosing should be highlighted as part of a MDT approach and, if appropriate, asked to attend a MDT meeting to see if the team can offer help to assist in compliance. The ongoing use of positive reinforcement is critical and it is important to notice, record and praise good compliance. Use of graphs to track ferritin levels and or R2 / T2* monitoring can be helpful in showing patients the result of good, or poor, compliance.

<u>6.3.3. Monitoring of Iron Overload</u>

<u>Clinical assessments</u> of iron loading are not helpful in routine practice: by the time there is obvious skin darkening, palpable hepatomegaly, cardiomegaly, or cardiac rhythm disturbance, iron loading is advanced and so investigations aiming to detect and enable correction of iron are required, on a regular basis, before these signs develop.

<u>Serum ferritin</u> levels should be **monitored at least every three months**; levels maintained in the range 500-1500 µg/l over the long term carry a relatively low risk, best if around / below 1,000 ng/ml. Remember that ferritin levels are often elevated in SCD, and also during intercurrent acute infections, chronic inflammatory conditions and chronic viral hepatitis, and this leads to an overestimate of the degree of iron loading. It is recommended to include full iron studies (TIBC, Fe and transferrin saturation) from time to time.

Magnetic resonance imaging (MRI).

T2* MRI is the best available method for detection of cardiac iron overload. There is evidence that T2* can be used as a marker for cardiac risk, and the result allows adjustment of chelation regime to reduce myocardial iron load and avoid clinical cardiac disease. There is a relationship between low T2* [lower numbers indicating higher iron level] and impaired LV function; LV impairment becomes increasingly likely when T2* falls below 20 milliseconds (ms). Although not specifically designed to measure liver iron, the T2* also gives an estimate of liver iron content; aim for a level of < 7 mg/ g dry weight.

As a guide, cardiac T2* MRI

- every 2 years if T2* >20 ms,
- every year if T2* 10-20 ms,
- 6 monthly if T2* <10 ms, and / or if any evidence of cardiac impairment.

R2 MR assessment scan, 'Ferriscan' is reported to be more accurate in quantifying liver iron levels. R2 should be requested if any of the following apply:

- the ferritin is consistently high, above 2,000 ng/ml
- liver function is abnormal without any other evident cause
- there is infection with hepatitis B or C, so that LFT might be unreliable, and it is especially important to keep liver iron levels low to reduce the risk of hepatocellular carcinoma

In practice, having this additional scan is now becoming standard care, and all patients are now referred for Ferriscan, first at aged 8, and then at intervals according to load / compliance with chelation:

- yearly if the liver iron is over 15 mg/g dry weight, up to
- 3 yearly if liver iron is below 5 mg/kg dry weight as long as other indicators of iron loading remain stable and low [ferritin, liver iron on T2*].

6.3.4. Modifying Chelation Treatment.

1 Patients with acceptable iron stores *(Serum ferritin consistently 1000±500 µg/l, liver iron < 7 mg/g dry weight, Cardiac T2* >20 ms.)* If patients are content to continue regular desferrioxamine, switching is not necessary. Maintain desferrioxamine 20-30 mg/kg 5 infusions per week, up to 50 mg/kg/day for adults. Oral chelation should be offered if patients would prefer, and there are no contra-indications. This will usually be deferasirox 14-21 mg/kg/day. In older children and adults, if there are adverse effects to desferrioxamine and deferasirox, deferiprone 75mg/kg/day in three divided doses may be considered.

It is important that a therapeutic index for desferrioxamine of < 0.025 is maintained at all times. Significant side effects as mentioned above are unlikely to occur when the mean daily dose (mg/kg) /current serum ferritin (microg/L) remains below 0.025

2 Patients with increasing or high iron stores and normal Cardiac T2* *(Serum ferritin consistently >1500 µg/l, and/ or liver iron >7 mg/g dry weight, Cardiac T2*>20 ms.)*

Patient on desferrioxamine: Can try optimising dosage and adherence as far as possible, but usually this will have been tried: try switching to deferasirox if no contra-indications.

Patient on deferasirox: Optimise dosage and adherence to deferasirox. For patients treated with deferasirox, it may take years for ferritin and liver iron to reach target levels. Deferasirox should be continued provided there is a trend to decreasing iron levels with dosage increases as required within the licensed range (up to 28 mg/kg/day) in increments of 5 mg/kg as tolerated.

3 Patients with increased cardiac iron *(Cardiac T2* <20 milliseconds.)*

Increased cardiac iron and high liver iron stores: (Serum ferritin consistently >1500 µg/l, and/ or liver iron >7 mg/g dry weight, Cardiac T2*<20 ms.) Switch to combination desferrioxamine 30 mg/kg x 5 per week plus deferiprone 75 mg/kg/day seven days per week. The dose and frequency of desferrioxamine and dose of deferiprone should be determined largely by the cardiac T2* value, pushing to deferiprone 100 mg/kg /day if cardiac iron is substantial, and as many desferrioxamine infusers per week [ideally 24/7] as the patient can manage to use.

Increased cardiac iron and acceptable liver iron stores: (Ferritin consistently 500-1500 µg/l, and liver iron <7 mg/g dry weight.) Consider switching to deferiprone pushing to 100mg/kg/day seven days per week.

4 Chelation in patients with iron-induced cardiac failure

It is imperative for the management of decompensated cardiac failure that early input from a cardiologist with experience of acute management of cardiomyopathy in general and haemoglobinopathies in particular is sought; refer immediately to a tertiary centre.

There is a concensus statement from the American Heart Association which outlines accepted best practice for this clinical emergency, in summary:

- 24 hour iv desferrioxamine [50 mg/kg/day]
- PLUS oral deferiprone pushing to to 33 mg/kg/day tds [100 mg/kg/day]
- *Avoid* inotropes – tolerate low BP if renal and cerebral perfusion is OK
- Maintain pre-load… *minimise* diuretics; filtration if need be
- Correct electrolytes
- Amiodarone for dysrhythmias, β blocker if BP allows
- Meticulous glucose control
- Hydrocortisone at replacement dose in case adrenal insufficiency
- Look for infection
- Maintain Hb 100 – 120 g/l

Cardiac function may recover relatively rapidly, but sustained compliance with an appropriate chelation regime over several years will be required for reversal of cardiomyopathy and normalisation of cardiac iron levels.

6.3.5. Administering chelators and monitoring for side effects

Desferrioxamine.

Patients should be taught how to administer subcutaneous desferrioxamine infusions. The

training and performance should be documented in the patient's records. Their technique should be assessed regularly. Means of facilitating the delivery of desferrioxamine such as Thalaset® needles, anaesthetic cream or freezing spray, disposable elastomeric pre-filled infuser pumps should be offered to all adults: a majority of patients find home reconstitution and the mechanical syringe drivers inconvenient / heavy, and they receive home delivered pre-filled 'balloon pumps'; see also comprehensive patient information sheet.
Ascorbic acid should be taken around the time of starting each desferrioxamine infusion, from about a month after starting to use regular desferrioxamine.
Offer / prescribe local anaesthetic cream or freezing spray to apply to the skin before needle insertion, for children and any adults who find it painful.

Monitoring for adverse effects should include:

- annual audiometry [checking for high tone hearing loss] in all ages, and
- annual ophthalmology checks in all ages.

Desferrioxamine should be stopped if there are symptoms of gastrointestinal disturbance (abdominal pain, severe diarrhoea) or high fever. Patients should be aware of the risk of overwhelming infection due to Yersinia and Klebsiella, and seek medical attention as soon as possible if they have symptoms or signs of severe infection

Deferiprone therapy [alone or in combination with desferrioxamine].
Patients should be monitored carefully for side effects of deferiprone, with ***frequent blood counts to detect neutropenia or agranulocytosis***. Patients should be regularly reminded of the side effects of deferiprone, and should understand that if they develop fever or symptoms of infection, they should ***stop the medication and immediately attend for a blood count.*** They should carry a treatment card indicating they take deferiprone, contact details of their treating doctor, and what action should be taken if they seek medical advice after becoming unwell.

Nausea / constipation may occur in the early weeks of use; if the child can persevere - at a reduced dose working up to full dose if necessary – these GI side effects often subside.
Joint pains or swelling are uncommon in children, but may occur in older children and adults. ANA / Rheumatoid factor should be checked. If the symptoms are severe, or there is any evidence of actual arthritis, more than just some discomfort, the medication may need to be stopped altogether and a different chelator regimen chosen instead.

Deferasirox
The current formulation is film coated, so is just to be swallowed with a drink, not necessarily on an empty stomach. It can be ground up and put into a spoonful of soft food such as yoghurt.
Patients should be monitored carefully for side effects of deferasirox, with urine analysis for proteinuria [request protein creatinine ratio], serum creatinine and liver function testing at baseline (in duplicate) and renal function and liver function checks weekly for the first month, and after increasing the dosage. These tests should be done monthly thereafter.
Audiometry and ophthalmology checks should be done at baseline and bi-annually thereafter.
Deferasirox should be interrupted if serum creatinine rises to 33% above average baseline

level or on appearance of significant proteinuria with no other cause [eg UTI] , or if transaminase rise is persistent or progressive.
A florid rash can occur, which necessitates stopping the medication. GI side effects can sometimes cause the patient to request transfer back on to another agent. Avoid other medications which can cause gastric irritation such as NSAIDs.

Table 2 summarises regular monitoring tests which should be performed for patients receiving chelation:

** indicates – as part of regular monitoring rather than for specific drug related side effect*
*** monitor more frequently again like this after dose change*

Medication	**Test**	**Required prior to commencing treatment**	**Then @ frequency :**	
Desferrioxamine Deferasirox Deferiprone	FBC	Yes* Yes* Yes	Pre –each transfusion Recommended weekly, in practice usually before each transfusion AND IF ANY FEVER OR SYMPTOMS / SIGNS OF INFECTION	
Desferrioxamine Deferasirox Deferiprone	Serum ferritin	Yes Yes Yes	3 monthly Monthly 3 monthly	Reduce dose when ferritin below 1000ug/l Reduce dose when ferritin below 1000ug/l, interrupt if < 300 ug/l Reduce dose when ferritin below 500ug/l
Desferrioxamine Deferasirox	Serum creatinine Serum creatinine [ctd]	Yes* Yes – on 2 occasions	Before transfusion Weekly for first 4 weeks, then monthly **	 Deferasirox: dose adjustments per renal function

Deferiprone		Yes*	Before transfusion	tests – see table 3 below Deferasirox is contra-indicated in patients with a creatinine clearance < 60ml/min. Return to checking weekly for 4 weeks after any dose adjustment.
Deferasirox	Urine protein : creatinine ratio	Yes	Monthly	For other chelators, uPCR not routine, only if concern about renal function, or symptoms, or other causes for proteinuria eg diabetes mellitus
Desferrioxamine Deferasirox Deferiprone	LFTs	Yes* Yes Yes*	Before transfusion 2 weekly for first 4 weeks, then monthly**	 Deferasirox: reversible mild increase in LFTs is a known side effect. Interrupt treatment there is a persistant or progressive increase in transaminases. Deferasirox is contraindicated in severe hepatic impairment [Child-Pugh class C].
Deferiprone	Zn		Yearly	

Desferrioxamine Deferasirox	Audiology and ophthalmology testing	Yes Yes	Yearly Yearly	Consider alternative chelator if affected

Table 3 – deferasirox dose adjustment according to renal function tests:

Reduction of daily dose by 7 mg/kg/day (film-coated tablet formulation), *if following renal parameters are observed at **two** consecutive visits and cannot be attributed to other causes*			
Adult patients	>33% above pre-treatment average	and	Decreases <LLN* (<90 ml/min)
Paediatric patients	> age appropriate ULN**	and/or	Decreases <LLN* (<90 ml/min)
After dose reduction, interrupt treatment, if			
Adult and paediatric	Remains >33% above pre-treatment average	and/or	Decreases <LLN* (<90 ml/min)
*LLN: lower limit of the normal range **ULN: upper limit of the normal range			

6.4. Vaccinations and hyposplenism

Patients with SCD should be on prophylactic dose penicillin 250mg p.o. b.d. as they are often functionally hyposplenic. If penicillin allergic prescribe erythromycin 500mg mg p.o. b.d.

Recommended Vaccinations for People with Sickle Cell Disease

Adults with sickle cell disease who have not received primary vaccination as part of the national schedule in the UK should be offered:

- One dose of HIB/Men C
- One dose of Men ACW&Y conjugate vaccine one month later
- Two primary doses of men B vaccine one month apart [this can be at the same visits as the other vaccinations above]
- A single 0.5 ml dose of pneumococcal conjugate vaccine (PCV13) [which should be given at least six months after pneumococcal polysaccharide vaccination (PPV23) if this has been previously administered]

Adults with sickle cell disease who received their primary vaccinations should also be offered:

- Pneumococcal polysaccharide vaccination (PPV23) [given 6-12 months post PCV13] and at five-yearly intervals thereafter.
- Annual influenza vaccination
- Hepatitis B vaccination if they have not previously received it and are non-immune (anti-HBs antibody titre < 100 mIU/ml).

6.5. Psychological Support

Sickle cell disorder (SCD) is a lifelong, life limiting inherited blood disorder. Patients with SCD may suffer with chronic anaemia, the alteration to red blood cells caused by the condition can result in blockages to small blood vessels leading to ischaemic damage to joints and organs and to chronic pain conditions. Chronic pain and episodes of acute pain known as a sickle crisis can result in the long term use of opioid analgesic medication with associated side effects of tolerance and dose escalation, physiological dependence and hyperalgesia. Patients with SCD are susceptible to infection and stroke and cognitive impairment as a result of chronic cerebral ischaemia. Additionally this is a BME group that may face societal discrimination as well as stigmatisation from within their own family and cultural groups leading to chronic loss of self-esteem and at times highly entrenched chronic shame. Socio-economic difficulties are common in this group as completing education and maintaining employment can be a challenge.

The 2018 Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK highlights the role of stress, depression, fear and anxiety in the pain experience of individuals with SCD and the importance of adopting helpful coping strategies when managing pain. The standards state that:

- All people with SCD should have access to psychology support.
- Core staffing of specialist centres should include a psychologist with specialist experience in SCD.
- Psychological assessment should be carried out at least annually
- Neuropsychological assessment should be carried out as appropriate

- Psychological therapies including CBT should be offered as required for individuals and groups.

Following the NHS England Service review, Specialist Haemoglobinopathy Teams (SHT) are required to provide adequate and accessible clinical psychology support for adults and children, adequate being defined as >0.5 WTE per 200 patients. This follows concerns about poor access to psychology that were highlighted after the Peer Review Programme for Health Services for People with Haemoglobin Disorders 2014-16. Many services lacked dedicated support from psychologists with specialist expertise in haemoglobin disorders; and many services had poor access to neuropsychology. Recommendations to NHS Trusts included a review of specialist psychology and neuropsychology provision available to services (www.wmqrs.nhs.uk/publications).

The role of the psychologist in the Haemoglobinopathy Team is defined as follows:

- Provide psychological assessment, psycho-education, and evidence-based therapy to patients and families
- Provide psychological support within the Transition Service for young people and their families
- Contribute to annual reviews of patients attending clinics by screening for concerns re mood, quality of life and coping.
- Attend multidisciplinary team ward rounds
- Provide neuropsychological assessment and recommendations or facilitate such assessments as necessary
- Facilitate support groups
- Offer consultation and support to staff
- Liaise with health, social and education professionals
- Contribute to multidisciplinary team guidelines, protocols, research and education.
- Support multidisciplinary chronic pain service

Further requirements for the Psychology Service:

- Permanent contracts are necessary to ensure consistency and stability in psychology provision. This is especially important when working with people with haemoglobin disorders where building trust over time is vital in order to engage patients with psychological support.
- Effectiveness of the psychologist will depend on factors such as: stability of the haemoglobinopathy team in terms of staff turnover; willingness of haemoglobinopathy team to take on board psychological approach to patient care; provision of clinical nurse specialists (who can provide level 2 psychological skills under supervision); administration support.

Psychologist Qualifications:

- If the service for people with haemoglobin disorders has a sole psychologist, they should be at least a band 8a or above.
- Psychology services can be provided by a clinical, health, or counselling psychologist provided they have the relevant competencies and experience required for this specialist area of work.

- Psychologists must have completed the British Psychology Society accredited doctoral training in clinical/health/counselling psychology (or statement of equivalence)
- Psychologists must be eligible for Health and Care Professions Council registration as Practitioner Psychologist (Modalities: Clinical or Health or Counselling Psychologist)

6.6. Travel and SCD

(Adapted from J Travel Med. 2014 Sep; 21(5): 332–339.)
There have been very few systematic studies or even case series of international travel in the SCD population. Still, the general theme emerges that as compared with otherwise healthy travellers, the SCD population is at substantial risk of a medical complication while abroad. The most frequent complications included:

- Veno-occlusive crises (precipitating factors associated with travel, include dehydration, infection, altitude, and weather changes)
- Bacterial infections (especially in children)
- Malaria

Travel vaccinations and prophylaxis:
All patients with SCD are recommended to have the routine vaccinations as specified under section 6.4: vaccinations and hyposplenism. Travel-specific vaccinations and prophylaxis will depend on the destination and a Travel Clinic can best provide information. Patients with SCD should have the same precautions as all other travellers. Hepatitis A should be considered for countries where this is optional. Live vaccines, such as yellow fever vaccination, may be given to SCD patients before travel to endemic areas in Africa or the Americas, but caution is recommended for patients on hydroxycarbamide. Both injectable and oral attenuated typhoid vaccinations are acceptable in SCD patients. There is no evidence that patients with SCD are at particular risk from the oral attenuated typhoid vaccine.

Air Travel and Altitude:
Flying in pressurized aircrafts usually poses no major problems for sickle cell patients, although occasionally severe and life-threatening complications have occurred during or several days after a flight. The most important considerations are to dress warmly, drink plenty of fluids, and to move about the cabin as often as possible. However, the cabin pressure on board most commercial aircraft is generally set to approximately 5000 to 7000 feet (1500 to 2100 meters) and this is associated with a drop in arterial oxygen pressure (PaO2) that may adversely affect patients with SCD. During air travel VOC may occur in up to 8.7% of patients with HbS. At mountain altitudes, patients with SCD may have a risk for developing VOC as high as 38%. Complications such as splenic infarction have been noted at high altitudes (over 10,000 feet or 3000 meters) even in patients with sickle cell trait! Children, HbSC an HbS/beta(+) patients appear more at risk of in-flight splenic sequestration, possibly because the more severe phenotypes will have had significant splenic infarction beforehand.

There is no evidence-based guidance on whether to use prophylactic oxygen during flights. Patients with a very severe phenotype would benefit from (exchange) transfusion prior to flying. Most Medical Professional Organisations recommend against routine prophylaxis; an

exception would be individuals with known hypoxic lung disease or patients already receiving oxygen at home. A careful history about previous exposure to flights and signs or symptoms, taking into account the severity of the phenotype is helpful for decision making. Others have propagated an hypoxic stress test prior to flying in order to assess the risk of developing VOC.

The Civil Aviation Authority takes a more defensive position and recommends that all SCD patients should travel on oxygen for flights of 5 hours and longer.

At present, in the absence of a clear indication as mentioned above, it is recommended that individuals with SCD can and should request oxygen if they become short of breath during air travel, similar to those passengers without SCD. Unfortunately, one has to take into account that rules and regulations with regards to the (very limited) availability of oxygen for medical use on board of aircraft vary between airlines and aircraft types. The safest recommendation would be to contact the airline at the time of booking and enquire about oxygen. If airlines are not willing to provide medical oxygen, it remains the patient's own responsibility to arrange for an appropriate supply. There are various commercial organisations hiring out equipment – see Appendix 6 for UNVERIFIED information as an example

Prolonged air travel is a well-established risk factor for venous thromboembolism (VTE). SCD itself is also a thrombophilic state. Current recommendations, however, rely only on individual assessment of thrombotic and bleeding risk factors. Knee-high graduated compression stockings or a single dose of low molecular weight heparin are options to prevent travel-associated VTE in select cases.

Travel letters and medical insurance:
Patients should also discuss their plans with their haematologist. All patients should plan to carry a letter from their haematologist explaining diagnosis, treatment plan (including prescription of narcotics and other medications), and complications of disease. This may serve to facilitate appropriate medical care overseas. Patients may also require permission to carry medications on board the aircraft. All medications should be appropriately and clearly labelled. This is particularly true for narcotic pain medications, which many patients with SCD require to manage pain crises. See appendix 5 for an example travel letter.

It is paramount to have proper travel insurance to cover any medical care or repatriation during travel, as well as a cancellation policy if applicable. Please note that insurance premiums are likely to be higher for people with sickle cell disorder. The Sickle Cell Society has published a list of insurers on their website who have treated SCD patients fairly.

7. OUTPATIENT MANAGEMENT AND ANNUAL REVIEW

All patients should be offered regular outpatient review to ensure screening for chronic disease complications and early instigation of treatment according to this guideline and national guidance. A comprehensive annual review by a specialist haemoglobinopathy team should be offered to all patients.

Organisational Considerations:

Where possible, adults with sickle cell disease (SCD) should be offered care close to home. Oversight of the clinical care is the responsibility of the regional specialist haemoglobinopathy team (SHT). To ensure that all SCD patients receive care in compliance with the standards the following organisational structures are suggested:

- Each individual hospital will need to make an annual inventory of patients with SCD attending their Trust and check if they are known to an SHT.
    - For patients known to the SHT, or new patients unaffiliated to an SHT, their details should be confirmed or updated to the SHT's data manager.
    - If the patient is known to an SHT outside the Trust's lot, the relevant SHT needs to be informed and discussed whether any local arrangements need to be made.
- The SHT is responsible for making sure that all patients within the area have a comprehensive annual review and that a specific management plan for the year is communicated to local teams where applicable.
    - Patients can be referred to the specialist clinic in the SHT
    - The SHT may also provide outreach clinics locally
    - The SHT may delegate the annual review to a local team with relevant expertise – the annual review report will still need to be forwarded to the SHT.
    - As an alternative, uncomplicated cases can be reviewed by the local team and discussed at the regional MDT chaired by the SHT.
    - A proforma should be used for the annual review visit to ensure thorough and consistent care and to facilitate data collection – this should also form the basis for the GP letter. Please see Appendix IV for an example of a proforma.
- In addition to the annual review agreements, all local hospitals should be linked with a named specialist centre with agreed pathways and protocols for advice and referral for acute and chronic complications. Please see Section 2 for all locally agreed pathways.
- All consenting patients should be registered on the National Haemoglobinopathy Registry (NHR) and annual review data and adverse events should be reported to the NHR. This is the responsibility of the SHT's data manager, unless agreed otherwise.
- All adverse events should be reviewed and discussed at the morbidity and mortality section of the regional MDT chaired by the SHT. See Section 2 for the MDT Terms of Reference and Proforma.
- The NHR/Annual Review data forms the basis for the continuous clinical governance by the SHT.
- In addition, specialist haemoglobinopathy teams should participate in a quality review programme of haemoglobinopathy services against nationally agreed standards.

Outpatient management and referrals:

Please refer to section 2 for local policies and pathways

Appendix I – Incentive Spirometry Protocol

PROTOCOL FOR THE USE OF INCENTIVE SPIROMETRY (I.S) IN SICKLE CELL DISORDERS

Patient Selection

All patients of 8 years of age or older who fulfil one or more of the following criteria:

1* Acute chest or back pain above the diaphragm
2* Receiving opiate analgesia
3* Clinical signs of respiratory infection
4* Consultant in change or patient specifically requests

Initiation of I.S. Programme by admitting doctor

5* Select patient for I.S. programme
6* Document selection in medical notes
7* Inform the nurse in charge of the ward on that shift
8* Refer any patient with signs of respiratory infection to the physiotherapist

The nurse in charge of the shift has responsibility for ensuring that the programme is commenced, and results documented.

Documentation

9* Incentive spirometry record sheets plus copy of the I.S. protocol should be kept with the patient's charts at the bedside.
10* A new I.S. record sheet should be completed for each 24-hour period.
11* On discharge, the ward clerk should photocopy the completed I.S. record sheets and place the copies in the I.S. folder. The originals should be kept with the patient's medical notes.

Incentive Spirometry (I.S.) programme

12* 10 maximal inspirations using incentive spirometer every 2 hours between 08.00 hr and 22.00 hr and while awake at night.
13* Completion of I.S. record sheet including measurement of pain scale and Sa02 prior to I.S. and recording of maximum inspiratory capacity achieved following I.S.
14* I.S. carried out with the patient sitting in an upright position.
15* Patients requiring >35% oxygen should continue with 02 therapy via nasal specs during I.S. breathing.

Discontinuation of I.S.

Medical staff responsible for deciding when to discontinue I.S. programme. Patients should fulfill all the following:-

16* Doctor considers patient unfit to continue for medical reasons
17* Chest and back pains subsided
18* Opiate analgesia discontinued
19* No clinical signs of respiratory infection

Appendix II – Protocol Acute Priapism

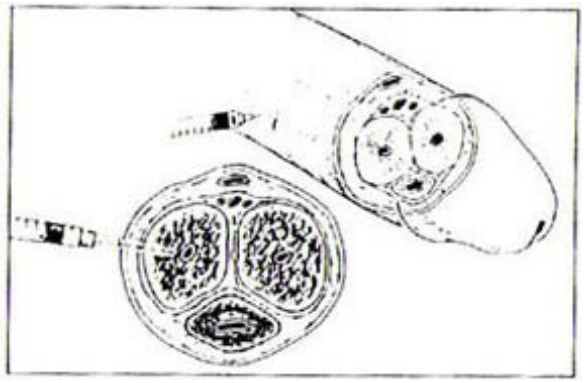
PROTOCOL FOR INTRACAVERNOSAL BLOOD ASPIRATION AND INJECTION
Modified from Whittington & UCH priapism guideline V2 October 2006

Requirements:

- Urethral catheterisation pack (if not available then dressing pack).
- Liquid skin antiseptic (chlorhexidine/povidone iodine)
- Green Butterfly needle (19 G needle)
- Heparinised (blood gas) syringe
- 20ml syringe for aspiration
- 10ml syringe for injection
- Phenylephrine 1% ie 10mg/ml - add 0.1 ml of phenylephrine 1% to 9.9ml of 0.9 saline or water for injection to produce 0.1mg/ml solution

PROCEDURE:

1. Written consent for procedure. Risks include pain and bleeding
2. Lay patient flat
3. Clean penis with antiseptic liquid
4. Hold penis by glans and insert needle into side of penis at midshaft level to a depth of 1cm (see diagram). Care should be taken to avoid the urethra and neurovascular bundle.
5. Aspirate blood with heparinised syringe and process through blood gas machine. At same time, send separate sample of penile blood in fluoride tube to Biochemistry for measurement of glucose.
6. Aspirate **up to 100ml blood** from penis with 20ml syringe. Blood should be thick and dark. Once blood becomes fresh, stop aspirating.
7. Inject phenylephrine 1ml every 5-10 minutes whilst monitoring the cardiovascular system.



APPENDIX III – Hydroxycarbamide Patient Information Sheet

North Middlesex University Hospital NHS
NHS Trust
Sterling Way
London N18 1QX
Direct Line: 0208 887 2428

Hydroxycarbamide [Hydroxyurea] treatment in sickle cell: Patient information sheet

Introduction

For decades, the treatment for sickle cell problems was limited to pain relief and fluids for pain episodes, antibiotics for infection, and blood transfusions for serious complications. Nor was it possible to alter the course of the condition, except by bone marrow transplant which is a complicated and risky treatment, not available in England for adults.

Since the early 1990's, a medication called **Hydroxycarbamide** [previously/also known as Hydroxyurea] has been found to help people with this condition a great deal. It increases the production of fetal (baby - type) haemoglobin. This is normally present in adults at a low level but if it is increased, it can reduce sickling. We know this because in newborn babies, when most of the blood is of the fetal type, sickling does not occur. Also, some people with sickle cell naturally go on making higher than usual levels of fetal haemoglobin as adults, and these people have fewer pain episodes and other complications, and also live longer. The medication also reduces the stickiness of the red blood cells and other blood cells, and most patients who take it find that it helps them.

What is Hydroxycarbamide?

Hydroxycarbamide is a drug that has been in regular use for decades, in the treatment of different blood disorders such as an over-active bone marrow, but more recently there has been a great deal of research into its use for people with sickle cell disorders.

What does it do for patients with sickle cell-disease?

The first strong evidence came from a large multi-centre study conducted in North America, and published in 1994. A large group of patients with sickle cell anaemia were entered into the study and received either Hydroxycarbamide capsules or an identical looking dummy drug called a placebo. Neither the patients nor doctors knew which they were taking, so that the benefits and any side effects could be monitored objectively. All patients were carefully followed up for a period of nearly two years initially. The majority of patients receiving Hydroxycarbamide noted significant clinical benefit, as compared with those taking the dummy drug. The improvements occurred in:

1* time from starting treatment to suffering a first pain episode
2* time after that to suffering a further pain episode
3* the number of episodes of chest crises, or lung sickling
4* the need for blood transfusion

Overall, the treated patients had fewer, less severe painful crises. About 8 out of 10 (80%) improved a great deal. In the years since this study was started, it has also become apparent that people taking the treatment are in better physical health (they can exercise longer, for

example) and that they are less likely to die than people with sickle cell who are not taking Hydroxycarbamide.

Over a prolonged follow up period, it has additionally now been shown that taking the medication can decrease mortality, or death from sickle related complications, by about 40%. There is also evidence that, with prolonged use, it can reduce the risk of sickle damage to some vital organs, for example the kidneys and liver.

How does it work?

It appears to work in a number of ways:

- It increases production of fetal haemoglobin, as described above. This takes some weeks or months to take effect.
- It decreases the stickiness of the young red cells: if these cells stick to the blood vessel lining, they may start a crisis. Hydroxycarbamide produces this effect much more quickly, in as little as a week or two and this is thought to be the reason why some patients notice that they feel better, with fewer pains, quite soon after starting the treatment
- It reduces the number of white blood cells (leucocytes) in particular neutrophils, which are often raised in number in people with severe sickle cell. This may be important because the white cells produce chemicals that can cause inflammation and might speed up sickling. Having fewer white blood cells makes this less likely.
- It improves levels of a chemical called nitric oxide in the blood; this helps the walls of the blood vessels to relax and so can help improve blood flow.

How do you take it?

Hydroxycarbamide comes in 500mg capsules that you take once a day by mouth. You begin at a low weight-related dose, and we can monitor how you respond to it – in yourself and in your blood counts. We usually increase the dose every 8 – 12 weeks until the medication is having its best effect for you.

What problems or side effects does it have?

All medication can have side effects; even drugs such as aspirin and Paracetamol, which people think of as safe, can occasionally cause serious problems. The risks associated with Hydroxycarbamide are low, but it has some side effects that you should be aware of:

a) It can cause a fall in your haemoglobin level, white blood count or platelets. For this reason you start on a low dose**,** working up to the dose that you need. You should have a blood test two weeks after starting, then further blood tests at 8 – 12 weekly intervals. When you have had a dose increase, again your blood should be checked after two weeks but then doesn't need to be checked again for a further 8 – 12 weeks. If at any stage your blood counts do fall, we will ask you to stop the medication until they recover, then re-start the medication, often at a slightly lower dose.

b) Therefore: at any time when you are on hydroxycarbamide, if you become unwell with sore throat, or any other symptoms or signs of infection and you take your temperature and find you have **a fever of 38 C or above**, you should inform a member of the Haematology Team right away, or come to the Emergency Department out of hours, for a blood check in case the white blood cells are low in which case we would start you on strong antibiotics.

c) It often causes some mild darkening of the skin and nails.

d) It can lead to some stomach or bowel disturbance, or to a degree of hair thinning, although these side-effects are not common.

e) It is important that you do not become pregnant, or make your partner pregnant while you are taking Hydroxycarbamide because it is possible that it could harm the baby if conception occurred while either parent was taking the drug. If you wish to start a pregnancy, you should stop taking Hydroxycarbamide for 3 months prior to becoming pregnant.

f) Although Hydroxycarbamide does not affect sexual function - the ability to have erections in men, or to produce eggs or have periods in women - there have been concerns that the drug may affect the sperm produced in men. Having severe sickle cell disease can itself cause this problem sometimes. At North Middlesex University Hospital, to be on the safe side we offer sperm analysis and sperm storage before starting Hydroxycarbamide therapy, until we have a clearer understanding of this possible effect.

g) People sometimes worry that Hydroxycarbamide could increase their risk of developing cancer or leukaemia. Now we have 20 years of long term follow up on many hundreds of patients taking it for long periods, we can reassure you that there is NO evidence of this; no increases in the numbers of cancers of any sort have been diagnosed in patients taking the medication.

In the UK, it is now recommended that we offer hydroxycarbamide to EVERYONE with sickle cell anaemia HbSS, or Hb Sβ^0 thalassaemia. This is on the basis of improved life expectancy, and reduced sickle damage to some vital organs including the kidneys and liver, as well as the expected benefits of reduced frequency and severity of pain crises, sickling in the lungs, and less need for blood transfusion.

People who have other types of sickle cell disease – Hb SC and Hb Sβ+ thalassaemia, may benefit from taking hydroxycarbamide as well, and in similar ways, although fewer research studies have been carried out in people with these conditions so the evidence is not so clear-cut.

You have been given this leaflet because the members of the Haematology Team at North Middlesex Hospital want you to be aware of the availability of this medication for you, and understand its use in sickle cell, and would like you to consider starting on it because of the expected benefits outlined here.

Please do read this leaflet, and discuss it with friends and family and read around it on the internet if you wish. The team will be happy to discuss it further in the Clinic and to answer any questions you have about Hydroxycarbamide treatment. After that, you would be free to start on it at any time.

A.Y November 1998. Revised November 2001, February 2007, September 2009, September 2012, November 2015, January 2019.

APPENDIX IV – Example of Annual Review Proforma

Patient's Name: **Hosp No:**

DOB: **Diagnosis:** **Performed by:**

Hospital: **Consultant:** **NHR: Y / N / Declined**

HISTORY				
Any subjective problems: Number of ED attendances / admissions in last 12 months:				
SOCIAL				
Education / Employment: Smoking: Alcohol:				
FAMILY PLANNING				
Children: Y / N Partner tested: Y / N Plans				
EXAMINATION				
Pulse:	BP:	O2 Sats:	Weight: ↑ ↓ Stable	Other:

Physical examination:	**Tick which apply:**
Heart Chest / Lungs Liver / Spleen Hips / Shoulders Other	Acute chest syndrome Priapism Pulmonary hypertension Renal dysfunction Retinopathy Ankle ulceration CVA Asthma VTE Alloantibodies AVN Hip / Shoulder Other

TREATMENT
Penicillin prophylaxis Y / N **Penicillin treatment dose when unwell** Y / N **Folic acid** Y / N **Hydroxycarbamide** Y / N Dose: Date commenced: Latest F%:

Analgesia (home / hospital):

Other medication:

BLOOD RESULTS REVIEW / date			
Hb g/l Neutrophils x 10 /l Platelets x 10 /l Creat umol/l Bili umol/l ALT u/l Vit D Urine PCR mg/mmol		Ferritin ng/ml Transferrin saturation % Hb S% or S+C % [if transfused] HbF % Others: [if iron overload] Glucose Calcium Thyroid function	

BLOOD TRANSFUSION

Blood Transfusion in last 12 months Y / N how many units
Lifetime cumulative <20 20-50 50-100 >100 units

Transfusion history: Top Up transfusions Y / N Exchange transfusions Y / N

Iron chelation currently receiving (ring and insert dose):

Desferrioxamine Deferiprone Deferasirox [Exjade]

SPECIALIST CLINICAL REVIEW IN LAST 3 YEARS

Ophthalmology date: outcome: Next review:

Echocardiogram date: outcome: Next review:

Other:

Virology / Vaccinations: Results /date HBsAg HBsAb HBcAb

HBsAb level: revaccination needed Y / N
Pneumovax II date: revaccination needed (date):
Prevenar date
Influenza vaccine: Yes / No date:

Hepatitis C Serology: HCV IgG Yes / No / NA Date:
Results:

Other

Summary of referrals / actions / management changes recommended:

1.

2.

3.

4.

5.

APPENDIX V: Example Travel Letter

North Middlesex University Hospital NHS
NHS Trust

Sterling Way
London N18 1QX

Direct Line 020 8887 2428
Direct Fax 020 8887 4034
Appointments 020 8887 2379

Haematology Department

Date: ……

TO WHOM IT MAY CONCERN

Re :

…… who is under the care of this hospital suffers from sickle cell ……., an inherited condition in which as well as anaemia there may be painful "crisis" affecting the bones or other organs. For this reason…. he/she …carries a small supply of strong painkillers. These are strictly for medicinal purposes and should not give rise to any concern. He/She…… is normally well, and there should be no problems during the flight provided the right preventive measures are taken.

1. He/She should be offered a drink frequently, at least hourly, as dehydration can precipitate crises.

2. He/She should be allowed to mobilise freely, when flight regulations allow.

3. If there is any suggestion of falling oxygen levels, he/she must be given inhaled oxygen immediately. For longer flights (over 5-6 hours), it is recommended that some patients travel on oxygen for the entire duration of the flight (CAA Guidelines). Since most airlines do not routinely carry extra oxygen, it is important that the passenger informs the airline in advance (ideally at the time of booking) about his/her requirements.

I would not expect her/him to experience any problem during the flight, but it would certainly help if the above could be observed.

Yours faithfully

Dr ……..
Consultant Haematologist

North Middlesex University Hospital
NHS Trust

North Middlesex University Hospital NHS
NHS Trust

Sterling Way
London N18 1QX

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Haematology Department

Date: ……

FLYING WITH SICKLE CELL ANAEMIA

Dear ……..,

Please find important information on flying with Sickle Cell Anaemia (SCA) below.

Whereas most people with SCA have travelled by air many times without any problems, the prolonged exposure to lower oxygen levels at cruising altitude can in fact trigger a crisis. These crises can be mild, but sometimes also severe and may either happen during the flight, but also a few days later.

The Civil Aviation Authority recommends that all patients with SCA should travel with, or at least have access to supplementary oxygen for the entire duration of the flight. Also, it is incredibly important **not to travel by air within 10-14 days after a sickle cell crisis**.

Most airlines will be able to supply oxygen to passengers on flights longer than 5-6 hours for free, provided that the **passenger will inform the airline in advance.** Important to realise is that most airlines limit the supply to very few passengers, sometimes only to one single passenger. If that is the case, the **passenger will need to arrange for their own portable oxygen** and inform the airline about their arrangements.

In brief, we recommend taking the following steps:

1. Discuss the need for supplementary oxygen well in advance with your consultant.
2. Please make sure you have appropriate travel insurance, covering medical costs abroad and/or repatriation. The Sickle Cell Society has published a list of insurers on their website that offer fair packages for people with sickle cell disorder.
3. At the time of booking the ticket, contact the airline about the need to travel with oxygen – also if this is for emergency use only.
4. The airline will most likely provide you with a form. Part 2 of this form will need to be completed and signed by your consultant.
5. If the airline indicates that they can't provide oxygen on board, it is your own responsibility to contact a supplier of portable oxygen and make further arrangements. The haematology department at North Middlesex University Hospital has an information leaflet with some suppliers, but we cannot actually arrange portable oxygen for you ourselves.

Yours faithfully

Dr …….
Consultant Haematologist

APPENDIX VI: Organisations providing holiday oxygen

NOTE: This is currently unverified information from the internet

Holiday information for people requiring Oxygen

This information leaflet aims to help you have a happy and relaxing holiday in the UK and abroad.
It is written for people who are using oxygen treatment, and who wish to travel by plane or go on a cruise with their families and carers. It contains guidance relating to a number of airlines that fly into and out of the UK, and summarises each one's policy for carrying and using oxygen on board. If you need oxygen for use throughout your holiday, you will need to make arrangements for the oxygen to be provided before you travel. Your home oxygen supplier will not be able to provide oxygen.
If you are travelling outside of Europe you will need to contact an oxygen company that supplies the country that you will be visiting. To find an oxygen provider you could contact the British consulate in the country you are travelling too.

Air Liquide: Your current supplier of oxygen at home
Contact number: 0808 143 9991

- Will supply oxygen to anyone travelling to a destination in England Scotland they will require at least 3 working day's notice.
- They will also supply oxygen to people who require it to fly but this will be at a charge. The charge will depend on how much oxygen you require. There is also a refund when the cylinders are returned back to Air Liquide.
- For patients travelling to Wales or Ireland you need to contact an alternative oxygen supplier called **Air Products** (0800 373 580) they will supply oxygen and will need at least 2 weeks notice. This is at a cost £66 per week for a concentrator they also supply portable cylinders at a cost depending on your requirements.

- This may be subsidised if you hold a EHIC (European Health Insurance Card (OLD E111)

Omega –Advanced Aeromedical (Cruises)
Contact 01273 308176 or 07860 458277

- Specialise in making it possible for the oxygen dependant patients to enjoy a much needed holiday break including cruises flights and hotels.
- They offer several rental programmes to suit each individual, as everybody's needs are different….some patients require it for 24hr/day some for bedtime only, some only on exertion
- They can supply oxygen equipment to cruise ships, including oxygen concentrators (compatible with cruise ship power supplies) Portable oxygen and Liquid Oxygen Therapy (LOX)
- You will need to provide a copy of your oxygen prescription
- All cruises out of Southampton Dover and Harwich are serviced by Omega Advanced Aeromedical.
- They are recognised by all major cruise and air liners
- Once you have confirmed your requirements, your oxygen equipment will be installed into your cabin prior to arrival.
- You are provided with a personal meet and assist service at the port to ensure your boarding is made easy

Omega-Advanced Aeromedical (Flight Oxygen)
Contact number: 01273 308176 or 07860 458277

- They recommend that patients requiring in-flight oxygen should book flights with an airline that provides in flight oxygen
- However if your airline does not provide oxygen contact omega to discuss your flight options.
- Whatever your oxygen requirements, they have the equipment and the expertise to deliver the right service to you

Pure 02 0800 145 59 02 (UK 9-5 pm) 0870 712 0202 (UK 24 hours)

- Pure 02 specialise in providing the latest portable and stationary concentrators for oxygen users whilst travelling
- Whether you live in the UK or are travelling abroad
- Rental department is open 24 hours day with all the advisors fully qualified to help make the most of your holiday.

• Before Pure 02 can hire (or sell) a concentrator they will need confirmation of your oxygen requirements. Patients will need to contact Pure 02 by phone and inform them of their oxygen requirements; they can fax or post a letter to them with their oxygen prescription.
• They deliver to fixed UK and European addresses, UK hotels or alternatively personal collection can also be arranged.
• All holiday rentals are VAT exempt for UK residents, with complementary delivery service and collection service once your holiday has ended.
• Prices vary depending on the patients' needs but start from £170

Tens Mecical Contact No: 0121 355 6555
Tens Medical Services Ltd is a family Business which started in 1996. The company grew at phenomenal rate and now the business specialises in a much wider variety of home health products – including the sale and hire of Oxygen Concentrators. For example:
Respironics SimplyGo
• Portable Concentrator
• 1-6l/min pulse dose
• 0.5-2l/min constant flow
• £155 a week to hire, additional weeks £100

£40 Delivery and collection (unless you collect yourself)
Respironics EverGo
• Portable Concentrator
• 1-6l/min pulse dose
• £135 a week
• £350pcm

European Health Insurance Card (OLD E111)
• We recommend you obtain the above card for added insurance
• The card is free to everyone and can be downloaded from the internet or obtained from the post office
• The card is not an alternative to travel insurance
• It will not cover any private medical healthcare
• It is important to have both EHIC and a valid private travel insurance policy.
• The card should be carried with you at all times when on holiday as some hospitals can be very particular when giving out treatment ie: if you can't produce the card there and then they may not treat you!!
• The EHIC entitles you to free or reduced cost medical treatment that becomes necessary during your trip if you are ill or have an accident.
• This includes treatment for long term or pre-existing medical conditions.
• The card gives access to state provided medical treatments only, and you will be treated on the same basis as someone who lives in the country you are visiting.
• This may not include all the things you would expect to get free of charge on the NHS.
• It may also mean that you have to pay something towards the cost of your care.
• The European Health Insurance Card (EHIC) can be used to cover any necessary medical treatment due to either an accident or illness within the European Economic Area (EEA)

Fitness to Fly
Most people with existing medical conditions are able to fly without difficulty, however occasionally certain precautions need to be taken. A fitness to fly form is required to be completed when:
• Fitness to travel is in doubt as a result of recent illness, hospitalisation, injury or surgery.
• If you have an existing unstable medical condition
• You wish to use medical equipment or therapeutic oxygen on board.
• These forms will be given to you by your airline or GP and come at a cost as your GP has to fill them in. **(They are not available from your Respiratory Nurses)**

Hypoxic Challenge Test (HCT)
This is used to assess whether Patients need in flight oxygen. Patients with severe airway disease, those recently hospitalised for acute respiratory illness or previous air travel tolerance with respiratory symptoms (shortness of breath, chest pain, confusion or syncope) require assessment before flying. This test is requested by your Consultant, Nurse, GP and will be performed in the hospital lung function laboratory. HCT (Hypoxic challenge test) stimulates cabin pressure using 15% oxygen.
Airline Oxygen Policies

- The following information is for people who require oxygen to fly
- It contains details of a number of commercial airlines that fly into and out of the UK
- Summarises each ones policy for carrying and using oxygen on board
- Different airlines require medical certificates or forms which can be obtained from your GP **(Not your Respiratory Nurse)**

EastJet Do not provide supplementary oxygen but you are allowed to carry 2 x oxygen cylinders of your own on board, you will need a medical certificate confirming the cylinders are required for medical reasons.
Oxygen concentrators (either mains or battery powered) are permitted on board and medical certificate is not required. Batteries will need to be use on board (be sure the batteries have enough power for the duration of the trip, including possible delays)
British Airways can provide in flight oxygen free of charge on all flights but this is restricted to one passenger per flight. Contact their passenger medical clearance unit for availability and advice about flow rates. British Airways cannot provide ground oxygen whilst in transit through the airport.
Virgin can provide in flight oxygen free of charge on all flights but this is restricted to one passenger per flight. Contact their passenger medical clearance unit for availability and advice about flow rates. Virgincannot provide ground oxygen whilst in transit through the airport.
Emirates can provide on board oxygen subject to availability and with at least 48 hour's notice. A Doctors certificate is required advising of the litres per minute. There is no charge for the service, although your GP may charge you for the certificate.
Jet2 is unable to supply oxygen for use on board its flights. However you may carry your own therapeutic oxygen, subject to having applied for and received appropriate medical clearance from the airline. You will need to provide a medical certificate confirming that oxygen is required for medical reasons and confirmation that you are fit to fly, for which you need to contact your GP.
Ryanair if passengers require oxygen for use during the flight they should notify the Ryanair special assistance line, preferably on the same day as the booking is made as there is limitation on this service. The airline will then send you a medical clearance form, which must be completed and returned to Ryanair. You must also carry your fitness to fly certificate with you.

SECTION 2: LOCAL PATHWAYS AND POLICIES AT NNUH

1. Haematology Team Contact Details:

Haematology Team

Consultants:	**Dr S Docherty** **Dr H Lyall** **(On call Consultant out of hours)**
Clinical Nurse Specialist	**Jo Read**
Transfusion Practitioners	**Ali Rudd, Kathy Ford, Janet Pring**
Specialist Trainees, ST doctors:	**DECT 2919**
Core Trainees, CT doctors:	**DECT 6043**
Haematology lab	**Extn 2909**
Blood transfusion lab	**Extn 2906**

Acutely Unwell adult patient with a Haemoglobin disorder

Local Hospital:

- Initial assessment by: Haematology team 08.30-18.30 (AMU team out of hours)
- Senior review by: Haematologist within 14h
- Please contact Haematology if patients with known haemoglobin disorders are admitted under other teams
- Local contact details haematology (24x7): SpR DECT 2919, Consultant DECT 6744, SHO DECT 6043

- Inpatient management:
    - Patients should go to Mattishall Ward if a bed is available under Haematology triage unless clear reason to triage to another specialty.

- Outpatient management:
    - Patients are seen in the M6 clinic (Drs Lyall/Docherty) and offered annual review in a specialist haemoglobinopathy clinic with a visiting haematologist from our Specialist Team (Dr Arne de Kreuk)

Escalation pathways:

- Agreed local ITU pathway / referral: patients who may need ITU escalation will be discussed with the ITU team by the attending Haematology consultant
- Facilities on site:
    - Top up blood transfusion 24x7
    - Manual exchange transfusion out of hours
    - Automated exchange transfusion Monday-Friday normal working hours – outside these times, patients will be discussed with the on call non-malignant haematologist at Addenbrookes
- Patients can be discussed with the SHT at North Middlesex Hospital

3. Local Referral Pathways

REFERRALS TO OTHER SPECIALITIES:

Summary of screening, management and referral for acute or chronic scenarios occurring in people with sickle cell disorders, from out-patient clinics.

Note! We are asked NOT to refer to colleagues for symptoms or problems unrelated to the primary diagnosis, unless clinically urgent [eg ? malignancy, 2 week maximum wait]. We can, however, refer for recognised complications, along established pathways, including:

Problem	What to do	When to refer	Who to refer to
Renal Disease	U&E, creatinine, eGFR + Urine for PCR at least annually In parallel with referral to Nephrology for those who need [see next column], request renal tract ultrasound and ensure recent calcium, phosphate, uric acid levels are available.	Heavy proteinuria, PCR >100mg/mmol Hypertension > 140/90 Declining e-GFR / rising creatinine. **Note!** Patients who have **normal renal function [e-GFR > 90 mls /min] and uPCR between 50 and 100 mg/mmol should be started on an ACE inhibitor** – usually perindopril 2 mg daily. Bring them back for a repeat uPCR after 2 months and if not improving, and blood pressure will tolerate it, increase to 4 mg, up to a maximum of 8 mg daily.	Consultant Nephrologist, NNUH
Haematuria	Urinalysis and MSU. Arrange US renal tract / IVU	Unless simple UTI and red cells clear from the urine after antibiotic treatment	Consultant Urologist NNUH
Priapism	Ask about this symptom routinely. For stuttering priapism, recommend trying emptying the bladder, hydration, oral analgesia, a warm bath and/or exercise such as jogging. Trial of medication: Ephedrine 15-30mg OD nocte or Etilefrine 25-50mg OD nocte	If symptom continues despite these measures	On call Urologist, NNUH
Retinopathy	Screen according to genotype and degree	routinely	Annual referral to Ophthalmology at

	of retinopathy		NNUH
Cardiac problem	If symptomatic, request ECG / 24 hour tape / echocardiogram as appropriate to symptoms. IF a patient with transfusional iron overload	Any abnormal findings on investigation which require specialist input	Refer to Consultant Cardiologist at NNUH Arrange cardiac MRI and discuss with SHT for advice
Pulmonary Hypertension	Routine echocardiogram, every 1 – 3 years, specifically asking for TR jet velocity	See flow chart below on page 32	Echo referral on ICE
Other chronic lung problems	Note history, request CXR / CT scan of chest as needed If chronic baseline oxygen, request lung function tests, sleep study and high resolution CT scan.	If suggestive of bronchiectasis or tuberculosis According to investigation results. If sleep disordered breathing	Consultant Respiratory Physician at NNUH Refer to Sleep Apnoea clinic
Symptoms suggestive of gallstones	Request ultrasound liver and biliary system	If gallstones identified, and any evidence of obstruction OR continuing symptoms, so that lap cholecystectomy would be considered	Consultant Surgeons NNUH
Orthopaedic problems	Examine range of movements at affected site. If pain in one joint for > 1 month – plain X ray and review with results. If no abnormalities seen but pain persists, request MR scan.	If evidence of AVN **shoulder** or impingement syndrome If evidence AVN **hip**	Consultant Orthopaedic Surgeon, NNUH

Ankle ulceration	Check appearance, take swab for MC&S, advise daily cleaning with saline solution, application of non-adherent dressing, firm strapping TOE TO KNEE all day, elevate when at rest. Give antibiotics to treat clinical infection / cellulitis [NOT just bacterial growth on swab, often colonised].	If not healing, deep, slough covered, heavy exudate.	If service not available through GP practice: Tissue Viability Nurse
Neurological problems	TIA / stroke usually presents acutely BUT if history of TIA or other neurology is given at clinic, do full neurological examination, request CT scan of brain + contrast	Always	On call Stroke Team via Stroke Alert Nurse ext 6588 if possible stroke/TIA
Patient requiring elective surgery	A discussion will be required in every case about the need for pre-operative blood transfusion and other preparatory management.	If surgery before next out-patient visit: Consultant will see the patient with you that day. Otherwise inform the patient that a management plan will be discussed and arranged with them by the Consultant at their next Haematology Clinic appointment.	Dr Docherty or Dr Lyall
		Also ask patient to inform Consultant via haematology secretary as soon as a date for surgery is confirmed.	
Chronic pain	Managed partially from clinic and in chronic pain MDT clinic	Discuss with patient referral to Psychology for help with non-pharmacological interventions. Consider if referral to	Outpatient referral to Pain Team at NNUH

		chronic pain team might be beneficial eg local nerve block etc	
Other issues in managing long term condition	Discuss in clinic and offer referral to counsellor as appropriate	When patient agrees it would be useful / accepts referral	**Ruth Marks**, Clinical Psychologist, NMUH, will take referrals from NNUH
Endocrinology	LH, FSH, testosterone / oestradiol R2 MRI scan of liver Bone mineral density scan (DEXA)	Abnormal findings or concerns	Consultant Endocrinologist NNUH
Fertility and Sperm Freezing		(Young) adult men prior to start hydroxycarbamide	Bourne Hall, Wymondham
Liver related problems	Conjugated and unconjugated bilirubin, Full LFTs, Abdominal ultrasound	Sickle cell hepatopathy, cirrhosis, unexplained hepatomegaly	Consultant gastroenterologist NNUH

4. Network MDT Terms of Reference

Haemoglobinopathy Network MDT Terms of Reference

Author: Arne de Kreuk, Consultant Haematologist
Date: September 2019

Background
Haemoglobinopathy Operational Delivery Networks (ODN) have been developed by NHS England to improve standards, quality and equity of care both regionally and nationally. The ODNs are commissioned centrally; the North Middlesex and East of England network operates a 'Hub and Spoke model'. North Middlesex Univrsity Hospital is the 'Hub' centre. During 2019/20, a haemoglobinopathy coordinating centre (HCC) will be allocated to oversee the quality and governance of the ODN.
The ODN Multidisciplinary Team Meeting (MDT) provides the means for thorough multidisciplinary review and discussion of patient management and care including the transition of teenagers. All ODN patients will be reviewed a minimum of annually. This can be via a face-to-face consultation during one of the outreach clinics in the local centres in the network, referral for annual review to the specialist centre or via a case review at this network MDT. However any patient can be (re-) referred at any time to the MDT. Morbidity and mortality will also be a fixed item on the agenda.

Organisation and Management of the MDT:
The meeting will be chaired by the hub and minimally attended by an adult consultant haematologist and a paediatric consultant haematologist.
Quorum: The meeting will be determined as quorate where there are either two NMUH consultants or one NMUH and one regional consultant present, and at least one CNS.

Meetings are held as follows (subject to change):

- **The second Tuesday of each even month from 11.00 -12.00**
- **The second Wednesday of each uneven month from 10.00 -11.00**

The MDT will be held via a telephone conference, allowing teams to dial in simultaneously.

The In the future, the aim will be to offer a video conference link as well but this is currently not feasible.
Any written patient communications are made via secure email @nhs.net

- The MDT coordinator at NMUH will send a reminder to the network members 1 week before the MDT meeting.
- An MDT proforma will need to be completed and returned for all referrals at the latest the Friday before the MDT.
- The discussion is typed into the proforma during the meeting, with the action/conclusion relayed to the team for agreement before moving on the next patient.
- Completed proforma are scanned and emailed to the presenting consultant, a copy retained at NMUH.

In case of a large number of referrals, the chair of the MDT will try to allocate a fair amount of time to all cases to be discussed or may choose to defer a case and/or discuss the case outside the MDT if appropriate. For practical reasons, it may be required to split the MDT in an adult and paediatric session in the future.

Data collection:
The network data manager will track the progress towards annual review of all patients within the network. Numbers of patients discussed at the MDT are collated, including where changes in management have been suggested.
Other key indicator data collected per centre include number of: admissions, ICU admissions, acute chest crises, manual exchange transfusion, deaths, new pneumococcal infection, pulmonary hypertension, strokes, priapism and other serious morbidity. This data forms the basis of an annual MDT report to be presented at the ODN each year.

Role of the MDT Chair:
The role of MDT chair is pivotal in ensuring that patients using the service are treated appropriately and to a high standard. The role involves monitoring and delivering performance according to national and local standards; ensuring that evolving requirements for the service are identified and action taken to support development. Specifically, it is the responsibility of the MDT Chair (this may or may not be the MDT clinical lead and should be nominated by the MDT core members) to:
1. Ensure that the team work effectively.
2. Ensure that care is given according to recognised guidelines with appropriate information being collected to support audit.
3. Lead on or nominate a lead for research to ensure mechanisms are in place to support entry of eligible patients into clinical trials, subject to patients giving fully informed consent.
4. Ensure attendance levels of core members are maintained. Poor levels of attendance will be addressed with individual members/Trusts.
5. Ensure that the meeting runs to time.
6. Ensure that each patient discussed has a clear discussion outcome documented.

Personnel Role/Service:
NMUH:
Dr Arne de Kreuk, network lead and MDT chair
Dr Marilyn Robert-Harewood, deputy MDT chair
Dr Olu Wilkey, lead for paediatric haemoglobinopathies
Dr Rosalind Mensah, deputy lead for paediatric haemoglobinopathies
CNS Liz ODeh (adults)
CNS Albin Bendiola (paediatrics)

Cambridge:
Dr Martin Besser, lead for adult haemoglobinopathies
Dr Emmy Dickens, lead for paediatric haemoglobinopathies
CNS Ruth Jolley, (adults)
CNS Clare Clarke, (paediatrics)

East & North Hertfordshire:
Dr Judith Hanslip, lead for adult haemoglobinopathies
Dr Fatima Kagalwala, lead for paediatric haemoglobinopathies

Norfolk & Norwich:
Dr Jo Ponnampalam, lead for paediatric haemoglobinopathies
Dr Suzanne Docherty, lead for adult haemoglobinopathies

Ipswich:
Dr Debo Ademokun, lead for adult haemoglobinopathies

Version 1.2 October 2019

5. Network MDT Proforma