

<b>CLINICAL GUIDELINE TITLE</b>	<b>Clinical Management of Sickle Cell Disease in Adults</b>
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### 1) SUMMARY

This guideline covers the management of clinically significant sickle cell disorders in adults and is directed at all clinical staff involved in the care of adults with sickle cell disease (SCD). SCD is associated with multiple disease-related complications the effective management of which requires a multidisciplinary approach. The most common indication for admission is acute painful crisis treatment of which should follow NICE guidance. Most adult patients with SCD will have been under follow-up since childhood but patients who present later in life with suspected SCD should be fully assessed to confirm the diagnosis and agree an individual management plan. All adults with SCD require regular follow-up to detect or prevent complications and identify the need for disease-modifying therapy. The patient and family should receive full and accurate information with support from experienced professionals.

### 2) INTRODUCTION

Sickle cell disease (SCD) comprises a group of conditions due to inheritance of the sickle gene and is now one of the most common genetic disorders in the UK with a birth prevalence of 1 in 2000. In developed countries most affected children survive to adulthood. The outcome for adults with SCD is less favourable with a significantly increased risk of early death in sickle cell anaemia the most common form of SCD. Prompt recognition and treatment of acute complications responsible for the majority of deaths in adults and early detection of secondary complications underpin effective clinical management of SCD.

### 3) DEFINITIONS

- A&E Accident and Emergency
- ACS Acute chest syndrome
- CMV Cytomegalovirus
- CNS Clinical Nurse Specialist
- CNS Central Nervous System
- CPAP Continuous positive airways pressure
- CRP C-reactive protein
- CT Computerised tomography
- CVS Cardiovascular System
- DFO Desferrioxamine
- DFP Deferiprone
- DFX Deferasirox
- FBC Full Blood Count
- HDCU Haematology Day Care Unit
- HDU High Dependency Unit
- HIV Human immunodeficiency virus
- ICHT Imperial College Healthcare NHS Trust
- IV Intravenous
- LDH Lactate dehydrogenase
- LFT Liver Function Test

MRI Magnetic resonance imaging  
MSU Mid-stream urine  
PCA Patient controlled analgesia  
PRN As needed  
SHO Senior House Officer  
SMAC Specialist Medicine Assessment Centre  
SpR Specialist Registrar  
U&E Urea and electrolytes

#### 4) SCOPE

This guideline is directed at all clinical staff involved in the care of adults with sickle cell disease (SCD). It applies to all patients known to have or who are diagnosed with SCD. SCD includes sickle cell anaemia (HbSS) as well as those compound heterozygous states (HbSC, HbSD, HbSO-Arab and sickle  $\beta$ -thalassaemia) and other less common conditions that give rise to a clinically significant sickling disorder. The guideline describes the clinical management of SCD. It should be read in conjunction with NICE Guidance on the management of sickle cell acute painful episode (<http://guidance.nice.org.uk/CG143>), BCSH Guideline on the management of Acute Chest Syndrome in Sickle Cell Disease 2015 (<http://onlinelibrary.wiley.com/doi/10.1111/bjh.13348/epdf>), RCOG Green-top Guideline No. 61 Management of sickle cell disease in pregnancy 2011 and Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK 2008.

The following aspects of care are described:

Criteria for urgent assessment and admission  
Admission procedure  
Management of acute complications  
Management of chronic complications  
Transition from paediatric to adult service  
Transfusion  
Reproductive health  
Surgery and Anaesthesia  
Hydroxycarbamide therapy  
Outpatient management

## 5) Full Guideline

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## **EMERGENCY ATTENDANCE: CRITERIA FOR URGENT ASSESSMENT AND ADMISSION**

If the patient presents with **any** of the following urgent medical assessment is mandatory

- **Septic shock (BP <90/60)**
- **Neurological signs or symptoms**
- **SpO2 <92% on air**
- **Symptoms/signs of anaemia Hb <50g/L or fall >30g/L from baseline**
- **Priapism >4 hours**

In addition to the above the following conditions require immediate admission:

- Extreme pain
- Pyrexia > 38°C (or hypothermia)
- Chest pain, tachypnoea or lung consolidation
- Abdominal pain or distension, diarrhoea, vomiting
- Acute hepatic/splenic enlargement
- Increasing jaundice
- Severe thoracic/back pain

## **ADMISSION PROCEDURE**

The haematology inpatient service is based at Hammersmith Hospital. All patients under regular follow-up have been issued with an access passport with information on how to contact and access the haematology triage service if they require urgent assessment for pain or other problems related to SCD. Patients should call the triage service which is staffed 24/7 by a nurse bleep holder on 020 3311 7788 and will be directed to attend either the ambulatory care pain management service located on the Haematology Day Care Unit in the Catherine Lewis Centre ( Mon – Sun, 8am-8pm; latest time for receiving patients 3pm) or to the Specialist Medicine Assessment Centre (SMAC) on B1 ward. The patient will be advised to dial 999 if clinically indicated (see below). On ambulatory care, patients are first assessed by the triage nurse and then the Haematology Day Care SpR or SHO (Bleep 9077). The patient must be assessed medically within 1 hour and if admission is deemed necessary transferred directly to a haematology ward or to SMAC if a haematology bed is not immediately available. The Red Cell SpR/SHO should be informed of all admissions from the Day Care Unit. Patients attending SMAC directly will be seen by the Red Cell SpR (Bleep 9240) or SHO (Bleep 9078) within working hours, and by the on call SHO covering haematology outside working hours. If the Red Cell team or on call SHO are unable to attend immediately then the acute medicine team will assess the patient, prescribe initial treatment including analgesia and monitor the patient until the haematology team arrives.

If a patient is very unwell they should dial 999 and present their access passport to LAS. They will be taken preferentially to Hammersmith Hospital, SMAC with the LAS team giving advance notification of their arrival. If a patient requires immediate treatment for a medical emergency they will be taken to the nearest hospital with an A&E service, usually St Mary's or Charing Cross Hospital (see also management of priapism page 19).

All adults presenting acutely should have a full assessment including history and examination, keeping in mind specific problems encountered in sickle cell disease (see below). All patients requiring admission should be discussed with the Red Cell SpR on bleep 9240 or the duty Red Cell haematology consultant and fast-tracked to the ward (usually D7 when possible). The Clinical Nurse

Specialist and Specialist Social Worker for Haemoglobinopathies should also be notified of all patients admitted.

### Clinical assessment

A full history and examination should be carried out, paying particular attention to symptoms/signs of life-threatening complications including acute chest syndrome, infection, hepatic/splenic sequestration or aplastic crisis.

The following should be recorded in the notes:

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

### Investigation

#### All patients:

FBC	Group and save
Reticulocyte count	Blood cultures if febrile
Renal profile, LFTs, LDH	CXR if fever or chest signs
CRP	Urine dipstick/MSU

#### If not seen before: including:

Hb electrophoresis	ABG if SpO <sub>2</sub> on air <92%
Extended red cell phenotype*	Parvovirus IgM if low Hb and retics
Hepatitis +/- HIV serology	Atypical pneumonia screen in acute chest syndrome
G6PD	
Ferritin	Amylase if abdominal pain
Parvovirus B19 serology	Yersinia blood and stool cultures if abdominal pain/diarrhoea and on iron chelation
Vitamin D	

#### Others as required (see below for specific complications)

Hb electrophoresis should be sent for HbS level (%) if transfused within past 3 months

\* Includes the following blood group antigens: C, c, D, E, e, K, k, Jk<sup>a</sup>, Jk<sup>b</sup>, Fy<sup>a</sup>, Fy<sup>b</sup>, Kp<sup>a</sup>, Kp<sup>b</sup>, M, N, S, s, Le<sup>a</sup> and Le<sup>b</sup>. If the patient has been recently transfused the red cell phenotype should be obtained from the referring hospital and if not available blood group genotyping should be arranged with Red Cell Immunohaematology, NHSBT, Filton, Bristol via the Transfusion Laboratory (extn. 34772 or 34790).

### Pain management

Where the primary diagnosis is a painful crisis, appropriate analgesia should be administered as soon as possible and within 30 minutes in all cases, if necessary before completing a full clinical assessment. The patient's individual analgesia protocol which is held in A&E or accessible from a Trust computer via Cerner or on the shared drive in the Clinical Haematology-Red Cell folders should be followed. When parenteral opioids are required and analgesia preference not known prescribe

diamorphine if no contraindication. Pethidine should be avoided and **only** given if specified in individual patient protocol.

**Note:** Pain as a presenting symptom is usually due to a painful crisis but alternative diagnoses should be considered especially if reported as atypical.

### **Discharge from A&E/HDCU**

If after discussion with the Haematology SpR the patient does not require admission ensure they should have:

- Instructions to maintain a high fluid intake
- Supply of appropriate oral analgesia
- Prophylactic penicillin (or erythromycin if penicillin allergic)
- Folic acid
- Follow-up appointment in Red Cell clinic or HDCU

## MANAGEMENT OF ACUTE COMPLICATIONS

### 1. Sickle pain crisis

Adapted from the NW London Haemoglobinopathy Network protocol for Early Management of Sickle Cell Crisis. See also NICE guideline CG143: Sickle cell acute painful episode: management of an acute painful sickle cell episode in hospital, June 2012 and NICE Quality Standard 58: Sickle cell acute painful episode, April 2014.

**O2** – initial FiO2 28% e.g. Venturi 28% 4-6l/min. This should be prescribed on the oxygen section of the drug chart. If the patient is hypoxic titrated to maintain SpO2 > 95% See explanatory notes below.

- **Analgesia** (within 30 mins) Diamorphine sc  
2.5mg (if weight < 50kg) 5mg (if weight > 50kg)

**Note:** Always follow individual patient protocol as diamorphine may not be appropriate. **Avoid** iv opioids.

- Give with cyclizine 50mg im/iv then 8 hourly prn po/im/iv
- Commence observations including fluid balance and pain assessment
- Intravenous access (mandatory if patient opioid naïve/unknown opioid requirements/changing opioid) and fluids. Suggested rate 3-4l/24hours if normal renal and cardiac function. If no iv access and oral intake inadequate consider nasogastric (if no vomiting/ileus) or sc fluids
- Keep patient warm

#### **Reassess at 15-20 minute intervals until pain adequately controlled:**

- Reassess pain using validated pain score, respiratory rate, SpO2 and sedation score
- Give 50-100% of opioid dose if still in moderate/severe pain
- This dose can be repeated every 15-20 minutes until pain is controlled as long as respiratory rate and sedation are carefully monitored

**If pain persists:** Set up subcutaneous Patient Controlled Analgesia (PCA) if available (see PCA guideline) with diamorphine or fentanyl as per individual protocol

#### **Adjuvants**

- Consider regular Paracetamol 1g qds - iv most effective
- Senna 2 tablets daily (if no abdominal signs) +/- lactulose 15mls bd
- Chlorpheniramine 4mg qds po prn or Hydroxyzine 25mg tds po prn for pruritus. **Caution for hydroxyzine especially in elderly. Do not prescribe in patients with prolonged QT or risk factors for QT prolongation. Maximum daily dose should not exceed 100mg (50mg in elderly)**
- Thromboprophylaxis: Enoxaparin 40mg od sc (20mg if creatinine clearance <30ml/min). Consider monitoring trough anti-Xa in renal impairment. Caution if thrombocytopenia/coagulopathy
- Incentive spirometry 2-4 hourly
- Folic acid 5mg daily

## Antibiotics

- If septic, chest signs or pyrexial  $>38^{\circ}\text{C}$  start cefuroxime 1.5g tds iv (adjusted according to renal function) or if history of severe penicillin allergy levofloxacin 500mg bd iv (Cautions: Isolated cases of haemolysis have been reported with other fluoroquinolones in G6PD deficiency; MHRA guidance on restricted use - see Drug Safety Update September 2012) after cultures (blood, urine and any other source indicated) have been taken. Note this differs from ICHT antibiotic guidelines.
- Clarithromycin 500mg bd po if respiratory symptoms/signs or symptoms unless levofloxacin prescribed - see Acute Chest Syndrome below.
- In severe sepsis ceftriaxone 2g od iv + amikacin 15mg/kg (adjusted according to renal function) stat iv then od iv as per Infection protocol below.
- For other specific infections (osteomyelitis, septic arthritis, biliary sepsis, meningitis) see relevant sections of guideline or discuss with Microbiology/Infectious Diseases.
- Consider co-amoxiclav 625mg tds po or doxycycline 200mg stat po then 100mg od if penicillin allergic if fever  $<38^{\circ}\text{C}$  and not unwell.
- Continue penicillin V/erythromycin prophylaxis if none of above indicated.
- If diarrhoea/abdominal pain and on iron chelation therapy stop chelator, send blood and stool for Yersinia culture and commence ciprofloxacin 400mg bd iv if G6PD status normal or ceftriaxone 2g od iv if G6PD deficient.

## Explanatory notes

- There is no evidence supplemental O<sub>2</sub> is beneficial if the SpO<sub>2</sub> is normal, however many patients report symptomatic relief. Caution should be exercised when prescribing oxygen to patients with known pulmonary hypertension and type 2 respiratory failure. SpO<sub>2</sub> should be recorded on air hourly then 4 hourly if stable and ABG performed if it falls below 92%. If this occurs discuss with Haematology SpR and follow acute chest syndrome protocol. Prolonged use of supplemental O<sub>2</sub> in the absence of hypoxia may be harmful and exacerbate anaemia.
- Pain relief should be given within 30 minutes of arrival in A&E and good pain control should be achieved within 60 minutes
- Diamorphine is suggested as first line as it causes less pruritis and is more soluble than morphine
- Cautions for diamorphine – opioid allergy, reduce dose in renal or hepatic impairment, patient on other CNS depressants, other opioid in past 24 hours
- Cautions for cyclizine – allergy, reduce dose in hepatic impairment
- Cautions for ibuprofen – NSAID allergy, avoid in renal and hepatic impairment, active gastrointestinal ulceration, pregnancy and breastfeeding
- Cautions for hydroxyzine – hepatic disease, pregnancy and breastfeeding, prolonged QT interval (see above)
- A validated pain chart should be used. The patient should initially be monitored every 20 minutes and then hourly for respiratory rate, SpO<sub>2</sub> on air, O<sub>2</sub> dose and sedation
- PCA comprising continuous background infusion and patient controlled boluses provides more effective analgesia and reduces opioid consumption. Subcutaneous administration is preferred because of difficulties with iv access
- If PCA is not available or declined, sc diamorphine (or alternative as per individual protocol) may be given up to 2 hourly at a dose sufficient to achieve effective pain control
- Morphine can be used as an alternative to diamorphine. Suggested initial sc dose is 5mg if  $<50\text{kg}$  and 10mg if  $>50\text{kg}$
- 5mg morphine sc is equivalent to 10 mg oral morphine, 3mg sc diamorphine or 3mg sc/5mg oral oxycodone
- Pethidine should not be prescribed for sickle crisis unless known severe allergy to all other opiates and specified on individual patient protocol
- Once the patient has moderate pain (VAS rating 3-7), parenteral opioids should be gradually decreased. When discontinued the patient should generally be maintained on oral analgesia for 12-24 hours before discharge. A suggested regime is regular ibuprofen 200mg – 600mg tds

in conjunction with either co-codamol (2 tablets qds), dihydrocodeine (30-60mg qds) or tramadol (50-100mg qds) prn

- Nitrous oxide/oxygen (Entonox) should only be used in the ambulance and should not be used frequently or for more than 30 minutes

## 2. Acute Chest Syndrome (ACS)

Refer to BCSH Guideline on the management of Acute Chest Syndrome in Sickle Cell Disease, 2015

Acute Chest Syndrome (ACS) is a medical emergency and the leading cause of death in adults with SCD. Its pathophysiology is multifactorial (infection, sludging/sickling or thrombosis of pulmonary arteries and fat embolism). It usually develops during a painful crisis. The risk is increased in the post-operative period and post-partum. Prompt diagnosis and management, with early involvement of the Haematology SpR and Red Cell Consultant, is essential.

### Symptoms

- Pain affecting chest, upper abdomen and/or thoracic spine.
- Dyspnoea
- Cough

### Signs

Clinical signs often precede CXR changes

- Fall in SpO<sub>2</sub> **on air** (measurement on O<sub>2</sub> may delay diagnosis) hypoxia
- Fever, tachypnoea, tachycardia
- Pain/tenderness in chest wall
- Signs of lung consolidation, typically basal and bilateral initially. Bronchial breathing may be striking. Wheezes occur less commonly
- CXR – New shadowing is usual but may lag behind other signs. Appearances may resemble lobar or bronchopneumonia. Diffuse irregular shadowing. Basal atelectasis is often an early sign.

### Differential diagnosis

ACS and pneumonia are clinically and radiologically indistinguishable. Pleuritic pain may be due to ACS, spinal/rib/sternal infarction, pulmonary embolism or sub-diaphragmatic inflammation.

Consolidation in the upper and/or middle lobes, without basal changes, is more suggestive of infection than ACS. Bilateral lung involvement is most likely to reflect ACS though atypical pneumonia should be considered.

### Investigation

- Arterial blood gases (ABG) on air
  - if SpO<sub>2</sub> on air <92% or >3% fall from baseline
  - if dyspnoeic or tachypnoeic
- Monitor SpO<sub>2</sub> on air and inspired O<sub>2</sub> 1-4 hourly
- CXR
- Measure peak expiratory flow (PEF)
- CTPA including HRCT cuts if pulmonary embolism suspected
- Blood, throat and sputum
- Blood tests as per emergency admission protocol plus respiratory infection serology including Mycoplasma, Chlamydia, Legionella, RSV and Parvovirus (if reticulocytes low)
- Legionella and Pneumococcal antigen
- NPA for virology

### Management

- Notify Haematology SpR immediately. Suspected ACS should always be managed with advice from attending/on-call Red Cell Consultant
- Seek ITU/Respiratory opinion early and consider transfer to ITU/HDU if unwell/deteriorating

- Analgesia and iv fluids as per pain crisis protocol (avoid respiratory depression and fluid overload)
- Give humidified O<sub>2</sub> (2-4l/min) to maintain SpO<sub>2</sub> 98% or patient's usual SpO<sub>2</sub>
- Monitor SpO<sub>2</sub> on air and O<sub>2</sub>, ABG, pulse, RR, abdominal girth, fluid balance, Hb and CRP
- Antibiotics (during which penicillin V/erythromycin prophylaxis can be suspended): cefuroxime 1.5g tds iv (adjusted according to renal function) + clarithromycin 500mg bd po or if history of severe penicillin allergy levofloxacin 500mg bd iv (Cautions: Isolated cases of haemolysis have been reported with other fluoroquinolones in G6PD deficiency; MHRA guidance on restricted use - see Drug Safety Update September 2012)
- CPAP +/- transfusion as indicated (see below)
- Incentive Spirometry +/- chest physiotherapy
- Nebulized salbutamol 2.5mg in 2.5 mls sodium chloride 0.9% qds if wheezes or history of asthma. Measure PEF pre and post salbutamol
- Avoid diuretics unless other signs of left heart failure (signs/CXR may mimic pulmonary oedema)
- Consider fat embolism syndrome if ACS accompanied by petechiae, confusion/other neurological signs, renal/hepatic dysfunction, hyponatraemia, thrombocytopenia or coagulopathy.
- Thromboprophylaxis: Enoxaparin 40mg od sc (20mg if creatinine clearance <30ml/min). Consider monitoring trough anti-Xa in renal impairment. Caution if thrombocytopenia/coagulopathy

### Indications for ventilation and exchange transfusion

PaO <sub>2</sub> on air	8.0 - 9.5 kPa	Trial of CPAP
	< 8.0 kPa	CPAP and discuss exchange transfusion with SpR/Consultant
	< 7.5 kPa	Exchange transfusion and CPAP
PaO <sub>2</sub> on 60% O <sub>2</sub> or CPAP	< 7.5 kPa	Intubate, IPPV and exchange transfusion
PaCO <sub>2</sub>	> 6.7kPa or rising and patient tiring	Exchange transfusion. Consider intubation and IPPV

Other potential indications for exchange transfusion include:

- Multilobar involvement on CXR
- Rapid fall in PaO<sub>2</sub>
- Failure to respond to increased FiO<sub>2</sub>%
- 25% drop in PaO<sub>2</sub> compared to baseline PaO<sub>2</sub> e.g. in patients with chronic hypoxaemia
- Exhaustion from respiratory effort

Before starting CPAP discuss with the SpR/Red Cell Consultant. If CPAP is not available consider a lower threshold for.. Initial top-up transfusion may be considered in patients whose Hb shows a significant drop from steady-state level. BiPAP may have a role as non-invasive ventilation in ACS (more efficient than CPAP in removing CO<sub>2</sub>) but should not delay institution of IPPV. Discuss with ITU/Respiratory team on individual basis.

### Exchange Transfusion

Once a decision is reached to proceed with red cell exchange this should be performed without delay by either automated erythrocytapheresis or isovolaemic manual exchange. The ICHT Standard Operating Procedure for Automated or Manual Red Cell Exchange should be followed.

Target HbS <30% (consider <20 % if in extremis) with maximum Hb and Hct of 10-11g/dl and 0.34. If Fat Embolism Syndrome suspected consider combined automated red cell and plasma or manual exchange.

### Follow up

- Check baseline SpO2 and request PFT at 6 weeks
- Echo, HRCT chest and respiratory referral to Dr Philip Ind if chronic sickle lung disease (CSLD) suspected
- For recurrent ACS recommend hydroxycarbamide therapy or transfusion programme
- Advice on vaccination if indicated

### 3. Infection

Infection is a common precipitating factor of painful crisis and other acute complications. Patients with SCD are immunocompromised with functional asplenia or hyposplenia irrespective of spleen size, resulting in increased susceptibility to infection, in particular with capsulated organisms such as *Pneumococcus*, *Haemophilus influenzae* and *Salmonella* – all of which can cause life-threatening sepsis. In SCD presenting with sepsis any history of overseas travel/residence, contact with other healthcare institutions and the sensitivities of preceding microbial isolates should be established and discussed with the Microbiology/Infectious Diseases team as this may influence choice of antibiotics.

#### Empiric antibiotic therapy

For empiric treatment of suspected infection during an acute pain crisis follow protocol above. For other specific indications the following antibiotics are advised:

- Severe sepsis – ceftriaxone 2g od iv + amikacin 15mg/kg (adjusted according to renal function) stat iv then od iv
- Chest signs and/or abnormal CXR – cefuroxime 1.5g tds iv (adjusted according to renal function) and clarithromycin 500mg bd po or if history of severe penicillin allergy levofloxacin 500mg bd iv (Cautions: Isolated cases of haemolysis have been reported with other fluoroquinolones in G6PD deficiency; MHRA guidance on restricted use - see Drug Safety Update September 2012)
- Abdominal pain and girdle syndrome – cefuroxime 1.5g tds iv (adjusted according to renal function) and metronidazole 500mg tds iv
- Suspected biliary sepsis – cefuroxime 1.5g tds iv (adjusted according to renal function) and metronidazole 500mg tds iv
- If symptoms/signs of focal infection are present (e.g. tonsillitis, UTI) follow current version of ICHT Adult Treatment of Infection Policy
- Abdominal pain and diarrhoea on iron chelation therapy - stop chelator, send blood and stool including *Yersinia* culture and commence ciprofloxacin 400mg bd iv if G6PD status normal or ceftriaxone 2g od iv if G6PD deficient
- For hospital acquired pneumonia or other infection piperacillin/tazobactam 4.5g tds iv

If antibiotics prescribed cover *Pneumococcus*, prophylactic penicillin/erythromycin may be suspended.

**Malaria** should be excluded if there is a history of travel to an endemic area within the past 12 months. See ICHT Guideline Adult Treatment of Malaria.

#### Osteomyelitis/septic arthritis

Bone/joint pain is usually due to vaso-occlusive crisis but the possibility of osteomyelitis/septic arthritis should always be considered. *Salmonella* is the commonest cause of osteomyelitis in sickle cell patients, others being *Staphylococcus aureus*, *S. pneumoniae* and other Gram negative enteric bacteria. The diagnosis is often difficult but should be suspected if persistent fever, local inflammation, swelling, pain or enteric symptoms are present. The CRP and WBC are often high but this may also be seen in uncomplicated vaso-occlusive crisis. Management depends on the index of suspicion and should be discussed with the Red Cell Consultant

#### Specific investigation

- Blood film (toxic neutrophils)

- Blood +/- stool cultures
- Plain X-ray (no specific changes in early osteomyelitis, lucent areas evident ~10 days after infection)
- Ultrasound (subperiosteal fluid is also seen in vaso-occlusive crisis, but high suspicion for osteomyelitis if fluid depth of >4mm)
- Gadolinium enhanced MRI (to localize lesions and monitor response to treatment)
- Bone/joint (if effusion seen on ultrasound) aspiration and culture

### **Management**

- Multidisciplinary approach - involving Orthopaedic/Rheumatology and Microbiology/Infectious Diseases (ID) teams
- If septic arthritis suspected joint aspiration should be undertaken urgently and samples sent for M,C and S
- In suspected osteomyelitis microbiological samples should be obtained wherever possible before commencing antibiotics. Empiric treatment should cover the above organisms e.g. ceftriaxone 2g od iv and clindamycin 600mg qds iv
- Tailor antibiotics once culture and sensitivity results are known
- Length of treatment depends on the certainty of diagnosis and clinical course but should usually be at least 6 weeks
- Patients should receive general supportive care as outlined in the sickle pain crisis protocol
- Screening family members of patients with Salmonella infection should be discussed with the ID team

#### 4. Acute abdominal pain/jaundice

Acute abdominal pain is common in sickle cell disease specific causes including:

- Vaso-occlusive ('mesenteric') crisis
- Biliary colic
- Acute cholecystitis
- Cholangitis
- Hepatic/splenic sequestration
- Ischaemic colitis (rare)
- Intrahepatic cholestasis
- Pancreatitis
- Pyelonephritis
- Splenic infarction
- Yersinia enterocolitis (if receiving iron chelation)

Causes unrelated to sickle cell disease eg acute appendicitis should be considered and surgical opinion sought at an early stage.

##### a) Abdominal (mesenteric) crisis including 'girdle syndrome'

###### Symptoms

- Abdominal pain (non-specific) often associated with bone pain
- Anorexia
- Constipation (especially if received codeine or other opiates)
- +/- Vomiting

###### Signs

- Abdominal distension
- Bowel sounds normal/reduced
- Abdominal tenderness – generalized without rebound
- Abdomen not rigid and moves on respiration

**Girdle syndrome** is defined by circumferential abdominal pain +/- ileus

- Abdominal distension
- Vomiting
- Reduced/absent bowel sounds
- Distended bowel loops with fluid levels on AXR
- +/- Hepatomegaly
- Risk of acute chest syndrome – CXR may show basal lung consolidation

###### Management

- IV fluids
- Analgesia as per pain protocol
- Nil by mouth +/- nasogastric suction if vomiting or reduced bowel sounds
- Antibiotics if pyrexial/unwell e.g. cefuroxime 1.5g iv tds (adjusted according to renal function) and metronidazole 500mg iv tds
- Consider red cell exchange if:
  - Hypoxic/respiratory signs
  - Failure to resolve with conservative management
- Monitor abdominal girth (at umbilicus) 1-4 hourly
- Measure liver size twice daily
- AXR and US
- Repeat AXR +/- CT abdomen if worsening abdominal pain/tenderness/distension

## **b) Sequestration syndromes**

In sequestration there is pooling of large numbers of red cells in the liver or spleen. This may lead to a rapid fall in haemoglobin and circulatory collapse. In adults hepatic sequestration is more common. Splenic sequestration is most common in infants and young children but may occur in adults without splenic atrophy such as those with sickle  $\beta$ -thalassaemia, HbSC and HbSS with a high HbF level. Both have a tendency to recur.

### **Splenic sequestration**

#### **Symptoms**

- Pain left hypochondrium
- Abdominal distension

#### **Signs**

- +/- Tenderness splenomegaly
- Tachycardia +/- hypotension
- Hypovolaemic shock
- Thrombocytopenia frequently present

#### **Investigation**

As per emergency admission protocol plus:

- Cross match
- Hepatitis serology
- US Abdomen
- Infection screen if febrile
- Parvovirus B19 Serology (concurrent sequestration and aplastic crisis may occur)

#### **Management**

- Fluid resuscitation if hypovolaemic
- +/- Antibiotics as per sickle pain crisis protocol
- Top-up transfusion if significant fall in Hb
- If transfused set lower target Hb to prevent hyperviscosity on reversal of pooling
- Monitor FBC closely as splenomegaly regresses and consider venesection if haematocrit > 0.36
- If splenic sequestration recurs consider splenectomy

### **Hepatic sequestration**

Hepatic sequestration may be precipitated by sepsis eg Salmonella and is associated with an increased risk of acute chest syndrome.

#### **Symptoms**

- Pain right hypochondrium
- Abdominal distension
- +/- Fever due to associated sepsis

#### **Signs**

- Tender hepatomegaly
- Increasing jaundice (predominantly conjugated)
- Tachycardia/hypotension - less common than in splenic sequestration

#### **Investigations**

As per emergency admission protocol plus:

- Cross match
- Coagulation screen

- Hepatitis serology
- Infection screen including blood cultures
- US Abdomen
- Split/Conjugated bilirubin

### Management

- Fluid resuscitation if hypovolaemic
- Treat with broad spectrum antibiotics e.g. cefuroxime 1.5g tds iv (adjusted according to renal function) and metronidazole 500mg tds iv
- Top-up or exchange transfusion
- If transfused set lower target Hb to prevent hyperviscosity on reversal of pooling
- Monitor FBC closely as hepatomegaly regresses and consider venesection if haematocrit > 0.36
- Consider plasma exchange if very high bilirubin

### c) Biliary tract

Pigment gallstones develop at an early age and are present in up to 70% of adults with sickle cell disease. They are often asymptomatic but may cause:

- Acute cholecystitis
- Chronic cholecystitis
- Biliary colic
- Obstruction of the common bile duct
- Cholangitis
- Acute pancreatitis
- Choledocholithiasis
- Empyema of the gall bladder

**Symptomatic gallstones** are an indication for elective laparoscopic cholecystectomy. Transfusion is recommended prior to cholecystectomy. The decision whether to undertake top-up versus exchange transfusion should be decided on an individual basis.

### Acute cholecystitis

- Blood tests as per emergency protocol plus Coagulation screen and Amylase
- Plain abdominal X-ray (50% of stones radio-opaque)
- US Abdomen
- Refer to hepatobiliary/on-call surgical team
- IV fluids
- Analgesia
- Antispasmodics: e.g. hyoscine butylbromide (Buscopan<sup>®</sup>) : 20mg qds po or im

Antibiotics e.g. cefuroxime 1.5g tds iv (adjusted according to renal function) and metronidazole 500mg tds iv

### Obstructive jaundice due to common bile duct obstruction

- Endoscopic retrograde cholangiopancreatography (ERCP) or emergency surgery - increased risk of sickle related complications including acute chest syndrome with ERCP especially if pancreatitis develops
- Consider red cell exchange prior to ERCP or emergency surgery
- Correct coagulopathy with vitamin K/FFP if indicated
- Antibiotics e.g. cefuroxime 1.5g tds iv (adjusted according to renal function) and metronidazole 500mg tds iv
- Refer to Hepatobiliary Surgery for elective laparoscopic cholecystectomy

## **d) Other causes of jaundice**

### **Intra-hepatic cholestasis**

Intra-hepatic cholestasis is caused by widespread sickling within hepatic sinusoids with resulting ischaemia and carries a significant mortality due to liver failure. This can be minimized by aggressive supportive care and red cell exchange. It is characterised by hepatomegaly with marked hyperbilirubinaemia (conjugated > unconjugated), moderately raised alkaline phosphatase and transaminases, fever, right upper quadrant pain in the absence of gallstones, coagulopathy and in some cases renal impairment.

### **Management**

- Correction of coagulopathy with vitamin K/FFP
- Antibiotics if febrile; e.g. cefuroxime 1.5g tds iv (adjusted according to renal function) and metronidazole 500mg tds iv
- Analgesia if required - caution as most opioids metabolised in the liver
- Red cell exchange - long term if recurrent
- Refer for hepatology opinion
- Liver biopsy carries an increased risk and if indicated should be performed by the transjugular route

### **Hyperhaemolysis syndrome**

Hyperhaemolysis syndrome is a rare and potentially life-threatening complication occurring after blood transfusion characterized by the development of severe anaemia with haemoglobinuria and hyperbilirubinaemia. The onset may be acute (< 7 days; DAT negative, no detectable red cell antibodies) or delayed (> 7 days; DAT positive, new red cell antibody identified). Typically after transfusion the Hb falls to below the pretransfusion level and the reticulocyte count is inappropriately low. Discuss with Red Cell Consultant immediately diagnosis is suspected. Management comprises avoidance where possible of further transfusion, high dose intravenous immunoglobulin, corticosteroids and erythropoiesis stimulating agents.

## 5. Acute neurological events

### a) Stroke

Stroke (ischaemic or haemorrhagic) occurs in all types of sickle cell disorder and at all ages. Its incidence is highest in homozygous sickle cell disease (HbSS). Cerebral infarction most often results from occlusion of major cerebral vessels particularly the middle cerebral artery. There is a high risk of recurrence (up to 90%) in the absence of specific treatment. Predictive factors include a history of transient ischaemic attacks, acute chest syndrome, hypertension, low Hb and low Hb F%. Precipitating factors include dehydration, fever and acute anaemic events.

### Investigation

- Urgent CT brain if out-of-hours (may be negative in early stages of ischaemic stroke)
- CT perfusion scan if presents within 3-4 hours of onset
- MRI + MRA/Contrast enhanced CT angiography
- MRV if cerebral venous thrombosis suspected on clinical grounds
- Blood tests as per emergency admission protocol plus cross match, ferritin, hepatitis B, C, HIV and CMV serology
- Lumbar puncture if signs of meningism to exclude infection or subarachnoid haemorrhage. Check coagulation normal first

### Management

#### 1) Immediate

- Rehydrate
- Regular monitoring of neurological status
- Refer to on-call Neurology SpR/Consultant
- Urgent red cell exchange to achieve HbS % <20% (haematocrit should not exceed 0.34)
- Anticonvulsant therapy if seizures occur
- Avoid/stop aspirin, NSAIDs and LMWH until haemorrhage excluded

#### 2) Long-term

- Regular exchange transfusion programme (every 4-6 weeks) to maintain HbS level below 30%
- MRA may help to determine the duration of the transfusion regimen The risk of recurrent neurological events is greatest in those with abnormal cerebral vasculature:
  - No occlusion, no neurological deficit: monitor without further transfusion
  - Occlusion of vessels and/or neurological deficit: regular transfusion for at least 36 months
- For TIA consider lifelong anti-platelet therapy if there is no contraindication
- Neurology review

### b) Subarachnoid haemorrhage

- May occur at any age (median 22 years)
- Multiple intracranial aneurysms common

### Investigation

- CT brain **plus**
- CT angiography with isotonic contrast (contraindications; renal failure and metformin)
- +/- LP

### Management

- Red cell exchange as for stroke
- Refer to on-call Neurosurgery SpR/Consultant at CXH
- Avoid/stop aspirin, NSAIDs and LMWH

### **c) Seizures**

Convulsions are not uncommon following stroke, subarachnoid haemorrhage and infections such as meningitis and are predictive of adverse outcome in SCD. Seizures can also occur following pethidine administration.

### **Investigations**

- Urgent CT or MRI
- EEG
- Consider MR angiography
- Infection screen including blood cultures +/- LP
- Toxicology screen for pethidine and metabolites (norpethidine) if indicated

### **Management**

#### **a) Immediate**

- Anticonvulsant therapy (as per NICE guidelines): lorazepam 4mg iv given at a minimum rate of 2mg/minute. This can be repeated after a minimum of 10 minutes if still fitting, to a maximum of 8mg  
Or give diazepam (as Diamuls®) 10mg IV at a rate of 5mg/minute to a maximum of 10-20mg (or PR if no IV access)
- For established status epilepticus – IV Phenytoin 15mg/kg at a maximum rate of 50 mg/minute (ECG monitoring required)
- Avoid/stop pethidine
- Refer to on-call Neurology SpR/Consultant
- Discuss need for urgent red cell exchange with Red Cell Consultant

#### **b) Long term**

- If no abnormality on EEG or CT/MRI and no recurrence watch and wait. Consider diagnosis of pseudoseizures
- If EEG abnormal, but CT/MRI and MRA are normal consider anticonvulsant therapy
- If infarct on CT/MRI, or vessel stenosis/occlusion on angiogram consider transfusion programme
- Neurology review

## 6. Priapism

Priapism occurs in up to 40% of males with sickle cell disease. It often develops at night in association with a full bladder and is more common in those sexually active. Untreated if prolonged it can lead to irreversible penile ischaemia and fibrosis resulting in permanent erectile dysfunction.

**If a patient contacts the haematology triage service for acute priapism they should be advised to immediately go to A&E at SMH as there is no urology service on the Hammersmith site.**

Types of presentation:

- **Acute fulminant** (> 4 hours)
- **Stuttering** (repeated but self-limiting painful erections lasting more than 30 minutes and up to 4 hours). Recurrent stuttering attacks may herald an acute fulminant episode

Precipitating factors: Dehydration, fever, exposure to cold

### Immediate management of acute fulminant priapism

- Rehydrate with iv fluids
- Opioid analgesia +/- sedation
- Catheterisation if necessary to empty bladder
- Pseudoephedrine 30-60mg qds po – monitor blood pressure
- Blood tests as per emergency admission protocol
- Contact on-call Urology SpR/Consultant at SMH

If priapism persists:

- Intracavernosal blood aspiration +/-cavernosal blood gas analysis with injection of phenylephrine 0.5mg ( $\alpha$  adrenergic agonist) **must only be carried out by an experienced urologist** – Avoid phenylephrine in patients with thyrotoxicosis or ischaemic heart disease
  - Injection can be repeated after 15 minutes
  - Monitor BP closely (may cause hypertension)
- If no/transient response consider emergency red cell exchange (maximum Hct 0.34)
- If intractable despite non-surgical measures a cavernous shunt procedure may be considered (carries risk of irreversible erectile dysfunction)

### Management of stuttering priapism

- Educate regarding measures of potential benefit
  - High fluid intake
  - Frequent bladder voiding
  - Warm bath/shower
  - Mild to moderate exercise
  - Ejaculation
- Oral analgesia
- Advise patient they **must** attend A&E if any episode > 3 hours
- Pseudoephedrine 30-60mg qds po
- Other prevention strategies that may be considered on an individual basis after discussion at Red Cell MDT Meeting include:
  - Red cell exchange programme
  - Hydroxycarbamide
  - Etilefrine
  - Phosphodiesterase inhibitors
  - Anti-androgens: Cyproterone 50mg bd (caution risk of thrombosis assess VTE risk) or Stilboestrol 5mg od (monitor LFTs)

## 7. Aplastic crisis

In patients with chronic haemolysis temporary red cell aplasia caused by parvovirus B19 can lead to a rapid fall in haemoglobin with profound anaemia accompanied by reticulocytopenia. There may be a history of prodromal illness but classical *erythema infectiosum* ('slapped cheek syndrome') is uncommon. Aplastic crisis may affect multiple members of a family concurrently or consecutively. Presentation is usually with symptoms of anaemia.

### Investigation

- As per emergency admission protocol
- Reticulocytes absent/low except in early recovery phase
- Parvovirus serology including IgM +/- Parvovirus DNA

### Management

- Urgent top-up transfusion - if Hb < 50g/L or drop of >20g/L from baseline or clinically compromised
- Monitor FBC & Retics - recovery is heralded by reticulocytosis +/- nucleated RBCs 1-10 days after presentation
- Reassure - recurrence does not occur as immunity to parvovirus B19 is lifelong

## 8. Renal

### a) Haematuria

Microscopic haematuria is common in sickle cell disease. Macroscopic haematuria may be due to urinary infection or papillary necrosis but unrelated causes should be considered and where indicated the patient referred to urology for further investigation and management. Sloughing and passing of renal papillae may produce renal colic and ureteric blockage. Haematuria can also occur in patients with sickle trait.

### Management

Painless haematuria on dipstix testing age < 40 yrs

- Renal ultrasound
- MSU
- Urine cytology

Painful haematuria on dipstix testing

- Above investigations + CT-KUB
- Refer to haematuria clinic after organizing above investigations

### b) Urinary tract infection

Urinary tract infections are more common in sickle cell disease especially in women during pregnancy. They should be investigated and treated vigorously based on antibiotic sensitivities to prevent more serious renal sequelae. Haematuria secondary to papillary necrosis may be complicated by UTI.

### Management

- Uncomplicated UTI in females: Cefalexin 500mg bd po for 3 days or Nitrofurantoin 50mg qds po for 7 days if not G6PD deficient (avoid if eGFR <30ml/min)
- Uncomplicated UTI in males: Cefalexin 500mg bd po for 7 days – if suspicion of prostatitis 14 days of Cefalexin 500mg bd po or Ciprofloxacin 500mg bd po if not G6PD deficient
- Recurrent UTI - imaging of the renal tract and consideration of antibiotic prophylaxis

### c) Acute renal failure/Nephrotic syndrome

Refer to Nephrology team and follow ICHT Renal guidelines.

## 9. Ophthalmic

### **Proliferative sickle retinopathy**

Sickle cell disease is associated with several ocular complications that carry a risk of visual loss. The most common is proliferative retinopathy. Infarction of the peripheral retina results in neovascularisation with proliferation of fragile, thin-walled blood vessels ('sea fans') which can lead to vitreous haemorrhage and retinal detachment. Proliferative retinopathy is most frequently detected in young adults and more prevalent in HbSC disease and sickle  $\beta^+$ -thalassaemia. Progression may occur during pregnancy.

### **Proliferative Sickle Retinopathy: Staging criteria**

*Stage 1:* Peripheral arteriolar occlusions

*Stage 2:* Peripheral arteriolar-venular anastomoses

*Stage 3:* Neovascular and fibrous proliferation

*Stage 4:* Vitreous haemorrhage

*Stage 5:* Retinal detachment

### **Traumatic hyphema**

Traumatic hyphema (anterior chamber haemorrhage) which usually follows blunt trauma carries a high risk of complications in sickle cell disease due to the consequences of raised intra-ocular pressure which may lead to retinal vessel occlusion with blindness.

### **Management**

- Patients should be advised to immediately attend the Western Eye Hospital A&E or their nearest eye casualty if they develop acute visual symptoms or suspected hyphema after eye injury
- Refer all new and pregnant patients to Western Eye Hospital (Mr Duguid) or CXH (Mr Kinnear) for initial ophthalmology assessment including fluorescein angiography
- For patients with retinopathy or those on regular desferrioxamine and deferasirox review at least annually is recommended
- Indications for panretinal laser photocoagulation therapy for proliferative sickle retinopathy should be considered on an individual basis
- Red cell exchange is recommended prior to surgery for retinal detachment, vitreous haemorrhage or hyphema

## MANAGEMENT OF CHRONIC COMPLICATIONS

### 1. Nephropathy

#### a) Screening in outpatients

- Urine protein:creatinine ratio (PCR) at least annually - if significant proteinuria request 24hr collection to quantitate
- Renal profile at each visit

#### b) Proteinuria

##### Management

- If dipstix negative and/or PCR < 50 repeat 6-monthly
- If dipstix positive for protein send for PCR and MSU
- If PCR > 50 on at least 2 occasions
  - Blood for ANA, ANCA, anti-GBM, C3 and C4, immunoglobulins, protein electrophoresis
  - Urine for BJP
  - US renal tract
  - Start ACE inhibitor e.g. ramipril 2.5mg od po initially increasing to maximum 10mg daily
  - Angiotensin receptor blocker (ARB) e.g. losartan if ACE inhibitor not tolerated
  - If proteinuria persists add ARB as long as potassium < 6mmol/l
  - Refer to Nephrology service if urine PCR persistently > 50 despite maximal ACE and ARB blockade
  - Avoid NSAIDs and pethidine

#### c) Hypertension

##### Management

- If no proteinuria treat if BP  $\geq$  140/90 mmHg
  - Aim for BP <140/90 mmHg
  - Manage according to the NICE/British Hypertension Society treatment algorithm. NICE guideline CG127 <http://www.nice.org.uk/nicemedia/live/13561/56008/56008.pdf>
  - Start calcium channel blocker (CCB) e.g. amlodipine as initial treatment if African/Caribbean of any age or non-African/Caribbean  $\geq$ 55 years; if non-African/Caribbean and < 55 years start ACE inhibitor or ARB e.g. losartan if ACE inhibitor not tolerated
  - Both ACE inhibitors and ARB contraindicated in pregnancy – caution in women of reproductive age
  - Advise GP to manage to target
  - If BP uncontrolled on monotherapy add the other class of drug i.e. add CCB to ACE inhibitor/ARB or vice versa
  - Avoid diuretics
- If proteinuria treat if BP  $\geq$  130/90 mmHg
  - Aim for BP <130/80 mmHg
  - Manage as for proteinuria above
  - Add CCB if BP uncontrolled despite maximal ACE and ARB blockade

#### **d) Chronic renal failure**

Chronic renal failure defined as an irreversible rise in creatinine > 132 µmol/L and steady state urea > 7 mmol/L due to glomerulosclerosis develops in around 4% of SCD patients. Predictors include progressive anaemia, hypertension, proteinuria, nephrotic syndrome, and microscopic haematuria. It is managed in conjunction with the West London Renal and Transplant Centre, Hammersmith Hospital.

#### **Investigation**

- FBC and reticulocytes
- Renal and bone profile, bicarbonate, urate
- Immunoglobulins, protein and urine electrophoresis, auto-antibodies (as above), C3 and C4
- Hepatitis B surface antigen, core and surface antibody
- Hepatitis C antibody and RNA
- HIV 1/2 antibody
- EPO level
- Vitamin D
- Parathormone
- Glucose +/- GTT (HbA1C not reliable in presence of Hb variant)
- Lipids
- Urine for BJP
- MSU for MCS
- US renal tract

#### **Management**

- Refer to Nephrology service
- Avoid dehydration - maintain fluid intake
- Treat proteinuria and hypertension as above
- +/- Statin
- +/- Allopurinol
- Avoid NSAIDs and pethidine
- Review iron chelation therapy if receiving - stop deferasirox (Exjade®)
- If anaemia severe consider erythropoiesis stimulating agent (often poor response in SCD) and/or transfusion regime - if regular transfusion required red cell exchange is preferable to limit iron loading
- Caution if receiving hydroxycarbamide (potentiated by renal impairment) - dose reduction may be necessary
- Consider renal transplantation

#### **e) Hyperuricaemia**

Hyperuricaemia is seen in up to 40% of adults with SCD due to a combination of increased production and decreased renal excretion. It may develop as a side-effect of hydroxycarbamide therapy. Hyperuricaemia may represent an early manifestation of renal dysfunction. Uric acid stones may develop but gout is uncommon. If there is evidence of renal impairment consider treatment with allopurinol.

## 2. Pulmonary and cardiac

### a) Pulmonary hypertension

See American Thoracic Society Clinical Practice Guideline: Diagnosis Risk Stratification and Management of Pulmonary Hypertension of Sickle Cell Disease 2013  
[www.atsjournals.org/doi/pdf/10.1164/rccm.201401-0065ST](http://www.atsjournals.org/doi/pdf/10.1164/rccm.201401-0065ST)

Pulmonary arterial hypertension is a predictor for premature death in patients with SCD. Transthoracic echocardiography with estimation of tricuspid valve regurgitant jet velocity (TRV) and BNP should be performed in all patients. Repeat echocardiography every 2 years if TRV < 2.5 m/s, annually if TRV > 2.5 m/s or earlier if signs of cardiac or pulmonary disease develop (e.g. decreased exercise tolerance, hypoxia or arrhythmia) develop. If TRV > 3.0 m/s in steady state refer to Pulmonary Hypertension team (Dr Simon Gibbs) for assessment and consideration of right heart catheterisation. Patients receiving regular transfusion should be monitored for evidence of myocardial iron overload (see below) though this is uncommon in SCD. Conventional cardiac risk factors should be treated (see section on hypertension above). Patients with SCD who develop cardiac failure may benefit from hydroxycarbamide or transfusion to increase their Hb. Elevated TRV or BNP is a biomarker of poor outcome and consideration should be given to hydroxycarbamide or transfusion therapy.

Patients who present with acute cardiac symptoms should be discussed urgently with the Cardiology SpR on bleep 9064 or Consultant of the week via the hospital switchboard (020 3313 1000). If the patient is known to have pulmonary arterial hypertension urgent advice should be sought from the National Pulmonary Hypertension Service, Hammersmith Hospital. Between 9.00 am and 5.00 pm contact the Pulmonary Hypertension SpR on bleep 9045 or Pulmonary Hypertension Nurses Office on 38072. Out of hours contact via bleep 9064.

### b) Sickle chronic lung disease

Patients with SCD can develop a respiratory defect due to chronic lung damage. There may be a history of recurrent acute chest syndrome (ACS) but patients without a prior history of ACS may also develop chronic pulmonary complications. A restrictive lung defect due to pulmonary fibrosis is most common. Reduced vital capacity (VC), total lung capacity (TLC) and a reduction in gas transfer (TLCO and kCO) are seen. As progression is insidious patients often do not complain of symptoms until the late stages of the disease when pulmonary hypertension and cor pulmonale may be present. There are four distinct stages of SCLD.

Clinical Marker	Stage 1	Stage 2	Stage 3	Stage 4
<b>Chest pain</b>	Recurrent substernal pain and chronic cough	Increase pain over stage 1	Severe midline crushing pain	Severe and prolonged pain with dyspnoea at rest
<b>Arterial blood gases</b>	Normal oxygen saturation	Normal oxygen saturation	Hypoxia with partial pressure oxygen (9.5 kPa) during stable periods	Partial pressure oxygen (8.0 kPa) during stable periods
<b>CXR</b>	Decreased distal pulmonary vascularity, hyperexpansion, evidence suggestive of increased interstitial markings	Diffuse, fine interstitial fibrosis involving all lobes of the lung	Pulmonary fibrosis	Severe pulmonary fibrosis

<b>Pulmonary Function Tests</b>	Decreased FVC, TLC, FEV1, (mild, 80% of predicted normal, or 1 SD below normal). Increased FEV1/FVC	Decreased FVC, TLC, TLCO, FEV1, (moderate, 60% of predicted normal, or 2 SD below normal). Increased FEV1/FVC	Decreased FVC, TLC, TLCO, FEV1, (severe, 40% of predicted normal, or 3 SD below normal). Increased FEV1/FVC	Patient frequently unable to complete testing due to degree of hypoxia
<b>ECG &amp; ECHO</b>	Left ventricular preponderance persists	Balanced ventricular hypertrophy	Right ventricular hypertrophy and right atrial enlargement Progressive increase in heart size	Severe right ventricular and right atrial hypertrophy. Ischaemic T waves in V1 and V2 and cor pulmonale.
<b>Pulmonary Artery Pressure</b>	Normal	Normal	Borderline elevation or normal	Markedly elevated with pulmonary hypertension

\* These measurements are based upon common methods for comparison of reference values. Abbreviations: FVC = forced vital capacity, TLC = total lung capacity, FEV1 = forced expiratory volume in 1 second

To detect chronic lung disease SCD patients should undergo lung function tests with estimation of gas transfer at least every 2 years. Abnormal lung function tests and high resolution CT (HRCT) chest scan are the most sensitive markers. Symptoms may overlap with those of pulmonary hypertension without underlying lung disease and chronic pulmonary thromboembolic disease. Echocardiography should also be performed at least every 2 years if patient has increasing dyspnoea or significantly impaired lung function.

### Investigation

- Chest X-ray
- Lung function tests including 6 minute walk test
- ECG and ECHO to determine ventricular hypertrophy and estimate pulmonary artery pressure
- ABG if SpO2 < 95%
- HRCT chest
- CT pulmonary angiogram or V/Q scan
- CRP - may be a useful marker
- $\alpha$ -1 antitrypsin status
- ACE, auto-antibodies including ANA

### Management

- Refer to Respiratory service – Dr Philip Ind
- Advice on smoking cessation if appropriate
- Prompt treatment of lower respiratory infection
- Ensure vaccination up to date

### 3. Chronic Pain

Refer to Trust guideline - Pain management guidelines for adult patients with acute or chronic pain 2013 ([http://source/prdcont/groups/extranet/@clinical/@guidelines/documents/ppgs/hhnt\\_000438.pdf](http://source/prdcont/groups/extranet/@clinical/@guidelines/documents/ppgs/hhnt_000438.pdf))

Chronic pain in patients with sickle cell disease refers to longstanding pain which occurs outside of an acute crisis. It is sometimes defined as pain which lasts more than 3 months or more simply “pain that does not go away”. There are 2 types of chronic sickle pain – that which is related to underlying pathology e.g. avascular necrosis or leg ulcers, or intractable pain with no obvious underlying cause; the latter is usually much more difficult to manage. Emotional distress, pain behaviours, altered mood, irritability, depression, anxiety, fear, sleep disturbance, loss of sexual drive, reduced self-esteem and family stress are all associated with chronic pain. These patients often access healthcare services frequently, require regular inpatient admissions and may take large doses of opioids and other analgesic drugs. The primary goal is to enable patients to manage their pain as effectively as possible while avoiding adverse effects associated with therapy.

Management should include:

- Thorough assessment and treatment of any underlying cause for the pain e.g. avascular necrosis
- Referral to the chronic pain service (refer to Dr Gillian Chumbley, Nurse Consultant, Chronic Pain Clinic, Charing Cross Hospital).
- Refer to clinical psychology (Dr Jeremy Anderson) for assessment and development of pain coping skills

Specific therapies indicated may include:

- Long-acting opioids – these can lead to tolerance or dependence so should be used with caution and closely monitored
- Adjuvant analgesics e.g. pregabalin, gabapentin
- Local anaesthetic/steroid injections
- Non-pharmacological therapies e.g. cognitive behavioural therapy, acupuncture, hydrotherapy
- Red cell exchange may be of benefit in individual patients

### 4. Avascular necrosis (AVN) of the hips and shoulders

AVN occurs in up to 20% of patients with SCD and often gives rise to chronic pain and limitation of movement due to joint damage. AVN of the femoral and humeral head are commonly associated. AVN typically develops from adolescence and reaches a peak incidence in young adults (25-35 years).

#### Symptoms

- Pain in the hip, leg, groin, knee or shoulder on movement e.g. walking
- Initially relieved by rest but later may become chronic
- Pain recurrent/prolonged - if > 8 wks should be investigated for AVN
- Limitation of movement; particularly abduction and external rotation of the hip, external rotation of the shoulder
- May be aggravated by or present in pregnancy

#### Differential diagnosis

- Osteomyelitis
- Septic arthritis
- Chronic pain syndrome

#### Investigations

- X-Ray
- MRI if XR normal

## Avascular necrosis of femoral head: Staging criteria

Stage	Clinical and Laboratory Findings
<b>0</b>	Patient is asymptomatic Radiography findings are normal Histology findings demonstrate osteonecrosis
<b>I</b>	Patient may or may not be symptomatic Radiography and CT scan findings are unremarkable AVN is considered likely based on MRI and bone scan results (may be subclassified by extent of involvement [see below]) Histology findings are abnormal
<b>II</b>	Patient is symptomatic. Plain radiography findings are abnormal and include osteopenia, osteosclerosis, or cysts Subchondral radiolucency is absent MRI findings are diagnostic
<b>III</b>	Patient is symptomatic Radiographic findings include subchondral lucency (crescent sign) and subchondral collapse Shape of the femoral head is generally preserved on radiographs and CT scans Subclassification depends on the extent of crescent, as follows: <ul style="list-style-type: none"> <li>- Stage IIIa: Crescent is less than 15% of the articular surface</li> <li>- Stage IIIb: Crescent is 15-30% of the articular surface</li> <li>- Stage IIIc: Crescent is more than 30% of the articular surface</li> </ul>
<b>IV</b>	Flattening or collapse of femoral head is present Joint space may be irregular CT scanning is more sensitive than radiography Subclassification depends on the extent of collapsed surface, as follows: <ul style="list-style-type: none"> <li>- Stage IVa: Less than 15% of surface is collapsed</li> <li>- Stage IVb: Approximately 15-30% of surface is collapsed</li> <li>- Stage IVc: More than 30% of surface is collapsed</li> </ul>
<b>V</b>	Radiography findings include narrowing of the joint space, osteoarthritis with sclerosis of acetabulum, and marginal osteophytes
<b>VI</b>	Findings include extensive destruction of the femoral head and joint

## Management

Treatment depends on the stage of disease and requires a multidisciplinary approach.

- Analgesia - NSAIDs and/or codeine derivative initially
- Rest and avoidance of weight bearing - often difficult in practice
- Physiotherapy/hydrotherapy
- Refer to Orthopaedic service - Mr Angus Lewis (Hip), Mr Peter Riley or Mr Andrew Forester (Shoulder)
- Core decompression may improve symptoms and delay progression
- Arthroplasty may be necessary if pain is continuous/severe or movement severely restricted
- Counsel preoperatively regarding the limitations of surgery including possibility of failure, likelihood of some residual pain/limitation of movement, greater risk of loosening and infection of the prosthesis in SCD and potential need for revision surgery due to life of the prosthesis
- Uncemented prostheses may carry lower complication rate
- Prior to surgery (ideally 3-5 days) perform red cell exchange to achieve HbS < 30%

## 5. Iron overload

Sickle cell patients are prone to iron overload due to increased intestinal absorption and multiple blood transfusions. The choice of iron chelators includes desferrioxamine (Desferal<sup>®</sup>), deferiprone (Ferriprox<sup>®</sup>) and deferasirox (Exjade<sup>®</sup>). **Note:** Deferiprone is not licensed for use in sickle cell disease but has been used in patients who are unable to tolerate licensed chelators or in those who develop cardiac iron overload.

See ICHT Guideline Clinical Management of Thalassaemia in Adults for individual drugs and their side-effects

### Indications

- Received >20 red cell units and on continuing transfusion programme
- Manual partial RCE programme - usually results in iron loading
- Patients on automated red cell exchange less prone to iron loading but still require monitoring for iron overload
- Ferritin should be checked on at least two occasions when the patient is in steady state prior to decision to start chelation therapy
- Ferritin should not be relied upon as the only criteria for initiating chelation treatment
- Other non-invasive methods of estimating iron loading should be used to guide the need for and monitor chelation therapy

### Investigation

- Baseline and annual ophthalmology and audiology review – if on desferrioxamine or deferasirox
- Glucose, cortisol, TSH+T4, FSH+LH, oestradiol/testosterone, PTH, IGF-1
- Creatinine Clearance/eGFR and urine PCR
- ECG and echocardiogram (if cardiac iron loading)
- If ferritin persistently raised (>1000µg/L) cardiac and liver iron estimation by MRI T2\* scan and liver R2 MRI (FerriScan)
- Renal profile and LFTs at least monthly (see below)
- 3 monthly ferritin and zinc (if on deferiprone)
- Alpha fetoprotein 6 monthly if confirmed/probable cirrhosis

### Monitoring of iron load

#### a) Serum ferritin

Serum ferritin is less reliable as a marker of iron overload in SCD as elevation may reflect an acute phase response.

#### b) Cardiac and hepatic T2\* MRI

Gradient-echo T2\* sequences are highly sensitive to magnetic properties of tissue iron. This technique provides accurate quantitation of cardiac iron load and function but estimation of hepatic iron the predominant site of loading in SCD is not quantitative. There is poor correlation between cardiac iron overload and serum ferritin or liver iron. The risk of impaired left ventricular function increases at T2\* values < 20 ms. Nearly all patients with clinical evidence of cardiac failure have a T2\* < 10 ms.

#### c) FerriScan<sup>®</sup> – R2 MRI

This is the preferred and only validated method for non-invasive quantitation of liver iron concentration (LIC). Results are unaffected by inflammation, fibrosis or cirrhosis unlike T2\* MRI. Dual analysis of cardiac T2\* and FerriScan can take place at the same visit to the MRI unit.

#### d) Liver biopsy

Ultrasound-guided percutaneous biopsy allows direct measurement of hepatic iron (as mg/g dry weight) and allows for assessment of hepatic fibrosis. The method is invasive and iron deposition can

be patchy and show variable reproducibility. This is not routinely performed in SCD and is reserved for individual patients e.g. suspected cirrhosis, or concomitant Hepatitis C infection in consultation with the Hepatology team.

### **Interpretation of liver iron concentration (LIC)**

A LIC <1.8 mg/g dry weight is normal. Levels of up to 7mg/g dry weight do not usually result in organ damage or endocrinopathy. A LIC >15 mg/g dry weight is associated with an increased risk of organ damage. The aim of chelation should be to achieve a LIC of 3-7 mg/g dry weight. At a LIC < 3mg/g dry weight there is a greater risk of chelator toxicity and dose reduction or treatment suspension should be considered.

### **Choice of chelator**

In SCD patients iron loading is predominantly hepatic for which the two options for first-line treatment are:

- Desferrioxamine by sc infusion
- Deferasirox po

Current or previous cardiac iron overload (uncommon in SCD):

- Consider Deferiprone
- For acute cardiac decompensation (e.g. cardiac failure or arrhythmia) desferrioxamine 40-50mg/kg/day by continuous IV infusion 24hrs/day 7 days/wk
- Once stabilized combination therapy should be considered

Nephropathy:

- Desferrioxamine may be given with caution with dosage adjustment
- Deferasirox (Exjade<sup>®</sup>) is contraindicated in patients with renal impairment though may be considered on an individual basis at reduced dose (5mg/kg/day initially) in patients with end-stage renal failure on dialysis with close monitoring of FBC and LFTs.

### **Dosing guide**

Previously untreated patients:

- sc Desferrioxamine 20-40mg/kg 5 nights/week over 10-12hrs via elastomeric infuser. Vitamin C enhances mobilization of iron stores and should be prescribed at a maximum dose of 100mg orally on days when the patient receives desferrioxamine. This should not be commenced until the patient has been on therapy for 6-8 weeks and must be avoided in patients with severe cardiac disease
- Deferasirox 20-30mg/kg/day

Deferasirox

- Initial dose 20mg/kg/day (can be increased up to 40mg/kg/day)
- Check Creatinine and measure eGFR before starting - contraindicated if <60ml/min
- Monitor FBC, Creatinine, LFTs, urine protein (dipstix) weekly for 1<sup>st</sup> month, then monthly
- Dosage reduction (by 10mg/kg/day) or discontinuation if progressive rise in Creatinine
- Measure Ferritin 3 monthly
- When dose increased or restarted after stopping monitor as above weekly for 1 month
- Patients with non-transfusional iron overload achieve negative iron balance at lower doses - start at 10-15mg/kg.

Deferiprone

- Initial dose 75mg/kg/day in divided doses (tds) - can be started at lower dose and increased over 4 weeks
- Maximum 100mg/kg/day in divided doses (tds)
- Weekly FBC

Combination therapy e.g. desferrioxamine 2-4 infusions/week + deferiprone 7 days/week

- Aim is intensive chelation rather than long-term therapy
- Risk of toxicity may be increased
- Close monitoring essential
  - Weekly FBC
  - 3 monthly biochemistry, Ferritin and Zinc levels
- 6 monthly T2\* MRI and liver FerriScan
- 6 monthly audiometry
- Review desferrioxamine frequency as ferritin falls
- When ferritin <1000 consider deferiprone monotherapy

For alternative combined chelation regimes see ICHT Guideline Clinical Management of Thalassaemia in Adults.

### Special considerations

- Patients with iron overload are at increased risk of infection due to siderophilic bacteria
- Iron chelation must be stopped and the patient admitted for treatment if there are any signs and symptoms of sepsis including Yersinia infection (abdominal pain and diarrhoea)
- Send blood and stool for culture including Yersinia - discuss with microbiology laboratory as culture conditions differ
- Antibiotics should include ciprofloxacin 400mg bd iv or ceftriaxone 2g od iv in G6PD deficiency if Yersinia infection is suspected
- Avoid nephrotoxic drugs and maintain hydration especially if on deferasirox
- Advise on need for rapid assessment of sepsis -1% risk of agranulocytosis and other cytopenias with deferiprone

## 6. Vitamin D deficiency

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

All patients with SCD should have vitamin D levels checked regularly (at least 6 monthly) and if deficient should be replaced according to ICHT Guidelines Vitamin D replacement in adults [http://source/prdcont/groups/extranet/@clinical/@guidelines/documents/ppgs/id\\_028408.pdf](http://source/prdcont/groups/extranet/@clinical/@guidelines/documents/ppgs/id_028408.pdf)

- Normal level 70-150 nmol/L
- Vitamin D level <40 nmol/L (deficiency) – prescribe loading dose colecalciferol 20,000 units weekly for 12 weeks followed by maintenance dose
- Vitamin D level 40- 69 nmol/L (insufficiency) – prescribe maintenance dose (either colecalciferol 20,000 every 2 weeks or Adcal D3 2 tablets daily)

## 7. Endocrinopathy

Endocrine complications can occur in patients with sickle cell disease as a consequence of iron overload or long-term opioid use. All patients at risk should have a full endocrine screen at least annually. Any new or suspected endocrine complications that develop should be discussed with the Endocrinology team with arrangement for specialist review according to urgency (Dr Jeannie Todd, Consultant Endocrinologist - extn. 34823)

Endocrine screen should include (see annual review proforma – appendix 3)

Glucose  
T4 and TSH  
Parathyroid hormone  
Cortisol  
Oestradiol/Testosterone  
LH and FSH  
IGF-1

## 8. Leg ulcers

Up to 20% of SCD patients develop leg ulcers. These are more common in males and frequently recur. Other causes including diabetes, venous insufficiency and connective tissue disorders should be excluded. Hydroxycarbamide has been associated with leg ulcers in other patient groups so should be used with caution in this setting. If leg ulceration develops while a patient is taking hydroxycarbamide this should be discussed with the Red Cell Consultant or at Red Cell MDT.

All patients who develop leg ulcers should be referred to a Tissue Viability service for assessment. The Haemoglobinopathy CNS will advise on the appropriate community service. Vascular imaging should be performed to identify patients with venous incompetence.

Management comprises:

- Swab for MCS
- Antibiotics if clinical signs of infection
- MRI if underlying osteomyelitis suspected
- Bed rest and elevation - effective but difficult to sustain
- Wet-to-dry dressings applied daily
- Zinc supplementation
- Compression stockings/Unna boots
- Topical morphine gel - may be effective if pain not relieved by oral analgesics
- Pregabalin/Gabapentin if neuropathic pain
- Consider transfusion programme (usually for 6 months) if recurrent or resistant
- Maggot debridement in individual cases

## **TRANSITION FROM PAEDIATRIC TO ADULT SERVICE**

A care plan should be agreed for all patients with sickle cell disease before they are transferred from Paediatric to Adult services. For adolescent and young adult patients attending ICHT this is developed jointly between the Paediatric Haematology and Adult Clinical Haematology teams in discussion with the patient during visits to the monthly Transition Clinic held at St Mary's Hospital. Details of the transition process are provided in the ICHT Policy for Transition of Haemoglobinopathy Patients From Paediatric to Adult Services 2014.

## TRANSFUSION

Transfusion is undertaken in SCD to improve haemoglobin level and/or reduce HbS%. There is little evidence that transfusion is of benefit in the management of an uncomplicated acute painful crisis. Regular transfusion reduces the risk of vaso-occlusive crisis, acute chest syndrome and stroke. Indications are discussed in more detail in individual sections of the guideline. The risks associated with transfusion include acute transfusion reactions, allo-immunisation against blood group antigens, transmission of viral infection and, in the long-term, iron overload. Serious hazards are rare and minimized by meticulous attention to protocols in transfusion practice (see ICHT Blood Transfusion Policy for Adults).

Elective transfusions are undertaken in the Haematology Day Care Unit at Hammersmith Hospital. For patients who require regular transfusions these should be arranged with minimum disruption to everyday life. To facilitate this the Day Care Unit (extn. 34594) operates 7 days a week with extended hours Monday to Friday. Transfusion should be commenced within 1 hour of the patient's attendance.

Patients with sickle cell disease often have poor peripheral venous access. It is recommended that no more than 3 attempts should be made by an individual practitioner. If initial attempts fail a more experienced practitioner should attempt cannulation. If unsuccessful after a maximum of 10 attempts, the Day Care or Red Cell SpR/SHO should decide on further management. This may involve further cannulation attempts using ultrasound guidance, insertion of a femoral line or seeking assistance from the anaesthetic team.

Patients on a regular transfusion programme should have an individual transfusion plan that is reviewed on a regular basis or if there is any notable change such as a new alloantibody or a significant transfusion reaction (see BCSH Guideline on the Investigation and Management of Acute Transfusion Reactions 2012). Pre- and post-transfusion Hb levels should be reviewed by the SHO/SpR responsible for Day Care and at outpatient visits. Hb and HbS% should be checked before and after each transfusion.

### Simple ('top up') transfusion

This may be given to correct acute anaemia e.g. aplastic crisis, splenic/hepatic sequestration or haemolysis.

- Indications include Hb < 50 g/l or fall in Hb > 30 g/l below steady state
- Target Hb 80-90 g/l - in splenic/hepatic sequestration top up to steady state level (see above)
- Maximum increment in Hb 40 g/l
- Keep haematocrit < 0.35 - higher levels may be detrimental in SCD due to increased blood viscosity
- Avoid diuretics

As a general guide transfusing a volume of 4ml/kg will typically give an increment in Hb of 10g/l. The concept that one unit of red cells gives a Hb increment of 10g/l is only applicable in a 70-80 kg patient and should not be applied to patients of lower body weight. In patients with normal cardiac function transfusion is administered at a rate of 2-3 hours per unit.

### Exchange transfusion

Exchange transfusion is indicated when a rapid reduction in the proportion of cells containing HbS is required or to maintain HbS < 30% in order to prevent specific complications. It may also be considered to limit iron overload in patients who require regular transfusion. The ICHT Standard Operating Procedure for Automated or Manual Red Cell Exchange should be followed.

## **Exchange transfusion must be approved by a Red Cell Consultant or at Red Cell MDT meeting**

Exchange transfusion is considered in the following situations:

### **a) Urgent exchange transfusion**

- Acute neurological events - stroke, subarachnoid haemorrhage
- Acute chest syndrome
- Multi-organ failure
- Severe sepsis
- Systemic fat embolism syndrome
- Progressive hepatopathy e.g. intrahepatic cholestasis
- Priapism - acute fulminant (refractory to pharmacological therapy/aspiration)
- Girdle syndrome
- Emergency surgery or endoscopic intervention

### **b) Elective exchange transfusion**

- Secondary stroke prevention
- Preparation for surgery
- Pregnancy - maternal sickle cell related complications
- Recurrent painful crises if hydroxycarbamide ineffective, refused or contraindicated
- Recurrent acute chest syndrome if hydroxycarbamide ineffective, refused or contraindicated
- Leg ulcers refractory to other measures
- Recurrent priapism
- Pulmonary hypertension
- Chronic sickle lung disease
- Anaemia due to chronic kidney disease if erythropoietin ineffective

### **Hypertransfusion**

A programme of hypertransfusion may be considered as an alternative to regular exchange transfusion in patients with chronic organ damage or intractable painful crises particularly those with poor vascular access. The aim is to keep the Hb level above the patient's steady state thereby suppressing endogenous erythropoiesis to maintain an HbS% below 30%. This usually requires transfusion every 4 weeks. More rapid iron overload is a disadvantage. Hypertransfusion should only be undertaken after discussion with the Red Cell Consultant or at Red Cell MDT meeting.

### **Consent**

The benefits and risks of transfusion must be explained to the patient and written information provided. Valid consent for blood transfusion should be obtained in accordance with Advisory Committee for the Safety of Blood Tissues and Organs guidance:

[https://www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/216586/dh\\_130715.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/216586/dh_130715.pdf)

Patient information sheets are available from NHS Blood and Transplant at:

<http://hospital.blood.co.uk/patient-services/patient-blood-management-resources/patient-information-leaflets/>

### **Pre-transfusion testing**

All patients should have extended red cell phenotyping prior to their first transfusion or genotyping (see above) if they have been recently transfused and information on their red cell phenotype is not available. For patients previously transfused elsewhere, historical allo-antibody status should be ascertained even if no allo-antibodies are currently detectable.

Outpatients attend the Haematology Day Care Unit for pre-transfusion testing. Cross-match samples must be collected no more than 72 hours prior to transfusion.

### **Virology**

All patients should be vaccinated against Hepatitis B if non-immune. Antibody levels should be checked at least every 5 years and booster doses given as needed. Hepatitis B surface antigen + HCV and HIV antibodies should be tested before transfusion and the latter repeated annually if receiving regular transfusion.

### **Selection of red cell units**

NHSBT supplies SAG-M blood which comprises packed red cells in preservative (saline, adenine, glucose and mannitol) with a haematocrit of 0.5 -0.7. For transfusion in SCD these should be:

- Matched for ABO, Rhesus (D, C, c, E, e) and Kell (K) blood group antigens
- HbS negative
- Where possible less than 7 days old
- Negative for blood group antigens to which the patient has developed alloantibodies

## REPRODUCTIVE HEALTH

### 1. Pregnancy

Adapted from the NW London Haemoglobinopathy Network protocol for management of pregnancy in women with SCD (2013)

#### Antenatal Care

Pregnancy in SCD has been associated with increased maternal and perinatal morbidity which can be minimised by careful management. This should be discussed before conception with advice to report pregnancy as soon as possible to facilitate arrangements for specialist antenatal care. Women with SCD who are pregnant should be managed at Queen Charlotte's and Chelsea Hospital(QCCH) under the joint care of Mr Andrew McCarthy, Consultant Obstetrician and Dr Mark Layton, Consultant Haematologist.

Referral to QCCH should be discussed at the earliest opportunity with any pregnant woman with sickle cell disease who presents to the antenatal clinic or haematology clinic. This referral can be made by either the obstetric or haematology team, whichever sees the patient first. The patient's GP should also be informed. A referral should be made to Mr McCarthy and to Dr Mark Layton as soon as possible, preferably before 12 weeks of gestation. The patient will be seen in the joint Obstetric Haematology on a Monday morning and followed up at QCCH until after delivery. The clinic is located on the the 2<sup>nd</sup> floor of QCCH in the Centre for Fetal Care (Tel: 020 3313 3998).

If the patient presents initially at their local antenatal clinic, the midwife should check that the woman's partner has been offered testing and his Hb status verified. Responsibility for this rests with the designated local specialist midwife or nurse. The specialist midwife/nurse will offer genetic counselling and if requested partner testing. If the couple is at risk of having a child with a major haemoglobinopathy they will be offered the option of prenatal diagnosis.

#### Referral

- Refer to QCCH as early as possible ideally before 12 weeks gestation
- Refer directly to Mr McCarthy, Consultant Obstetrician and Dr Layton
- Contacts:

Mr Andrew McCarthy  
Bleep 5116  
Secretary: 0203 3133514  
Fax: 0203 3133521  
Email: [andrew.mccarthy@imperial.nhs.uk](mailto:andrew.mccarthy@imperial.nhs.uk)

Jeanette Kerr, Specialist Midwife, QCCH  
Tel: 0203 3135108  
Fax: 0203 3133507  
Email: [Jeanette.Kerr@imperial.nhs.uk](mailto:Jeanette.Kerr@imperial.nhs.uk)

- Referral letter should include:
  - Biographical details including telephone number
  - Summary of obstetric and medical history
  - Details of any alloimmunization against blood group antigens
  - G6PD and hepatitis status
  - Latest FBC and iron status
  - Partner's haemoglobinopathy status if known
  - Analgesic preference or individual analgesia protocol
  - Details of specific therapy e.g. hydroxycarbamide, transfusion

## Initial assessment

- Normal antenatal booking procedure
- Booking bloods should include:
  - FBC and reticulocytes
  - HbS, F and A2 quantitation
  - Renal profile
  - LFTs
  - Extended red cell phenotype (if not known) and antibody screen
  - Ferritin, iron and TIBC
  - G6PD status if not known
  - Malaria screen if history of travel to endemic area within the past 12 months
- Nuchal/Combined screening test (CST) scan should be offered if appropriate
- US to estimate gestational age
- Urinalysis and MSU
- SpO2 on air
- Echocardiogram – to screen for pulmonary hypertension
- Pulmonary function tests if resting SpO2 <95%
- Refer to Ophthalmology if not assessed within last 6 months or history of retinopathy
- Review vaccine history
- Offer genetic counselling if applicable – information leaflets for carriers and couples at risk of having a child with a clinically significant haemoglobin disorder are available in the joint clinic and at:
  - Adult carriers: sickle cell, thalassaemia, unusual haemoglobin – GOV.UK
  - or
  - <http://www.chime.ucl.ac.uk/APoGI/>

## Medication

- Iron supplements should **only** be given if deficiency is confirmed biochemically
- Folic acid 5mg od po if not already receiving - continue throughout pregnancy
- Penicillin V 250mg bd po
- Commence low dose aspirin (75mg daily po) - to reduce pre-eclampsia risk
- Avoid NSAIDs
- If requiring long term opioids for pain discuss implications for neonate including abstinence syndrome
- Iron chelation therapy should be stopped preferably 3 months prior to conception or immediately after confirmation of pregnancy
- Hydroxycarbamide should be stopped at least 3 months prior to conception - if not counsel about risk of teratogenicity

## Follow up

- Frequency of review
  - 12-24 weeks 4 weekly
  - 24-36 weeks 2 weekly
  - 36 weeks to term Weekly
- Frequency will be increased if there are any concerns
- Monitor for pre-eclampsia at each visit - weight, blood pressure and proteinuria
- If significant red cell alloantibodies are detected serology should be repeated every 2 weeks from 16 weeks gestation and if indicated fetal anaemia assessed by MCA velocity on Doppler US
- Discuss timing and mode of delivery

### **Ultrasonography**

- 12 weeks Nuchal/Combined screening test (CST) scan
- Booking Routine booking scan
- 20 weeks Anomaly scan (with uterine artery Doppler)
- From 26 - 28 weeks until term At least monthly growth scan
- Risk of IUGR increased - US combined with Doppler of umbilical artery and liquor volume estimation

### **Other investigations**

- FBC monthly
- Renal function should be checked every 4 - 8 weeks - more frequently if initially abnormal
- Monitor anti-Xa assay if on treatment dose LMWH or at risk of accumulation
- MSU if UTI suspected clinically/on urinalysis – UTI is common and often asymptomatic

### **Thromboprophylaxis**

- It is recommended prophylactic LMWH is started at booking in women with
  - Previous thrombosis
  - Family history of thrombosis
  - Genetic or acquired thrombophilia
  - Other high risk factors e.g. age, BMI
- Standard regime is enoxaparin 40mg od sc (20mg if creatinine clearance <30ml/min) self-administered in the morning
- Prophylactic LMWH should be offered to all woman post-delivery and continued for 6 weeks
- Introduce earlier if additional risk factors develop during pregnancy e.g. pre-eclampsia, immobility, nephrotic syndrome

### **Blood Transfusion**

- Routine blood transfusion is not indicated for the majority of women with SCD during pregnancy
- Red cell transfusion must only be given antenatally in discussion with the Red Cell SpR or Consultant
- Transfusion should be considered in women who are severely affected prior to pregnancy (particularly if previously on long term transfusion or hydroxycarbamide) or who develop complications during pregnancy
- Indications include frequent pain episodes, chest crisis, severe anaemia (symptomatic with Hb < 60g/l or >15% reduction in Hb from steady state), pre-eclampsia, recurrent pregnancy loss, multiple pregnancy, and IUGR
- Once initiated transfusion (top up or exchange) will often be continued on a regular basis every 4-6 weeks until term
- Red cell exchange should achieve a target Hb of 100-110g/l/Hct 0.32 – 0.34) and maintain the HbS <30%. Care must be taken to avoid volume fluxes which can precipitate labour
- Blood should be matched for ABO, full Rh and Kell blood groups, HbS negative and CMV negative. The request form should clearly identify that the patient has SCD and is pregnant

### **Admission with acute complications during pregnancy**

- < 20/40 admit to HH or local hospital if non-HH patient
- > 20/40 admit to QCCH via Delivery Suite
- If admitted to QCCH inform Haematology SpR and attending/on-call Red Cell Consultant
- Manage acute complications according to relevant sections of Adult Sickle Cell guideline
- Follow patient's agreed individual pain protocol
- 3L intravenous fluids/24 hours if renal function normal
- Monitor fluid balance

- If there is evidence of pre-eclampsia fluid replacement should be given more cautiously
- Hourly observations including SpO2 **on air**
- If SpO2 < 95% on air oxygen via mask
- If SpO2 < 92% on air perform ABG and inform Haematology SpR
- If significant fever or symptoms of infections – cefuroxime iv and clarithromycin po
- Commence enoxaparin 40mg od sc (20mg if creatinine clearance <30ml/min) if not already receiving
- At least daily review by Red Cell team

## Delivery

- On admission to QCCH (Delivery Suite or Antenatal Ward) in labour notify:
  - Obstetrics - SpR and Consultant
  - Anaesthetics - SpR and Consultant
  - Haematology – Red Cell/On-call SpR and Red Cell Consultant
- The Haematology SpR or Red Cell Consultant should be informed immediately if there are any impending or actual complications
- Routine blood tests (FBC and Retics, U&Es, LFTs, Coagulation screen, Group and Save) should be taken
- During labour, induction and delivery a fluid intake of 3-4 L/day should be maintained (unless there are features of pre-eclampsia) with analgesia as required
- Delivery should be covered with prophylactic antibiotics as per Trust maternity guideline.
- Epidural anaesthesia/Regional block for labour analgesia or Caesarean section should be discussed with the on-call anaesthetist
- If receiving prophylactic LMWH an anti Xa assay should be performed. If this is normal or it is >12 hours since the last dose and coagulation screen normal it is safe to proceed with epidural anaesthesia. If no anti Xa assay is available and it is < 12 hours since the last dose or coagulation screen abnormal discuss with the on call anaesthetist
- If general anaesthesia is required discuss indication for blood transfusion prior to surgery with Haematology SpR or Red Cell Consultant
- Continue intravenous hydration (3-4 L/day) and supplemental oxygen for 24 hours post delivery with close monitoring of fluid balance
- SpO2 on air should be checked hourly and the Haematology SpR notified immediately if it falls below 92%
- After Caesarean section monitor on Delivery Suite for at least 24 hours with incentive spirometry every 2-4 hours
- All women with SCD should be reviewed by the physiotherapist post-delivery
- Early ambulation should be encouraged
- In high risk patients consider continuous positive airways pressure (CPAP) post Caesarean section
- Diclofenac pr may be useful for moderate-severe pain post Caesarean section
- Review at least daily by the Red Cell team
- The patient should not be discharged for at least 48 hours post delivery
- If there is a risk of a major haemoglobinopathy in the neonate the option of screening on a liquid sample should be discussed and arranged if requested - All neonates undergo neonatal screening for haemoglobinopathies via the Guthrie card
- There should be an agreed discharge plan

## Postnatal follow up

- Review 6 weeks in joint clinic at QCCH
- If complications develop before this see at QCCH with joint review by Red Cell and Obstetric teams
- Discuss contraceptive options
- Arrange follow up in Red Cell clinic Hammersmith/St Mary's Hospital or at local centre

## **2. Contraception**

The progestogen only pill, medroxyprogesterone acetate by im depot or subdermal progesterone implant are preferred methods because of their reliability and the theoretically increased risk of stroke and venous thromboembolism with the combined oestrogen containing contraceptive pill (COCP). However if these methods are unacceptable or unsuitable a low dose COCP can be considered after discussion with the patient. A copper intrauterine contraceptive device ('coil') suffers the disadvantage it may carry a risk of menorrhagia or infection. The Mirena coil reduces menstrual loss by up to 80% and should be considered.

## **3. Termination of pregnancy**

Surgical termination of pregnancy should be avoided, where possible, as it carries a risk of post-operative complications. Medical termination is preferable where practical. Follow procedure for anaesthesia and surgery (see below) if indicated.

## **4. Fertility**

Fertility in women with SCD is not impaired. In men a variety of factors including priapism, testicular infarction, hypogonadism and possibly hydroxycarbamide therapy may contribute to reduced fertility. Patients with irreversible erectile dysfunction due to priapism should be offered referral for consideration of implantation of a penile prosthesis. Couples who have not conceived after 1 year of regular unprotected sexual intercourse should be offered assessment through the Assisted Conception Unit (Mr Stuart Lavery).

## **SURGERY AND ANAESTHESIA**

Surgery in SCD is associated with increased peri-operative risk. Close collaboration between the surgeon, haematology team and anaesthetist in formulating an individual management plan is essential to minimize this. The Red Cell SpR/Consultant or Haemoglobinopathy CNS must be informed of any patient with SCD who is due to undergo surgery. The patient should be listed for elective surgery well in advance of the operation date (a minimum of 2 weeks) to allow pre-operative assessment and time to plan red cell exchange if indicated.

### **1. Pre-operative assessment**

- Assess cardiac, pulmonary and renal function before intermediate/high risk surgery to identify patients at higher risk of peri-operative complications
- Arrange HDU bed if required
- Identify any special analgesic requirements
- Consider the need for pre-operative transfusion or exchange blood transfusion

### **2. Procedure for surgery and anaesthesia**

- Admit to the ward the day before procedure - Day case surgery is contraindicated
- Assess for recent complications including vaso-occlusive crisis during the past week
- Elective surgery should be cancelled if the patient is febrile or has a sickle cell crisis and the Red Cell/on-call Haematology SpR contacted
- Check bloods including FBC and reticulocytes, renal profile, LFTs, coagulation screen and group and save/cross match
- Start iv fluids as soon as nil by mouth and continue until able to take oral fluids freely
- Hyperoxygenation with 100% oxygen at induction and reversal of anaesthesia
- Monitor SpO<sub>2</sub> from pre-medication until at least 24 hours after surgery and provide supplemental O<sub>2</sub> to maintain normoxaemia – inform Red Cell/on-call Haematology SpR immediately if SpO<sub>2</sub> < 92%
- Antibiotic prophylaxis (see ICHT Surgical Prophylaxis guideline)
- Keep the patient normothermic throughout the perioperative period
- Intraoperative blood salvage is contraindicated
- Avoid tourniquet use unless absolutely essential and patient exchange transfused (see below)
- For thoracic, abdominal, pelvic and airway related surgery, CPAP on HDU or ITU post operatively for a minimum of 24 hrs is recommended
- Prophylactic post-operative chest physiotherapy, including incentive spirometry if not on CPAP, should be instituted
- Ensure adequate analgesia taking account of preoperative requirements and opioid tolerance

### **3. Pre-operative transfusion**

The need for pre-operative transfusion in SCD should be decided well in advance taking account of the clinical status of the patient and type of surgery planned. In some patients undergoing minor surgery transfusion may be avoided. A recent UK-led multi-centre, randomised control trial of patients with HbSS and HbSβ<sup>0</sup> thalassaemia looked at the benefit of pre-operative transfusion in low and medium risk surgery e.g. cholecystectomy, joint replacement, tonsillectomy (TAPS study, Lancet 2013; 381: 930–38). The incidence of adverse events (mainly chest crisis) was significantly higher in the non-transfused group. Pre-operative transfusion may therefore be of benefit even in relatively low-risk surgery.

A lower threshold for exchange transfusion may be applied in patients who are severely affected particularly if they have impaired cardiac or pulmonary function. The timing of transfusion in relation to surgery is important so it is essential that once set the date of the procedure is not changed. The optimal time to undertake transfusion is 3-5 days before surgery. Guidance on indications is provided below but this does not replace the need for individual discussion.

### **a) Top up transfusion**

Indications

- Low/Medium risk surgery if Hb < 90g/l

The target Hb should not exceed 100-110g/l and the patient should have no additional significant risk factors (see below).

### **b) Exchange transfusion**

Indications for exchange transfusion - target HbS < 30%

- High risk surgery
- History of significant risk factors e.g. acute chest syndrome, frequent painful crises, chronic lung disease, pulmonary hypertension
- Low/Medium risk surgery if Hb > 90g/l

Mandatory indications for exchange transfusion include:

- Eye surgery (excluding cataract)
- Neurosurgery
- Organ transplantation
- Cardiothoracic including bypass surgery (involves hypothermia)
- Orthopaedic procedures requiring tourniquet

## HYDROXYCARBAMIDE THERAPY

Adapted from NW London Haemoglobinopathy Network Hydroxycarbamide Guideline for the Treatment of Sickle Cell Disease (2015).

### 1. Background

Hydroxycarbamide (HC), also known as hydroxyurea, is the first drug shown to ameliorate the clinical severity of SCD. HC decreases the frequency of painful crises, reduces the number of episodes of acute chest syndrome (ACS) and reduces blood transfusion requirements. It also has a role in children with some forms of transfusion dependent anaemias such as haemoglobin E  $\beta$ -thalassaemia and may improve growth and prevent hyposplenism in children with SCD. Evidence indicates HC improves survival in SCD. The mechanism of action is not fully understood but it is known to increase fetal haemoglobin (HbF), improve red cell hydration, and reduce the leucocytosis and thrombocytosis commonly seen in SCD. This guideline focuses on the role of HC in sickle cell anaemia (HbSS). While HC has been shown to be of benefit in other sickle disorders e.g. HbSC disease its use in this setting should be discussed on an individual basis.

HC therapy should be used with caution but offered to all patients who may benefit. It is not currently recommended as an alternative to transfusion in patients with known stroke risk. HC is cytotoxic and causes dose-dependent myelosuppression. The clinically effective dose may approach or overlap with that causing myelosuppression. Patients receiving HC must therefore be monitored regularly. Those recently started on treatment, medically unstable or receiving maximum tolerated dose (MTD) require more frequent follow-up.

HC has been used for over twenty years in SCD and studies show it to be effective and safe. There remains some uncertainty surrounding its long-term safety and side effects however among patients with severe SCD overall survival is better in those who receive HC. These issues must be discussed with the patient prior to commencing treatment with HC.

### 2. Indications and exclusions

#### Indications

HC is recommended for patients with clinically severe or moderate SCD defined by any of the following:

- 3 or more admissions with painful crises in the previous 12 months or recurrent crises at home requiring frequent time off work or affecting normal daily routine
- 2 or more episodes of acute chest syndrome
- 1 episode of ACS requiring IPPV

Other potential indications should be discussed on an individual basis in the Red Cell MDT meeting or with the Red Cell consultant.

#### Exclusions

- Pregnancy or breast-feeding
- Risk of pregnancy - patient not using contraception
- Liver disease - ALT  $>2$  x upper limit of normal unless due to hepatic iron overload in which case use with caution
- Likely poor adherence with monitoring
- On transfusion programme (unless decided on individual basis to establish patient on HC therapy before discontinuing regular transfusion)
- Renal impairment - if considered reduce dose due to increased risk of myelosuppression

HC should be used with caution in patients with a history of leg ulcers.

### 3. Information and consent

- Explain and document potential benefits and known side effects/toxicity including risk of cytopenia (low if monitored and reversible), nail pigmentation (common but reversible), skin pigmentation (rare but reversible), evidence of reduction in sperm count in some cases and theoretical long-term risk of leukaemia (for which in SCD there is currently no evidence) or other malignancy
- Provide copy of HC information leaflet to patient, GP and Community Haemoglobinopathy Nurse/Counsellor
- Advise on avoidance of live vaccines while taking HC
- Provide local Clinical Haematologist and Nurse Lead (if applicable), GP and Community Haemoglobinopathy Nurse/Counsellor with copy of HC guideline
- Obtain written consent from patient (and parent if under 18 years).

### 4. Initiation and monitoring

Before initiating HC therapy assess risk of pregnancy and document LMP. Patients should be provided with contact details for clinical advice, warned about the potential danger of cytopenia and instructed to seek medical advice urgently if they develop petechiae, bruising, bleeding or fever.

All males should be offered sperm cryopreservation (via the Andrology Department at Hammersmith Hospital) prior to commencing HC.

Start at 15 mg/kg/day to nearest 500 mg (HC is available as 500mg capsules) increasing after intervals of 4 weeks by 5mg/kg/day. To achieve the correct average daily dose it may be necessary to alternate doses or omit the drug on certain days. The usual maximum dose is 15-30mg/kg/day (a few patients tolerate up to 35mg/kg).

To achieve MTD:

- Escalate HC dose as above
- Follow monitoring schedule in section 6 below
- Stop HC if cytopenia develops

This is defined by **any** of the following:

Neutrophils  $< 1.5 \times 10^9/L$  (consider a lower figure if there is evidence of ethnic neutropenia)  
Platelets  $< 80 \times 10^9/L$   
Reticulocytes  $< 1\%$   
Haemoglobin  $> 30g/l$  below baseline

- Monitor FBC weekly (or more frequently if indicated) until neutrophils  $> 1.5 \times 10^9/L$  and platelet and reticulocyte count are in the normal range (generally 1-2 weeks)
- Reintroduce HC at 2.5mg/kg/day or 500mg daily/alternate days **below previous dose**
- Monitor FBC weekly for 2 weeks at this dose
- If blood counts remain stable this constitutes MTD

Some patients show significant clinical benefit at doses below MTD. If sustained a decision may be taken to continue at a fixed dose rather than escalate to MTD.

Clinical benefit may not be apparent for several months (until the proportion of HbF containing cells increases). It is important to encourage the patient to persevere with treatment until a therapeutic dose is reached. Consider stopping HC therapy if after 12 months there has been no significant benefit.

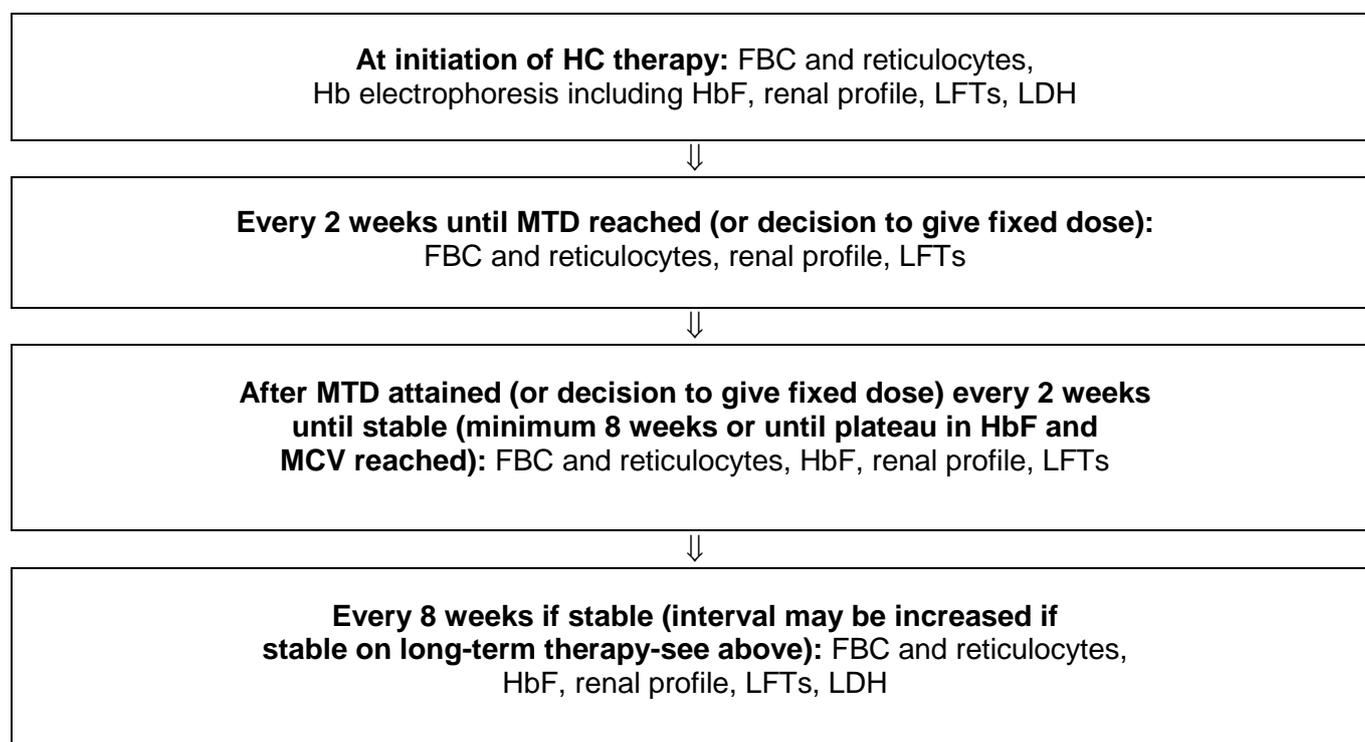
At each attendance include documentation of:

- Frequency of painful episodes
- Other clinical benefit
- Any side effects
- Adherence with treatment and monitoring
- Spleen size (splenic regrowth associated with risk of sequestration has been described in children)

Once established on HC therapy the suggested frequency of review is:

- MTD regime - 6-12 weeks
- Fixed dose regime 2-6 months

Follow the schedule below for laboratory tests:



## 5. Management of side effects

### a) Myelosuppression

If clinically significant cytopenia develops:

- Stop HC
- Consider G-CSF or blood product support
- Monitor FBC weekly or more frequently if indicated
- Reintroduce HC as per schedule above for MTD

### b) Rise in haemoglobin

Venesect if Hb rises to > 120 g/l or > 30 g/l above baseline **with** symptoms of hyperviscosity

## OUTPATIENT MANAGEMENT

Clinics for patients with haemoglobinopathies are held weekly at Hammersmith Hospital (Thursday afternoon) and St Mary's Hospital (Friday morning). The CNS for Haemoglobinopathies, Specialist Social Worker and Clinical Psychologist attend the clinic on a Thursday afternoon.

### 1. First appointment (New Patients)

#### History and examination

- Take full medical, psychosocial and family history
- Record weight, height, BP and SpO<sub>2</sub>
- Complete a full examination including cardiorespiratory and abdominal examination (record liver and spleen size if enlarged)
- Check for pallor and jaundice
- Document immunisation record including Pneumovax<sup>®</sup> II, Hib, meningococcal, hepatitis B and seasonal influenza vaccines
- Assess compliance with prophylaxis
- Explain diagnosis, its medical and genetic implications
- Discuss acute complications and their management
- Arrange screening for chronic complications including echocardiogram, pulmonary function tests, urine PCR and ophthalmology assessment
- If needed prescribe penicillin V 250mg bd po (erythromycin 250 mg bd if allergic) and folic acid 5 mg od
- Check the patient is registered with a GP
- Provide written information on SCD and details of Sickle Cell Society and local support group
- Issue a haemoglobinopathy card, and ensure patient has a haematology "passport" plus contact details for the hospital (Ambulatory care pain service, outpatient clinic, Day unit, consultant's secretary, haemoglobinopathy CNS and Specialist Social Worker)- Please refer to the separate pain service protocol and patient admission pathways on the source [http://source/prdcont/groups/extranet/@clinical/@guidelines/documents/ppgs/hhnt\\_000438.pdf](http://source/prdcont/groups/extranet/@clinical/@guidelines/documents/ppgs/hhnt_000438.pdf)
- Provide patient information leaflet and record consent if given for entry to National Haemoglobinopathy Registry (NHR)
- Assess need for psychosocial support
- Refer to MDT if indicated
- Arrange follow-up appointment

#### Investigation

- Confirm diagnosis with quantitative Hb separation (HbS, A<sub>2</sub>, F+/- other structural Hb variant)
- Check FBC, reticulocytes, renal profile, LFTs, LDH, ferritin, immunoglobulins, blood group and antibody screen, extended red cell phenotype (if not previously known and transfused within 3 months arrange blood group genotyping via NHSBT, Filton, Bristol), G6PD activity and vitamin D
- Hepatitis (ABC) and parvovirus B19 serology
- Full virology screen if due to undergo automated erythrocytapheresis
- Malaria screen if history of travel to endemic area within the past 12 months
- Urine PCR (protein:creatinine ratio)
- Baseline lung function, echocardiogram and eye review

### 2. Follow-up checklist

- Document any sickle-related or other health concerns since last visit
- Check immunisations are up to date
- Check compliance with Penicillin V and folic acid
- Record weight, BP and SpO<sub>2</sub>
- Cardiorespiratory and abdominal examination (record liver and spleen size if enlarged)
- Check for pallor and jaundice

- FBC and reticulocytes, renal profile, LFTs each visit
- Ferritin at least annually or 3 monthly if on iron chelation
- HbF if on hydroxycarbamide
- Urine PCR at least annually
- Complete annual review proforma(s) if indicated (see Appendix 3)
- Assess need for psychosocial support
- Refer to MDT if indicated
- Arrange follow-up appointment
- Enter data on NHR if patient previously consented

Stable patients without active complications are usually seen 3-6 monthly. Those with acute or chronic complications require more frequent assessment.

## 6) IMPLEMENTATION

Training required for staff	Yes
If yes, who will provide training	Mark Layton, Asad Luqmani, Lydia Alexander and Jeremy Anderson
When will training be provided?	Rolling programme of training for medical (including Haematology SHO and SPR induction), nursing and Acute Medicine staff
Date for implementation of guideline	October 2015

## 7) MONITORING / AUDIT

When will this guideline be audited?	October 2016 – Management of acute painful crisis in sickle cell disease
Who will be responsible for auditing this guideline?	Mark Layton
Are there any other specific recommendations for audit?	<ul style="list-style-type: none"> <li>- Monitoring of iron overload in thalassaemia and sickle cell disease</li> <li>- Effectiveness of exchange transfusions in sickle cell disease.</li> <li>- Hydroxycarbamide therapy in sickle cell patients.</li> <li>- Screening for endocrinopathy in sickle cell disease</li> <li>- Uptake of vaccination and penicillin prophylaxis</li> </ul>

## 8) REVIEW

When will this guideline be reviewed?	<p>Clinical treatment - 3 years (Mark Layton, Asad Luqmani and Diana Hagger)</p> <p>Drug related guidance – 2 years (Stephanie Kirschke)</p>
<p>Please indicate frequency of review:</p> <p>As a guide:</p> <ul style="list-style-type: none"> <li>• Drug related guidance should be reviewed every 2 years</li> <li>• Therapy related guidance should be reviewed every 5 years</li> <li>• Clinical treatment guidance should be reviewed every 3 – 5 years</li> </ul>	
Date of next review	October 2017

## 9) REFERENCES

Imperial College Healthcare NHS Trust (ICHT) (Dec 2014) Adult Treatment of Infection Policy

Imperial College Healthcare NHS Trust (ICHT) (Oct 2015) Guideline: Paediatric Sickle Cell Disease

Imperial College Healthcare NHS Trust (ICHT) (Oct 2015) Guideline: Clinical Management of Thalassaemia in Adults

Imperial College Healthcare NHS Trust (ICHT) (Dec 2014) Infection Prevention for Adult Patients with an Absent or Dysfunctional spleen

Imperial College Healthcare NHS Trust (ICHT) (Aug 2014) Policy for Transition of Haemoglobinopathy Patients From Paediatric to Adult Services

Imperial College Healthcare NHS Trust (ICHT) (Aug 2014) Blood Transfusion Policy for Adults

Imperial College Healthcare NHS Trust (ICHT) (Jan 2014) Adult Treatment of Malaria

## 10) GUIDELINE DETAIL

Start Date: (date of final approval by CPG)	October 2015	
Dates approved by:	<b>Divisional Guidelines Group (if applicable):</b> <b>Policies, Procedures and Ratification Meeting (PPRM)</b>	02.09.15
	<b>Directorate Quality and Safety Committee</b>	10.09.15
Have all relevant stakeholders (Trust sites, CPGs and departments) been included in the development of this guideline?	<p>Red Cell clinical team</p> <p>Surgery - Justin Vale, Justin Cobb</p> <p>Respiratory – Philip Ind</p> <p>ICU – Stephen Brett</p> <p>Ophthalmology – Graham Duguid</p> <p>Nephrology – Elaine Clutterbuck</p> <p>Microbiology – Claire Thomas</p> <p>Pharmacy – Stephanie Kirschke</p> <p>Obstetrics – Andrew McCarthy</p> <p>Paediatrics – Kirstin Lund</p>	
Who will you be notifying of the existence of this guidance?	<p>Divisional Directors</p> <p>Divisional Quality Leads</p> <p>Specialty Leads</p>	
Related documents:		
Author/further information:	<p>Dr Mark Layton            Consultant Haematologist            Surgery Cancer and Cardiovascular Division            Hammersmith Hospital            Telephone 31320  <a href="mailto:mark.layton@imperial.nhs.uk">mark.layton@imperial.nhs.uk</a></p>	
Document review history:	<p>Asad Luqmani September 2015</p> <p>Mark Layton October 2015</p>	
Next review due	October 2017	
THIS GUIDELINE REPLACES:	<p>Clinical Management of Sickle Cell Disease in Adults v1.0  <a href="http://source/prdcont/groups/extranet/@clinical/@guidelines/documents/ppgs/id_038400.pdf">http://source/prdcont/groups/extranet/@clinical/@guidelines/documents/ppgs/id_038400.pdf</a></p>	

## 11) INTRANET HOUSEKEEPING

Key words	Sickle cell disease Clinical management Adult
Which Division/Directorate category does this belong to?	Surgery, Cancer and Cardiovascular
Which specialty should this belong to when appearing on the Source?	Clinical Haematology
Title for the intranet if different from the document ( <i>please note that documents sit alphabetically so should <b>not</b> start with "guideline for..."</i> )	Sickle Cell Disease: Clinical Management (Adult)

## 12) Equality Impact of guideline

Is this guideline anticipated to have any significant equality-related impact on patients, carers or staff?

**No**

## Appendix 1: Prevention of infection in patients with sickle cell disease

### Antibiotic prophylaxis

- Penicillin V 250mg bd po (or erythromycin if penicillin allergic)
- In patients who decline to take long-term antibiotic prophylaxis it is recommended they are provided with a supply of broad spectrum antibiotics (e.g. co-amoxiclav 625mg tds po or if penicillin allergic doxycycline 200mg stat then 100mg od) to be taken for 7 days in the event of fever or other symptoms of infection

### Vaccination

a) Current British Committee for Standards in Haematology (BCSH) guidelines 2012 ([http://www.bcsghguidelines.com/documents/Review\\_of\\_guidelines\\_absent\\_or\\_dysfunctional\\_spleen\\_2012.pdf](http://www.bcsghguidelines.com/documents/Review_of_guidelines_absent_or_dysfunctional_spleen_2012.pdf)) recommend the following vaccinations to protect against infection for adults with splenic hypofunction such as in sickle cell disease:

- Polyvalent polysaccharide pneumococcal vaccine against 23 serotypes (PPV; Pneumovax<sup>®</sup> II). Ideally antibody response should be assessed 4-6 weeks after the initial vaccination. Serial measurements may guide the timing of booster vaccination. A small number of patients may be non-responders to PPV. These patients should be offered two doses of pneumococcal conjugate vaccine (PCV 13; Prevenar 13<sup>®</sup>) given 2 months apart.
- PPV should be repeated every 5 years.
- Haemophilus influenza b vaccine (Menitorix<sup>®</sup>; combination with meningitis C conjugate)
- Meningitis C conjugate vaccine followed 1 month later with 1 dose Men ACWY conjugate vaccine
- Influenza vaccine annually

In addition Meningitis B vaccine is recommended in hyposplenic patients (ICHT Guideline Infection Prevention for Adult Patients with an Absent or Dysfunctional spleen).

b) Prevention of transfusion acquired hepatitis B

All patients should be vaccinated against Hepatitis B if non immune. Antibody levels should be checked after completing vaccination, a minimum of 5 yearly thereafter and booster doses given as required.

### Other measures to prevent infection

SCD patients should be educated regarding food hygiene and the risks of infection with Salmonella and Yersinia (avoid unpasteurised dairy products and raw/undercooked pork) as well as overseas travel with specific reference to malaria and unusual infections, for example those resulting from animal bites and must be advised to take effective prophylaxis and precautions against malaria if travelling to an endemic area.



**Surgery in the last 12 months:** .....

**Blood transfusion/red cell exchange:** (dates) .....

(if regular complete Form 1b)

Any pregnancies / children within last 12 months.....

**Medications:**

**Individual analgesia protocol for initial management of acute pain crisis (drug/ suggested starting dose)**

.....  
.....

Penicillin Y/N Folic Acid Y/N

Hydroxycarbamide Y/N Dose.....

Iron chelation Y/N Medication/dose.....

Other medications (dose)

.....  
.....  
.....

**Known allergies:** .....

**Immunisations:** (dates given)

Pneumovax:..... Hepatitis B: .....

Hib/Meningitis C: .....

Influenza vaccine:.....

**Examination:**

Hepatomegaly: Yes/No Size(cm)..... Splenomegaly: Yes/No Size(cm).....

CVS.....Respiratory.....

Other .....

.....

**Annual investigations:**

1. Blood tests:

Steady state Hb.....

Retics.....

Hb F% (if on HCH ) ..... Hb S % ( if on Tx );.....

Creatinine/eGFR ) ..... Bilirubin..... ALT..... Calcium/Phosphate .....

Glucose..... Thyroid function..... Vitamin D ..... Ferritin.....

(Fasting if random > 6).....

Hepatitis B surface antibody..... Parvovirus status (if IgG negative) .....

2. Urine tests:

Dipstix/MSU.....

Protein/creatinine ratio.....

If persistently >50 have the following tests been checked? ANA, GBM, ANCA,C3, C4, serum and urine electrophoresis Y/N

Normal/abnormal (give details) .....

3. Echo: .....

(2 yrly if TR jet velocity < 2.5m/s, annual if > 2.5m/s or clinical need. Discuss at MDT meeting and refer to Pulmonary Hypertension service if >3.0m/s or if > 2.5m/s and symptomatic)

4. Pulmonary function tests: (2 yrly) .....

5. Imaging studies:

a) If on regular transfusion (also complete Form 1b) or if Ferritin consistently > 1000

Cardiac and liver T2\* (ms) on MRI .....

Liver Iron Concentration (Ferriscan) .....

b) DEXA scan (5 yrly) .....

c) Other.....

6. Retinopathy screen: .....

(All patients at diagnosis then as per clinical need)

**Management changes:**

**Name of person completing annual review:.....**

**IMPERIAL COLLEGE HEALTHCARE NHS TRUST:**

**Additional information regarding adults with Sickle Cell Disease receiving regular transfusion/exchange transfusion (Form 1b)**

Name:  
D.O.B:  
Hospital number:

Top up Tx Y/N  
Red cell exchange programme Y/N  
On iron chelation therapy: Y/N  
Deferasirox (Dose) .....  
Deferoxamine (Dose) .....  
Deferiprone (Dose) .....

Vascular access: Central/Peripheral

Transfusion interval ( weeks ) ..... Target end HCT:.....

Transfusion total;

Top up (units/year or mls/kg) .....

RCE (units per year ) .....

Pre-transfusion HbS% or S+C% ( range ) .....

Pre-transfusion Hb g/dl ( range ) .....

Serum Ferritin (last 3 results/dates).....

Red cell allo-antibodies- (specify antibody and if new).....

Other transfusion/chelation issues.....

Hepatitis B s Ag..... Hepatitis C antibody.....HIV.....

**Additional tests for adults on regular transfusion/RCE with iron overload**

TSH /T4..... FSH/LH..... Testosterone/oestradiol .....

Cortisol/ synacthen test .....

Calcium..... Parathormone ..... Glucose /GTT..... Zinc.....

Liver iron concentration (Ferriscan) .....

Cardiac T2\* MRI .....

Liver T2\* .....

If on iron chelation:

Audiology review date ..... Ophthalmology review date .....