NHS
West London
Haemoglobinopathy
Coordinating Centre

GUIDELINES FOR THE MANAGEMENT OF SICKLE CELL DISEASE IN ADULTS

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1) 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.

2) 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
ESRF	End stage renal failure
FBC	Full Blood Count
HCC	Haemoglobinopathy Coordinating Centre
HDCU	Haematology Day Care Unit
HDU	High Dependency Unit
HIV	Human immunodeficiency virus
HH	Hyperhaemolysis
ICHT	Imperial College Healthcare NHS Trust
IV	Intravenous
LDH	Lactate dehydrogenase
LFT	Liver Function Test
LNWUH	London North West Healthcare NHS Trust
MRI	Magnetic resonance imaging
MSU	Mid-stream urine
PCA	Patient controlled analgesia
PRN	As needed
RHTU	Renal Haematology Triage Unit
SDB	Sleep disordered breathing
SHO	Senior House Officer

SpR	Specialist Registrar
SGH	St George's University Hospitals NHS Foundation Trust
U&E	Urea and electrolytes

3) SCOPE

This guideline is directed at all clinical staff within the West London HCC 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 β-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(https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg61/)., BCSH Guidelines on the Management of sickle cell disease in pregnancy, for the monitoring and management of iron overload in patients with haemoglobinopathies and rare anaemias, for the use of hydroxycarbamide in children and adults with SCD and red cell transfusions in SCD part 1 and part 2 and Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK 2018

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

4) FULL GUIDELINE AND INDEX

1) INTRODUCTION 3

2) DEFINITIONS 3

3) SCOPE 5

4) FULL GUIDELINE AND INDEX 6

RED CELL TEAM 9

1. MANAGEMENT OF ACUTE COMPLICATIONS 10

1.1a Sickle pain crisis 10

1.1b Patient controlled analgesia (PCA) 17

1.2 Acute Chest Syndrome (ACS) 21

1.3 Infection 24

1.4 Acute abdominal pain/jaundice 27

a) Abdominal (mesenteric) crisis including 'girdle syndrome' 27

b) Sequestration syndromes 28

c) Biliary tract 30

d) Other causes of jaundice 31

1.5 Neurological complications 37

a) Stroke 37

b) Subarachnoid haemorrhage 38

c) Seizures 38

d) Headaches 39

e) Neurocognitive impairment 39

1.6 Priapism 40

1.7 Aplastic crisis 41

1.8 Renal 42

1.9 Ophthalmic Complications 43

2. MANAGEMENT OF CHRONIC COMPLICATIONS 45

2.1 Nephropathy 45
a) Screening in outpatients 45
c) Proteinuria 45
d) Hypertension 46
2.2 Pulmonary and cardiac Complications: 48
a) Pulmonary hypertension 48
b) Chronic Sickle lung disease (CSLD) 49
2.3 Chronic Pain 51
2.4 Avascular necrosis (AVN) of the hips and shoulders 52
2.5 Iron overload 55
2.6 Vitamin D deficiency 60
2.7 Endocrinopathy 60
2.8 Leg ulcers 60
3. TRANSITION FROM PAEDIATRIC TO ADULT SERVICES 62
4. TRANSFUSION 62
5. REPRODUCTIVE HEALTH 66
5.1 Pregnancy 66
5.2 Contraception (discussed at 6 week post-natal follow up appointment) 73
5.3 Termination of pregnancy 73
5.4 Fertility 73
6. SURGERY AND ANAESTHESIA 74
6.1 Pre-operative assessment 74
6.2 Procedure for surgery and anaesthesia 74
6.3 Pre-operative transfusion 75
a) Top up transfusion 75
b) Exchange transfusion 75
6.4 Emergency surgery 76
6.5 Patients who cannot be transfused 76

7. HYDROXYCARBAMIDE THERAPY 77

7.1 Background 77

7.2 Indications and exclusions 77

7.3 Information and consent 78

7.4 Initiation and monitoring 78

7.5 Management of side effects 80

a) Myelosuppression 80

b) Rise in haemoglobin 80

8. Other Disease Modifying Therapies 81

9. OUTPATIENT MANAGEMENT 81

9.1 First appointment (New Patients) 81

9.2 Follow-up checklist 82

10. Bone Marrow Transplant 83

11. HCC MDT 84

REFERENCE LIST 85

APPENDIX 1: PREVENTION OF INFECTION IN PATIENTS WITH SICKLE CELL DISEASE 86

APPENDIX 2: ANNUAL REVIEW PROFORMAS 88

APPENDIX 3: HCC OBSTETRIC SICKLE CELL – ANTENATAL REFERRAL PROFORMA 90

Appendix 4: NURSING TRAINING 92

Appendix 5: SICKLE CELL PATIENT CONTROLLED ANALGESIA (PCA) OBSERVATIONS AND COMPLICATIONS 93

APPENDIX 6: HCC CONTACT DETAILS 95

APPENDIX 7: HCC MDT REFERAL FORM 97

APPENDIX 8: MANUAL EXCHANGE PROTOCOL 99

RED CELL TEAM

Please find contact details for the respective Specialist Haemoglobinopathy Teams in the HCC in Appendix 6 of this document.

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1. MANAGEMENT OF ACUTE COMPLICATIONS

1.1a Sickle pain crisis

INTRODUCTION

This guideline is directed at all clinical staff caring for patients with sickle cell disease (SCD). It applies to all patients known to have SCD or who are diagnosed with SCD. SCD includes patients with sickle cell anaemia (HbSS) as well as those with compound heterozygous states (HbSC, HbSD, HbSO-Arab and sickle β-thalassaemia) and other less common conditions that give rise to a clinically significant sickling disorder. The guideline describes the clinical management of a sickle pain crisis and should be read in conjunction with NICE Guidance on the management of sickle cell acute painful episode (http://guidance.nice.org.uk/CG143).

This is an overarching guideline covering the principles of how to manage a sickle pain crisis. Local protocols should be referred to for specific management plans including drug choice and dosages

ACUTE ADMISSIONS PATHWAY

Local admissions procedures should be followed. All patients should be triaged urgently and receive their first dose of analgesia within 30 minutes of arrival.

ICHT

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. Patients should contact the triage service which is staffed 24/7 and will be directed to attend the Renal Haematology Triage Unit (RHTU).

If a patient is very unwell they should dial 999 and present their access passport to LAS. They will then be taken to RHTU at the Hammersmith Hospital. If the patient requires urgent treatment for a medical emergency they will be taken to their nearest A&E, usually St. Mary's or Charing Cross Hospital.

All patients requiring admission should be discussed with the Red Cell SpR or attending Red Cell Consultant Haematologist. The Clinical Nurse Specialist and Specialist Social Worker for Haemoglobinopathies should be notified of all patients admitted.

LNWUH

Patients needing urgent assessment, will be reviewed in A&E at Northwick Park.

All patients requiring admission should be discussed with the haematology SpR or the attending Red Cell Consultant Haematologist.

SGH

Patients are reviewed in the Emergency Department. Those requiring admission should be discussed with the Red Cell Haematology SpR (Bleep 7080) or on call haematology SpR if out of hours via switchboard. The Haemoglobinopathy CNS should be informed of all admissions.

For all sites

Patients should be reviewed by the attending red cell consultant haematologist or on call consultant haematologist or alternative senior decision maker at the earliest available opportunity aiming to meet the national target of 14 hours and in any event within 24 hours.

LHTs

Patients are reviewed in their local Emergency Department and those requiring admission will be admitted under the haematology or acute medicine team as per the local pathway. In the event of an acute complication which requires red cell exchange transfusion or other specialist input, the LHT consultant should assess the need to transfer the patient to the responsible SHT and contact the SHT consultant for advice, this should be a consultant to consultant decision.

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If direct transfer to ICU is required LHT consultant should discuss urgently with their SHT. A conversation between the SHT, LHT & ICU consultant(s) should take place.
Blood transfusion should be advised of any need for emergency transfusion planning with advanced warning where possible.

EMERGENCY ATTENDANCE: CRITERIA FOR URGENT ASSESSMENT AND ADMISSION

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

- Septic shock
- Neurological signs or symptoms
- SpO2 ≤94% on air
- Symptoms/signs of anaemia with Hb <50g/L or fall >30g/dl 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

All patients with the above presentations should be escalated to a senior decision maker at the earliest opportunity.

CLINICAL ASSESSMENT AND INVESTIGATIONS

Clinical assessment

Analgesia should be administered within 30 mins when the primary diagnosis is a painful crisis in accordance with NICE guidance.

Painful bony crises can occur with or without a trigger and occur as a result of tissue (bone) hypoxia, which is a consequence of the rigidity of the red blood cells. These crises can occur without warning but well recognised triggers include cold weather, infection, hypoxia, dehydration, pregnancy and menstruation and these should be considered and asked about.

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. Early discussion with the attending red cell consultant is advisable for those presenting with potentially life-threatening complications.

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, baseline pulse oximetry on air
- Blood pressure
- Liver and spleen size (in centrimetres beyond the costal margin)
- Degree of pallor and jaundice
- Any neurological signs

Investigations

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:	**Others as required** *(see below for specific complications)* **including:**
Hb electrophoresis	ABG if SpO_2 on air ≤94%
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	Blood and stool cultures for Yersinia if abdominal pain/diarrhoea and on iron chelation. Please inform laboratory if requesting Yersinia stool cultures
Vitamin D	

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^a, Jk^b, Fy^a, Fy^b,Kp^a, Kp^b, M, N, S, s, Le^a and Le^b. 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.

Transfusions are rarely required to help manage simple painful crises.

Patients should not be transfused without discussion with the haematology team first. If requesting blood it is imperative that the blood transfusion laboratory is aware that the receiving patient has sickle cell disease.

PAIN MANAGEMENT

Where the primary diagnosis is a painful crisis, appropriate analgesia should be administered as soon as possible and within 30 minutes (if necessary before completing a full clinical assessment), using the patient's individual analgesia protocol if available or the ED guidelines on management of a sickle pain crisis. Pethidine should be avoided and **only** given if specified in a patient's individual 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.

Note: Always follow individual patient protocol. Analgesia decisions should be discussed with patients where appropriate. Avoid iv opioids. If there is no individual patient protocol please follow analgesia guidance below:

1st line opioid - morphine

(body weight<50kg) morphine subcutaneous 2.5-5mg 2 hourly as required; (body weight ≥50kg) morphine subcutaneous 5-10mg 2 hourly as required.

Second line - oxycodone

(body weight <50kg) oxycodone subcutaneous 1.25-2.5mg 2 hourly as required;
(body weight ≥50kg) oxycodone subcutaneous 2.5-5mg 2 hourly as required

Note: Check renal and liver function and adjust dose if indicated

- **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.
- Give with ondansetron 8mg IV then 8-12 hourly prn po/iv or cyclizine 50mg po or IM (NOT IV) 8 hourly prn. **In patients with prolonged QT interval or risk factors for QT prolongation use cyclizine.**
- **Alternative anti-emetics include metoclopramide (body weight < 60KG) Up to 500 micrograms/kg daily in 3 divided doses; (body weight ≥ 60kg) 10mg every 8 hours prn or levomepromazine 6.25mg OD PRN po/SC. Can be increased to BD if necessary. Can also cause QT interval prolongation.**
- Commence observations (frequency adjusted according to NEWs score) including pain assessment
- Monitor fluid balance
- Intravenous access (mandatory if patient opioid naive/unknown opioid requirements/changing opioid) and fluids. Suggested rate 3-4l/24hours if normal renal and cardiac function, but consider smaller volumes in patients weighing <50kg. If no iv access and oral intake inadequate consider nasogastric (if no vomiting/ileus) or sc fluids
- Keep patient warm

Reassess at 30 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 20-30 minutes until pain is controlled as long as respiratory rate and sedation are carefully monitored

If pain persists:

ICHT/LNWUHT/LHT

Set up subcutaneous Patient Controlled Analgesia (PCA) if available (see PCA guideline with morphine, oxycodone or fentanyl as per individual protocol).

If PCA is not available or declined, sc opioids may be given up to 2 hourly at a dose sufficient to achieve effective pain control.

SGH

Manage with regular 2 hourly subcutaneous morphine (or oxycodone) injections. Breakthrough injections should not be prescribed and if pain control is not achieved then the dose of the 2 hourly injections should be increased.

Some patients on very high doses of parenteral opiates may require continuous subcutaneous infusions – these patients should have individual pain protocols.

Adjuvants

- Consider regular paracetamol (body weight ≥ 50kg)1g qds po or iv; (body weight < 50kg 15mg/kg every 4-6 hours, maximum 60mg/kg per day – some patients may find iv more effective and ibuprofen 400mg po every 8 hours (be aware of patients with nephropathy and avoid NSAIDs).
- Senna 15mg tablets at night (if no abdominal signs) +/- lactulose 15mls bd
- Chlorphenamine 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 hydroxyzine daily dose should not exceed 100mg (50mg in elderly).**
- Thromboprophylaxis (please refer to local guidelines): enoxaparin 40mg od sc (20mg if creatinine clearance <30ml/min or weight < 50 kg) or dalteparin 5000 units od (UFH 5000 units BD if creatinine clearance <30 ml/min) depending on local guidelines. Consider monitoring trough anti-Xa in renal impairment. Caution if thrombocytopenia/coagulopathy.
- Incentive spirometry 2-4 hourly
- Naloxone 100 micrograms IV prn as required for opiate-induced respiratory depression or sedation

Discharge from A&E/RHTU

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 250mg twice a day (or erythromycin 500mg twice a day if penicillin allergic)
- Folic acid 5mg daily
- Follow-up appointment in Haematology clinic

Explanatory notes

- There is no evidence supplemental O2 is beneficial if the SpO2 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. SpO2 should be recorded on air hourly then 4 hourly if stable and ABG performed if ≤94%. If this occurs discuss with Haematology SpR and follow acute chest syndrome protocol. Prolonged use of supplemental O2 in the absence of hypoxia may be harmful and exacerbate anaemia. Prolonged use of high-flow oxygen should be avoided, and flow rate should be guided by saturations.

- Pain relief should be given within 30 minutes of arrival in A&E/RHTU and good pain control should be achieved within 60 minutes
- Hourly observations to monitor pain, sedation, vital signs, respiratory rate and oxygen saturation for the first 6 hours and 4 hourly thereafter until they leave hospital or the episode has ended. Staff should be alert to potential risk of opiate toxicity and act on any concerning observations.
- Cautions for morphine – 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 gastro-intestinal ulceration, pregnancy and breastfeeding
- Cautions for chlorphenamine – hepatic impairment, may cause drowsiness.
- Cautions for hydroxyzine – hepatic disease, pregnancy and breastfeeding, prolonged QT interval (see above)
- A validated pain chart should be used.
- 5mg morphine sc is equivalent to 10 mg oral morphine (please see Opioid conversion table below for other agents)

Opioid conversion table

The conversions are provided only as an approximate guide to equivalences and individual patient variability needs to be considered when switching from one opioid to another.

Drug Name	Route	Dose	Equivalent dose of Oral Morphine	Conversion Ratio to Oral Morphine
Diamorphine	IV/SC	5mg	15mg	**1:3**
Fentanyl	IV/SC	200microgram	30mg	**1:150 (note evidence base varies from 1:100 to 1:150)**
Morphine	IV/SC	5mg	10mg	**1:2**
Oxycodone	Oral	5mg	10mg	**1:2** (note some evidence for ratio of 1:1.5)
Oxycodone	IV/SC	5mg	20mg	**1:4** (note evidence from 1:2 – 1:4)
Adapted from UCLH Palliative Care Quick Reference Guide Guideline, November 2021				

- 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 can 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 – contains paracetamol (2 tablets qds) or dihydrocodeine (30-60mg qds) or tramadol (50-100mg qds) prn. The patient's individual protocol should be followed.
- Nitrous oxide/oxygen (Entonox) should only be used in the ambulance and should not be used frequently or for more than 30 minutes

1.1b Patient controlled analgesia (PCA)

The guidance below applies to the use of Subcutaneous PCA local trust should follow their local standard operating procedures and competency assessments.

- PCA is a mechanical device which allows the patient to regulate the amount of analgesia received from their assessment of the magnitude of their pain. PCA aims to provide a safe and effective analgesic regime that is applicable to the individual and allows them to play an active role in the management of their pain. A PCA pump may provide a constant continuous (background) infusion rate plus patient controlled boluses. PCA avoids the peaks and troughs in blood plasma levels that are associated with injections if the continuous infusion rate is available. It is recommended avoiding repeated painful injections as PRN due to the risk of local infection, tissue damage and the unpredictable rate of absorption with injections. Patients should also be prescribed naloxone 100 micrograms IV prn as required for opiate-induced respiratory depression or sedation.

Inclusion criteria

To be eligible for PCA, adult patients with sickle cell must:

- Have consented to administering their own analgesia
- Be conscious, appropriately responsive and able to obey commands
- Have a respiratory rate >12/min
- Be able to operate the PCA handset effectively

Exclusion criteria

Patients should be excluded if:

- They decline PCA
- Are confused or do not understand the concept of self-administration
- Are unable to press the handset
- The use of morphine, oxycodone or fentanyl is contra-indicated

Starting the PCA

The PCA must be prescribed on the drug chart **and not prescribed with other opioids**, either strong or weak.

Patients must be instructed how to use the PCA to manage their pain by nursing staff trained in the use of PCA.

Recommended Subcutaneous PCA regimes

Regimen	Morphine	Oxycodone	Fentanyl
Amount	200 mg/100 ml 0.9% Sodium Chloride	100 mg/100 ml 0.9% Sodium Chloride	3 mg/300 ml 0.9% Sodium Chloride
Concentration	2 mg/ml	1 mg/ml	10 mcg/ml
Background continuous infusion rate	0-3 mg/hour	0-2.5 mg /hour	0-20 mcg/hour
Lockout time	10 minutes	10 minutes	10 minutes
PCA bolus dose range	0-2 mg	0-1 mg	0-20 mcg

Prescribe and start S/C injections initially until the PCA bag is ready to start. Once the PCA has started then stop sub/cut injections as they cannot be used in combination.
A background infusion may be suitable in patients who are long-term users who show high opioid requirements when on S/C opioids and complain of waking in the night with severe pain. Use background rate with caution in opiate naïve patients due to risk of respiratory depression and drowsiness. The background/ continuous infusion rate should start at a low dose and alter the bolus doses as appropriate.

Procedure

- All patients starting on PCA/parenteral opioids should have vital signs documented on observation chart, pain score obtained, nausea score, sedation score and respiratory rate prior to commencing PCA.
- Explain the procedure to the patient
- Check the drug prescription chart and prepare the solution by two registered nurses who are intravenous medication trained.
- Programme the pump in accordance with the prescription
- The PCA infusion, the prescription and the PCA programme must be checked by two registered nurses (Intravenous medication trained) one of whom has completed the PCA in-house training.
- Identify the patient, checking the patient's hospital number on the ID bracelet and the drug chart match.
- Using an aseptic non-touch technique (ANTT) guidelines (follow infection control guidelines. Once the needle is inserted a bio-occlusive dressing should be applied and dated. Clearly label the PCA giving set with date, time and drug according to trust protocol then attach the PCA to the patient...
- Press the start button, sign the drug chart and re-check that the patient understands how to use the PCA.
- Commence care and observation monitoring as appropriate.

Subcutaneous (S/C) needle insertion, use and care for PCA and injections
Patients should have flow-safe winged infusion set sub/cut butterfly needle (that adheres to the EU sharps safety directive).The date of the insertion should be recorded within nursing documentation and needle should be removed at 72 hours. When the insertion site becomes painful, red or after 3rd bag of PCA infusion set is change every 24 hours.

Placement and insertion of the needle should be in the following areas only; they must be rotated regularly to avoid abscess formation and scarring;

In order of preference:

- Anterior abdominal wall
- Upper thigh
- Deltoid area (upper aspect of the non-dominant arm if possible)

The sub/cut insertion site must be observed regularly (at least every shift) for signs of infection, abscess formation or leakage.
Only the opioid is to be delivered through the butterfly needle.
A separate cannula should be used if any other drugs are prescribed via sub/cut or Intravenous route administration.

Care and monitoring of the patient
Patients must be advised not to leave the ward while on the PCA or parenteral opioids. If the patient repeatedly leaves the ward despite warnings the continuation of this treatment should be discussed with the haematology consultant/team.

Respiratory function
Assessment of the patient's respiratory function should begin with an overview of the patient's general appearance and by measuring their respiratory rate and oxygen saturations on room air. Normal involuntary respirations are regular, effortless and quiet. Irregularities in breathing may relate to rate, rhythm or volume**. If the patient's oxygen saturations and respiratory rate are stable there is little evidence available that oxygen therapy for a painful crisis is of any benefit.** Therefore only administer for a patient with acute chest syndrome, unknown hypoxia or chronic lung changes on an individual basis (normal respiratory rate range 12-20 per minute and oxygen saturations, normal range over 94% on air).

Respiratory complications
If the respiratory rate falls to below 10/minute or oxygen saturations on room air below 92% the PCA should be stopped. Treat patient with a potential risk of respiratory depression and inform doctor immediately.
An increase in respiratory rate of >24/min may signify acute chest syndrome and also warrants urgent medical assessment.
If respiratory depression is triggered the following should be done:

- Stop the PCA/inject able parenteral opioids
- Stimulate the patient
- Administer oxygen therapy via a re-breath mask for up to 15/litre until O2 saturations are greater than 96%

- Summon emergency assistance
- Commence pulse oximetry, blood pressure, pulse and respiratory rate monitoring every 15 minutes.
- Naloxone must be given with great caution to patients who have received longer-term opioid/opiate treatment for pain control or who are physically dependent on opioids/opiates. Naloxone must be available and prescribed. Naloxone by intravenous injection: initially 100-200 micrograms, then 100 micrograms for up to 2 doses at 1 minute intervals if no response to preceding dose. Further doses maybe given if respiratory function deteriorates on the advice of the medical team or emergency team give a further 2mg dose (4mg may be required in seriously poisoned patients), then review diagnosis. Further doses may be required if respiratory function deteriorates following initial response, intravenous administration has a more rapid onset of action, doses may be given by intramuscular route but only if intravenous route is not feasible. If naloxone is given the medical team must be informed and observations made every 15 minutes in the first instance for one hour. Be aware naloxone will reverse the analgesic affect quickly due to a short half-life and patient will be in pain again quickly. Therefore use a reduced sub/cut parenteral opiate dose by 50% and monitor closely.
- A bag and mask must be available to ventilate the patient if necessary.

Sedation

The cause of an abnormal decrease of consciousness may be related to unintentional overdose of opioids. However in SCD there may be other associated causes e.g. stroke or meningitis.

- The level of sedation should be recorded every 15/30 minutes for the first 2 hours and then 4 hourly intervals unless clinically indicated. If the patient is sedated review 2 hourly and seek medical attention.
- If the PCA bolus/rate or lockout times are increased or parenteral opioids are increased the above observations should be repeated.
- If the patient becomes unresponsive or if the sedation score is 3 or 4 (use scoring on early warning score), then disconnect the handset, stop the PCA and contact the doctor immediately. (Follow respiratory function guidelines)

Nausea and Vomiting

There are common side-effects of parenteral opioids which can be spontaneous but often brought on by movement. The presence of nausea should be assessed 4 hourly. Ensure suitable anti-emetics are prescribed and given regularly to the patient. If problems persist contact the medical team to review and change the anti-emetic regimen.

Pruritus

This is a common side-effect with opioids which can manifest as localised itching or generalised itching. If this occurs prescribe hydroxyzine 25-50mg TDS orally or other locally used anti-histamines. If pruritus persists consider changing to an alternative opioid i.e. oxycodone or fentanyl.

Constipation
Reduced bowel motility is a complication of opioid therapy and requires daily monitoring of bowel function with documentation. Encourage the patient to modify their diet, increase fluid intake and the medical team to prescribe laxatives regularly.

Setting-up Patient-Controlled Analgesia (PCA) CME Pump
Follow PCA for post-operative and acute pain: Clinical nursing guidelines for adult patients (Imperial College Healthcare NHS Trust2020) and CME Pump manual information.

Stopping the PCA or sub/cut opioids
Patients can be weaned off once they have met following criteria:

- The patient has a pain score of none or mild pain.
- The patient is able to tolerate oral medication.
- The patient has reduced the amount of PCA boluses or parenteral opioids in the previous 24 hours.

a) If the patient fulfils the above criteria they can be prescribed suitable oral analgesia and then stop the PCA or parenteral opioids. **Do not step down on to sub/cut opioids if stopping a PCA.**
b) Dose reduction should, whenever possible, be implemented in the morning and the patient's pain closely assessed. For example stop the continuous infusion first then wean the bolus dose until stopping.
c) Upon discharge please make sure the patient has an adequate supply of analgesia and a follow up outpatient appointment.

1.2 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

- Hypoxia - fall in SpO2 **on air** (measurement on O2 may delay diagnosis)
- Fever, tachypnoea, tachycardia
- Pain/tenderness in chest wall
- Signs of lung consolidation, typically basal and bilateral initially. Bronchial breathing may be striking. Wheeze occurs 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. COVID-19 pneumonitis should also be considered as a potential cause of ACS.

Investigation

- Arterial blood gases (ABG) on air
  - if SpO2 on air ≤94% or >3% fall from baseline
  - if dyspnoeic or tachypnoeic
- Monitor SpO2 on air and inspired O2 1-4 hourly
- FBC, group & save
- CXR
- Measure peak expiratory flow (PEF) if symptoms or history of obstructive airways disease
- CTPA including HRCT cuts if pulmonary embolism suspected
- Blood, throat and sputum cultures
- 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
- Nasopharyngeal aspirate (NPA) for virology
- SARS-CoV2 PCR

Management

- Notify Haematology SpR immediately. Suspected ACS should always be managed with advice from attending/on-call Consultant
- Seek ITU/Respiratory opinion early and consider transfer to ITU/HDU if unwell/deteriorating. If ITU/HDU support is not required, patients should be managed on a haematology ward.
- Analgesia and iv fluids as per pain crisis protocol (avoid respiratory depression and fluid overload)
- Give humidified O2 (2-4l/min) to maintain SpO2 >95% or within 3% of patient's baseline. Prolonged treatment with high flow oxygen should be avoided, and flow rate should be guided by saturations.
- Monitor SpO2 on air and O2, ABG, pulse rate, respiratory rate, abdominal girth, fluid balance, Hb and CRP
- Antibiotics (during which penicillin V/erythromycin prophylaxis can be suspended):
  ICHT
  Ceftriaxone 2g od iv (adjusted according to renal function) + clarithromycin 500mg bd po
  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)

LNWUH

Co-amoxiclav 1.2g tds iv + clarithromycin 500mg po/iv bd

If history of severe penicillin allergy give teicoplanin iv (see London NW Teicoplanin guidance) + clarithromycin 500mg bd po/iv

SGH

Co-amoxiclav 1.2g tds iv + clarithromycin 500mg po/iv bd

If history of severe penicillin allergy give levofloxacin 500mg bd iv (see caution above)

- CPAP +/- transfusion as indicated (see below)
- Consider BiPAP (bi-level positive airways pressure) if Type 2 respiratory failure
- 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: Give Low Molecular Weight Heparin as per local Trust guidelines. Consider monitoring trough anti-Xa in renal impairment. Caution if thrombocytopenia/coagulopathy. It can be difficult to clinically exclude a pulmonary embolism and so initially therapeutic anticoagulation may be indicated.

Indications for ventilation and exchange transfusion

- A simple top-up transfusion should be considered in patients with a PaO2 of < 9.0 kPa on room air but may also be needed at less severe hypoxaemia depending on the patient's history, clinical features and if there is a rapid increase in oxygen requirement.
- An exchange transfusion is indicated for those with severe clinical features, those who deteriorate despite a top-up transfusion and in those with a higher haemoglobin (>90 g/L).
- Early discussion with ICU is advised to discuss the role of advanced respiratory support (High Flow nasal oxygen/CPAP/BiPAP) in those with worsening hypoxaemia, severe dyspnoea and increasing hypercapnia causing a respiratory acidosis.
- Invasive ventilation (endotracheal intubation and ventilation) will be required in patients with worsening acute respiratory failure despite maximal NIV or CPAP or with a reduced level of consciousness and therefore unable to protect their airway.

Other potential indications for exchange transfusion include:

- Multilobar involvement on CXR
- Rapid fall in PaO_2
- Failure to respond to increased FiO_2%
- 25% drop in PaO_2 compared to baseline PaO_2 e.g. in patients with chronic hypoxaemia
- Exhaustion from respiratory effort

Before starting CPAP discuss with the SpR/Red Cell Consultant. **Caution in Type 2 respiratory failure.** If CPAP is not available consider a lower threshold for transfusion. 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 CO2) but should not delay institution of IPPV. Discuss with ITU/Respiratory team on individual basis.

Exchange Transfusion

If automated erythrocytopheresis is not available, early discussion with the on-call consultant is essential to decide if the patient requires transfer to a Specialist Haemoglobinopathy team (SHT) to perform automated erythrocytopheresis. If the patient is not safe to transfer, an isovolaemic manual exchange will need to be performed locally.

The apheresis teams at ICHT and SGH offer 24/7 apheresis services and should be contacted as soon as the decision has been made to perform a red cell exchange transfusion. For LNWUH, please refer to the local apheresis pathway.

The target HbS is <30% (consider <20% if in extremis) with a maximum Hb and Hct of 100-110 g/L and 0.34, respectively. If Fat Embolism Syndrome suspected /multi organ failure consider combined automated red cell and plasma exchange.

Follow up

- Check baseline SpO2 and consider requesting PFT if ongoing symptoms
- Echocardiogram, HRCT chest and respiratory referral to Respiratory team (Dr Vincent Mak at ICHT, Dr Susannah Leaver at SGH and Dr Ian Stone at LNWUH) if chronic sickle lung disease (CSLD) suspected
- For prevention of recurrent ACS recommend hydroxycarbamide therapy or red cell exchange transfusion programme if hydroxycarbamide is not effective or declined. Where available, patients should be made aware of trial options.
- Ensure that all patients are offered penicillin V prophylaxis, or erythromycin if penicillin allergic, pneumococcal polysaccharide vaccination in addition to pneumococcal conjugate vaccine, seasonal influenza vaccination and COVID-19 vaccination.

1.3 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 patients with 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.

Patients with sickle cell disease are advised to seek medical attention early if they have any signs of infection (for example, a fever >38^{o}C).

Empiric antibiotic therapy

Please refer to individual trust antimicrobial guidelines for more detailed information and guidance on

the treatment of other specific infections not listed in this guideline (e.g. tonsillitis, UTI, meningitis).

ICHT ICHT Adult Treatment of Infection Policy
LNWUHT Please see micro guide
SGH St George's NHS Trust antibiotic policy (https://viewer.microguide.global/sguh/adult)

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

	ICHT	SGH
Severe sepsis	Ceftriaxone 2g iv od + amikacin* 15mg/kg (adjusted according to renal function) stat iv then iv every 24 hours.	Co-amoxiclav 1.2g iv stat then iv tds + gentamicin*
Chest signs and/or abnormal CXR	Ceftriaxone 2g IV od iv (adjusted according to renal function) + clarithromycin 500mg bd po. 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)	Co-amoxiclav 1.2g tds iv + clarithromycin 500mg po bd. If history of severe penicillin allergy levofloxacin 500mg bd iv.
Abdominal pain and girdle syndrome	Cefuroxime 1.5g tds iv (adjusted according to renal function) + metronidazole 500mg iv tds	Co-amoxiclav 1.2g iv tds + gentamicin* If history of severe penicillin allergy/other beta-lactam allergy give vancomycin (see SGH High Dose Vancomycin Guidelines for Adult Patients) + ciprofloxacin 400mg iv bd + gentamicin* + metronidazole

		500mg iv tds
Biliary sepsis	Cefuroxime 1.5g tds iv (adjusted according to renal function) and metronidazole 500mg tds iv	Co-amoxiclav 1.2g iv tds + gentamicin*
Diarrhea /abdominal pain on iron chelation	Stop iron chelator, send blood and stool including Yersinia culture and commence ciprofloxacin 400mg iv bd if G6PD status normal or ceftriaxone 2g od iv if G6PD deficient	Stop chelator, send blood and stool including Yersinia culture and commence ciprofloxacin 400mg iv bd if G6PD status normal or ceftriaxone 2g od iv if G6PD deficient
	Refer to ICHT Amikacin Once Daily Guideline (Adults) for dosing and monitoring	*see SGH Adult Gentamicin Dosing and Monitoring Guideline

Malaria should be excluded if there is a history of travel to an endemic area within the past 12 months. Patients with SCD can contract malaria even though many patients may think they are immune and malaria should be investigated if there is clinical suspicion. See individual trust guidelines on the management of malaria (ICHT Guideline Adult Treatment of Malaria, SGH Treatment of Malaria policy).

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 investigations

- Blood film (toxic neutrophils)
- Blood +/- stool cultures
- Plain X-ray (no specific changes in early osteomyelitis, lucent areas evident ~10 days after infection)
- Ultrasound (sub periosteal 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 & 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.

1.4 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 (see local guideline on the management of infection in sickle cell disease)
- 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 β-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 and parvovirus DNA (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 billirubin

Management

- Fluid resuscitation if hypovolaemic
- Treat with broad spectrum antibiotics e.g. cefuroxime 1.5g tds iv 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

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 : 20mg qds po or im
- Antibiotics as per local guidelines

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 as per local guidelines
- 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.

Emergency exchange transfusion should be considered for acute intrahepatic cholestasis – patients suspected to have this diagnosis should be discussed with the On call/attending Consultant immediately.

Management

- Correction of coagulopathy with vitamin K/FFP
- Antibiotics if febrile (as per local guidelines)
- 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

Blood transfusion is an important treatment in the management of patients with sickle cell disease (SCD) and other haemoglobinopathies, however, about one third of transfused SCD patients develop antibodies to red cell antigens, becoming allo-immunised, and around 10% develop the most serious consequence of this allo-immunisation which is a delayed haemolytic transfusion reaction (DHTR).

In some Haemoglobinopathy patients presenting with DHTR, the patient's ***haemoglobin level fall below*** the pre-transfusion level suggesting destruction of transfused RBCs as well as the patient's own RBCs. This is referred to as hyperhaemolysis (HH).

It is characterised by rapid haemolysis and may be associated with fever and with pain typical of sickle cell disease. The direct antiglobulin test (DAT) may be either negative or positive and new red cell allo-antibodies are not usually identified but may be present. There may be a reticulocytopenia.

Hyperhaemolysis can recur in such patients following blood transfusions several months or years after the initial episode.

Patients with hyperhaemolysis should be treated with intravenous immunoglobulin (IVIg) and IV methylprednisolone. Additional transfusion has been associated with increasing haemolysis and worsening anaemia, and should be avoided if possible. However, in cases where there is very rapid haemolysis and critical anaemia, transfusion is required and should be preceded with IVIg. Follow local trust guideline for prescribing and authorisation.

Erythropoietin and haematinic replacement should be considered.

Diagnosis

Hyperhaemolysis should be suspected in any patient with a haemoglobinopathy who presents with increasing haemolysis after a blood transfusion, typically, 1 week post transfusion, but may occur earlier or later.

Clinical features: Increasing jaundice, dark urine ('Coca-Cola' coloured), and anaemia. They may also have fever, Vaso Occlusive symptoms e.g. back, leg or abdominal pain, hepatomegaly or right upper quadrant pain.

Investigations:

- **FBC**: Worsening anaemia – Hb may fall to below the pre-transfusion level.
- **Reticulocytes:** May be raised (in keeping with haemolysis) or decreased, due to suppression of red cell production.
- **Direct Antiglobulin Test (DAT):** Usually negative but can be positive, transfusion laboratory should send for an eluate if DAT is positive.
- **Group and screen:** New allo-antibodies may be found but are usually absent.
- **Haemoglobin electrophoresis to measure HbS% and HbA%:** this is useful to quantify how much, if any, HbA (transfused blood) remains.
- **Haemoglobin electrophoresis to measure Hb S% and Hb A% in urine if available although not currently a standardised test :** HbS and HbA are present on serial analysis of urine
- **B12, folate and iron studies :** to exclude coexistent haematinic deficiency
- ***Other markers of haemolysis***:
    - Raised Bilirubin

- Raised LDH
- Haptoglobins
- Hyperferritinaemia may also be seen as a marker of macrophage activation

Treatment

- All haemoglobinopathy patients with suspected hyperhaemolysis must be discussed with a Sickle (red cell) Consultant during normal working hours or the on-call Haematology Consultant covering non-malignant haematology if out-of-hours.

- Supportive management should continue with analgesia, hydration and oxygen therapy as required.
  - Prescribe folic acid 5mg daily.
  - Consider treatment with erythropoietin and providing IV iron replacement if not iron replete (i.e. if ferritin <100ng/ml).
  - Consider B12 replacement.

- Primary treatment is with IV Methylprednisolone and IVIg.
- Blood transfusion should be avoided but may be necessary if clinically indicated for profound symptomatic anaemia, but should only be given after discussion with the Haematology Consultant.

- Phenotyped blood should be given (CDE and Kell matched).

- When a case of hyperhaemolysis is suspected, and having discussed with the Haematology Consultant, it is important to communicate the suspected diagnosis to the transfusion biomedical scientist who will add a comment to the patient record.

Dosage

- **Intravenous immunoglobulin (IVIg)**

1g/kg once daily for 2 days (total dose = 2g/kg). Dose should be based on dose determining weight (refer to local trust guideline).
Administration and the choice of preparation is according to individual Trust guidance. Dose should be rounded down to the nearest vial size to prevent wastage.

- **Methylprednisolone**

Adults: 500mg IV for 2-3 days. Prescribe concurrent proton pump inhibitor e.g. omeprazole 20mg daily whilst prescribed steroids.

- **Erythropoietin**

NeoRecormon 300 iu/kg once daily for 5 days.
Then 300 iu/kg once daily on alternate days (i.e. 3 times per week).
Alternative regimen include NeoRecormon 10-20000 units sc 3 times a week

- **Eculizumab and Rituximab**

There are case reports of successful outcomes using eculizumab and rituximab which are now recommended as a treatment option through routine commissioning within set criteria outlined by NHS England. All cases should be discussed with the specialist haemoglobinopathy team (SHT) and or the Haemoglobinopathy Co-ordinating Centre (HCC). All cases will be required to seek approval (ideally before administering treatment) from the HCC. Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined. All cases must be referred to the National Haemoglobinopathy Panel (NHP) for retrospective discussion of indications and outcomes

In the non-emergency situation, patients with previous DHTR/HH despite pre-transfusion treatment with IVIg and steroids who need elective transfusion therapy should be referred to the HCC MDT for discussion/approval and also (if time allows) to the NHP prior to treatment being given. As with the above, all cases must then be referred to the NHP for retrospective discussion of indications and outcomes. Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Management of DHTR/HH

Second line treatment with eculizumab should be considered in patients when the rate of rapid haemolysis WITH symptomatic anaemia OR compromise of another organ system (e.g. respiratory failure, renal failure, neurological symptoms) continues despite first line treatment with IVIg and steroids. Third line treatment with rituximab should be considered in patients when all criteria for giving eculizumab has been met AND there is a need for ongoing blood transfusion therapy.

Dose

- Eculizumab in adult patients: 900mg IV ONCE and a second dose 7 days if there is evidence of efficacy of treatment but ongoing haemolysis. No further doses/ courses are permitted.

Stopping Criteria:
Eculizumab
One dose to be given initially and no further dose given if there is:

- A complete response
- No evidence of response.
- An adverse event.

Dose
Rituximab: 2 doses of 375mg/m2 IV to a maximum of 4 doses given 7 days apart, depending on response and the need for further blood transfusions. Hepatitis B status should be checked in all patients prior to rituximab. Refer to local trust guideline. Ensure paracetamol, chlorphenamine and hydrocortisone administered 30 -60 minutes prior to rituximab to prevent infusion related reactions. Refer to local IV guide for administration and monitoring.

Stopping Criteria:
Rituximab
Following initial dose(s) no further doses given if there is:

- No further transfusion is needed.

- An adverse event of a severity such that the balance of risks and benefit do not support further use.

Prevention of Hyperhaemolysis

Rituximab should be considered as second line treatment for the prevention of hyperhaemolysis in patients requiring elective blood transfusion who have:

- had DHTR/HH previously despite pre-transfusion treatment with IVIg and steroids

OR

- multiple red cell alloantibodies where compatible blood is not available.

Dose

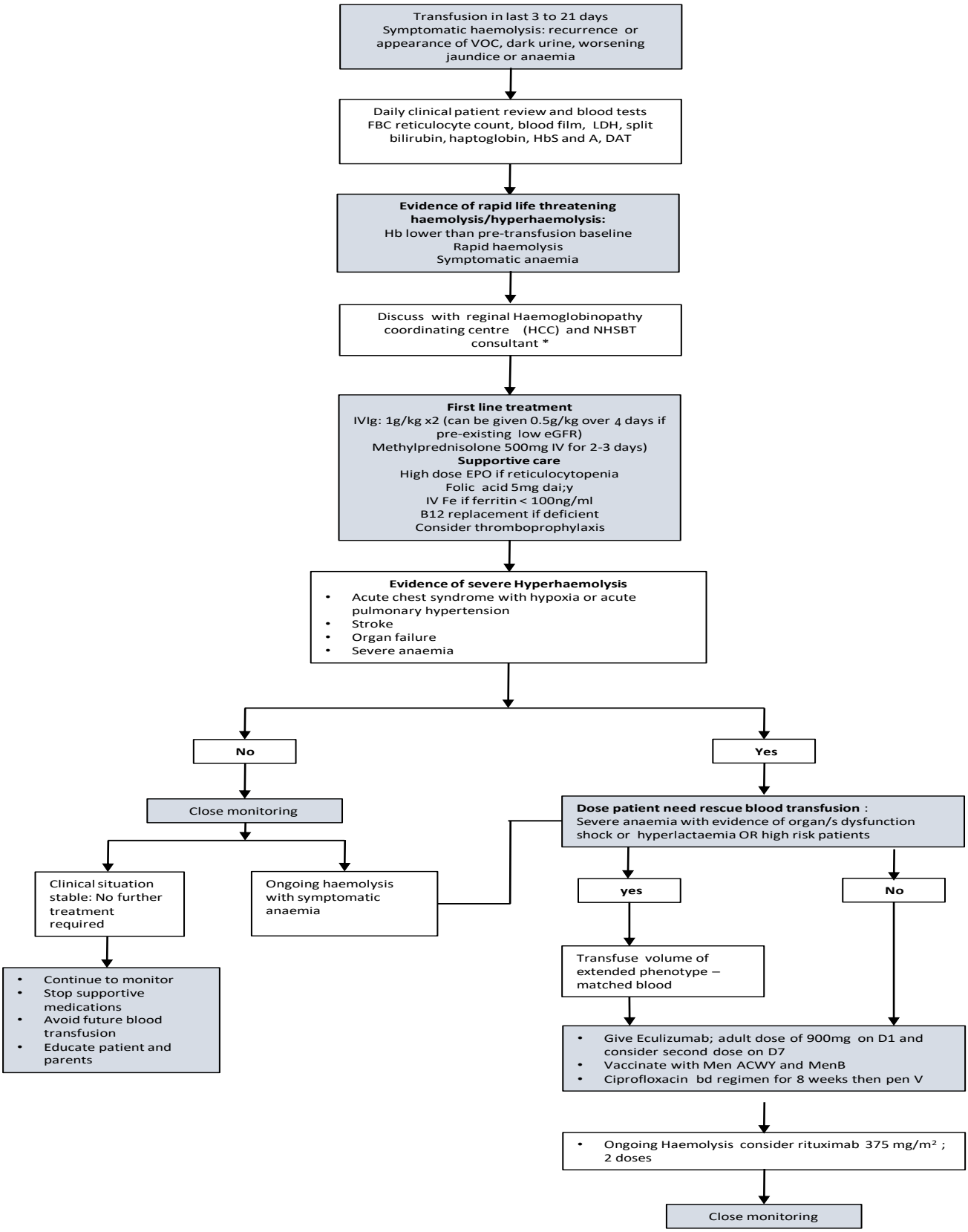
Rituximab 2 doses of 375mg/m2 IV given 7-14 days apart. Hepatitis B status should be checked in all patients prior to rituximab. Refer to local trust guideline. Ensure paracetamol, chlorphenamine and hydrocortisone administered 30 -60 minutes prior to rituximab to prevent infusion related reactions. Refer to local IV guide for administration and monitoring.

Monitoring

Principle long-term adverse effects of rituximab include neutropenia and hypogammaglobulinaemia from prolonged B-cell depletion. The product license for rituximab recommends regular measurement of blood neutrophils which would be part of ongoing monitoring.

Following eculizumab administration, ciprofloxacin 500mg bd should be administered for 8 weeks from the last dose, once completed long term prophylactic penicillin (Penicillin V) or erythromycin (if penicillin allergic) should continue. Patients receiving Eculizumab should be vaccinated with Meningitis A,C,W,Y, and Meningitis B. Complete “Certificate – UK: vaccination and/or prophylactic antiobiotics” form as the Pharmacy Department will need to submit this to Alexion (eculizimab manufacturer) for further supply.

Patient Pathway



1.5 Neurological complications

Central nervous system (CNS) complications in Adults with SCD cause significant morbidity and mortality. Early recognition of acute neurological complications is vital, alongside rapid diagnosis and appropriate management. Adults with SCD are at increased risk of both acute ischaemic and haemorrhagic stroke with the risk of acute ischaemic stroke increasing with older age

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. Older patients may have other co-morbidities including hypertension, diabetes, hyperlipidaemia, renal dysfunction, impaired cardiac systolic function, and atrial fibrillation which are all recognised cardiovascular risk factors in adults without SCD.

Acute haemorrhagic strokes are reported at increased rates in adults with SCD. Hypertension and multi-organ failure are risk factors for cerebral haemorrhage. Aneurysms, which are reported in 10.8% of adults with SCD, can rupture, typically leading to subarachnoid haemorrhage, most commonly in young adults. Low steady state Hb concentration, high steady state white cell count and transfusion within the previous 14 days have been identified as risk factors for haemorrhagic stroke.

Extradural and subdural haemorrhage is also recognised and may occur in the absence of head trauma.

Investigation

- Urgent CT brain within one hour of presentation 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
- CTV/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 and Red Cell Consultant at ICHT/ SGH
- Urgent red cell exchange to achieve HbS % <20% (haematocrit should not exceed 0.34)

- Anticonvulsant therapy if seizures occur, give IV lorazepam 2-4 mg over 2 minutes, discuss with Neurology SpR oncall
- Avoid/stop aspirin, NSAIDs and LMWH until haemorrhage excluded
- Limited data on use of thrombolysis in patients with SCD are available. The sickle standards suggest that adults with SCD with acute ischaemic stroke may benefit from both thrombolysis and acute red cell exchange. Management will need careful collaboration between the hyperacute stroke team and haematologists to decide whether to offer exchange transfusion, thrombolysis, or both. This decision will need to consider the patient age, genotype, phenotype, MRI findings, and traditional risk factors.

2) Long-term

- Regular exchange transfusion programme (every 4-6 weeks) to maintain HbS level below 30%
- Hydroxycarbamide should be considered for prevention of recurrent stroke where transfusion is not possible or acceptable
- Sibling allogenic bone marrow transplantation should be considered in select cases and require referral to the National Haemoglobinopathy Panel (NHP)
- 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 Charing Cross Hospital/SGH
- 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
- CTV/MRV if cerebral venous thrombosis suspected on clinical grounds Infection screen including blood cultures +/- LP
- Toxicology screen for pethidine and metabolites (norpethidine) if indicated

Management

1) 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 Diazemuls®) 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 at ICHT/ SGH
- Discuss need for urgent red cell exchange with Red Cell Consultant at ICHT/SGH

2) Long term

- If no abnormality on EEG or CT/MRI and no recurrence watch and wait. Consider diagnosis of psychogenic non epileptic seizures - prolactin measurement may be useful
- 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

d) Headaches

There is no evidence base for the management of chronic headaches or migraines in adults with SCD. Referral to headache clinic at ICHT/SGH may be needed. Headaches do seem to be more frequent than the general population. Analgesia, particularly opioids, may contribute. For the diagnosis of migraine, family history is an important factor. Headaches are throbbing in nature and may be associated with photophobia or phonophobia more commonly than with aura. Triggers include stress, red wine, some foodstuffs, menstruation and missing meals.

- Triptans (serotonin receptor agonists) are most effective and should be offered
- Prophylaxis with propranolol or other agents may be needed if migraine frequency is greater than four per month

e) Neurocognitive impairment

Neurocognitive decline is recognised in patients with SCD and may be related to silent cerebral ischaemia and small vessel vasculopathy. Memory loss is not uncommon in these patients. Patients

should be discussed at MDTs for possible referral to neuropsychology for full neuro-cognitive assessment.

Mood disturbance may or may not be related to SCD and after exclusion of organic causes these patients should be discussed at MDTs to ensure appropriate medical and psychological follow up and possible referral to neuropsychology for full neuro-cognitive assessment and advice on adaptation and adjustment, as appropriate

Other neurological presentations to consider are Silent infarcts and PRES (Posterior reversible encephalopathy syndrome)

1.6 Priapism

Priapism has a lifetime incidence of up to 35-90% in male patients with SCD with the majority of first episodes occurring before the age of 20 years. Priapism is categorised as either ischaemic (low flow) or arterial (high flow) in origin. Priapism in SCD is of the low flow ischaemic type. 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.

Types of presentation:

- **Acute fulminant** (> 3 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
- Keep warm – DO NOT USE LOCALLY APPLIED ICE PACKS
- Opioid analgesia +/- sedation
- Catheterisation if necessary to empty bladder
- Alpha adrenergic agent (usually etileferine), if not available, Pseudoephedrine 30-60mg qds po – monitor blood pressure
- Blood tests as per emergency admission protocol
- Contact on-call Urology SpR/Consultant- the longer the ischaemic priapism has persisted, the greater the need for surgical intervention. Recent British Association of Urological Surgeons (BAUS) genital emergencies guidelines have separated ischaemic priapism into 3 categories by time since onset:
  - < 48 hrs
  - 48-72 hrs
  - 72 hrs

If priapism persists but < 48hrs:

- Intracavernosal blood aspiration +/-cavernosal blood gas analysis with injection of phenylephrine 0.5mg (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 intractable despite non-surgical measures a cavernous shunt procedure may be considered (carries risk of irreversible erectile dysfunction)
- For those presenting at > 72 hrs the BAUS emergencies guidelines recommend referral of the patient to a specialist unit to consider a primary penile implant. At SGH, refer to Professor Nick Watkin at ICHT and LNWUH refer to Professor Suks Minhas
- No randomised trial evidence for either simple or exchange transfusion to treat prolonged priapism. Blood transfusion should be considered when acute priapism does not settle with conservative measures and prior to surgery.

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 > 1 hour
- Alpha adrenergic agent (usually etilefrine up to a maximum of 25mg per day in divided doses), if not available, pseudoephedrine 30-60mg qds po
- Other prevention strategies that may be considered on an individual basis after discussion at HCC MDT Meeting include:
- Pseudoephedrine 30-60mg qds po – monitor blood pressure
- Phosphodiesterase inhibitors
- Anti-androgens: cyproterone 50mg bd (caution risk of thrombosis assess VTE risk)
- Diethylstilboestrol
- Red cell exchange programme
- Hydroxycarbamide

1.7 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. Associated symptoms may include fever, headache, myalgia, arthralgia, respiratory and

gastrointestinal symptoms. 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
- Non-immune close contacts with haemolytic anaemia may develop red cell aplasia and should be monitored with baseline FBC and reticulocyte count
- In hospital, isolation facilities should be utilised particulalry as a precaution for pregnant staff, as infection may result in hydrops fetalis, foetal death, or congenital anaemia

1.8 Renal

Renal complications (sickle cell nephropathy, SCN) occur in approximately 60% of patients with the more severe forms of SCD at some point during their lives. In most cases, SCN develops insidiously over time, starting in the very young with glomerular hyperfiltration and leading to microalbuminuria in late childhood early adulthood. The majority of patients do not progress further, but a number will develop slowly progressive chronic kidney disease. These patients are at increased risk of acute kidney injury (AKI) complicating vaso-occlusive crises or other interim illness. End stage kidney disease (ESKD) is an uncommon complication, though the incidence is on the rise.
The mechanisms of disease and the impact of treatment options are poorly characterised but an increase in glomerular blood flow, reduction in medullary blood flow from ischaemia, papillary necrosis, and the use of NSAIDs are all recognised contributors to sickle nephropathy.

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 the patient indicated 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. Patients with renal medullary carcinoma may also present with haematuria, sometimes with additional back or abdominal pain and weight loss. This rare and aggressive cancer is virtually restricted to those with the sickle gene, particularly sickle cell trait, sickle cell/haemoglobin C disease and occasionally sickle cell anaemia. It has usually metastasised at the time of presentation and has a very poor prognosis with a median survival of less than one year from diagnosis.

Management

Painless haematuria on dipstick testing age < 40 yrs

- Renal ultrasound
- MSU
- Urine cytology

Painful haematuria on dipstick testing

- Above investigations + CT-KU

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: nitrofurantoin 100mg modified release bd po for 3 days if not G6PD deficient (do not use if eGFR <30ml/min). If pregnant or breastfeeding: cefalexin 500mg bdpo for 7 days.
    - Uncomplicated UTI in males: nitrofurantoin 100mg modified release bd po for 7 days (do not use if eGFR <30ml/min)– if suspicion of prostatitis 14 days of 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

1.9 Ophthalmic Complications

SCD can cause many problems within the visual system from vascular occlusions to problems in both the posterior and anterior segments. Patients with sickle cell/haemoglobin C compound heterozygosity have a higher risk of sickle retinopathy than patients with homozygous sickle cell anaemia. All patients with SCD should have baseline retinopathy screening.

Sickle retinopathy is the most common ophthalmic complication of SCD and can be sub classified into non-proliferative and proliferative forms. It is characterised by mechanical obstruction of the retinal capillaries by sickling although endothelial damage may also contribute. Patients with early stage retinopathy are generally asymptomatic but it can lead to vitreous haemorrhage and retinal detachment resulting in loss of vision. Drug-induced retinopathy can arise from iron chelating agents and so the detection of retinal toxicity is particularly important through retinopathy screening.

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

Indications for panretinal laser photocoagulation therapy for proliferative sickle retinopathy should be considered on an individual basis.

There is no clear evidence base for the benefit of strict annual screening but patients should be asked about visual symptoms at each clinic appointment and given advice to seek urgent medical attention via the eye casualty department or the emergency department and be encouraged to visit their optician for routine review

Refer all new and pregnant patients to Western Eye Hospital, Moorfield's Eye Hospital at SGH or Ophthalmology Clinic at Central Middlesex Hospital, for initial ophthalmology assessment including fluorescein angiography.

Patients with evidence of retinopathy should have at least annual ophthalmic review.

SCD can also affect the anterior segment of the eye. Anterior segment involvement includes conjunctival vascular lesions (corkscrew and comma-shaped vessels), sectoral iris atrophy and pupillary abnormalities. Central and peripheral retinal arterial occlusion have been reported.

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, Moorfield's at SGH , or their nearest eye casualty if they develop acute visual symptoms or suspected hyphema after eye injury
- Red cell exchange is recommended prior to surgery for retinal detachment, vitreous haemorrhage or hyphema

Ophthalmological Review When On Iron Chelation

Desferrioxamine

Asymptomatic patients when starting desferrioxamine should have a baseline review including electrophysiology and retinal imaging preferably within 6 weeks of starting treatment and annually thereafter. Symptomatic patients should be discussed with ophthalmology urgently as desferrioxamine can be retinotoxic.

Deferasirox and Deferiprone

There is less clear evidence of any retinotoxicity and so these patients should be monitored clinically and discussed with ophthalmology if there are concerns of any symptoms. A baseline ophthalmology review in asymptomatic patients is recommended prior to commencing treatment. BCSH guidance recommends annually for those on desferasirox and 6-12 monthly if deferiprone is used in combination with another iron chelator

2. MANAGEMENT OF CHRONIC COMPLICATIONS

2.1 Nephropathy

a) Screening in outpatients

- Patients with an albumin to creatinine ratio (ACR) persistently >30 mgmmol should be monitored using the unselective protein to creatinine ratio (PCR) as this will more accurately reflect their total protein loss.
- Urine protein:creatinine ratio (PCR) at least annually - if significant proteinuria consider 24hr collection to quantitate
- Renal profile at each visit

b) Hyposthenuria

Due to an increased glomerular filtration rate (GFR) in these patients from early childhood to young adulthood there is an increase in the proximal tubular function and an inability to concentrate the urine. This manifests clinically as a susceptibility to dehydration which can trigger crises. Patients therefore must be encouraged to drink adequate volumes. Patients may also have an incomplete form of distal renal tubular acidosis leading to acidosis and hyperkalaemia this can usually be corrected with dietary potassium restriction and oral sodium bicarbonate however this should be discussed with a nephrologist if persistent.

c) 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
    - consider adding hydroxycarbamide
    - Avoid NSAIDs and pethidine, and any other nephrotoxic drugs

d) Hypertension

Management

- If no proteinuria treat if BP ≥ 140/90 mmHg
    - Aim for BP <140/90 mHg
    - 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 ≥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 ≥ 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

BP targets should be adhered to strictly in SCD since BP is typically lower than that of matched controls.

e) 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.

Creatinine levels are often low in people with sickle cell anaemia and sickle cell/β0 thalassaemia due to hyperfiltration and increased proximal tubular excretion, resulting in a high estimated glomerular filtration rate (eGFR).

Increased rate of change of creatinine may, therefore indicate declining renal function before the value moves out of the normal range.
Anyone with an eGFR which is declining by >5 ml/min/year or an absolute value <60 ml/min should be identified and discussed with a nephrologist.
Urinary tract infections should be promptly treated with suitable antibiotics.
Long-term use of NSAIDs should be avoided in patients with an eGFR <60 m/min; if unavoidable, regular monitoring of renal function is recommended.

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
- Parathyroid Hormone PTH
- Glucose +/- GTT (HbA1c not reliable in presence of Hb variant, Fructosamine level can be checked instead)
- 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 and any nephrotoxic drugs
- Review iron chelation therapy if receiving - stop deferasirox (Exjade®)
- If anaemia severe/symptomatic 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. (Patients with CKD and symptomatic anaemia may benefit from erythropoietin therapy, with or without hydroxycarbamide, although high doses are often required. Please discuss this in an MDT setting.
- Caution if receiving hydroxycarbamide (potentiated by renal impairment) - dose reduction may be necessary

f) 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 occur as a side-effect of hydroxycarbamide therapy. Hyperuricaemia may be associated with the development of uric acid stones or gout. And represent an early manifestation of renal dysfunction. In the presence of symptomatic hyperuricaemia or renal impairment consider treatment with allopurinol.

g) End Stage Renal Failure (ESRF)

This is managed by the nephrologists and should include early discussion of renal replacement therapy options including transplant and dialysis.

Patients with renal failure associated anaemia can be considered for erythropoietin therapy as in the non-sickle population, but the haemoglobin target should be tailored to the historical baseline haemoglobin of the patient. Patients with SCD on dialysis will require higher than the average dose when erythropoietin is used to correct anaemia. This should be done in discussion with the haematologists and nephrologist.

h) Dialysis & Renal Transplantation

Haemodialysis (HD) and peritoneal dialysis (PD) are both options for management of end-stage renal failure in the Sickle cell patients with some precautions such as warming the PD fluid prior to insertion and ensuring the HD machine is kept at a reasonable temperature while the blood is flowing through the circuits.
When possible, renal transplantation provides sickle cell patients with the best quality of life.
Each patient being considered or on the list for a renal transplant should be discussed between haematology and nephrology to cover the following:

- Transfusion programme prior (increased blood transfusions can increase risk of antibody formation therefore needs to be with antigen matched blood)
- Surgical and anaesthetic plan for the procedure
- Post and peri-transplant management to try to protect new transplanted kidney.

- Most patients will be considered for a transfusion programme (this maybe exchange blood transfusion to reduce hyperviscosity) following the procedure.
- Special focus to fluid balance, haematocrit, peripheral perfusion, temperature and oxygenation peri-procedure and any venous access issues
- Likely need for more frequent than average follow-up in outpatients in relation to fluid balance, immunosuppressant levels, renal function, and anaemia.
- Patients need to be counselled re: possibility of recurrence of sickle cell damage to transplanted organ

Survival of patients with SCD on haemodialysis is reduced compared with other causes of ESKD of non-diabetic origin.
Delayed graft function and increase in frequency of painful crises in individuals post-renal transplantation has been noted.
Exchange blood transfusion (EBT) or hydroxycarbamide should be considered in patients on the transplant waiting list and with functioning grafts.

2.2 Pulmonary and cardiac Complications:

a) Pulmonary hypertension

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 NT-pro BNP should be performed in all patients. Repeat echocardiography every 3 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 Service (Dr Gulum Haji ICHT and Professor Brendon Madden SGH) 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.

Patients who present with acute cardiac symptoms should be discussed urgently with the Cardiology

SpR locally or Consultant of the week via the hospital switchboard. 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) Chronic Sickle lung disease (CSLD)

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 due to recurrent sickling.
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 CSLD.

Clinical Marker	Stage 1	Stage 2	Stage 3	Stage 4
Chest pain	Recurrent substernal pain and chronic cough	Increase pain over stage 1	Severe midline crushing pain	Severe and prolonged pain with dyspnoea at rest
Arterial blood gases	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
CXR	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
Pulmonary Function Tests	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
ECG & ECHO	Left ventricular preponderance persists	Balanced ventricular hypertrophy	Right ventricular hypertrophy and right atrial enlargement Progressive	Severe right ventricular and right atrial hypertrophy. Ischaemic T

			increase in heart size	waves in V1 and V2 and cor pulmonale.
Pulmonary Artery Pressure	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

Abnormal lung function tests (PFT) and high resolution CT (HRCT) chest scan are the most sensitive markers of chronic lung disease. 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.

Routine pulmonary function tests (PFTs) in asymptomatic adult patients are ***not*** recommended

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 ≤ 94%
- NT-Pro BNP
- HRCT chest
- CT pulmonary angiogram or V/Q scan
- CRP - may be a useful marker
- α-1 antitrypsin status
- ACE, auto-antibodies including ANA

Management

- Refer to Respiratory service (Vincent Mak- Imperial, Dr Susannah Leaver at SGH and Dr Ian Stone at LNWUH
- Advice on smoking cessation if appropriate
- Prompt treatment of lower respiratory infection
- Ensure vaccination up to date

Sleep disordered breathing

Sleep diordered breathing (SDB) is a group of conditions characterised by complete or partial cessation of normal respiration during sleep resulting in nocturnal hypoxia or obstructive sleep apnoea (OSA). Both are common in SCD and have been correlated with morbidity including frequent painful VOC, risk of future CNS events and priapism. OSA has been reported in up to 60% of adults with SCD.

A sleep study should be recommended in all patients with:

- Self-reported disturbance of sleep
- Excessive daytime sleepiness (Epworth sleep score >10)
- Oxygen saturations awake < 95%
- A history of snoring, priapism or early morning headaches

2.3 Chronic Pain

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.

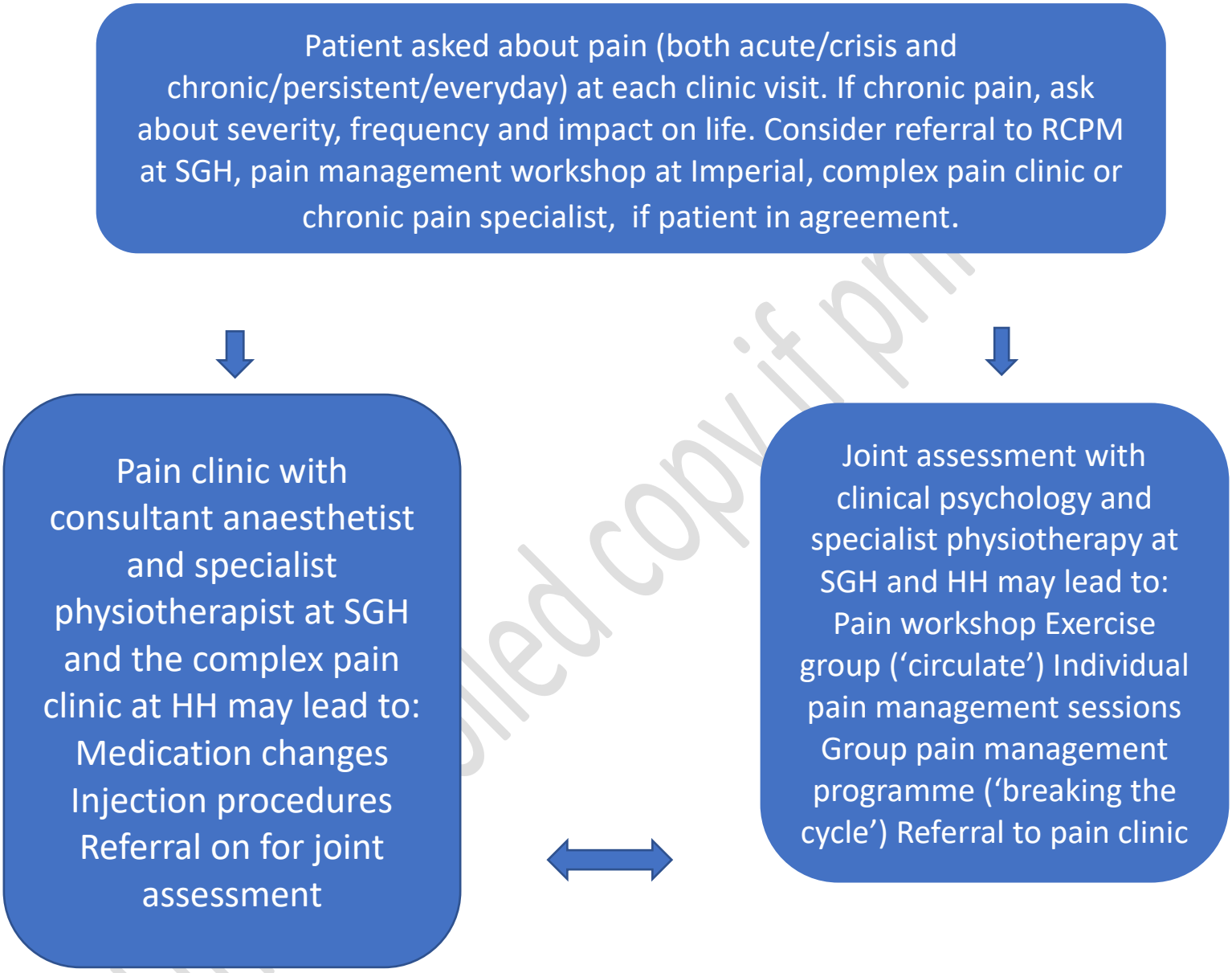
Management should include:

- Thorough assessment and treatment of any underlying cause for the pain e.g. avascular necrosis
- Referral to the complex pain clinic coordinated by Dr Steven Okoli, or chronic pain service provided by Dr Arun Bhasker at ICHT and the Red Cell Pain Management Service (RCPMS) at SGH.
- Refer to clinical psychology Dr Jeremy Anderson at ICHNT or Dr Kofi Anie at LNWUH and Dr Yvonne Whelan or Dr Anna Mathieson at St Georges for assessment and development of pain coping skills. Suitable patients can be referred to the Comprehensive Pain Management Programme based at HH or the Pain clinic with Consultant Anaesthetist and Specialist Physiotherapist at SGH

Specific therapies indicated may include:

- Long-acting opioids – these can lead to tolerance or dependence so should be used with caution and closely monitored. At doses of more than 120 mg oral morphine equivalent a day there is increased risk of harm, with no increased benefit and the likelihood that opioid-based medication is not working (BMA board of science, 2017).
- Adjuvant analgesics e.g. pregabalin, gabapentin
- Local unaesthetic/steroid injections
- Radiofrequency neurotomy
- Non-pharmacological therapies e.g. cognitive behavioural therapy, acupuncture, hydrotherapy
- Red cell exchange may be of benefit in individual patients.

Flow chart for managing chronic pain



2.4 Avascular necrosis (AVN) of the hips and shoulders

Avascular necrosis may affect up to 50% of patients with sickle cell disease and often gives rise to chronic pain and limitation of movement due to joint damage. It affects most commonly the femoral head (Issa et al., 2013) and the humeral head and they are commonly associated, although it has also been reported to affect multiple other joints including the knees, feet and back. It commonly affects

multiple joints. 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 at rest
- Pain recurrent/prolonged - if > 8 weeks 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

- Plain X-Ray
- MRI if XR normal

Avascular necrosis of femoral head: Staging criteria

Stage	Clinical and Laboratory Findings
0	Patient is asymptomatic Radiography findings are normal Histology findings demonstrate osteonecrosis
I	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 sub classified by extent of involvement [see below]) Histology findings are abnormal
II	Patient is symptomatic. Plain radiography findings are abnormal and include osteopenia, osteosclerosis, or cysts Subchondral radiolucency is absent MRI findings are diagnostic
III	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 Sub classification depends on the extent of crescent, as follows: - Stage IIIa: Crescent is less than 15% of the articular surface - Stage IIIb: Crescent is 15-30% of the articular surface - Stage IIIc: Crescent is more than 30% of the articular surface

IV	Flattening or collapse of femoral head is present Joint space may be irregular CT scanning is more sensitive than radiography Sub classification depends on the extent of collapsed surface, as follows: - Stage IVa: Less than 15% of surface is collapsed - Stage IVb: Approximately 15-30% of surface is collapsed - Stage IVc: More than 30% of surface is collapsed
V	Radiography findings include narrowing of the joint space, osteoarthritis with sclerosis of acetabulum, and marginal osteophytes
VI	Findings include extensive destruction of the femoral head and joint

Management

AVN is a complex condition, and there is inadequate evidence to guide practice (Martí-Carvajal et al., 2016)

Treatment depends on the stage of disease and requires a multidisciplinary approach, involving a specialist orthopaedic surgeon and haematologist.

Treatment is broadly divided into conservative and surgical approaches with non-surgical management largely the preserve of early stage disease.

1- Conservative or non-surgical management:

Although helpful, conservative treatment of AVN alone does not provide prolonged symptomatic relief and does not prevent disease progression.

- Analgesia - NSAIDs and/or codeine derivative initially, Gabapentin and pregabalin are alternative options
- Rest and avoidance of weight bearing - often difficult in practice.
- Walking aids.
- Physiotherapy/hydrotherapy
- Injection of local anaesthetic into the joint; Refer to Orthopaedic service

ICHT: at Charing Cross Hospital - Mr Angus Lewis (Hip), Mr Peter Riley or Mr Andrew Forester (Shoulder), LNWUH: refer to Orthopaedic department at NPH/CMH, Dr Abdul-Jabbar. Nick Ferran Shoulder. SGUH refer to Orthopaedic department at St Georges, Dr John Stammers and Dr Alazzawi Sulaiman.

2- Surgical management

- 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%

Recommendations

- The anaesthetic and pain management team should be involved in preoperative management of patients with SCD prior to joint replacement surgery.
- Core decompression can be considered in selected cases of non-collapsed femoral head in the young patient.
- The use of cementless prosthetic devices is preferred for hip replacement surgery in SCD.
- Post-operative infection prophylaxis and thromboprophylaxis are recommended as per local trust policies unless contra-indicated.

2.5 Iron overload

This should be read in conjunction with the BCSH guidelines for the monitoring and management of iron overload in patients with haemoglobinopathies and rare anaemias

Sickle cell patients are prone to iron overload due to multiple blood transfusions. Ferritin levels need to be monitored in frequently transfused patients in order to assess the need to start chelation, gauge the efficiency of their chelation regimen and ensure timely changes are made as needed. Iron levels also help to assess compliance.

If the patient **does** receive regular transfusions then ferritins should be measured at each transfusion and reviewed at Apheresis meetings and also with the patient in clinic. Other patients should have regular monitoring of ferritin levels as part of the annual review.

The choice of iron chelators includes desferrioxamine (Desferal®), deferiprone (Ferriprox®) and deferasirox FCT (Exjade®). **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.

Indications

- Received >10 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
- All patients with serum ferritin persistently raised >1000 µg/l who have been previously transfused should have quantitative monitoring of liver iron concentration using magnetic resonance imaging (MRI).
- Iron chelation is recommended in patients who have a liver iron concentration of > 7mg/g dry weight on MRI scanning.
- Patients receiving long term blood transfusion should have regular monitoring for iron overload and appropriate iron chelation therapy according to their iron burden.
- All patients receiving iron chelation therapy should be regularly monitored for therapeutic effect and chelator toxicity.
- Support should be provided to patients to help improve adherence to chelation therapy

Investigation

Baseline and annual ophthalmology and audiology review – if patient is on desferrioxamine . There is less clear evidence of any retinotoxicity with **deferasirox and deferiprone** and so these patients should be monitored clinically and discussed with ophthalmology if there are concerns of any symptoms

- Glucose, cortisol, TSH+T4, FSH+LH, oestradiol/testosterone, PTH, IGF-1
- Creatinine Clearance/eGFR and urine PCR weekly for the first month of initiation or modification of therapy and monthly thereafter
- 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

Deferasirox

Deferasirox (DFX) is an orally active iron chelator, given once daily. The starting dose of the film coated tablet is 14 mg/kg/day. Maximum dose is 28 mg/kg/day. Serum ferritin should be monitored monthly and the dose adjusted every 3 to 6 months, Advised dose escalation is 3.7-7.5mg/kg/day if required. In patients whose serum ferritin level has reached the target (usually between 500 and 1,000 µg/l), dose reductions in steps of 5 to 10 mg/kg should be considered. Interruption of DFX should be considered if ferritin is persistently < 500 µg/l..

Dose alterations due to hepatic impairment

 Interrupt treatment if persistent or progressive increase in liver enzymes.

Serum transaminases, bilirubin and alkaline phosphatase should be checked before the initiation of treatment, every two weeks during the first month and monthly thereafter. Deferasirox may be a contributing or aggravating factor for hepatic failure, but the most common cause of liver dysfunction and failure in the iron loaded patients is the iron itself.

If there is a persistent and progressive increase in serum transaminase levels that cannot be attributed to other causes, deferasirox should be interrupted. Once the cause of the liver function test abnormalities has been clarified or after return to normal levels, cautious re-initiation of treatment at a lower dose followed by gradual dose escalation may be considered**.** Deferasirox is not recommended in patients with severe hepatic impairment

Contraindications

It is contraindicated in patients with a creatinine clearance/eGFR <60ml/min

Monitoring / Tests

Prior to initiating treatment, the patient requires serum ferritin, renal and liver biochemistry and urine PCR. *Audiology and ophthalmology review at baseline and then annually*

First month, renal and liver biochemistry weekly and then monthly

Urine dip and urine PCR for protein assessment

Desferrioxamine (Desferal)

Desferrioxamine (DFO) is usually given as a subcutaneous infusion, most often 8-12 hours overnight but can also be given as a continuous intravenous infusion in heavily iron-loaded patients. Patients are usually treated between four and seven days per week depending on the degree of iron overload. DFO can also be given by continuous intravenous infusion to reverse cardiac dysfunction, but this is rarely needed in patients with SCD

Dose

- 20–40 mg/ kg as a subcutaneous infusion over 8-12 hours on 4-7 days each week
- Consider oral vitamin C (200mg oral ascorbic acid) to be taken separately to food to enhance chelation

In cases of cardiac iron overload it can be used in combination with deferiprone. This must only be initiated via the haematology consultant

Monitoring

- Annual ophthalmology and audiology review including baseline
- Monitor ferritin and MRI scan to ensure response

Desferrioxamine must be stopped and patients admitted for treatment and investigation if they develop sore throat, abdominal pain and diarrhoea. *Yersinia* infection must be excluded.

Deferiprone (Ferriprox)

Deferiprone is an oral chelation agent which may be used in dual therapy with deferasirox in patients where optimum chelation is not being achieved. It can also be used as a single agent in patients who cannot tolerate desferrioxamine or deferasirox.

On initiation, regular FBC should be monitored weekly as there is a risk of drug induced neutropaenia (agranulocytosis) with this medication.

Doses usually start around 25mg/kg tds (75mg/kg) and do not exceed 100 mg/ kg / day

It is not licensed for use in SCD. Consequently, patients should be made aware of this and the reasons for its use should be clearly documented in the notes.

Adverse effects include agranulocytosis and arthropathy, as well as gastro-intestinal disturbance, intermittent elevation in alanine transaminase (ALT) and zinc deficiency. Deferiprone therapy has been given in combination with desferrioxamine in patients with significant iron overload and it is thought to have a particular benefit in those with cardiac iron overload. Combination therapy should only be instigated after discussion with a specialist centre.

Routine Test	DFO	DFP (or combination with DFO)	DFX
Neutrophil count	Not required	Weekly during therapy	Not required
Creatinine	Not required	Not required	Twice before start, then weekly during first month after initiation

			and change of dose. Thereafter monthly
ALT	Monthly	Monthly	Twice before start, then 2 weekly for first month after initiation of therapy. Thereafter monthly
Urinalysis	Not required	Not required	Twice before start, then weekly during first month after initiation and change of dose. Thereafter monthly
Pure tone audiometry	Annual	6-12 monthly for combination DFO and DFP, not if used as single agent	Annual
Ophthalmology	Annual	6-12 monthly for combination DFO and DFP, not if used as single agent	Annual

Monitoring of iron load

a) Serum ferritin

Serum ferritin remains a convenient, cheap and widely used way of assessing body iron but levels can be very variable. 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.. Cardiac iron loading is rare in Sickle cell patients. **The frequency of scanning depends on the degree of iron loading and the clinical picture.**

c) FerriScan® – 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 ultrasound perform annually if LIC > 7mg/g DW

e) Liver elastography (Fibroscan) - If evidence of chronic liver disease on ultrasound or persistently elevated LIC

f) 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 3-5 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.

Routine Test	Frequency
Serum ferritin	1-3 monthly
Cardiac T2* MRI	2 yearly if >20ms
	Annual 10-20ms
	Six monthly < 10ms
FerriScan	1-2 yearly 1.8-7mg/g DW
	Annual >7<15mg/g DW
	6-12 monthly > 15mg/g DW

2.6 Vitamin D deficiency

There is a high prevalence of vitamin D deficiency (VDD) 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 as below:

- Normal level 50-150 nmol/L
- Vitamin D level <40 nmol/L (deficiency) – prescribe loading dose colecalciferol 20,000 - 25,000 units weekly for 12 weeks followed by maintenance dose
- Vitamin D level 40- 49 nmol/L (insufficiency) – prescribe maintenance dose (either colecalciferol 20,000-25,000 every 2 weeks or Adcal D3 2 tablets daily

2.7 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, Consutant Endocrinologist - extn. 34823 at Imperial or Dr Wing May at the LNWUH or Dr Gul Bano at St George's Hospital)

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

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

2.8 Leg ulcers

Up to 20% of SCD patients develop leg ulcers. These are more common in males and frequently recur. They most commonly occur around the ankle area and are often secondary to trauma. Other causes including diabetes, venous insufficiency and connective tissue disorders should be excluded.

The pathophysiology of leg ulcers in SCD is not fully understood but there is an association with higher levels of haemolysis and it's thought that hypercoagulability, thrombosis, mechanical obstruction and venous incompetence may play a role in their development.

A multidisciplinary approach should be taken in the treatment of leg ulcers and should include haematologists, vascular surgeons, dermatologists and the tissue viability service. Specialist pain team input may be required as leg ulcers can cause severe pain.

All patients who develop leg ulcers should be referred to a tissue viability service/wound care specialist for assessment. The Haemoglobinopathy CNS will advise on the appropriate community service.

Referrals to the Vascular team
All patients with leg ulcers should be referred to their local Vascular team for review to identify those with venous incompetence.

SGH refer to the Vascular team at SGH
ICHT refer to the Vascular team at Charing Cross Hospital
LNWUH refer to the vascular team at Northwick Park Hospital

Hydroxycarbamide
Hydroxycarbamide has been associated with leg ulcers in other patient groups although this association has not been proven in patients with SCD. However, hydroxycarbamide 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 the Red Cell MDT.

Transfusion
A trial of transfusion (usually for 6 months) may be appropriate in patients with intractable leg ulcers, particularly if they are significantly anaemic. This should be discussed at the Red Cell MDT.

Other management includes:

- 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 – zinc levels should be measured and supplements offered to those with deficiency
- Compression stockings/Unna boots, particularly in patients with evidence of venous insufficiency
- Topical morphine gel - may be effective if pain not relieved by oral analgesics
- Pregabalin/gabapentin if neuropathic pain
- Maggot debridement in individual cases
- Lumbar Sympathectomy (on recommendation of pain specialist)

3. TRANSITION FROM PAEDIATRIC TO ADULT SERVICES

Please refer to the separate HCC guideline on the transition of haemoglobinopathy patients.

4. TRANSFUSION

Transfusion in patients with Sickle Cell Disease (SCD) is increasing rapidly across the UK but with variability in indications and lack of robust evidence in many cases. Guidance is now issued by both the British Standards of Haematology (2016) and from the Standards of Clinical Care for adult patients with SCD in the UK. These guidelines describe the indications, management and process (including safety and selection) for blood transfusion in SCD and thalassaemia.

Transfusion is undertaken in SCD to improve haemoglobin level and/or reduce HbS%. “Top up” transfusions are generally required to achieve the first aim and exchange blood transfusions usually achieve the second goal. The decisions to top up or exchange transfuse an adult or paediatric patient with sickle cell disease (SCD) needs the input of a clinician with appropriate experience. Specialist advice should be obtained for the management of patients with complex transfusion requirements
Transfusion in SCD requires careful consideration of both the haemoglobin concentration (Hb) and/or percentage of sickle haemoglobin (%HbS) in order to ensure maximal oxygen delivery to tissues without increasing overall blood viscosity to detrimental levels. 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 Local Blood Transfusion Policy for Adults).

A transfusion history should be obtained in all SCD patients requiring transfusion, whether elective or emergency. Close communication is essential between clinical and laboratory teams so that appropriate blood is given, please also refer to SpICE (national database on transfusion history and genotype)

- Individuals with SCD are high-risk surgical patients. Close liaison between all clinical teams is essential with preoperative optimisation and appropriate postoperative care, whether transfused or not
- Virology testing [hepatitis B, hepatitis C and human immunodeficiency virus (HIV)] should be undertaken at presentation and hepatitis B vaccination should be given to all patients with SCD, irrespective of previous or prospective planned transfusions. SCD patients on regular transfusions should be screened annually for hepatitis B, hepatitis C and HIV
- The choice of transfusion method, i.e., simple (top up) or exchange, should be based on clinical judgement of individual cases, taking into account the indication for transfusion, the need to avoid hyperviscosity and minimise alloimmunisation, maintenance of iron balance, venous access issues and available resources
- Patients with SCD must also have extended red blood cell (RBC) antigen typing performed (either extended phenotyping or if recently transfused genotyping) , which may assist with further serological testing and selection of red cell units if there are haemolytic reactions and complex transfusion requirements. “* Includes the following blood group antigens: C, c, D, E, e, K, k, Jk^a, Jk^b, Fy^a, Fy^b,Kp^a, Kp^b, M, N, S, s, Le^a and Le^b. 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

- Blood provided for SCD patients should be HbS negative and, where possible, should be <10 days for top up and <7 days for red cell exchange transfusion.

Elective top up transfusions are undertaken in the Haematology Day Care Unit at HH and SGH, and Medical Day Care Unit at Central Middlesex Hospital (LNUWH). Exchange transfusions are carried out on designated Apheresis units at HH and SGH. Both centres offer 24/7 service. Elective RCEx transfusion is offered at Northwick Park Hospital on Tuesdays, Wednesdays and Thursdays only. Emergency RCEx is performed at the Northwick Park site when necessary.

Patients with sickle cell disease often have poor peripheral venous access. It is recommended that no more than 3 attempts at should be made by an individual practitioner. If initial attempts fail a more experienced practitioner should attempt cannulation.

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 >.20 g/l below steady state.(BSH guidelines 2016)
- 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. Depletion RCEx should be used where clinically appropriate.

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) in preparation for Surgery
- Girdle syndrome
- Emergency surgery or endoscopic intervention

b) Elective exchange transfusion

- Primary Stroke prevention in patients transitioning from Paediatrics
- Secondary stroke prevention
- Preparation for surgery
- Pregnancy - maternal sickle cell related complications
- Recurrent painful crises if hydroxycarbamide ineffective, declined or contraindicated
- Recurrent acute chest syndrome if hydroxycarbamide ineffective, declined or contraindicated
- Leg ulcers refractory to other measures
- Recurrent priapism for failed pharmacological measures.
- 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 Haemoglobinopathy Coordinating Centre 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

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, Rh (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

5. REPRODUCTIVE HEALTH

5.1 Pregnancy

Pregnant women with Sickle Cell Disease

Pregnancy in SCD has been associated with increased maternal and perinatal morbidity which can be minimised by careful management. Maternal complications include increased mortality, increased sickle complications (acute pain crisis, acute chest syndrome, and infection, particularly urinary tract infection) and increased pregnancy complications (pre-eclampsia, pregnancy-induced hypertension, thromboembolism and caesarean section). Fetal complications include increased rate of miscarriage, still birth, premature labour, fetal growth restriction and perinatal mortality. This should be discussed before conception with advice to report pregnancy as soon as possible to facilitate arrangements for specialist antenatal care.

Pre-conception counselling

From adolescence, the intentions of women with SCD regarding pregnancy and contraception should be documented at each contact with their sickle haematology team.

Women with SCD should be seen pre-conceptually by a specialist in sickle cell disease to receive information about how SCD affects pregnancy and how pregnancy affects sickle cell disease, and how to improve outcomes for mother and baby. This consultation should include optimisation of management and screening for end organ damage.

Patients with SCD should be encouraged to have the haemoglobinopathy status of their partner determined before they embark on pregnancy. If identified as an 'at risk couple', as per National Screening Committee guidance, they should receive counselling and advice about reproductive options.

Penicillin prophylaxis or the equivalent should be prescribed.

Vaccination status should be determined and updated before pregnancy.

Folic acid (5 mg once daily) should be given both pre-conceptually and throughout pregnancy.

Hydroxycarbamide (hydroxyurea) should be stopped at least 3 months before conception.

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers should be stopped before conception.

Antenatal Clinic & Haematology Clinic management

This guideline applies to all women who are known to have sickle cell disease and present to the antenatal clinic, and those who are diagnosed with sickle cell disease at booking in the antenatal clinic (antenatal screening). Sickle cell disease includes the following genotypes: HbSS and compound heterozygotes (HbSC disease, HbSBeta thalassaemia,
HbSD, HbSE and others).

In North West London a specialist service is provided at Queen Charlotte's and Chelsea Hospital (QCCH) for the care of pregnant women with SCD. In the South West London, this is provided at St Georges University Hospital (SGH). It is recommended that these women should be managed in a specialist joint Obstetric-Haematology clinic. At QCCH this is provided by a Consultant Obstetrician and specialist midwife at QCCH and a Consultant Haematologist with expertise in management of SCD from Hammersmith Hospital (HH). At SGH this is provided in a hybrid model by consultant obstetrician, haematologist, case load midwife and anaesthetist, see Appendix 3 for contact details

Referral to the joint Obstetric-Haematology service should be arranged at the earliest opportunity with any pregnant woman with SCD who presents to antenatal clinic or haematology clinic. This referral can be made by the obstetric or haematology team or whoever sees the woman first.
The referral to the joint Obstetric-Haematology service should be made as soon as possible, preferably before 10 week's gestation.
The woman will be seen regularly in the joint Obstetric -Haematology Clinic at QCCH on a Monday morning throughout the pregnancy. At SGH the High Risk Obstetric clinic is on a Monday afternoon 2-5pm.

All women with sickle cell disorders should be offered care in a mutlidisiplinary setting which includes obstetric and specialist haemoglobinapthy input. If the woman presents in a local antenatal clinic, the midwife should check that the woman's partner's has been tested and his haemoglobinopathy status has been identified by contacting the specialist nurse / midwife who is responsible for the area. If this has not been done the specialist nurse / midwife will invite the woman / couple for genetic counselling and partner testing in order to identify an at-risk pregnancy as early as possible. Referral should be done preferably by 10 weeks gestation in order to meet national standards if prenatal diagnosis is required.

Referral for specialist care
Refer as early as possible – ideally before 10 weeks of pregnancy.
Refer directly to the joint Obstetric- Haematology Monday morning clinic this is held in the de Swiet Obstetric Medicine Unit, 2nd floor, Queen Charlotte's and Chelsea Hospital.
Direct telephone number 0208 383 3998 (reception)
0208 383 5108 (obstetric medicine midwife)

SGH : refer to the high risk obstetric clinic held in the Antenatal Clinic, ground floor of Lanesborough Wing on Mondays at 2-5pm.
020 8672 1255 ext 3664/1911 (Haemoglobinopathy Specialist Midwife)
Inform local haematologists.
Instigate a referral to Consultant Haematologist at Hammersmith Hospital,
Haemoglobinopathy clinic.
Refer to Consultant Haematologist, Red Cell and Haemoglobin Disorders Unit, St George's Hospital. Clinics held on Wednesday afternoons in Haematology and Oncology Outpatient Clinic, ground floor of St James' Wing

Referral letter must include:

- Woman's biographical details including telephone/ mobile number
- Summary of obstetric and medical history (inc. transfusion etc.)
- Details of known red cell alloimmunisation
- G6PD status, Hepatitis status and iron status if known
- Details of partner's haemoglobin type if known
- Analgesic preference or individualised pain protocol if available
- Whether the woman is on Hydroxycarbamide and the date this was stopped
- Routine medications (including penicillin, folic acid, chelation therapy).

Initial assessment at Booking

Normal booking procedure and booking bloods. These should also include:

- Full blood count
- Reticulocyte count
- Hb S, F and A2 quantification
- Renal profile
- Liver function tests
- Extended red cell phenotype (if not known) and antibody screen
- Ferritin, Fe and TIBC
- G6PD status if not known
- Malaria screen, if history of travel to an endemic area within the past 12 months.

Other investigations include:

- Nuchal / Combined screening test (CST) scan should be offered if appropriate
- Booking USS should be performed as normal
- Urinalysis and MSU
- Urine for protein: creatinine ratio
- SpO2 on air
- Echocardiogram – to screen for pulmonary hypertension
- Pulmonary function tests if resting PO2 <95 %
- Refer to Ophthalmology if not assessed within the last 6 months or if there is a 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.

Medications

- Iron supplements should only be given if deficiency is confirmed biochemically
- Folic acid 5mg orally once a daily if not already receiving - continue throughout pregnancy
- Penicillin V 250mg orally twice a day
- Commence low dose aspirin (75mg daily orally) - 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 3 months prior to conception or immediately after confirmation of pregnancy due to risk of teratogenicity
- Hydroxycarbamide should be stopped at least 3 months prior to conception - if not counsel about risk of teratogenicity
- Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers should be stopped.

Follow up

Frequency

The Sickle cell standards suggest:

10-24 weeks – 4 weekly

24-34 weeks – 2weekly
34 weeks to term – weekly

- The frequency will be increased if there are any concerns
- Monitor for pre-eclampsia at each visit (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 middle cerebral artery (MCA) velocity on Doppler US.

The influenza vaccine should be recommended if it has not been administered in the previous year. The COVID- 19 vaccine, Pfizer/BioNTech or Moderna vaccine should be recommended if unvaccinated Women with SCD should be offered anaesthetic assessment in the third trimester of pregnancy.

Ultrasound Scans
Women should be offered the following ultrasound scans:

- A viability scan at 7–9 weeks of gestation
- 11-14 weeks – Booking and Nuchal / Combined Screening Test (CST) scan
- 18-20 weeks - Anomaly scan (and uterine artery Doppler)
- 24 weeks until term - 4 weekly growth scans. Risk of IUGR is increased, therefore

fetal biometry scan, Doppler of umbilical artery and liquor volume estimation.

Other Investigations

FBC should be checked monthly

Renal function should be checked every 4-8 weeks and more frequently if initially abnormal.
Consider monitoring anti-Xa levels if on treatment dose LMWH or at risk of accumulation (extremes of body weight and/or abnormal renal function).

Urinalysis should be performed at each antenatal visit and MSU sent monthly. UTIs should be treated promptly with antibiotics as they are common in this group of women who are 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.

It should be considered in all pregnant women with SCD from 28 weeks gestation

Introduce earlier if additional risk factors develop during pregnancy e.g. pre-eclampsia, immobility, and nephrotic syndrome

Thromboprophylaxis should be routinely prescribed during antenatal hospital admissions.
Dosing should be based on local guidelines on thromboprophylaxis in pregnancy.
Prophylactic LMWH should be offered to all women post-delivery and continued for 6 weeks.

Blood Transfusion

Routine blood transfusion is not indicated for the majority of women with SCD during pregnancy. Blood transfusions must only be given after discussion with the haematology SpR or Consultant.

Blood transfusion may be considered in women who are severely affected prior to pregnancy (particularly if on a long- term transfusion programme or hydroxycarbamide) or those who develop complications during pregnancy.

Possible indications for blood transfusion include recurrent pregnancy loss, multiple pregnancy, severe anaemia (symptomatic or >15% reduction in Hb from steady state), frequent pain episodes, chest crisis, pre-eclampsia and IUGR.
Once initiated transfusion (top- up or exchange) will usually 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 affect uteroplacental blood flow.
CTG monitoring during transfusion not routinely required.

Blood should be matched for ABO, full Rh and Kell blood groups and be HbS negative.
The request form should clearly identify that the woman has SCD and their ethnic origin.
Blood used for transfusion in pregnancy should be cytomegalovirus CMV negative.

Admission with acute complications during pregnancy

Gestation and place of admission:

- <20/40 present to Renal Haematology Triage Unit at HH and A and E at SGH. At SGH women with haematology problems will be admitted to Golden Smith ward or Ruth Myles Unit and those with obstetric problems will be admitted to the gynaecology ward.
- >20 weeks admit to Delivery Suite at SGH

  At QCCH (Queen Charlotte's & Chelsea) 20-23/40 admit to HH if indication for admission is sickle cell crisis; admit to QCCH if indication for admission is obstetric

  >23 weeks admit to QCCH and inform haematology SpR at HH

Inform haematology SpR/on-call haematologist:
For admissions with sickle cell crisis, care should be led by haematology team with regular review and adjustments of pain relief by haematology specialist nurses and doctors.

Manage according to the sickle cell guidelines (see hospital intranet).
Intravenous fluids 3 litres /24hours if renal function normal. Monitor fluid balance using standard chart.

IF THERE IS EVIDENCE OF PRE-ECLAMPSIA FLUID REPLACEMENT SHOULD BE GIVEN MORE CAUTIOUSLY

Follow patients agreed individual analgesia protocol. Hourly observations including pO2 on air

- If pO2<94% on air, oxygen via mask, perform arterial blood gasses and inform haematologist.
- If significant fever or symptoms of infections – follow local trust guidelines
- If afebrile/no symptoms of infection – consider oral Amoxycillin 500mg TDS or oral cephalosporin e.g. cephalexin 500mg BD.

Commence LMWH thromboprophylaxis if this has not already been done.
At least daily review by Red cell team who are responsible for adjustments in analgesia. It is recommended that any woman with SCD on labour ward with a sickle cell crisis should be reviewed at start of the day and end of the day if possible.

Timing and mode of delivery
Pregnant women with SCD who have a normally growing fetus should be offered elective birth through induction of labour (IOL), or by elective caesarean section if indicated on obstetric grounds, after 38+0 weeks of gestation. The pregnancy should not continue beyond the due date without MDT discussion.

SCD should not in itself be considered a contraindication to attempting vaginal delivery or vaginal birth after caesarean section.

In women who have had hip replacements (because of avascular necrosis) it is important to discuss suitable positions for delivery.

Delivery
On admission to the Delivery Suite or Antenatal Ward in labour inform:

- Consultant or SpR Obstetrician
- Consultant or SpR Anaesthetist
- Consultant or SpR Haematologist

The haematology consultant or SpR should be informed immediately if there are any impending or actual complications.

Delivery will usually be at Queen Charlotte's and Chelsea Hospital or SGH but women may present in labour to the other hospitals.

During induction, labour and delivery the woman should have a fluid intake of 3-4 l/day and analgesia and oxygen as required (unless there are features of pre-eclampsia, when fluid replacement should be more cautious).

Delivery should be covered with prophylactic antibiotics as per local maternity guideline on safety of anti-infectives in pregnancies.

Routine blood tests (FBC and reticulocytes, U+Es, LFTs, coagulation screen, Group and Save) should be taken.

Blood should be cross-matched for delivery if there are atypical antibodies present (since this may delay the availability of blood), otherwise a 'group and save' will suffice.

Regional analgesia is recommended for caesarean section.
If the woman is on LMWH thromboprophylaxis and it is >12 hours since the injection, it is safe to proceed with the epidural. If it is <12 hours since the last dose of LMWH or the coagulation is abnormal, the on-call anaesthetist should be contacted and will decide on the most appropriate form of analgesia/ anaesthesia.

If the woman is on treatment dose LMWH and it is >24 hours since the last injection, it is safe to proceed with an epidural. If it is <24 hours since the last dose of LMWH or the coagulation is abnormal, the on call anaesthetist should be contacted and will decide on the most appropriate form of analgesia/ anaesthesia.

The obstetric team should make a risk analysis of any woman who has had LMWH halted during induction of labour or during labour to ascertain if further dosing is required during
IOL / labour. Thromboprophylactic dosing of LMWH can be given 2 hours following insertion of an epidural and discussion with the anaesthetist. TED stockings should be used and consideration given to using FLOWTRON boots.

If a general anaesthetic is required and the woman has not been receiving regular blood transfusion during pregnancy, consider blood transfusion (top up or exchange) prior to surgery and discuss with the haematologist. **A blood transfusion should only be given on the haematologist's advice.**
Continuous intrapartum electronic fetal heart rate monitoring is recommended owing to the increased risk of fetal distress which may necessitate operative delivery.

Avoid the use of Pethidine due to the risk of CNS toxicity and seizures

The neonatal team should be present at the time of delivery for women who have been on high doses of opioids antenatally or in labour

The neonatal team must be told about the opioid dosing and duration during pregnancy as the neonate may need to be admitted and monitored for signs of withdrawal

Post Delivery
Intravenous hydration (3-4 l/day) and supplemental oxygen is required for the first 24 hours post delivery. Oxygen saturations on air should be checked hourly, and the haematologist should be contacted if they fall below 94%.

If a caesarean section is performed, post delivery monitoring on the intensive care unit or obstetric high dependency unit is necessary for a minimum of 24 hours. Regular incentive spirometry must be performed by the patient post caesarean section. If the patient is not able to perform this and/or oxygen saturations <94% on room air, start continuous positive airways pressure (CPAP) and maintain for 12 – 24 hours.

Early ambulation should be encouraged.
All women should be reviewed by the physiotherapist.
Continue broad spectrum antibiotics for five days post delivery if clinical signs of infection. In the absence of infection a single dose should be given and discussed with microbiology if unsure

Diclofenac by rectal route can be used as analgesia post caesarean Section or vaginal birth, if the woman is experiencing moderate-severe pain. Diclofenac should not be used if the woman has pre-eclampsia.
The woman should be reviewed by the haematologist before discharge.
The woman should not be discharged for at least 48 hours post delivery.
The woman should be reviewed by the haematologist before discharge.
If the couple are known to be at-risk of having a child with a major haemoglobinopathy, inform paediatrician of the birth and arrange blood to be taken from the baby and sent to the neonatal screening laboratory as soon as possible after birth (do not use cord blood), if the mother has requested.
All neonates will have routine neonatal screening for haemoglobinopathies via the national new born screening programme at 5 - 8 days of age.

Postnatal follow up
Review at 6 weeks in joint obstetric haematology clinic at QCCH at SGH follow up is arranged in the haematology clinic and or postnatal clinic as required.
If complications develop before this see at QCCH / SGH with joint review by Red Cell
Haematology and Obstetric teams
Discuss contraceptive options.
Arrange on-going routine follow up in Red Cell clinic or at local centre.

5.2 Contraception (discussed at 6 week post-natal follow up appointment)

Progestogen-containing contraceptives such as the progesterone only pill (Cerazette®), injectable contraceptives (Depo-Provera®) the levenorgestrel intrauterine system
(Mirena®) and the subdermal implant (Nexplanon®) are safe and effective in SCD.
Depot Provera has been shown to reduce the number of sickle cell crises in women and is administered 3 monthly.
Oestrogen-containing contraceptives should be used as second-line agents. There is a theoretically increased risk of stroke and venous thromboembolism with the combined oestrogen containing contraceptives such as the combined oral contraceptive pill (COCP).
If progestogenic methods are unacceptable or unsuitable, a low dose COCP can be considered after discussion with the patient. A copper intrauterine contraceptive device (‘coil’) can also be used. Disadvantages of the copper coil are an increase in menorrhagia and a slight increased risk of infection.

5.3 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 if indicated.

5.4 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 Andrology Service at Imperial College
Healthcare NHS Trust, see section 7.4 for contact details.

6. SURGERY AND ANAESTHESIA

Surgery is associated with a higher risk of peri-operative complications in patients with SCD, including an increased risk in peri-operative mortality, vaso-occlusive crisis, acute chest syndrome and infection. Close collaboration between the surgeon, specialist haemoglobinopathy team and anaesthetist in formulating an individual management plan is essential to minimize this risk. 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 4 weeks) to allow pre-operative assessment and time to plan a red cell exchange transfusion or top-up transfusion if indicated.

6.1 Pre-operative assessment

- Assess cardiac, pulmonary (consider echocardiogram) and renal function before intermediate/high risk surgery to identify patients at higher risk of peri-operative complications
- Arrange HDU bed if required (should be considered for those with a severe disease phenotype or with chronic respiratory disease)
- Identify any special analgesic requirements
- Consider the need for pre-operative transfusion or exchange blood transfusion
- For elective surgery, patients should be placed at the beginning of the theatre list to reduce the risk of cancellation, particularly if they have been transfused pre-operatively.
- Each patient should have an individualised management plan which will depend on the risk of the procedure and the patient's risk factors. This should be communicated to the surgical and anaesthetic teams and uploaded to the patient's medical records.

6.2 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 (patients should have repeat group and save samples on admission being aware that these patients are NOT suitable for rapid crossmatch).
- 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 SpO2 from pre-medication until at least 24 hours after surgery
- and provide supplemental O2 to maintain normoxaemia – inform Red Cell/on-call Haematology SpR immediately if SpO2 ≤ 94%
- Antibiotic prophylaxis (according to local guidelines)
- 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
- VTE prophylaxis should be prescribed unless contraindicated. Follow local guidelines on extended prophylaxis depending on the type of surgery.

6.3 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 UK-led multi-centre, randomised control trial of patients with HbSS and HbSβ0 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:

- HbSS or HbSβ0 having low/intermediate risk surgery if Hb < 90g/l

The target Hb should not exceed 100 g/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 in all genotypes
- History of significant risk factors e.g. acute chest syndrome, frequent painful crises, chronic lung disease, pulmonary hypertension
- HbSS or HbSβ0 having 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

* In this situation a target HbS of <20% is recommended in HbSS/HbSβ-thalassaemia and <10% in compound heterozygous states e.g. HbSC and HbAS. This should be discussed by the multidisciplinary team, including haematology, cardiothoracic and anaesthetic teams.

Patients with HbSC and other milder phenotypes (non-HbSS or HbSβ0) undergoing low/intermediate risk surgery without additional risk factors should be considered for transfusion on a case by case basis taking into consideration preoperative Hb, type of surgery and disease phenotype.

6.4 Emergency surgery

Following emergency surgery, the majority of patients should be admitted to HDU/ICU. These patients should be discussed urgently with the Red Cell/on-call Haematology SpR or consultant. Pre-operative transfusion may not be possible but may be indicated post-operatively.

6.5 Patients who cannot be transfused

Rarely, alternatives such as hydroxycarbamide and erythropoietin may be indicated, for example, if the patient has a history of delayed haemolytic transfusion reactions (DHTR) such as hyperhaemolysis, rare alloantibodies or is a blood-refuser.

Patients who have had DHTR despite steroid and IVIg treatment should be discussed in the HCC MDT pre-operatively and considered for rituximab treatment.

For patients who decline blood products, a clear advance directive must be documented and shared with the anaesthetic, surgical and haematology teams.

7. HYDROXYCARBAMIDE THERAPY

7.1 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 hospitalisation, reduces the number of episodes of acute chest syndrome (ACS) and reduces blood transfusion requirements.

Evidence indicates HC improves survival in SCD, and potentially modifying the natural history of SCA including the onset or progression of end organ damage. 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 severe SCD (sickle cell anaemia (HbSS), and S/β 0 thalassemia). 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. 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 thirty years in SCD and studies show it to be effective and safe.

BCSH guidance hydroxycarbamide
https://b-s-h.org.uk/guidelines/guidelines/guidelines-for-the-use-of-hydroxycarbamide-in-children-and-adults-with-sickle-cell-disease
https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.15235

7.2 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
- Severe symptomatic anaemia that interferes with quality of life (QOL) or activities of daily living (ADL).
- Secondary stroke prevention if transfusion contra indicated
- Sickle Nepropathy with persistent proteinuria despite ACEi/ARB (caution if EGFR reduced)

Other potential indications should be discussed on an individual basis and should be referred to the HCC MDT

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)

Caution:

- 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.

7.3 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 (reversible).

- Provide copy of HC information leaflet to patient, GP and Community Haemoglobinopathy Nurse/Counsellor

- Advise on avoidance of live vaccines while taking HC (like Shingles or yellow fever vaccine).

- Provide local Clinical Haematologist and Nurse Lead with copy of HC guideline (if applicable).

- Obtain and document informed consent from patient (and parent if under 18 years, or both in some cases especially between 16-18 years).

7.4 Initiation and monitoring

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

All males should be offered sperm cryopreservation (via the Andrology Department at Hammersmith Hospital) prior to commencing HC.(An email should be sent to Andrology clinic HH, imperial.andrology.queries@nhs.net). A negative pregnancy test should be obtained in females of reproductive age before initiaiting therapy.

Start at 15 mg/kg/day to nearest 500 mg (HC is available as 500mg capsules) increasing after intervals of 8 weeks by 5mg/kg/day, aiming towards MTD. To achieve the correct average daily dose it may be necessary to alternate doses or omit the drug on certain days. The usual dose is 15-35 mg/kg/day (a few patients tolerate up to 35mg/kg), although the MTD typically averages 25mg/kg/day. Older patients

often require lower doses of HC, and this should be taken into consideration if starting HC in someone over 60 years of age.

To achieve MTD:

- Escalate HC dose as above
- Follow monitoring schedule as outlines below.
- Stop HC if cytopenia develops

This is (Cytopenia) defined by any of the following:

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

- Neutrophils < 1.0 x10^9/L (consider a lower figure if there is evidence of ethnic neutropenia)
- Platelets < 80 x 10^9/L
- Reticulocytes < 1% (Absolute Reticulocyte Count < 80.).

Haemoglobin < 45g/l or drop >30g/l below baseline

- Monitor FBC weekly (or more frequently if indicated) until neutrophils
- 1.5 x 10^9/L and platelet and reticulocyte count are in the normal range (generally 1-2 weeks)
- Reintroduce HC at 2.5mg-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

If MTD has been achieved, this should be clearly documented.

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

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:

At initiation of HC therapy: FBC and reticulocytes,
Hb electrophoresis including HbF, renal profile, LFTs, LDH

⇓

Every 2 weeks until MTD reached (or decision to give fixed dose):
FBC and reticulocytes, renal profile, LFTs

⇓

After MTD attained (or decision to give fixed dose) every 2-3 months: FBC and reticulocytes, HbF, renal profile, LFTs

⇓

Every 3 months if stable (interval may be increased if stable on long-term therapy-see above):
FBC and reticulocytes,
HbF, renal profile, LFTs, LDH

7.5 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

Consider venesection if Hb rises to > 120 g/ and patient has hyperviscosity symptoms
l or > 30 g/l above baseline with symptoms of hyperviscosity

8. OTHER DISEASE MODIFYING THERAPIES

Crizanlizumab – a monoclonal antibody that binds to P selectin has been approved for use in the UK by NICE by a Managed Access Programme. Please note liscence was revoked by MHRA in Jan 2024 based on evidence from the Stand Trial, saying benefits did not outweigh potential risks.

Voxelotor – is currently undergoing regulatory approval in the UK. It binds reversibly to haemoglobin, stabilizing the oxygenated haemoglobin state and preventing HbS polymerization by increasing haemoglobin's affinity for oxygen

Several candidate disease modifying therapies are undergoing clinical trials within the HCC. These should be considered on an individual basis.

9. OUTPATIENT MANAGEMENT

The aims of outpatient management of adults with SCD are to promote health maintenance and to recognize and manage emerging disease complications in a multidisciplinary setting. Patients and their families should be fully informed about the sickle condition, kept up to date about changes to their therapy and be made aware of new and evolving therapy options including clinical trials.

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. Adult clinics at LNWUH are held on Tuesday morning, Adult clinics are held at St Georges on Wednesday afternoons. All sickle patients within the network should be seen at a tertiary centre for annual review.

9.1 First appointment (New Patients)

History and examination

- Take full medical, psychosocial and family history
- Record weight, height, BP and SpO2
- 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® II, meningococcal C/HIB, meningococcal ACWY and meningococcal B , hepatitis B, seasonal influenza and COVID vaccines
- Assess compliance with prophylaxis and disease modifying treatment if relevant
- Explain diagnosis, its medical and genetic implications
- Discuss acute complications and their management
- Arrange screening for chronic complications including echocardiogram, 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
- At ICHT, Issue a haemoglobinopathy card, and ensure patient has a haematology "passport" plus contact details for the hospital (RHTU, , outpatient clinic, Day unit, consultant's secretary, haemoglobinopathy CNS and Specialist Social Worker)-

- Discussion or confirmation of the personalised analgesia plan for pain crisis
- Review of chronic pain and prescriptions used to treat this. Refer to chronic pain specialist where appropriate, see chronic pain management section
- Inform about the National Haemoglobinopathy Registry (NHR)
- Discussion about contraception, fertility, pregnancy and (where appropriate) genetic information
- Assess need for psychosocial support
- Refer to MDT if indicated
- Arrange follow-up appointment

Investigation

- Confirm diagnosis with quantitative Hb separation (HbS, A2, 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 (A,B,C), HIV 1 and 2 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, echocardiogram and ophthalomology review

9.2 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, folic acid and other disease modifying therapies if relevant
- Record weight, BP and SpO2
- 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 due (see Appendix 2)
- Assess need for psychosocial support
- Refer to MDT if indicated
- Arrange follow-up appointment
- Assess eligibilty for clinical trials and observational studies

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

10. BONE MARROW TRANSPLANT

Sibiling allogenic bone marrow transplant is an option in a select group of patients this would need to be discussed at the HCC and NHP. The following guidance should be read in conjunction with local guidelines/ SOPs for transplantation in adult sickle cell disease at ICHT and SGH.

Inclusion criteria

HSCT should only be considered in those adults with severe SCD where the benefits outweigh the risks.

- History of >= 3 severe pain crises or other acute complications per year despite institution of supportive care measures (optimal treatment with hydroxycarbamide (HC) or transfusion therapy).

Other acute complications would include acute hepatopathy or splenic sequestration or acute priapism

- Recurrence of acute chest syndrome despite optimum treatment with hydroxycarbamide (HC) or transfusion therapy
- Clinically significant neurologic vascular event or deficit lasting over 24 hours and confirmed radiologically (i.e. stroke) or progressive cerebral vasculopathy
- Administration of regular transfusion therapy, either by simple transfusion or exchange transfusion with the aim to prevent severe sickle complications by maintaining a low HbS%. Severe sickle complications include a history of >= 2 chest syndromes, >= 3 painful crises or severe recurrent priapism
- Patients assessed as requiring transfusion but with red cell allo-antibodies/very rare blood type, rendering it difficult to continue/commence chronic transfusion
- Patients requiring hydroxycarbamide/transfusion for treatment of SCD complications who cannot tolerate either therapy due to significant adverse reactions
- Established end organ damage relating to SCD including but not limited to progressive sickle vasculopathy and hepatopathy.

To determine fitness to proceed to HSCT, patient should meet the following criteria:

1. Karnofsky score >60
2. Cardiac function: LVEF >45% or shortening fraction >25%. Note: For subjects who have history of iron overload or serum ferritin levels >1000 ng/mL, a cardiac MRI is required. Cardiac T2* <10 ms results in exclusion.
3. Lung Function: FEV1, FVC and DLCO >50%
4. Renal function: EDTA GFR >40 ml/m2 /1.73m2
5. At least one first degree relative willing to act as a donor and confirmed as fully matched sibling donor.

11. HCC MDT

The purpose of the HCC MDT is to provide multi professional input for adults and children with Sickle Cell disease served by the West London HCC

The HCC Network Manager (or deputy) will forward out invitations for the scheduled HCC MDT in advance of the meeting. Included in the invitation will be case referral forms and adverse event report form for the MDT and criteria for referral, referrals to the MDT will be submitted at latest the day before the MDT to allow time for the coordinator to collect and circulate the cases in advance to the attendess. A reminder/call for cases will be sent out to clinicians two weeks in advance of the HCC MDT occuring. Patient identifiers should be anonmyised. Referrals will be collated, anonymised if further required and a patient list created. The HCC Network Manager (or deputy) will respond to referral email with confirmation that patient is on the list.

Any issues with referrals to be clarified with lead clinician and referring team (e.g. doesn't meet the criteria, information not clear). Referrals that don't meet the criteria will be returned to clinician with a request for clarification. It is incumbent on the clincians referring that they collect all necessary medical information (scans, results, notes etc.) in advance of presenting the case at the meeting.

The Meeting is chaired by the West London HCC MDT Lead or nominated deputy.

Cases are presented by the referring clincian.

In the event of rare or extremely complex cases or the consideration of Novel Therapies cases may be referred through to the National Haemoglobinopahty Panel.

All serious adverse events should be discussed at the HCC MDT held on on alternating Wednesdays and Fridays afternoons each month.There is also a specific MDT for discussing and recording adverse events by the HCC. These include, acute chest syndrome, complications during pregnancy, cardiac dysfunction, end stage renal failure (ESRF) requiring dialysis, hyperhaemolysis, bacteraemic sepsis, pneumococcal sepsis, multi-organ failure and fat embolism syndrome, post operative complications, unplanned PICU/ICU admissions, stroke, drug related adverse events and aplastic crisis.

REFERENCE LIST

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

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT).

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 then100mg od) to be taken for 7 days in the event of fever or other symptoms of infection.

GP to prescribe the above on regular prescription.

Vaccination

Please refer to the Green Book for most up to date advice (Public Health England, 2023)

Adults SCD (all genotypes) patients should be adequately vaccinated against the following infections:
1- Invasive pneumococcal disease
2- Haemophilus influenza type B
3- Neisseria meningitis ACWY and B
4- Hepatitis B
5- Influenza
6- Covid-19

GP and SCD Specialist should ensure that adults with SCD should have been offered:
1- Pneumococcal polysaccharide vaccination (PPV23) at five yearly intervals; and

2- A single 0.5 ml dose of pneumococcal conjugate vaccine (PCV13) which should be given at least six months after PPV.

3- One dose of Hib/Men C. Haemophilus influenza b vaccine (Menitorix®; combination with meningitis C conjugate)

4- One dose Meningococcal A,C,W135 and Y conjugate vaccineshould be given 1 month after Meningitis C conjugate vaccine.

5- Two primary doses of MenB vaccine one month apart [this can be at the same visits as the other vaccinations above].

6- Influenza vaccine annually

7- Covid-19 vaccination

8- Hepatitis B vaccination (if they have not previously received it and are non-immune. Give a booster dose if Hepatitis B Surface Antibodies less than 100 mIU/ml

The patients' primary care team should be responsible for keeping clear records of vaccination and revaccination status for patients with SCD and the status documented at annual review and included in hospital records.

Other measures to prevent infection

Patients should be periodically warned about the increased risk of invasive pneumococcal disease (IPD) and other forms of sepsis. They should also be educated about symptoms which might indicate infection and to attend for medical assessment if temperature ≥380C.

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.

Discussion of oral antibiotic prophylaxis should be undertaken on transition to adult care and at annual review. Adults with SCD who choose not to continue regular oral prophylaxis should ensure they have received pneumococcal vaccination and should be provided with a supply of appropriate antibiotics for emergency use as above.

Travel vaccinations and antibiotics

Patients should be encouraged to seek travel advice and to accept all the offered immunisations relevant to the area to which they are travelling; this includes live vaccines such as yellow fever.
Patients with SCD should receive malaria prophylaxis when travelling to malarial areas, in line with general guidance for the area of travel
All chemoprophylactic agents are acceptable in patients with SCD although it should be noted that there is an increase of glucose-6-phosphate-dehydrogenase (G6PD) deficiency in this patient group and in these patients certain agents should be avoided.

APPENDIX 2: ANNUAL REVIEW PROFORMAS

Annual Review NHR Template – 2023/24

Patient Name:
Hospital Number:
NHS Number:

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

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

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

Patient received psychology support:
Yes No Unknown

Patient required other mental health support services:
Yes No Unknown

Patient accessed haemoglobinopathy community services:
Yes No Unknown

Patient discussed at National MDT panel:
Yes No Unknown

Disease Modifying Therapy

Patient eligible for hydroxycarbamide:
Yes No Unknown

Patient offered for hydroxycarbamide:
Yes No Unknown

Patient declined hydroxycarbamide:

○ Yes ○ No ○ Unknown

Patient currently receiving hydroxycarbamide:

○ Yes ○ No ○ Unknown

Reproduction

Fathered a child this year?

○ Yes ○ No ○ Unknown

APPENDIX 3: HCC OBSTETRIC SICKLE CELL – ANTENATAL REFERRAL PROFORMA

HCC Obstetric Sickle Cell – Antenatal referral proforma

Name
DOB
NHS number
GP name / address
Referring centre and consultant

Diagnosis		
EDD + gestation		
Previous Obstetric History		
Sickle History (multiple admissions, ICU admissions, acute chest syndrome, stroke, pulmonary hypertension, proteinuria, avascular necrosis, previous surgery)		
Other relevant social and family history including mental health concerns, HADS score		
Normal pain protocol		
Transfusion History		
Regular RCE/ transfusion programme		
Historical/ current red cell allo-antibodies		

History of hyperhaemolysis			
Investigations			
Bloods	FBC, reticulocyte, HbS/F/A2, Renal profile, LFT, Ferritin, Fe, TIBC		
	Antibody screen		
	Others:	G6PD status	Malaria (if travel history)
Ultrasound	Dating scan	CST	Anomaly scan
	Growth scans	24/28/32/36 weeks	
Urine	MSU	UPCR	
sP02			
Echocardiogram			
Lung function test (if resting p02 <95%)			
Ophthalmology			
Vaccine history			
Partner status			
Genetic counselling			
Medications	Folic acid 5mg od	Penicillin V 250mg po bd	Low dose aspirin 75mg od
	Prophylactic LMWH	Influenza vaccine	Covid vaccine
	STOP – iron chelation/ hydroxycarbamide/ ACE/ ARB NSAIDS and TRAMADOL should be stopped during pregnancy		

APPENDIX 4: NURSING TRAINING

Qualified nursing staff pre-requisites for managing a patient on parenteral opioids and PCA:

a) Registered nurses require:

- Intravenous medication administration competence

- Training in pain management and care of sickle cell patients as per trust policy attended the Trust pain study day and sickle cell study sessions.

- Completion of a period of supervised practice and assessed as competent in the care of patients receiving parenteral opioids and PCA.

- Be ANTT compliant

b) The following staff may be authorized to prepare and commence a PCA and to change the size of the bolus, lockout and drug reserve and administer a bolus:

- Clinical nurse specialist for Haemoglobinopathies (Adult) who have fulfilled the trust requirements/competencies for this procedure

- Registered nurses at band 6 and 7 and experienced band 5 nurses who have fulfilled the trust requirements/competencies for this procedure

- Site practitioner who have fulfilled the trust requirements/competencies for this procedure

- Clinical Nurse Specialist in the pain team who have fulfilled the trust requirements/competencies for this procedure

-

c) Registered nurses may change the prescribed PCA bag, clear air in the line, change the batteries and discontinue a PCA who have fulfilled the trust requirements/competencies for this procedure

d) Student nurses should be encouraged to observe and learn about PCA but cannot participate in the above procedures.

Training

Managers have a responsibility for ensuring that as many qualified nurses as possible attend training sessions. The standard is for 75% of qualified nurses in a clinical area to have the training for PCA according to local policy. Applicants must have the support of their line manager and clinical nurse specialist in Haemoglobinopathies (Adult) or Clinical nurse specialist for pain. Advanced training to programme PCA pumps is arranged with the clinical nurse specialist for haemoglobinopathies (adult) or Clinical Nurse Specialist for pain. All nurses must fulfil all competencies for PCA before being independent with this practice (See appendix three). Reassessment of competencies must be performed annually to ensure that the nurse remains competent and confident to deliver care.

APPENDIX 5: SICKLE CELL PATIENT CONTROLLED ANALGESIA (PCA) OBSERVATIONS AND COMPLICATIONS

Sickle Cell Patient Controlled Analgesia (PCA) Observations and Compilations

All Sickle patients starting on PCA/Parental opiods should be nursed in a ward where nursing staff are familiar and have experience with managing PCAs. Pathway is A&E- James Ward – Drake Ward

The observations below must be carried out and recorded on the Observation chart and the Sickle adult PCA monitoring chart. Cumulative number of administrations and demands and total amount of drug administered must be recorded at the same time.

Timing	Observations required	Frequency
Base line observation- prior to commencing PCA.	Temperature, Blood pressure, Pulse, Respiratory rate, Oxygen sat, Pain score, Sedation score, Nausea and Vomiting Score	Baseline
1st-6th hour	Temperature, Blood Pressure, Pulse, Respiratory rate, Oxygen sat, Pain score, Sedation score, Nausea and Vomiting Score	Every 30 minutes until pain is controlled or responding. (pain score reduced by 2 from admission) Then every hour to a total of 6 hours
7th hour until the PCA has stopped	Temperature, Blood Pressure, Pulse, Respiratory rate, Oxygen sat, Pain score, Sedation score, Nausea and Vomiting Score	Every 2 hours
Following any change to the pre-set protocol	Temperature, Blood Pressure, Pulse, Respiratory rate, Oxygen sat, Pain score, Sedation score, Nausea and Vomiting Score	Restart frequency from the 1st hour as outlined above

Respiratory complication

If the respiratory rate falls to below 12/minute or oxygen saturations on room air below 95% the PCA should be stopped immediately. Treat patient with a potential risk of respiratory depression.

If respiratory depression is triggered, do the following:

- Stop the PCA/injectable parenteral opiods/and all opiod based analgesia
- Try to rouse the patient
- Administer oxygen therapy via a non-rebreather mask at 15litre/minute until O2 stats are > 95%
- Put MET call out and summon emergency assistance

Sedation

Opioid overdose may lead to reduced conscious level, in SCD there may be other causes for reduced concious level e.g. stroke or meningitis

- The level of sedation should be recorded as indicated in the above table.

If the patient is unarousable (sedation score of 3)

- Stop the PCA/injectable parenteral opiods/and all opiod based analgesia
- Put MET call out and summon emergency assistance.
- Inform the haematology doctor on call.

If the patient has ascore of 1 or 2 the anit-emetic therapy must be reviewed.

Patients receiving opiate subcutaneously by PCA can only be cared for by registered nurses who have been trained and are competent in the use of Perfusor Space PCA Syringe Pump or who have been assessed as competenet by the Haemoglobinopathy Clinical Nurse Specialist or a senior nurse who has been trained, skilled, deemed competent and authorised to do this task.

Sedation	Score
Fully Alert	0
Drowsy but easy to rouse	1
Responds to verbal comments	2
Unresponsive to verbal commands	3

Nausea/Vomitting	Score
No nausea/vomitting	0
Nausea	1
Vomitting	2

Sedation	Score
Fully Alert	0
Drowsy but easy to rouse	1
Responds to verbal comments	2
Unresponsive to verbal commands	3

Nausea/Vomitting	Score
No nausea/vomitting	0
Nausea	1
Vomitting	2

APPENDIX 6: HCC CONTACT DETAILS

	Telephone	Bleep
In Hours SpR advice numbers (9am-5pm		
Imperial College Healthcare NHS Trust	02033131000	9071
St George's University Hospitals NHS Foundation Trust	02086721255	7080
London North West University Healthcare NHS Trust	020 8864 3232	Haematology registrar – 071 Haematology SHO - 244 Sickle cell MET calls (A&E only) – 152
Out of Hours Call numbers		
Imperial College Healthcare NHS Trust	02033131000	9071
St George's University Hospitals NHS Foundation Trust	02086721255	6068
London North West University Healthcare NHS Trust	020 8864 3232	Haematology registrar –via switch board Haematology SHO - 244 (until 9pm) The MET call bleep for sickle cell does not operate after 5pm
CNS		
Imperial College Healthcare NHS Trust	Afoke Arigbe 0203 3138553 07776227760	
St George's University Hospitals NHS Foundation Trust	Carol Rose 07825978812	
London North West University Healthcare NHS Trust	Christiano Mbonaz Ondandu - 07796705607	
Community Nurses	Elizabeth Erikodi 07769243591/02072668892	
SWL- Wandsworth	Leteshia Abrahams-Dixon: 07586549350/ 0330 058 1679	
NWL- H&F, K&C, Westminster	Elizabeth – 07769243591/ 02072668892	
NWL- Brent	Christiano Mbonaz Ondandu - 07796705607	
Psychology		
Imperial College Healthcare NHS Trust	020 3313 8119	
St George's University Hospitals NHS Foundation Trust	07798581198	
London North West University Healthcare NHS Trust	02084532050	

HCC leads		
Mark Layton	Imperial College Healthcare NHS Trust	0208 3832173 (Direct) 0208 3831320 (Secretary HH) 0203 3126806 (Secretary SMH)
Julia Sikorska	St George's University Hospitals NHS Foundation Trust	0208 725 0885 (Direct)
Muhsin Almusawy	London North West University Healthcare NHS Trust	02084642121 (Northwick park) 02084532112 (CMH secretary)
In Hours SpR advice numbers (9am-5pm)		
Imperial College Healthcare NHS Trust	02033131000	9071
St George's University Hospitals NHS Foundation Trust	02086721255	7080
London North West University Healthcare NHS Trust	020 8864 3232/2121	Haematology registrar – 071
Out of Hours Call numbers		
Imperial College Healthcare NHS Trust	02033131000	9071
St George's University Hospitals NHS Foundation Trust	02086721255	6068
London North West University Healthcare NHS Trust	020 8864 3232	Haematology registrar –via switch board

APPENDIX 7: HCC MDT REFERAL FORM

MDT Referral Form

To discuss the management of a patient with a haemoglobinopathy, please complete the form below and email it to the MDT Co-ordinator

Ralph.brown@nhs.net

Patient Details		**Consultant Details**	
Initials:		**Referring Consultant:**	
DOB:		**Hospital/Clinic:**	
		Contact Number:	

Primary diagnosis	
Medical History	
Investigation results	
Is radiology review required? ☐Y ☐N Please state date and nature of investigation to be reviewed	
Is the patient on a clinical trial? ☐Y ☐N **Please provide details**	
Reasons for referral and question(s) to be addressed at MDT	
Final recommendation by MDT and agreed management plan (to be completed during the meeting)	

Signed _____ Dr Asad Luqmani Date: _____

APPENDIX 8: MANUAL EXCHANGE PROTOCOL