Whittington Health NHS

Sickle Cell Disease in Adults

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This guideline should be used in conjunction with the following guidelines:

1. Priapism in sickle cell anaemia, Management of
2. Sickle cell disease in pregnancy
3. Sickle cell leg ulcers, Management of
4. Sickle cell disease in adults – Perioperative management
5. Iron chelation therapy for iron overload
6. Sickle cell disease in childhood – Management
7. Oxygen therapy: Safe oxygen therapy in adult patients

➢ About this document

This document aims to present an overview of the clinical management of sickle cell disease (SCD) in adults at the Whittington Hospital. **Clinical management is covered in Sections 3-11)** and **Section 12 gives information on the set up of the sickle service.** Where appropriate, links have been provided to other existing clinical guidelines or documents. Appendices that are relevant to particular situations have been included and can be downloaded, printed off and completed as necessary.

The clinical problems described are not exhaustive. Adults with sickle cell disease may suffer from additional conditions related to SCD and other unrelated medical conditions. Sickle cell disease is a complex, multi-system condition requiring a multi-disciplinary approach and it is hoped that this document will facilitate effective and efficient management of patients with this condition. It has been written with junior doctors and nurses in mind, but senior help should always be sought in the case of any ill patient or for clarity.

➢ Acknowledgement

Thanks to our colleagues up and down the country who have shared their experience of the management of sickle cell disease with us. Special thanks to Dr Jo Howard for offering the St. Thomas's Hospital guideline.

CONTENTS

1.0 INTRODUCTION

- Sickle cell disease (SCD) is the commonest genetic disorder in the U.K.
- There are estimated to be 12,500 people with sickle cell disease in England
- 80% of sickle cell patients live in London
- Patients with SCD may suffer a variety of acute and chronic complications
- SCD is complicated and may lead to rapid clinical deterioration. It is therefore essential that patients are managed with reference to this guideline and with timely involvement of the haematology team.
- **Please note that there is a separate guideline covering the management of sickle cell disease in pregnancy. When a pregnant woman with sickle cell disease presents to A&E, the A&E and medical consultants should be notified immediately of her presence. They should communicate promptly with the on-call Obstetrics, Haematology and Anaesthetics consultants particularly if she is in the 3rd trimester.**

2.0 INCLUSION/EXCLUSION CRITERIA

- This guideline covers all genotypes of sickle cell disease including HbSS, HbSC, HbSβ^{o} thalassaemia, HbSβ^{+} thalassaemia HbSD^{Punjab}, HbSO^{Arab} , and other genotypes.

- Homozygous sickle cell disease (SS) is the commonest type (around 70% in the UK) and usually the most clinically severe; HbSC accounts for most of the remaining cases.

- Sickle cell trait is defined as HbS coinherited with normal haemoglobin (HbA) and is not covered by this document.

3.0 THE ACUTELY ILL PATIENT: GENERAL PRINCIPLES OF MANAGEMENT

3.1 Acute Attendance

All sickle genotypes can present with sudden and rapid clinical deterioration. Rapid assessment and treatment are essential in achieving a successful outcome.

3.2 Admission Pathways

- All sickle cell patients will be admitted through A&E.
- Initial triage, assessment and management in A&E will be performed by A&E staff, who should then refer to the appropriate on call team (e.g. on-call medical or surgical registrar).
- Patients with uncomplicated sickle cell crisis will be under the care of the medical team until formally transferred to the haematology team.
- For patients with high risk disease or who are very ill, the haematology team will review the patient in A&E where possible and coordinate their care with the admitting medical team.

3.3 Approach to assessment and management

- **Ensure that pain relief is administered promptly; this will enable better assessment of the patient.**
- Each attendance should be treated as a new episode of illness worthy of full evaluation and management. Infrequent attendees usually only attend hospital when they are really sick. Frequent attendees can also become very sick.
- Sickle cell patients often have a problem unrelated to sickling; therefore keep an open mind.
- Sickle problems are frequently precipitated by problems unrelated to sickle cell disease.
- Sickle cell patients are often sicker than first appearances might suggest. The inflammatory response (eg. fever, CRP rise) may be delayed.
- Sickle cell patients may deteriorate quickly and unexpectedly, they often have very little reserve.
- Sickle cell patients usually have sub-normal creatinine levels because they hypersecrete creatinine through the proximal tubules. Therefore high normal levels or an increase from baseline creatinine into the normal range may suggest acute kidney injury.
- For new patients or if the diagnosis is in doubt, HPLC (Haemoglobinopathy Screen) can quickly establish the diagnosis but is not usually done out of hours. If it is imperative to confirm the diagnosis out of hours, please discuss with the haematologist on call.

3.4 Nursing Care

See RCN Nursing Competencies for Sickle Cell and Thalassaemia:
http://sct.screening.nhs.uk/getdata.php?id=11791

- Observations:
    - Monitor vital signs as per Whittington Adult Observation Chart.
    - Within A & E, observations should be recorded hourly until pain is controlled. Frequency is then dictated by clinical need.
    - Monitor pain, nausea and sedation scores as per Whittington Adult Observation Chart.
    - **Record O2 saturations on room air.**
    - Any patient who presents with neurological symptoms such as fits, numbness, limb weakness, or confusion requires neurological observations and urgent medical review.

- To ensure the safety of the patient they should be nursed in full open view and not behind closed curtains.

- If the patient declines observations, this should be documented in the medical notes.

3.5 Criteria for escalation to acute medical consultant and haematology

Please escalate promptly if any of the following features are present:

- Severe pain unresponsive to usual analgesia protocol
- Chest pain or thoracic spine pain
- Fever or signs of sepsis
- Symptomatic anaemia
- Respiratory symptoms
- Clinical or radiological signs of chest consolidation
- Abdominal symptoms – pain, diarrhoea, vomiting, distension
- Neurological symptoms
- Priapism
- If concerned about the patient's condition for any other reason

3.6 Criteria for Critical Care Outreach Team (CCOT) and ITU referral

The CCOT team are experienced in the management of sickle patients and are happy to discuss and if necessary review patients whose condition is giving cause for concern. This includes:

- Any patient meeting Trust guidelines for CCOT involvement http://whittnet.whittington.nhs.uk/document.ashx?id=3530
- Any patient with signs of physiological deterioration
- Patients with specific sickle complications as detailed in Section 4.0 of this guideline

3.7 Pain Management

See section 4.1.6.1 (pain management in vaso-occlusive crisis) for further details

- **NICE quality standards stipulate that pain relief should be delivered within 30 minutes of A&E attendance and pain should be under control within two hours.**

- Electronic copies of PATIENT-SPECIFIC and GENERIC analgesia protocols can be found in the “SICKLE CELL PROTOCOLS” folder on the I drive [**I:\Doctors' Shared Folder\Junior Doctors Shared Folder\A&E\SICKLE CELL PROTOCOLS**].

- Proper use of pain protocols:

    - Pain relief is given according to the patient-specific protocol.

    - The generic pain protocol should be used if no patient-specific protocol is available.

    - If the patient is known to another hospital, their protocol should be sought from their usual hospital and in the interim the generic pain protocol should be followed.

    - The pain protocols are just a guide. Please do not deny the patient more analgesia if their protocol is clearly not adequate or keep rigidly to their protocol if they are clearly showing signs of excess opiates.

- If respiratory rate falls to <12/min all opioids should be stopped and doctors informed urgently.

- Pain assessment should be recorded prior to the delivery of analgesia and 20 minutes post administration of each dose.

- Inadequate pain control should be reported to the haematology team. Out of hours the Anaesthetist on call and in hours the Acute Pain team can support the prescription and choice of pain relief.

- Adjuvant medicines should be prescribed for patients on opioid regimens e.g. anti-pruritics, laxatives, anti-emetics.

- Patients should be encouraged to gradually reduce analgesia during admission and to commence their normal oral analgesia prior to discharge.

- Psychological distress magnifies pain and pain causes significant psychological distress. Any psychological issues that emerge should be brought to the attention of the haematology team for involvement of the clinical psychologists.

3.8 Infections and antibiotic choice

- Sickle cell patients are functionally hyposplenic and should take long-term prophylactic penicillin 250mg PO BD or amoxicillin 250mg BD (clarithromycin or erythromycin if penicillin allergic)

- If unwell, a low threshold for antibiotic treatment is appropriate. If a source is clear, antibiotics should be chosen as per Trust protocol. There is no basis for doubling prophylactic penicillin dose empirically if unwell.

- If there is no clear source of infection but the patient is mildly unwell and pyrexial, commence broad spectrum antibiotics such as co-amoxiclav. Discuss antibiotics with Microbiology and Haematology if more severely unwell.

- A septic screen (no LP unless clinically indicated) should be completed prior to starting antibiotics

- Sickle cell patients are prone to unusual infections:

    - Pneumococcal septicaemia is common due to hyposplenism, and can be rapidly life threatening. Haemophilus influenzae is also common

    - Sickle cell patients are very susceptible to Salmonella, which can cause osteomyelitis and septicaemia in all age groups. Consider Salmonella infection in patients with a history of food poisoning or gastroenteritis with no clear cause.

    - Other infections such as staphylococcal osteomyelitis, mycoplasma pneumonia, and E Coli UTI may be seen.

    - Parvovirus infection is the usual cause of an 'aplastic crisis' (see section 4.6.1)

    - If patients on Desferrioxamine (DFO) have diarrhoea and/or abdominal pain, the DFO should be stopped. Ciprofloxacin should be started immediately but can be stopped if diagnosis of Yersinia has been excluded.

3.9 Hydration and Diet

- Oral fluids should be encouraged, preferably water and juice; aim for 3 litres in 24 hours. Fluid balance charts should be maintained. Ensure that fluids are within easy reach and offer assistance to those with difficulties drinking.

- Intravenous fluids should be prescribed if patient is clinically dehydrated, Nil by Mouth or unable to drink adequately because of pain. Avoid unnecessary intravenous cannulation to reduce future difficulties with venous access.

- Anti-emetics should be encouraged if the patient is nauseated. **Cyclizine must not be given intravenously under any circumstances.**

- A normal diet should be encouraged and assistance with feeding offered where necessary.

3.10 Toileting/Environment

- Dipstick urine analysis should be recorded on attendance to A&E.

- Patient in acute pain should be encouraged to take analgesia prior to using the commode/bed pan or mobilising to the toilet. Physical assistance with toileting may be required.

- Difficulties in passing urine (including acute urinary retention) can sometimes occur secondary to opioids or because of priapism in men. Any difficulties should be recorded and reported to the haematology team.

- Laxatives should be prescribed for patients on opioid therapy and bowel movements noted.
- Patients should be nursed in warm environments and kept away from draughty or open windows, particularly in winter.

- Patients with Parvovirus infection should be nursed in isolation, and pregnant women should avoid contact. Family members with sickle cell disease or who are pregnant will need to be screened.

4.0 MANAGEMENT OF SPECIFIC SICKLE COMPLICATIONS

4.1 Vaso-Occlusive (Painful) Sickle Cell Crisis (VOC)

Key points

- This is the commonest acute presentation of sickle cell disease
- Painful crises increase the risk of life-threatening sickle complications such as acute chest syndrome and must be treated effectively.
- VOC should be distinguished from other non-sickle causes of pain
- VOC may be superimposed on chronic pain for which the patient may already be taking substantial regular opioids.
- Rapid and effective pain relief is key to management

4.1.2 Precipitating factors

Factors that may precipitate or aggravate acute vaso-occlusive crisis include:

- Infection
- Dehydration
- Cold or damp conditions
- Unaccustomed exercise
- Emotional stress

4.1.3 Characteristics of vaso-occlusive crisis

- There is no uniform description of sickle pain; however patients can usually differentiate what is sickle pain from what is not.
- Crises are unpredictable in onset, location and severity.
- The pain may be localised, multi-focal or migratory.
- Attacks are self-limiting; they typically last a few days. However, attacks may persist for several weeks if there are other co-morbidities or if the pain is not rapidly and effectively controlled.
- Patients may have typical patterns of vaso-occlusive crisis and the haematology consultants may be familiar with these.
- Most patients manage less severe episodes at home and only present to hospital when the pain in severe and uncontrolled.

4.1.4 Medical Clerking

For patients whose care is based elsewhere, contact their hospital for a patient-specific protocol. This contains important clinical information and is vital for optimal management.

Current episode

- Nature of pain – is it typical of sickle pain?
- Sites and severity of pain
- How typical is the current episode compared to their usual crisis
- Shortness of breath, fever, other symptoms
- Precipitating factors (see 4.1.2)
- Recent analgesia use

Past Medical History – check patient-specific protocol and notes

- Previous sickle-related complications, particularly acute chest syndrome
- Previous ITU admissions and whether ventilated
- Any recent transfusions and whether on long-term transfusion programme
- Hydroxycarbamide use
- Baseline haemoglobin, reticulocytes, creatinine and bilirubin if known

4.1.5 Investigations

Initial routine investigations:

- FBC + reticulocytes
- Biochemistry: U&Es, LFTs, bone profile, CRP
- Haemoglobinopathy screen if patient new to the Whittington, transfused in last 3 months or no record of genotype on system
- Group and save. **Clearly indicate on request form "FOR SICKLE CELL PATIENT".**

Common additional investigations when indicated:

- Coagulation screen
- Septic screen including pneumococcal antigen
- Chest X-ray - If respiratory symptoms/signs, or low O2 sats.
- Arterial blood gases - If O2 sats on room air are ≤94% or ≥3% less than baseline, abnormal CXR or respiratory symptoms/signs. Should be done on oxygen if the patient is in obvious respiratory distress or if O2 saturation falls <85% on air
- Viral serology: Parvovirus +/- Mycoplasma serology if low reticulocyte count
- Viral swab for respiratory viruses

4.1.6 Management of VOC

Key points:

- **Rapid and effective pain relief is key.** The national standard is for the first dose of analgesia to be given within 30 minutes of arrival and effective control of pain within 2 hours of arrival.
    - Electronic copies of PATIENT-SPECIFIC and GENERIC analgesia protocols can be found in the "SICKLE CELL PROTOCOLS" folder on the I drive. [I:\Doctors' Shared Folder\Junior Doctors Shared Folder\A&E\SICKLE CELL PROTOCOLS].
- **Whittington patients:** Refer to the patient-specific analgesia protocol. If the patient clearly requires more pain relief than is stipulated on their protocol, discuss with haematology.
- **Non-Whittington patients:** If the patient's usual care is based elsewhere, contact their hospital to request their protocol. If it is not possible to obtain this, use the generic protocol
- Explain and discuss your analgesia plan with the patient
- Opioid addiction is rare and it is unhelpful to suggest this without strong suspicion
- The haematology team are available at all times to discuss analgesia if required

The following section covers:

- Pain management
- Fluid management
- Oxygen
- Respiratory support
- Psychological support
- Adjuvant medication

4.1.6.1 Pain management

- Vaso-occlusive pain necessitating admission typically requires strong opiate treatment.
- Sensitivity to opiates is highly variable therefore regular assessment is vital.
- Atypical pain: If the pain is atypical and/or the patient says the pain is not like their usual sickle pain other diagnoses should be considered.

<u>Moderate pain</u>

Give oral analgesia according to the WHO ladder e.g.

- Paracetamol – some patients find IV paracetamol more effective than oral

- Ibuprofen – avoid in patients with renal impairment
- Dihydrocodeine or codeine

Severe pain

- The majority of patients presenting acutely to hospital will fall into this category. Most patients require bolus sc diamorphine or morphine for the duration of admission.

- Some patients will be able to move onto oral opiates earlier and this should take place as soon as possible where effective.

- Daily opiate requirement can be calculated and converted into MST slow release tablets with oral morphine tablets or solution for breakthrough pain

- Wherever possible, use paracetamol, ibuprofen and weaker opioids such as codeine concomitantly, taking patient preference into account.

1. **Diamorphine**

    - Advantages: Can be administered in small volumes allowing sc bolus injection or infusion, this is particularly useful in patients with poor IV access. Usually highly effective.
    - Disadvantages: Can cause more side effects than other opiates, such as dysphoria, itching, sedation and respiratory depression.
    - Young adults recently transitioned from the paediatric services may require oral morphine only or may be able to rapidly transfer from diamorphine to oral morphine
    - Dosing: consult generic protocol for patients without a personalised protocol.

2. **Alternative opiate analgesia**

- Some patients cannot tolerate diamorphine. Consult patient-specific protocols or generic protocols for dosing. Pharmacists can provide advice on choice of medication or dosing.

- Alternative drugs include:

    - **Morphine**
    - **Oxycodone**. Formulations are Oxynorm and Oxycontin (slow release). These are expensive and should only be used if diamorphine or morphine cannot be given.
    - **Fentanyl.** This is usually prescribed as PCA by the Acute Pain Team. Please do not prescribe without discussion with them.

    DO NOT USE:

    - **Pethidine**
        - Pethidine is no longer given for sickle cell pain as it is short acting and its metabolite norpethidine may cause seizures.
        - Very occasionally, a patient may request Pethidine because of “allergy” to morphine or diamorphine. Offer Oxycodone to such individuals.
    - **Entonox**
        - Entonox causes metabolic inhibition of B12 which can result in bone marrow and neurological toxicity.
        - There are also issues with dependency.

3. Patient Controlled Analgesia (PCA)

- Any patient requiring or requesting PCA should be discussed with the Acute Pain Team during normal working hours or the anaesthetic team out of hours.
- PCA boluses without background can be managed on Mary Seacole South ward.
- When PCA is indicated for severe unremitting pain or if background infusion is required, the patient should be transferred to ITU.
- PCA for post-operative pain should be administered on the relevant surgical ward or ITU if indicated.

4. Difficult cases of pain management

- **Difficulties managing acute pain.**

The Acute Pain Team should be contacted within hours. Out of hours the Anaesthetic Registrar should be contacted.

Patients requiring background PCA infusion or other drugs such as ketamine infusion will normally be managed on ITU.

- **Postoperative pain relief.**

This can be difficult, especially in patients who take long-term opiates. Many patients will require the same analgesia regimen they would receive for an acute vaso-occlusive crisis. Please discuss post-operative pain management with the haematology team.

Any sickle patient who is planned for elective surgery should be brought to the attention of the Acute Pain Team.

See Whittington Guideline: Sickle Cell Disease in Adults - Perioperative Management

4.1.6.2 Fluid management

- **The treatment most likely to influence the resolution of a vaso-occlusive crisis is hydration.** Patients become dehydrated because they cannot concentrate urine. Increased blood viscosity exacerbates sickling.
- Encourage oral fluids; however, if the patient is unwell, intravenous fluids may be needed.
- Patients need a total fluid intake of 70-90 ml/kg body weight per 24 hours (approximately 3L in 24h for most adults) as maintenance fluid, but may require more rapid fluid resuscitation as clinically appropriate.
- Start a fluid balance chart.
- Care should be taken not to fluid overload as some patients have compromised cardiac reserve or abnormal renal function
- Monitor creatinine and check U&E for hypokalaemia

- Central lines should be avoided unless absolutely necessary and removed after a maximum of 48 hours (due to the high risk of thrombus formation and infection) unless discussed with consultant.

4.1.6.3 Oxygen

- There is no objective benefit from oxygen therapy in the absence of hypoxia. However, many patients report symptomatic benefit and oxygen should be prescribed at the patient's request, even if their O2 saturation is normal.

- Monitor pulse oximetry **OFF oxygen** unless there is significant respiratory distress.

- If sats are <94% on air or oxygenation falls ≥ 3% from baseline, an ABG on air should be performed and the possibility of acute chest syndrome should be considered.

- If suspected respiratory depression from excess opiates:
    - Stop opiates and closely monitor patient
    - Avoid naloxone if at all possible. Most patients will "sleep off" the effects of opioids but must be monitored closely. Injudicious use of naloxone can cause recurrence of severe pain that may be difficult to control.

NB. Some patients will have low baseline oxygen saturations due to underlying chronic lung disease. In general, a fall in oxygen saturations of ≥ 3% from baseline should be interpreted as a significant drop. **Do not assume chronic hypoxia unless clearly documented in the patient's clinical records.**

4.1.6.4 Respiratory support

a) Chest physiotherapy

- This is essential in patients with acute chest syndrome or at high risk of developing it (see acute chest syndrome section 4.2.6)
- Involve physiotherapists early for such patients

b) Incentive spirometry and IPPB Bird device

- The use of Incentive Spirometry and Intermittent Positive Pressure Breathing (IPPB) using the Bird machine can reduce the risk of acute chest syndrome and should be considered particularly for patients with chest pain.

- Appropriate use will be advised by the physiotherapists.

c) Non-invasive ventilation

- See acute chest syndrome section 4.2.6

4.1.6.5 Psychological and general supportive care

The pain in VOC is severe and relentless. Analgesia can be mind-altering. Patients may have had previous traumatic experiences associated with painful episodes.

Treating patients with kindness and compassion is essential to optimal care. Unhelpful attitudes from healthcare workers can delay a patient's recovery and have long term consequences.

For those who appear to particularly struggle with these episodes, refer to the Clinical Psychologist for ongoing support.

4.1.6.6 Adjuvant Medication

1. Anti-emetics

- Not required routinely, but opioid use may cause nausea in some patients
- **Do not prescribe IV cyclizine** – some patients develop dependency if used by this route

2. Laxatives

- Opioids can cause constipation, as can VOC through reduced fluid intake or immobility
- Prescribe laxatives before the onset of constipation, usually on admission.
- Commonly used laxatives include senna, sodium docusate, lactulose, Movicol

3. Anti-pruritics

- Some patients develop severe pruritus when taking morphine or diamorphine.
- Hydroxyzine is often effective. Prochlorperazine or chlorpheniramine (Piriton) can be used as an alternative. Check patient's preference

4.1.7 VTE prophylaxis

- Patients with sickle cell disease are at a medium risk of VTE (see Trust guidelines for VTE prophylaxis) UNLESS they have had previous VTE in which case more intensive VTE prophylaxis may be required, following discussion with the haematology team.

4.1.8 Antimicrobials

- Sickle cell patients are functionally hyposplenic and should take long-term prophylactic penicillin 250mg PO BD or amoxicillin 250mg BD (clarithromycin or erythromycin if penicillin allergic)

- In patients with VOC, investigate for infection as a precipitating factor. Respiratory tract infection is a risk factor for the development of acute chest syndrome.

- A low threshold for antibiotic treatment is appropriate. If a source is clear, antibiotics should be chosen as per Trust protocol.

- If there is no clear source of infection but the patient is mildly unwell and pyrexial, commence co-amoxiclav and clarithromycin. Discuss antibiotics with Microbiology and Haematology if more severely unwell.

- Patients with sickle cell disease are prone to unusual infections. See section 3.8 for further details

4.1.9 Discharge

- Patients should be supplied with oral analgesia as TTAs as recommended by Haematology.

- If a patient attends A&E and is fit for discharge, small supplies of simple analgesics (NOT strong opioids) can be issued for a few days if appropriate. Please email the haematology consultants if a patient attended A&E and was well enough to be discharged.

- Following opioid injection, patients must remain for 2 hours for observation within A&E.

- If you feel a sickle cell patient requires home follow up by the specialist nursing community team please liaise with the haematology team.

- Patients should be encouraged to make their own arrangements for transport home and to avoid public transport in the winter months. Patients should be advised not to drive whilst on opioids.

- Outpatient follow-up should be scheduled. If the patient's usual care is based elsewhere, send a copy of their discharge summary to their usual haematology consultant.

4.2 Acute Chest Syndrome

Key points:

- Acute chest syndrome (or “chest crisis”) is defined as an acute illness with fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on chest x-ray. Degree of hypoxia is a predictor of severity and outcome.
- It is the second most common cause for hospitalisation in sickle cell disease and a leading cause of morbidity and mortality in adults.
- Acute chest syndrome is unique to sickle cell disease and may mimic bacterial pneumonia.
- It is not necessary to differentiate between acute chest syndrome and pneumonia; all patients with acute chest syndrome must be presumed to have an infection and treated with antibiotics.
- Acute chest syndrome may follow a severe clinical course and progress rapidly from mild hypoxia to respiratory failure and death. Early recognition and prompt treatment is essential to achieving a successful clinical outcome.
- Acute chest syndrome may be precipitated by a vaso-occlusive crisis, post-operatively or by hypoventilation secondary to opiate overuse

4.2.1 Clinical features

- Shortness of breath
- Pain (often pleuritic) in chest wall, sternum, upper abdomen, and/or thoracic spine.
- Wheezing and haemoptysis may occur
- Cough may be a late symptom and may be productive
- Fever and rigors
- Hypoxia, tachypnoea, tachycardia
- Signs of lung consolidation; usually bilateral and generally basal.
- **Physical signs often precede X-ray changes**

4.2.2 Investigations:

- FBC and reticulocytes
- Haemoglobinopathy screen (HPLC) if recently transfused, on chronic transfusion programme or baseline unknown
- Biochemistry: U+Es, creatinine, LFTs, CRP
- Atypical pneumonia serology and urine for pneumococcal and legionella antigen
- Nasopharyngeal aspirate for respiratory viruses if patient has coryzal symptoms
- Blood cultures, sputum culture and other infection screen, as clinically indicated
- Crossmatch 8 units red cells immediately. **NOTIFY TRANSFUSION LABORATORY THAT THE BLOOD IS REQUIRED FOR A SICKLE CELL PATIENT.**
- Arterial blood gases on room air if O2 saturation ≤94% or >3% fall from baseline. Should be done on oxygen if patient is in obvious respiratory distress or if O2 saturation falls <85% on air
- Chest x-ray.

4.2.3 Notable investigation findings:

- Evidence of systemic inflammation: leucocytosis, raised inflammatory markers
- Evidence of haemolysis: acute drop in Hb, increased LDH and bilirubin
- Platelet drop: a platelet count of ≤200 x10^9/l is an independent predictor of severe acute chest syndrome with neurological complications and requiring mechanical ventilation
- Chest x-ray: alveolar consolidation affecting at least one segment, most commonly lower lobes; may be delayed by up to 12 hours

4.2.4 Differential Diagnoses

- **Pulmonary embolism**
  A CTPA is indicated for suspected PE. In acute chest syndrome, a V/Q scan can be indistinguishable from multiple pulmonary emboli. D-dimers are unhelpful in sickle cell disease as levels are usually elevated

  If there is a high clinical suspicion of pulmonary embolism (eg chest pain not typical of sickle pain, sudden onset unilateral pain, normal chest X-ray), treat for both conditions pending CTPA. Occasionally, acute chest syndrome is complicated by PE and treatment will be required for both conditions simultaneously.

- **Fluid overload**
  Fluid replacement is an integral part of the management of acute chest syndrome. However, over-hydration may lead to pulmonary oedema, especially in patients with impaired cardiac function. Close attention should be paid to fluid balance. Deterioration in a patient after blood transfusion should prompt consideration of this complication.

- **Opiate toxicity**.
  Careful attention should be paid to avoid opiate toxicity. Respiratory rate, sedation and pain scores should be monitored.

- **Hypoventilation due to pain**.
  Chest splinting due to chest or thoracic spine pain may lead to atelectasis and precipitate or aggravate acute chest syndrome. Effective analgesia is necessary.

4.2.5 Management

Notify the haematology registrars immediately, BOTH DURING AND OUT OF HOURS.

Haematology SpR to:

- Review patient urgently (out of hours this will be the medical team). Inform blood bank immediately
- Discuss the case with the Haematology ward nursing team to arrange emergency exchange transfusion or top up transfusion as determined by clinical need
- Inform Consultant immediately
- Assess need for and arrange central venous access
- Involve CCOT

4.2.6 Treatment

All patients with chest syndrome should be managed with the CCOT or ITU team.

- **Pain relief** – effective analgesia to allow good respiratory effort in patients with chest or thoracic spine pain

- **Antibiotics:**
  - IV co-amoxiclav and oral clarithromycin is the first line. IV co-amoxiclav may be converted to oral after 48 hours if improving.
  - IV Tazocin for patients with severe sepsis or with progression of acute chest syndrome on IV co-amoxiclav.
  - Liaise with microbiology regarding penicillin-allergic patients.

- **Oxygen therapy** to maintain oxygen saturations ≥95% on room air or within 3% of the patient's baseline. An increasing oxygen requirement denotes progression of acute chest syndrome.

- **Intravenous fluids (crystalloids)** – aim for 3 litres/24 hours if there is normal cardiorespiratory reserve. Strict fluid balance chart to avoid fluid overload.

- **Bronchodilators –** not required routinely, but should be considered if there is evidence of reversible airways disease, a history of asthma or acute bronchospasm.

- **Thromboprophylaxis** as per Trust guidelines

- **Blood transfusion** can be life-saving but the decision to transfuse can be difficult in milder cases. A consultant haematologist must be involved in the decision making.

  - **Top up (simple transfusion):** should be considered in patients with milder disease (PaO2 >8.0kPa on room air), or if Hb < 60 g/l

  - **Exchange transfusion:** patients with severe disease (PaO2 <8.0 kPa on room air), patients who deteriorate despite initial top up transfusion, patients with a higher Hb (>90g/l), patients with evidence of widespread sickling and/or multi-organ failure. See protocol in Appendix 2.

- **Chest physiotherapy** for all patients. In very sick patients, chest physiotherapy must be instituted promptly even outside normal working hours

- **More intensive respiratory support** will be required by some patients and any patients potentially requiring NIV or mechanical ventilation should be discussed with the Haematology Consultant on call:

  - **Non-invasive ventilation** use should be determined by the CCOT or ITU team and will normally be administered in ITU. Some patients with high risk disease (eg limited pulmonary reserve, multiple red cell alloantibodies, previous hyperhaemolysis, refusal of blood transfusion) may require NIV at an earlier stage.

  - **Mechanical ventilation** – the need for intubation and mechanical ventilation will be decided by the ITU team

4.2.7 Monitoring of patients with acute chest syndrome

- Hourly observations if unstable, deteriorating or on PCA. Less frequently as clinically appropriate.
- Oxygen saturation monitoring can take place on oxygen in established cases.
- Strict fluid balance chart
- Serial Chest X-rays if deteriorating
- Daily full blood counts, electrolytes, liver function tests, CRP

- Discuss transfer to ITU if
    - PaO_2 on inspired oxygen is < 8.0 kPa OR
    - $PaCO_2$ > 6.7 kPa OR
    - Fulfils any criteria for CCOT

4.3 Acute multi-organ failure syndrome

Key points:

- This is a life-threatening syndrome that may accompany a severe vaso-occlusive crisis and is characterised by failure of lungs, liver and/or kidneys.
- It is particularly likely to occur in patients with otherwise mild sickle cell disease and relatively high baseline haemoglobin.
- It may be precipitated by infection
- Deterioration is rapid and unexpected
- Early recognition and prompt, aggressive management are essential to prevent death.

4.3.1 Clinical features:

- Multi-organ failure – respiratory, hepatic, renal.
  - Acute respiratory failure is usually associated with development of acute chest syndrome.
  - Liver failure with marked elevation of conjugated and unconjugated bilirubin, liver enzymes and coagulopathy.
  - Acute renal failure is associated with a rapid rise in serum creatinine, with or without oliguria and hyperkalaemia.
- Fever
- Rapid fall in Hb and platelet count
- Rhabdomyolysis
- Non-focal encephalopathy

4.3.2 Investigations

- FBC and reticulocytes
- U&Es, LFTs, Bone profile, CK, CRP
- Coagulation screen
- Septic screen
- Chest X-ray
- Blood gases – venous and arterial
- Crossmatch 8 units red cells

4.3.3 Management

- Escalate to CCOT and ITU team; arrange urgent transfer to ITU
- Supportive treatment on ITU
  - respiratory support with oxygen, NIV or mechanical ventilation as required
  - Renal support with haemofiltration as required
  - Management of hepatic failure
- Immediate institution of transfusion – exchange transfusion wherever possible or top up transfusion as guided by haematology
- IV antibiotics if infection suspected

4.4 Acute Abdominal Pain

Key points:

- Abdominal pain is common in patients with sickle cell disease, and can be due to complications of sickle cell, **or any of the causes of abdominal pain in other patients.**
- Sickle cell patients with acute abdominal pain should be assessed and managed both medically and surgically. Purely surgical causes can be complicated by widespread sickling.
- Several of the sickle-related causes, in particular mesenteric syndrome, can closely mimic a surgical abdomen and the patient must be properly assessed, to avoid unnecessary investigations and surgical intervention.
- Acute chest syndrome can often follow episodes of abdominal pain, as there is splinting of the chest wall. Monitor oxygen saturations on air carefully
- Additional to analgesia and fluids:
    - If there is vomiting, or the abdomen is distended, or bowel sounds are absent, give nothing by mouth and consider nasogastric suction. Monitor liver size.
    - If cholecystitis/cholangitis is suspected consider antibiotics as per Trust guidelines

Sickle-related causes of abdominal pain:

1. Mesenteric syndrome (girdle syndrome)
2. Gallstone-related disease
3. Acute Intrahepatic cholestasis
4. Constipation secondary to opiate analgesia
5. Acute splenic sequestration (see under Acute Anaemia – section 4.6.2)
6. Acute hepatic sequestration (see under Acute Anaemia – section 4.6.3)

4.4.1. Mesenteric / Girdle syndrome

- This is a severe sequestration syndrome characterised by sickling and sequestration in the mesenteric vascular bed, liver and lungs**. It can be easily confused with an acute surgical abdomen.**

Symptoms and signs:

- Preceding pain in the abdomen, lumbar spine and limbs is common
- Abdominal tenderness and rigidity mimicking peritonitis
- May progress to ileus, with silent, distended abdomen without localising signs or rebound
- Some hepatic enlargement
- Often associated with bilateral basal lung consolidation; acute chest syndrome frequently develops due to splinting of chest wall as a result of abdominal distension
- Distended bowel loops or fluid levels on X-ray

Investigations:

- FBC and reticulocytes
- U&Es, LFTs, CRP, serum amylase

- Crossmatch 8 units of blood for exchange transfusion
- Chest x-ray
- Abdominal x-ray and erect chest x-ray or CT abdomen as discussed with surgeons

Management:

- It is essential to distinguish this syndrome from other causes of abdominal pain. Girdle syndrome will settle with conservative management:

    - Pain relief
    - IV fluids
    - Exchange transfusion
    - Antibiotics as per Trust Guidelines for an acute abdomen, including cover for Salmonella
    - Incentive spirometry is important, however there is no evidence for other respiratory support unless there is chest syndrome or other chest problems
    - Nasogastric suction. Sips by mouth only.
    - Measure abdominal girth (at umbilicus, in cms) at hourly intervals

- **No surgical intervention should occur without consultant level discussion between the surgeons and haematologists.**

4.4.2 Gallstones

Key points:

- Occur in at least 30% of children and over 70% of adults
- Usually pigment stones due to chronic haemolysis
- Often asymptomatic but can cause:
    - Acute cholecystitis
    - Chronic cholecystitis
    - Biliary colic
    - Obstruction of the common bile duct
    - Ascending cholangitis
    - Acute pancreatitis
    - Can precipitate abdominal painful crises and the girdle syndrome

Symptoms and Signs:

- Often asymptomatic but can cause biliary colic
- Signs of local complications eg acute cholecystitis, chronic cholecystitis, obstructive jaundice, acute pancreatitis
- Signs of sickle complications: e.g. acute chest syndrome and abdominal crises

Investigations:

- Plain abdominal X-ray (as many as 50% of stones may be radio-opaque)
- Ultrasound to look for biliary obstruction / stones
- MRCP (discuss with gastroenterologist)

Differential diagnosis:

- Hepatitis including viral
- Peptic ulcer
- Vaso-occlusive episodes
- Hepatic sequestration
- Chest syndrome

Management:

- Pain relief
- IV fluids
- Surgical referral
- IV antibiotics for acute cholecystitis, ascending cholangitis, acute pancreatitis as per Trust Guidelines
- Prophylactic antibiotics (ciprofloxacin) for biliary obstruction if no cholangitis present
- Urgent ERCP and removal of stone from common bile duct if obstructed
- Consider exchange transfusion for patients who are septic or sick

Indications for interval cholecystectomy (usually laparoscopic)

- Severely symptomatic biliary colic
- Acute cholecystitis
- Painful chronic cholecystitis
- Acute biliary obstruction
- Ascending cholangitis
- Acute pancreatitis

4.4.3 Acute Intrahepatic cholestasis

Key points:

- Severe hyperbilirubinaemia (conjugated and unconjugated), associated with fever and hepatic pain in the absence of demonstrable gallstones.
- These episodes are thought to be due to severe intrahepatic sickling.
- The rise in bilirubin is out of proportion to any rise in alkaline phosphatase.
- Liver can be enlarged but can be differentiated from sequestration because in the latter, liver function tests are only mildly elevated

Symptoms and Signs:

- Sudden onset of right upper quadrant pain
- Fever
- Increasing jaundice
- Progressively enlarging and exquisitely tender liver
- Light coloured stools

Investigations:

- FBC and reticulocytes – thrombocytopenia may be present
- U+E, bone profile
- LFTs - usually extreme hyperbilirubinaemia, both conjugated and unconjugated, elevated alkaline phosphatase, variable levels of transaminases
- Clotting screen – coagulopathy may be present
- Blood cultures
- Crossmatch 8 units of red cells for exchange transfusion

Management:

- Analgesia (with care as most opioids are metabolised in the liver)
- Hydration
- Antibiotics as per Trust guidelines for ascending cholangitis
- Monitoring as for hepatic sequestration
- Monitor for complications such as sequestration, chest syndrome etc
- Exchange transfusion is usually needed
- Surgical review

4.5 Stroke and other CNS complications

Common CNS complications in SCD include:

1. Ischaemic or haemorrhagic stroke
2. Subarachnoid haemorrhage
3. Seizures
4. Headache
5. Venous sinus thrombosis

4.5.1 Acute stroke

Key points:

- Ischaemic stroke is most common in children and those >30 years; may occur at any age
- Often occurs in context of a vaso-occlusive crisis, acute chest syndrome or other acute illness causing dehydration and fever
- May be silent and only detected on neuropsychological assessment; if cognitive impairment is suspected, refer to clinical psychologists.
- Cerebral infarction may be due to causes other than sickle, and the patient must be investigated for these

Symptoms and signs:

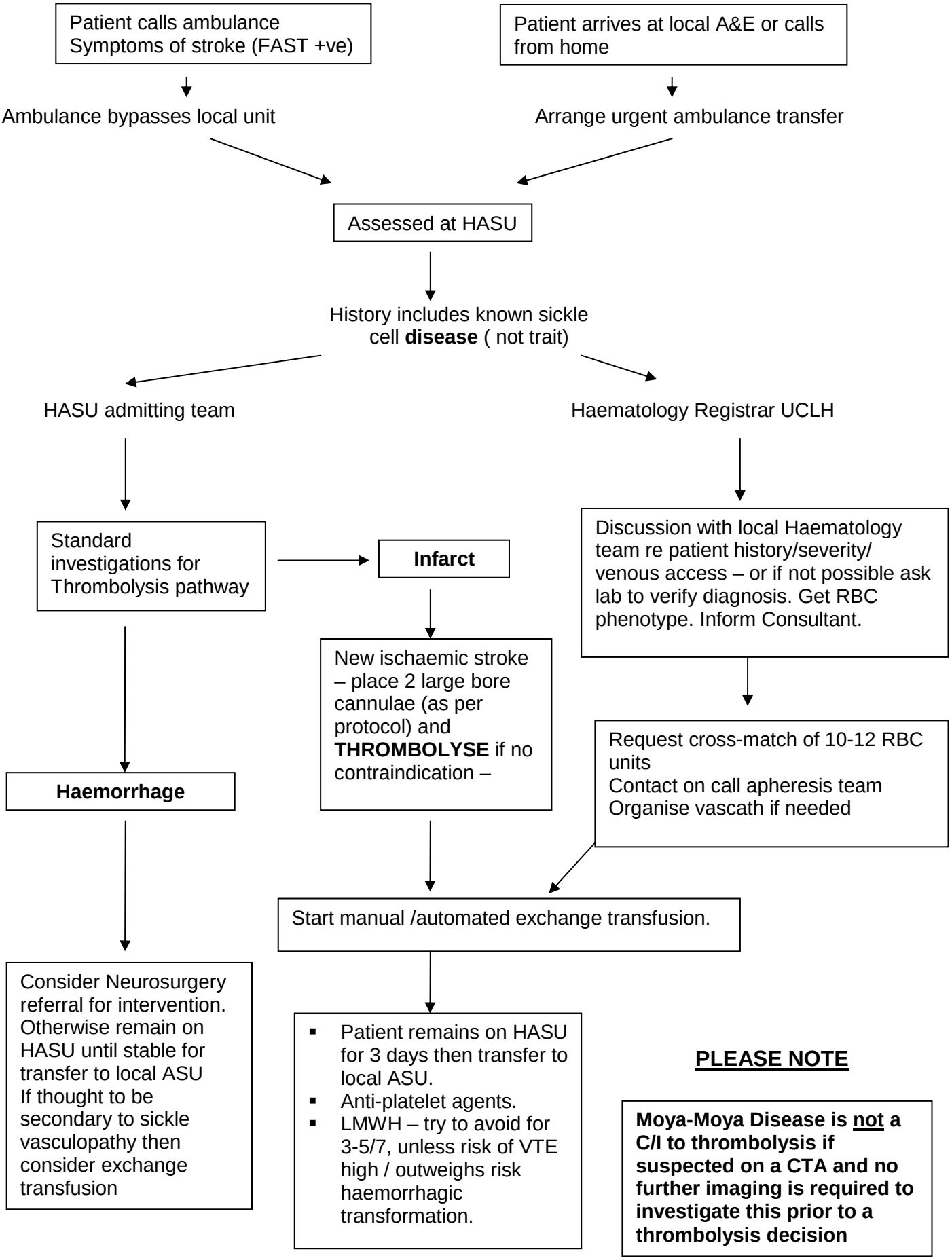
- Limb or facial weakness, or slurred speech
- Paraesthesia
- Seizure
- Acute confusion

Investigations:

- Early CT/MRI scan is essential to exclude haemorrhage; a negative scan at an early stage does not exclude infarction.
- MR angiography

Management:

- Contact the haematology team immediately if a stroke is suspected in a SCD patient
- Transfer to UCLH HASU as per pathway below
- Inform both Stroke Team and Red Cell Registrar at UCLH about the transfer
- Ensure that Whittington Transfusion Laboratory liaises with UCLH Transfusion Laboratory regarding patient's red cell phenotype and red cell antibody status
- The UCLH Stroke Team should contact the UCLH Red Cell Registrar **immediately** on patient's arrival, who will start urgent exchange transfusion to achieve Hb S < 30%, preferably <20% and Hb≤110 g/l. If scans are delayed, exchange transfusion should be commenced if there is strong clinical suspicion of stroke


Patient calls ambulance
Symptoms of stroke (FAST +ve)
Patient arrives at local A&E or calls from home
Ambulance bypasses local unit
Arrange urgent ambulance transfer
Assessed at HASU
History includes known sickle cell **disease** (not trait)
HASU admitting team
Haematology Registrar UCLH
Standard investigations for Thrombolysis pathway
Infarct
Discussion with local Haematology team re patient history/severity/ venous access – or if not possible ask lab to verify diagnosis. Get RBC phenotype. Inform Consultant.
New ischaemic stroke – place 2 large bore cannulae (as per protocol) and **THROMBOLYSE** if no contraindication –
Request cross-match of 10-12 RBC units
Contact on call apheresis team
Organise vascath if needed
Haemorrhage
Start manual /automated exchange transfusion.
Consider Neurosurgery referral for intervention.
Otherwise remain on HASU until stable for transfer to local ASU
If thought to be secondary to sickle vasculopathy then consider exchange transfusion
Patient remains on HASU for 3 days then transfer to local ASU.
Anti-platelet agents.
LMWH – try to avoid for 3-5/7, unless risk of VTE high / outweighs risk haemorrhagic transformation.
PLEASE NOTE
Moya-Moya Disease is not a C/I to thrombolysis if suspected on a CTA and no further imaging is required to investigate this prior to a thrombolysis decision

Ischaemic stroke prevention

Primary stroke prevention:

- In children, the presence of a raised Transcranial Doppler blood flow >200cm/s is associated with increased stroke risk. However in adults there is currently no evidence for a role of Transcranial Doppler in primary stroke prevention.

- For children who have been commenced on long term blood transfusion regimens following an abnormal Transcranial Doppler scan, there is no clear evidence of how long transfusions should continue for and therefore current practice is to continue transfusions long-term into adulthood.

Secondary stroke prevention

- The recurrence rate of ischaemic stroke is very high without transfusion.

- All patients who have had a sickle-related ischaemic stroke should go onto a long-term exchange transfusion programme.

Secondary prevention of silent cerebral infarcts

- Silent cerebral infarcts may have effects on IQ and cognitive performance, including memory.

- In patients with subtle neuro-cognitive defects, investigation with MRI/MRA scans and neuropsychological testing may be appropriate. The latter can be obtained by referral to the haemoglobinopathy clinical psychologists.

- All such patients should be evaluated by Haematology Consultant and designated Neurologist.

- The role of long-term transfusion for adult patients who have identified silent cerebral infarcts in the absence of symptoms has not been established.

4.5.2 Subarachnoid haemorrhage

Key points:

- Occurs at all ages, but commonest age group is 20-30 years

- Multiple aneurysms may be present most commonly at bifurcation of internal carotid artery and middle cerebral artery

Management and investigation:

- Exchange transfuse as for ischaemic stroke; refer to neurosurgeons; neurological observations
- If sickle cell vasculopathy is thought to have precipitated this event then consider long term exchange transfusion programme.

4.5.3 Seizures

Key points:

- Common after stroke or subarachnoid haemorrhage
- May be caused by pethidine (still administered at some centres) due to accumulation of the metabolite norpethidine.
- Withhold opioids until recovered

Investigations:
- EEG
- CT or MRI/A to exclude vascular event

Management:
Immediate:
- Stop pethidine / opioids
- Anticonvulsants, usually diazepam (slow IV injection or rectally)
- Neurological observations

Definitive:
- If no abnormality on EEG and no recurrence, no long term intervention is necessary, except to avoid pethidine
- If infarction on scan, or vessel stenosis/occlusion on angiogram, exchange transfuse and consider long term transfusion programme
- Further management as advised by Neurology

4.5.4 Headaches

A. Acute severe headache

Acute severe headache should be evaluated as an emergency and the diagnoses of intracranial haemorrhage or venous sinus thrombosis considered

B. Chronic headache

Key Points:

Chronic headache is common in sickle cell disease

Intracranial haemorrhage or venous sinus thrombosis should be considered if there is a change in the pattern of headache.

Causes:
- Migraine
- Benign intracranial hypertension (presumably as a consequence of venous sinus thrombosis)
- Sleep apnoea
- Tension

Management:
- Patients with persistent chronic headache should be referred to Neurology.

4.6 Acute Anaemia

Key Points:

- **Acute anaemia in SCD can progress rapidly to become life-threatening. It is crucial to be aware of the causes of acute anaemia specific to SCD and to recognise them early.**
- Baseline (steady state) Hb varies between genotypes and individuals.
- Typical Hb values are 60-90 g/l in HbSS, 70-90g/l in HbS/β^o thalassaemia, 90-120 g/l in HbSβ^+ thalassaemia and 90-140 g/l in HbSC.
- Steady state anaemia is well tolerated and does not require transfusion in health. An acute decrease in haemoglobin (> 20g/l below baseline) should prompt a review for aetiology
- Similarly, reticulocyte counts vary between genotypes and individuals but are usually high compared to the normal range.
- Changes in reticulocyte count may be helpful in identifying the cause of worsening anaemia. An inappropriately low count indicates a failure of production (eg aplastic crisis, drugs), whereas a high count indicates increased consumption (sequestration, haemolysis).

Causes of acute anaemia in sickle cell:

- **Aplastic crisis** – most often caused by Human Erythrovirus (formerly Parvovirus) B19
- **Acute splenic sequestration** – mainly in children
- **Acute hepatic sequestration**
- **Haemolytic transfusion reactions** (see section 8.4.1)
    - Classical delayed haemolytic transfusion reaction
    - Hyperhaemolysis
    - ABO incompatible transfusion
- **Exacerbation of background haemolysis**
    - Severe sickle cell crisis
    - Acute chest syndrome (see section 4.2)
    - Acute multi-organ failure syndrome (see section 4.3)
    - Severe sepsis
- **Other causes**
    - Acute haemorrhage
    - Myelosuppression due to Hydroxycarbamide

General principles of management of acute anaemia:

- **Manage cardiovascular compromise**
  - Large bore intravenous access
  - FBC, reticulocytes, Renal Function, Liver Function, LDH.
  - Closely monitor FBC until stabilised and then as clinically indicated
  - Crossmatch 4 units urgently, send several samples to blood bank if anaemia may be due to a haemolytic transfusion reaction.

- Note size of liver and spleen
- Urine dipstick and microscopy
- Obtain urine sample for HPLC if transfusion reaction or hyperhaemolysis is suspected. If hyperhaemolysis considered, keep serial urines for comparison to observe resolution of haemolysis.
- Septic screen, including virology and atypical serology and parvovirus serology
- Inform haematology registrar and haematology consultant on call

4.6.1 Aplastic crisis

Key Points

- **Most commonly caused by Human Erythrovirus (Parvovirus) B19**
- Severe anaemia with **reticulocytopenia.** Mean fall in Hb approximately 40g/l below baseline
- Occasionally presents with life-threatening complications including acute chest syndrome, acute splenic sequestration, or acute neurological syndromes including stroke.
- The characteristic prodromal illness of erythema infectiosum ('slapped cheek syndrome' or 'fifth's disease') is not always present and may be hard to recognise on pigmented skin.
- **Any person** in whom parvovirus infection is suspected should be isolated to protect patients with haemolytic anaemia, pregnant women and those who are immunocompromised.
- Enquire about household contacts, particularly any with haemoglobinopathy. All susceptible contacts should be screened (FBC, reticulocyte counts and parvovirus serology)
- Immunity to parvovirus is usually life-long, so second infections in individuals with normal lymphocyte function are very rare.

Investigations:

- FBC shows severe anaemia
- Reticulocytopenia and absence of nucleated red blood cells on blood film despite low Hb.
- Parvovirus IgM present. It may be absent in very immunocompromised patients in whom viral DNA may need to be assayed.

Management:

- Urgent red cell transfusion is usually necessary. Top up to baseline haemoglobin. If Hb is very low, transfuse in two stages to avoid rapid changes in blood viscosity.
- Spontaneous recovery is heralded by return of nucleated RBCs and reticulocytes to peripheral blood.

4.6.2 Acute splenic sequestration

Key points:

- Acute splenic sequestration is characterised by an acute fall in Hb, reticulocytosis and sudden splenic enlargement
- Typically occurs in children < 5 years but can occur in adults with milder disease such as HbSC or patients with high levels of HbF whose spleens have persisted into adulthood
- Often associated with septicaemia, particularly pneumococcal. High mortality, usually from hypovolaemia or severe anaemia.
- May go on to develop chest syndrome or other complications of sickle cell disease.

Symptoms and signs:

- Shock and sudden circulatory collapse
- Rapidly enlarging, painful spleen
- Abdominal pain (pulling legs up to abdomen)
- Acute worsening anaemia with reticulocytosis
- Signs of sepsis

Investigations:

- FBC and reticulocytes
- Biochemistry (U&Es, LFTs, CRP)
- Blood cultures and Viral serology
- Cross match

Management:

- Supportive (treatment of shock)
- Emergency (top-up) transfusion to no higher than baseline Hb. In extreme emergency with life-threatening hypovolaemia, can give uncrossmatched O negative blood. Discuss first with consultant haematologist.
- Broad spectrum antibiotics to cover Pneumococcus and Haemophilus
- There is a high rate of recurrence and splenectomy is usually advised in patients who have two or more episodes.

Splenectomy

Key Points:

- Splenectomy is usually needed in childhood.
- Indications include:
    - Sequestration – chronic, recurrent or a single life-threatening episode
    - Unexplained splenomegaly if causing significant symptoms or secondary cause suspected.

Management:

- Refer to upper GI surgeons
- Ensure up to date with Pneumococcal, meningococcal and Haemophilus influenzae immunisations
- Transfuse pre-operatively to prevent sickle complications (see Pre-operative guideline)

4.6.3 Acute hepatic sequestration

Key points:

- Liver enlargement is common in sickle cell crisis due to hepatic congestion.
- Hepatic sequestration is a far more serious cause of acute hepatomegaly
- Presents with acute fall in Hb, reticulocytosis and acute liver enlargement.
- Most reported cases are associated with infection, often Pneumococcus and Salmonella.
- More common in adults

Symptoms and signs:

- Shock and circulatory collapse; less frequent and sudden than with splenic sequestration
- Rapidly enlarging, painful tense liver, often hypochondrial pain
- Progressive jaundice can occur
- Acute worsening anaemia with reticulocytosis
- Signs of sepsis
- If patient develops tachypnoea, chest signs, hypoxia, treat as acute chest syndrome.

Investigations:

- FBC and reticulocytes
- Biochemistry (U&Es, LFTs, CRP)
- Blood cultures and Viral serology
- Cross match
- ABG if features suggestive of acute chest syndrome

Management:

- Supportive - treatment of shock and anaemia
- Emergency (top-up) transfusion to no higher than baseline Hb.
- Broad spectrum antibiotics to cover Pneumococcus and Salmonella

4.6.4 Delayed haemolytic transfusion reaction including Hyperhaemolysis

Can rapidly become life threatening and should be suspected in any recently transfused patient presenting with anaemia +/- pain – see section 8.4.1

4.7 Priapism

- Please refer to trust guidelines for management of priapism in sickle cell disease http://whittnet/document.ashx?id=3935

4.8 Renal complications

Key points:

- Sickle cell patients, especially older ones, frequently have precarious renal function. Avoid NSAIDS in all patients with known renal impairment
- Always compare creatinine levels with baseline.
- Patients cannot concentrate their urine making them vulnerable to acute kidney injury if dehydrated.

Complications include:

- Acute kidney injury
- Haematuria
- Hyperuricaemia
- Urinary tract infections
- Chronic kidney disease

4.8.1 Acute kidney injury

Key Points:

- Sickle cell patients are susceptible to acute kidney injury because of:
    - Unrecognised pre-existing renal impairment
    - their inability to concentrate their urine; as a result they are easily tipped into AKI due to intravascular volume depletion when their fluid intake is reduced
- Acute kidney injury can be precipitated by dehydration, sepsis, drugs or in the context of multi-organ failure.
- All patients admitted to hospital should be assessed for renal damage, and their fluid balance should be monitored throughout their admission.
- People with sickle cell disease have a low baseline creatinine and thus a rise in creatinine may represent acute kidney injury without exceeding the normal range.
- Remember that just because the patient has sickle cell disease this does not exclude other causes of acute kidney injury.

Investigations:

- USS renal tract
- Bloods: FBC, U&E, LFT, Group and save, reticulocytes, haemoglobinopathy screen
- Urine MC+S, and protein/creatinine ratio and dipstick.
- Tests for other causes of renal failure e.g. autoimmune disease, sepsis, PSA

Management:

- Assess and treat for underlying precipitant
- Careful fluid balance monitoring
- Discuss with renal team
- Discuss with ITU re: filtration if required

4.8.2 Haematuria

Key Points:

- Microscopic haematuria is common in SCD, and is usually due to sickle nephropathy.
- Frank haematuria is usually due to acute papillary necrosis, but may occur without any demonstrable pathology. Passing of renal papillae can cause renal colic and ureteric blockage.
- Other non-sickle related causes must be considered e.g. UTI/renal tract malignancy.
- Clearly differentiate between haemoglobinuria and haematuria using microscopy. Haemoglobinuria in the context of recent transfusion usually implies hyperhaemolysis, which can rapidly become life-threatening.

Investigation:

a) Painless, <40 years
- Renal ultrasound if not performed in previous year
- MSU and Urine cytology

b) Painful < 40 years
- Renal ultrasound
- CTKUB
- MSU and Urine cytology

c) All patients >40 years
- Refer to renal team for full work-up after ordering the investigations above

Management of frank haematuria:

- Intravenous fluids
- Treat infection
- Contact Haematology and refer to urology

4.8.3 Hyperuricaemia

Key Points:

- 40% of adults and 15% of children with SCD have hyperuricaemia, due to a combination of decreased urinary clearance and increased production of urate.
- Uric acid stones are common, as is clinical gout.

Investigations:

- Serum uric acid and renal function

Management:

- Good hydration
- Treatment of gout as in a non-sickle cell patient

4.8.4 Urinary tract infections

Key Points:

- Common, particularly in women with SCD (especially during pregnancy).
- Should be vigorously treated to prevent serious renal pathology.
- Haematuria, secondary to papillary necrosis, can precipitate UTI, but other factors must be excluded.

Investigation:

- MSU
- Bloods including renal function
- Blood cultures if unwell and/or febrile
- Renal tract ultrasound

Management:

- If well, give antibiotics as per Trust guidelines for UTI
- If unwell, give antibiotics as per Trust guidelines for pyelonephritis (consider previous positive culture results) and admit.
- Note that sloughed renal papillae can act as foreign bodies in the bladder predisposing to recurrent UTIs. Those with recurrent UTIs need a urology referral for a cystoscopy and further investigation.

4.8.5 Chronic kidney disease

Key Points:

- Chronic kidney disease occurs in 4-18% of people with sickle cell disease, the prevalence rising with age.
- Recognition of early CKD is important because sickle cell patients hypersecrete creatinine at the proximal tubules; there may be significant renal impairment before the serum creatinine rises.
- Presentation
  - Proteinuria – up to 68% in some studies; some patients have nephrotic range proteinuria
  - Hypertension is present in about a third of patients prior to developing CKD.
- Aggressive management of hypertension and proteinuria is the cornerstone of prevention.

A. Hypertension

- Sickle cell patients have a lower mean blood pressure than the general population.
- There is a growing recognition of hypertension as a cause of renal dysfunction in SCD

Management:

- Refer to renal team (Dr Mark Harber or Dr Robin Woolfson)
- If no proteinuria treat if BP >140/90 mmHg.
  - Aim for target of <130/80 mmHg.
  - Start ACE inhibitor (ACEi) e.g. ramipril 2.5mg, increasing up to a maximum of 10mg per day
  - If ACE inhibitor is not tolerated, change to angiotensin receptor blocker (ARB) e.g. candesartan
- If proteinuria is present, treat if BP > 130/80 mmHg
  - Aim for target of 120/80 mmHg
  - Treatment as above

B. Proteinuria

Management

1. Dipstick negative for protein: repeat 6 monthly
2. Dipstick proteinuria: send for urine protein-creatinine ratio (PCR) and MSU
3. PCR >50mg/mmol (on at least 2 occasions) with or without haematuria

   i) Refer to the Renal Team

   ii) Full renal investigation including:

- Immunology (autoimmune profile, immunoglobulins, complement)
- Viral serology – hepatitis B and C, HIV, Parvovirus B19 (if new onset nephrotic syndrome or recent aplastic crisis)
- Serum ACE
- Myeloma screen if >40 years old
- Renal ultrasound
- CT and urine cytology if haematuria present
- Renal biopsy as determined by renal team

iii) If other secondary causes excluded, treatment as per renal team eg:

- ACE inhibitor or angiotensin receptor blockers
- Consider disease modifying treatments (ie. hydroxycarbamide, long-term exchange transfusion)

NB: Exclude pregnancy and provide contraceptive advice to women of childbearing age before initiating an ACE inhibitor

4.8.6 Advanced renal disease

May require:

- Erythropoietin stimulating agents
- Renal replacement therapy in end stage renal disease as advised by the renal team
- Renal transplantation where indicated. Consider regular exchange transfusion if planning renal transplant.
- Post-renal transplant – automated exchange transfusion programme as advised by a haematology consultant

Role of erythropoietin (EPO)

- Consider in patients with eGFR <60ml/min and Hb <65 g/l and/or absolute reticulocyte count <150 x 10^9/l. These patients should be referred to the renal team.

Note: EPO will increase the rate of the sickle reticulocyte production and may compound sickling and further renal damage. Consider concurrent use of hydroxycarbamide (see Appendix 1)

4.8.7 Suggested criteria for renal referral

a) Hypertension with evidence of renal damage

b) Proteinuria - Urine PCR ≥50mg/mmol

c) Investigations reveal a non-sickle cause for renal disease

d) Worsening creatinine/eGFR

e) Candidate for EPO

4.9 Ocular complications

Key points:

- Chronic ocular complications include proliferative sickle retinopathy and vitreous haemorrhage.
- They occur in up to 50% of patients with sickle cell disease and are found more frequently in individuals with HbSC and HbSS

4.9.1 Proliferative sickle retinopathy

- Vascular damage due to SCD can cause retinal change, classified as non-proliferative or proliferative.
- Infarction of the peripheral retina results in the proliferation of fragile, thin-walled blood vessels ('sea fans') which are at high risk of bleeding and neovascularization.
- Onset before adolescence is rare.

Staging criteria:

Stage	Retinal characteristics
Stage I-II	Peripheral arteriolar occlusions and vascular remodelling
Stage III	Neovascularisation and sea fan formation
Stage IV	Vitreous haemorrhage
Stage V	Retinal detachment

Management:

- All patients over 18 years should be reviewed annually by ophthalmology to monitor for retinopathy. This may commence in childhood if there are any concerns.
- The Ophthalmology Consultant may advise a two year review if the patient is otherwise well.
- It is not clear however, whether early intervention has any benefit as the majority of patients with early retinopathy will have complete spontaneous resolution.
- Proliferative sickle retinopathy is commonly managed with laser photocoagulation.

- Surgical intervention, including vitrectomy may be indicated to treat vitreo-retinal complications refractory to medical treatment.

- Patients should be informed about the risks of ocular complications and **advised to attend Moorfields A&E urgently for review if they develop any acute visual symptoms**.

4.9.2 Vitreous Haemorrhage and Retinal Detachment

- More common in Hb SC and Hb Sβ Thalassaemia, especially in pregnancy. Usually presents as sudden loss of vision.

Patients with any visual symptoms should be advised to attend Moorfields A&E urgently

4.9.3 Ocular complications of iron chelation therapy

- There is a risk of retinopathy in patients on desferrioxamine and annual ophthalmic review is recommended.

4.10 Pulmonary and cardiac disease

Includes:

- Sickle cell chronic lung disease
- Obstructive sleep apnoea
- Pulmonary hypertension
- Reversible airways disease

4.10.1 Sickle Cell Chronic Lung Disease

Key Points:

- 90% of adult patients with HbSS have abnormalities on lung function tests. There are four stages of the disease (see Table 1 below); it is not clear whether patients inevitably progress through the stages or whether early intervention is of benefit.
- It may occur as a result of recurrent episodes of acute chest syndrome.
- Enquire about smoking history, asthma, previous episode(s) of acute chest syndrome and pneumonia, occupational history.
- Oxygen saturation should be measured in clinic, and if low, or if the patient has symptoms, they should be investigated as below.

Investigations:

- Chest X-ray
- Lung function tests – most common abnormalities are mild restrictive defects (74%) and isolated low diffusing capacity for carbon monoxide (13%)
- ECG and ECHO
- Arterial blood gases to confirm low PaO_2.
- High resolution CT scan of chest

Management:

- Refer to Respiratory Physician. Patients may require home oxygen +/- NIV.

Table 1: Sickle Chronic Lung Disease – Staging Criteria

Clinical Markers	Stage 1	Stage 2	Stage 3	Stage 4
Chest pain	Recurrent substernal pain and chronic cough	Increased pain over stage 1	Severe midline crushing pain.	Severe and prolonged pain with dyspnoea at rest.
Blood gases	Normal oxygen saturation	Normal oxygen saturation	Hypoxia with partial pressure oxygen (9.5 kPa) during stable periods	Hypoxia with partial pressure oxygen (8.0 kPa) during stable periods
X-Ray	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, FEV_1 and FEV_1/FVC ratio (mild, 80% of predicted normal or 1 SD below normal)	Decreased FVC, TLC, DCO, FEV_1 and FEV_1/FVC ratio (moderate, 60% of predicted normal or 2 SD below normal)	Decreased FVC, TLC, DCO, FEV_1 and FEV_1/FVC ratio (severe, 40% of predicted normal or 3 SD below normal)	Patient frequently unable to complete testing due to degree of hypoxia
ECG and ECHO	Left ventricular preponderance persists	Balanced ventricular hypertrophy	Right ventricular hypertrophy and right atrial enlargement. Progressive increase in heart size.	Severe right ventricular and right atrial hypertrophy. Ischaemic T waves in V1 and V2 and cor pulmonale
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, FEV_1= forced expiratory flow rate, DCO = diffusing capacity for carbon monoxide

4.10.2 Obstructive sleep apnoea

Key Points:

- This is common in SCD and may be due to adeno-tonsillar hypertrophy.
- Overnight hypoxia can be associated with painful sickle episodes and neurological events.
- Overnight sleep studies should be performed on those who are hypoxic at rest, have symptoms of daytime somnolence or have a high Epworth score.

Investigations:

- Hypoxia on pulse oximetry should be confirmed by arterial blood gas on air with co-oximetry. This information should be recorded in any referral.
- Posterior nasal space x-ray
- Sleep study

Management:

- Patients with abnormal sleep studies should be discussed with the Haematology consultant and referred to Respiratory and ENT Team
- Treatment options include CPAP and surgery, including adeno-tonsillectomy.

4.10.3 Pulmonary hypertension

Key Points:

- All patients with sickle cell disease should be reviewed annually with echocardiography
- Any patient who is symptomatic with shortness of breath or hypoxia should be investigated for pulmonary hypertension.
- Patients with suspected pulmonary hypertension should be referred to Dr Malcolm Walker's specialist cardiology clinic for sickle cell patients at UCLH
- All patients with pulmonary hypertension should be offered annual review with dedicated Respiratory Consultant also.

- Causes include:
  - Chronic haemolytic anaemia – causes pulmonary arterial hypertension
  - Left ventricular systolic dysfunction – causes pulmonary venous hypertension
  - Chronic lung disease
  - Chronic thromboembolic disease
  - Unclear mechanisms

- Symptoms:

    - Shortness of breath on exertion
    - Fatigue and lethargy
    - Chest pain
    - Palpitations
    - Syncope
    - Peripheral oedema
    - Decreased appetite

Investigations:

- Echocardiography
    - A raised tricuspid regurgitant jet velocity (TRV) >2.5ms may be suggestive of pulmonary hypertension in patients with SCD.

- TRV may be transiently elevated during vaso-occlusive crisis or acute chest syndrome; therefore perform echocardiogram when the patient is in steady state in order to determine baseline value.

- In patients with confirmed pulmonary hypertension, systemic hypertension, chronic lung disease, chronic thromboembolic disease, chronic hypoxia, and obstructive sleep apnoea should be excluded.

- Definitive diagnosis of pulmonary hypertension is made by right heart catheterisation and direct measurement of the pulmonary artery pressure.

Management:

- Patients with pulmonary arterial hypertension should be managed by a specialist pulmonary hypertension service. Refer to Dr Walker.

- Long-term exchange transfusion is usually recommended but the effectiveness of this or hydroxycarbamide for reducing mortality is unknown

- Other treatments such as bosentan have been used

4.10.4 Reversible airways disease

Key Points:

- Some patients with sickle cell disease have bronchial hyper-reactivity and may respond well to bronchodilators. This is particularly common in children though also occurs in adults.

4.11 Orthopaedic complications

4.11.1 Osteomyelitis

Key points:

- Sickle cell patients are susceptible to osteomyelitis.
- Symptoms can be identical to those of an acute painful crisis; the latter is much more common and also usually multi-focal in location.
- Patients often have a good idea as to whether this is their usual vaso-occlusive crisis or not.
- Therefore, treat as vaso-occlusion and only investigate for osteomyelitis if pain or fever is persistent or if there is any other suggestion of osteomyelitis.
- Common organisms
    - Salmonella species
    - Staphylococcus aureus
    - Gram negative bacteria

Signs and symptoms

- Local tenderness and warmth
- Bony swelling
- Fever

Investigations

- Bloods for inflammatory markers and blood cultures
- Plain X-Rays are usually normal
- USS can show increased subperiosteal fluid >4mm (smaller amounts of fluid are associated with painful crises)
- MRI scans with gadolinium may help diagnosis, but without contrast do not differentiate between infarction and infection
- Bone scans and radio labelled leucocyte scans will not differentiate between infarction and infection
- Bone aspiration
    - **Bone aspiration may introduce infection, so should only be done after discussion with the Haematology and Orthopaedic Consultants and if there are persistent symptoms.**

Management

- Start antibiotics if there is a strong clinical suspicion e.g. ceftriaxone with Microbiology advice
- Involve Microbiology early
- Treat for six weeks or as advised by Microbiology
- Accumulation of fluid may require drainage, consult with orthopaedics

4.11.2 Avascular Necrosis

Key Points:

- Occurs in approximately 10% of all patients and about 50% of HbSS patients by the age of 33 years.
- The normal age of onset is adolescence and young adulthood, and it is uncommon as a new presentation after the age of 30 years.
- Sickle cell genotypes that are associated with relatively mild anaemia (eg. HbSC, Hb Sβthalassaemia) are at particularly high risk of AVN at an earlier age.
- Avascular necrosis (AVN) of the hip is most common, but it can occur in other joints, in particular the shoulder.
- Early referral to orthopaedics is important in assessment and management

Symptoms and Signs:

- Pain in the affected joint on movement, later at rest. Hip AVN may be referred to the leg, groin or knee.
- Limitation of movement; particularly abduction and external rotation of the hip, and external rotation of the shoulder.
- May be triggered or exacerbated by pregnancy (even when transfused).

Diagnosis:

- Clinical
- Radiological: X-ray or MRI

Avascular Necrosis of Femoral Head: Staging Criteria

Stage	Radiological signs
EARLY: Stage 0 Preclinical	None; marrow necrosis may be present histologically
EARLY: Stage I. Pre-radiographic	None; abnormal MRI with marrow and bone necrosis
EARLY: Stage II. Before flattening of head or sequestrum formation	Diffuse porosis, sclerosis or cysts
TRANSITION	Femoral head flattening Crescent sign
LATE: Stage III. Collapse	Broken contour of head Sequestrum Joint space normal
LATE: Stage IV. Osteoarthritis	Flattened contour Decreased joint space Collapse of head

Management:

Treatment depends on the stage of the disease

Early

- Avoidance of weight bearing and rest are sometimes recommended, however their role remains uncertain;
- Analgesia with non-steroidal anti-inflammatory agents or codeine derivatives. Long acting opioids may be considered, e.g. Morphine sulphate slow release tablets.

Late

- Refer to the orthopaedic team
- Early disease, prior to collapse of the femoral head, can be treated surgically with core decompression.
- Joint replacement may be indicated for severe or chronic pain, and if the patient's mobility is seriously affected.
- Patients with ongoing pain following joint replacement, or who do not want a joint replacement, should be referred to the chronic pain team

4.12 Leg Ulcers

Please see Trust Guidelines on the intranet: http://whittnet/document.ashx?id=7129

5.0 OBSTETRICS AND GYNAECOLOGY ISSUES

5.1 Pregnancy

Please see Trust Guidelines on the intranet http://whittnet/document.ashx?id=4410

5.2 Contraception

A full range of contraceptive choices can be offered to women with SCD. Sickle patients requiring contraceptive advice may discuss with their GP or family planning clinic. Patients may also be referred to Miss Amma Kyei-Mensah for specialist advice. All changes of medication should be communicated to the Haematology Team.

- **Progestogen-only contraceptives** (pill, depot or implant) have no significant adverse effects in women with SCD. The control of cyclical hormonal changes may have a beneficial effect on symptoms such as painful crises.

- **The Combined Oral Contraceptive pill** has not been widely used in women with SCD in the past due to concerns about increased risk of venous thromboembolism. Newer formulations have shown no additional risk. The benefits of contraception outweigh the risks in this population

- **Intrauterine devices**. The Mirena coil is the preferred choice of IUD in this population.

5.3 Termination of pregnancy

- Terminations should take place in a hospital where there is appropriate haematology cover.

- Patients should be referred urgently to the gynaecology department and an individualised management plan formulated for each patient.

5.4 Delayed puberty

Key Points

- Common, particularly in boys
- Related to lower body mass for age in children with SCD
- Reassure, as most will progress to normal puberty despite the delay
- Most patients will have undergone puberty by the time of transition to adult services but if not they will need continued management involving the endocrinologists.
- Delayed puberty may be linked to problems with body image, confidence and low mood. Consider referral to psychology in this case.

Management:

- In underweight patients, encourage improved quantity and quality of nutritional intake in order to increase body weight
- Check testosterone/oestradiol, FSH, LH and SHBG. Where a hormonal deficiency can be demonstrated, refer to endocrinologists.
- Exceptionally, infarcts in the hypophysis and hypothalamus are responsible. Refer to a specialist for appropriate replacement therapy.
- Regular transfusion for 6 - 12 months may initiate puberty but is rarely required.

5.5 Menorrhagia/ Painful periods

Key Points

- In some women, sickle crises may be triggered pre-menstrually
- These women should be offered referral to a gynaecologist (Miss Kyei-Mensah) for consideration of management options.

5.6 Fertility

Key Points

- Women with SCD usually have normal fertility, whereas many men with Hb SS and Hb Sβ^{o}thalassaemia have reduced sperm counts and reduced sperm motility.
- Couples with problems conceiving should be referred to Mr Gidon Lieberman.
- Some men may have erectile dysfunction because of past priapism. They should be referred to the Andrology team for further management (Mr Ralph, UCLH).
- Hydroxycarbamide may cause long term reduction in sperm counts, and male patients embarking on hydroxycarbamide treatment should have counselling, and if required sperm counts and sperm banking.
- Psychosexual counselling can be obtained via the psychologists.

5.7 Genetic counselling

- Patients with sickle cell disease wishing to have children should be offered partner screening for haemoglobinopathies and genetic counselling, offered by the Islington Sickle Cell and Thalassaemia Centre.
- More complicated cases e.g. silent beta thalassaemia can be referred to Dr Sara Trompeter/Dr Mary Petrou at the Haemoglobinopathy Genetics Service, UCLH.

6.0 SURGERY AND A6.0 SURGERY AND ANAESTHESIANAESTHESIA

Please refer to Guideline for the peri-operative management of haemoglobinopathies on the intranet: http://whittnet/document.ashx?id=7128

7.0 IMMUNISATIONS

Immunisations

- Immunisations should be performed by the General Practitioner
- In addition to routine childhood vaccinations (polio, pneumococcus, diphtheria, tetanus, BCG) people with sickle cell disease, as with other hyposplenic patients, require:
    - **Pneumococcal C vaccine**: adults and children >2years should receive the unconjugated vaccine (Pneumovax II). Vaccination should be repeated every 5 years.
    - **Influenza Vaccine** (annually)
    - **Haemophilus influenza type b vaccine**: a single dose should be given if not already received as part of primary child immunisation schedule
    - **Conjugated Meningococcal C vaccine**: a single dose should be given
    - **Conjugate Meningococcal B vaccine** if not already received as part of primary child immunisation schedule
    - **Hepatitis B Vaccine:**
      Hepatitis B vaccination should be given as 3 injections at months 0,1 and 6. Hepatitis B surface antibody levels should be checked 1 month after the 3rd dose to ensure an adequate response (>100 iu/ml). A second full course should be offered if response is poor. Thereafter, antibody levels should be checked every 5 years and a booster given if levels are sub-optimal.

8.0 BLOOD TRANSFUSION IN SICKLE CELL DISEASE

8.1 Introduction

Red cell transfusion in the management of sickle cell disease reduces disability and can be lifesaving. However, it can be associated with serious complications and mortality if used injudiciously. Therefore the decision to transfuse a sickle cell patient should involve the input of a consultant haematologist or doctor with appropriate experience, and specialist advice should be obtained for the management of patients with complex transfusion requirements.

Goals of transfusion

There are 2 main goals of blood transfusion in SCD:

- To correct anaemia and so improve the oxygen-carrying capacity of blood
- To prevent or reverse the complications of SCD by reducing the percentage of HbS in relation to HbA.

Strategies of transfusion

- Simple or top up transfusion – generally used to correct anaemia
- Exchange transfusion – this can be done either manually or with an automated red cell separator and is generally used to reduce HbS.

Both top up and exchange transfusion can be used in the emergency setting or electively to prevent the development or progression of chronic complications.

Indications for transfusion

See Table 2 below for indications where transfusion is of proven benefit.
There is no evidence that transfusion shortens the duration of a painful crisis; transfusion is not indicated in uncomplicated sickle cell crisis but should be considered if there is a substantial drop in baseline Hb, haemodynamic compromise or impending critical organ dysfunction.

Access to exchange transfusion for patients on long-term transfusions

All patients on long-term transfusions have access to automated exchange transfusions. Patients requiring automated exchange transfusion (either pre-operatively or long-term) are referred by the haematology team to the Red Cell Team at UCLH.

Some patients are maintained on manual exchange transfusions which are carried out on the Thalassaemia Unit at Whittington Health by specialist haemoglobinopathy nurses.

Protocol for carrying out manual exchange transfusion

The protocol for carrying out a manual exchange transfusion in the emergency setting can be found in Appendix 2.

Table 2: Indications for blood transfusion in sickle cell disease

Goal of transfusion	Indication	Type of transfusion[1]
Correction of acute anaemia – in general, aim to restore haemoglobin to patient's baseline value	Aplastic anaemia	Top up
	Acute splenic sequestration	Top up
	Acute hepatic sequestration	Top up
	Delayed haemolytic transfusion reaction[2]	Top up
	Hyperhaemolysis[2]	Top up
Reduction of HbS concentration in relation to HbA – prevention or reversal of sickle cell complications	Acute chest syndrome	Top up or exchange[3]
	Acute stroke or neurological deficit (eg TIA)	Exchange transfusion
	Acute multi-organ failure	Exchange transfusion
	Mesenteric/girdle syndrome	Exchange transfusion
	Severe sepsis	Exchange transfusion
	Acute intrahepatic cholestasis	Exchange transfusion
	Primary stroke prevention	Top up or exchange
	Secondary stroke prevention	Top up or exchange
	Surgery	
	• Elective low or medium risk surgery	Top up or exchange
	• Elective high risk surgery	Exchange transfusion
	• Emergency surgery	Individual considerations[4]

	Pregnancy	
	• Severe anaemia	Top up
	• Sickle complications (eg. painful crises, chest crisis, stroke)	Top up or exchange
	• High obstetric, medical or fetal risk	Top up or exchange
	Recurrent acute chest syndrome[5]	Top up or exchange
	Recurrent painful crises[5]	Top up or exchange

[1]Individual patient factors and consideration of complications such as iron overload must be taken into account
[2]Transfusion should be avoided unless the anaemia is severe or life-threatening
[3]Top up transfusion may abrogate mild cases of acute chest syndrome but exchange transfusion should be performed from the outset in severe cases or if there is progression despite initial top up transfusion in mild cases.
[4]Decisions to transfuse or choice of transfusion should be based on individual patient factors and considerations such as urgency or complexity of surgery.
[5]Hydroxycarbamide is first-line. Transfusion should be considered for those failing or not accepting hydroxycarbamide or if it is contraindicated

8.2 Blood Products

Key Points:

- Trust transfusion policy and guidelines on the use of blood products should be used
  http://whittnet/document.ashx?id=800
  http://whittnet/document.ashx?id=799

- **Label the blood transfusion request form: "SICKLE CELL DISEASE".** The information from the other forms does not reach blood transfusion. This should ensure that the patient receives the correct phenotyped blood

- Blood for sickle cell patients should be
  - ABO compatible
  - Rh matched
  - Kell matched (or K negative)
  - Sickle negative
  - Negative for any alloantibodies they may have
  - It is preferable, if it does not result in a delay in treatment, to use blood:
    - <7 days old for exchange transfusions
    - <10 days old for top-up transfusions

- Patient should have a full red cell phenotype recorded on the computer system. If not, contact the blood transfusion laboratory because the red cell phenotype may be held as legacy data.

- If the transfusion laboratory has no record of the patient's red cell phenotype, send an additional sample to the transfusion laboratory labelled as per blood transfusion guidelines. Mark form "FOR FULL RED CELL PHENOTYPE". The Rh phenotype can be determined quickly by the hospital transfusion department if not already known.

- Inform Blood Bank if the patient is known to another hospital and in particular if transfused there.

- In an emergency setting CALL blood bank immediately and discuss the decision to transfuse with the Biomedical Scientist (BMS). INFORM THE BMS THAT THE BLOOD IS REQUIRED FOR A SICKLE CELL PATIENT.

- If there is insufficient blood on site meeting the specific requirements you should consider accepting alternatives, for example slightly older blood, if delay may cause harm. Discuss with a Consultant if there are any concerns regarding this. There is usually blood in the blood bank that could be used in an emergency.

8.3 Outpatient transfusion arrangements

Investigations and vaccinations prior to first transfusion
Investigations to be carried out prior to the first transfusion are as follows:

- FBC & reticulocyte count
- Transfusion
    - ABO and Rh (D)
    - Extended red cell phenotype
    - Antibody screen
- U&Es, LFTs, bone profile, LDH
- Serum ferritin, serum iron, TIBC, transferrin saturation
- Virology
    - Hepatitis B surface antigen and antibody
    - Hepatitis C antibody
    - HIV antigen and antibody

Vaccinations prior to first transfusion
All patients should be fully immunised against hepatitis B prior to the first transfusion. Hepatitis B surface antibody levels must be checked every year together with Hepatitis B surface antigen, hepatitis C and HIV serology in patients on long-term transfusions. Patients who are non-immune for hepatitis B should be given a booster to maintain immunity.

Review by specialist nurse or doctor prior to transfusion to ensure that each transfusion is appropriate
All patients attending for transfusion will be reviewed by the haemoglobinopathy specialist nurses or the haematology registrars to ensure that they are fit for transfusion and that each transfusion is appropriate.

Areas where transfusions will usually be given
The Thalassaemia Unit offers a 7-day 9am-5pm transfusion service. Overnight blood transfusions usually take place on Victoria ward. Staff on the Thalassaemia Unit can be contacted on 020 7288 5225.

Recommended number of phlebotomy and cannulation attempts and waiting time for setting up of the blood transfusion (for pre-ordered blood)
Patients attending for transfusion should not be kept waiting longer than 30 minutes to be cannulated and the transfusion set up. The recommended number of attempts at phlebotomy and cannulation is two.

8.4 Complications of transfusion

Transfusion reactions
Please adhere to the Trust guidelines: **http://whittnet/document.ashx?id=701**

Haemolytic transfusion reactions are a particular concern in sickle cell disease.

8.4.1 Haemolytic transfusion reactions

Key Points:

- Sickle cell patients are at increased risk of haemolytic transfusion reactions due to:
  - A high rate of red cell alloimmunisation
  - Previous antibodies that are currently undetectable
  - Increased likelihood of urgent transfusion out of hours
  - Transfusion in multiple different hospitals

- **A haemolytic transfusion reaction should be strongly suspected in patients presenting with acute anaemia following a recent transfusion ,with or without pain typical of a vaso-occlusive crisis**

- **PLEASE INFORM HAEMATOLOGY IMMEDIATELY IF YOU SUSPECT A HAEMOLYTIC TRANSFUSION REACTION.**

Types of haemolytic transfusion reaction:

- **Acute** – haemolysis occurs during transfusion
  - ABO incompatibility – this is a never event; it is rare and is due to the transfusion of ABO incompatible red cell units. See Transfusion guidelines: **http://whittnet/document.ashx?id=701**

- **Delayed** – haemolysis occurs a few days after transfusion
  - Classic delayed haemolytic transfusion reaction accounts for most cases (see 8.4.2)
  - Hyperhaemolysis (see 8.4.3)

Investigations of haemolytic transfusion reactions:

- FBC and Reticulocytes,
- U&E, LFT, LDH
- Group and save (transfusion laboratory staff may ask for additional samples in order to investigate the haemolytic transfusion reaction)
- DAT
- Coagulation screen
- Haptoglobins
- Urine HPLC and dipstick and microscopy

8.4.2 Classical DHTR

- Most commonly occurs 7-10 days after transfusion
- Fever, jaundice and anaemia which may be accompanied by sickle pain
- Laboratory evidence of haemolysis (reticulocytosis, raised unconjugated bilirubin, raised LDH, reduced haptoglobin)
- Positive DAT and new red cell alloantibody or antibodies

Management:

- Inform Haematology Consultant and senior transfusion laboratory staff
- The patient should be carefully monitored

- Management is supportive.
- Prescribe folic acid tablets 5mg daily
- Delayed haemolytic transfusion reactions are usually self-limiting.
    - Avoid further transfusion if patient stable and anaemia not life-threatening.
    - May need top up transfusion if anaemia is severe or life-threatening.

- **If a new red cell antibody is found, the patient should be issued with an antibody card**. This is particularly important as these antibodies often become undetectable and are found again only after they have caused haemolysis following a further blood transfusion in another hospital.

8.4.3 Hyperhaemolysis – defined as destruction of both transfused and autologous red cells

- A distinct form of life-threatening haemolytic anaemia following transfusion
- Characteristically presents with severe sickle cell pain, fever and haemoglobinuria
- Haemoglobinuria is due to intravascular haemolysis
    - Dark or black urine ('Coca Cola' coloured)
    - The colour of the urine may be red if intravascular haemolysis is brisk; this must be distinguished from haematuria which will have intact red cells on urine microscopy

- **May be missed because it is assumed that the patient's symptoms are due to a sickle cell crisis**

- Laboratory features include:
    - Post-transfusion Hb is lower than before transfusion
    - A fall in the absolute reticulocyte count (from patient's usual level); this contrasts with classical DHTR where reticulocytes are raised
    - Haemoglobinuria - HbS and HbA in serial analysis of urine on HPLC
    - HbA falls or disappears in blood (on HPLC)
    - Usually DAT negative and with absence of new red cell alloantibodies (which distinguishes hyperhaemolysis from classical DHTR)
    - Additional transfusion may exacerbate haemolysis

Management

- Inform haematology registrar who must inform Consultant IMMEDIATELY
- CCOT review and discussion with ITU
- Inform blood bank and cross match 6 units - blood should be available on site even if not immediately required
- Treatment is focused on resuscitating the patient and controlling immune destruction
- Prescribe folic acid tablets 5mg daily and consider B12 replacement
- Primary treatment is immunosuppression: IV Methylprednisolone and IVIg (see below for dosing).
- Consider treatment with erythropoietin and IV iron replacement

- Further blood transfusion should only take place after discussion with the haematology consultant and should only occur when absolutely necessary – i.e. if compromised, Hb rapidly dropping, Hb <45 g/l.

- If transfusion indicated, do so cautiously– eg. one unit at a time
- FBC will need to be checked frequently initially e.g. 4 hourly, do not reduce frequency unless discussed with consultant.

Dosage of IVIg and methylprednisolone

- **Intravenous immunoglobulin (IVIg) -** 1g/kg once daily for 2 days or 0.4g/kg/day for 5 days (total dose = 2g/kg)
  - Round dose to nearest vial size (5g or 10g vials available)
  - Out of hours contact the on call pharmacist. This product is stocked in the emergency drug cupboard.

- **Methylprednisolone -** 500mg to 1g IV once daily for 2 days
  - Review dose after 2 days.

- **Erythropoietin -** Neorecormon 300iu/kg once daily for 5 days. Then 300iu/kg once daily alternate days (i.e. 3 times per week)

- **Ferritin, B12 and Folate**
  - Erythropoietin requires adequate haematinics to work effectively.

  - If ferritin <100ng/ml – prescribe IV iron infusion
  - If ferritin >100ng/ml – prescribe oral iron (ferrous sulphate)

  - B12: prescribe if B12 <200 pg/ml
  - Folate: prescribe Folic acid 5mg once daily

Management of subsequent transfusion episodes following hyperhaemolysis

- Similar episodes of hyperhaemolysis are likely on re-exposure to blood products, so further transfusions ought to be considered only after discussion with the consultant. IVIg and methylprednisolone should be given prior to any transfusion.

- **Issue the patient with a Transfusion card stating the diagnosis of hyperhaemolysis.** The patient must be instructed to show this card to medical and nursing staff whenever they are admitted to hospital or when they transfer their care to another hospital.

8.4.4 Non-haemolytic transfusion reactions

These are transfusion reactions due to anti-WBC/platelet antibodies. Treat with antipyretics, antihistamines, etc. See transfusion guidelines: **http://whittnet/document.ashx?id=701**

8.4.5 Iron overload and its sequelae

Please refer to the chronic iron overload guideline for guideline on iron chelation treatment: **http://whittnet/document.ashx?id=7131**

9.0 OUTPATIENT ATTENDANCES

9.1 Haematology outpatients

- There is no dedicated outpatient clinic for adult sickle cell patients at the Whittington. The majority of patients are seen in Dr Davis' clinics on Tuesdays in Clinic 3B. A few patients are seen in the thalassaemia Thursday evening clinic, also in Clinic 3B.

- Dr Davis will see patients with difficult or complex issues in his office on Wednesday afternoons for longer appointments.

9.2 Referrals

- External referrals can be made through "Choose and Book" to Dr Davis or Dr Shah. They can also be made by writing to the consultants or by discussion with one of the team, although a follow up written referral is needed to secure the appointment.

- Internal referrals should be made via the registrars on bleep 3060 or 3037. A red top referral can be written for non-urgent cases.

  The following details are necessary:
  - Patient name
  - Hospital ID number
  - Date of Birth
  - Whether the patient is an inpatient or an outpatient and planned date of discharge
  - Address and telephone number for the patient if an outpatient
  - Current problems and relevant past medical history
  - Your name and contact details

- If these details are not included, it is not possible to prioritise the referral and there may be a delay in contacting your patient.

- To prevent referrals waiting in an e-mail inbox while somebody is away it would be appreciated if ALL referrals could be made using one of the above routes.

9.3 Staffing

- Haematology Medical Staff: Haematology Consultants and Specialist Registrars
- Nursing Staff: Clinic Nurses & Health Care Assistants
- Sickle Cell Community Matron as required
- Phlebotomists
- Administrative Staff

9.4 First outpatient appointment

Clinical assessment

1. Full history to include:
- Sickle cell genotype if known
- When and where diagnosed
- How diagnosed

- Clinical severity
    - Frequency, severity and duration of crises
    - Number of admissions a year or number of days off sick from education or work
    - Previous sickle complications and their treatment, especially acute chest syndrome
    - Previous ITU admissions
    - Transfusion history – episodic vs regular; indications, when and where last transfused, previous transfusion complications
    - Antibody card – check patient's knowledge and understanding of how to use card
- Other past medical history
- If previous pregnancies, what were outcomes
- Social history – education & training, work
- Immunisations – check if has card
    - Pneumococcal
    - Meningococcal
    - Haemophilus influenza type B
    - Influenza
    - Hepatitis
- Drug history
    - Penicillin or substitute if penicillin allergic
    - Folic acid
    - Usual way patient manages pain at home – which analgesics, check has adequate supply. If opiates, who is prescribing them
    - Usual pain management in hospital – check with referring hospital
    - Hydroxycarbamide – see Appendix 1
    - Other including iron chelators
    - Allergies

2. Full clinical examination including

- Height, weight, BMI
- O2 saturation (pulse oximetry)
- Urinalysis

3. Investigations

- FBC & reticulocyte count
- Haemoglobinopathy screen to confirm sickle genotype
- G6PD assay
- Transfusion
    - ABO and Rh (D)
    - Extended red cell phenotype
    - Molecular genotype if patient is on a chronic transfusion programme and not previously phenotyped
    - Antibody screen
- U&Es, LFTs, bone profile, LDH
- B12, folate, iron studies
- Vitamin D
- Virology
    - Hepatitis B surface antigen and antibody – all
    - Hepatitis C if transfused, from high risk area or high risk activity
    - HIV if transfused, from high risk area or high risk activity
- Urine protein/creatinine ratio

Discuss

1. Management plan
2. Any patient queries or concerns

Provide/Organise/Prescribe
1. Penicillin V and folic acid
2. Other medications as required – see Appendix 1 (hydroxycarbamide)
3. Immunisations
4. Haemoglobinopathy card
5. Contact details for the hospital, including clinical nurse specialist and consultant
6. Splenectomy/hyposplenism instructions +/- card
7. Referral to any other specialist as required
8. GP information flyer and Patient information leaflets
10. Consent for NHR
11. Follow-up appointment

9.5 Routine follow-up appointment

Visit frequency
The majority of patients are seen twice yearly, and one of these visits will be a comprehensive annual review. Patients with complex medical needs, those requiring chelation, or who are taking hydroxycarbamide and need regular blood monitoring will be seen more frequently.

Assessment for each visit

1. History and examination as appropriate
2. Record significant events in notes – clinical, psychosocial etc
3. Medication and allergies
4. Height, weight, BMI
5. Urinalysis
6. Urine protein/creatinine ratio if proteinuria
7. Routine blood tests
    - FBC, reticulocytes
    - U&Es, LFTs, LDH
    - Ferritin if on transfusion programme
    - Vitamin D (if not done previously)
    - Haemoglobinopathy screen if not done previously or if recently transfused
    - G6PD if not done previously
    - Full red cell phenotype if not recorded
    - Antibody screen if recently transfused (antibodies may disappear with time, so important to "capture" them when likely to be detectable)

9.6 Annual Review

This is a more comprehensive visit and should cover psychosocial issues, discussion of research or new therapies and genetic counselling. It also incorporates the dataset outlined by the National Haemoglobinopathy Registry.

Consent for National Haemoglobinopathy Registry
- Patient information leaflet
- Enter registry consent onto patient database
- Written consent not required

Crises – state where treated
- Number of crises during review period
- Number of admissions during review period
- Days off school or work during review period

Clinical examination to include height, weight and BMI

Yearly investigation review and results
- Ophthalmology
- Echocardiography
- Lung function tests
- Trans-cranial Doppler (<18years only)
- HIV, HCV, HBsAb, HbSAg (verbal consent) – if regularly transfused
- Audiology and electroretinography if on desferrioxamine
- Urine protein/creatinine ratio if on Deferasirox

Counselling – lifestyle issues, genetic counselling, education

Transfusion history
- Ad hoc/acute – state indication, where transfused and any complications
- Long term transfusion regimen
- Record any new antibodies

Immunisations – state date last given
- Pneumococcal
- Influenza
- Hepatitis B
- Haemophilus influenza type B
- Meningococcal B, C, ACWY
- Others

Serious adverse events
- ITU admission
- Acute chest syndrome
- Stroke
- Pneumococcal infection
- Other bacteraemia
- Renal dysfunction requiring dialysis
- Pulmonary hypertension

Pregnancy
- Outcomes – sickle problems, obstetric and medical complications, transfusions, mode of delivery, birth outcome (eg. live birth) etc

9.7 Phlebotomy service

- The phlebotomy service is located in the Haematology Department, 5th Floor of the Diagnostic Block, opening hours 8.30am to 4.30pm, Monday to Friday.

  A phlebotomy service is also available in Clinic 3B for all haematology clinics.

- Patients on Hydroxycarbamide can have their blood test on arrival to clinic with results ready within 10-15 minutes.

Sometimes it may be appropriate for patients with difficult venous access or indwelling central venous catheters to have their bloods performed in the Thalassaemia Unit. This is at the discretion of the Thalassaemia Unit nurses.

10.0 DAY CARE SERVICES

10.1 Introduction

- Day care facilities on the Thalassaemia Unit are available only to sickle cell patients on regular or intermittent blood transfusions due to limited space.

- Services provided in the Thalassaemia Unit include:
  - Blood tests
  - Blood transfusion
  - Red cell exchange transfusion (manual)
  - Advice over the telephone where appropriate
  - Management of indwelling lines e.g. Port-a-caths.
  - Clinical review of patients at the discretion of the haematology registrars or consultants. Please inform Emma Prescott or Niamh Malone about any such reviews so the patient can be accommodated.

- Patients may also be seen in the Ambulatory Care Unit at the discretion of the Ambulatory Care and Haematology teams. Referrals to Ambulatory Care should be made on Anglia ICE after discussion with the Haematology team and the Ambulatory Care consultant on call.

10.2 Unwell patients

- Patients should be advised to attend A&E if they are unwell.

- Patients who are taken ill whilst on the Thalassaemia Unit will be reviewed by the registrars and/or consultants. Those requiring admission will be transferred to the care of the medical on-take team in A&E after discussion with the DMR.

10.3 Prescriptions

- Ad hoc prescriptions may be issued from the Thalassaemia Unit at the discretion of the doctors, however in general routine prescriptions should be obtained from a patient's General Practitioner.

10.4 Staffing

The Thalassaemia Unit is staffed by a team of experienced nurse specialists and other staff. The haematology registrars and consultants provide medical cover.

10.5 Location and opening times

- The Thalassaemia Unit is situated on the 4th Floor of the new hospital wing and is adjacent to Mercers Ward and the Chemotherapy Suite.

- The Thalassaemia Unit is open Monday to Sunday from 9.00am to 5pm. There is an overnight transfusion service which is available for thalassaemia patients only.

- If an elective exchange transfusion overruns, the patient must be transferred to Victoria Ward for completion of the procedure. Elective weekend exchange transfusions can occasionally be arranged at the discretion of Emma Prescott or Niamh Malone.

11.0 TRAVEL

11.1 General Arrangements

- Travel can lead due to an increased risk of crises due to thrombosis, infection, fatigue, dehydration and climate change.
- Sickle cell patients wishing to travel abroad must be encouraged to inform their consultant well in advance of the trip, so that appropriate preparation can be undertaken, particularly in relation to travel letters, air travel, insurance, immunisations and malaria chemoprophylaxis.

11.2 Long distance Travel

- Patient should be advised to keep well hydrated and mobile (walk around at least every half hour where possible), and not to drink alcohol
- Most SCD patients do not need O2 in a pressurised aircraft. Assist patients to complete relevant forms for airlines if they request oxygen, but different airlines have different rules (some carriers will not accept sickle cell patients requesting oxygen).
- Some patients with chronic lung disease will require oxygen on the flight.
- There is a possible increased risk of splenic infarction from air travel, and this should be considered in patients with left hypochondrial pain.

11.3 Travel Insurance

- Patients should obtain travel insurance, declaring their sickle cell disease and recent admissions. The Sickle Cell Society can provide details of willing insurers.

11.4 Medications for Travel

Antibiotics

- Standard penicillin prophylaxis
- Patients should have a 'rescue pack' of antibiotics available
- Advise to seek treatment for dog bites (e.g. C canimorsus infection) and tick bites (e.g. Babeosis infection)
- Seek early treatment for other infections and diarrhoea
- Explain hyposplenic state

Anti-Malarials

- Sickle cell patients are at increased risk of malaria, even if previously resident in malarial area
- Protective clothing, insect repellent and mosquito nets should be used
- Prophylactic anti-malarials are essential. These should be started two weeks before travel if not taken before to ensure tolerability of the drug
- Advise to carry curative anti-malarials (e.g. quinine) if staying far from medical care facility.
- Check G6PD status

12.0 CONTACTS

Name	Telephone/Email
Dr Bernard Davis* Consultant Haematologist (Lead, Adult Sickle Services)	020 7288 5437 bernard.davis1@nhs.net
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Deborah Wellington Family Psychotherapist	deborahwellington@nhs.net

***OUT OF HOURS: VIA HOSPITAL SWITCHBOARD 020 7272 3070**

Referral Pathways

Clinical Problem	Named Consultant
Acute stroke (via UCLH HASU)	Dr David Werring (UCLH)
Neurology (not stroke)	Dr Katie Sidle
Upper GI Surgery	Mr Hasan Mukhtar
Colorectal Surgery	Mr Hasan Mukhtar
Dental	Dr Navdeep Kumar (UCLH)
Hepatology (iron)	Dr Deepak Suri
Hepatology (viruses)	Prof. Geoff Dusheiko (RFH)
Gynaecology	Miss Amma Kyei-Mensah
Obstetrics	Miss Amma Kyei-Mensah
Fertility	Mr Gidon Lieberman
Leg ulcers	Matty Asante-Owusu
Acute pain	Dr Samina Ishaq
Chronic pain	Dr Roman Cregg (UCLH)
Orthopaedics – Hips	Mr Ian Bacarese-Hamilton
Knees	Mr Harry Charalambides
Shoulders	Mr Omar Haddo
Urology and Andrology	Mr Suks Minhas (UCLH)
Cardiology	Dr Malcolm Walker (UCLH)
Endocrinology	Dr Karen Anthony
Diabetes	Dr Maria Barnard
Anaesthetics	Dr Catherine Shaw
Renal	Dr Mark Harber

13.0 REFERENCES used in production of guideline

Cullis, J. O., N. Win, et al. (1995). "Post-transfusion hyperhaemolysis in a patient with sickle cell disease: use of steroids and intravenous immunoglobulin to prevent further red cell destruction." Vox Sang **69**(4): 355-357.

Porter, J. B. and E. R. Huehns (1987). "Transfusion and exchange transfusion in sickle cell anaemias, with particular reference to iron metabolism." Acta Haematol **78**(2-3): 198-205.

Society, S. C. (2008). Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK**:** 112.

Talano, J. A., C. A. Hillery, et al. (2003). "Delayed hemolytic transfusion reaction/hyperhemolysis syndrome in children with sickle cell disease." Pediatrics **111**(6 Pt 1): e661-665.

Win, N., H. New, et al. (2008). "Hyperhemolysis syndrome in sickle cell disease: case report (recurrent episode) and literature review." Transfusion **48**(6): 1231-1238.

Win, N., T. Yeghen, et al. (2004). "Use of intravenous immunoglobulin and intravenous methylprednisolone in hyperhaemolysis syndrome in sickle cell disease." Hematology **9**(5-6): 433-436.

Rees, D.C., A.D. Olujohungbe et al. (2003). "Guidelines on the management of the acute painful crisis in sickle cell disease." British Journal of Haematology **120**: 744-752,

NHLBI (2014) Evidence-Based Management of Sickle Cell Disease: Expert Panel Report, 2014. National Heart, Lung, and Blood Institute, Bethesda, MD.

Howard, J., Hart, N., Roberts-Harewood, M., Cummins, M., Awogbade, M., Davis, B. & Committee, B. (2015) Guideline on the management of acute chest syndrome in sickle cell disease. British Journal of Haematology, **169**, 492-505.

Standards for the Clinical Care of Adults with Sickle Cell Disease, 2008 (Sickle Cell Society)

A Sickle Crisis? A Report of the National Confidential Enquiry into Patient Outcome and Death, 2008 (NCEPOD)

Sickle Cell Disease in Childhood: Standards and Guidelines for Clinical Care, 2010 (NHS Sickle Cell and Thalassaemia Screening Programme)

Caring for People with Sickle Cell Disease and Thalassaemia Syndromes. A Framework for Nursing Staff, 2011 (Royal College of Nursing)

Quality Standards: Health Services for People with Haemoglobin Disorders Version 2.1 (WMQRS 2014)

Guidelines for the management of the acute painful crisis in sickle cell disease, 2003 (British Journal of Haematology 2003, 120:744-752)

Sickle cell acute painful episode: management of an acute painful sickle cell episode in hospital. (NICE clinical guideline 143, 2012)

14.0 APPENDICES

14.1 - Appendix 1 Hydroxycarbamide (Hydroxyurea) Protocol

Indications:
Adults and children with Sickle Cell Disease who have any of the following:
- >3 admissions with painful crises in the previous 12 months, or
- >1 admission with painful crisis in the previous 12 months, and are symptomatic in the community, or
- >1 life threatening complications of the disease, such as acute chest syndrome, or
- Other indications (such as secondary stroke prevention, pulmonary hypertension) - must be discussed with the consultant in charge of the patient.

Exclusions:
- Pregnancy or not practicing active contraception (if sexually active)
- Active hepatitis

Requirements
- Discuss the possible risks of infertility with male patients and offer sperm count and banking before commencement of the drug.
- Warn patient that hydroxyurea can cause darkening of finger and toe nails. This is a cosmetic blemish and is not dangerous.
- Informed written consent
- Give Hydroxycarbamide patient information leaflet

Regimen details:
- Commence at 15mg/kg once daily to nearest 500mg if an adult as capsules only come in 500mg.
- Children less than 50kg should be given the exact dose to start; they can be given the liquid formulation. This has to be ordered in especially by pharmacy.
- The liquid formulation may also be used for selected adult patients
- Note that there is a very short expiry on the liquid (4-6 weeks) so children and adults should be given tablets where possible.
- If there is a good clinical response, continue on this dose (Minimal effective dose)
- If clinical response is sub-optimal, increase by 2.5 - 5mg/kg every 4 weeks until clinical response achieved or toxicity seen.
- Most people tolerate a maximum dose of 35mg/Kg daily.

Toxicity:
Neutrophils < 1.0 x 10^9/l
Platelets < 80 x 10^9/l
Reticulocytes < 10 x 10^9/l
Haemoglobin <20g/l from baseline

- These are not absolute and if concerns discuss with Consultant.
- If any of the above problems with FBC are encountered, stop hydroxycarbamide, until full blood count has recovered. Restart at 2.5mg/kg (or 1 capsule – 500mg) lower than the previous toxic dose. This is the maximum tolerated dose (MTD)

Caution:
- If there is a significant rise in Hb (e.g. >110g/l) decrease the hydroxycarbamide or consider venesection because of the risk of hyperviscosity.
- If there is a downward trend in FBC parameters, increase frequency of monitoring
- Use with caution in renal impairment: start at a lower dose and increment more cautiously

- If Creatinine Clearance < 60ml/min, commence at 50% dose (7.5mg/kg)

Administration:
Orally. Available as 500mg strength tablets or liquid formulation.
Note: liquid formulation is expensive and has short shelf life. It is therefore much more desirable for patients to be taking tablets.

Frequency:
Continuous

Extravasation:
N/A

Regular investigations:
- Fbc and reticulocytes
- Haemoglobinopathy screen (%HbF)
- U+Es and LFTs
- Urate
- LDH

14.2 – Appendix 2

Emergency, Isovolaemic, Manual Red Cell Exchange Transfusion in Adults with Sickle Cell Disease

Governance
All exchange transfusion procedures should be carried out by trained staff under the authorisation of a consultant haematologist.

The number of red cell units transfused and post-transfusion targets will be decided by the attending consultant haematologist.

Preparation
- Blood tests – FBC, reticulocytes, U&Es, LFT, LDH
- Crossmatch 8 units of blood
- Secure high flow venous access – either multi-lumen standard central line or Vascath, or two large bore peripheral vein cannulae (one on each arm, minimum grey (16G) Venflon).
- Prepare equipment as described below:

Equipment required:
- sterile gloves x 1 pair per venesection
- disposable apron x 1 per venesection
- saline 0.9% (500ml or as prescribed)
- 1 x fluid administration set
- drip stand
- sterile dressing pack and sterile dressing towel
- venesection bags x 1 per venesection (obtained from Blood Bank)
- blood administration sets (to be changed after every third unit or after 12 hours)
- bung with injectable membrane (Vygon) x 1 per venesection
- Sani-Cloth 2% wipes x 4 per venesection
- 10 ml syringes (luer lock) x 2 per venesection
- 19G needles
- saline 0.9% 10ml x 1 per venesection
- heparin sodium flushing solution 100iu/ml (8ml per venesection)
- blood units as required
- blood weighing scales (located in thalassaemia unit)

Procedure (for total exchange transfusion via central/femoral line).

- check blood units have been issued and exchange transfusion prescribed
- identify correct patient
- explain procedure to patient and gain consent
- ensure patient in comfortable position
- baseline observations (temperature, pulse, blood pressure, oxygen saturations and respiration rate)
- clean dressing trolley and gather equipment as required
- apply apron and wash hands thoroughly
- open dressing pack, sterile gloves, bungs, syringes, needles, wipes, heparin and 0.9% saline 10ml
- prime fluid administration set with saline 0.9% 500ml (or as prescribed)
- repeat hand washing
- apply sterile gloves

- place sterile paper towel under central / femoral line lumens
- identify proximal lumen (shorter lumen), clean with Sani-Cloth wipe and attach saline 0.9% 500ml (or as prescribed)
- infuse saline 0.9% at prescribed rate (usually 30 minutes)
- once saline infusion completed repeat hand washing and apply clean pair of sterile gloves
- identify distal lumen (longer lumen) and attach sterile bung
- clean bung with Sani-Cloth and flush lumen with 8ml saline 0.9%
- insert venesection bag needle into injectable membrane on bung
- ensure venesection bag is lower in position than patient to allow gravity flow
- observe patient throughout
- weigh venesection bag and disconnect when 620ml (500ml plus 120ml bag weight), clamp, sheath needle, cut tube below needle, dispose of needle into sharps bin and 'double bag' venesected blood (yellow bags)
- clean bung with Sani-Cloth wipe and flush lumen with 8ml heparin sodium 100iu/ml, clamp lumen
- check blood unit as per hospital transfusion policy
- prime blood administration set
- clean proximal lumen (shorter lumen) with Sani-Cloth wipe and attach blood administration set
- infuse as prescribed, regular observations as per hospital transfusion policy
- document volume venesected and blood volume transfused
- repeat procedure as prescribed
- once exchange transfusion completed flush both lumens with sodium heparin 8ml (100iu/ml)

Summary of total manual exchange procedure (for standard '3units in, 4 units out' procedure)

- Infuse 500 ml of 0.9% saline over 30 minutes
- Venesect 500 ml of blood over 15-30 minutes
- Transfuse 1st unit of blood over 30-40 minutes
- Venesect 500 ml of blood over 15-30 minutes
- Transfuse 2nd unit of blood over 1 hour
- Venesect 500 ml of blood over 15-30 minutes
- Transfuse 3rd unit of blood over 2 hours
- Venesect 1 unit of blood over 15-30 minutes
- Make up any shortfall in fluid balance with 0.9% saline.

Assess clinical response, check FBC and %HbS and discuss with haematology.

Further exchange transfusion:
Continue above cycle without interruption if insufficient clinical improvement or reduction in %HbS. Above cycle can be repeated the following day if good clinical response to first cycle

Following each exchange transfusion cycle, assess clinical response, check %HbS and discuss with haematology.

On call haematologist will advise on further steps as appropriate to achieve desired final Hb and %HbS.

Key points to note

- If pre-transfusion Hb <60 g/l, give top up transfusion first to Hb 80-100 g/l. Formal exchange transfusion will be required if insufficient clinical improvement despite initial top up transfusion.
- Ensure that the blood to be transfused is set up before venesecting the patient, to avoid hypotensive emergencies and to ensure a degree of warming of the blood prior to transfusion.
- The procedure should be performed more slowly than described in patients with significant renal or cardiac abnormalities, or if acutely cardiovascularly unstable.
- The patient should be kept in overall fluid balance throughout the procedure. This may require the infusion of additional saline.
- Always request a haemoglobin S % pre and post exchange, to gauge efficacy of the exchange transfusion.

Appendix 3 – Duties and Responsibilities

3.1 Expectations

- It is the responsibility of the patient's consultant to ensure that members of his/her team are managing patients in accordance with these guidelines
- It is the responsibility of the nurse in charge to ensure that his/her team are managing patients in accordance with these guidelines
- Where patients are not admitted under the haematology team, it is the responsibility of the consultant of the admitting team to inform the haematology team of the patient's attendance. This may be delegated. All admitted patients on outlying wards should be jointly managed with the haematology team.
- Where unsure about diagnosis or treatment decisions it is the responsibility of the nurse or doctor to escalate until there is a satisfactory outcome.

3.2 Specific responsibilities of individuals

- All patients with sickle cell disease should be reviewed every day by the haematology registrars or by the on-call SHO at weekends.
- The haematology registrars should contact the consultant at the end of the ward round or earlier if required to apprise them of the clinical situation
- The haematology consultants will review all patients on scheduled consultant ward rounds (twice a week). In addition, the haematology consultants will be available to review individual patients as frequently as is dictated by their clinical needs.
- If the haematology registrars are away appropriate handover and cover must be organised and the consultants informed.
- The haematology registrars are expected to keep a list of tests and investigations ordered on the patients, to chase up the results and act upon them in a timely manner. If they are on leave, then this must be handed over.

To be completed and attached to any procedural document when submitted to the appropriate committee for consideration and approval

		Yes/No	Comments
1.	**Does the procedural document affect one group less or more favourably than another on the basis of:**		
	• Race	No	
	• Ethnic origins (including gypsies and travellers)	No	
	• Nationality	No	
	• Gender	No	
	• Culture	No	
	• Religion or belief	No	
	• Sexual orientation including lesbian, gay and bisexual people	No	
	• Age	No	
	• Disability - learning disabilities, physical disability, sensory impairment and mental health problems	No	
2.	**Is there any evidence that some groups are affected differently?**	No	
3.	**If you have identified potential discrimination, are any exceptions valid, legal and/or justifiable?**	No	
4.	**Is the impact of the procedural document likely to be negative?**	No	
5.	**If so can the impact be avoided?**	N/A	
6.	**What alternatives are there to achieving the procedural document without the impact?**	N/A	
7.	**Can we reduce the impact by taking different action?**	N/A	

If you have identified a potential discriminatory impact of this procedural document, please refer it to the Director of Human Resources, together with any suggestions as to the action required to avoid/reduce this impact.
For advice in respect of answering the above questions, please contact the Director of Human Resources.

Checklist for the Review and Approval of Procedural Document

To be completed and attached to any procedural document when submitted to the relevant committee for consideration and approval.

	Title of document being reviewed:	Yes/No	Comments
1.	**Title**		
	Is the title clear and unambiguous?	Yes	
	Is it clear whether the document is a guideline, policy, protocol or standard?	Yes	
2.	**Rationale**		
	Are reasons for development of the document stated?	Yes	
3.	**Development Process**		
	Is it clear that the relevant people/groups have been involved in the development of the document?	Yes	
	Are people involved in the development?	Yes	
	Is there evidence of consultation with stakeholders and users?	Yes	
4.	**Content**		
	Is the objective of the document clear?	Yes	
	Is the target population clear and unambiguous?	Yes	
	Are the intended outcomes described?	Yes	
5.	**Evidence Base**		
	Are key references cited in full?	N/A	
	Are supporting documents referenced?	N/A	
6.	**Approval**		
	Does the document identify which committee/ group will approve it?	Yes	
7.	**Dissemination and Implementation**		
	Is there an outline/plan to identify how this will be done?	Yes	
8.	**Document Control**		
	Does the document identify where it will be held?	Yes	
9.	**Process to Monitor Compliance and Effectiveness**		
	Are there measurable standards or KPIs to support the monitoring of compliance with and	Yes	

	Title of document being reviewed:	Yes/No	Comments
	effectiveness of the document?		
	Is there a plan to review or audit compliance with the document?	Yes	
10.	**Review Date**		
	Is the review date identified?	Yes	
	Is the frequency of review identified? If so is it acceptable?	Yes	
11.	**Overall Responsibility for the Document**		
	Is it clear who will be responsible for co-ordinating the dissemination, implementation and review of the document?	Yes	

Executive Sponsor Approval			
If you approve the document, please sign and date it and forward to the author. Procedural documents will not be forwarded for ratification without Executive Sponsor Approval			
Name		Date	
Signature			
Relevant Committee Approval			
The Director of Nursing and Patient Experience's signature below confirms that this procedural document was ratified by the appropriate Governance Committee.			
Name		Date	
Signature			
Responsible Committee Approval – only applies to reviewed procedural documents with minor changes			
The Committee Chair's signature below confirms that this procedural document was ratified by the responsible Committee			
Name		Date	
Name of Committee		Name & role of Committee Chair	
Signature			

Tool to Develop Monitoring Arrangements for Policies and guidelines

What key element(s) need(s) monitoring as per local approved policy or guidance?	Who will lead on this aspect of monitoring? Name the lead and what is the role of the multidisciplinary team or others if any.	What tool will be used to monitor/check/observe/Assess/inspect/ authenticate that everything is working according to this key element from the approved policy?	How often is the need to monitor each element? How often is the need complete a report ? How often is the need to share the report?	What committee will the completed report go to?
Element to be monitored	**Lead**	**Tool**	**Frequency**	**Reporting arrangements**
Care of sickle cell inpatients – adherence to section 3 and section 4 of guidelines, and appropriate referral.	**Dr Bernard Davis**	**Audit**	**Two-yearly**	**Haematology internal meeting**