THALASSAEMIA INTERNATIONAL FEDERATION

Guideline for the Emergency Department for the acute treatment of patients with Sickle Cell Disease

THALIA

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This publication is based on the "Guidelines for Adults with Sickle Cell Disease: Acute Presentation", as developed by University Hospitals of Leicester. Authored by Dr. Amy Webster, Consultant Haematologist and Clinical Lead for the East Midlands Sickle Cell and Thalassaemia Network (EMSTN).

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1. Introduction and Who the Guideline applies to

This guideline outlines the management of patients with sickle cell disease who are admitted acutely to hospital. Sickle cell disease includes HbSS and compound heterozygous states including HbSC and HbS β thalassaemia. The commonest reason for admission to hospital is acute pain, which can occur in any part of the body, in adults most often affects the waist, back, and / or limbs. Sickle pain is usually very severe and often requires opiate analgesia. Patients often have analgesia at home which they take before coming into hospital and can often describe if this is their 'usual' sickle pain.

The pathogenesis of sickle cell pain is thought to be due to deoxygenated sickle haemoglobin forming large polymers which cause red cells to become deformed and obstruct small blood vessels; neutrophils, platelets, and endothelium also contribute to the 'vaso-occlusion'. Triggering factors include fever / infection, cold weather, dehydration, stress and pregnancy, but often no cause is found.

These guidelines may be used by medical and nursing staff in any clinical area. They outline the care of patients admitted with acute complications of sickle cell disease.

Any admission of a patient with sickle cell disease should be discussed with the Attending Team .

2. Guideline Standards and Procedures

This guideline outlines the management of patients with sickle cell disease presenting with acute complications. As described, the commonest reason for admission is acute pain but other, potentially life threatening complications are also discussed.

- A summary of this guideline document is available in Appendix 1

Arrangement for admission

- All patients known to the service should have been made aware of how to contact the clinical teams for advice, including out of hours. Each hospital will have their own system for ensuring open access for urgent medical review.

Immediate assessment

- Baseline observations including pulse, blood pressure, temperature and respiratory rate must be performed as standard and documented.
- If opiates have been administered by the ambulance crew, this MUST be documented clearly.
- Baseline oxygen saturations must be documented ON AIR. If <95%, supplementary oxygen should be given by mask or nasal prongs. Repeat saturation monitoring should be recorded with the mask / prongs OFF for ~ a minute.
- If $SpO_{2\ is}$ ≤ 94% on air or there is a fall in SpO_2 of 3% or more from baseline, arterial blood gases should be performed with urgent escalation to more senior medical opinion to assess for acute chest syndrome.
- Suspected sepsis should be managed in line with local policy

1. Acute Painful episode

1.1 Pain management

- A pain score MUST be documented. Analgesia should be addressed as a priority and **analgesia must be administered within 30 minutes of admission.**
- IV access is NOT mandated in all patients and delays for attempted cannulation is not an acceptable reason for not meeting this target.
- Entonox may be required until the first dose of analgesia is administered but must not be continued after opiate analgesia has been given.
- Individualised care plans may be available on local hospital systems. If unavailable, patients should be managed as per a painful crisis flowchart (an example is given in Appendix 2).
- If the pain is their 'usual sickle pain', patients will often have taken their own analgesia at home. This should be taken into consideration when prescribing analgesia. Opiate analgesia is most often required, providing baseline observations are stable.
- Opiate naïve patients should be assessed based on their pain score and analgesia offered in line with the WHO analgesic ladder (below):

Step 1: mild pain
Non-opioid ± adjuvant: Paracetamol 500mg-1000mg + Ibuprofen 400mg TDS or equivalent non-steroidal anti-inflammatory drug. Do not give NSAIDs if there is renal impairment.
Step 2: moderate pain
Weak opioid (or low dose of strong opioid) ± non-opioid ± adjuvant: As above for mild pain + Dihydrocodeine 30-60mg (maximum dose 180mg daily)
Step 3: severe pain
Strong opioid ± non-opioid ± adjuvant As above for moderate pain + Morphine sulphate (see text)

- For severe pain, there are a number of strong opioid regimens in use *[could refer to our Pain chapter on HCP platform here].* For simplicity, this guideline uses an intermittent subcutaneous morphine regimen. Some patients, including those recently transitioned from paediatric care, may prefer oral morphine and this should be encouraged. Intravenous morphine is not recommended as routine.

- **<u>If the patient does not have a dedicated analgesia plan, then give based on weight:</u>**
    - If ≤50kg, give 5mg morphine sulphate SC stat
    - If >50kg, give 10mg morphine sulphate SC*:*

Patient's weight [kg]	*Initial dose subcut morphine [mg]*
40	*8*
50	*10*
60	*12*
70	*14*
<u>></u>75	*15*

For patients who are opiate naïve, or whose drug history is unknown, start towards the lower end of the dose range. Efficacy of analgesia should be assessed after **30 – 60 minutes** and a further dose of SC morphine administered provided that there is no evidence of opioid toxicity. The second and ongoing doses are usually slightly lower at 0.1 - 0.15 mg/kg, but **are tailored to the individual patient's response on this occasion.** Higher doses may be required in people who more frequently use opiate analgesia.

- If the RR is <10 per minute, omit opioid analgesia
- If RR < 8, give naloxone 100microgram every 2 minutes as necessary

Pain should then be reassessed every 30 minutes until adequate pain control achieved.

If pain control is inadequate despite 2 doses of morphine:

- Discuss the case with the Attending Team.
- Consider changing to patient controlled analgesia where available
- Consider alternative causes of pain if out of context with 'usual' sickle pain.
- Once pain is controlled, regular adjunct analgesia and PRN opiate analgesia (morphine 0.05- 0.1mcg/kg to nearest mg every 3 hours) should be prescribed.

Adjunct analgesia	
Paracetamol 1gram IV/PO	Up to 4 gram in 24 hours
Ibuprofen 400mg PO	Up to maximum dose of TDS unless contraindicated (such as patients with renal impairment)
Dihydrocodeine 30-60mg PO	Up to maximum dose of 180mg daily
Lidocaine 5% topical patches to the affected area	Offer to all patients unless contraindicated
Non-pharmacological methods: Local heat packs TENS machine	 May be available from haemoglobinopathy team If available

Alternative analgesics such as oxycodone, ketamine, methadone and fentanyl should only be used after discussion with a senior member of the Attending Team. unless specifically indicated in the patients care plan documentation. Pethidine should not be used because of the risk of seizures.

Requirements for analgesia should be reconsidered with the patient on at least a daily basis by nursing and medical staff.

1.2 Adjunct medication

Antipruritics:

- Prescribe PRN chlorphenamine 4mg 6 hourly PO or hydroxyzine 25mg two – three times daily

Antiemetics:

- First line: Ondansetron 4mg BD IV/PO
- IV cyclizine use should be avoided

Laxatives:

- Ensure regular laxatives are prescribed if on regular morphine. Patient's choice should be taken into consideration.

Stomach protection:

Give concurrent PPI (Lansoprazole 30mg) if on NSAIDs Oxygen:

- There is no evidence for this being used routinely in call cases of painful crisis, although some patients find it comforting.
- Its use should be dictated by the clinical situation and oxygen saturations
    - If sats ≤ 95% on air, give supplementary oxygen to maintain at 98% or above
    - If sats ≤94% on air, or 3% lower than the patient's baseline, perform ABG and give supplementary oxygen to maintain sats 98% or above

If sats are < 94% on air in a patient whose usual levels are normal, or there is increasing oxygen requirement, urgent medical review is required to assess for acute chest syndrome

Antibiotics.

- Most patients will be on long term prophylaxis with penicillin 250mg BD [or erythromycin if penicillin allergic].. If admitted and therapeutic antibiotics are not required, these should continue
- If there is fever or other signs of infection, broader spectrum antibiotics should be started after taking the relevant specimens for microbiology investigation [see Other Considerations section below].

1.3 Baseline Investigations

- Blood tests: FBC, Reticulocytes, Biochemistry (U&Es, LFTs, LDH, CRP), group and save serum G&SS
- Reasonable attempts should be made to perform baseline investigations in admission area. If unsuccessful due to difficult venous access this can be deferred until the patient is admitted and settled after analgesia, **unless more urgent results are clinically indicated.**
- Haemoglobin electrophoresis only indicated if a new patient or patient recently transfusedIf recently transfused (within 12 weeks), also request DAT (via blood bank)
- If appropriate: Blood cultures, Urine dipstick +/- MSU, Throat swabs (if viral symptoms), viral serology, COVID swab
- CXR **not** routinely required: perform if there is dyspnoea, cough, fever or chest pain, O2 sats <95%, increased respiratory rate, , with or without focal chest signs on auscultation.
- It is not helpful to X ray bones and joints which are the site of pain; this may become necessary later if there is persistent fever and failure for symptoms to resolve, raising the possibility of osteomyelitis or septic arthritis

1.4 Other considerations

Hydration:

- Not all patients require IV fluids but all patients should be on a fluid balance chart and supplementary fluids given if necessary
- Those who cannot take plentiful oral fluids will often require additional fluid supplementation; this can be ng or iv.
- Fluid requirements should be individualised and be guided by the patient's fluid balance and cardiopulmonary status. Care must be taken to avoiding fluid overload and the development of acute pulmonary oedema. Accurate monitoring is necessary, using a fluid balance chart of input and output with a daily target.

Antibiotics:

- If the patient is febrile or has a history suggestive of an infective cause of the sickle cell crisis they should be commenced on antibiotics in line with the local microbiology guidelines. Do not wait for the results of cultures and other microbiology tests before commencing them.

Thromboprophylaxis:

- Sickle cell disorders are associated with an increased risk of thrombotic complications
- All patients should be VTE assessed on admission and offered LMWH prophylaxis, unless contraindicated
- Anti-embolic stockings are uncomfortable, and are not required in addition to chemoprophylaxis.

Transfusion:

- See local transfusion guidelines ..
- Any transfusion in sickle cell patients, other than for life threatening haemorrhage, should be discussed with the a senior member of the Attending Team, and ideally also with the Haematology team.

Ongoing patient monitoring:

- Observations should be carried out every half hour until pain is controlled.
- Sedation score, respiratory rate and O2 saturation should be checked 1-2 hourly while on opiate analgesia.
- Temperature, BP and pulse rate, and fluid balance should be reviewed 4 hourly.

2. Other acute presentations

2.1 Acute Chest Syndrome (ACS)

This is a life threatening complication of sickle cell disease and can arise during a painful crisis or occur on admission.

Clinical Features - some, but not all, of the following may be present:

Symptoms:

- Feeling short of breath
- Chest pain
- Cough

Signs:

- Raised respiratory rate
- Raised pulse rate
- Fever
- Wheeze
- Crackles or bronchial breathing on auscultation of the chest
- Hypoxia [sats <95% or $\underline{\geq}$ 3% lower than the person's usual level
- Fall in haemoglobin level

Differential Diagnosis:
Acute Infection (including COVID-19 infection)
Pulmonary Embolism
Opiate Toxicity
Fluid overload
Hypoventilation due to pain
Asthma exacerbation

Diagnosis and Investigations

Based on:

- Clinical suspicion (low sats, hypoxia, new chest signs)
- CXR: new pulmonary infiltrate – this defines the condition.
-
- Perform baseline investigations (as above)
- Microbiology: blood and sputum culture, l serology for 'atypical' organisms esp mycoplasma, flu swabs (if applicable)

Management

- Preventative measures:
    - Vigilance
    - Incentive spirometry for all patient if chest/rib pain on admission (and use as adjunct to treatment)
    - Early treatment of pain and infection with careful monitoring for opioid toxicity
    - Careful hydration management to avoid fluid overload
    -
- Intervention if ACS suspected:
    - Inform senior member of Attending Team (if not already aware)
    - Early liaison with HDU/outreach team as transfer to Critical Care may be necessary, for intensive monitoring and assisted ventilation.
    - Start appropriate antibiotics to include atypical cover – include a macrolide antibiotic
    - Chest physiotherapy
    - Nebulised bronchodilators may be useful

- Role of transfusion:
    - Simple top up may be adequate initially, especially if Hb significantly decreased from baseline; aim for the person's own steady state Hb level
    - Urgent manual or automated exchange transfusion is indicated in deteriorating patient or risk of hyperviscosity due to baseline Hb (see transfusion guidelines)

2.2 Acute Anaemia

- Presentation with pallor, extreme lethargy, and / or shortness of breath
- Investigations: FBC and reticulocytes, usual biochemistry, plus parvovirus serology and urgent request red cell units for transfusion
- Consider underlying pathology including parvovirus infection – which causes transient red cell aplasia, sequestration [liver or spleen], iron or folate deficiency or acute oxidative haemolysis if known G6PD deficiency. Screen for delayed haemolytic transfusion reaction / hyperhaemolysis if transfusion within the preceding 28 days [samples to Transfusion Department].
- Check parvovirus PCR if serology negative and high clinical suspicion.
- Especially if the reticulocyte count is low, blood transfusion should be considered if the Hb declines by more than 20 g/l from the person's baseline, particularly for patients who are symptomatic or show any signs of cardiovascular compromise. The haemoglobin should be watched over several days as if red cell production remains very low, reflected by low reticulocyte count, a second transfusion is sometimes necessary

2.3 Acute Stroke

- May be ischaemic or haemorrhagic
- Patients should be assessed and initially managed in line with the local acute stroke guideline with urgent CT scan of the head, although in a person with sickle cell disease preparations for transfusion should take place simultaneously.
- Haemorrhagic stroke will usually be obvious on CT scan, but ischaemic lesions are often not seen until several hours after the event, and if the CT scan is negative, an MR scan should be requested at the earliest possible time. If clinical suspicion of acute ischaemic stroke is high, transfusion management should proceed even in the absence of radiological confirmation.
- Thrombolysis should be considered in sickle cell patients with acute cerebral thrombosis who otherwise meet current national recommendations, but these cases should be discussed with a senior haematologist and stroke physician
- Urgent exchange transfusion should be performed for acute ischaemic stroke to reduce HbS% to <30%. Acutely, this may need to be performed as a manual exchange with an automated exchange at the earliest opportunity.
- Exchange blood transfusion is not always indicated in acute haemorrhagic stroke, but may be necessary if GA intervention [for example for coiling of an aneurysm] is planned.
- Following acute intervention, an MRI/A head should be performed to assess for sickle related vasculopathy and determine long term management
- Other causes of stroke seen in adults without sickle cell disease should also be considered, especially in the older patient.

~~2.5~~2.4 Acute Sequestration

- Sudden enlargement of the spleen (or more rarely, liver) in which blood is pooled in the organ leading to a severe reduction in circulating red cells and profound anaemia. This is common in children but occasionally also occurs in adults
- Abdominal examination will reveal an enlarged spleen or liver
- Urgent FBC and retics followed by urgent request of red cell units for a 'top up' transfusion aiming for the person's baseline haemoglobin level.

~~2.6~~2.5 Abdominal Pain

Patients can present with abdominal pain for a number of reasons. The differential diagnosis includes (not exhaustive list):

Gallstones – cholecystitis or biliary colic	Referred pain	Acute splenic/hepatic sequestration
Pancreatitis	Appendicitis or other infection	Constipation
Splenic infarct / abscess	Thrombosis eg renal vein	Vaso-occlusion – 'mesenteric syndrome' causing bowel ischaemia

Investigations:

- FBC, retics, U&Es, LFTs, clotting screen, Amylase, Blood cultures, MSU
- Relevant imaging, as guided by clinical features/findings

~~2.7~~2.6 Priapism

Defined as a prolonged painful penile erection which is maintained without sexual stimulation and persists despite ejaculation and orgasm.

There are two types:

Stuttering (recurrent episodes lasting < 60mins)

Ischaemic fulminant (> 4 hours) – should be treated as a medical emergency.

Management of fulminant priapism

- Hydration, analgesia, encourage micturition
- Etilefrine 50mg may be given by mouth
- Urgent referral to on call urology team
- Aspiration of corpora cavernosa (with or without irrigation) may be required with the instillation of adrenergic agonist e.g phenylephrine, progressing to a surgical shunt procedure if not successful
- Transfusion therapy is not thought to be useful in acute presentation although it may be considered if all other treatment is ineffective and in preparation for surgery.

~~2.8~~2.7 Sepsis – including osteomyelitis

- Patients with sickle cell disease are immunocompromised and organisms more readily disseminate, causing bacteraemia and sepsis. Careful monitoring for this is essential in any patient who has fever and other signs of infection
- Osteomyelitis or septic arthritis should be considered in any patients with persistent fevers, and a continuingly hot and painful limb
- XR should be performed, but may be normal and MRI is likely to be required
- Blood cultures should be sent in any febrile patient, and local / joint aspiration considered.
- Microbiology advice should be sought for suspected cases to ensure adequate pathogen cover in line with local policy

~~2.9~~2.8 Renal complications

- Patients with sickle disease are at increased risk of nephropathy and renal impairment. Urinary tract infections are also common. U&Es and MSU / urine dipstick should be performed as part of baseline investigations for all patients presenting to hospital.
- Haematuria may occur and can be associated with papillary necrosis. This may be associated with ureteric colic and can lead to significant blood loss. Treatment is supportive and urological support may be required.
- Other causes of renal impairment and haematuria should also be considered.

~~2.10~~2.9 Visual loss

- Sickle cell disease is associated with retinopathy and any visual loss should be considered a medical emergency
- Patients should be advised to attend the nearest emergency department with an eye

casualty department, stressing the need to inform the assessing team that they have sickle cell disease, and requesting contact with their usual Haematology team as soon as possible for joined management.

Appendix 1

Flow Chart for management of acute sickle cell admission with painful crisis

Full baseline observations including respiratory rate, oxygen sats on air and documentation of pain score.

Administer analgesia in line with WHO analgesic ladder (Box A), within **30 minutes** of arrival

Re-assess after 20 minutes

Is pain adequately controlled?

N

Y

Box A: Management of pain: See patients individualised care plan (if available).

Mild pain: Offer paracetamol (0.5-1g) +/- dihydrocodeine 30-60mg +/- ibuprofen 200-400mg

Moderate/severe pain: Morphine sulphate SC first weight based dose – 0.2 mg/kg : see guideline page 4.

BOX B: General measures

For ALL patients:

Keep warm and well hydrated.

Avoid IV cannulation unless clinical need / inadequate oral fluid intake

Assess fluid status and commence fluid balance

Assess for sepsis and treat with antibiotics if indicated

Document patient's weight

BOX C: Routine Investigations

Bloods: FBC, U&E, reticulocytes, LFT, CRP, G&S

+/- cultures (if indicated)

Urine dipstick
+/- MC&S (if indicated)
+/- Pregnancy test (if indicated)

Imaging: CXR if dyspnoea, cough, chest pain, Sp02 <95%, fever, chest signs

Assess for opiate toxicity

RR<10 , new oxygen requirement or sats <95%, drowsy or pin point pupils

If none of the above are present, administer a 2nd dose of SC morphine sulphate at 0.1-0.15 mg/kg

Re-assess after 20 minutes

Is pain adequately controlled?

Y

N

Full patient assessment

History and clinical examination (to include potential triggers, infective signs/symptoms, history of sickle cell complications, transfusion history)

Continue general measures (Box B)

Complete routine investigations (Box C)

VTE risk assessment: Offer LMWH unless contra-indicated

Are there any features of a red flag event? See Box D

Y

N

Escalate to Haematology team:

- *Consult local policy for advice on contacting haematology in the trust.*
- If outside these hours or patient clinically unwell, call on-call haematology registrar via switchboard

BOX D: Red flag events (see overleaf for further details)

- Acute Chest Syndrome
- Aplastic Crisis
- Stroke
- Priapism
- Acute Abdomen
- Splenic Sequestration
- Suspected delayed haemolytic transfusion reaction

Ongoing assessment

Monitor observations every 30 minutes if morphine administered

If unable to tolerate oral fluids, start IV fluids at 10-20mls/kg

Ensure regular analgesia prescribed

Review results of investigations

Not for blood transfusion unless discussed with haematology

Acute Chest Syndrome

- Life threatening acute complication; defined by fever and/or respiratory symptoms in presence of new infiltrates on CXR. New hypoxia should trigger investigation (sats <95% air or >3% decline from baseline)
- Infective cause common and antibiotic therapy (including atypical cover) should be initiated
- Perform ABG if sats ≤94% **on air** or >3% decline from baseline. Discuss all hypoxic patients with a senior member of the Attending Team . Ensure routine investigations completed.
- Transfusion should be considered early (top up or exchange) and refer early for HDU/ITU input

Stroke

- Assess initially in line with local acute stroke and TIA guideline.
- Inform Haematology / Attending Team on arrival.
- Emergency management of acute ischaemic stroke in SCD patients includes:
    - Need for urgent exchange blood transfusion. Ensure G&SS has been sent as part of routine investigations to allow for efficient blood ordering.
    - Consideration of thrombolysis in patients who otherwise fulfil local criteria. All cases should be discussed with the Consultant on the Attending Team.

Priapism

- Defined as fulminant if > 4 hours duration
- Offer analgesia in line with acute painful crisis protocol; ensure hydration and encourage micturition
- Inform attending and urology teams on patient's arrival
- Give etilefrine 50mg PO stat (unless contraindicated)
- Consider aspiration of corpora cavernosa if persistent

Suspected Delayed Haemolytic transfusion reaction

- Sickle cell patients are at increased risk following transfusion
- Any patient presenting within 28 days after a transfusion with signs of a crisis should be investigated for evidence of DHTR.
    - May also present with symptoms of anaemia, jaundice +/- 'Coca-Cola' coloured urine
- In addition to routine investigations, request a Direct Antiglobulin Test (DAT) via blood bank
- Manage crisis in line with acute painful crisis protocol

Seek advice from Consultant Haematologist before giving any further transfusion

Acute Vision Loss

- Sickle cell patients are at increased risk of retinopathy
- Any patient experiencing symptoms of vision loss should be seen and assessed in Eye Casualty (or ED if not available) and managed jointly by Ophthalmology and the Attending Team.

Appendix 1: Guideline Summary (Quick Reference Guide)

Acute Presentation	Best Practice	Where can further guidance be found?
Pain	Rapid assessment (basic observations, pain score): Appropriate pain relief within **30 minutes** – in line with policy or patients care plan Monitor every 30 mins till pain relieved then 2 hourly Thorough investigation (FBC, Retics, U+Es, LFTs, CRP, G&SS, LDH, blood cultures if fever, haemoglobinopathy screen if indicated), ADD laxative, thromboprophylaxis, paracetamol, NSAID unless contraindicated IV fluids if insufficient oral intake; Supplemental oxygen if <SO2 ≤95%	EMSTN guideline page 2
Chest Syndrome	**Prevention! Adequate pain relief, monitor for opioid toxicity, incentive spirometry** Warning signs : any of - shortness of breath, chest pain, chest signs, falling oxygen saturation [measured ON AIR] Do CXR (look for widespread infiltrate but may be normal) and do ABG on air if sats ≤ 94% Liaise with HDU/ ITU transfer Consider transfusion (top up/exchange based on patient factors)	EMSTN guideline page 6
Anaemia	Symptomatic anaemia (SOB, lethargy, pallor) with haemoglobin usually falling by 25% of baseline or less 20g/l from steady state level Top –up transfusion may be necessary – discuss with Consultant on the Attending Team. Exclude other causes (e.g. parvovirus, bleeding, folate deficiency)	EMSTN guideline page 7
Stroke	Acute ischaemic or haemorrhagic stroke possible Urgent imaging and liaison with local stroke team Thrombolysis indicated as for non-sickle patient Urgent red cell exchange required for ischaemic stroke	
Sequestration	Sudden enlargement of spleen (occasionally liver) with blood pooling resulting in profound anaemia Urgent blood transfusion usually required	
Abdominal Pain	Investigate cause Ensure adequate analgesia Imaging as guided by clinical features	
Priapism	If prolonged can be medical emergency (exercise, warm bath can help) Analgesia Early discussion with urology if >3 - 4 hours, may need to aspirate Alpha adrenergic blocker e.g. etilefrine may help Acute transfusion therapy probably not helpful	EMSTN guideline page 8
Sepsis	Take blood cultures and MSSU, other cultures if symptoms Identify cause and treat within local guidance Low threshold for antibiotics and suspend penicillin V if on broad spectrum antibiotics Consider osteomyelitis in any febrile patient with swollen painful limb: Xray may not be helpful especially initially. MRI may be required	
Renal Complications	Check renal function in any acute presentation If painless haematuria, consider papillary necrosis (pain only if accompanied by obstruction) US may be helpful, otherwise CT.	
Vision Loss	Any acute symptoms should be seen urgently - eye casualty; subsequent management between Ophthalmology and Attending Team.	