This guideline is intended to cover the management of acute inpatient complications of sickle cell disease.

Every patient with sickle cell disease who attends A&E/admitted needs referring to haematology and informing on arrival via SpR during normal working hours or on-call consultant out of hours.

Who gets acute sickle complications- patients with HbSC, HbSS and HbSBthal are susceptible to the acute complications of sickle disease including- acute chest crisis, hyperhaemolysis and other transfusion reactions, priapism, vasoculsive crisis, thrombosis, sequestration, pregnancy and surgery related complications. Any patient with sickle disease needs urgent haematology input prior to going for acute or elective surgery. Patients with sickle cell disease are at risk of rapid deterioration particularly in medical emergencies such as sepsis, stroke, MI and PE.

Contents

Routine investigations

1- FBC, retics, Haemoglobin electrophoresis only in new patients, G&S (stating patient with sickle cell), U&E, LFTs, LDH, baseline Sats on air
2- If indicated blood cultures, virology, urine dip plus MSU, rapid COVID screen
3- Additional- **CxR-** chest signs or temp >38degrees, **ABG-** if sats on air <94%, other microbiology samples, amylase/ abdo X-ray if abdominal pain, malarial films if travel history, pregnancy test if female of childbearing age

General measures

1- **Hydration-** IVI if oral intake is inadequate (<3L per 24 hours) and fluid balance chart
2- **Oxygen-** Measure sats hourly for first 6 hours of admission. Record baseline on air, ABG if <94%. Many patients have symptomatic benefit from oxygen therapy and should be prescribed irrespective of saturations if patient requests. If sats <94% OA see acute chest crisis section
3- **Antimicrobial-** if apyrexial and no clinical infection continue prophylactic Penicillin V 500mg bd or erythromycin 500mg bd if penicillin allergy. If infection present stop prophylactic antibiotics and after appropriate microbiology samples taken, give infections as per focus or augmentin if unclear and no penicillin allergy. Sickle patients are at increased risk of pneumococcal sepsis, gram negative sepsis, lower respiratory tract infections including viral, UTI, osteomyelitis, Malaria, parvovirus and Yersinia- particularly if on iron chelation.
4- **VTE assessment** Unless contraindication should be given as increased thrombosis risk in this group of patients.
5- **Other pharmaceutical interventions** Antipruritics, antiemetics, laxatives, folate, prophylactic antibiotics if not on treatment antibiotics.
6- **Transfusion support**- Extended phenotype matched and sickle negative blood should be used. Always inform transfusion blood is for a sickle patient. Extended red cell phenotype should be sent prior to first transfusion.

   Indications for transfusion- severe anaemia due to sequestration, aplastic crisis, acute CVA/TIA, multi-organ failure, severe sepsis, surgery, pregnancy complications.
   Not in routine vasooclusive crisis. Top up transfusion contraindication if pre transfusion Hb >90 or Hct >0.3, need to consider exchange transfusion in this circumstance.
   Post-transfusion, should not exceed Hb 100g/L or HCT >0.3 due to risk of thrombosis from viscosity. Discuss any transfusion with haematology prior to giving.

   Exchange transfusion - Aim to reduce Hb S% to <30-50% and required in acute chest syndrome, Severe sepsis, acute stroke, hepatic sequestration, fulminant priapism and life-threatening conditions

Problems of transfusion

Anaphylactoid reactions due to anti-WBC/platelet antibodies. Treat as NHTR (non haemolytic transfusion reaction) with antihistamines, etc.

Delayed haemolytic transfusion reactions are more common in patients with SCD. They typically present 8-12 days following a transfusion with increased haemolysis (anaemia, jaundice, dark urine), but can present with symptoms suggestive of a painful crisis. The patient should be carefully monitored, and samples taken to check DAT test and antibody screen. If a new red cell antibody is found, the patient should be issued with an antibody card.

Hyperhaemolysis is a syndrome in which there is destruction of both donor and recipient red cells following transfusion. Patients present with a severe anaemia, typically about a week after transfusion, and symptoms suggestive of a painful crisis. Further transfusion should be avoided, and treatment with intravenous immunoglobulins and steroids may be required.

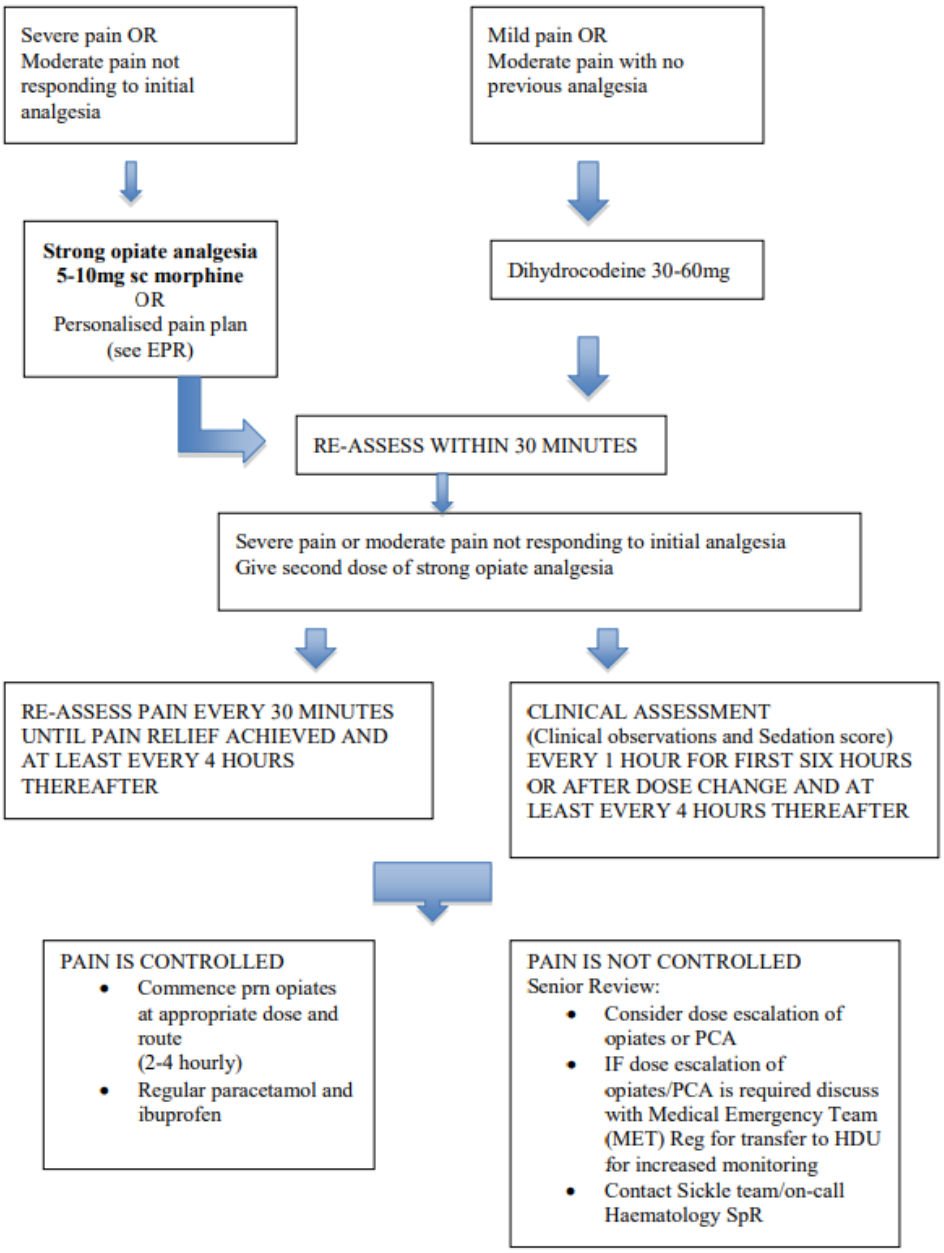
Acute anaemia

In HbSS disease Hb is usually 60-90g/L and well tolerated. A rapid drop in Hb >20g/L from baseline may lead to typical anaemia symptoms.

Causes- acute painful episode may be associated with increased haemolysis and cause a drop in Hb. Transient red cell aplasia due to parvovirus B19 infection. Acute splenic and hepatic sequestration. Acute haemolysis due to malaria, G6PD deficiency, blood loss, transfusion reactions included delayed haemolytic or hyperhaemolysis.

Analgesia-Analgesia should be given within 30 minutes of the patient presenting to A+E as per NICE Guidelines see algorithm below if opiate naïve or unknown to UHS. Vaso-oclusive sickle cell crisis can be precipitated by infection, dehydration, hypoxia and stress. The patient is an expert in their condition and their views should be listened to and management discussed with them. Refer to patients individual care plan.

Severe pain- entonox can be given until first dose of opiate, opiate only given S/C. Pethidine is not recommended. If not contraindicated give paracetamol, NSAID and dihydrocoodeine as per WHO analgesia ladder. **Reassess after 30mins and titrate as needed, reassess 4hourly when adequate analgesia achieved.** Patient controlled analgesia can be used as needed via anaesthetics if adequate analgesia is not achieved.


Severe pain OR
Moderate pain not responding to initial analgesia
Mild pain OR
Moderate pain with no previous analgesia
Strong opiate analgesia
5-10mg sc morphine
OR
Personalised pain plan
(see EPR)
Dihydrocodeine 30-60mg
RE-ASSESS WITHIN 30 MINUTES
Severe pain or moderate pain not responding to initial analgesia
Give second dose of strong opiate analgesia
RE-ASSESS PAIN EVERY 30 MINUTES UNTIL PAIN RELIEF ACHIEVED AND AT LEAST EVERY 4 HOURS THEREAFTER
CLINICAL ASSESSMENT
(Clinical observations and Sedation score)
EVERY 1 HOUR FOR FIRST SIX HOURS OR AFTER DOSE CHANGE AND AT LEAST EVERY 4 HOURS THEREAFTER
PAIN IS CONTROLLED
Commence prn opiates at appropriate dose and route (2-4 hourly)
Regular paracetamol and ibuprofen
PAIN IS NOT CONTROLLED
Senior Review:
Consider dose escalation of opiates or PCA
IF dose escalation of opiates/PCA is required discuss with Medical Emergency Team (MET) Reg for transfer to HDU for increased monitoring
Contact Sickle team/on-call Haematology SpR

Acute chest syndrome

Definition Acute illness charactierised by fever and or respiratory symptoms, accompanied by new pulmonary infiltrate on CxR. Severe hypoxia is a useful predictor of severity and outcome. **ABG** if O2 sats <94% on air. If diagnosed warrants ITU review. If difficulties with IV access do not wait for CEPOD insertion of vascath, must be done urgently if needed.

Can occur at any point during admission, vigilance and early recognition is vital. Acute chest crisis is one of the most common causes of death in patients with sickle cell disease

Symptoms and signs Hypoxia, chest/upper abdominal/spinal pain, lung consolidation, fever, tachypnoea, tachycardia, shortness of breath and cough

Differential diagnosis PE (d-dimers are unhelpful in SCD), fluid overload, opiate narcosis, MI, alveolar hypoventilation secondary to pain

Investigations- CxR, FBC, U&E, LFTs, crossmatch (sickle negative, fully matched Rh and Kell, Ag negative for current/previous antibodies) blood culture, sputum MC&S, NPA for respiratory viruses, COVID rapid PCR

Management- immediate aim is to prevent or reverse acute respiratory failure. Discussion with haematology, HDU/ITU referral, pain relief (PCA if needed), antibiotics, exchange transfusion if Hb >70g/L/p02 <9.0kPA (cross matched 8 units of sickle negative blood, arrange suitable access and monitor for transfusion reactions, VTE prophylaxis, oxygen to maintain sats >95%, hydration, chest physiotherapy

Prevention- when recovered discuss hydroxycarbamide or chronic transfusion, penicillin V prophylaxis, annual influenza, pneumococcal and COVID vaccine

Acute abdominal pain

Common presentation in sickle patients that can be due to disease complications or unrelated. Always involve haematology especially if may be heading to surgery. Always perform pregnancy test in females of childbearing age.

Differential diagnosis

Splenic sequestration or infarction, Acute cholecystitis/cholangitis, Biliary colic, Pancreatitis, Mesenteric syndrome, Acute appendicitis, Splenic abscess, Ischaemic colitis, Peptic ulcer, Vaso-occlusion, Constipation, Hepatic sequestration or infarction and Dysmenorrhea

Management

Additional to analgesia and fluids; If there is vomiting, or the abdomen is distended, or bowel sounds are absent, make nil by mouth and consider nasogastric suction, monitor liver size, if cholecystitis/cholangitis is suspected consider appropriate antibiotics, Acute chest syndrome can

often follow episodes of abdominal pain, due to splinting of the chest wall. Monitor oxygen saturations on air regularly and act accordingly if they fall < 94 % on Air (See acute chest syndrome page).

Abdominal crisis (Girdle syndrome or Mesenteric syndrome)

Patients may present with mild abdominal pain in the context of an acute painful crisis.

With abdominal crisis of mild-moderate severity the abdomen may be soft with mild tenderness but if severe examination may show a silent, distended abdomen without localising signs or rebound. Some hepatic enlargement and preceding pain in back, abdomen, or limbs is common. Often associated with bilateral basal lung consolidation. Characteristic distended bowel loops or fluid levels on X-ray.

Management: Oxygen and analgesia, Nasogastric suction, Sips by mouth only, Surgical intervention is not usually required but other causes of abdominal pain should be considered and surgical review is usually required, Simple (top-up) transfusion if Hb has fallen >30g/l below baseline- see transfusion section. Consider exchange transfusion if condition is severe or is complicated by acute chest syndrome or other acute complication.

Splenic sequestration

Splenic sequestration is most common in children with Sickle Cell Disease, but can occur in patients with Hb SC disease or with high levels of fetal Hb, who have not experienced splenic infarction in childhood.

Often leads to shock and sudden collapse, rapidly enlarging, painful spleen, abdominal pain (pulling legs up to abdomen), Hb drops by at least 20g/l from the stable state, often associated with septicaemia, particularly pneumococcal, high mortality

Investigations : Hb, reticulocytes, blood cultures, virology, cross match and extended phenotype if new patient

Management: Supportive (treatment of shock), emergency (top-up) transfusion (Group and RhD compatible, and phenotyped), broad spectrum antibiotics to cover pneumococcus and haemophilus

Hepatic sequestration

Causes abdominal distension with hypochondrial pain, enlarging, tense liver, sometimes increasing jaundice, collapse is less frequent and sudden than with splenic sequestration.

May need urgent (top-up) transfusion, may be associated with infection therefore consider broad spectrum antibiotic cover. If the patient becomes tachypnoeic, develops chest signs, or cyanosis, then arterial blood gases and treat as acute chest syndrome- see section

Gall stones

Demonstration of gall stones in a patient with abdominal pain does not mean that the gall stones are the cause of the pain, they are present in over 70% of adults most often asymptomatic but can cause: Acute cholecystitis, Chronic cholecystitis, Biliary colic, Obstruction of the common bile duct, Related acute pancreatitis. Also can precipitate abdominal painful crises and the mesenteric syndrome.

Management: Acute episode: Antispasmodics, Hydration, if acute cholecystitis/cholangitis is suspected prescribe appropriate antibiotics, avoid pethidine in view of risk of fits.

Common bile duct obstruction: Surgical review for MRCP or Endoscopic retrograde cholangiopancreatography (ERCP) or emergency surgery

Once acute episode has settled: Elective cholecystectomy; generally laparoscopy

Do not take to theatre without haematology review

Sickle hepatopathy (Intrahepatic cholestasis):

Some patients experience episodes of severe hyperbilirubinaemia, associated with fever and hepatic pain in the absence of demonstrable stones. These episodes are thought to be due to severe intrahepatic sickling.

Management: Analgesia (care as most opioids are metabolised in the liver), hydration, antibiotics, close monitoring of liver function tests.

Stroke and other CNS complications

Stroke is a common complication of sickle cell disease and can present with the typical features of stroke: limb weakness, paraesthesia, fits, acute confusion.

Acute ischaemic stroke may occur at all ages, but most common in children and >30 years
Precipitating factors: dehydration, fever, sometimes in well patients

Acute haemorrhagic stroke (includes intracerebral, intraventricular and subarachnoid haemorrhage)
Occurs at all ages, but median age of onset is 22 year, often occur in context of acute illness (e.g. sepsis)

Pathophysiology and treatment of stroke in patients with SCD differs from acute ischaemic stroke in non-sickle patients. Early exchange transfusion will be indicated in some cases in addition to, or instead of acute stroke treatment. Always discuss with haematology. Each case needs individual assessment but

Patients <50 years with no thrombotic risk factors are likely to have a sickle-related stroke and should have exchange transfusion

Patients 70 years or younger patients with thrombotic risk factors are less likely to have a sickle-related stroke

2. **Headaches**

The first episode of acute severe headache or a significant change in type of headache should be evaluated as an emergency and the diagnoses of intracranial haemorrhage or venous sinus thrombosis considered. Discussion with the neurology team and appropriate imaging should be considered. If acute or prolonged migraine attack suspected, discuss with neurology team. Consider treatment with high dose NSAIDs (oral if tolerated: e.g. 900mg Dispersible aspirin or 800mg Ibuprofen or 750mg Naproxen), prokinetic antiemetics (e.g. Domperidone or Metoclopramide) if able to tolerate orally. If significant vomiting, treat with IV fluids (with supplemental IV magnesium, e.g. 1g in 1L saline), Consider a triptan if within the first 6-12 hours of an attack

Secondary headaches (including Medication Overuse Headache and Headache associated with sleep apnoea)

Fits – treat as in non-sickle population. Screen for acute ischaemic stroke or haemorrhage.

Venous sinus thrombosis – may have an increased complication rate in SCD. Diagnosis made by MRVenogram and treated with anti-coagulation

Posterior reversible encephalopathy syndrome (PRES) – seen typically in context of child with severe ACS and occasionally in adults and in pregnancy. Characterized by neurological deterioration, headache and seizures. Diagnosis made by MRI and treatment is supportive.

Silent cerebral infarction – these are common in children and adults with SCD. They are characterized by MRI lesions without overt neurological impairment and are associated with cognitive impairment. In patients with subtle neuro-cognitive defects, investigation with MRI/MRA scans and neuropsychological testing may be appropriate.

Acute renal complications

Avoid NSAIDs in patients with known renal impairment

The kidney is susceptible to defects in tubular and glomerular function which start early in life causing hyposthenuria (an inability to concentrate urine) which can lead to dehydration. Increased renal cortical blood flow leads to glomerular hyperfiltration and a raised glomerular filtration rate (GFR). This subsequently leads to microalbuminuria, proteinuria and loss of renal function with a decreasing GFR throughout adulthood which can lead to chronic renal failure and end stage renal failure.

Acute kidney injury (AKI)

Can be precipitated by dehydration, sepsis, drugs or in the context of multi-organ failure. Monitor U&Es and fluid balance. Exclude reversible cause, aggressive fluid replacement accounting for

cardiovascular co-morbities. Good blood pressure control and oxygenation. Renal USS to exclude post-renal cause, renal replacement therapy as indicated, hyperkalaemia is common (due to tubular defects) and needs careful monitoring.

Haematuria

Microscopic haematuria is common due to renal microscopic infarcts. Frank haematuria is also common and is often due to renal papillary necrosis. This can be profuse. It may also occur in patients with sickle cell trait. It is usually painful and passing of renal papillae can cause renal colic and ureteric blockage.

In patients >40 years or with painless haematuria, alternative diagnoses should be considered (eg bladder tumours) and they should be referred to Urology. Ultrasound scan is the first line of investigation.

Management: FBC, U&E and Group and Screen/Cross match, IV fluids, treat infection. Avoid NSAID's
NB: Patients with delayed haemolytic transfusion reaction or hyperhaemolysis can present with 'coca cola' coloured urine. Therefore always ask for history of recent transfusion.

Hyperuricaemia Some 40 % of adults have hyperuricaemia, due to a combination of decreased urinary clearance and increased production. Uric acid stones are common, as is clinical gout.
Investigations: Monitor serum uric acid

UTIs are particularly common 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.

Pulmonary and cardiac disease

Patients with sickle cell disease should have biannual echocardiograms to screen for pulmonary hypertension. Any patient who is symptomatic with shortness of breath or hypoxia should be investigated for chronic pulmonary disease or pulmonary hypertension.

Orthopaedic complications

Osteomyelitis

Suggested by local tenderness, warmth, bony swelling, fever, raised WBC/CRP but these can also be present with an acute painful crisis. Consider osteomyelitis if evidence of infection- positive cultures/fever/raised CRP, atypical infection, failure to settle with acute painful crisis management.

Plain x-rays are usually normal, bone scans and radiolabelled leucocyte scans will not differentiate between infarction and infection, MRI scans with gadolinium may help diagnosis, but without contrast do not differentiate between infarction and infection.

Treatment- Antibiotics if strong clinical suspicion, positive cultures (Salmonella spp, Staphlococcus aureus, Gram negative bacteria are the commonest organisms. Involve microbiology early, accumulation of fluid may require drainage.

Avascular necrosis

Loss of blood supply to the bone underlying the articular surfaces leads to ischaemia and infarction or osteonecrosis. This occurs typically in the distal end of long bones, most commonly the hip. Occurs in up to 50% of adults.

Presentation: Pain in the affected joint on movement; later at rest. Hip AVN is typically felt as groin pain. Reduce range of movement.

Diagnosis: X-ray initially and MRI only if X-ray is normal.

Management: Early - Physiotherapy may be of benefit. Analgesia with non-steroidal anti-inflammatory agents or codeine derivatives. Late - Joint replacement may become necessary if pain is continuous or very severe or mobility seriously affected. Exchange transfuse pre-operatively.

Leg ulcers

Leg ulcers are a common problem in sickle cell disease and are notoriously difficult to treat and recurrent. If a patient attends with a new leg ulcer:

Check for fever: if > 38° undertake blood cultures

Check FBC, retics, CRP

Swab the wound for MC&S

Dress wound – Non adherent dressing and a bandage

Commence antibiotic therapy if clinically required: Trust guidance for cellulitis is flucloxacillin

Request ABPI (ankle brachial pressure index) and Doppler USS: Compression bandage should only be commenced following completion of this investigation

Pregnancy

Complications for women with SCD can occur during the antenatal period, labour, and the puerperium. Including , Infection (UTI, Pneumonia, Puerperal sepsis) , Acute chest syndrome (Fever, tachypnoea, pleuritic chest pain) , thrombosis, increased incidence of preterm labour, pre-eclampsia and caesarean section. Increased risk of maternal death (approx. 1%). In addition to risks to fetus.

Women with sickle cell disease are at risk of a sickle crisis in pregnancy, labour and the early puerperium, particularly if they become dehydrated, acidotic or infected. Their care should involve specific measures to prevent these complications. **Please inform haematology if pregnant women with sickle cell disease becomes pregnant and if admitted to hospital.**

Women of child bearing age should have pregnancy test if being admitted to hospital with a complication of sickle cell disease.

References

GSTT sickle guidelines

BCSH Guidelines on red cell transfusion in sickle cell disease. Part I: principles and laboratory aspects

https://doi.org/10.1111/bjh.14346

BCSH Guidelines on red cell transfusion in sickle cell disease Part II: indications for transfusion

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All-party parliamentary group on sickle cell and thalassaemia
All-Party Parliamentary Group for Sickle Cell and Thalassaemia - SCTAPPG (sicklecellsociety.org)

BCSH Guideline on the management of acute chest syndrome in sickle cell disease

https://doi.org/10.1111/bjh.13348