Standards for the clinical care of adults with Sickle Cell Disease in the UK (2018, 2nd edition)

Summary by M Qureshi (not to be used for the delivery of clinical care – please refer to original guideline)

Introduction

- Substitution of C for A at codon 6 of the B globin gene → B^S → HbSS (Sickle cell anaemia)
- SCD includes HbSC, HbSD ^{Punjab}, HbSO ^{Arab}, HbSE
- High proportion of intracellular HbF inhibits HbS polymerisation at birth. Pathological effects start to happen as proportion of HbS increases during first year of life.
- Laboratory tests:
  - → Sickle solubility test (if HbS >15% of total haemoglobin)
  - → Hb electrophoresis
  - → HPLC
  - → Tandem mass spectroscopy
  - → DNA analysis
- Neonatal screening: Heel prick bloodspot sample on all babies at 5-7 days of age.
- Antenatal screening: Testing for carrier status is universal in high prevalence areas in the UK, and targeted using a questionnaire in low prevalence areas.
- When both parents are carriers → regarded 'at risk' → prenatal diagnosis is offered

Organisation of care

Standards

- Adults with SCD should be **offered care as close to home** where possible, but should also have **access to highly specialist multidisciplinary care** including specialist nursing support.
- All patients should have a **named key contact** and a number to phone if needing advice.
- All hospitals with emergency departments should have **protocols** to guide management of uncomplicated acute presentations of SCD.
- All **local hospitals should be linked with a named specialist centre** with agreed pathways and protocols for advice and referral for acute and chronic complications including when to seek specialist advice.
- All adults with SCD should be offered **comprehensive review from a specialist centre at least annually**.
- All patients should have access to **specialist psychology support**.

Specialist Haemoglobinopathy Team

- MDT team: consultants, trainees, specialist nurses, community staff, psychologists
- Based at a **Specialist Haemoglobinopathy Centre** but work cross-site in **outreach clinics**
- Develop and review **individual care plans**
- Responsible for **governance: audit, mortality reviews, guidelines, protocols**
- Specialist Haemoglobinopathy Centres should participate in rolling programme of audit against their clinical guidelines
- Ensure **patient participation in service development** and quality reviews
- Provide specialised acute and chronic pain service
- Provide patient information and education
- Ensure **data sharing** between LHT, SHT and **National Haemoglobinopathy Registry**

Networks

- Wide geographical variation in prevalence of SCD across the UK
- **Care networks should ensure equitable care for every patient in the UK**, irrespective of their location
- In low-prevalence areas, a **'hub and spoke' clinical model** may be appropriate.

Transition services

- Specialist teams should have a policy and dedicated team for transition, which should include a **named transition lead**.
- Transition teams → **improved concordance, reduced hospitalisation**.
- Young people must be treated as **equal partners** in the transition process. Take their views into account, and involve them in evaluation.
- A **profile or 'passport' document** can be used to enable the Transition Lead to work with the young person and to assess when they are ready for transition.

National Haemoglobinopathy Registry

- Over 10,000 patients with SCD from 55 centres registered at time of publication.
- Individuals added with consent, but the NHR can also be used to report adverse events for anonymised patients who do not consent to their individual details being added to the registry.
- NHR has developed minimum data set for annual review, which can then be accessed by other hospitals.
- NHR data is also collated into an annual report: registrations per centre, genotype, gender, age, ethnicity, adverse events and specific treatments (transfusion, HC, iron chelation).

Primary care

Standards

- All adults with SCD should be registered with a GP.
- Primary care teams should maintain good communication with the specialist and local haemoglobinopathy teams, enabling two-way exchange of expertise to optimise the care of their mutual patients.
- Each SCD patient should be offered **routine primary health care services at their GP surgery.**
- **Specialist haemoglobinopathy teams** should develop locally agreed **shared care protocols with GPs defining the roles and responsibilities of each**.

- **Specific responsibilities of the primary care team** include (Patel, 2016):
  - → **Early treatment of infections to prevent sepsis**
  - → Prescription of antibiotic prophylaxis
  - → Ensuring **vaccinations** are up to date
  - → Early referral of pregnant women
  - → Reproductive provision to include contraceptive advice, pre-conceptual counselling and partner testing. They may also be involved in shared antenatal care with the specialist centre.
  - → Referral for psychological support and counselling (including neuropsychological support)
  - → Encourage **treatment compliance**
  - → **Patient education** and self-management of mildly painful episodes
  - → Support during transition and the move onto further education

- Other recommendations for primary care:
  - → **Blood pressure monitoring** should happen at every GP visit.
  - → **Annual vitamin D levels** and replacement if required.
  - → Consider bone mineral densitometry.
  - → Regular dental care (can trigger crisis).

Prevention of infection

Poor splenic function → susceptibility to infection (especially **invasive pneumococcal disease**, also **salmonella organisms**)

Standards

- Specialist and local haemoglobinopathy teams and GPs should ensure that adults with SCD are adequately **vaccinated**:
  → Invasive **pneumococcal disease (PPV23 every 5 years, and PCV13 once)**
  → Haemophilus influenza type B (**one dose of Hib/Men C**)
  → **Neisseria meningitis ACWY and B** (one month after Hib/Men C)
  → **Hepatitis B**
- Influenza vaccine should be offered annually.
- **Hepatitis B immunity (HBsAb)** should be reviewed annually and a **booster offered if levels are <100** IU/ml.
- Patients should be periodically warned about the increased risk of IPD and other forms of sepsis. They should also be educated about symptoms which might indicate infection and be **advised to keep a thermometer at home to check for fever and to attend for medical assessment if ≥ 38°C**.
- Adults with SCD who have had a **splenectomy or a history of IPD → lifelong penicillin prophylaxis**.
- A discussion of oral antibiotic prophylaxis should be undertaken on transition to adult care and at annual review. **Adults with SCD who choose not to continue regular oral prophylaxis** should ensure they have received pneumococcal vaccination and should be provided with a **supply of appropriate antibiotics for emergency use** (Penicillin V 500mg qds, Amoxicillin 500mg tds or Erythromycin 500mg qds).

Acute pain

- NICE: Acute sickle crisis is a medical emergency → **analgesia within 30 minutes → review every 30 minutes until pain is under control, then four hourly.**
- Moderate pain and no prior analgesia → NSAID or weak opioid
- Severe pain or persistent moderate pain → Strong opioid up front (s/c)
- **Consider PCA** if pain persists despite repeated boluses of strong analgesics.
- Opioid adjuncts: Laxatives, anti-emetics, anti-pruritics.
- **IV hydration** if unable to take oral fluids.
- **Oxygen therapy if saturation <95%**
- **Incentive spirometry**.
- Discharge planning: Information on pain management at home, access to specialist advice at home, repeat prescriptions and adequate supplies of analgesia.
- **Consider Day care management of patients who present frequently with uncomplicated pain, however overnight admission is preferable for patients who present infrequently**.

Chronic pain

- PiSCES study concluded that adult patients reported pain on 54.5% of surveyed days, with 29% of patients experiencing pain on more than 95% of days.
- **Central sensitisation and hyperalgesia**.
- Ask about chronic pain and review opioid use at annual review.
- All healthcare professionals should be aware of prescribing plans for opioids and who the key prescriber is.
- **Seek out underlying cause of chronic pain** and treat if appropriate (eg **avascular necrosis**, ongoing leg ulcer).
- Consider specific analgesia for **neuropathic pain**.
- Refer patients with **complex pain to a chronic pain team**.
- Physical dependence on analgesia should be differentiated from addiction.

Acute stroke

- Patients presenting with suspected transient ischaemic attack (TIA) or stroke should have urgent neuroimaging.
- Adults presenting with TIA or stroke should be managed within a hyperacute stroke unit with access to multidisciplinary support from a haemoglobinopathy specialist centre, vascular interventional neuroradiology, neurology and neurosurgery.
- **Urgent red cell exchange is recommended for patients with a sickle related acute ischaemic stroke**.
- **Thrombolysis should be considered for patients with acute ischaemic stroke** who meet current UK national recommendations for stroke treatment if there are no contraindications.
- CT can rule out haemorrhagic stroke. **For ischaemic stroke: MRI, MRA, possibly MRV to exclude CSVT**.
- **Stroke prevention**:
  - → There is **no verified imaging technique such as TCD to identify adults at risk of stroke**.
  - → **Adult patients who experience an acute ischaemic stroke attributed to sickle cell disease should be offered long term transfusion therapy**.
  - → Patients who have been started on chronic transfusion therapy for **primary prevention during childhood** should be assessed by an expert in SCD at transition to adult care to discuss the risks and benefits of ongoing transfusion. They **should be offered continuation of transfusion therapy or hydroxycarbamide if they have had a previous abnormal transcranial Doppler (TCD) that has normalised and there is no evidence of vasculopathy**.
  - → Patients who have been started on chronic transfusion therapy for **secondary stroke prevention during childhood should be offered continuation of transfusion therapy**.
  - → Patients who have been started on hydroxycarbamide for primary stroke prevention during childhood should be offered ongoing hydroxycarbamide therapy after transition to the adult service.
  - → Anti-platelet therapy should be considered in patients with acute ischaemic stroke as per national stroke guidelines unless there are any contra-indications.
  - → Hydroxycarbamide should be considered for prevention of recurrent stroke where transfusion is not possible or acceptable.

Acute chest syndrome

- Fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on CXR.
- Investigations: CXR, FBC, biochemistry, G&S, blood cultures, sputum, **NPA for viral testing**.
- **Evidence of severe disease: Worsening hypoxia (Pa O2 <9 kPa), increasing respiratory rate, fall in Hb and platelet count**.
- **Give ABX which cover Strep pneumonia and atypical organisms even if blood and sputum culture are negative**.
- **Anti-virals if clinical suspicion of influenza A**.
- Consider early simple 'top-up' transfusion in hypoxia, but exchange transfusion will be required if progression or severe clinical features.
- Consider: High flow oxygen, **CPAP, bronchodilators, incentive spirometry**.
- HC for prevention of recurrent ACS.
- Consider chronic exchange transfusion programme.

Chronic respiratory complications

- Assess all patients for respiratory symptoms and with respiratory examination at each annual review.
- Monitor oxygen saturation SpO2 at least annually.
- Patients with respiratory symptoms or chronic hypoxia should be investigated with:
  - → **Spirometry with transfer factor / pulmonary function tests**
  - → **HRCT of the lung**

- A sleep study should be recommended in all patients with:
  → Self-reported disturbed sleep
  → excessive daytime sleepiness (Epworth sleep score >10)
  → oxygen saturations awake <95%
  → a history of snoring, priapism or early morning headaches.
- Patients with suspected chronic lung disease or abnormal sleep studies should be referred to a respiratory physician for review and consideration of therapy.

Cardiac complications

- Assess all patients for cardiac symptoms (dyspnoea, dizziness, chest pain, ankle swelling) and perform cardiac examination that includes assessment for **signs of right heart strain** at each annual review.
- Patients with cardiorespiratory symptoms and signs should be evaluated with electrocardiography **(ECG) and echocardiography**.
- In patients with sickle cell disease **echocardiography should be performed at initial presentation to adult service and at least once every three to five years even in asymptomatic patients** (or earlier if patients are symptomatic or hypoxic).
- **Echocardiography** should be repeated **annually in patients with previously elevated tricuspid regurgitant jet velocity (TRV)** who have not had **right heart catheterization** (RHC).
- Patients should be **referred to a pulmonary hypertension specialist centre for consideration of RHC** if:
  → **TRV >290 cm/sec**
  → TRV 250-290 cm/s and symptoms suggestive of pulmonary hypertension.
- Patients with PH should be evaluated for thromboembolic disease, chronic lung disease, hypoxaemia, sleep-disordered breathing, HIV infection and autoimmune disease.
- Evaluation for risk factors of PH should include assessment of renal function, liver function and systemic hypertension.
- **Disease modifying therapy with hydroxycarbamide or blood transfusion should be considered in patients with pulmonary hypertension**.
- Consideration should be given to the use of vasodilator therapy for select patients with precapillary PH under the supervision of a pulmonary hypertension specialist.
- Note that **cardiac iron overload is uncommon in SCD, compared to thalassemia**, but can be diagnosed with **cardiac T2* MRI**.

Renal and urological complications

- **Sickle Cell Nephropathy is found in 60% of patients with HbSS**, and some can develop into proteinuria and CKD.
- **Monitoring renal function: Hyperfiltration and increased proximal tubular excretion of creatinine in SCD → creatinine levels are often low → monitor declining renal function rather than values out of 'normal' range**
- AKI or declining renal function → manage jointly with a renal physician.
- Rigorous bp control. Patients with hypertension and ACR <3.5 mg/mmol should be treated with a BP target of <140/90 mmHg. Patients with hypertension and ACR >3.5 g/mmol should be treated with a target of <130/80 mmHg.
- Patients with urine PCR >50 mg/mmol → ACE inhibitors ARBs, and consider Hydroxycarbamide
- Patients with end-stage kidney disease (ESKD) should be considered for renal replacement therapy including transplantation.
- Hyposthenuria is universal → can lead to nocturnal enuresis and dehydration → All patients with SCD should be encouraged to have fluid intake of minimum 3L per day.
- Avoid long-term use of NSAIDS if eGFR < 60ml/min.

- **Haematuria** can be caused by **renal papillary necrosis or renal calculi**, but also by **renal medullary carcinoma** (rare and aggressive cancer, virtually restricted to the sickle gene) → **New-onset haematuria should be investigated, regardless of age, to exclude malignancy**.

Priapism

- All men should be educated about priapism and should be **asked about both stuttering and fulminant priapism as part of their annual review**.
- MDT should include **urologist with a specialist interest in SCD-related priapism**.
- Each haemoglobinopathy unit should have an emergency pathway and access to emergency urology services for cases of fulminant priapism.
- Patient education: Gentle exercise, trying to urinate, keeping warm, keeping hydrated at bedtime
- Management:
  - → If lasts more than one hour > attend A&E > **pain relief, hydration, oxygenation and alpha adrenergic agent (eg etilefrine)**.
  - → If <48 hours, then urology for **penile aspiration and concomitant injection of alpha adrenergic agent directly into the corpus cavernosa**.
  - → If this fails, then **surgical intervention with a distal shunt procedure**.
  - → If this fails, then **consider red cell exchange before T-shunt** (see below), which is major surgery.
  - → If 48 to 72 hours, then **definitive T-shunt by specialist urologist**.
  - → If present at >72 hours, then place a **primary penile implant**.

Orthopedic complications

- **Osteomyelitis**
  - → Look for osteomyelitis if bone pain is persistent and/or associated with fevers
  - → Blood cultures
  - → Radiological exam (x-ray → lucent areas, **USS → subperiosteal fluid >4mm**)
  - → Consider bone biopsy/aspiration for cultures (but infection risk)
  - → Most common cause: **Salmonella, Staph aureus, gram negative enteric bacilli**
  - → **Antibiotics +/- drainage**

- **Avascular necrosis**
  - → Bone death due to loss of blood supply, most commonly in head of femur or humerus (hip or shoulder pain)
  - → Plain x-ray → MRI if x-ray is normal
  - → Conservative management: Analgesia and physiotherapy at early stages
  - → Surgical: **Core decompression, joint arthroplasty**
  - → Post-operative infection prophylaxis and thromboprophylaxis

Gastroenterological complications

- LFTs (including unconjugated/conjugated bilirubin) at least annually.
- Symptomatic gallbladder stones should be treated with laparoscopic cholecystectomy because of the shorter hospital stay and fewer immediate surgical complications.
- **Exchange transfusion should be considered early in the presentation of patients with intrahepatic cholestasis** (severe RUQ pain, acute hepatomegaly, coagulopathy, extreme conjugated hyperbilirubinemia)
- Simple transfusion to baseline haemoglobin can be considered for patients with acute hepatic sequestration associated with anaemia.

Opthalmology complications

- All patients with SCD should be informed about the risk of ophthalmic complications and asked about visual symptoms at their annual review.
- **All patients with SCD should have baseline retinopathy screening**.
- Patients should be educated about acute symptoms (including trauma) and how to access help.
- **Patients with visual symptoms should be referred for ophthalmic review**.
- **Patients with a history of retinopathy should have regular (annual) ophthalmic review**.
- Patients with **HbSC who have no proven retinopathy should have review every 3 years**.
- Patients on **desferrioxamine or deferasirox should also be monitored for visual problems** due to the development of drug-induced retinopathy.
- Sickle retinopathy can be non-proliferative or **proliferative**. The **latter is more prevalent in HbSC disease**, and may result in visual loss.
- **Laser photocoagulation therapy** should be considered for patients with **proliferative sickle retinopathy**.

Anaemia

- **Transient red cell aplasia** (reticulocytopenia, **parvovirus** IgM or DNA)
- **Splenic sequestration** (splenomegaly, profound anaemia, reticulocytosis, circulating NRBCs, thrombocytopenia) → **cautious transfusion to avoid hyperviscosity when splenic RBCs return to circulation**
- **Delayed transfusion reactions**
- **G6PD deficiency**

Leg ulcers

- Annual review should include questioning about leg ulceration and inspection of the lower extremities for active or healed leg ulcers.
- Patients with leg ulceration should be treated by a **MDT which includes wound care experts, dermatologists, vascular/plastic surgeons**.
- Patients with **sickle-related leg ulcers should be assessed for venous insufficiency with venous reflux studies**.
- Multi-component compression bandaging should be offered, particularly in patients with evidence of venous insufficiency.
- **Zinc levels** should be measured in patients with leg ulcers and supplements should be offered to those with deficiency.
- There is **insufficient evidence of HC causing leg ulcers in SCD → should not interrupt treatment if ulcers develop**.

Reproductive health

- Pregnancy planning:
  - → Ensure immunisations, penicillin prophylaxis, **regular folic acid**
  - → **Stop HC, ACE inhibitors and chelation**
  - → **Screen for organ damage: proteinuria, echo (pulmonary HTN), opthalmological review**
  - → **Partner screening (HbS, HbC, beta thalassemia)**
  - → Offer **pre-implantation/prenatal diagnosis**
- Pregnant women with SCD should be managed by a **MDT** of obstetricians, midwives and haematologists with an interest in SCD **in a unit that manages high risk pregnancy**.
- VTE assessment at 12/40. Women with SCD are intermediate risk for VTE → **Consider LMWH thromboprophylaxis from 28/40 and continue until 6/52 postpartum**.

- SCD causes **increased risk of pre-eclampsia** and pregnancy-induced HTN → **offer aspirin to all women with SCD**.
- **Review monthly to 24/40, fortnightly to 34/40, and weekly thereafter**. Regular **bp monitoring and urinalysis**.
- **Viability scan at 8/40, routine first trimester scan at 12/40, detailed anomaly scan at 20/40**.
- **Foetal growth monitoring: every 4 weeks from 24/40**
- **Routine prophylactic transfusion is not recommended during pregnancy for women with SCD but is indicated in certain situations**.
- **Do not recommence HC until after breastfeeding has stopped**.

Surgery

- **SCD testing and HPLC should be performed at pre-assessment visit in all non-Northern Europeans**.
- In emergencies, **most cases of SC anaemia can be identified by a positive sickle solubility test, FBC showing anaemia, and blood film**.
- **For patients with known SCD: FBC, red cell phenotype, and pre-operative antibody screen. Rh and Kell typed cells should be available before surgery**.
- **Preoperative plan**:
  - → Perioperative **hydration, oxygenation, warmth**.
  - → **IV fluids** for patients who are NBM for more than 4 hours.
  - → Regular **monitoring of oxygen saturation**.
  - → Respiratory support with **incentive spirometry or CPAP post-operatively**.
  - → **Prophylactic antibiotics**.
  - → **VTE risk assessment**.
  - → Local or regional anaesthesia where possible.
  - → Adequate analgesia post-operatively (**involve acute pain team in the plan**)
- **Low/Medium risk surgery → Preoperative transfusion** (simple transfusion to Hb 100 g/l if Hb <90 g/l or partial exchange if Hb >90g/l)
- **High risk surgery → Exchange transfusion**
- Preoperative transfusion should be considered for patients with non-SCA genotypes undergoing low and moderate risk surgery taking into account previous history and complexity of surgery.

Hydroxycarbamide

- **MSH trial** (1995):
  - → **Lower annual rates of pain crises**
  - → **Lower incidence of ACS**
  - → **Reduced need for blood transfusion**
  - → **Increased total Hb and HbF**
- **Indications**:
  - → Adults with **SCA and HbS/β0** with **three or more moderate to severe pain crises in a 12 month period**
  - → Adults with SCA and HbS/β0 who have a **history of severe and/or recurrent ACS**
  - → Adults with SCA and HbS/β0 who have **sickle associated pain or severe symptomatic anaemia that interferes with quality of life or ADLs**
  - → **Possibly adults with HbS/β+ or HbSC** who have three or more moderate to severe VOC in a 12 month period, a history of severe/recurrent ACS or recurrent pain that interferes with QOL or ADL
- HC starting dose 15mg/kg/day, then titrate up by 5mg/kg/day increments, **aiming for a Maximum Tolerated Dose** with increased HbF, neutrophil count of 1.5 – 2.0 x 10^9/L, and absolute reticulocyte count of 100 – 200 x 10^9/L. Stop if neutrophil count <1.0 x 10^9/L.
- HC shows **no increased risk of stroke, MDS, leukaemia or cancer**.
- In the MSH trial, there were no birth defects in patients exposed to HC at conception.

- There is conflicting evidence regarding azoospermia/oligospermia → sperm banking should be offered prior to commencing HC.

Blood transfusion

- An **extended phenotype (or genotype) including C, c, E, e, K, k, Jka, Jkb, Fya, Fyb, M, N, S and s** should be performed at baseline. **If the patient is S- s-, then U typing** should be performed.
- **If the patient has not been transfused within three months then testing can be undertaken serologically, otherwise genotyping is needed**.
- Red blood cell transfusion requirements:
  - → **ABO Rh (D, C, c, E, e) and Kell compatible**
  - → Haemoglobin **S negative**
  - → If there are clinically significant red cell antibodies (current or historical) then the red cells selected should be **negative for the corresponding antigens**.
  - → If possible, **red cells should be < 10 days old for simple transfusion and < 7 days old for exchange** transfusion.
- Transfusion is not recommended in uncomplicated vaso-occlusive crisis.
- Simple transfusion to steady state haemoglobin concentration (Hb) may be indicated for patients with acute exacerbation of anaemia due to aplastic crisis or sequestration crisis.
- **Risk of hyperviscosity → Post-transfusion Hb target should not exceed 110 g/L, and do not increase Hb by > 40 g/L in 24 hours**.
- Exchange transfusion recommended for:
  - → ACS
  - → Ischemic stroke
  - → **Acute multi-organ failure**
  - → Severe sepsis
  - → **Mesenteric girdle syndrome**
  - → **Acute intrahepatic cholestasis**
  - → Acute priapism – under certain conditions (see above)
- **DHTR typically presents 5-15 days following red cell transfusion**:
  - → Varies in severity. More severe presentations may include pain, rapid decrease in Hb, **cola-coloured urine** and renal dysfunction accompanied by increased haemolytic markers and a **new allo-antibody**.
  - → There is observational evidence of **response to methylprednisolone and high dose IVIg** in addition to erythroid stimulating agents.
  - → Rituximab or eculizumab have been used in cases resistant to these therapies.
- **Hyperhaemolysis is rapid decrease of Hb below the pre-transfusion level**:
  - → Both transfused red cells and the patient's own red cells are destroyed.
  - → **Evidence of HbS and HbA in the urine by HPLC**.
  - → Can be triggered by a new red cell antibody, however there is frequently no evidence of an allo-antibody.
  - → Treat with **methylprednisolone and high dose IVIg**.
- **Report adverse events to the National Haemoglobinopathy Registry, SHOT/SABRE, and MHRA**.

Iron chelation

- **Iron tends to accumulate in the liver rather than the heart in patients with SCD**, in contrast with thalassemia and other iron loading conditions → Quantitative liver iron concentration if serum ferritin persistently raised >1000 μg/l.
- **Iron chelation is recommended in patients who have a liver iron concentration of > 7mg/g dry weight**.
- All patients receiving iron chelation therapy should be **regularly monitored for therapeutic effect and chelator toxicity**. Support should be provided to help improve adherence to chelation therapy.