Anaesthesia 2021, 76, 805–817 doi:10.1111/anae.15349

Guidelines

# Guideline on the peri-operative management of patients with sickle cell disease

## Guideline from the Association of Anaesthetists

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## Summary

Sickle cell disease is a multisystem disease characterised by chronic haemolytic anaemia, painful vaso-occlusive crises and acute and chronic end-organ damage. It is one of the most common serious inherited single gene conditions worldwide and has a major impact on the health of affected individuals. Peri-operative complications are higher in patients with sickle cell disease compared with the general population and may be sickle or non-sickle-related. Complications may be reduced by meticulous peri-operative care and transfusion, but unnecessary transfusion should be avoided, particularly to reduce the risk of allo-immunisation. Planned surgery and anaesthesia for patients with sickle cell disease should ideally be undertaken in centres with experience in caring for these patients. In an emergency, advice should be sought from specialists with experience in sickle cell disease through the haemoglobinopathy network arrangements. Emerging data suggest that patients with sickle cell disease are at increased risk of COVID-19 infection but may have a relatively mild clinical course. Outcomes are determined by pre-existing comorbidities, as for the general population.

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Accepted: 18 November 2020
Keywords: haemoglobinopathy; peri-operative; sickle cell anaemia; sickle cell disease
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This is a consensus document produced by expert members of a Working Party established by the Association of Anaesthetists. It has been seen and approved by the Board of Directors of the Association of Anaesthetists of Great Britain and Ireland. It has

been endorsed by the Royal College of Anaesthetists, the Association of Paediatric Anaesthetists of Great Britain and Ireland, the Obstetric Anaesthetists' Association and the Sickle Cell Society.

## Recommendations

1 Clinical teams should work in partnership with patients and their families, and endeavour to make sure they are kept informed of clinical decisions relating to their care at all times.
2 The lead clinician in the Department of Anaesthesia is responsible for making sure that there is local departmental guidance for the peri-operative management of patients with sickle cell disease, developed in partnership with the haematology team. The Department may wish to identify a specific lead for this role.
3 All patients at risk of haemoglobinopathy should be screened for haemoglobinopathy before surgery but unnecessary repeat screening should be avoided.
4 There should be a nominated lead haematologist (or for children, a lead paediatrician or paediatric haematologist) when a patient with sickle cell disease undergoes surgery. The nominated leads are responsible for deciding the peri-operative transfusion plan, with support of the specialist centre where relevant.
5 Local governance arrangements should be in place so that the surgical team booking the patient for surgery communicates the sickle cell disease diagnosis at all stages of the patient pathway, and documents this clearly in the patient record so that the relevant teams are aware: haematology; anaesthesia; transfusion laboratory; waiting list co-ordinators; pre-assessment; and ward nursing staff.
6 Patients with sickle cell disease presenting for elective surgery should be reviewed in a pre-assessment clinic, with input from the nominated lead haematologist (or for children a paediatrician/paediatric haematologist). The haematology team must be informed if a patient with sickle cell disease is admitted for emergency surgery.
7 The acute pain team should be notified in advance if a patient with sickle cell disease is undergoing major surgery, particularly if the patient has a history of chronic pain.
8 Patients with sickle cell disease should be scheduled early on the operating list to avoid prolonged starvation. Last minute cancellations for administrative reasons should be avoided, particularly if the patient has received a blood transfusion in preparation for surgery.
9 Patients are at increased risk of sickle complications (acute chest syndrome, pain, acute renal insufficiency or stroke), sepsis and venous thromboembolism in the peri-operative period. The majority of complications occur postoperatively, and there should be a low threshold to admit patients to high dependency or intensive care.
10 Patients require meticulous peri-operative care to avoid factors that may precipitate sickling: dehydration; hypoxia; acidosis; hypothermia; and pain. Routine surgery should be avoided if the patient is febrile or having a painful crisis.
11 Pregnancy confers an increased risk for patients with sickle cell disease. Patients should be managed by a multidisciplinary team and be encouraged to give birth in hospitals able to manage high-risk pregnancies and complications of sickle cell disease.
12 Patients should be managed according to standard COVID-19 care pathways, striking a careful balance between limiting hospital contact to minimise the risks of viral exposure and avoiding delays to essential treatments.

## What other guidelines are available on this topic?

There are existing evidence-based guidelines and quality standards relating to the care of patients with sickle cell disease published by the National Institute for Health and Care Excellence [1,2], British Committee for Standards in Haematology [3], British Society for Haematology [4], Sickle Cell Society [5], UK Forum on Haemoglobin Disorders/West Midlands Quality Review Service [6], NHS screening programme [7], Royal College of Obstetrics and Gynaecology [8] and US National Institute of Health [9].

## Why were these guidelines developed?

Sickle cell disease is one of the most common serious inherited single gene disorders worldwide and has a major impact on the health and life expectancy of the affected individual. Peri-operative complications are higher for patients with sickle cell disease than for the general surgical population, but outcomes can be improved with careful

peri-operative care and the involvement of specialist teams. Peri-operative complications may be sickle-related, transfusion-related, or related to surgery or anaesthesia. These guidelines were developed to highlight advances in peri-operative care of patients with sickle cell disease; to provide anaesthetists with a better understanding of sickle cell disease; and to make recommendations about the organisation of care for this complex group of patients.

## How does this statement differ from existing guidelines?

This is the first anaesthetic-led multidisciplinary statement on peri-operative management of patients with sickle cell disease presenting for routine and emergency surgery in all hospital settings in Great Britain and Ireland. It is the collaborative effort of sickle haematologists, transfusion medicine specialists, patient representatives, anaesthetists and surgeons. It draws together current best evidence for management of patients with sickle cell disease in the peri-operative period, particularly relating to blood transfusion, and prevention and management of complications. It has been written to clarify organisational aspects of care and to support anaesthetists who manage patients with sickle cell disease, either on a regular or occasional basis.

## Introduction

Sickle cell disease is one of the most common serious inherited conditions globally, diagnosed in more than 1:2000 live births in England annually (up to 1:300 births in some cities). Patients may be homozygous for the sickle gene (sickle cell anaemia, HbSS), or have a compound heterozygous state with another abnormal haemoglobin (e.g. ß-thalassaemia, haemoglobin C, D, E or $O_{Arab}$). The heterozygous carrier state HbAS is a mostly benign condition that only becomes important at extremes of physiology (e.g. in severe sepsis) and is not considered further in these guidelines.

It is estimated there are approximately 14,000 patients with sickle cell disease in the UK (approximately 240,000 healthy carriers with sickle cell trait), and approximately 500 patients with sickle cell disease in the Republic of Ireland [10,11]. The National Haemoglobinopathy Registry (NHR) was established in England in 2008; 98% of patients registered are of African or Caribbean background. Sickle cell disease is also seen in families originating in the Middle East, India and the southern and eastern Mediterranean. Approximately two-thirds of patients with sickle cell disease in the UK live in London, one third in cities in the North West, West Midlands, East Midlands or Yorkshire and Humber [10].

Sickle cell disease is characterised by a chronic haemolytic anaemia, painful vaso-occlusive crises and acute and chronic end-organ damage. Management of patients with sickle cell disease has improved markedly in recent decades. Care is focused on prevention and management of complications from birth, and death in childhood is uncommon in the UK (1–2%). Survival up to the 7th decade can be expected with optimal multidisciplinary care in a specialist haematology clinic [12].

Patients with sickle cell disease may present for elective or emergency surgery to manage the complications of sickle cell disease (cholecystectomy, splenectomy, tonsillectomy, hip replacement, bone and joint infection), or for incidental surgery such as appendicectomy or caesarean section. Patients are at increased risk of peri-operative complications compared with the general surgical population, both sickle-related (acute chest crisis, acute painful crisis or stroke) and non-sickle-related (infection or thrombosis). Many complications can be mitigated with careful planning, assessment of comorbidities and multidisciplinary team working.

## Pathophysiology of sickle cell disease

Normal adult haemoglobin comprises the haem molecule and two alpha and two beta globin chains (HbA, $\alpha_2ß_2$). The genetic mutation in HbS is a C to A substitution at codon 6 of the beta globin gene with replacement of glutamic acid by valine. This results in an abnormal beta globin gene ($ß^s$) and formation of abnormal haemoglobin, HbS ($\alpha_2ß^s{}_2$). In HbA, when oxygen binds to haem, the shape of the haemoglobin molecule changes facilitating further oxygen binding and carriage. These interactions are not as effective in HbS and abnormal polymerisation of the HbS occurs [13].

The severity of sickle cell disease varies according to genotype and within genotype. HbSS, HbS$ß^0$-thalassaemia and HbSD disease are associated with severe sickle cell disease, early onset of painful crises, and severe anaemia, with typical haemoglobin levels of between 60 and 90 $g.l^{-1}$. Fetal haemoglobin (HbF) reduces the polymerisation of the HbS molecules, and offers some protection in sickle cell disease. Patients with high HbF levels (> 8%) tend to have mild phenotype with fewer symptoms. Hydroxycarbamide raises the HbF level and is now recommended as standard therapy for many patients [14]. Patients with HbSC disease typically have a higher haemoglobin level and generally have fewer symptoms, but if they require blood transfusion when acutely unwell are more likely to require exchange transfusion due to a higher haemoglobin (see Table 1).

The main pathology in sickle cell disease arises from the propensity of HbS molecules to form polymers when de-

 

**Table 1** Common forms of sickle cell disease and related haemoglobinopathies (modified from Ware 2017 [12]).

| | Haemoglobin type (% total) | | | | | | |
|---|---|---|---|---|---|---|---|
| **Sickle cell disease genotype** | **HbA** | **HbS** | **HbC** | **HbF** | **$HbA_2$** | **Clinical course** | **Prevalence in UK sickle cell disease population** |
| Sickle cell anaemia (HbSS) | 0 | 80–95% | 0 | 5–15% | < 3–5 | Severe | 50–60% |
| Sickle-C disease (HbSC) | 0 | 50–55% | 40–45% | < 3% | < 3–5 | Moderate | 25–30% |
| Sickle $ß^0$ thalassaemia (HbS $ß^0$ thal) | 0 | 80–90% | 0 | 5–15% | > 3–5 | Severe | 1–3% |
| Sickle $ß^+$ thalassaemia (HbS $ß^+$ thal ) | 10–25% | 70–80% | 0 | < 3% | > 3–5 | Mild | 5–10% |
| Other sickle variant (HbS other) | 0 | 50–60% | 0 | Variable | < 3–5 | Variable | 1–2% |
| Sickle trait HbAS | 55–65% | 30–40% | 0 | < 1% | < 3–5 | Benign | |
| Normal adult haemoglobin | 95–98% | 0 | 0 | < 1% | < 3–5 | | |

oxygenated, which causes the red cells to deform into the characteristic sickle shape. The polymers disaggregate with oxygenation so there is a continuous cycle of sickling and un-sickling as red cells travel to the peripheries and return to the lungs. If the red cells are delayed in their return to the lungs the polymerisation becomes more extensive. Extensive polymerisation of HbS causes damage to the red cell membrane and cytoskeleton, leading to the formation of irreversibly sickled cells and red cell haemolysis. Damaged red cells are removed by the reticulo-endothelial system. Changes in the red cell membrane cause increased adherence to the vascular endothelium, which leads to vaso-occlusion, ischaemia-reperfusion injury and end-organ damage. Intravascular haemolysis leads to nitric oxide depletion and release of free haem, which in turn may worsen vascular endothelial damage. Repeated cycles of haemolysis, ischaemia and inflammation result in the acute and chronic features typical of sickle cell disease. Haemolysis results in anaemia. Vascular endothelial damage is responsible for complications such as stroke, pulmonary hypertension and priapism. Vaso-occlusion causes acute and chronic ischaemia, acute painful crises and end-organ damage.

## Clinical features of sickle cell disease

The clinical features in sickle cell disease relate to acute painful crises, anaemia and infection, or acute or chronic end-organ damage. The clinical picture varies with age and is very variable between patients. Acute sickle-related complications are described in Table 2 and chronic sickle-related complications in Table 3. End-organ dysfunction associated with sickle cell disease and increased susceptibility to infection contributes to the increased risk of surgery in patients with sickle cell disease, particularly in older patients.

## Pre-operative screening for sickle cell disease

It is recommended that all patients at risk of haemoglobinopathy are screened for haemoglobinopathies before surgery, but repeated unnecessary screening should be avoided. In practice, this means all patients should be considered for screening, unless they are ethnically of solely northern or eastern European, Jewish or South-East Asian heritage, or have been screened previously.

The NHS sickle cell and thalassaemia screening programme was established in 2001 as part of the NHS Newborn Blood Spot screening programme, and was fully established in England by 2006, in Scotland by 2010, Northern Ireland by 2012 and Wales by 2013 [7]. This means that if a child was born in the UK after the introduction of the screening programme in their area, they will have been screened, the parents informed if they have sickle cell disease and the child referred to specialist care (see Fig. 1) [15]. Directed voluntary screening is used in the Republic of Ireland [11].

Hospital laboratories use their own local algorithm for screening. They may choose to do a rapid sickle solubility test to detect the presence of HbS and, if positive, then perform a full haemoglobinopathy screen using high performance liquid chromatography, capillary electrophoresis, mass spectrometry or gel electrophoresis, or they may choose to do the full haemoglobinopathy screen first. The haemoglobinopathy screen is highly sensitive, reliable and reproducible and detects those who are homozygous or heterozygous for HbS or other haemoglobinopathies. A positive sickle solubility test should not be used in isolation as it does not differentiate between heterozygous, compound heterozgous or homozygous states, and can give false negative results in neonates or in a heavily transfused patient.

**Table 2** Acute sickle-related complications in children and adults.

| Complication | Description |
|---|---|
| Acute painful crises | Affects fingers in infancy (dactylitis), long bones, sternum, ribs or back in older children and adults |
| Hyposplenism | Within first few years of life due to repeated vaso-occlusion and splenic infarction. |
| Adenotonsillar hypertrophy | Obstructive sleep apnoea, sleep disordered breathing, nocturnal hypoxia |
| Priapism | 'Stuttering' or acute fulminant. Occurs due to sickling localised to the penis, may result in impotence if prolonged. |
| Acute splenic sequestration crisis | Potentially life-threatening complication in 5 month–2 year-olds associated with massive splenomegaly, acute anaemia (Hb 10–30 $g.l^{-1}$), and hypovolaemic shock. |
| Aplastic crisis | Commonly parvovirus B19 infection (or Epstein-Barr virus or streptococcal). Aplasia may last 5–10 days. |
| Acute chest syndrome | New onset respiratory symptoms (chest pain, fever, tachypnoea, cough and wheeze), and new pulmonary infiltrates on chest X-ray. Common complication following surgery. |
| Neurological | Stroke seen in up to 10% of children. All children and young people aged < 17 years with sickle cell disease should undergo regular screening with trans-cranial Doppler to assess the risk of stroke, and the results should be available before elective surgery.<br>Ischaemic stroke/intracranial haemorrhage in adults. 'Silent' infarction seen in 40% of adults on MRI. May be associated with cognitive impairment. |

MRI, magnetic resonance imaging.

**Table 3** Chronic sickle-related complications in adults.

| | Complication |
|---|---|
| Renal | Hyposthenuria (all patients)<br>Proteinuria (40% adults)<br>Renal insufficiency (20% adults) |
| Cardiorespiratory | Obstructive sleep apnoea<br>Chronic lung disease (restrictive disease in 70%)<br>Congestive cardiac failure<br>Pulmonary hypertension (6% adults) |
| Orthopaedic | Avascular necrosis of the femoral head<br>Osteomyelitis |
| Surgical/urological | Cholelithiasis<br>Erectile dysfunction |
| Ophthalmological | Retinopathy |
| Dermatological | Leg ulcers |
| Infection-related | Gram negative sepsis – urinary tract infection, biliary sepsis, non-typhi salmonella infection |
| Transfusion/ treatment-related | Acquired red cell antibodies<br>Iron overload<br>Neutropenia (hydroxycarbamide treatment)<br>Hyperhaemolysis |

## Clinical networks and organisation of care

National Quality Standards require that patients with sickle cell disease be managed in a clinical network with an annual specialist review [1,2,6]. Planned surgery should ideally take place at a designated sickle centre with automated or manual exchange transfusion available on site, or with appropriate arrangements made in advance to access this if it is required [16]. Specialist advice must be sought if a patient is admitted to a hospital where there is no sickle haematology expertise.

There should be a nominated lead haematologist when an adult with sickle cell disease undergoes surgery, and for children a lead paediatrician or paediatric haematologist. Where surgery is planned outside the usual designated sickle centre, the patient's haematologist/paediatrician must be included in communications relating to the surgery. The haematologists are responsible for developing the peri-operative transfusion plan. The lead clinician in the Department of Anaesthesia is responsible for making sure that there is local departmental guidance for the peri-operative care of patients with sickle cell disease, developed in partnership with the haematology team. The Department may wish to identify a specific lead for this role; or may absorb this role into an existing role. The surgical team booking the patient for surgery is responsible for communicating the sickle cell disease diagnosis and for documenting this clearly in the patient record so that the relevant teams are aware at all stages of the patient pathway: haematology; anaesthesia blood; transfusion laboratory; waiting list co-ordinators; pre-assessment; and ward nursing staff. The surgical team must inform the haematology team (and paediatric team if a child) as soon

 

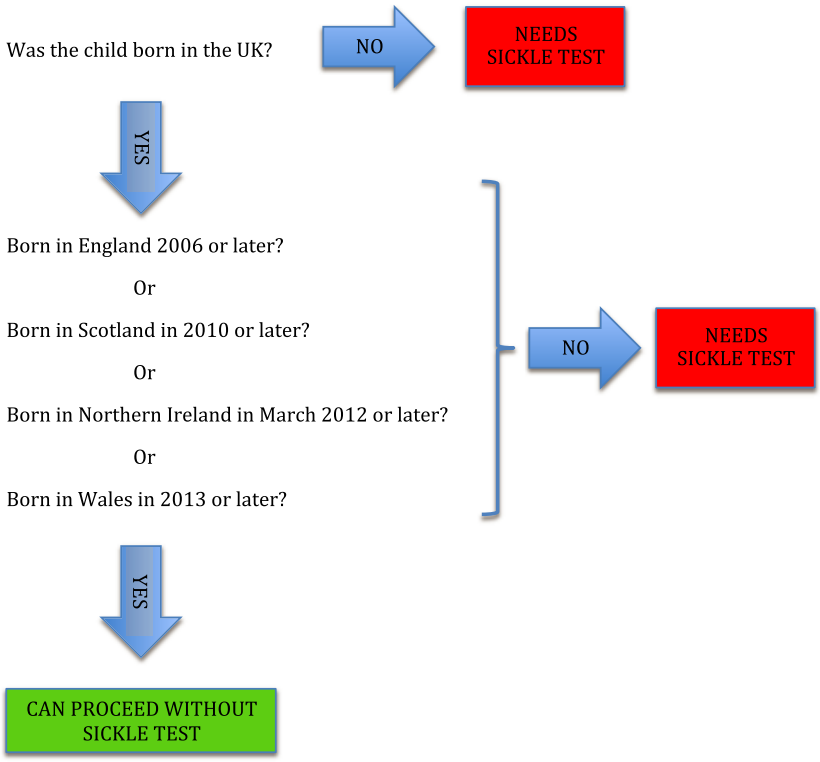


**Figure 1** Pre-operative sickle screening guideline for children and young people [15] (redrawn with permission). Consider the sickle cell status of an 'at risk' child using the flowchart. The sickle cell status should be known pre-operatively. [Colour figure can be viewed at wileyonlinelibrary.com]

as a date for surgery is known. The patient should be scheduled early on the operating list. The lead haematologist for the patient is responsible for arranging transfusion preparation when indicated and for informing the admitting team of the post-transfusion results. Last minute cancellations for administrative reasons must be avoided if the patient has been transfused pre-operatively, particularly if blood has been difficult to access due to alloimmunisation or previous transfusion reactions.

## Pre-operative assessment and preparation

A senior member of the anaesthetic pre-assessment team should review all elective patients in the pre-assessment clinic to assess arrangements for pre-operative transfusion, requirement for an ICU bed, or suitability for day surgery. The patient's existing pain management plan should be reviewed when discussing peri-operative analgesia, and the pain management team alerted if the patient is receiving treatment for chronic pain. Venous access should be discussed, particularly if known to be difficult.

All patients require a full blood count, urea and electrolytes and group and full red cell antibody screen before surgery. If the patient is transfused before surgery, or within the last 3 months, a repeat full blood count and antibody screen will be required < 72 h before the operation. It is important to make it clear on the sample request forms that the patient has sickle cell disease. The blood transfusion laboratory must be contacted directly with the patient details (including NHS number and transfusion history) so that the staff have time to find the relevant information from the hospital where the patient has been transfused, and also NHS Blood and Transfusion, and they can add the relevant flags on the transfusion laboratory information management system (LIMS).

Baseline oxygen saturation should be measured in the pre-assessment clinic. Symptoms of sleep disordered breathing should be sought, and overnight saturation measurement or formal sleep study undertaken if there is a suspicion of severe obstructive sleep apnoea. An echocardiogram should be considered for adults with symptoms suggestive of pulmonary hypertension ($S_pO_2$ < 94%, reduced exercise capacity). For children < 16 years old, the results of transcranial Doppler assessment should be available and documented from within the previous 12 months or, in the case of patients with HbSC or HbSBeta + thalassaemia, the last 2 years. If abnormal, there should be a multidisciplinary discussion as to how the child should be managed. An MRI/magnetic resonance angiogram may be required to determine whether there is any cerebral vasculopathy [13].

Some patients may be suitable for day surgery if they are undergoing a low-risk procedure and they are otherwise well. They can be discharged when they meet standard discharge criteria but should be scheduled early in the day to allow time for identification of any potential complications. The patient must have clear instructions about postoperative analgesia and mobilisation, and who to contact in case of concerns when they are at home.

Patients admitted as an emergency require special consideration as emergency surgery conveys a higher risk, and the patient is more likely to have a sickle crisis, either as the precipitating cause of the admission (e.g. priapism) or as a complication of surgery. The haematology team must be informed when a patient with sickle cell disease is admitted and requires emergency surgery. Communication with the transfusion laboratory (as per above) is important.

## Peri-operative management of patients with sickle cell disease

Surgery (emergency or elective) and pregnancy present particular physiological challenges to the patient with sickle cell disease and meticulous anaesthetic care is required. Surgery is associated with increased risk of sickle-related complications (acute chest syndrome, painful crisis, acute renal insufficiency or stroke) and surgical complications such as infection and venous thrombosis. Routine surgery should be avoided if the patient is febrile or having a painful crisis. There should be a low threshold for admitting patients to the high dependency or intensive care unit after surgery, depending on the surgical risk and patient comorbidities.

There are few formal studies to guide anaesthetic management in sickle cell disease; the following description is based on expert consensus opinion. The choice of anaesthetic technique (general +/- regional) depends on considerations such as the age and preference of the patient, the surgery planned and the preference of the anaesthetist and surgeon. The risks and benefits of regional anaesthesia should be considered in all cases, either as a sole technique or to provide supplementary analgesia for a patient undergoing general anaesthesia. There may be fewer sickle-related complications associated with spinal or epidural anaesthesia compared with general anaesthesia. The particular advantages of regional anaesthesia include excellent quality postoperative analgesia and improved peripheral blood flow secondary to sympathetic blockade. Regional anaesthesia may cause hypotension and hypoperfusion, and this should be treated early with vasopressors and intravenous fluids. Note that if a male patient has altered sensation due to regional anaesthesia they may not notice the presence of priapism. Men receiving regional anaesthesia will need to be counselled for this and be regularly examined to ensure that no priapism has occurred.

Standard monitoring should be used, as per Association of Anaesthetists guidelines [17]. If neuromuscular junction blocking drugs are used, neuromuscular monitoring must be used to ensure full reversal before awakening and tracheal extubation. Near-infrared spectroscopy should be considered to monitor cerebral oxygenation.

Pain may be a dominant clinical feature throughout the lives of patients with sickle cell disease [1,2,6]. Acute painful crises are common and postoperative pain can be difficult to manage, particularly if the patient has a chronic pain condition. Baseline analgesic use should be noted, and long-acting opioid medication should be continued in the peri-operative period. Opioid dependency is rare in sickle cell disease patients; opioid sensitivity is more common. The anaesthesia plan should include consideration of multimodal postoperative analgesia techniques (local/regional blocks, patient-controlled analgesia, nurse-controlled analgesia, oral analgesia). Patients may be familiar with patient-controlled analgesia techniques from management of pain associated with acute painful crises. The pain team should be notified in advance if a patient with sickle cell disease is undergoing major surgery, particularly if there is a history of opioid tolerance. An appropriate validated pain assessment scale should be used, and pain re-assessed regularly. The patient should be encouraged to report pain, particularly pain that is similar to their usual sickle pain and not associated with the surgical wound.

Patients with sickle cell disease have impaired urinary concentrating ability and become dehydrated easily. Dehydration must be avoided, particularly in patients with pre-existing renal dysfunction.

Starvation instructions should be documented clearly and reinforced with the patient and their family. Oral hydration is preferred, and patients should be encouraged to take free clear fluids up to 1–2 h before surgery, according to local protocol. A common scenario is that the patient is starved for too long. If oral hydration is not possible, or is likely to be inadequate, intravenous fluids should be considered. Meticulous intra-operative fluid management is required, with accurate measurement and replacement of fluid losses. Measurement of urine output, central venous pressure and cardiac output monitoring should be considered for major surgery. Postoperatively, intravenous fluids should be continued until the patient is

 

able to tolerate an adequate intake of oral fluids. Fluid balance should be monitored.

Baseline oxygen saturation should be documented pre-operatively and monitored if sedative premedication is given. Do not give continuous oxygen therapy unless necessary. Pre-oxygenation is recommended before induction of general anaesthesia. Hypotension should be avoided and, if the patient's trachea is intubated, controlled ventilation should be used to achieve good oxygenation and normocarbia. Postoperatively, oxygen should be administered continuously to keep the $SpO_2$ above baseline or 96% (whichever is the higher) for 24 h or until the following morning if the patient is able to mobilise freely. Oxygen saturation should be monitored continuously until it is maintained at baseline in air. Oxygen therapy may be required at night for several nights, particularly following thoracic or abdominal surgery. Early mobilisation, physiotherapy and support such as incentive spirometry every 2 h (or for young children, blowing bubbles) should be promoted after moderate or major surgery. Continuous positive airway pressure, high-flow nasal oxygen therapy, or a nasopharyngeal prong airway may be useful. Bronchodilator therapy should be considered for patients with a history of small airways obstruction, asthma or acute chest syndrome.

Patients should be normothermic during the peri-operative period, and hypothermia must be avoided as this will lead to shivering and peripheral stasis, which in turn leads to hypoxia and increased sickling. Avoid heat loss by active warming in the anaesthetic room and in the operating theatre, increasing the ambient temperature in theatre, avoiding unnecessary exposure and by using warmed fluids. Active warming should be continued in the post-anaesthesia care unit (recovery) or until the effects of anaesthesia and sedation have worn off. Temperature should be monitored regularly postoperatively. Note that a spike in temperature may be an early sign of sickling.

## Postoperative care

Patients with sickle cell disease have an increased risk of deep vein thrombosis. Thromboprophylaxis should be used for all peri- and post-pubertal patients as routine, and mobilisation encouraged postoperatively. Patients with additional risk factors such as continuing immobility, previous venous thromboembolism or indwelling lines (including children) may need special precautions. Expert guidance from a haematologist specialising in coagulation may be able to provide additional support and advice in such situations.

Patients with sickle cell disease are more susceptible to infection than the general population, including respiratory and postoperative wound infections. Infection in the peri-operative period may precipitate sickle complications such as painful crisis or acute chest syndrome. Antibiotic prophylaxis should be administered as dictated by the surgical procedure and local policy. Prophylactic penicillin can be temporarily halted in the peri-operative period if the patient is receiving gram-positive cover for the surgical procedure. Postoperatively, chest physiotherapy should be provided if the patient is unable to mobilise. Intravenous cannula sites should be inspected regularly for phlebitis and removed immediately if there are signs of redness or swelling. Patients should be encouraged to report symptoms of infection, such as shivering, muscle aches or productive cough. Blood cultures should be taken if the patient becomes pyrexial and antibiotics started if the temperature is $\geq 38.0^{\circ}C$ or if there are signs of sepsis.

Patients undergoing surgery should receive multidisciplinary care, with daily assessment by a haematologist (or paediatrician if a child) after moderate or major surgery. Sickle complications may be difficult to differentiate from postoperative pain or surgical complications, but a high index of suspicion should be maintained. General supportive therapy should be provided as above (warmth, hydration, analgesia, oxygen therapy). Regular monitoring of $SpO_2$ provides early warning of acute chest syndrome. Patients who have received a recent blood transfusion should be monitored for a transfusion reaction. Patients with acute life-threatening complications such as acute chest syndrome, stroke or sepsis should be admitted to intensive care and may require emergency exchange transfusion, as directed by the haematology team.

## Blood transfusion in patients with sickle cell disease

The British Society of Haematology has issued guidance on transfusion in sickle cell disease, including in the peri-operative period [3,4]. The risks and benefits of transfusion must be considered carefully and discussed with the haematologist and transfusion laboratory. The benefits of transfusion include increased oxygen carrying capacity, increased haemoglobin, suppression of sickle erythropoiesis and reduced risk of vaso-occlusion due to dilution of HbS. The risks of transfusion include hyperviscosity and increased sickling due to over-transfusion, allo-immunisation leading to haemolytic transfusion reactions, non-haemolytic transfusion reactions, hyperhaemolysis and transmission of infection. The

incidence of allo-immunisation is particularly high in patients in sickle cell disease, in part thought to be due to the inflammatory state of the patient at the time of transfusion, but also due to mismatch in the red cell pheno/genotype between the donor and recipient populations. Allo-immunisation is estimated to occur in 7–30% of patients with sickle cell disease. The provision of ABO, full Rh and Kell compatible blood reduces the risk of allo-immunisation, but does not eliminate it completely [18,19].

There is a paucity of high-quality data to inform transfusion decisions in sickle cell disease, particularly in adults > 40 years-old, those with co-existing medical complications, those undergoing emergency surgery or who have sickle genotypes other than HbSS. However, there are a number of key studies that have looked at the role of transfusion pre-operatively [20–23]. Howard et al. [23] provided the most compelling evidence to support pre-operative transfusion in HbSS patients undergoing low- and medium-risk surgery.

If transfusion is required, it is better to perform this electively to minimise transfusion reactions and reduce the risk of needing an emergency unplanned peri-operative transfusion. Pre-operative transfusion should be arranged by the haematology team, according to written clinical guidelines, depending on the sickle genotype, the age of the patient, comorbidities, type of surgery (low- medium- or high-risk, and transfusion history (see Appendix 1; Table 2) [4,23]. Transfusion may be given as a simple 'top-up' or as a partial or full exchange transfusion to reduce the HbS% to a target level. The transfusion method will depend on the baseline Hb, the health of the patient and the bleeding risk associated with the procedure. The target Hb should be around 100 $g.l^{-1}$ to avoid hyperviscosity and should not be increased by more than 40 $g.l^{-1}$ in a single transfusion episode. Patients of all genotypes undergoing high-risk surgery or those with significant comorbidity are likely to require pre-operative transfusion. An exchange transfusion should be considered in these patients. High-risk patients on a long-term transfusion programmes, for example, for primary or secondary stroke prevention, should have their sickle cell percentage optimised to < 30% pre-operatively. Note that some patients (e.g. with HbSC) have a relatively high resting Hb, sometimes up to 120 $g.l^{-1}$. Lowering the HbS% by partial exchange transfusion can potentially allow a higher Hb as the viscosity from the HbS is less contributory, so the target Hb suggested may be > 100 $g.l^{-1}$. These decisions should be guided by an expert in sickle cell disease (Table 4).

Patients undergoing emergency surgery should receive a simple top-up transfusion pre-operatively to a target of 100 $g.l^{-1}$ if the Hb is low, provided this will not delay surgery. If the Hb is ≥ 90 $g.l^{-1}$ and the risk of surgery is low, it is reasonable to proceed to surgery without delay and transfuse the patient intra-operatively or postoperatively if necessary. If there is any doubt about pre-operative transfusion preparation, the consultant anaesthetist should contact the relevant consultant haematologist.

The hospital transfusion laboratory may need to order special blood supplies from the appropriate transfusion service. Patients with sickle cell disease are advised to carry a transfusion card that includes information about allo-antibodies and their full red cell phenotype or genotype. Donor red cells should be HbS negative and must be compatible for ABO, Rh and Kell antigens and for additional known allo-antibodies. Blood should ideally be < 10 days old for simple transfusion and < 8 days old for exchange transfusion. Older blood may need to be given in difficult to transfuse patients or in an emergency. If the patient has been transfused within 28 days. there should be a minimum of 72 h between the group and save specimen and blood cross match for surgery. Patients with allo-antibodies or complex transfusion requirements may be more difficult to cross match and should have suitable blood on site even if the risk of transfusion is small.

## Obstetrics

Women with sickle cell disease should ideally be managed in an obstetric unit with a special interest in sickle cell disease [8]. Mothers with sickle cell disease have been over-represented in the Confidential Enquiries into Maternal Deaths, with estimated mortality around 1–3%. Perinatal mortality rates are also high, between 1 and 8%. Sickle complications may be precipitated by the physiological changes of pregnancy (increased metabolic demand, susceptibility to infection, pro-thrombotic state and aortocaval compression). Obstetric complications are also increased, specifically pre-eclampsia, intra-uterine growth retardation, preterm labour, antepartum haemorrhage and infection. A national study of maternal and fetal outcomes in patients with sickle cell disease showed a high incidence of painful crises (57%), caesarean delivery (38%), ICU admission (23%), low birth weight (23%) and premature delivery (5–6%). A high rate of complications was seen in patients with HbSS and HbSC, although sickle-related complications were more common in patients with HbSS [24]. Recent data from large centres with specialist services for sickle cell disease have reported no maternal deaths [25].

Antenatal assessment of patients should include specific consideration of the complications of sickle cell

 

**Table 4** Suggested transfusion strategy before elective surgery.

| Genotype | Surgical risk category | Baseline Hb ($g.l^{-1}$) | Suggested pre-operative transfusion |
|---|---|---|---|
| All genotypes | High-risk | – | Exchange transfusion aiming for Hb of 100 $g.l^{-1}$ |
| HbSS/HbSß$^0$ | Low- or medium-risk | < 90 $g.l^{-1}$ | Top-up transfusion aiming for Hb of 100 $g.l^{-1}$ |
| HbSS/HbSß$^0$ | Low- and medium-risk | ≥ 90 $g.l^{-1}$ | Partial exchange transfusion aiming for Hb of 100 $g.l^{-1}$ |
| HbSC | Medium-risk | – | Top-up transfusion or partial exchange transfusion aiming for Hb 100 $g.l^{-1}$ |

Transfusion decisions in other sickle variants (HbSD, HbS/HPFH, HbSß$^+$ thalassaemia, $HbSO_{Arab}$ should be made on a case-by-case basis, in discussion with the sickle haematologist, depending on the history/phenotype of the patient and the type of surgery.

disease [8]. Prophylactic transfusion is not routinely offered except for high-risk patients or multiple pregnancies [3]. All patients should be offered an anaesthetic assessment as a routine in the third trimester, and high-risk patients should be referred earlier during pregnancy. The obstetric anaesthetist should be informed if a patient is admitted with a sickle cell crisis during pregnancy or when labour commences.

Epidural analgesia is ideal for labour, particularly if there is opioid tolerance or sickle-related pain in the lower body. Thromboprophylaxis should be given, but attention must be paid to the timing of low molecular weight heparin when planning central neuraxial blockade. Regional anaesthesia is preferred for caesarean section as general anaesthesia carries additional risks compared with the non-sickle cell disease population [8]. If general anaesthesia is required, particular attention should be given to effective oxygenation during intubation. Passive nasal oxygenation using nasal cannulae or high-flow nasal oxygenation will prolong the apnoeic period before desaturation occurs. 'Ramping' should be considered using an Oxford Head Elevating Laryngoscopy Pillow (HELP®, Alma Medical, New Haven, UK) or similar, especially for the obese parturient, to optimise the position for intubation [26].

Labour and the early puerperium are high-risk periods for patients with sickle cell disease. High-dependency or ICU care should be considered, especially following general anaesthesia [27]. Postoperative analgesia after caesarean section should be optimised. Post-partum low molecular weight heparin should be prescribed with advice from the haematologist. The dose calculation should be based on post-delivery weight and usually continued for 6 weeks after caesarean section.

## Cardiac surgery

Although cardiac surgery using cardiopulmonary bypass would appear to be a hazardous undertaking in individuals with sickle cell disease, several publications detail the successful use of this technique in adults requiring heart valve surgery and children requiring surgery for congenital cardiac disease [28].

A variety of approaches are detailed including exchange transfusion before surgery, exchange transfusion during surgery and simple top-up transfusion before and during surgery. Even complex surgery (such as pulmonary endarterectomy) and techniques such as deep hypothermic circulatory arrest have been performed successfully [29]. One series described a matched pair analysis comparing the outcomes of patients with HbSS, HbSC and HbAS without pre-operative transfusion to controls with normal haemoglobin. HbSS, HbSC and HbAS patients received standard bypass care using systemic hypothermia, aortic cross-clamping and cold crystalloid antegrade cardioplegia, with simple top-up transfusion during and after bypass only. There was no significant difference in outcome between sickle cell disease or trait patients and matched controls [30]. Where automated apheresis is available (as it is in the UK), exchange transfusion is the preferred transfusion modality before cardiac surgery.

All these studies have emphasised the importance of cooling to the minimum temperature necessary and of careful monitoring and management of arterial and mixed venous oxygen and pH levels.

## Ear, nose and throat surgery in children

Adenotonsillar hypertrophy is common in children with sickle cell disease. Adenotonsillectomy is indicated for children with severe obstructive sleep apnoea and nocturnal desaturation on sleep study, particularly those at risk of stroke. While the surgery itself may be relatively minor, it represents a challenge in these children and is graded as moderate risk due to oedema after surgery and the potential for airway obstruction/hypoxia in the postoperative period. Children who are < 5 y with severe obstructive sleep apnoea are at particular risk of postoperative oxygen desaturation.

Children should be prepared for surgery with pre-operative transfusion, as per standard guidance. Blood

should be available in case of a sickle cell disease complication in the peri-operative period. Special care is required for young children with high transcranial Doppler flows who are at risk of stroke. Children < 5 years old or with a history of severe obstructive sleep apnoea may require admission to paediatric ICU/HDU for postoperative monitoring. In some centres, a nasopharyngeal airway is inserted routinely as this avoids postoperative hypoxia, and may also avoid the requirement to admit the patient to paediatric ICU [31]. The nasopharyngeal airway should be the same size as an age-appropriate tracheal tube and should be placed in theatre under direct vision by the ENT surgeon. The nasopharyngeal airway should be secured carefully and suctioned regularly to make sure it remains patent. It is usually left in place for one to two nights after surgery, in discussion with the ENT surgeons. It should not be replaced if it falls out due to the risk of bleeding from the surgical site [31].

The child should be kept well hydrated and intravenous fluids continued until the child is drinking. Postoperative nausea and vomiting are common after adenotonsillectomy and should be treated promptly. Standard analgesia regimens should be used and should take account of the fact that sore throat may last for 8–10 days postoperatively.

## Use of a surgical tourniquet

Use of a tourniquet to reduce blood loss during surgery remains an area of debate due to the theoretical risk of sickling in the limb to which the tourniquet is applied, or following reperfusion of the affected limb, but there is little high-quality evidence to support practice. Pre-operative transfusion and meticulous peri-operative care may reduce the risk of sickling in this context. If the benefits of a tourniquet are deemed to outweigh the risks, the limb should be exsanguinated carefully before inflation of the tourniquet and the surgical time and tourniquet time should be kept to a minimum [32]. Sickling would theoretically be less in a patient well transfused with a low HbS%.

## Management of the difficult to transfuse patient

Patients with sickle cell disease may be difficult to transfuse due to the presence of specific rare or multiple red cell allo-antibodies or a history of hyperhaemolysis. In this situation there will need to be careful multidisciplinary team discussion about the risks and benefits of pre-, peri- or postoperative transfusion and a detailed transfusion plan should be produced by the haematologists. These cases should be discussed in the multidisciplinary team meeting with support from the allocated transfusion consultant where this facility exists. In some situations, it may be appropriate to use pre-operative erythroid-stimulating agents or hydroxycarbamide to optimise pre-operative haemoglobin and reduce the chance of sickling. Likewise, premedication with intravenous immunoglobulin and steroids in those with previous severe transfusion reactions may be considered. For those who are difficult to transfuse, in all but the most minor of surgery, blood ought to be available on site on the day of surgery even if transfusion is not planned.

In patients who refuse blood transfusion (e.g. Jehovah's Witnesses), the risks of proceeding without blood transfusion are higher than in non-sickle patients. This should be discussed with the patient and the discussion documented in the patient record. The use of pre-operative erythroid-stimulating agent or hydroxycarbamide may be appropriate.

The use of cell salvage for peri-operative blood conservation has been described in recent Association guidelines [33]. The concern about cell salvage in sickle cell disease is whether the cells would withstand the environment of the extracorporeal circulation, but there are no randomised controlled trials to guide practice. There have been reports of high rates of haemolysis in salvaged red blood cells rendering them unsuitable for re-infusion [34]. There are two case reports showing that cell salvage may be effective in adults; in one of these, the patient had received a full exchange transfusion before surgery and their HbS% was only 25%, and in the other, the patient received one unit of previously donated autologous blood [35,36]. Several sickle centres use cell salvage routinely in adult patients with sickle cell disease who have had a red cell exchange pre-operatively [JH, ST personal communication]. Cell salvage may also have a role in the difficult to transfuse patient or for urgent surgery in a patient with very low haemoglobin. Further investigation of the role of cell salvage in sickle cell disease patients is needed.

## COVID-19 pandemic

The COVID-19 pandemic is a current concern, and knowledge is evolving rapidly. Latest guidance should be consulted (e.g. National Haemoglobinopathy Panel (NHP) [37], Public Health England [38], the British Society for Haematology [39], Royal College of Paediatrics and Child Heath [40]). Emerging data suggest that patients with sickle cell disease are at increased risk of severe COVID-19 infection but those with otherwise uncomplicated disease can have a relatively mild clinical course with very good outcomes [38–44]. It is important that essential treatments (such as transcranial Doppler screening in children or blood

 

transfusion for stroke prevention) are not delayed unnecessarily [39]. Patients may present with vaso-occlusive crisis due to COVID-19 infection. They are susceptible to bacterial infection due to functional hyposplenism and should be assessed if they develop a fever to avoid confusion between bacterial sepsis and coronavirus infection [39]. Patients with sickle cell disease should be managed according to standard COVID-19 treatment protocols and should be included in potentially life-saving interventions such as respiratory support, depending on pre-existing comorbidities.

## Acknowledgements

JH has received funding from Global Blood Therapeutics, Imara Inc, Novartis, Novo Nordisk, Forma and Agios for consultancy work. DW has received lecture and advisory fees from Aguettant Ltd, Medtronic and BD, all donated to the Lifebox Foundation and the World Federation of Societies of Anaesthesiologists. No other competing interests declared.

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# Appendix 1 Classification of surgical procedures, adapted from [20].

## Low-risk procedures

Surgery involving the eyes, skin, nose, ears and distal extremities as well as those pertaining to the dental, perineal, and inguinal areas (e.g. inguinal hernia repair, myringotomy, and dilatation and curettage).

## Moderate-risk procedures

Surgery involving the throat, neck, spine, proximal extremities, genito-urinary system, and intra-abdominal areas, such as caesarean section, splenectomy, cholecystectomy and hip replacement.

## High-risk procedures

Surgery involving the intracranial, cardiovascular and intrathoracic systems (e.g. craniotomy and heart valve replacement).

 