Update on sickle cell disease

Sickle cell disease is thought to affect 1/2000 births in the UK, with 12 500 affected patients across the country (NHS Sickle Cell and Thalassaemia Screening Programme, 2010). However, its increasing prevalence is not necessarily matched by an increased awareness among patients and doctors of its complications and management, and the average life expectancy of patients with sickle cell disease extends only to the fifth decade (Platt et al, 1994).

This article focuses on the practical management of patients with some of the acute complications of sickle cell disease that may be encountered in general and emergency medicine, before outlining approaches to long-term management.

What are the sickling disorders?

Homozygous haemoglobin S (HbSS), termed sickle cell anaemia, is the commonest of the sickling disorders, although other genotypes can also result in sickling (*Table 1*). While these conditions may have subtly different clinical pictures, the paucity of clinical trials in this field means that their management is often equivalent.

Pathophysiology

Sickle cell disease has been described as the first 'molecular' disease. In 1949 it was demonstrated that sickled red cells (*Figure 1*) are the consequence of a structural defect in the haemoglobin molecule. Shortly thereafter, the precise amino acid abnormality was defined (β6Glu>Val), itself caused by a single nucleotide substitution in the β-globin gene (reviewed in Orkin and Higgs, 2010).

Although superficially simple at a genetic level, the sickle mutation provokes a cascade of changes in the vasculature resulting in a complex multisystem disorder. However, despite an advancing understanding of its pathophysiology, there has been little translation into therapeutics and patients with sickle cell disease still face substantial challenges to the effective management of their disease. In each of the following acute presentations, early specialist input from haematologists is essential.

Acute presentations

Vaso-occlusive crises

Vaso-occlusion, with downstream ischaemia and reperfusion damage, is the hallmark of sickling disorders. Vaso-occlusive crises are also the commonest acute complication encountered by hospital physicians, with painful crises being the prompt for over 80% of admissions for patients with sickle cell disease in the UK (Brozovic and Anionwu, 1984).

The mechanisms by which vaso-occlusive crises arise are more complex than the simple blockage of small vessels by sickled red cells. Many additional abnormalities have been defined, including enhanced leucocyte adhesion to the vascular endothelium, endothelial cell activation and platelet activation (*Figure 2*) (Conran et al, 2009; Rees et al, 2010).

While these findings suggest targets for future treatments, management currently remains supportive. Practically, this means effective analgesia and efforts to circumvent any ongoing prompts to sickling. Since

Figure 1. The blood film in sickle cell disease shows frequent 'sickled' or boat-shaped cells. Several additional features also present in this film: nucleated red cells (arrowed) and target cells (arrowhead). There is also evidence of polychromasia (cells with a more bluish tinge, because of their increased RNA content), which reflects an increased reticulocyte count.

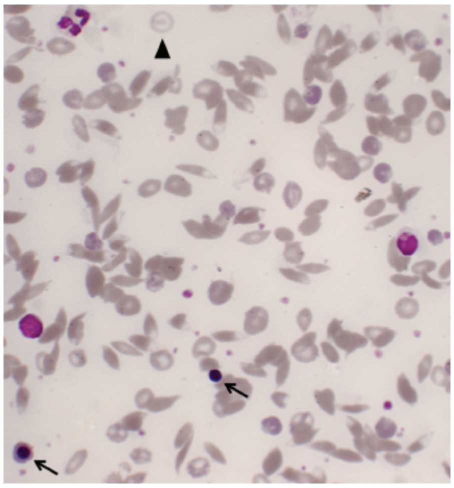

Table 1. Sickling disorders	
Genotype	**Comment**
HbSS, sickle cell anaemia	Commonest sickling disorder
HbSC	Common sickling disorder
HbS β thalassaemia	Inheritance of β_0 with β_s is clinically similar to HbSS; β+ allele with β_s gives a milder phenotype
HbS/DPunjab	Seen most commonly in patients of north Indian ethnicity
HbS/E	Uncommon
HbS/OArab	Rare
Several other genotypes described	All rare

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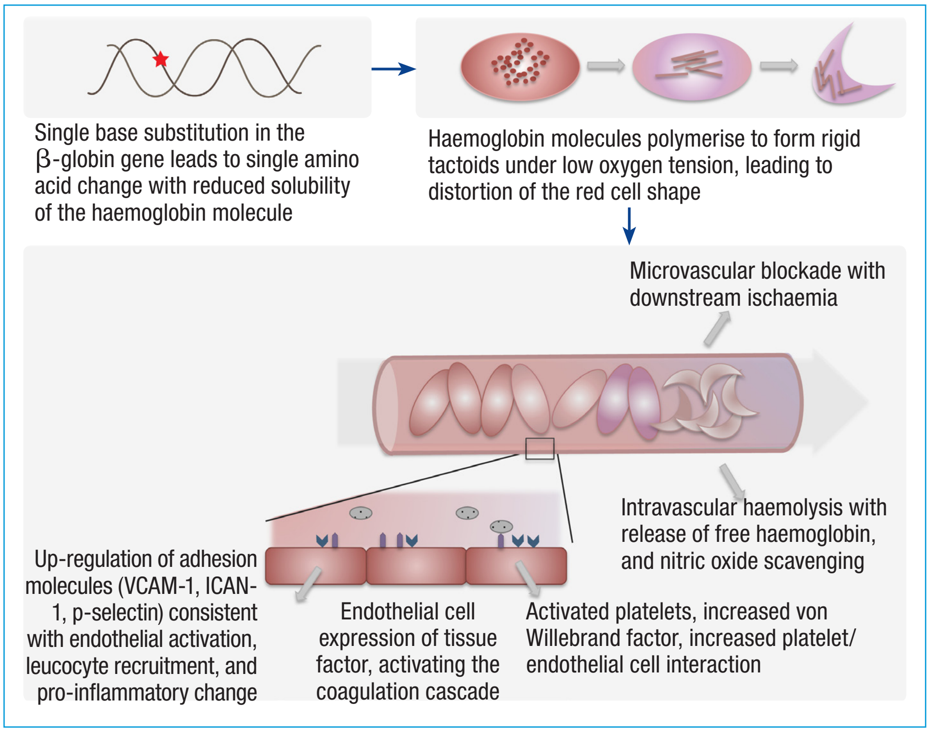

Figure 2. Mechanisms of disease. The genetic change in sickle cell anaemia results in a haemoglobin molecule that is less soluble than normal under hypoxic conditions. Polymerizing haemoglobin molecules cause the formation of insoluble tactoids, which result in the distortion of the red cell into the characteristic sickle shape. Recurrent vaso-occlusion, ischaemia and reperfusion damage occurs. Studies have also demonstrated increased expression of markers of the activation of endothelial cells, platelets and the coagulation cascade, giving a pro-inflammatory picture. The presence of intravascular haemolysis also releases free haemoglobin which is capable of scavenging nitric oxide – a key regulator of normal vascular tone and reactivity.

patients with sickle cell disease often have strategies for managing pain at home, many will present only once they are no longer coping with simple analgesics; this is emphasized in a guideline from the National Institute for Health and Care Excellence (2012), which advocates formal pain scoring and the use of parenteral opiates as immediate management for patients who have already used non-opiate analgesics at home. A cycle of assessment, analgesic dosing and reassessment is needed, with subsequent use of patient-controlled analgesia. A possible treatment algorithm is shown in *Figure 3*.

In most cases, the precipitant of a painful crisis is unknown. However, cold, dehydration and infection are commonly associated with the onset of vaso-occlusive crises (Serjeant et al, 1994), and should be treated promptly. The functional hyposplenism of patients with sickle cell disease necessitates a low threshold for empirical treatment of suspected infections.

Treatments for vaso-occlusive crises that address the underlying disease mechanisms are few, but early phase studies suggest that agents including pan-selectin inhibitors might abbreviate painful crises and reduce opiate requirements (Telen, 2014). For patients with frequent painful crises (>3/year) evidence from large-scale randomized controlled trials supports long-term treatment with hydroxycarbamide (Charache et al, 1995).

Acute chest syndrome

The acute chest syndrome is the outcome of several possible insults including pulmonary infection, fat embolism, sickling within the pulmonary microvasculature, and painful crises affecting the chest, back and ribs. It is characterized by progressive hypoxia and the development of pulmonary infiltrates on the chest X-ray along with fever, chest pain, tachypnoea and wheeze or cough, and it can herald a vicious cycle in which hypoxia and sickling in the pulmonary vasculature become mutually reinforcing. The urgency of recognizing this presentation is underscored by the observation that 13% of patients with acute chest syndrome will require invasive respiratory support. Even with optimal management, there is a mortality of 3% (Vichinsky et al, 2000), and acute chest syndrome is implicated in 25% of deaths in patients with sickle cell disease (Paul et al, 2011). Clinicians must maintain a high index of suspicion for incipient acute chest syndrome in any sickle cell disease patient with chest or back symptoms.

The focus of treatment is on increasing oxygenation and stalling the sickling process, and high-flow supplemental oxygen is essential. Since the radiological and clinical features of acute chest syndrome overlap with those of pneumonia, appropriate antibiotic cover is also prudent. Top-up transfusions may improve oxygenation and limit sickling if the patient's resting haemoglobin permits (Emre at al, 1995; see Transfusion, below), but in many cases the downward spiral of sickling and hypoxia can be halted only by a major reduction in the proportion of HbS – i.e. by red cell exchange transfusion. In most UK centres, exchange is performed using an automated system, although in emergency situations a manual exchange can also be attempted. Typically, the exchange aims to give an HbS level of <30% with a haematocrit of <30%, although the evidence base for these targets remains poor.

Following acute chest syndrome, there is randomized controlled trial evidence to support the use of oral hydroxycarbamide to reduce the risk of further episodes (Charache et al, 1995).

Fever and infection

Splenic autoinfarction and functional hyposplenism is apparent early in life for patients with homozygous sickle cell disease, and is likely to be caused by chronic sickling in the spleen. Consequently, the risk of bacterial sepsis particularly from encapsulated organisms, such as *Streptococcus pneumoniae* and *Neisseria meningitidis*, is increased; until recently, this was the leading cause of mortality in children with sickling disorders. The immunization programme for patients with sickle cell disease mirrors that for asplenic patients, and all children with sickle cell disease should be treated prophylactically with penicillin or a suitable alternative if allergic. Many centres advocate ongoing penicillin prophylaxis in adults, although evidence for this remains incomplete.

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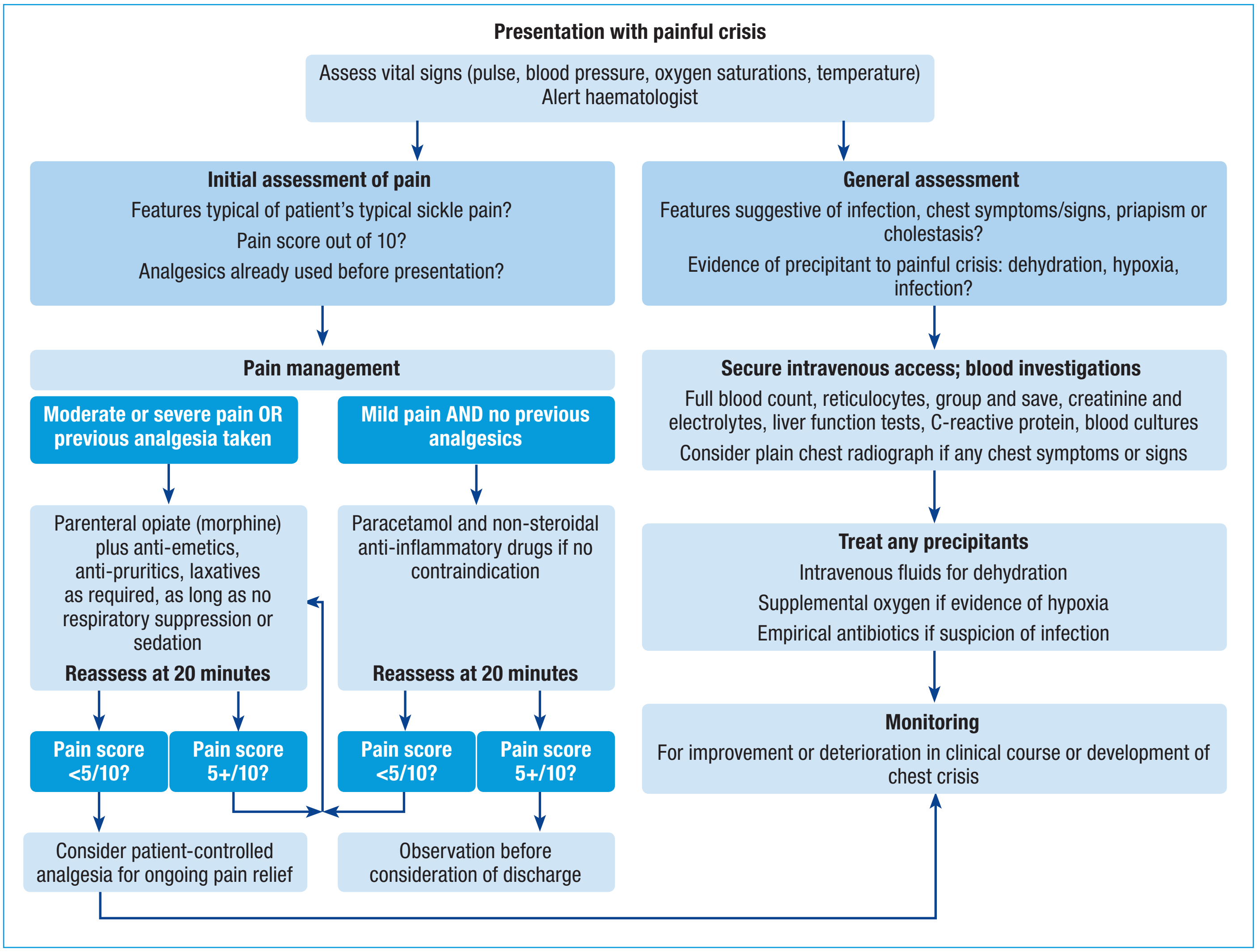
Figure 3. Painful crisis. A schedule of repeated assessment, parenteral analgesic and reassessment is needed for the rapid resolution of the sickle painful crisis. Management of precipitating factors and careful monitoring for the development of complications such as acute chest syndrome is also essential. N.B. Centres will have local protocols for the management of painful crises; not all centres use the ten-point pain scale suggested here.



Nevertheless, patients may still present with acute infective complications, and prompt empirical antimicrobial treatment is warranted. Atypical organisms such as *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae* are among the commonest infective causes of acute chest syndrome (Booth et al, 2010). Infection with *Salmonella* species is more common than in the general population, perhaps as a result of sickling in the gut lumen and impaired mucosal integrity; it is one of the commoner organisms identified in sickle cell disease patients with osteomyelitis.

Stroke

This can be a devastating complication of sickle cell disease, with up to 25% of patients suffering a stroke before the age of 45 years. The incidence of stroke in patients with sickle cell disease is highest in early childhood, peaking at >1% per year for children aged 2–5 years (Verduzco and Nathan, 2009).

The pathological basis of stroke in sickle cell disease is the subject of debate. Many of the aspects of sickle pathophysiology represented in *Figure 2* will be implicated, but the involvement of larger vessels as well as the microvasculature suggests that the pathophysiology here is incompletely understood. Strokes may also be haemorrhagic, either secondary to cerebral artery aneurysms or to the formation of abnormal arterial collaterals around stenosed major vessels.

The management and, critically, the prevention of stroke in this population has been the focus of randomized controlled trials. In children, Doppler estimation of middle cerebral artery blood velocity correlates with the risk of stroke (with higher velocities in more stenotic vessels). The STOP1 trial (Lee et al, 2006) demonstrated that the incidence of stroke in a high-risk population could be diminished by regular transfusions to reduce the circulating HbS percentage. The optimal long-term management of these patients remains to be defined, although many centres continue with a regular transfusion programme into adulthood, with a requirement for iron chelation. The possibility of switching from chronic transfusion to hydroxycarbamide treatment in secondary stroke prevention (aiming in part to prevent iron overload) has been assessed in children, but was not superior to transfusion therapy (Ware et al, 2012); however, for primary stroke prevention in children with sickle cell

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disease, hydroxycarbamide has been found to be useful in selected high risk patients (Ware et al, 2016). In adults, the data remain limited but do not suggest a convincing role for hydroxycarbamide alone in stroke prevention.

Aplastic crises

Parvovirus B19 infection is the classic cause of an aplastic crisis in patients with sickle cell disease (and other haemolytic anaemias). The virus binds to the P-antigen on the surface of erythroid precursors and induces a maturation block. The consequence is a failure of production of mature red cells, manifest by a complete reticulocytopenia and an acute drop in haemoglobin. Serological (IgM) or polymerase chain reaction positivity confirms the diagnosis. Affected patients need transfusion to maintain their haemoglobin until the virus is cleared and erythropoiesis resumes.

Transfusion in patients with sickle cell disease

Transfusion plays an important role in the management of patients with sickling disorders. Although the haemoglobin level may be markedly low, this in itself is not a reason for transfusion: the haemoglobin dissociation curve in sickle cell disease is shifted to the right, facilitating oxygen delivery. Patients presenting with painful crises also do not typically need transfusion. However, simple top-up transfusions are likely to form part of the initial management of patients with acute chest syndrome and aplastic crises. Exchange transfusions are important in established acute chest syndrome and acute stroke, where a more rapid reduction in HbS% is needed.

Table 2 highlights some of the generally accepted indications for transfusion in patients with sickle cell disease. Where a top-up transfusion is planned, the aim should be to maintain a haematocrit of <30%, to avoid increased viscosity.

The differences in blood group antigen patterns between patients with sickle cell disease and the majority of UK blood donors mean that alloimmunization can be a problem (Yazdanbakhsh et al, 2012). Therefore, all patients with sickle cell disease should receive blood that is phenotyped not only for ABO and RhD, but also for groups C, c, E, e and Kell as a minimum.

Chronic complications and proactive management

As well as the acute complications described above, patients with sickle cell disease also have chronic subclinical sickling leading to a gradual deterioration in vital organ function. The resulting complications include those in *Table 3*; although a detailed review of these is beyond the scope of this article, it is important to remember that patients may present acutely with decompensation of any of these longstanding problems.

Delaying or preventing the development of these life-limiting conditions is one of the primary aims of long-term sickle cell disease management. There are few high-quality trials to guide management, but a multicentre trial with a 17-year follow-up suggests a survival benefit for patients treated with hydroxycarbamide (Steinberg et al, 2010). This remains the only agent shown to improve long-term outcomes in sickle cell disease to date.

Modifying the phenotype and curative strategies?

An intriguing aspect of sickle cell disease is the wide variation in phenotype that patients manifest. In some, the clinical picture is dominated by frequent vaso-occlusive crises, while in others haemolysis is a more prominent feature. Still others will have a very mild clinical picture, being only rarely affected by crises of any type.

The determinants of this variation are important, since they may provide a means of modifying the clinical phenotype of severely affected patients. The best known modifier to date is the level of fetal haemoglobin (HbF): patients who co-inherit hereditary persistence of HbF alongside their sickling disorder tend to have a more benign clinical course (Murray et al, 1988), suggesting that increasing HbF might be a useful therapeutic goal. This is one of the mechanisms by which hydroxycarbamide acts, but its impact is often limited and it can be difficult to predict which patients are likely to respond.

A more definitive solution would be to reactivate the natural production of HbF, and attempts to reverse the switch between fetal γ-globin and adult β-globin gene expression, thereby reactivating HbF production, are the focus of intensive research. In this respect, the study of these diseases is in the vanguard of efforts to modulate gene expression for therapeutic purposes (Bauer et al, 2012). Disrupting the expression of BCL11a, one of the key transcription factors responsible

Table 2. Possible indications for blood transfusion in sickling disorders

Top-up transfusion	Exchange transfusion
Acute chest syndrome (early stages) (Vichinsky et al, 2000) Preoperative (Vichinsky et al, 1995; Howard et al, 2013) Aplastic crisis* Sequestration crisis* Severe vaso-occlusive crisis*	Acute chest syndrome (Vichinsky et al, 2000) Ischaemic stroke in children Preoperative (major surgery)* Intrahepatic cholestasis*

** Widely performed, but without optimal supportive evidence*

Table 3. Chronic complications of the sickling disorders

Complication	Comment
Pulmonary hypertension	Common complication, monitoring by regular echocardiogram assessment of right atrial pressure and tricuspid regurgitation
Chronic kidney disease	Sickle cell nephropathy (heralded by proteinuria), renal papillary necrosis, renal medullary carcinoma
Sickle liver disease	Including gallstones, hepatic sequestration, intrahepatic cholestasis
Skeletal complications	Avascular necrosis of the femoral or humeral head, generalized osteopenia, vertebral collapse
Leg ulcers	Especially common at the malleoli
Proliferative retinopathy	Especially common in patients with haemoglobin SC disease

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for silencing fetal haemoglobin production, significantly ameliorates the severity of disease in a mouse model of sickle cell anaemia (Xu et al, 2011). However, finding a way to translate this into the clinical setting is challenging.

Such strategies remain experimental, and at present the only potentially curative approach to sickle cell disease is haematopoietic stem-cell transplantation. The decision to proceed to transplantation is fraught with difficulties, and the availability of matched donors can be limiting. Together these factors may explain why relatively small numbers of patients with sickle cell disease have been transplanted to date.

As our understanding of the nature of sickling disorders expands, new potential targets for treatment are being uncovered, and there are many agents currently being investigated in clinical trials. A phase 3 trial of the selectin inhibitor rivipansel aims to determine whether this agent can shorten the duration of painful crises and reduce the need for opiates. Vorinostat, a histone deacetylase inhibitor, is another agent in active clinical trials: as well as being an HbF inducer in erythroid cells, vorinostat is also thought to inhibit VCAM-1 expression (*Figure 2*). Drugs targeting the inflammatory and oxidative processes in sickle cell disease include *N*-acetylcysteine, and this is the subject of a phase 3 trial to assess whether it is able to reduce the frequency of painful crises.

Conclusions

Sickle cell disease is a complex multisystem disorder that exacts a heavy price in terms of morbidity and mortality. Although treatments are currently largely supportive, progress in understanding the pathophysiology of sickle cell disease holds promise for future therapies. Until curative strategies are widely available, however, a combination of patient education, proactive management by an effective multidisciplinary team, and an awareness of the major acute complications will be the mainstay of care for this growing population. **BJHM**

Conflict of interest: none.

KEY POINTS

- Sickling disorders include sickle cell anaemia, haemoglobin SC disease and sickle β thalassaemia.
- Painful vaso-occlusive crisis is the commonest presentation.
- Painful crises require urgent analgesia, and a cycle of pain scoring, analgesic dosing and reassessment is essential for optimal management.
- Acute chest syndrome is a serious acute complication with a high mortality rate.
- Exchange transfusion to lower the HbS percentage is required in acute chest syndrome.
- Blood transfusions in sickle cell disease should be subject to extended phenotyping, and the post-transfusion haematocrit should be no higher than 30% to avoid increased viscosity.
- Mechanisms for increasing haemoglobin F levels (including hydroxycarbamide) are likely to improve the outcome for patients with sickle cell disease.

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