

# Understanding sickle cell anaemia

Sickle cell awareness day (4 July) kicks off a campaign that runs to the end of the month. In this article, **Susan Allen** helps pharmacists understand the medical needs of — and support required by — patients with sickle cell anaemia

**Q**uality of life and life expectancy for patients with sickle cell disease has improved considerably over the past 25 years. In 1973, their average life-span was 14 years. Now, it is closer to 50 years.<sup>1</sup>

The birth incidence of haemoglobinopathies in the UK is approximately 250 per annum. This now exceeds cystic fibrosis and phenylketonuria births. The UK has an estimated 12,500 adults and children with a sickle cell disease.<sup>2</sup> This term describes inherited abnormal haemoglobin formation due to the presence of haemoglobin S (HbS). There are three types of sickle cell disease: sickle cell anaemia, haemoglobin sickle cell disease and sickle beta thalassaemia. Of these, sickle cell anaemia is the most common.

An individual's haemoglobin (Hb) is determined by his or her genetic make up. There are over 300 types of Hb, the most common being HbA, which refers to adult haemoglobin. Usually, one HbA gene is inherited from each parent. A healthy combination of two HbA genes (HbAA) results in the manufacture of HbA in red blood cells. These cells efficiently transport oxygen and maintain their flexible, round shape so they can easily travel through the body's smallest capillaries.

Individuals who inherit an abnormal Hb gene from one parent and a normal HbA gene from the other have no disease, but are said to have a trait. An estimated 170,000 people in the UK have sickle cell trait.<sup>3</sup> Estimates suggest that the sickle cell trait (HbAS) is present in<sup>3</sup>:

- One in four west Africans
- One in 10 Afro-Caribbeans
- One in 20–50 Asians
- One in 100 northern Greeks

The only time someone with sickle cell trait may be vulnerable is if there is limited oxygen (eg, at high altitudes or if under anaesthesia). A more common concern for people with the trait is if they have a child with another person also with the trait or with a carrier of another significant variant haemoglobin. Their child would have a 1 in 4 risk of being born with a sickle cell disease.

The sickle gene mutation arose in tropical areas. Children with the sickle cell trait are more resistant to falciparum malaria than those with two normal HbA genes (HbAA). However, those with two sickle cell genes (HbSS) will have sickle cell anaemia.

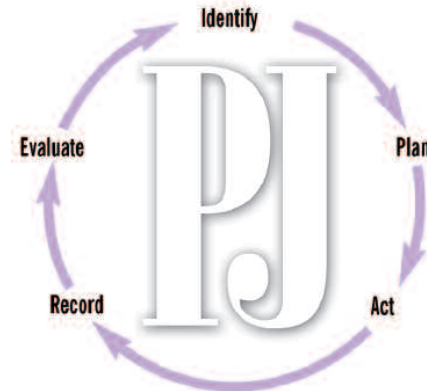
## HbSS and sickle cell anaemia

A red blood cell containing only HbS and no normal HbA is capable of carrying oxygen but when the HbS gives up its oxygen to the



Dr Gopal Murthi/SPL

**Sickle-shaped red blood cells have shortened life spans and carry less oxygen than normal red cells**



## Identify knowledge gaps

1. What are the symptoms of sickle cell anaemia?
2. What drugs are involved in the management of sickle cell anaemia?
3. What support can pharmacists give to patients with sickle cell anaemia?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in "Plan and record", (available at: [www.rpsgb.org/education](http://www.rpsgb.org/education)). This article relates to "drug therapies" (see appendix 4 of "Plan and record").

tissues, the HbS molecules can crystallise. These crystals are sticky and stack-up to form long rods, distorting the red cell, making it rigid and sickle shaped.

When the sickle-shaped red blood cells are reoxygenated they regain their original round shape but, with repeated oxygenation and deoxygenation, they become increasingly hard and brittle and, eventually, irreversibly sickled. Once irreversibly sickled, the cells are destroyed by the reticulo-endothelial system. Depending on the severity of the disease, sickle cells live for between five and 30 days, compared with the 120-day lifespan of normal red blood cells. The shortened life-span of red cells leads to haemolytic anaemia. It is important to note that this is not the same as iron deficiency anaemia because the iron component of destroyed red blood cells is stored for reuse.

**Symptoms and complications** Despite advances, there is considerable morbidity and mortality associated with sickle cell disease. The many health problems associated with sickle cell anaemia arise because of the red cells' sickle shape, rigidity, shortened life-span and inefficient oxygen transportation.

Sickle cells tend to clog together, causing occlusion of the smaller blood vessels and

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## Panel 1: Symptoms and complications of sickle cell anaemia



**The lower back is a common site of pain in patients with sickle cell anaemia**

**Pain** The pain of sickle cell anaemia varies widely. Some patients are pain-free most of the time, while others frequently suffer severe pain. The most common sites of pain in children and adolescents are the hands, arms, legs, chest and lower back. Different patients have tried to describe their pain:

- "A constant hammering inside your bones"
- "A real crisis when it comes...there is no magic, nothing you can do...there is nothing because it comes full on".

**Infection** People with sickle cell anaemia are particularly prone to both minor and life-threatening infections. The reason for this susceptibility is complex and includes reduced splenic function and abnormalities of antibody production and leukocyte function. In those with sickle cell, septicaemia and meningitis due to *Streptococcus pneumoniae* is the most common cause of death in early childhood — they have an estimated 400-fold increased risk compared with children without sickle cell. Bacteria rapidly take hold and an infant can die from a bacterial infection in as little as nine hours from the onset of fever. Fever in patients under five-years old often indicates life-threatening bacterial infection and must be treated rapidly and aggressively. As the child grows, immunity develops and pneumococcal infections become less frequent. However, other infections in areas damaged by ischaemia or necrosis, such as the lungs, urinary tract and bones (osteomyelitis) occur more often.

**Haemolytic anaemia** The bone marrow can have difficulty maintaining a sufficient level of red blood cells in sickle cell anaemia. Haemoglobin and haematocrit levels can fall and the patient experiences the symptoms of anaemia, such as fatigue, headaches and cardiac failure.

**Jaundice** A yellowing of the skin and eyes is a sign of rapid breakdown of red blood cells and is often seen in people with sickle cell anaemia. It is not a cause for concern unless it worsens. This can warn of an impending crisis.

**Stroke** Sticky, sickled red blood cells adhere to blood vessel walls causing narrowing and sometimes occlusion, leading to a life-threatening stroke. Ten per cent of patients will have a stroke before they

reach the age of 20. The most common deficit following a stroke in childhood is diminished mental function, and children with sickle cell anaemia tend, on average, to have a lower IQ than those without. Children over two years of age should receive annual transcranial Doppler screening and, where necessary, subsequent transfusion to reduce the incidence of stroke.

**Priapism** Unwanted persistent and painful erections can occur in males. Associated embarrassment and delay in seeking medical help is dangerous because it can lead to impotence.

**Eye problems** Blockage of vessels at the back of the eye can result in retinal damage and sight impairment. Regular ophthalmic checks are, therefore, needed.

**Hand-foot syndrome** Painful swelling of hands or feet or both (dactylitis), usually occurs before the age of one year and is often the first sign of sickle cell anaemia.

**Acute chest syndrome** Acute chest syndrome is a life-threatening condition caused by a sickle cell blockage in the lung and is the second most common cause of admission to hospital (after pain) for patients with sickle cell anaemia. It is characterised by chest pain, fever and an abnormal chest x-ray and may be accompanied by asthma. Over one third of adults develop pulmonary hypertension, a common cause of death.

**Bone and joint problems** Orthopaedic problems begin early on. Hyperplasia of the bone marrow can cause growth disturbances and osteopenia (low bone density), and childhood growth is often slowed. Avascular necrosis of the weight-bearing joints (hip and shoulders) causes chronic pain and can require surgical intervention in adulthood.

**Splenomegaly** Repeated crises commonly cause enlargement of the spleen in children under 10 years as the organ becomes packed with trapped broken red blood cells. This can result in a sharp decrease in haemoglobin concentration and a further rapid enlargement of the spleen, which may be life-threatening. The spleen can be felt under the ribs on the left side and parents are trained to monitor spleen size in children because there is a danger of rupture if the organ becomes too large. In adults, a damaged spleen renders the immune system deficient and patients become susceptible to infection by pneumococcus and *Haemophilus influenzae*.

**End-stage organ disease** Organ damage (due to ischaemia or necrosis) is an ongoing problem but is often silent until at an advanced stage, so pulmonary, renal and cardiac function need to be monitored closely. Early lesions in the kidneys can cause enuresis (bed-wetting) in children and dehydration. Later, damage to the distal tubule can cause renal acidosis and haematuria (which always requires investigation). Chronic renal failure occurs in up to 5 per cent of patients with sickle cell anaemia.

**Leg ulcers** Leg ulcers are a common complication of sickle cell disease, but are rare before the age of five years. Blood vessel occlusion, increased venous pressure and low oxygen can lead to tissue hypoxia and poor healing of minor wounds which then have a predisposition to ulceration.

intimal hyperplasia of larger vessels, slowing blood flow. If this situation is not rectified, a sickle cell crisis with its associated severe pain, tissue ischaemia and organ damage is the result. A sickle cell crisis can be precipitated by: hypoxia, dehydration, sudden changes in temperature, physical activity (causing tissue anoxia),

extreme fatigue, acidosis, infection, stress and anxiety, pregnancy or physical trauma.

Some indicators of severe sickle cell disease include hand-foot syndrome before the age of one year, a haemoglobin level of less than 7g/dL (normal levels are between 12 and 18g/dL) and a raised white cell count in

the absence of infection. Symptoms of sickle cell anaemia are described in Panel 1.

**Screening** Ideally, people from at-risk ethnic groups who wish to have children should be screened to detect their Hb type. Where both potential parents are identified as having a sickle cell or other trait, they are offered counselling. Where Hb type has not previously been identified, this screening is offered at antenatal clinics. As a result of the NHS Plan, universal antenatal screening now takes place in many parts of the UK. Potential carriers of the sickle gene should also be screened before anaesthesia and surgery.

Today's multicultural society means that it is increasingly difficult to predict which newborn babies are at risk of sickle cell disease. A phased programme (due to be completed by the end of this year) is currently being rolled out, where all babies in England are screened for sickle cell disease at six days old as part of the neonatal screening tests.<sup>3</sup>

Symptoms of sickle cell disease do not appear until some three months after birth. This is because fetal haemoglobin (HbF) dilutes any HbS and prevents the sickling mechanism. As the baby grows, the HbF gradually disappears, allowing the sickling mechanism to develop. By adulthood, HbF production has usually stopped completely. Most of the serious complications from sickle cell anaemia occur in the first two years of life. Early diagnosis is vital, allowing treatment to be started immediately and maximising its benefits. This reduces the incidence of later complications.

### Management of sickle cell anaemia

Much can now be done to improve patient quality of life and reduce the incidence of crises and complications that arise as a result of infection and vessel occlusion. Regular health maintenance is critical and patients should have frequent health checks. They and their families should be taught to recognise early warning signs of impending crises, infection and organ damage.

Although people with sickle cell anaemia should be helped to live as normal a life as possible, they should take practical precautions to reduce the incidence and severity of crises (see Panel 2).

**Pharmacological management** The mainstay of pharmacological management of patients with sickle cell anaemia include vaccinations, prophylactic antibiotics and analgesics.

**Immunisations** The poorly developed immune system in sickle cell anaemia means that it is vital for babies to receive all the recommended childhood immunisations, plus pneumococcal vaccine (although this does not protect against all strains of pneumococci). A polyvalent pneumococcal polysaccharide conjugated vaccine (Prevenar) has been especially developed for use in children aged between two months and two years of age and who are at special risk of pneumo-

coccal disease. Children over two years of age may be given the unconjugated polyvalent pneumococcal polysaccharide vaccine (Pneumovax II or Pnu-Imune).

**Prophylactic antibiotics** At around two months of age, babies with sickle cell anaemia should begin taking phenoxymethylpenicillin. This significantly reduces the morbidity and mortality associated with infection in children aged under five years. Twice daily dosing is preferred, but if compliance is an issue, once daily dosing is acceptable. There is some disagreement about the duration of prophylaxis with penicillin and whether it should be for the first five or six years of life or throughout life. Erythromycin tends to be used for patients who are allergic to penicillin.

**Folic acid** Folic acid supplements are sometimes recommended for people with sickle cell anaemia if normal dietary levels are not sufficient to keep up with the manufacture of red blood cells. Some centres give 5mg a day to their patients, especially children, but others consider supplementation less critical because the UK diet tends to be folate rich.

**Analgesics** Most patients manage their pain at home and only go to hospital if the pain becomes unbearable. Uncontrolled pain accounts for 90 per cent of sickle cell patient hospital admissions. Patients and parents of children with sickle cell anaemia follow an analgesic ladder of pain management (see Figure 1, p28, for an example). Self-help measures include rest, keeping warm and increasing fluid intake. Pharmacists should be sensitive to the anxiety and stigma some patients with sickle cell anaemia feel about needing to take analgesics. Patients may be concerned about having inadequate analgesia and having to suffer long periods of pain as a consequence. Some worry that others might think they are addicts.

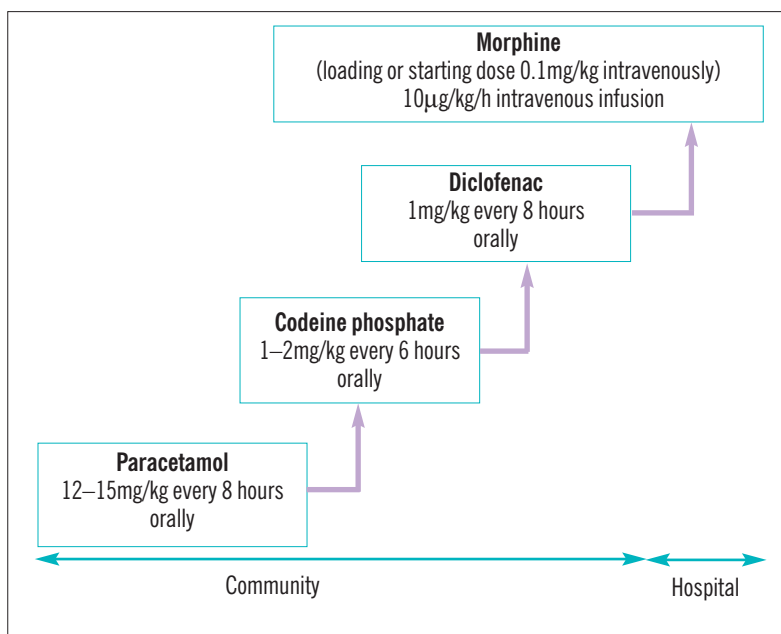
Complementary therapies, such as massage, aromatherapy and cognitive behavioural therapy, have all proved helpful in dealing with chronic and recurrent pain.

**Blood transfusions** Where sickling crises occur frequently, or where there is splenic enlarge-

## Uncontrolled pain accounts for 90 per cent of sickle cell patient hospital admissions

### Panel 2: Practical precautions

- Avoid dehydration because this will increase blood viscosity and exacerbate symptoms. (Patients should drink as much fluid as possible. Ideal volumes to be consumed in 24 hours by children with sickle cell anaemia are 150ml/kg body weight if under 10kg; 80ml/kg body weight if 10–20kg and 40ml/kg body weight if over 20kg. Adults should drink 3–5 litres per day.)
- Keep warm and dry to limit vasoconstriction and avoid sudden changes in temperature. (This not only reduces the likelihood of crises, but can ease a current crisis. Strenuous activity should be avoided in cold or wet weather. Children should only swim in warm water and avoid getting cold when leaving the water.)
- Maintain a healthy diet, sufficient in folates.
- Get enough sleep, rest when feeling tired and avoid over-exertion.
- Be adequately prepared when travelling. (Avoid dehydration on flights, take pain killers on holiday and make sure that appropriate malaria prophylaxis is taken — unlike sickle cell trait, sickle cell anaemia offers no protection against malaria.)



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**Figure 1: Management of pain in sickle cell anaemia**

ment or haemolytic anaemia, blood transfusions are given to increase the number of normal red blood cells. It has also been demonstrated that regular transfusions prevent further strokes in children who have suffered at least one stroke. However, regular blood transfusions can lead to iron overload and its subsequent risk of cardiac complications. This problem is treated with an iron chelating drug, such as desferrioxamine or, less frequently, deferiprone.

Patients with severe sickle cell anaemia may be offered bone marrow transplantation.

**Hydroxycarbamide** Hydroxycarbamide has been shown to restimulate fetal haemoglobin production, so reducing organ damage and maintaining splenic function. It is sometimes used for patients with severe and frequent crises. However, its use in sickle cell anaemia is unlicensed.

### Panel 3: The community pharmacist's role

- Stressing the importance of adhering to a regimen of penicillin prophylaxis
- Encouraging patients to take folic acid when prescribed and when planning a pregnancy
- Being aware of the potential for withdrawal symptoms following hospital stays and treatment with morphine or other opiates
- Being sensitive to patient concerns about stereotyping with respect to analgesic use
- Encouraging patients to adopt general good health care measures such as a healthy diet, avoidance of alcohol (and its dehydrating effects) and stopping smoking (adding to circulatory problems)
- Encouraging mothers to breast feed to boost infant immunity
- Promoting the importance of maintaining a high fluid intake
- Referring patients who show any signs of febrile illness to their GP without delay
- Promoting the importance of adhering to immunisation programmes and having regular health and eye checks
- Sickle cell patients are more prone to glucose-6-phosphate dehydrogenase deficiency and pharmacists need to be aware of this when dispensing prescriptions
- Clearly explaining the dosage schedule when starting to take hydroxycarbamide and stressing the importance of regular blood checks
- Highlighting the importance of avoiding unplanned pregnancies
- Encouraging patients to carry their haemoglobinopathy card at all times

Hydroxycarbamide is well tolerated in children but regular blood tests are needed to screen for cytopenias, particularly neutropenia. This toxic effect is reversed if treatment is stopped. Hydroxycarbamide capsules can be made into a suspension for once daily administration. Starting doses (15mg/kg/day) may be increased by 5mg/kg/day until crises are controlled or the dose is not tolerated. Both males and females must stop taking hydroxycarbamide at least six months before a planned pregnancy.

There has been a shift in the care of sickle cell patients from hospitals to the community and there are now 37 sickle cell and thalassaemia centres in cities (15 in London) across the UK, supporting patients and their families. Patients with sickle cell anaemia will be regular visitors to the pharmacy to obtain their prescriptions and for minor ailment guidance. Panel 3 suggests the role pharmacists can play in the care of these patients.

### Useful websites

- [www.sicklecellsociety.org](http://www.sicklecellsociety.org)
- [www.sickle-thalassaemia.org](http://www.sickle-thalassaemia.org)
- [www.blackhealthcare.com/bhc/sicklecell](http://www.blackhealthcare.com/bhc/sicklecell)

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### Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

1. Read the section on pneumococcal vaccines in the British National Formulary (section 14.4).
2. Find out if there is a sickle cell centre near you and make contact with the nurse counsellor.
3. Find out which drugs and foods pose a risk in patients with a glucose-6-phosphate dehydrogenase deficiency (see section 9.1.5 in the BNF).

### Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities. Answer the following questions: What have you learnt? How has it added value to your practice? (Have you applied this learning or had any feedback?) What will you do now and how will this be achieved?