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CLINICAL REVIEW

Management of sickle cell disease in the community

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Sickle cell disease is characterised by unpredictable episodes of acute illness, progressive organ damage, and a lack of effective treatments. It is one of the most common inherited conditions, although its prevalence varies widely. Median life expectancy is currently 40-60 years in high income countries but much less in low income areas.[1 2] It is associated with protean clinical complications. Patients present to all medical specialties and increasingly to general practitioners. This review aims to provide an evidence based update on how to manage patients with this disease in the community. It does not consider sickle cell trait, which is largely asymptomatic.

What is sickle cell disease?

Sickle cell disease is a recessive condition, caused by a mutation in the β globin gene, which changes the sixth amino acid from glutamic acid to valine. Sickle haemoglobin (HbS) is insoluble when deoxygenated, forming long polymers. These polymers damage the red cell membrane, resulting in rigid sickle shaped cells with a tendency to cause vaso-occlusion and a cascade of pathological events, including infarction, vasculopathy, haemolysis, oxidative stress, hypercoagulability, and inflammation (figure⇓).[3]

At least 15 different genotypes cause sickle cell disease, although all include the HbS allele. Homozygous disease (HbSS), usually called sickle cell anaemia (SCA), is the most common and severe type of disease in most populations. HbSC disease and HbS/β thalassaemia are the two other common genotypes.[4]

Where is sickle cell disease common?

About 300 000 babies with sickle cell disease are born worldwide each year, with an estimated 90 000 births in Nigeria and 40 000 in the Democratic Republic of Congo in 2010. Around 40 000 affected children are born in India each year, with 10 000 in the Americas, 10 000 in the Eastern Mediterranean, and 2000 in Europe.[2] Numbers are increasing, and sickle cell disease is thought to be the most common severe genetic disease in the United Kingdom and France, with 10 000-15 000 patients in each country.[5] The condition was traditionally found in populations of African descent in northern Europe, but this is changing with increasing numbers of mixed race people, particularly in large cities such as London and Paris.

How do we screen for sickle cell disease?

Many countries, including England, have antenatal screening programmes to identify couples at risk of having an affected baby. Screening is usually community based, with the doctor or midwife who sees the woman when she is first pregnant requesting haemoglobinopathy screening according to local or national guidelines. Typically, in high prevalence areas all women are screened, whereas in lower prevalence areas only those at high risk because of their ethnic origin are screened.[6] If a woman is found to carry a serious haemoglobinopathy, her partner will be offered testing, and if he is also a carrier (or affected) the couple will be counselled about prenatal diagnosis and selective termination of affected pregnancies.

Many countries have established neonatal screening programmes that can identify children with sickle cell disease before they present with potentially fatal sepsis. Heel prick blood spots are usually collected three to 10 days after birth and haemoglobin analysed. This reliably identifies affected babies and allows penicillin to be started by 3 months of age. England, the Netherlands, the United States, and some Middle Eastern countries have national screening programmes, and several Brazilian states also have systematic screening.[7] Other countries, such as France, target high prevalence areas or identify children at risk owing to their ethnic origin, but this approach is becoming unsustainable because of increasing numbers of mixed race families.[8]

African countries have no established national screening programmes. Individual hospitals or clinics may practise neonatal screening for local patients, but most babies present with anaemia, death, or invasive infection.[7] Childhood mortality is high, with one study showing an under 5 mortality rate of 7.3

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Summary points

All children with sickle cell disease should take penicillin twice a day until 5 years of age at least

Acute neurological symptoms in children and adults with sickle cell disease necessitate urgent referral to hospital

All patients should receive annual vaccination against influenza and other appropriate vaccinations where available

Patients living in most parts of Africa should use insecticide treated bed nets and take malarial prophylaxis

Children with severe types of sickle cell disease (HbSS and HbS/β^0 thalassaemia) should be offered primary stroke prevention with annual transcranial Doppler scans and blood transfusion when resources allow this

Children and adults should be offered treatment with hydroxyurea if they have two or more episodes of severe acute pain in a year, or acute chest syndrome

Children, families, and adults should be offered education about sickle cell disease and managing its complications

Sources and selection criteria

We searched Medline, the Cochrane Database, and ClinicalTrials.gov using the term "sickle" together with certain complications including pain, infection, enuresis, renal failure, spleen, acute chest syndrome, leg ulcers, and stroke. Preference was given to randomised clinical trials, and when these were unavailable large case series were sought. We prioritised newer studies over older ones.

per 100 patient years (95% confidence interval 4.8 to 11).[9] However the disease is clinically variable and some patients may present in adulthood, diagnosed on incidental blood testing.

How do patients with sickle cell disease present?

The first symptom in infants is typically dactylitis, or hand-foot syndrome—painful swelling of the hands or feet as a result of vaso-occlusion. This affects 30% of patients in the first year of life and usually resolves in a few days.[10] Treatment with simple analgesia is often sufficient, although severe episodes may require admission to hospital for opiates, particularly if this is the first presentation or the diagnosis is uncertain. Dactylitis is uncommon after 2 years of age.[10]

Invasive infection with encapsulated bacteria can be a presenting feature, related to functional hyposplenism, which is seen in 90% of 5 year olds with HbSS disease.[11] The relative risk of *Streptococcus pneumoniae* infection in young children with this disease compared with normal controls is 300-600,[12] with a mortality rate of 15%.[10] The relative risk of invasive infection with *Haemophilus influenzae* is 20-100, with a mortality rate of about 20%. Two randomised controlled trials found that penicillin prophylaxis significantly reduces morbidity and mortality associated with pneumococcal infection in children under 5,[13 14] with oral prophylaxis reducing pneumococcal septicaemia by 84%.[13]

In the absence of neonatal screening, most cases of sickle cell disease present with symptoms in infancy or early childhood. However, patients with milder forms, such as HbSC disease, may be diagnosed as adults with acute pain, or on incidental blood testing, particularly during pregnancy.

What acute complications occur in sickle cell disease?

Here we describe the common acute complications of sickle cell disease and offer advice for GPs on assessing and managing these problems in the community and when to refer. The feasibility of managing acute complications in the community varies geographically, depending on provision of community care and home circumstances. The box lists indications for urgent referral to hospital. In some high prevalence areas, such as London, community nurse specialists with specific knowledge of sickle cell disease can advise families on managing acute illness and may be able to make home visits.

Pain

Acute pain is the most common manifestation of the disease in all age groups. Pain is thought to be caused by vaso-occlusion, which results in ischaemic tissue damage and subsequent inflammation and pain. It can affect any part of the body, although the limbs and back are most commonly involved. The US Cooperative Study of Sickle Cell Disease (CSSCD) found an incidence of 0.8 episodes of acute pain per patient year in HbSS and 0.4 in HbSC disease. Pain was most common in 10-30 year olds, and high pain rates were associated with increased mortality after 20 years of age. Increased pain rates were associated with low levels of fetal haemoglobin (HbF) and high total haemoglobin levels.[15] Initial assessment should include an estimate of pain severity, looking for evidence of infection, severe dehydration, or other precipitating factors that would necessitate referral to hospital. General advice includes keeping warm; drinking plenty; and taking simple analgesia, such as paracetamol, ibuprofen, and weak opioids if pain is severe. There is no good evidence to support any particular form of analgesia, although many patients will prefer a certain drug or combination. Children are more likely to be managed at home, with parents acting as carers. A study of children with sickle cell disease in south London showed an admission rate of 41 per 100 patient years in 2009, compared with 111 per 100 patient years 30 years earlier.[16]

Most episodes of acute pain can be managed at home with simple analgesia. Severe pain usually lasts one to five days, with full recovery after one week, but this varies widely. Severe pain is usually managed in hospital with opiates, as recommended by National Institute for Health and Care Excellence guidelines.[17]

Acute chest syndrome

Acute chest syndrome is defined as a new pulmonary infiltrate on chest radiography in a patient with sickle cell disease, accompanied by symptoms such as chest pain, cough, dyspnoea, or tachypnoea. It occurs at all ages and has a peak incidence of 34 per 100 patient years at the age of 3 years.[10] The underlying lung disease involves a combination of infection, vaso-occlusion, endothelial dysfunction, and fat embolism in some cases.[4] A CSSCD study of 671 episodes identified infectious agents in 249 cases. The most common agents were chlamydia, mycoplasma, and respiratory syncytial virus; *S pneumoniae* was relatively uncommon, probably as a result of penicillin prophylaxis and vaccination.[18] Acute chest syndrome is serious because increasing hypoxia creates a vicious circle of increasing

Indications for urgent referral to hospital in sickle cell disease

- Severe pain not controlled by simple analgesia or low dose opioids
- Dehydration caused by severe vomiting or diarrhoea
- Severe sepsis: temperature >38.5°C or >38°C if under 2 years old, temperature <36°C, or hypotension
- Symptoms or signs of acute chest syndrome including tachypnoea, oxygen saturation more than 5% below steady state, signs of lung consolidation
- New neurological symptoms or signs
- Symptoms or signs of acute fall in haemoglobin
- Acute enlargement of spleen or liver over 24 hours, particularly in young children
- Marked increase in jaundice
- Haematuria
- Fulminant priapism lasting more than two hours or worsening of recurrent episodes

vaso-occlusion and worsening hypoxia. Patients usually present to their GP with respiratory tract infections, and most improve with simple outpatient management. Refer patients to hospital if they have a high fever, clinical evidence of lung consolidation, widespread wheezing, signs of respiratory distress, or new hypoxaemia as assessed by pulse oximetry. Patients with coexisting asthma are particularly vulnerable.[19] In the CSSCD study, 13% required mechanical ventilation and 3% died. Hospital management of the syndrome is based on evidence from case series, and involves broad spectrum antibiotics, bronchodilators, ventilatory support, and blood transfusion in severe or deteriorating cases.[18]

Neurological problems

Worldwide, HbSS disease is probably the most common cause of stroke in children. In the absence of stroke prevention programmes, these patients have an incidence of infarctive stroke of 0.61 per 100 patient years, with a peak incidence of 1.02 per 100 patient years in children aged 2-5 years.[20] Infarctive stroke is caused by vasculopathy of the large arteries, typically the middle cerebral artery.[21] Stroke can present in many ways including hemiparesis, speech problems, seizures, or altered levels of consciousness. Acute management is largely based on expert opinion and involves urgent transfusion to correct anaemia and reduce the amount of HbS in the blood.[21] The incidence of intracranial haemorrhage is also increased, mainly in young adults.[20] Bleeding occurs from fragile new arteries, which grow in response to ischaemia, and from aneurysms, which result from progressive vasculopathy. Over the past decade, the incidence of stroke in high income countries has fallen owing to primary stroke prevention based on transcranial Doppler scanning to identify children at high risk and selective use of regular blood transfusions.[22 23] Silent cerebral infarcts are seen on magnetic resonance imaging in about 30% of children. Although these are not associated with overt neurological events, they are associated with seizures, cognitive impairment, and headaches.[24] Urgently refer any patient with sudden onset headaches, reduced levels of consciousness, limb or facial weakness, or acute cognitive impairment to hospital.

Around 30% of adults and children have neurocognitive and behavioural problems as a result of cerebrovascular disease and need multidisciplinary support,[24] including neuropsychology, educational psychology, physiotherapy, occupational therapy, and social services.

Anaemia

Haemoglobin levels in HbSS disease are typically 70-80 g/L, and this chronic anaemia is well tolerated. Although any febrile illness or vaso-occlusive complication can worsen anaemia, the two main causes of an acute fall in haemoglobin of more than 20% below the baseline level are splenic sequestration and parvovirus B19 infection. Splenic sequestration is often triggered by sepsis and occurs when the spleen rapidly enlarges and traps red blood cells. It typically occurs in children under 5 years and is potentially fatal without urgent blood transfusion. If two or more episodes occur, splenectomy is often recommended, on the basis of case series that show a high rate of recurrence.[25] Parvovirus B19 infection causes slapped cheek syndrome and also infects erythroid cells, causing transient reticulocytopenia, which last about a week. Because sickled red cells have a shorter survival time than normal ones, reticulocytopenia can result in severe anaemia requiring blood transfusion, with recovery occurring after about seven days.[26] Increased anaemia can also be associated with folate and iron deficiency, and renal impairment, although this is usually of gradual onset.

Acutely anaemic patients may present to GPs with increased exertional dyspnoea or other cardiovascular symptoms, although anaemia is often part of a more apparent infective or vaso-occlusive picture. Examination should include assessment of pallor, jaundice, and hepatosplenomegaly. Urgently refer patients with cardiovascular signs or symptoms, or new enlargement of the liver or spleen, to hospital. Blood tests should include a full blood count, reticulocyte count, haematinics, and parvovirus B19 serology. Patients should be referred to or discussed with a specialist sickle cell disease team in the hospital if haemoglobin is more than 20 g/L below their known steady state.

Infection

Acute infection is one of the most common causes of admission to hospital in patients under 10 years. In a CSSCD study of 694 infants followed prospectively, bacteraemia had a peak incidence of 9.9 per 100 patient years in the first year of life and steadily declined with increasing age.[10] *S pneumoniae* is an important pathogen at all ages, and salmonella infections are particularly associated with osteomyelitis.[27] The spectrum of infections changes with age, and Gram negative bacterial and staphylococcal infections are more important in adults.

Suspect infection in the presence of a fever or localising symptom, as in any other patients. Particular concerns when assessing and treating sickle cell disease include increased risk of osteomyelitis and acute chest syndrome. Patients with clinical evidence suggesting either of these conditions should be urgently referred to hospital. Infections of the upper respiratory tract, urinary tract, ear, and skin can usually be managed in the community with oral antibiotics if necessary, unless features in the box are also present.

Many patients are already on regular penicillin prophylaxis; this should be changed to an alternative if antibiotic treatment is needed and subsequently restarted.

Sickle cell disease can affect every organ in the body and a wide range of other acute problems can occur (table⇓).

What chronic complications are common in sickle cell disease and how are they managed in the community?

Chronic complications increase with age and are becoming more common in high income countries as people live longer. Chronic complications are largely managed in the community, through a combination of families, GPs, community paediatrics, nurse specialists, and voluntary agencies. The most common chronic problem is pain, and management relies on physiotherapy and psychological support.[28] Pulmonary complications, including restrictive lung disease and pulmonary hypertension, are prevalent in older teenagers and adults. Pulmonary hypertension, confirmed on cardiac catheterisation, affects about 6% of adults and is associated with premature death.[29] Management includes regular blood transfusion, hydroxyurea, and drugs used in idiopathic pulmonary hypertension, such as endothelin receptor antagonists and prostaglandins. Community support including home oxygen is necessary with increasing disability.[4] Locomotor and neurological disabilities are increasingly recognised in older patients and again require multiagency community support.

Psychological problems are also common, as for many chronic diseases, and community support is important, particularly during the transition from paediatric to adult hospital care, when GPs offer continuity.[30]

Nocturnal enuresis

Glomerular hyperfiltration and reduced sensitivity to desmopressin are detectable at 13 months in children with HbSS disease.[31] This causes the production of large volumes of dilute urine and a high prevalence of nocturnal enuresis in older children with the disease. A survey of 213 children with HbSS disease in the US found that 42% of 6-8 year olds reported enuresis at least once a month, and 9% over 18 years still reported nocturnal enuresis as a problem.[32] There is no good evidence on how to manage this. Advice about not drinking at night and waking the child during the night to pass urine is sometimes helpful. Desmopressin has been used, and a small study of 10 patients reported a 60% response rate,[33] although benefit has not been confirmed in larger trials.

Chronic pain

Pain occurring daily for more than three months is unusual in children with sickle cell disease. However, estimates suggest that chronic pain may occur in 5-10% of adults,[34] although accurate figures are not available. Chronic pain can be related to tissue damage, such as leg ulcers, avascular necrosis of femoral or humeral heads, or chronic osteomyelitis, and specific treatment of these problems is important. It is increasingly recognised that some patients report severe pain with no obvious cause. Such pain has some features of neuropathic pain and may be related to increased central sensitisation to painful stimuli. Neuropathic chronic pain is more difficult to manage but drugs such as gabapentin and psychological therapies may be helpful.[28] All types of chronic pain in sickle cell disease require multidisciplinary support, with the general approach being similar to other types of chronic pain[35]; community provision of psychology and physiotherapy are particularly important.

Chronic renal disease

Blood is exposed to hypoxic and acidic conditions in the renal medulla, and in sickle cell disease this promotes HbS polymerisation and vaso-occlusion, which causes ischaemic damage. In addition, glomerular hyperfiltration is present in these patients from infancy, although the glomerular filtration rate falls progressively with age, contributing to renal failure in older adults.[36] Renal dysfunction is apparent from an early age—microalbuminuria is common in childhood and 20% of adults develop nephrotic range proteinuria. Chronic renal failure develops in 30% of adults.[36] A study of US mortality statistics from 1999 to 2009 showed that chronic renal failure caused 7% of deaths, making it the third most common cause of death in sickle cell disease.[1] Six year survival was 70% in 106 adults with sickle cell disease undergoing renal transplantation in the US between 2000 and 2011, significantly higher than survival on dialysis.[37] Patients are monitored for microalbuminuria yearly and usually treated with a combination of hydroxyurea and an angiotensin converting enzyme inhibitor when this approaches the nephrotic range. Case series suggest that these drugs reduce protein loss, although it is unclear if this approach reduces the number of patients who develop renal failure.[38]

Chronic leg ulcers

Chronic leg ulcers, typically just above the ankle, affect about 10% of adults with the disease in the US, but 50-75% in Jamaica, and are much less common in children. This difference may reflect the incidence of minor leg trauma. Leg ulcers are often painful. No treatments have a strong evidence base, but small studies suggest that many heal within six months with regular dressings and compression bandages. Other treatments that may accelerate healing include blood transfusion, skin grafting, hyperbaric oxygen, zinc supplements, arginine butyrate, and topical growth factors.[39] All these approaches seem promising in case reports or small series, but none has been validated in larger studies.

Proliferative retinopathy

Proliferative retinopathy (stages III-V) occurs in about 20% adults with HbSS disease and 50% of those with HbSC disease.[40] This can be progressive and lead to vitreous haemorrhage and retinal detachment, although visual loss affects less than 1% patients. Laser treatment may be beneficial for progressive retinopathy, but it is unclear whether routine retinal examination is beneficial. Warn patients about the importance of visual symptoms and refer urgently to ophthalmology if these occur.[41]

How can complications be prevented?

Prevention of infections

Penicillin prophylaxis is central to the management of children with the disease. In some countries this is continued throughout life, whereas in others it stops at age 5 years. Routine childhood vaccinations include protection against *H influenza* type B and conjugated vaccines against *S pneumonia* in most high income countries. Children should also receive unconjugated pneumococcal vaccine from 2 years of age, repeated every three to five years, and immunisation against meningococcus, influenza, and hepatitis B.[42]

Prevention of acute vaso-occlusive complications

Many patients report exposure to cold or dehydration as precipitants of acute pain. Studies in tropical countries suggest

increased frequency of acute pain during the rainy season, whereas in the northern hemisphere windy weather is associated with increased hospital admissions.[43] Advise patients to dress appropriately for the weather and ensure adequate hydration. It is important for children and adults to be physically active, although sports involving prolonged exertion or exposure to cold may provoke vaso-occlusion. Advise patients not to ski as anecdotally this can precipitate acute complications, because of cold temperatures and low oxygen levels at high altitude. Flying on commercial airlines is well tolerated and does not usually require prophylactic blood transfusions or supplemental oxygen, unless the patient has pre-existing hypoxia or cardiopulmonary problems. Patients should not fly if they have acute pain or other acute illness.

Hydroxyurea is the only drug that reduces the frequency of acute vaso-occlusive complications. In a double blind randomised controlled trial, 152 adult patients with HbSS disease were given hydroxyurea and 147 assigned placebo. Hydroxyurea was associated with a significant reduction in episodes of acute pain (median 2.5 *v* 4.5 episodes/year; P<0.001), acute chest syndrome, and blood transfusion.[44] Subsequent trials showed similar reductions in pain frequency in children, but provided no evidence that hydroxyurea protects against organ damage, despite observational studies suggesting reduced mortality.[45] In Europe, hydroxyurea is usually started if more than two episodes of acute pain occur each year, or after a severe episode of acute chest syndrome. Use is limited, partly because of theoretical concerns about the side effects of a cytotoxic drug and the potential increased risk of cancer and subfertility. These risks are unquantified, but seem to be small. In England, 15-30% of patients are currently taking hydroxyurea,[4] and it is often stated that it is underused. In the US, hydroxyurea is more widely prescribed for a wide range of indications, including hypoxia, severe anaemia, pulmonary hypertension, renal impairment, and cerebrovascular disease.[46]

Primary prevention of stroke in children

Regular blood transfusion can reduce the risk of stroke by about 90% in children with abnormal intracranial blood flow identified by transcranial Doppler screening. In the Stroke Prevention in Sickle Cell Anemia trial, one infarction occurred in 63 children randomly assigned to transfusions compared with 10 infarctions in 67 children receiving standard care.[22] Adoption of this approach in high income countries has significantly reduced the incidence of stroke. In California, the first stroke rate in children with HbSS disease fell from 0.88/100 patient years in 1991-1998 (before screening was introduced) to 0.17 in 2000 (P<0.005 for trend), when primary stroke prevention was fully implemented.[23] Patients on regular blood transfusions require iron chelation, usually with the oral iron chelator deferasirox. Community and psychological support is often needed to maximise adherence to iron chelation, which is essential to avoid organ damage (particularly the liver) owing to iron overload.[47]

Haematopoietic stem cell transplantation

Haematopoietic stem cell transplantation is potentially curative but is currently used only in patients with a severe clinical course and a matched sibling donor. Its use is limited by the toxicity of the procedure and the availability of suitable donors, although protocols are being developed that may improve both these problems and make this approach more widely used.[48]

How should pregnant women with sickle cell disease be managed in the community?

Women with sickle cell disease have near normal fertility. There has been concern that hormonal contraception might increase the risk of acute complications and venous thrombosis in women with sickle cell disease. Although no large studies have looked at this population specifically, a recent systematic review of eight non-randomised and cross sectional studies found no evidence that hormonal contraception was associated with an increased risk of complications in sickle cell disease, although there were no studies of venous thrombosis.[49] This review found that progestin-only and combined hormonal contraception were safe in women with sickle cell disease.

A large database study of 18 000 deliveries to women with sickle cell disease in the US showed that all complications were increased compared with controls. For example, the odds ratio was 2.5 (1.5 to 4.1) for deep vein thrombosis, 2.2 (1.8 to 2.6) for intrauterine growth retardation, and 6.8 (4.4 to 10.5) for sepsis.[50] Complications of sickle cell disease are also increased, with 50% of women developing episodes of acute pain.[51]

Women with sickle cell disease should receive preconceptual counselling about prenatal diagnosis and the risks associated with pregnancy; prenatal diagnosis should also be discussed when they are first seen during pregnancy. Hydroxyurea, which is potentially teratogenic, should ideally be stopped three months before becoming pregnant, and definitely when pregnancy is suspected or confirmed.[52] Pregnancy outcomes depend greatly on the facilities and expertise available. There is no established evidence base on managing pregnant women with sickle cell disease, although regular blood transfusions are typically used in those with a severe clinical course, such as those developing frequent episodes of pain, acute chest syndrome, or those with previous complicated pregnancies. Women should be referred to an obstetric team with experience of high risk pregnancies, and followed in a specialist sickle cell disease pregnancy clinic where available.[53]

What treatments are available in Africa?

Studies in Africa in the late 1970s reported childhood survival of less than 2% in sickle cell disease.[54] With improvements in healthcare, this has increased to nearly 50%.[9] Specific clinics for children and adults with sickle cell disease are available in several African countries, often in partnership with specialist clinics in high income countries. Unfortunately, few countries have newborn screening programmes, and although penicillin and vaccinations are available in most health facilities, few children receive them. In malaria endemic areas it is recommended that patients use insecticide treated bed nets and are promptly treated for malaria.[55] Proguanil, pyrimethamine, or mefloquine may be used for chemoprophylaxis. Measures to prevent and treat other infections, particularly gastroenteritis, are particularly important in children with sickle cell disease, although there is little evidence to support any particular intervention.

As in Western countries, pain is managed with paracetamol, ibuprofen, and opioids, although opioids are not readily available in rural settings. Severe anaemia is common.[9] Although blood transfusion services have improved in many African countries, there are challenges with supply, transfusion transmissible infections such as hepatitis B and C, and blood selection to reduce red cell alloimmunisation. Transcranial Doppler scanning for the detection of children at risk of stroke is feasible in Africa,

but it is not part of routine care and is of limited value because regular blood transfusions are not widely available.[56] Hydroxyurea is being used in some African hospitals, with frequent pain and secondary stroke prevention being the usual indications. However, patients may have to pay for treatment and it is not used in areas where diagnostic facilities to monitor blood counts are unavailable because of the risk of hydroxyurea induced neutropenia. The focus of management of sickle cell disease in Africa is health education to allow early and accurate diagnosis; better management of pain; and the prevention and prompt treatment of bacterial infections, malaria, and severe anaemia.

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Tips for non-specialists

- Sickle cell disease is very variable, with some patients having severe symptoms every month and others being largely asymptomatic
- Encourage adherence to penicillin prophylaxis whenever possible, and facilitate this by providing appropriate access to repeat prescriptions
- Ensure that all patients receive recommended vaccines, including annual vaccination against influenza in many countries
- Many episodes of uncomplicated acute pain can be managed at home with simple analgesia and community support
- Ensure children and adults who were born overseas in high prevalence countries are offered haemoglobinopathy screening (full blood count, haemoglobin analysis)

Additional educational resources

Resources for healthcare professionals

- National Heart, Lung and Blood Institute (www.nhlbi.nih.gov/health/prof/blood/sickle/sc_mngt.pdf)—American website with information on diagnosis and management of all aspects of sickle cell disease for high-income countries; free resource, no registration
- NHS Sickle Cell and Thalassaemia Screening Programme (www.sct.screening.nhs.uk)—Information on antenatal and neonatal haemoglobinopathy screening in England, with guidelines and standards on diagnosis, clinical management, and patient information leaflets; free, no registration.
- Global Sickle Cell Disease Network (www.globalsicklecelldisease.org)—Information on sickle cell centres and meetings across the world, with names of sickle cell disease specialists across the world; free, registration for full access
- South Thames Sickle Cell and Thalassaemia Network (www.ststn.co.uk)—Information on meetings, and access to guidelines covering diagnosis and management; free, no registration

Resources for patients

- Sickle Cell Society (www.sicklecellsociety.org)—Website of UK Sickle Cell Society with news, information, and patient leaflets; free, no registration
- NHS choices (www.nhs.uk/conditions/Sickle-cell-anaemia/Pages/Introduction.aspx)—Patient information on NHS screening programme for sickle cell disease; free, no registration
- Sickle Cell Disease Association of America (www.sicklecelldisease.org)—American website with news, guidelines, and information; free, no registration
- Rofsed (www.rofsed.fr)—French language website for children, parents, and professionals; particularly good for teenagers; free, no registration

Areas for future research

- The value of aggressively treating all children with sickle cell disease with interventions such as hydroxyurea, regular blood transfusion, or haematopoietic stem cell transplantation to prevent organ damage and premature death
- The value of simple commonly used interventions during acute admissions, including intravenous fluids, oxygen, thromboprophylaxis, and antibiotics
- The development of specific treatments to shorten the length and severity of acute vaso-occlusive pain
- The discovery and development of drugs designed to treat sickle cell disease, including those that promote haemoglobin F synthesis, prevent red cell dehydration, and inhibit HbS polymerisation
- The validation of DNA, plasma, and imaging biomarkers that can identify infants at risk of severe complications early
- The development of evidence based interventions in low and middle income countries, particularly African and Asian ones

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Table

Table 1| Acute complications of sickle cell disease

Complication	Features	Treatment	Estimated incidence in SCA*
Acute abdominal sickling (girdle syndrome)	Severe pain, abdominal distension, constipation	Analgesia, laxatives, intravenous fluids	Fairly rare: 0.1 episode/patient year[10 15]
Cholecystitis	Increased incidence of gallstones from haemolysis	Surgical management with transfusion before surgery	Common: 30-50% of patients by age 30[15]
Fulminant priapism	Painful, unwanted erection lasting more than two hours	Analgesia, α adrenergic agonists, penile aspiration and irrigation	Common: 30% of men by age 30[4]
Macroscopic haematuria	Usually painless; associated with renal papillary necrosis	Conservative management with hydration; transfusion as necessary	Common: 20% adults at some point; also common in sickle cell carriers[36]
Acute visual loss	Caused by proliferative retinopathy or retinal artery occlusion	Urgent referral to ophthalmology. Possible exchange transfusion	Fairly rare: 1% of patients by age 30[40]

*SCA=sickle cell anaemia (HbSS disease).

Figure

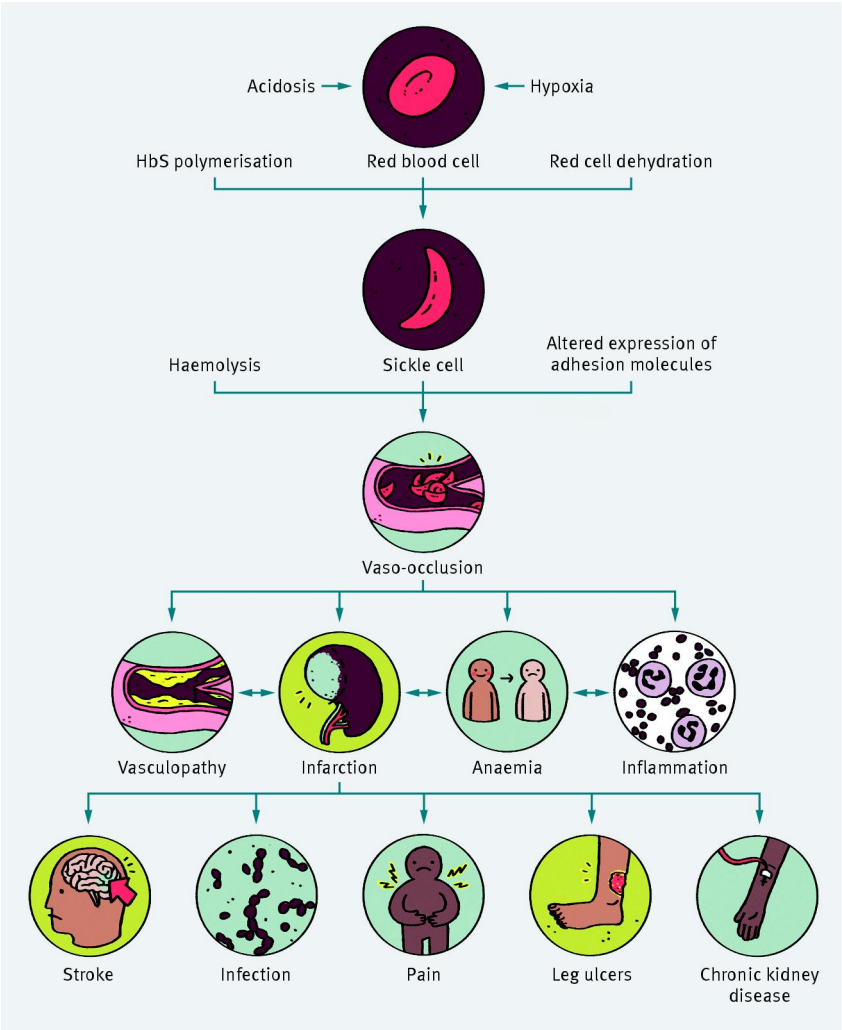

Diagram showing the pathophysiology and some of the major clinical complications of sickle cell disease. HbS=sickle haemoglobin