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Sickle cell disease

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Sickle cell disease (SCD) affects 12,000 individuals in the UK[1] and imposes a severe health burden on many. Frequent crises mean interrupted education and cause employment difficulties. In the third and fourth decades, chronic end-organ damage may predominate. Median life expectancy is reduced to the mid-40s even with optimal care[2].

Although some complications require hospital admission, a wider care model is appropriate involving health and social care agencies across acute and community boundaries. Full involvement of patients and carers in developing services is critical.

The term 'SCD' includes:

- homozygosity for the β^S gene, resulting in sickle cell anaemia (HbSS), usually the most severe form of SCD, and
- compound heterozygosity with other abnormal β genes, resulting in HbSC, Sβ thalassaemia, SD^{Punjab}, SE and SO^{Arab}, and some rarer phenotypes such as SLepore.

Abnormal β globin chains cause deranged conformation of haemoglobin molecules producing distorted erythrocytes, some sickle-shaped. Erythrocyte survival is shortened, rheology deranged with disturbed interaction between erythrocytes and vascular endothelium, and dysregulation of vascular reactivity. Small and large vessel occlusions result. Lack of significant morbidity for HbAS heterozygotes (sickle cell trait) and their relative protection against death from malaria in childhood are well documented. Current theories of pathogenesis are reviewed by Steinberg[3] (also at www.asheducationbook.org/current.shtml).

Screening

Up to 40% of African, Afro-Caribbean, Asian, South-East Asian and Mediterranean populations are carriers. Only in people of strictly Northern European origin are carriers rare.

Key Points

Sickle cell disease affects people from a wide range of ethnic origins. There are about 12,000 affected individuals in the UK, many of whom have major chronic health problems

Antenatal screening and counselling give carrier parents informed choice regarding their options in pregnancy. Neonatal screening identifies affected babies and reduces their risks

Pneumococcal infection has a high mortality, especially in infants. This can be reduced by regular penicillin prophylaxis and immunisation

Vaso-occlusive painful crises, often severe, dominate the clinical course but there are many additional acute and long-term complications, some life-threatening

Most pain episodes are managed at home. Although hospital analgesia has usually been with parenteral opiates, there is evidence in children that oral morphine is as effective

Management requires a comprehensive long-term multidisciplinary approach with full involvement of the patient and carers

Treatment with oral hydroxyurea and allogeneic bone marrow transplantation can change the course of the disease. These options should be discussed fully with potentially suitable, severely affected patients and families

Antenatal screening

The aim of antenatal screening is to give informed choice to parents at risk of having an affected child. If both partners are carriers, there is a 25% risk that the infant will have SCD. Prenatal diagnosis is offered, usually by first trimester chorionic villus biopsy, as is termination of an affected pregnancy. In areas with a high proportion of ethnic groups (the current 'cut-off' is 15% or above), universal screening is recommended. Selective or targeted screening, using one of several imperfect ethnic monitoring tools, is usual elsewhere.

Neonatal screening

The aim of neonatal screening, which may be universal or selective depending on the population, is to detect affected infants, educate parents about SCD, and start treatment and follow-up to pre-empt early complications.

'Steady state' management

Educating the family of a newly diagnosed individual is critical. This includes discussion of problems for which the child should be brought to hospital and how to manage uncomplicated pain episodes at home. In families where this is confidently handled, individuals can more often cope with pains outside hospital[4]. Regular measurement of growth and discussion of pains or social or educational difficulties can lead to early detection of problems. Teaching parents how to detect an enlarged spleen reduces morbidity from splenic sequestration through earlier presentation. Blood pressure monitoring, retinopathy screening and renal assessments become important in adulthood.

Determining steady-state haematology (haemoglobin, reticulocyte count, ferritin, creatine and also SaO_2, by pulse oximetry) highlights deviations from the individual's normal when ill. Extended red cell phenotype enables selection of appropriate blood, with reduced risk of antibody formation, should transfusion be required.

Prophylaxis against pneumococcus reduces deaths from infection in childhood[5]. Oral phenoxymethylpenicillin should start at three months, and regular immunisation with Pneumovax II offered. The value of prophylactic antibiotics in adults is controversial, but rapid treatment with penicillin at the first sign of infection may be life-saving.

The need for daily folic acid is uncertain. Dietary intake usually suffices, but evidence that increased homocysteine can contribute to hypercoagulability suggests that it may be valuable. Women with SCD who are contemplating pregnancy should be given folic acid.

Table 1. Acute complications of sickle cell disease.

Complications	Features
Vaso-occlusive	
Painful crises	More than 60% of patients, very variable frequency Mostly bone and joint pains
Stroke	About 10% of children Silent CNS damage, with or without cognitive impairment, in an additional 10%
Acute chest syndrome	40% of patients overall, more frequent in children, more severe in adults Watch for chest wall pain, tachypnoea + increasing chest signs
Priapism	Up to 90% of males If severe/prolonged, causes impotence
Splenic sequestration	Usually children <6 years Infection, especially with parvovirus, may precipitate
Abdominal pain episodes	May be fever, vomiting, guarding Mesenteric sickling may give distended, silent abdomen Can mimic other causes of acute abdomen
Leg ulcers	
Avascular necrosis, ball-and-socket joints	10–50%
Thrombosis	
Proliferative retinopathy	Over 30% in HbSC
Renal insufficiency	5–20% of adults
Haemolytic	
Anaemia	Haemolysis less and Hb higher in HbSC than HbSS
Cholelithiasis	Frequent, mainly asymptomatic but can require cholecystectomy
Infectious	
Streptococcus pneumoniae	10% of children <5 years
Chest infection	Variety of organisms including *Mycoplasma pneumoniae*
Osteomyelitis	Salmonella or staphylococcus
Escherichia coli sepsis	Usually secondary to urinary tract infections
Aplastic crises	Due to parvovirus B19 Rapidly developing severe anaemia

CNS = central nervous system; Hb = haemoglobin; HbSS = sickle cell anaemia.

Acute presentations

The acute complications of SCD are summarised in Table 1. The main ones are discussed below.

Painful ('vaso-occlusive') crises. These are usually managed at home. Over a third of patients with HbSS appear not to have pain severe enough to cause presentation to hospital, the median is 1/year; 1%

patients present >6 times/year[6]. A minority have pain almost constantly. Infection, extremes of temperature, dehydration and physical and emotional stresses may precipitate crises. Bone pain can be extremely severe, and may often require opiate analgesia. Co-analgesics such as NSAIDs and phenothiazines may be useful.

The question of which opiate to use, and by which route, continues to engender debate among service providers and users. In the 1980s and early 1990s, intramuscular pethidine was most often offered to patients presenting to hospital for acute pain management. However pethidine, especially if used at repeated high dose, can cause grand mal fits due to accumulation of its neuro-irritant metabolite, norpethidine, which has a longer half-life than the parent compound[7]. There are reported fatalities[8]. Together with pethidine's short duration of action (less than 2 hours) leading to uneven pain control, and its tendency to cause fibrotic muscle scars at injection sites with mobility problems after prolonged use, this has led to its use being discontinued by most units in the UK.

Diamorphine or morphine are preferred by prescribers for their longer duration of action, and the lack of these specific side-effects. Unfortunately, some patients experience increased nausea, itching or dysphoria with these. Standard anti-emetics and anti-histhamines can counter these side-effects effectively in many; hydroxyzine seems to be particularly effective for associated itching.

These agents can also be offered by patient-controlled analgesia pumps, set to give a low background infusion with small frequent boluses or less frequent larger boluses, as the patient prefers. Fentanyl has also been used successfully by this route. Theoretically this method gives smoother pain control, with less dependence on others for timely analgesia; some patients find it most effective while others continue to prefer intermittent injection.

Oral morphine is well documented to be effective in children for acute sickle cell pain[9]. In our experience it gives very satisfactory, smooth analgesia and is routinely used by patients up to 16 years of age. It has allowed some families to manage even severe pain episodes at home, as long as there are no other complications. It is hoped that children who learn to trust this form of analgesia will avoid some of the complications associated with frequent injections and repeated hospital-managed episodes in later life. In adulthood, familiarity with injections can make patients sceptical and mistrustful about the efficacy of oral or other forms of analgesia. 'Therapeutic dependency' on opiates is rare, but can occur.

Fear, including fear of dying from pain, is common and reassurance is crucial. Complementary approaches to pain management, including cognitive behavioural therapy, have been successful; this and other input from clinical psychology is valuable, especially where hospital admission for management of pain has become unduly frequent or prolonged.

Concurrent treatment includes:

- hydration, oral if possible
- correction of hypoxaemia, and
- management of any precipitant (eg infection).

Stroke. Ten per cent of children with HbSS suffer a stroke, although there is radiological evidence of silent infarction in 20%, and 50% have recurrence within three years. A regular transfusion programme, maintaining the HbS level below 30%, reduces recurrence to 10%. The difficult issue is when to stop, as allo-immunisation, vascular access and iron overload become troublesome. Transfusions should be offered as primary prevention to those at high risk of stroke, identified by increased cerebral flow rates on transcranial Doppler ultrasonography. Indications for blood transfusion are shown in Table 2. A two-year primary prophylactic transfusion study demonstrated reduction in stroke from 16% to 1.6%[10].

Acute chest syndrome. The development of pulmonary infiltrates, usually associated with tachypnoea, pain in the thoracic cage and worsening hypoxaemia, which inhaled oxygen corrects only partially or not at all, is known as acute chest syndrome (Fig 1). Auscultation reveals crackles and/or bronchial breathing. In 50% of cases, a cause is identified including infection, fat embolism or lung infarction. In a large multicentre study, 13% required ventilation, 11% developed neurological events and 3% died[11]. Management includes:

- analgesia
- hydration
- improving oxygenation
- incentive spirometry
- antibiotics, probably including a macrolide
- exchange transfusion (often urgently necessary).

Table 2. Indications for blood transfusion.

Note: Some of these indications are not absolute, but are circumstances in which transfusion is often offered

(a) Additive or 'top-up' transfusion	• For anaemia of compromising severity (not usually needed if Hb >5 g/dl) • Aplastic crisis with reticulocytopenia • Splenic sequestration
(b) 'Exchange' blood transfusion (with the aim of non-sickling Hb 75%)	• Stroke (and continued to prevent recurrence) • Severe chest syndrome • Severe mesenteric sickling • Priapism if prolonged • Pre-operatively (selected cases) • Pregnancy (selected cases) • Unresolving pain crisis (occasionally)

Hb = haemoglobin.

Priapism. A common problem is priapism. It occurs from young childhood onwards and may be either 'acute' and prolonged or 'stuttering' over long periods. Patients may not volunteer the symptom and should be asked about it.

Splenic sequestration. Splenic sequestration occurs in children. Sudden splenic enlargement accompanies a dramatic fall in haemoglobin. It is associated with parvovirus infection. Red cell transfusion is frequently necessary. Attacks may be recurrent and can be fatal. Splenectomy should be considered.

Thrombosis. There is an increase in thrombotic problems, especially during pregnancy and post-partum. Peripartum anticoagulation is recommended by many haematologists.

Haemolytic complications

Acute aplastic crises. Sudden worsening of anaemia, marked reticulocytopenia and marrow red cell aplasia characterise acute aplastic crises. Most are caused by parvovirus B19 infection. Although self-limiting; transfusion support may be life-saving.

Infectious complications

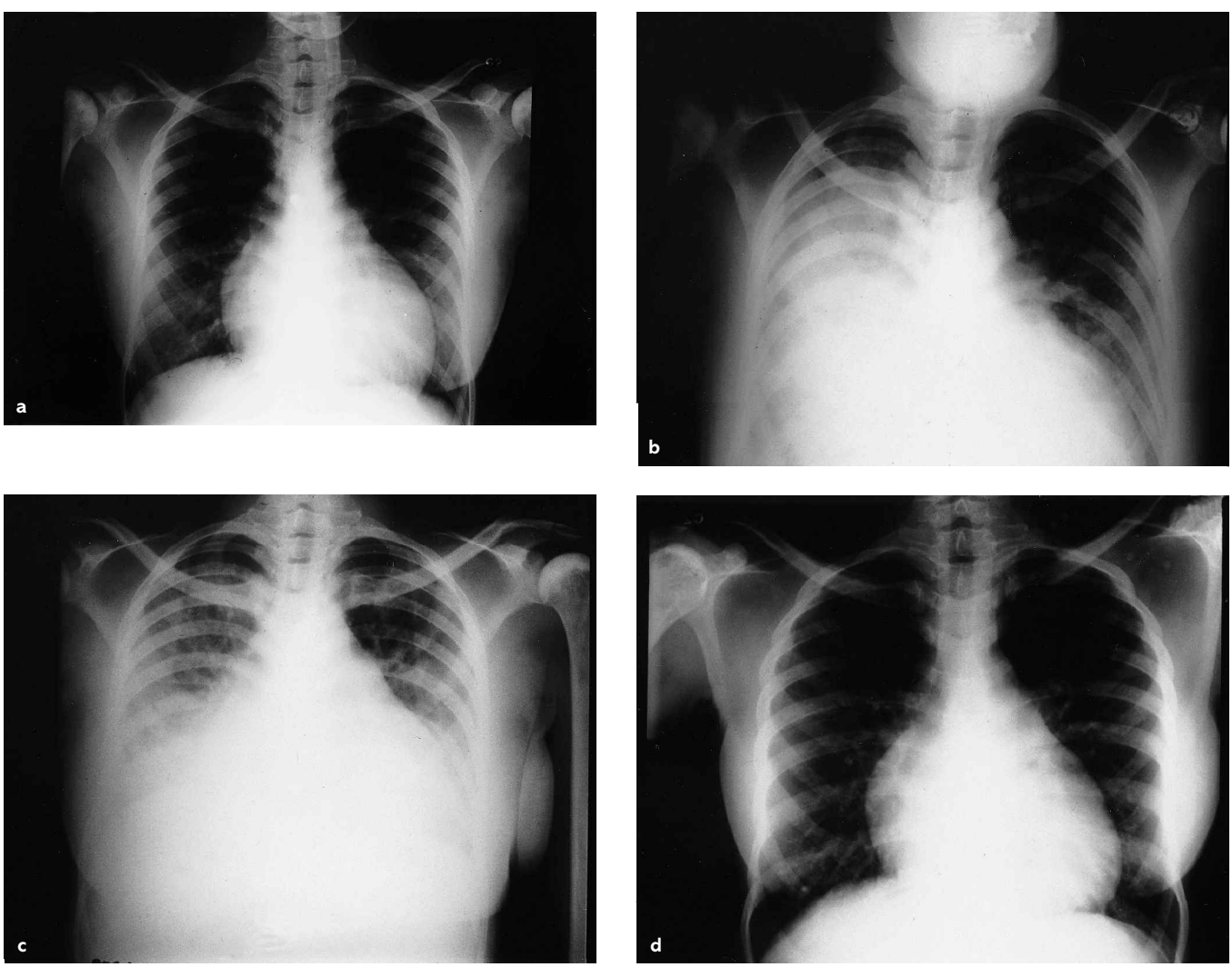
Penicillin prophylaxis[5] reduces the risk of pneumococcal meningitis, pneumonia and septicaemia which are major causes of death in children under three years. Infection with other encapsulated organisms such as *Haemophilus influenzae* are more frequent, as are pulmonary and urinary infections.

Chronic complications

Lung disease

Repeated 'chest syndrome' leads to permanent structural changes and chronic lung disease. Mild reduction in lung volumes, with or without an obstructive element, progresses through hypoxaemia at rest to severe fibrosis with pulmonary hypertension.

Fig 1. (a) Admission CXR of 24-year-old female with HbSS, rib pain, no chest signs. (b) Same patient 36 hours later, widespread bronchial breathing heard on right and some crackles starting on left. **(c) 24 hours later,** after exchange blood transfusion. Increased shadowing now on left with some clearing in right lung. **(d) Four days later,** showing near complete resolution.



Renal disease

Frank haematuria, usually self-limiting, can result from renal papillary necrosis. Investigation is mandatory as there is an increased incidence of medullary renal carcinoma. Renal failure causes death in 10% of adults with SCD. Predictors are increasing anaemia, hypertension, proteinuria, microscopic haematuria and nephrotic syndrome[12]. Angiotensin-converting enzyme inhibitors reduce hypertension and albuminuria, and may delay the progression of renal disease.

Eye disease

Proliferative retinopathy can result from retinal ischaemia. It is more frequent in SC than SS disease (36% vs 10% in young adults). Fragile new vessels can leak causing vitreous haemorrhage, or fibrose causing traction and retinal holes or detachment. Visual loss may be permanent.

Joint disease

Avascular necrosis affecting the shoulder and especially the hip (Fig 2) may cause chronic pain. Symptoms may force surgical intervention, but almost 59% of hip prostheses need revision in a median time of seven years.

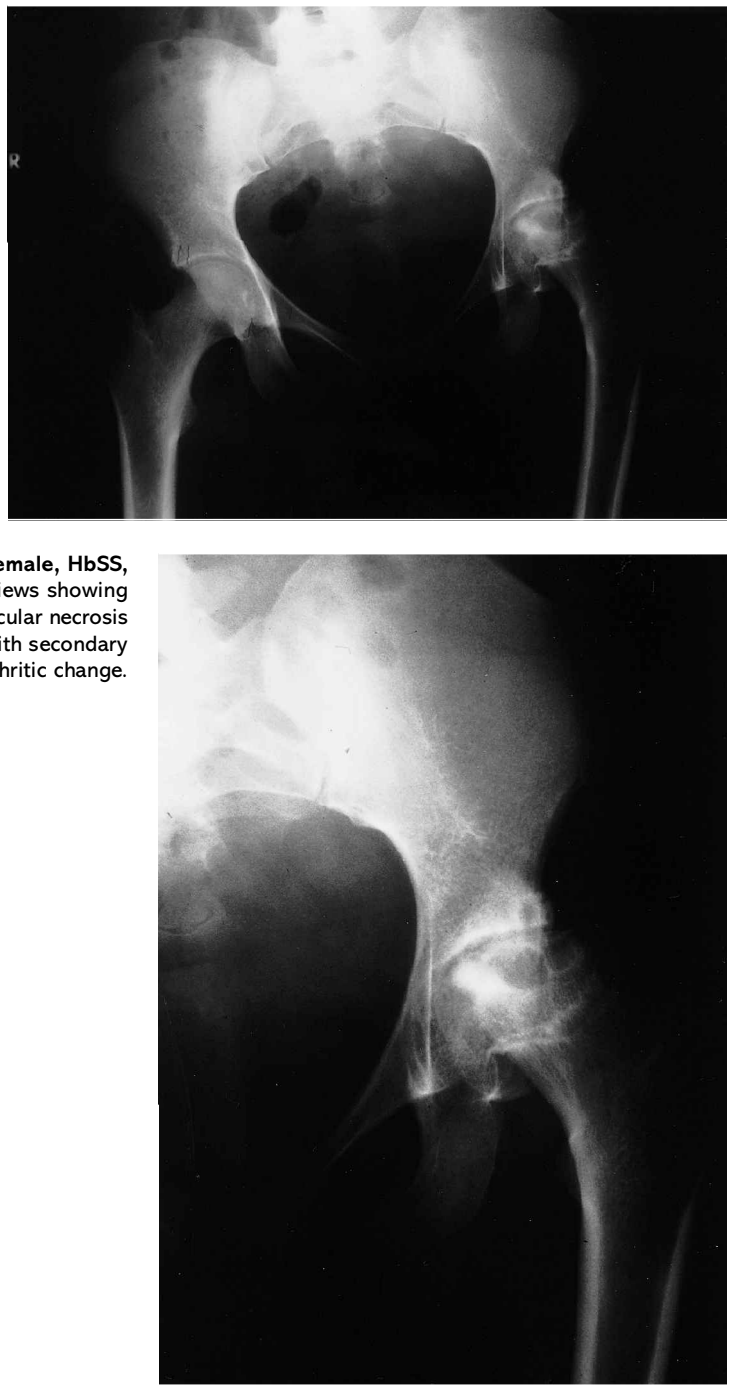


Fig 2. Female, HbSS, age 27. Views showing advanced avascular necrosis in left hip, with secondary arthritic change.

Leg ulcers

Painful and disfiguring malleolar ulcers (Fig 3) affect about 5% of adult patients in the UK, and more in Jamaica and Africa. Failure to heal is reported in over 50%, and recurrence is common.

Newer treatment strategies

Hydroxyurea. In patients with HbSS, there is a clear association between high fetal haemoglobin levels (>9%), a milder disease course and increased life expectancy. Hydroxyurea increases γ globin chain production and HbF%; it may also act by reducing both red cell adhesion molecules and neutrophils. In the largest study[13], 299 patients were randomised to hydroxyurea or placebo for two years. Pain episodes, chest syndrome and blood transfusion requirements were reduced in those on hydroxyurea.

Adverse effects include marrow suppression, potential teratogenicity and a possible (but not established) risk of carcinogenicity, but hydroxyurea can be life-transforming in badly affected patients. The drug is licensed for sickle cell disease in the USA, and is widely used there in both adults and children. Data are emerging that it may improve survival.

Allogeneic bone marrow transplantation. Allogeneic bone marrow transplantation is potentially curative but there are problems, first, in selecting patients with a sufficiently severe phenotype to justify the associated risks and, secondly, due to the lack of HLA-matched sibling donors[14]. Approximately 200 allografts for SCD have been performed to date, 20

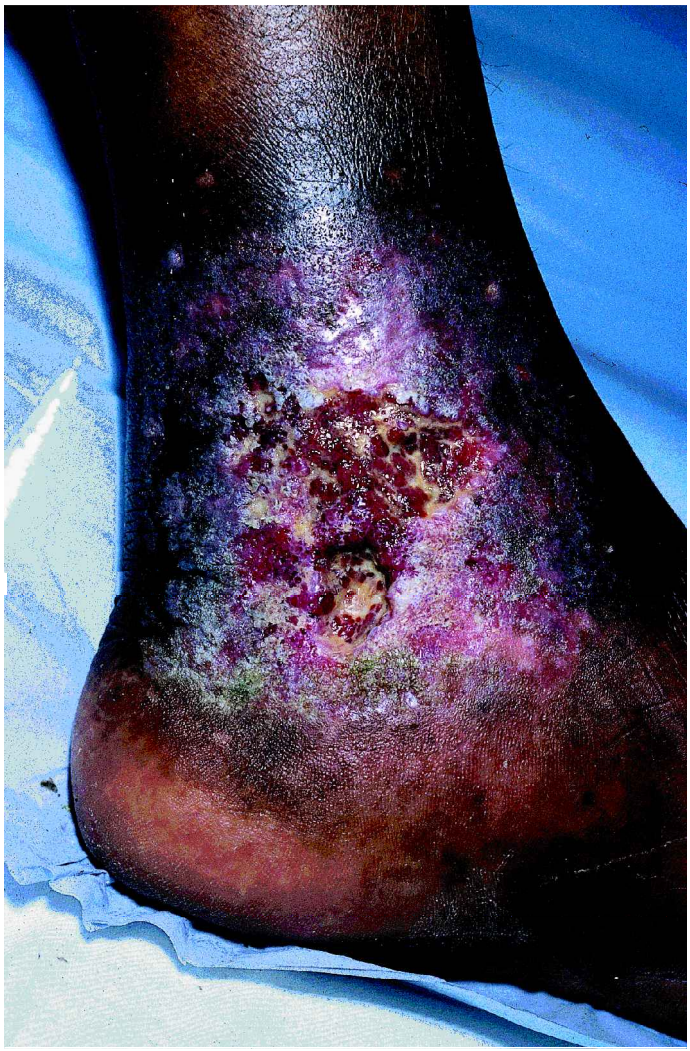


Fig 3. Male, 45 years old, Hb Sb thalassaemia. Extensive ulceration over the left medial malleolus.

of them in the UK, with overall survival about 88%. Low intensity conditioning regimens (mini-allografts) may become applicable for SCD.

Summary

SCD is a major health problem requiring lifelong multidisciplinary care to manage the wide range of medical and social consequences. A number of new approaches offer the potential to have an impact on the natural history of this disease.

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