SICKLE CELL SOCIETY

Sickle Cell Disease in Childhood

Standards and Recommendations for Clinical Care

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Clinical disclaimer

The content of this document is evidence based, as far as available evidence allows, and reflects the experience and opinions of its authors. However, they, the Sickle Cell Society, and Public Health England can take no responsibility for clinical problems arising in individual patients managed in line with its content. New evidence made available since publication should be taken into account when using this document.

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Foreword

Sickle cell disease is one of the most common serious genetic diseases in England and, as such, it must be viewed as a mainstream issue for the National Health Service (NHS). Since universal newborn screening using blood spot samples was instituted in 2005, over 3000 children have been diagnosed with the condition. Many of these children come from disadvantaged communities in urban centres and require services at local hospital and community level, as well as specialist services that match those available for other conditions (such as cancer and cystic fibrosis) to foster health equalities and to provide a better quality of life for both the child and their family.

There have been two previous editions of Clinical Recommendations and Standards for Care of Children with Sickle Cell Disease. The first in 2006 was intended to provide guidance for areas where sickle cell disease was not prevalent and to support the roll out of universal newborn screening in England. The second edition in 2010 highlighted areas where there was new guidance, for example in providing transcranial Doppler screening for the recognition of those children who might be at higher risk of stroke – a devastating consequence for children and their families. This third edition reflects what has been learned from peer reviews of hospital trusts across the country (2010–11 and 2014–16), which looked at what services were being delivered measured against quality indicators and standards, and also includes the recent guidance from NHS England on specialist services and networks. It updates clinical recommendations in several key areas and emphasises the importance of collecting data and measuring outcomes against robust standards.

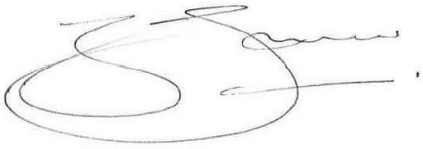
The All Party Parliamentary Group for Sickle Cell & Thalassaemia was set up in response to the report *A Sickle Crisis?* by the National Confidential Enquiry into Patient Outcome and Death (2008) and to concerns about inequity of access to medication to control iron overload due to the need for regular transfusions. Its stated purpose is to reduce health inequalities by improving standards of care and by addressing other critical issues recommended by stakeholders. One initiative has involved discussions with relevant Royal Colleges to increase training on haemoglobinopathies for all healthcare workers.

Other initiatives to improve services include data collection and the development of the National Haemoglobinopathy Registry (NHR) so that patient numbers and outcomes can be accumulated over time, thereby offering a comprehensive picture for commissioners to substantiate the need for clinical networks and services across the country. An electronic system for notifying newborns with sickle cell disease has been launched in 2019 to ensure that no infant is lost to follow-up after screening at birth and that there will be easy links with the NHR

when parents have given consent for their child to be included. In addition, the National Congenital Anomalies and Rare Diseases register (NCARDRS) in Public Health England will be monitoring the incidence of haemoglobinopathies and importantly looking at mortality data. This will provide the basis for a cohort study and will give valuable information on outcomes, which is not currently available in England.

We share a great sense of satisfaction in seeing this third edition of the Clinical Recommendations and Standards published; in particular that it has once again been the result of collaboration between clinicians, parents and carers, the Sickle Cell Society and the UK Forum on Haemoglobin Disorders, together with the NHS Sickle Cell and Thalassaemia Screening Programme and Public Health England. However, we remain conscious that there is still work to do to ensure the best possible healthcare is available for sickle cell patients wherever they live.

Rt Hon Pat McFadden MP, Chair, Sickle Cell and Thalassaemia All-Party Parliamentary Group



John James, OBE, Chief Executive, Sickle Cell Society

Dr Farrukh Shah, Chair, UK Forum on Haemoglobin Disorders

Abbreviations

A&E	Accident and emergency
CAMHS	Child and adolescent mental health services
GP	General practitioner
Hb	Haemoglobin
HCC	Haemoglobinopathy coordinating centre
HDU	High dependency unit
HPFH	Hereditary persistence of fetal haemoglobin
LHT	Local haemoglobinopathy team
MDSAS	Medical Data Services and Solutions
MRI	Magnetic resonance imaging
NCARDRS	National Congenital Anomaly & Rare Disease Registration Service
NHR	National haemoglobinopathy registry
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PHE	Public Health England
PICU	Paediatric intensive care unit
PPV	Polysaccharide pneumococcal vaccine
RCPCH	Royal College of Paediatrics and Child Health
SATs	Standard attainment tests
SCD	Sickle cell disease
SHT	Specialist haemoglobinopathy team
TCD	Transcranial Doppler
UKAS	UK accreditation service

Introduction to the 3rd edition

Sickle cell disease (SCD) is now the most common serious genetic disorder in England, affecting over 1 in 2000 live births. The majority of cases occur in cities, where expertise and resources tend to be concentrated[1]. Nevertheless, with the introduction of universal newborn screening for SCD in England through the NHS Sickle Cell and Thalassaemia Screening Programme, implemented since 2006, affected infants have been identified in all parts of the country[2]. SCD can therefore be regarded as a mainstream health issue in England.

The original standards and guidelines document was published as an 'executive summary' in September 2006; to support the introduction of universal newborn screening in England. A 2nd edition was published in 2010 with updated information and reference to other related documents and aimed to provide a more comprehensive overview of care that might be useful for a wider readership and not just clinicians. Since 2010 there have been two national peer reviews of clinical services for children with SCD (2010–11 and 2014–16), carried out by the West Midlands Quality Review Service, which were informed by the 2nd edition[3]. There has also been a specialist commissioning review of services for patients with haemoglobinopathies[4].

It is proposed that a clinical network should consist of local haemoglobinopathy teams (LHTs) and specialist haemoglobinopathy teams (SHTs) who will work with a specific haemoglobinopathy coordinating centre (HCC) to ensure that the roles and responsibilities for its caseload of patients are clear. Note: in some areas, the LHT and SHT may be the same. The SHTs and HCCs will be identified through a compliance exercise and will be required to deliver services through revised service specifications with contracts starting after 1 April 2019. HCCs will receive funding to coordinate a support team with multidisciplinary specialists.

Changes to this edition

This 3rd edition has been revised to reflect research and guidance published in the past 10 years. These include the guidance for preoperative transfusion[5], the long-term management of stroke and switching to hydroxycarbamide (previously known as hydroxyurea)[6] and the recommendation to offer hydroxycarbamide to all children from the age of 9 months regardless of their clinical status[7]. Most of the clinical recommendations remain the same; however, it is expected that, over the next 5 years, this will change as new medications come on the market and a new edition will be needed at this juncture. As well as clinical updates, the standards have been improved and extra ones incorporated to provide more consistent and rigorous definitions, with the aim of collecting better data on clinical outcomes.

Data collection is important to monitor the success of the newborn screening programme and to measure clinical outcomes, such as the incidence of stroke and early mortality in children. It is recognised that collection of data, although understood to be important by clinicians, also adds extra work to busy

caseloads. To mitigate this, Public Health England (PHE) and Medical Data Services and Solutions (MDSAS) has been developing an electronic system for newborn screening results that will link in with the requirements of the National Haemoglobinopathy Registry (NHR), the specialist commissioning dashboard and the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS). NCARDRS has the responsibility for maintaining a register of all children with SCD in England, and recording all who have died and whether the death was directly related to the condition. This register does not require consent and is not anonymised. It therefore provides an extremely valuable resource for the future.

Specific revisions to be noted include:

- The standards are defined in line with PHE guidance and Metric Definition Sets that inform the Specialised Services Quality Dashboard commissioned by NHS England to aid consistent monitoring.
- Where relevant, standards conform or refer to other related standards e.g. the newborn screening programme, transcranial Doppler (TCD) screening.
- New standards include the coverage of children offered hydroxycarbamide therapy, coverage of children on the NHR and the number of children having an annual review.
- Links have been provided for all other standards in order for the most up-to-date version to be available at all times.
- The recommendations on cerebrovascular disease, preoperative transfusion and hydroxycarbamide therapy have been updated.
- The section on delivery of healthcare has been expanded to acknowledge the effect that socioeconomic determinants have on health.
- A new information technology system for referring infants from newborn screening into treatment is introduced.

Aims of this document

These recommendations have been written to support clinicians and to ensure that every infant has access to the same quality of care wherever they live. They are written for paediatricians, haematologists, specialist nurses and psychologists, and for those responsible for monitoring outcomes i.e. hospital trusts, commissioning authorities and peer-review services.

The document is not intended to provide extensive clinical guidance for the management of acute complications. Prior to 2010, clinical guidelines were available mainly from the USA. Since the last edition, there have been clinical guidelines produced by the British Society for Haematology on transfusion in SCD[8,9], acute chest syndrome[10] and hydroxycarbamide therapy[11]. There has been National Institute for Health and Care Excellence (NICE) guidance on the management of pain in hospital[12] and a NICE-accredited Royal College of Paediatrics and Child Health (RCPCH) guideline on stroke[13], updating the 2004

document. Most hospital trusts will now have their own clinical guidelines and these are readily shared within and between networks and are available online.

This document outlines a model of care for children with SCD who have been identified through the newborn screening programme. It extends from newborns until transition into adult care – which is usually between 16 and 18 years. It will also have relevance for the care of children who may have missed out on newborn screening before the programme was introduced, or who have come from abroad and been diagnosed after the newborn period. It is based on a consensus of clinicians with experience in the UK, Jamaica and the USA.

Note: throughout this document, text that is underlined indicates a link either to a relevant section within this document or to an external website that the reader may wish to view; Ctrl + Click will allow the reader to follow the link.

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Background to sickle cell disease in children

Conditions to be treated

SCD denotes all genotypes containing at least one sickle gene in which HbS makes up at least half the haemoglobin (Hb) present. In addition to sickle cell anaemia (this will be referred to as HbSS in future in this document), there are other compound heterozygous conditions that occur in the UK. Conditions to be treated include:

- Haemoglobin SS (sickle cell anaemia)
- Haemoglobin SC*****
- Haemoglobin SD^{Punjab}
- Haemoglobin SE
- Haemoglobin S/β thalassaemia (β+, $β^0$, δβ and Lepore)
- Haemoglobin SO^{Arab}.

*** Note: areas where the management of HbSC differs from HbSS will be shown in this document in green.**

Haemoglobin S/HPFH (hereditary persistence of fetal haemoglobin) is indistinguishable on neonatal screening from HbSS and HbS/$β^0$ thalassaemia. Family studies and DNA testing may clarify the diagnosis. HbS/HPFH is not thought to cause clinical complications and there is no evidence as to whether children with this should be followed up regularly. There is no evidence that HbS/HPFH leads to splenic hypofunction and prophylactic penicillin is not recommended. However, in the absence of both parental phenotypes, it is best to start penicillin prophylaxis until such time that the diagnosis is confirmed. HbS/HPFH should not be confused with the more common HbSS where the child continues to produce relatively large amounts of fetal haemoglobin (HbF) beyond early childhood.

Incidence, prevalence and survival

SCD is one of the commonest serious genetic conditions in England, affecting approximately 1 in 2226 live births (2018 to 2019 annual data report). The birth prevalence in some urban areas may be as high as 1 in 325[1]. It is found at a low frequency in all populations, the highest prevalence occurring in people of African and African-Caribbean origin. Cases also occur in families originating from the Middle East, India and the eastern Mediterranean, with increasing numbers of cases in mixed-race families. A recent analysis of multiple databases concluded there are 14,000 people with a diagnosis of SCD living in the UK[2].

Considered a disease of childhood 30 years ago, at least 99% of children in London are now expected to survive until adulthood[3]. Life expectancy has improved owing to newborn screening and early administration of antibiotic prophylaxis, improved recognition and better management of acute episodes and screening for children at high risk of stroke. The introduction of neonatal screening programmes in parts of the USA dramatically improved healthcare, and childhood mortality is now about 1–2% in some areas[4].

However, in the USA there is a marked geographic difference in the mortality of young children with SCD, which greatly exceeds the mortality of black children without the disease[5,6]. This highlights the importance of having a robust clinical programme with clear guidelines, evidence-based standards of care and access to high-quality clinical care wherever a child with SCD lives. Studies in London suggest that the survival of children with SCD is very similar to that in the non-sickle population[2].

A US multicentre study in 1994 reported a median survival in people with HbSS of 42 years for men and 48 years for women; in those with HbSC disease of 60 years and 68 years, respectively[7]. Survival estimates for HbSS in Jamaica, based on a clinic population, suggested median survival for men of 53 years and for women of 58.5 years[8]. A recent study in the UK suggested a median survival of 67 years for adults with HbSS/HbSβ^0 thalassaemia[9] probably reflecting that the NHS is available to all residents, free at the point of use.

Pathophysiology

A single nucleotide substitution in the seventh codon of the β globin gene results in the substitution of valine for glutamic acid on the surface of the variant β globin chain. This change causes HbS to polymerise when deoxygenated, the primary event in sickle cell pathology. Polymerisation is dependent on intra-erythrocytic HbS concentration, the degree of haemoglobin deoxygenation, pH and the intracellular concentration of HbF. The polymer is a rope-like fibre that aligns with others to form a bundle, distorting the red cell into the characteristic sickled forms.

These deformed sickle red cells can occlude the microvascular circulation producing vascular damage, organ infarcts, painful episodes and other symptoms associated with SCD. HbS polymerisation and vaso-occlusion lead to a cascade of inter-related pathological processes, including anaemia, haemolysis, disturbed nitric oxide metabolism, inflammation, hypercoagulability, oxidative stress, hypoxia and vascular-endothelial dysfunction.

A recent review gives a comprehensive account of the current understanding of the pathophysiology in SCD[10].

Presentation

There is a wide range of clinical presentations and severity. In the unscreened population, infants may present with sudden death from pneumococcal sepsis due to splenic hypofunction or with acute splenic sequestration, before a diagnosis is made. Dactylitis is a common presenting symptom in infants between 9 and 18 months, but many children do not experience this and may only present later with vaso-occlusion affecting the long bones.

Possible complications may include:

- Painful episodes due to vaso-occlusion – the most common complication, accounting for the majority of hospital admissions
- Stroke:
  - silent strokes (with changes seen on magnetic resonance imaging [MRI]) occur in up to 20% before the age of 20 years, and may cause cognitive or psychological problems
  - overt strokes are less common since the introduction of routine transcranial Doppler (TCD) but previously affected 5–10% of the paediatric population
- Acute chest syndrome – a serious and common cause of morbidity and mortality, which may be precipitated by infection, infarction or a combination of the two
- Other complications:
  - lung damage
  - hepatobiliary disease
  - renal disease
  - osteomyelitis
  - avascular necrosis
  - eye complications
  - hearing impairment
  - priapism
  - leg ulcers.

Variability

Some children with SCD are severely affected, while others remain largely symptom-free in terms of painful episodes. However, many children who do not experience pain go on to suffer other complications, including progressive organ damage and vasculopathy.

This variability is not completely understood but may be due to inheritance of other genes that either affect the types and levels of Hb produced along with HbS or affect vaso-occlusive events:

- HbSC – co-inheritance of HbC with HbS results in a generally milder condition (typically half the number of acute painful episodes, less risk of splenic hypofunction and low risk of stroke)
- HbF level – once the level has stabilised during infancy, it is constant through life and a relatively good predictor of disease severity[11]
- concurrent α thalassaemia carrier status – episodes of acute pain are more common, but severe, life-threatening complications are less common.

In addition, a number of socioeconomic factors can affect variability.

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Overview of healthcare delivery for children with SCD

Challenges and requirements

The provision of equitable and comprehensive care for children with SCD is uniquely challenging, given the wide geographical variation in prevalence and known variability in the severity. Care must be delivered at an optimal level both close to the patient's home and via access to an SHT. In addition, services should support young people, parents and family carers to manage the condition at home where appropriate.

As SCD becomes more common across the UK, every hospital should be able to provide basic inpatient and outpatient care for local patients. All hospitals with an emergency department and/or acute paediatric unit should be able to provide emergency care of acute sickle problems, most commonly severe pain. Units need to have guidelines to manage acute anaemia that is getting worse, respiratory problems and more infrequent sickle cell complications, along with protocols for when these children need to be transferred to a specialist unit.

Health and wellbeing

SCD should be considered as a chronic long-term, life-limiting condition with acute exacerbations that have far-reaching disabling consequences for education, family life, social integration and the emotional wellbeing of the child and family. This requires those working in secondary and tertiary care to work with those in primary care, social care, education and public health, in addition to third-sector, voluntary organisations. Care therefore needs to be provided by a multidisciplinary team, working across sectors and different agency boundaries, with consistent clear communication being vital. An effective team has a clear strategy for sharing information, plus sharing and agreement of common goals, alongside an understanding of each other's respective responsibilities, experience, skills and knowledge.

The model of local and specialised centres is well established for the treatment of such conditions as cystic fibrosis, cancer and haemophilia. The value of haemoglobinopathy centres has been well documented in the USA[1].

The specialist haemoglobinopathy services specification[2] has proposed that there should be a number of HCCs across the country to provide a coordinated leadership function within their area, supporting SHTs and LHTs in the delivery of clinical care, and strengthening the network concept. All children with SCD should have access to those with specialist knowledge and an annual review in conjunction with an SHT is recommended, along with a transition policy for transfer to adult care when appropriate. Shared care arrangements will vary according to local needs and circumstances. It may be appropriate in some areas for the SHT to visit the local unit and in others for children and their families to travel to the centre in which the SHT is based.

When organising care, it is important to take into account local community support and health provision, including child and adolescent mental health services (CAMHS), education, social services and self-management, as well as hospital care. Training for general practitioners (GPs), community nursing and local authority employees will be needed, along with inter-agency agreement on criteria for referral to social services and education services for additional support. The voluntary sector (e.g. the Sickle Cell Society) plays an important part.

Parents should be encouraged to know and use their community teams and to make use of primary care. Parents who are knowledgeable about their child's condition will however often know when home treatments are not working or when an emergency necessitates them taking their child straight to hospital. Young people are also increasingly empowered to make choices about their care options.

Children, young people and their families who have a clear understanding of their condition are more likely to manage their disease optimally[3]. An emphasis on family education and independent self-care is therefore fundamental to successful outcomes, particularly given the uncertainties associated with SCD[4].

Non-clinical care interventions

In addition to clinical interventions, there are a number of other important non-clinical interventions that can help towards improved patient wellbeing[5].

Interventions that promote public health, improve outcomes in primary and social care, and facilitate successful education have the potential to transform lives, particularly for those with longstanding conditions[6]. People with SCD are more likely to be exposed to social factors that contribute to health inequalities, which can become disabling and create barriers to social inclusion[5]. These risks factors include lack of physical activity, social isolation and poor diet, alongside issues associated with education and employment opportunities, poverty and poor housing, and inequitable access to health and social care[7]. Tackling inequalities, which may cause enduring lifelong effects, is especially important for children[8].

Although sometimes neglected, primary care, public health and more socially orientated provision have important roles to play in supporting those with SCD. The scope of primary and community provision is necessarily broad. This highlights the importance of coordination, communication and team-working between the different stakeholders.

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Standards and recommendations

Basis of recommendations

Recommendations are based on evidence, which may have been obtained by:

- randomised controlled trials
- good clinical studies
- clinical opinion based on expertise.

Examples of a strong evidence base in the management of HbSS and HbS/β^0 thalassaemia include the use of prophylactic penicillin in children, routine TCD screening to identify children who might be at risk of stroke and prescription of hydroxycarbamide to reduce the frequency of painful episodes and acute chest syndrome.

Grading of recommendations

For the recommendations, the letter in brackets following the recommendation refers to its grading, as based on the US Agency for Health Care Research and Quality recommendations.

A	Requires at least one randomised trial as part of the body of literature of overall good quality and consistency addressing the specific recommendations
B	Requires availability of well-conducted clinical studies, but no randomised clinical trials, on the topic of the recommendations
C	Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality

Standards

The standards are linked to the strong recommendations and provide a mechanism by which laboratory, nursing and medical care can be assessed across the country. Some standards are already in use through the NHS Sickle Cell and Thalassaemia Screening Programme or have been agreed by NHS England in the specialist commissioning dashboard. Some are already part of the quality standards agreed by the UK Forum for Haemoglobin Disorders in collaboration with the West Midlands Quality Review Service. The Screening Programme, after much consultation and several re-iterations, include in their standards a description of the standard, the rationale behind the standard, a definition, up to two performance thresholds and appropriate reporting mechanisms. The value of this approach has been to ensure a clear pathway for monitoring and recording, thereby allowing for ease of comparison across different units. For this reason, the same format has been adopted for the standards in this document.

Target thresholds

All centres should aspire towards attaining and maintaining performance at the achievable threshold. All centres are expected to exceed the acceptable threshold. Centres not meeting the acceptable threshold are expected to implement changes to ensure sustained improvement. For some of the standards, it has not been possible to set an acceptable or achievable standard e.g. the coverage of hydroxycarbamide. These will be suggested once the peer-review process gives feedback on current practice.

Grouping of recommendations

The recommendations have been divided into the following sections:

- Organisation of care (community- and hospital-based care)
- Pathway of care (from newborn screening to transition to adult care)
- Ongoing issues (often managed at home/in the community)
- Chronic complications (usually requiring hospital care)
- Acute complications (usually requiring urgent inpatient care)
- Elective surgery and perioperative care
- Specific treatments.

These are followed by the eight standards, which cover:

- reporting of newborn screen-positive results to parents
- timely follow-up, diagnosis and treatment of newborn infants with a positive screening result
- timeliness of penicillin prophylaxis
- coverage of pneumococcal immunisation
- coverage of TCD scanning
- offer of/treatment with hydroxycarbamide
- registration on the NHR
- performance of an annual review.

Organisation of care

Community-based services/individuals involved in the care of children with SCD

Primary care

With improved staff knowledge and training, primary care is increasingly important in the management of SCD, although its potential is not always realised[1,2]. The primary care team may be involved in:

- genetic screening
- offering reproductive and health advice
- providing routine screening and testing
- preventive care such as immunisation
- follow-up after emergency admission
- coordination of care, including for patients who may have multiple co-morbidities and unrelated health issues alongside SCD – liaison with the sickle cell team is important before referring for any potentially SCD-related problem (e.g. hip pain).

Practical information that needs to be given by the acute hospital to the general practitioner includes:

- steady state values
- the information that has been given to parents
- dosages of medications
- when children can be managed at home or need to be seen in hospital.

Sickle cell and thalassaemia community centres

In areas of high prevalence, there may be sickle cell and thalassaemia community centres that provide an information resource, support and advice to families, training for health and other professionals, as well as genetic counselling and specialist nursing. A list of centres is available from the Sickle Cell Society. Where possible, parents should be put in touch with their local centre.

Community specialist nursing and counselling

Models of community specialist nursing for sickle cell care vary across the country and there are no nationally agreed models of nursing care. Community nursing teams make an important contribution to care. This may include social, psychological support, genetic counselling and more practical nursing support (such as review of medications and pain management).

Community nursing may be provided as a standalone community service, often as part of a community sickle cell and thalassaemia community centre or as part of a wider community NHS directive. They may also be integrated with the acute haemoglobinopathy team.

Local authorities

Local authorities are now responsible for commissioning health visiting and school nursing services. Since the 2012 Health and Social Care Act, local authorities have set up health and wellbeing boards that bring together the NHS, public health, adult social care and children's services, including elected representatives and Local Healthwatch, to plan how best to meet the needs of their local population and tackle local inequalities in health.

Every local authority must protect and promote the welfare of children in need in its area. To do this, it must work with the family to provide support services that will enable children to be brought up within their own families.

Children in need are defined in law as children who are aged under 18 and:

- need local authority services to achieve or maintain a reasonable standard of health or development
- need local authority services to prevent significant or further harm to health or development
- are disabled.

The local authority must keep a register of children with disabilities in its area but does not have to keep a register of all children in need.

Local authorities provide for children with SCD as they do for other children who may be ‘in need’ or experience an ongoing disability. Children with SCD, unless they have a chronic disability such as stroke, do not fulfil the criteria for acceptance onto the disability register for social services departments. This is despite the fact that frequent acute exacerbations disrupt normal life and may be as disabling as other chronic conditions.

Unfortunately, with no clear guidelines on what services should be available to them, it can be difficult for families to negotiate social care provision.

Welfare benefits

While children and their families may not be able to access a social worker, there may be welfare benefits that can mitigate some of the problems they face. In some areas, a welfare benefits adviser is an integral part of the community sickle cell centre. In other areas, it should still be possible to refer parents to their local welfare benefits advisor. However, it may still not be easy to claim benefits, especially as SCD can cause intermittent problems, meaning needs can fluctuate. Because information on benefits can change frequently, details of benefits that it may be possible to claim will not be listed in this document.

Provision of suitable housing is also key as cold damp conditions can precipitate painful episodes. Ease of access with the minimum of stairs may also be important for some.

Education

Education can mitigate against the impact of longstanding conditions, having an important long-term role in improving quality of life[3]. Educational qualifications can protect against socioeconomic disadvantage, but education providers can struggle to accommodate the needs of children with SCD[4]. For example, children with SCD are only monitored if they have been found to have a learning disability and defined special educational needs[5]. Even then, most special needs resource has been devolved to the local school, who provide only as much extra support as they can afford. Most children, when well, should however be able to attend school regularly and take part in all school activities.

There is a particular need to inform school teachers that overt or silent stroke can cause cognitive impairment that leads to learning difficulties[6], occurring in about 20% of those with SCD under 20 years. These acquired impairments may be missed in children who when they started school had no difficulties. It is vital that teachers liaise with the clinical nurse specialist if they become aware of any decrease in cognitive functioning. A formal neuropsychology assessment, which can be performed either by a neuropsychologist or an educational psychologist, is likely to be required.

Many children can attend school, despite having mild-to-moderate pain, if there is a care plan in place. It is of great concern that some children have a very low school attendance because of parental concerns that they will not be managed appropriately[4]. There is Department of Health policy for managing medical conditions in schools[7] and parents and clinicians should be aware of this and work closely with the school nursing service and the school to ensure its implementation.

Most children should be encouraged to take part in all school activities. Children who need additional and specialist help in school to access learning should be able to achieve this through the special educational needs process[8]. Helpful information is available in the leaflet *Sickle Cell and Thalassaemia: Education, Health and Care. A guide to School Policy* and the booklet *A parent's guide to managing sickle cell disease*.

Community paediatrics

Community paediatricians already have extensive experience in coordinating community services and liaising with education, social services, the voluntary sector, CAMHS and the acute sector. They can therefore be a valuable resource.

CAMHS and other psychological interventions

CAMHS are available in every borough, although they have limited resources to manage children who do not have a mental health diagnosis. Counselling services can be accessed in some schools. These community services need to link to those in hospital departments where there is specialist sickle cell psychology provision.

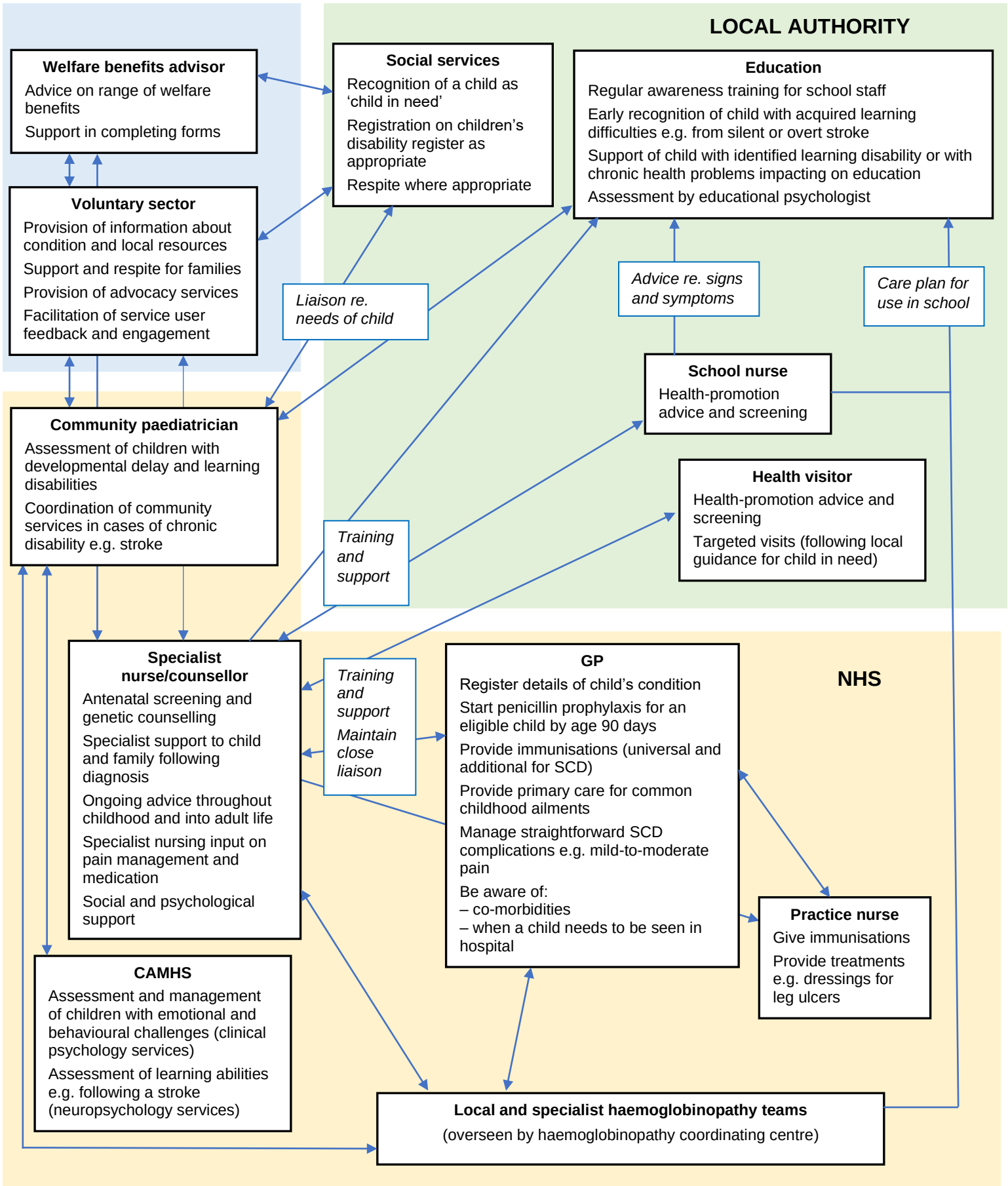
Psychological interventions can be especially valuable in helping children and families build resilience[1]. SCD can pose multiple and severe psychological challenges to children, young people and their families, although health and social care agencies can sometimes struggle to accommodate these challenges[2]. Psychosocial issues for people with SCD and their families can result from the impact and disruption due to pain and other symptoms on their daily lives. For example, stress, depression, fear or anxiety may affect the experience of pain. Psychological therapies with children and young people have been shown to be effective in reducing pain and, therefore, hospital admission[3]. While group psychoeducation for families of children and adolescents with SCD has shown improvements in understanding[1].

Roles and responsibilities of those providing community services

The roles and interlinkages of those providing care to children with SCD in the community are shown in the flowchart on the following page.

Recommendations

- There should be a network of care based on local community care, including GPs, the local sickle cell and thalassaemia centre (if available), health visitors, voluntary sector and school nurses, with links to the relevant haemoglobinopathy teams. (C)
- Parents should be put in touch with local and national voluntary organisations and local sickle cell and thalassaemia centres. (C)
- GP and community nurses should be kept informed about patients on a regular basis. (C)
- There should be community paediatric services to coordinate the community needs of the child and to liaise with CAMHS, local authority services and the voluntary sector as needed. (C)
- Local authority services (including education and social services) should be aware of the specific needs of children with SCD and their families. (C)
- Any child with a deterioration in cognitive functioning should be assessed by an educational psychologist or clinical/neuropsychologist. (C)
- CAMHS should be aware of the specific emotional and learning needs of children with SCD and their families. (C)
- Parents need to know how to access welfare benefits. (C)


LOCAL AUTHORITY
Welfare benefits advisor
Advice on range of welfare benefits
Support in completing forms
Social services
Recognition of a child as 'child in need'
Registration on children's disability register as appropriate
Respite where appropriate
Education
Regular awareness training for school staff
Early recognition of child with acquired learning difficulties e.g. from silent or overt stroke
Support of child with identified learning disability or with chronic health problems impacting on education
Assessment by educational psychologist
Voluntary sector
Provision of information about condition and local resources
Support and respite for families
Provision of advocacy services
Facilitation of service user feedback and engagement
Liaison re. needs of child
Advice re. signs and symptoms
Care plan for use in school
School nurse
Health-promotion advice and screening
Community paediatrician
Assessment of children with developmental delay and learning disabilities
Coordination of community services in cases of chronic disability e.g. stroke
Health visitor
Health-promotion advice and screening
Targeted visits (following local guidance for child in need)
Training and support
NHS
Specialist nurse/counsellor
Antenatal screening and genetic counselling
Specialist support to child and family following diagnosis
Ongoing advice throughout childhood and into adult life
Specialist nursing input on pain management and medication
Social and psychological support
Training and support
Maintain close liaison
GP
Register details of child's condition
Start penicillin prophylaxis for an eligible child by age 90 days
Provide immunisations (universal and additional for SCD)
Provide primary care for common childhood ailments
Manage straightforward SCD complications e.g. mild-to-moderate pain
Be aware of:
– co-morbidities
– when a child needs to be seen in hospital
Practice nurse
Give immunisations
Provide treatments e.g. dressings for leg ulcers
CAMHS
Assessment and management of children with emotional and behavioural challenges (clinical psychology services)
Assessment of learning abilities e.g. following a stroke (neuropsychology services)
Local and specialist haemoglobinopathy teams
(overseen by haemoglobinopathy coordinating centre)

Hospital-based care for children with SCD

Role of the haemoglobinopathy coordinating centre (HCC)

Responsibilities include:

- supporting local providers to ensure all patients are registered on the NHR
- ensuring local and national guidelines are in place
- identification of a TCD screening lead
- ensuring NICE guidance is followed for automated red cell transfusions.

Full details and a list of indicators are available in the HCC service specification (https://bit.ly/HCCservicespec).

Definition of specialist haemoglobinopathy team (SHT)

SHTs should fulfil the following criteria:

- have a designated paediatrician/paediatric haematologist/haematologist with a specific interest in paediatric haemoglobinopathy
- have a lead nurse
- have a designated paediatric haemoglobinopathy clinic (which may be part of a larger clinic)
- provide paediatric high dependency and intensive care, or have established protocols for the referral of patients to a hospital with a paediatric high dependency or intensive care unit (HDU/PICU) with experience and protocols for the management of SCD in children
- have clinical pathology (CPA)-accredited laboratory facilities for accurate haemoglobinopathy diagnosis
- have established links with local neonatal screening programme and sickle cell counsellors
- have access to TCD scanning
- have links with clinical psychology for specialised treatment and neuropsychological assessment or cognitive testing
- participate in the peer-review process.

Role of SHT

The SHT will:

- work with a specific HCC to ensure the roles and responsibilities for its caseload of patients is clear
- agree and monitor compliance with network care pathways and treatment protocols
- support the provision of coordinated expert care and advice within the network

- provide 24/7 advice for other clinical teams both within the hospital and at other local hospitals
- support the provision of routine non-complex care for its local population and be responsible for ensuring all of their patients have an annual review
- ensure all consented patients in their network are registered on the NHR.

All SHTs should provide:

- paediatric and adult outpatient review and care; annual reviews; referral for specialist diagnostic investigations; discussion of disease modifying treatments; discussion of new treatments and new trials; and neurocognitive assessment and review (see Standard 8)
- nursing care by staff with experience in haemoglobinopathies
- transition care from paediatric to adult services
- support from a psychologist with a specialist interest in haemoglobinopathies
- specialist support and advice on conditions such as transfusion reactions, severe or recurrent painful vaso-occlusive episodes, acute sickle chest syndrome and aplastic crisis
- advice on complex care surgery
- initiation of hydroxycarbamide treatment, blood monitoring and dose escalation as appropriate
- advice on acute organ failure
- transfusion management including decisions regarding initiation and cessation of elective transfusion programmes
- prescription and routine monitoring of iron chelating drugs.

They should also provide or have clear referral pathways within their network to provide the following:

- neurocognitive assessment and review
- MRI assessment of liver and cardiac iron
- management of complications related to iron overload, endocrine and growth issues
- management of complex patients and those with co-morbidities
- advice and referral for stem cell transplant, novel and curative therapies
- specialist advice for the management of pregnancy in conjunction with expert obstetric teams.

Further details are available in the SHT service specification (https://bit.ly/SHTservicespec).

Role of the local haemoglobinopathy team (LHT)

The LHT, which in some places is the same as the SHT, should:

- have a named paediatrician to link in with the SHT and neonatal screening laboratory
- arrange initial contact with the family and provide a paediatric clinic for routine outpatient management
- promote and support management at home by the parents, GP and community sickle cell and thalassaemia centre (if available)
- manage severe acute pain and acute anaemia, and provide initial care for other complications before transfer to the SHT according to shared guidelines and protocols
- liaise with the SHT for annual review
- follow-up children who fail to attend, reporting to the SHT on annual activity as part of a network review meeting
- liaise with local authorities e.g. education and social services
- manage transition to the adult service
- provide accurate, comprehensive and timely data to the Newborn Outcomes system to enable the outcomes of newborn screening to be evaluated
- complete and update entries into the NHR (when consent has been given).

Recent peer reviews reveal very wide discrepancies in staff resources across different units. The areas most affected are medical and specialist nursing provision together with psychology support. Some variation in staffing is inevitable as it will depend on other factors such as number of available supporting staff and case mix. However, an expected minimum requirement might be: one whole-time equivalent (WTE) consultant paediatric haematologist (or paediatrician with expertise in haemoglobinopathy disorders) and one WTE specialist nurse for every 200 patients with a major haemoglobin disorder based at any centre, with one WTE psychologist recommended by the British Psychological Society (BPS) for every 300 patients. In addition, the following was suggested after a survey of medical specialists treating haemoglobinopathy patients in England[1]:

- 0.25 programmed activities (PAs) for continuing professional development (CPD) per consultant
- 1.5 PAs for every 50 patients for direct clinical duties
- 1 PA for the geographical area clinical lead
- Additional PAs as required (e.g. for specialist training, laboratory work, research, outreach clinics).

Recommendations

- Organisation of care at the LHT and SHT levels should be in line with the findings of the specialist review. (C)
- The LHT and SHT should work closely with the HCC. (C)
- There should be a named paediatrician responsible for follow-up in the LHT. (C)
- There should be a named paediatrician and/or paediatric haematologist in the SHT. (C)
- There should be access to nurses experienced in caring for children with SCD. (C)
- There should be access to clinical psychology services. (C)

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Hospital-based care

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Pathway of care

Initial identification of disease

Parents of all babies born in England, Wales, Scotland and Northern Ireland are offered screening for SCD as part of the newborn bloodspot screening programme.

National blood spot laboratories are assessed by the UK Accreditation Service (UKAS) and must meet ISO 15189. The newborn screening programme set standards for the initial contact with the parent and registration in paediatric follow-up.

Communication of initial screening result

Bloodspots samples are sent to one of 13 newborn screening laboratories and the results of all infants who may have a type of SCD are sent as a matter of urgency to the nominated coordinating centre and the named individual. The centre confirms receipt.

Data is shared with NCARDRS who have permission from the National Information Governance Board under section 251 the NHS Health Act 2006 and the authority of the Health Service (Control of Patient Information) Regulations 2002 to collect patient-identifiable data without the need for individual informed consent for the purposes of congenital anomaly and rare disease registration. As from 2019 this system will be automated by the Newborn Outcomes System, improving the effectiveness of the whole system.

The NHR is commissioned by NHS England, with data collected from clinicians in haemoglobinopathy teams. It is a database of patients with haemoglobino-pathies living in England, its central aim being to improve patient care – initially it was set up to aid the planning of service delivery but recently it has become more of a clinical registry. NHR users are able to view and use the Newborn Outcomes System but the NHR is a consented registry and no data crosses into it until consent has been explicitly recorded. Additional data items recorded on the NHR are not shared back to the Newborn Outcomes system.

Information about what personally identifiable information is used by the screening programmes and why it is required is provided in *Screening tests for you and your baby*, a booklet issued to all pregnant women in England, with more detailed information on the Gov.UK website. This includes the parent's right to opt out of their data being held in NCARDRS under Section 251 approval.

More information on the NHR can be found on their website and includes a patient information leaflet.

Informing parents

The parents of every child found to have a probable significant haemoglobinopathy should be informed by personal contact from the designated healthcare professional by 28 days after the birth of the child (see Standard 1). Every area has a named healthcare professional, who may be a paediatrician or a nurse. In some high prevalence areas, the nurse will be a specialist in SCD.

Although women and their partners should have been offered antenatal screening and counselling, and should have been fully informed of their risk, this may not always be the case in reality. It may still come as a shock to learn the diagnosis[1]. Early communication from the local named healthcare professional, in a culturally sensitive way[2], is important to provide accurate information and to ensure that the infant has timely access to prophylactic treatment. Parents may find these leaflets useful: *Information and choices for women and couples at risk of having a baby with sickle cell disease* and *A parent's guide to managing sickle cell disease*.

The primary care team needs to know the diagnosis as soon as possible to provide ongoing medical and emotional support, and to begin penicillin treatment and appropriate immunisations. Arrangements for outpatient follow-up should be made so that the infant is seen by 90 days of age.

Recommendations

- Newborn screening laboratory scientists and clinicians responsible for the care of screen-positive infants must use PHE's Newborn Outcomes System to refer screen-positive infants from screening into treatment services. (C)
- All parents/carers of infants where SCD is suspected via the newborn screening programme should be given the result by the time the child has reached 28 days (see Standard 1). This should be done in a culturally sensitive manner, respecting the parents' dignity and individuality. An interpreter should be provided where necessary. (C)
- The result should be communicated to the family GP and health visitor as soon as it is received by the specialist nurse counsellor, or named healthcare professional. (C)
- Newborn infants with a positive screening result should be seen at a paediatric clinic to confirm the screening result or be discharged having been found to have a clinically insignificant result by ≤90 days of age. (C)
- Penicillin prophylaxis should be offered to all children with SCD (A) and should be initiated by 90 days of age. (C)
- Appropriate written information about the condition should be provided for carers. (C)
- Parents should be given the opportunity to have genetic counselling, especially if they did not take up this option before their child was born. (C)

Confirmation of diagnosis

Screen-positive infants must have a second sample taken by 90 days so that the screening test can be confirmed. This is usually done at the first sickle cell clinic visit, but in some areas may be requested before the child attends clinic. A confirmatory test is important in case of laboratory or administrative error.

Samples for diagnostic testing should be sent to a laboratory that is UKAS-accredited and takes part in quality control schemes for haemoglobinopathy testing. There should be organised links with the neonatal screening laboratory to feedback about cases identified by the newborn screening programme.

In the absence of the father's haemoglobin phenotype, it may be difficult to get a definitive diagnosis, as HbSS, HbS/β^0 thalassaemia and HbS/HPFH all have an FS phenotype on screening. If there is any doubt, DNA analysis should be requested from a specialist unit.

Penicillin prophylaxis should be instituted for all children whilst waiting for the diagnosis to be confirmed. There is no evidence that infants with HbS/HPFH need ongoing care and prophylactic treatment. This diagnosis must however not be confused with HbSS and a persisting high level of HbF, which is a relatively common finding, as these children require antibiotic prophylaxis. If there is doubt, the child should be treated having HbSS until confirmatory testing is complete.

Recommendations

- A blood sample to confirm the screening result should be taken at or before the first sickle cell clinic visit and sent to a laboratory accredited by UKAS to carry out haemoglobinopathy testing. (C)
- DNA analysis should be requested in cases where the diagnosis is unclear. (C)
- Penicillin prophylaxis should be started while waiting for confirmation of the final diagnosis. (C)

Outpatient care

Organisation of follow-up

The majority of a child's care will take place at home, in an outpatient department or in a GP surgery. Many children require hospital admission at some point, but only a minority will require frequent admissions. As SCD is a lifelong condition, it is important to engage with the family early, not only to establish the diagnosis and start treatment, but also to provide advice, education and support.

The US Department of Health and Human Services' clinical practice guideline[1] outlines the importance of early entry into care for pneumococcal prophylaxis and the parents' ability to recognise and manage the signs and symptoms of illness. In a Jamaican cohort study, parents were able to accurately define spleen size in

cases of acute splenic sequestration, a potentially fatal complication if presentation is late[2].

It is generally accepted that penicillin prophylaxis should start by 90 days of age, as the level of HbF starts to decline and the risk of splenic hypofunction increases. The Cooperative Study of Sickle Cell Disease, initiated in the USA in 1978, showed a significant number of acute events, including bacterial meningitis and sepsis, before the age of 6 months[3]. Although there is no evidence for early splenic hypofunction in HbSC and HbS/β^+ thalassaemia, the Cooperative Study showed a significant incidence of pneumococcal infections in HbSC in the first years of life, indicating that these children should receive the same treatment and education as children with HbSS. In order to ensure this is achieved, children should be registered for follow-up in the sickle cell clinic by 90 days of age.

The value of specific follow-up programmes for SCD, particularly after identification by neonatal screening, has been confirmed over the past 30 years. A cohort study in Jamaica showed improved survival rates[4] and enlistment in follow-up programmes following neonatal screening in the USA was found to reduce morbidity and mortality to about 1%[5]. More recently, a review of children with SCD identified by universal birth screening in East London showed that a program of hospital- and community-based care, which included penicillin V prophylaxis and appropriate vaccinations against pneumococcal infection, was able to virtually eliminate childhood mortality due to SCD[6].

An evaluation of the newborn sickle cell screening programme in England from 2010 to 2016 confirmed that the programme identified all infants and those resident in England were all in follow-up[7]. A further benefit of screening is the offer of regular TCD scans to identify those children at risk of cerebrovascular disease, with the aim of preventing stroke[8].

The aims of regular attendance at a designated sickle cell clinic should be to:

1. encourage adherence to treatment – particularly penicillin prophylaxis and immunisation programmes
2. continue education on the recognition of signs and symptoms to ensure early access to medical care when appropriate
3. offer screening tests for other complications of SCD
4. monitor general health, nutrition and growth
5. discuss treatment options, including hydroxycarbamide and stem cell transplantation.

Treatment options can be offered depending on the nature of complications and transition to the adult clinic can be organised in a timely fashion. A policy for the frequency of attendance at the specialist sickle cell clinic can be helpful e.g. a minimum of 3 monthly during the first 2 years; 6 monthly until the age of 5 years; and annually thereafter.

Every child with SCD, regardless of where they live, should be offered annual access to a full range of specialist professionals within the SHT and services to ensure that their care is optimised. Every network should determine how this should be organised. In some areas, shared care works well, with an annual visit to the specialist centre. In others, outreach clinics are much more readily accessed by parents and carers and the visit can be coordinated with the annual TCD. Communication between centres is key to effective shared care.

It is important that all families feel supported and have access to specialist advice and treatment. A qualitative study of pain management[9] showed that where families were supported and able to cope with their child's condition, the young adult was more likely to be able to manage their condition.

There should be regular communication with primary care and, where appropriate, the wider multidisciplinary team; the parent-held book (provided to all newborns) should be completed at every visit. Arrangements for follow-up and shared care should be made explicit. A policy for tracking children who do not attend should be in place.

The benefits of entering their child's details onto the NHR should be explained to parents as soon as the child's screening test is confirmed. Verbal consent should always be sought from parents.

Recommendations

- An infant screened as having a possible significant haemoglobinopathy through the newborn screening programme should be seen in a designated sickle cell clinic by 90 days of age. (C) See Standard 2.
- At the first visit, the family should meet with a doctor and/or nurse experienced in the management of SCD who can give them accurate information and advice. (C)
- The parents should be encouraged to consent to their child being entered on to the National Haemoglobinopathy Registry. (C) See Standard 7.
- Confirmation of the diagnosis, date of first clinic attendance and date of starting prophylactic penicillin should be returned to MDSAS electronically. (C)
- There should be regular communication between the SHT, the LHT, primary care and the community nursing teams. (C)
- There should be a policy for monitoring attendance in clinic and for following up those families who fail to attend. This should include documentation of children who have moved to another area. (C)
- There should be ongoing support for the family and promotion of management of straightforward illness, including uncomplicated pain, at home. (C)

- There should be access to specialist assessment and treatment when required. (C)
- Every child should be reviewed at least once a year by the SHT; this may be by direct consultation, in an outreach clinic or within a multidisciplinary team setting as appropriate. (C)

The consultation

The following gives a guide as to what should be included in each consultation. The list is not comprehensive.

The history should include:

- current symptoms and a review of painful episodes, illnesses, any accident and emergency attendances or hospital admissions since the last consultation
- a focused enquiry about symptoms e.g. abdominal pain, pica, enuresis, priapism, headaches, snoring, other neurological symptoms suggestive of ischaemia
- adherence to penicillin prophylaxis
- adherence to vaccination programme
- a review of how pain and fever is managed at home
- regularity of school attendance and reasons for absence
- outcome of developmental screening tests, school progress and achievement in national tests (e.g. standard attainment tests [SATs], GCSEs)
- travel plans, in particular if involving air travel, which is associated with increased risk of complications[10]. Airlines will have their own regulations and the need for in-flight oxygen should be discussed with the SHT in advance.

The examination should include:

- an assessment of growth and development
- a general physical examination, taking particular note of pallor, jaundice, spleen size, presence of a heart murmur
- blood pressure.

At the first consultation, investigations should include:

- full blood count
- haemoglobin electrophoresis
- reticulocyte count
- blood group and extended red cell phenotype (and genotype where possible).

As glucose-6 phosphate dehydrogenase (G6PD) deficiency is common in the same ethnic groups and also induces haemolysis, it is advisable to test for G6PD

at the first newborn visit when the degree of reticulocytosis is unlikely to produce falsely elevated results.

Subsequent consultations: it is not necessary to take blood and urine tests at every visit. It is usually advised that steady state investigations (full blood count, renal and liver function tests) are carried out at 1 year of age to give a baseline. It is then possible to assess the severity of any subsequent acute problem.

The frequency of further investigations will depend on the clinical picture but they would not be routinely performed more than once a year. Blood and urine tests and other screening tests are performed in well children to provide a baseline should the child become unwell, and to screen for conditions that may benefit from treatment. Steady-state oxygen saturations should also be recorded.

TCD scans should be carried out annually from age 2 years (or earlier at the discretion of the clinic).

Provision of transcranial Doppler ultrasonography

Annual TCD ultrasound assessment of children with SCD from the age of 2 years is recommended. This is based on the findings of a randomised controlled trial on the benefits of transfusion in children with raised cerebral blood-flow velocities[11].

The UK Forum for Haemoglobin disorders has published *Transcranial Doppler Scanning for Children with Sickle Cell Disease*. Most of the proposed SHT centres have now developed TCD scanning for children with SCD or have strong links and referral systems to other specialist centres. Supervision of this TCD programme is the responsibility of the SHT.

Education about SCD

Certain topics should be emphasised at every clinic visit or contact with the team. The aim being to:

- educate parents (and then the children themselves) to manage uncomplicated problems at home
- teach them to recognise the onset of serious complications so that the child is brought promptly for hospital treatment when indicated.

Where possible, this information should be backed up by written material in the first language of the parents, and interpreters should be available during discussions as required.

Topics covered should include (the following list is not comprehensive):

- a simple understanding of the condition
- the importance of penicillin
- the importance of staying up to date with all vaccinations
- management of pain at home

- the need to seek early advice, along with how to access that advice and seek admission if necessary, for
    - fevers
    - respiratory symptoms or other signs of infection
    - priapism
    - unusual pallor
    - weakness (without pain), tingling, loss of speech, or any neurological complications
- how to detect an enlarged spleen by palpation
- how to recognise dactylitis and other painful episodes
- symptoms and signs of priapism
- when to consult the GP
- when to come to hospital in an emergency
- the need to report any visual symptoms immediately, especially in children with HbSC
- the need to report any developmental concerns or falling-off in school achievement
- general advice regarding not getting cold, care when swimming, maintaining a good fluid intake
- information that should be shared with the child's school
- the need for any planned surgery to be managed jointly with the surgeon, anaesthetist and the SHT +/− LHT
- travel advice, including the need to:
    - discuss plans with the team in advance
    - inform travel companies of the child's diagnosis
    - take out appropriate travel insurance
    - for long journeys (e.g. on a plane), keep warm, drink plenty of fluids and move around when possible
- genetic counselling, contraception
- advice on avoidance of smoking and alcohol.

Recommendations

- Every outpatient visit should provide an opportunity for ongoing education of the child and family. (C)
- There should be a systematic approach to education, which will vary at different ages. (C)

The annual review

This should include assessment of progress in general and a review of the patient's and family's knowledge of the condition by an experienced doctor, clinical nurse specialist or nurse counsellor from the SHT. If possible, a clinical psychologist should be available at the same visit.

The annual review can take place at either the SHT or LHT site, depending on local circumstances. In practice, with the advent of electronic patient records, it is possible to keep a running assessment of many of the issues outlined below. The annual review does however give a chance for the annual TCD to be performed and for updating of the NHR. There should be a written policy on annual review devised by the SHT.

Issues covered should include:

- review of information provided by the LHT including any investigations undertaken and treatment given
- clinical review:
  - number of hospital admissions
  - number and severity of painful episodes (including days off school)
  - other complications e.g. splenic sequestration, aplastic crisis, priapism, gallstones, chest syndrome, stroke
  - nocturnal enuresis in children aged >6 years
  - assessment of child development
  - (for children on regular transfusions) blood volume transfused in past year
- review of infection prevention:
  - penicillin V dosage and compliance
  - immunisation record
  - (for children on regular transfusions) hepatitis A, B and C serology, including Hep B surface antibody titre, and CMV serology
- clinical tests (undertaken at visit or performed since last review):
  - clinical examination of heart, lungs, liver and spleen
  - assessment of growth and development
  - blood pressure
  - oxygen saturation
  - urinalysis, including urine albumin:creatinine ratio
  - ferritin
  - (for children on regular transfusions) pretransfusion HbS percentage
  - TCD screening and risk of stroke
  - (for children on regular transfusions for cerebrovascular disease) MRI/magnetic resonance angiogram (MRA) of brain
  - (for children on regular transfusions) T2*MRI heart and ferriscan of liver
- consideration and discussion of other treatments e.g. hydroxycarbamide, stem cell transplantation.

The annual review also provides an opportunity for collection of data as suggested by the NHR.

Inpatient care

SCD is characterised by both acute and chronic complications. Acute complications will usually present initially to local hospitals and may be associated with significant mortality in childhood. Mortality rates have however been reduced through effective antimicrobial prophylaxis, parental education and appropriate acute intervention coordinated in dedicated sickle centres employing experienced and well-trained staff[1,2]. Protocols should be in place to manage worsening anaemia, febrile episodes, severe acute pain, acute neurological complications, acute chest syndrome and priapism.

Every LHT and SHT should have a designated consultant paediatrician and/or paediatric haematologist responsible for the management of children with SCD. There should also be a named deputy. Junior doctors involved in the assessment and treatment of children with acute sickle complications should be made aware of the possible conditions and their local treatment protocols through regular education/training sessions.

Provision of PICU/HDU

Some of the proposed SHT centres and many of the LHTs do not have provision for PICU/HDU or MRI scanning. Arrangements will need to be made to develop shared protocols with regional paediatric and PICU units where required e.g. for the assessment and management of acute neurological complications, for exchange transfusions in an acutely unwell child and for children needing ventilatory support.

Provision of stem cell/bone marrow transplantation

There are a limited number of units in England that are accredited to provide haemopoietic stem cell (or bone marrow) transplantation for children. Clinicians in both LHTs and SHTs should have patient information available on the eligibility criteria for referral for haemopoietic stem cell transplantation and information regarding the process. There should be good links between the referring hospital and the specialist stem cell transplant unit, with agreement in particular about follow-up arrangements.

Recommendations

- Parents and carers should be made aware of the symptoms and signs associated with severe and life-threatening complications and know where to take their child if these occur. (C)
- A care pathway should be in place in the LHT for assessment of the child in accident and emergency (A&E) and for transfer to a designated ward if admission is necessary. (C)

- Protocols should be available to cover the management of all acute sickle cell complications. These should include worsening anaemia, febrile episodes, severe acute pain, acute neurological complications, acute chest syndrome and priapism. (C)
- A designated consultant paediatrician and/or paediatric haematologist, with a named deputy, should be responsible for the management of all children in the LHT and SHT. Junior doctors involved in assessment and treatment of acute sickle admissions should be made aware of acute complications and the local treatment protocols through regular education/training sessions. (C)
- Communication and transfer to a specified PICU should be readily available according to an agreed procedure. (C)

Transition to adult service

Transition is 'the purposeful planned movement of adolescents and young adults with chronic physical and medical conditions from child-centred to adult-oriented healthcare systems'[1].

The importance of transitional care has been highlighted in the *Getting the Right Start: National Service Framework Standard for Hospital Services*, *Transition: getting it right for young people – Improving the transition of young people with long-term conditions from children's to adult health services* and the intercollegiate report *Bridging the gaps: health care for adolescents*. This includes a requirement for children and adult services to take the needs of this group of patients into consideration when planning and developing services.

The National Service Framework document *Children and Young People who are ill* emphasised the importance of transition and stated that ideally within 10 years: 'Transition to adult services for young people is planned and coordinated around the needs of each young person to maximise health outcomes, their life chance opportunities and their ability to live independently.'

There is a need to involve the GP and community services early in the process, as they may be expected to take on a wider role as children leave the holistic care of paediatric outpatients.

In paediatric care, services place very few medical management expectations on the adolescent (these being placed instead on their parents) and clinicians are generally knowledgeable about the patient's condition. In contrast, adult healthcare services may know less about their patients and/or how their condition affects them, but generally have higher expectations for medical self-management. In addition, young adults/adolescents, by definition, have to cope with numerous changes as they develop their individual identity and deal with personal priorities of school, work, friends, family, social relationships and independent living.

Perhaps the biggest fear for adolescents is how their painful episodes are going to be managed when they need to be admitted to an adult ward.

Likely differences include:

- significantly lower supervision and direct nursing care on the adult ward
- a reasonable expectation that the adolescent will take a more active role in managing painful episodes
- fewer visits from doctors
- less structured activity, including school or work supervision
- medical staff, at least initially, being unfamiliar with the individual
- the 'adult' analgesic regimen possibly being different from the paediatric one
- a different visiting schedule, usually more limited and with specific visiting times, whereas a parent is often allowed to stay at all times on a paediatric ward.

This all occurs at a time when young people become more at risk of major complications.

Research indicates that adolescents with SCD have concerns, opinions and expectations about their future healthcare and medical management. They need guidance, support and information about available services to help meet daily challenges[2]. Adolescents with SCD may have problems of adjustment during a transition phase and it is important to identify factors that would guide appropriate interventions[3].

Transition care is particularly important as studies have indicated that a risk of increased mortality and morbidity occurs among young people with SCD if a robust care pathway is not in place[4]. In an ideal world, where numbers of adolescents with SCD are appropriate, there should be:

- an adolescent clinic with both paediatric and adult consultants and multidisciplinary team members, 'the joint approach'
- a transition clinic, run in the adult outpatient department, preferably in the evening as this reduces failure to attend rates; this clinic allows familiarity with teams and enables young people to conduct their own clinic appointments in a supportive environment
- a transition nurse specialist/key support worker who will follow these patients through to their early 20s, ensuring that the vital period between formal discharge from paediatrics and beginning adult services is supported, and that the risk of falling between these two services are minimised
- regular patient meetings, transition workshops/'adolescent days' and other engagement meetings held throughout the year.

Arrangements need to be flexible[5], as children reach maturity at different ages and puberty is often delayed in children with SCD. Hospital policy may demand that all children are admitted to adult wards at the age of 16 years, even when they are emotionally immature.

The National Children's survey 2014 found that older children were often not involved in decisions about their care, which was particularly worrying for children with long-term conditions who were preparing to make the transition into the adult service[2]. Evidence to support the transition process in improving patient outcome is lacking and requires prospective well-designed qualitative studies. However, patient and clinician experience clearly highlight the need for a well-structured and supportive transition process. The recommendations made in this document are based on experience from existing transition clinics in certain SHTs.

Recommendations

- There should be an accessible hospital transition policy in place and the introduction of a key support worker, with the aim to start preparation and planning at an early age e.g. 13–14 years. (C)
- A detailed review should be carried out at 15–16 years to assess the patient's knowledge of their condition and treatment concordance, understanding about SCD management, concerns about healthcare in an adult setting, emotional readiness for transition, self-efficacy and general readiness to transfer. (C)
- A transition or adolescent clinic should be available to allow the adolescent to meet the adult sickle cell team and for a formal review and handover to take place. (C)
- Adult and paediatric protocols for managing complications, in particular painful episodes, should correspond as much as possible. (C)

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Ongoing issues

Prevention of infection

A major aim of neonatal screening and follow-up care is to reduce the morbidity and mortality from preventable disease by antibiotic prophylaxis and immunisations.

Splenic hypofunction resulting from splenic infarction, usually from the first 6 months of life, means that children are at a greatly increased risk of infection by organisms expressing polysaccharide antigen, such as *Streptococcus pneumoniae* (pneumococcus) and *Haemophilus influenzae*. A national observational cohort study (2010–15) in England showed that children with HbSS had a 49-fold higher risk of invasive pneumococcal disease compared with their peers without SCD[1].

Children with SCD are more likely than the general population to be transfused for complications such as acute splenic sequestration or aplastic crisis; some 5–10% may be enrolled on a chronic transfusion programme at some time in their life. All neonates in the UK have been vaccinated against hepatitis B since August 2017. Older children with SCD should be offered vaccination against hepatitis B if not already vaccinated.

Meningitis ACWY is now advised for all children with SCD in infancy. This should be offered to older children, especially those travelling to parts of the world where these serotypes are prevalent.

Malaria is likely to be a serious issue due to splenic hypofunction and appropriate prophylaxis for the area of travel should be offered. Families should be aware that having SCD or sickle cell trait does not make a person immune to malaria.

Antibiotic prophylaxis

Penicillin prophylaxis has been shown in a randomised controlled trial to be effective in reducing mortality from pneumococcal sepsis[2]. Published guidelines recommend that penicillin prophylaxis is lifelong. As compliance is likely to decline and the incidence of pneumococcal infection in the community reduces significantly after the age of 5 years[3], the emphasis should be on excellent adherence in early childhood.

Penicillin V should be offered to all children according to the following dosage schedule:

- 62.5 mg per orally twice daily for those <1 year
- 125 mg per orally twice daily for those 1–5 years
- 250 mg per orally twice daily for those >5 years.

Erythromycin is a suitable alternative if penicillin allergy is documented.

Immunisations

Children with SCD should follow the UK schedule of routine immunisations, which is updated regularly in the 'Green Book'. Children arriving in the UK after the newborn period who have not received the complete vaccination schedule should follow the guidance provided in the document *Vaccination of individuals with uncertain or incomplete immunisation status*.

Children with SCD are also recommended to receive the following additional vaccinations:

- for a child diagnosed in the first year of life, two doses of MenACWY 1 month apart (in practice this probably means giving two doses of MenACWY in the second year of life)
- for children not given Prevenar 13 (a pneumococcal conjugate vaccine, also sometimes called PCV) during the first year of life, two doses of Prevenar 2 months apart in the second year
- for all children aged 6 months to 2 years, the intramuscular flu vaccine
- for all children aged 2 years to 17 years (the licensed age groups), Fluenz tetra nasal spray (a live attenuated vaccine), given annually – increasing numbers of children will receive this vaccination in school as the programme is gradually rolled out to children without specific conditions
- polysaccharide pneumococcal vaccine (PPV) at 2 years and 5 yearly thereafter.

Although all children are now offered the conjugate pneumococcal vaccine Prevenar 13, there is evidence of a rise of infections causing invasive pneumococcal disease that are not prevented by vaccination and emphasis must remain on children continuing to take regular penicillin in addition to immunisations[1].

Furthermore, in order to ensure maximum coverage with PPV, there needs to be a robust local system for policing the administration and recording of the PPV vaccine; consideration should be given to administering this at the hospital appointment, as is done in some large units, particularly in London, rather than in primary care.

Travel requirements

Children with SCD should receive:

- meningitis ACWY if travelling to sub-Saharan Africa and Saudi Arabia if not already received
- other recommended travel vaccinations for the country being visited
- malaria prophylaxis.

Recommendations

- Twice-daily penicillin prophylaxis or alternative should be prescribed by 90 days of age and continued throughout childhood. (A) See Standard 3.
- Local negotiation should be carried out between hospital, GPs and pharmacies to ensure a reasonable length of prescription to encourage compliance. (C)
- Reasons for parents not giving their children penicillin should be explored and addressed as fully as possible. (C)
- Immunisation against pneumococcal infection should include Prevenar 13 and PPV according to national schedules. (C) See Standard 4.
- Two doses of MenACWY should be given in either the first or second year of life. (C)
- A robust local policy should be in place to ensure that children receive PPV (in hospital or primary care) and this information should be recorded and shared between primary and secondary care. (C)
- Annual influenza immunisation should be offered. (C)
- When appropriate, malaria prophylaxis should be strongly recommended and current guidance sought for the area of travel. (C)
- Parents should discuss with their medical team before their child travels by plane. (C)

Management of pain at home

Most episodes of pain occur and are managed at home. Usually these are mild-to-moderate painful episodes and it is not be necessary to bring the child to hospital. Frequent pain may however lead to other problems, including negative mood and considerable loss of schooling. Children should therefore be encouraged to identify and avoid factors that regularly trigger acute pain (e.g. exposure to cold or windy weather, excessive physical activity and dehydration). This information should also be passed on to the school by a competent healthcare professional.

It is important for older children, parents/carers and family members to know how to manage pain at home with appropriate analgesia for the level of intensity. In addition, other coping strategies should be considered, including distraction techniques like games, computers and television, as these have been shown to predict both pain experience and the utilisation of health services[1].

It is usual to advise an increase in fluid intake if the child is unwell, as dehydration will tend to prolong the painful episode. Paracetamol and ibuprofen are the analgesics of choice in mild-to-moderate pain. Weak opiates can be added at home for more severe pain: dihydrocodeine can be used in those under 13 years of age and codeine after this age, depending on local prescribing practices; it should be recognised that at least 20% of children will not respond to codeine because they lack the enzyme needed to convert it to morphine[2].

If there is no response to this regimen, the child should be assessed in hospital. Children should not be treated with morphine at home, apart from in exceptional circumstances and with individualised care plans.

If a child has more than two admissions in a year, an individual care plan should be available in the A&E department (or children's ward if there is a direct admissions policy).

Hydroxycarbamide should be recommended if a child is getting significant episodes of pain at home, even if these do not require medical attention.

Recommendations

- Parents/carers and older children should be given clear guidance on how to assess and manage pain at home, including the type and dose of analgesia to be used for different levels of pain intensity, and when to seek medical advice. (C)
- Parents/carers should be informed about non-pharmacological therapies for pain, such as massage. Children should be encouraged to use psychological coping strategies, including distraction techniques such as games, computers and television. (C)
- Children should be encouraged to identify and avoid factors that regularly trigger acute pain, such as exposure to cold or windy weather, excessive physical activity and dehydration. This information should also be passed on to the school by a competent healthcare professional. (C)
- Hydroxycarbamide should be recommended to children getting significant episodes of pain at home. (C)

Nutrition and growth

The importance of nutrition in children with SCD is rarely discussed in the UK and those with SCD are seldom referred to dieticians. This may be a missed opportunity, as advice on healthy eating could enhance the general wellbeing of children and young people with SCD[1]. Impaired growth, poor nutritional status and delayed skeletal and sexual maturation are common in children with SCD. In HbSS, growth retardation may become apparent after 6 months of age, possibly due to decreased absorption of nutrients and/or an increase in metabolic rate. Poor appetite is frequently reported, and anorexia associated with febrile or painful episodes is common.

Pica – the eating of non-food stuffs – is frequently reported by parents and also by adults with SCD. Although this can be associated with nutritional deficiencies (e.g. iron), in most cases no nutritional deficiency is found. Psychological management can help, particularly if the pica becomes a more generalised eating disorder[2].

Studies of body composition in children with SCD show a significantly lower fat mass in prepubertal children and lower fat-free mass in all children, with muscle

wasting and low protein stores[3]. In extreme cases, growth can be accelerated by providing extra calories via nasogastric feeding, although this is rarely necessary[4].

There is little evidence of specific nutrient deficits, although a randomised controlled trial showed some improvement in height and weight after supplementation with zinc sulphate[5]. Another controlled trial also showed a reduction in infections and hospital admissions in those taking zinc supplements[6].

As a hypochromic microcytic blood picture may be caused by an associated thalassaemia trait, iron supplementation should be given only if iron deficiency is confirmed, typically by a low serum ferritin. There is no evidence that folic acid supplementation is beneficial, although many parents choose that their children should take it[7,8].

Vitamin D deficiency is very prevalent in non-white children of all ages in the UK[9,10] and there has been a resurgence of rickets. Advice should be given regarding vitamin supplementation, an adequate calcium intake and exposure to sunlight. If children are found to have vitamin D deficiency, therapeutic vitamin D supplementation should be prescribed, depending on local prescribing guidelines.

Some clinicians recommend the use of ethnically appropriate growth charts[11], but not specific sickle cell charts. Puberty may be delayed by about 6 months in HbSC and by 2–3 years in HbSS[12]. However, delayed skeletal maturation during adolescence allows for a longer growth period in the long bones, which results in normal adult height, so children and their parents can usually be reassured. Hormonal treatment may be indicated in children with physiological delay if they are very concerned by their short stature.

An endocrinology opinion should be sought if there are no physical signs of puberty in a girl at 14 years and a boy at 14.5 years[13]. It should also be recognised that children on long-term transfusion programmes with significant iron overload may develop pituitary +/- primary gonadal deficiencies.

Recommendations

- Height and weight should be measured at each visit and plotted on appropriate growth centile charts. (C)
- Referral to a dietitian should be made to consider extra caloric input if the child is hospitalised for frequent or long periods. (C)
- Zinc supplementation should be considered if growth is impaired. (B)
- Advice should be given on avoiding vitamin D deficiency, and vitamin D deficiency should be treated. (C)
- Children with delayed growth should be reassured if there is evidence of delayed skeletal maturation; however, they should be referred to a

paediatric endocrinologist if there are no physical signs of puberty at 14 years in a girl and 14.5 years in a boy. (C)

- Pica can usually be managed with explanation; a referral to a clinical psychologist is recommended if the pica is part of a more generalised eating disorder. (C)

Nocturnal enuresis

Nocturnal enuresis is common in all children – approximately 15% of children aged 5 years and 3% of 15-year-old children still wet the bed more than once per week.

There is an increased rate of nocturnal enuresis in children with SCD, particularly in boys with HbSS; the reason for this is not entirely clear. Children with SCD pass large quantities of dilute urine and have nocturia, but this should not necessarily lead to incontinence. Overnight urinary volumes greater than maximum functional bladder capacity have been posed as a possible cause[1]. Parents often report that their children are heavy sleepers. It has been shown that children with adenoidal hypertrophy and obstructive apnoea are more likely to have nocturnal enuresis[2] and it is possible that hypoxaemia plays a role in the aetiology of nocturnal enuresis.

As in the normal population, most cases will resolve spontaneously. On the whole, children with SCD do not respond to behavioural management techniques, such as star charts or mattress alarms, but can be ‘trained’ by intermittent alarms and parental waking to achieve continence. Despite nocturia, they learn to wake themselves up and pass urine during the night without enuresis. Many children respond to oral desmopressin and this is a useful adjunct, particularly for school trips.

Recommendations

- If nocturnal enuresis is present over the age of 6 years, this should be documented and parents should be given information and advice on treatment, including avoidance of drinking at night time. (C)
- If the history is suggestive of sleep-disordered breathing, this should be documented, overnight oxygen saturations should be measured and a referral made for an ear, nose and throat (ENT) opinion. (C)
- Desmopressin therapy should be considered in those children who do not respond to routine advice and management. (C)
- The child should be referred for specialist management (e.g. an enuresis clinic) if there is no response to basic measures after the age of 7 years. (C)

Dental health

Oral health and dental care are integral parts of general health and wellbeing and may impact on the general wellbeing of those with SCD[1]. SCD may be associated with dental problems, which may influence the quality of life of affected individuals. Dental infections, for example, can lead to an increased likelihood of triggering a painful sickle cell episode[2].

It is important to ensure there is good liaison between dentists treating children with SCD and the paediatric/haematology team, especially if any child needs a general anaesthetic.

Psychological issues

Psychological issues for people with SCD and their families result mainly from the impact of pain and symptoms on their daily lives and society's attitudes to the condition and those affected.

There is considerable variability in how people with SCD cope with their condition. People with SCD experience different levels of health and such variations can lead to differences in psychosocial functioning. Some people cope relatively well, attend school or work and are active physically and socially. Their efforts should be recognised and encouraged where necessary. Others lead more limited and secluded lives. Nonetheless, this may not necessarily be a consequence of severe disease and the reasons should be sought and addressed.

Quality of life in people with SCD may therefore be lower than that of the general population and, for those with severe disease, may deteriorate as people grow into adulthood. Children are also at greater risk of stroke with consequent impairment of their psychosocial functioning and cognition.

Studies on providing psychological therapy as a standard adjunct to routine medical management have shown encouraging results[1]. The overall goal is to help patients cope better, fulfil roles and achieve a better quality of life. In addition, there are specific indications for psychological intervention in the management of pain and stroke. Reviews of psychosocial interventions for pain and other outcomes[2–4] demonstrate that cognitive behavioural techniques are probably efficacious in treating sickle cell pain.

Psycho-education

Psycho-educational interventions primarily focus on improving knowledge and the understanding that patients have about their illness, while at the same time providing psychological support. Group interventions have been shown to identify issues and concerns in children and adolescents with SCD[5] and family interventions improve knowledge[6]. The rationale behind this approach is that

information can lead to improved knowledge and better coping with the condition[7] and children who feel isolated may benefit from the support and motivation of others through shared experience.

Cognitive behavioural therapy

Cognitive behavioural therapies (CBT) are a range of talking therapies based on the theory that thoughts, feelings, what we do and how our body feels are all connected. If we change one of these, we can alter the others. When people feel worried or distressed, we often fall into patterns of thinking and responding that can worsen how we feel. CBT works to help us notice and change problematic thinking styles or behaviour patterns so that we can feel better. CBT has been shown to reduce pain, health service utilisation and coping in children and adolescents with SCD[4,8].

Recommendations

- All children and their families should have access to a clinical psychology service. (C)
- CBT should be offered in addition to standard management in children experiencing frequent pain episodes and emotional difficulties. (A)

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Chronic complications

Cerebrovascular disease

In the multicentre Cooperative Study of Sickle Cell Disease in the USA, the overall incidence of stroke in HbSS was 0.6/100 patient-years. The highest incidence was in children aged 2–5 years (1.02/100 patient-years) and, by the age of 20, about 11% of people with SCD had had a clinically evident stroke[1]. In the absence of primary screening and prophylaxis, there is no reason to expect rates to differ in the UK.

In children, the cerebral ischaemic damage is often in the supply territory of the internal carotid/middle cerebral artery (ICA/MCA). However, damage in a watershed distribution, between either the MCA and anterior cerebral artery (ACA) or the MCA and posterior cerebral artery, is also commonly observed. Stroke is associated with cerebrovascular stenotic lesions, commonly in the distal ICA and proximal portions of the MCA and ACA. The high blood flow velocities through these stenotic segments can be detected using TCD ultrasound scanning.

Risk factors

A large prospective follow-up study showed that a high-risk group for stroke can be identified by time-averaged mean velocities in the ICA/MCA/ACA segments >200 cm/sec[2]. The risk is also increased, to a lesser extent, in those with conditional velocities (170–200 cm/sec) and in those with absent or low signal.

Another important indicator of risk for stroke is a history of transient ischaemic attacks. Other reported risk factors, such as low baseline Hb, high baseline white cell count, low overnight oxygen saturation[3], acute chest syndrome in the previous 2 weeks, frequent episodes of acute chest syndrome and high systolic blood pressure[4], are too insensitive to be of any value in evaluating a child, although high blood pressure obviously requires appropriate investigation and management.

Stroke is more prevalent in HbSS and HbS/β^0 thalassaemia compared to HbSC and HbS/β^+ thalassaemia, although there is limited information.

Haemorrhagic stroke is relatively rare in childhood, becoming more common in the third decade. Identified risk factors include low Hb and high white cell count. Intracerebral aneurysms are more common in those with SCD and can be multiple. The pathogenesis is unclear. There are no established or proven ways of screening for increased risk of haemorrhagic stroke.

Primary stroke prevention

A randomised controlled trial has shown that the risk of a first stroke can be reduced by 90% by regular blood transfusions in children with SCD and abnormal TCD scans (mean velocities >200 cm/sec)[5].

The TWiTCH study looked at the safety of switching children with abnormal TCDs from regular transfusions to hydroxycarbamide and found that hydroxycarbamide was equivalent to transfusion, with no increase in TCD velocities or cerebrovascular events[6]. Children entered into the study had been transfused for at least a year and did not have severe vasculopathy (multiple stenoses, moyamoya). Regular transfusions were continued until the maximum tolerated dose of hydroxycarbamide was established.

The role of neuropsychology

Cerebrovascular disease in SCD can result in both obvious and subtle neuropsychological deterioration. An overt stroke may cause intellectual impairment with an increase in frontal lobe problems of attention and executive functioning[7]. However, children who have silent infarcts also experience learning and behavioural problems and are twice as likely to have school difficulties as other children[8,9].

The Intercollegiate Working Party for Paediatric Stroke[10] and the British Psychological Society Special Interest Group in Sickle Cell Disease and Thalassaemia recommend a detailed assessment of the child's cognitive and social functioning following a stroke. There is evidence that neurocognitive screening provides a useful means of identifying those who may have suffered silent stroke[8]. MRI should be performed in any child with significant neurocognitive problems, but is not currently routinely recommended for all children.

Silent cerebral infarcts

About 20% of children with sickle cell anaemia have silent cerebral infarcts on MRI scan that are not associated with overt neurological episodes or symptoms. These are relatively small white-matter lesions, often in the anterior watershed distribution. They are associated with mild cognitive impairment and may be suspected following neurocognitive testing[11].

TCD screening in these patients shows normal results in 75% of cases. A randomised trial in children with silent cerebral infarcts showed that regular transfusions reduced the number of further neurological events compared with monitoring alone[12]. There is no evidence on how best to screen children for silent cerebral infarcts, although there should be a low threshold for performing brain MRI when there are concerns about the cognitive performance of a child, including poor school performance. When silent cerebral infarcts are found on MRI, the option of starting regular blood transfusions should be discussed with the parents and child.

The relative hazard for progression to overt stroke is approximately 14 times for a patient with a silent infarct compared with those with a normal MRI. This compares to 18 times normal in a patient with a high-risk TCD[13].

Secondary stroke prevention

Chronic transfusion has been established as effective secondary stroke prevention, reducing the risk of recurrent stroke from 50–75% to about 13%[14]. The aim of the transfusion regimen is to maintain the HbS level <30%. Some patients may be able to reduce the intensity of transfusions after 3 years to maintain HbS at 50%.

The SWiTCH study showed that hydroxycarbamide was less effective at secondary stroke prevention than continued transfusion[15], and hydroxycarbamide is only considered as an option when regular transfusions are contraindicated (multiple alloantibodies, uncontrolled iron overload) or unacceptable owing to sincere personal beliefs (most often Jehovah's Witnesses)[16]. This trial in children with HbSS in the USA recommended that transfusion therapy should be continued throughout childhood. This is because a significant number of children reverted to the high-risk range of TCD velocities or developed overt stroke after discontinuation[16].

As iron overload is a serious consideration in long-term transfusion therapy, iron chelation should be started when the patient has received approximately 1 year's worth of transfusions, has a serum ferritin >1000 ng/mL on two successive readings 4 weeks apart, or has evidence of iron overloading in the liver on MRI.

Recommendations

- Annual TCD scans should be performed on all children with HbSS and HbS/β^0 thalassaemia from age 2. For children with abnormal TCD velocities, the risks and benefits of starting regular blood transfusions and/or other treatments should be fully discussed by an appropriate multidisciplinary team with parents/carers. (A) See Standard 5.
- The option of switching from transfusions to hydroxycarbamide should be discussed with eligible children and families. If it is agreed to switch to hydroxycarbamide, transfusions should be continued until the child is stabilised on the maximum tolerated dose of hydroxycarbamide. (A)
- The symptoms and signs of stroke should be discussed with parents/carers in the first 2 years of life, with information given on what action to take should the child develop neurological symptoms. (C)
- Appropriate imaging studies to assess the extent of cerebrovascular disease should also be arranged if TCD scanning is abnormal, or there are learning difficulties, atypical symptoms such as unusual behaviour during acute pain, frequent headaches, fits or other unexplained neurological, psychiatric or psychological symptoms. (C)
- The advantages and disadvantages of starting regular blood transfusions should be discussed with all children and families if the child has one or more silent cerebral infarcts on MRI. (A).
- Blood pressure should be measured and recorded annually. (C)

- Overnight oxygen saturation monitoring should be performed if a child has low steady-state oxygen saturations on air (<95%). (C)
- Children should have access to a clinical, educational or neuro-psychologist to assess cognitive function, learning and behavioural difficulties. (C)
- A comprehensive neuropsychological assessment should be carried out and repeated annually in all children who have had a stroke. (C)
- Cognitive (or where available, neuropsychological) assessment should be conducted in children with abnormal TCD or abnormal brain MRI. (C)
- Information about developmental progress and school performance should be ascertained for all children annually; if there are significant concerns, further assessments should be considered including cognitive or neuropsychological assessment and brain MRI scan. (C)
- Transfusion therapy should be offered throughout childhood for the secondary prevention of stroke. (B)

Priapism

(see also management of fulminant priapism)

Priapism, a sustained, painful and unwanted erection, mainly affects adolescents and adults, and may go unreported.

Bicorporal priapism occurs in 3–5% of pre-pubertal boys and has a better prognosis for normal erectile function than tricorporal priapism in post-pubertal boys. Events may be classified as stuttering (occurring for <3 hours but several times a week), minor (isolated or infrequent episodes of <3 hours) or fulminant (events lasting >3 hours).

Fulminant episodes are often preceded by bouts of stuttering priapism. Bladder emptying, exercise such as jogging, warm baths and analgesia may help abort an attack. Oral etilefrine may reduce the frequency of stuttering priapism[1] and, in a prolonged episode, aspiration and irrigation of the corpora cavernosa with epinephrine or etilefrine is now the treatment of choice[2].

Children and their carers should be advised to seek treatment early and should attend hospital as an emergency if priapism persists for >2 hours.

Recommendations

- All boys and their parents/carers should be warned early in childhood about priapism being a complication of SCD. (C)
- Adolescent boys and their parents/carers should receive further information about priapism and know to seek treatment early. (C)
- An enquiry about priapism should be included as part of the outpatient consultation for pubertal boys. (C)

- For minor events, complete bladder emptying before sleep, pain relief and warm baths should be recommended. (C)
- Oral etilefrine should be considered in cases of stuttering priapism. (C)

Avascular necrosis of the femoral and humeral head

This may occur in all types of SCD and children with high HbF levels are not protected. The shoulder joint is more likely to be affected in older age groups. Although weight-bearing makes femoral head necrosis more likely to cause severe joint destruction, healing with minimal destruction may be the outcome if it occurs before closure of the femoral epiphysis.

X-ray changes will not be apparent until the repair process has changed the density of the bone. Therefore, MRI scanning is the investigation of choice in a patient with persistently painful hip or shoulder.

Typically, some form of radiological staging is used to evaluate the development and progression of the disease[1]. Initial treatment should be conservative, with analgesia, partial weight-bearing on crutches and physiotherapy support. There is some evidence that decompression in the early stages may be beneficial, at least in relieving pain.

Recommendations

- An MRI scan should be carried out where there is persistent pain in the hip or shoulder. (C)
- The radiological stage of avascular necrosis should be documented. (C)
- Referral to an orthopaedic surgeon with an interest in SCD should be made if pain persists or if avascular necrosis is at stage III or more. (C)

Liver disease

Gallstones occur in over 50% of children with SCD over the age of 10 years in the UK[1]. They are usually asymptomatic and may not be the cause of intermittent abdominal pain, which is relatively common. There is no evidence to recommend cholecystectomy in asymptomatic cases, but it is advised for those with symptomatic biliary disease.

Recommendations

- Annual steady-state liver function tests should be carried out; children with evidence of progressive hepatopathy (increasing bilirubin, persistently high ALT) should be referred to a paediatric hepatology service with experience of SCD. (C)
- Recurrent episodes of abdominal pain should be investigated with an ultrasound of the liver and biliary tree. (C)
- Elective cholecystectomy should be carried out in symptomatic biliary disease. (C)

Kidney disease

Renal complications are relatively common in SCD, particularly with increasing age.

Renal failure primarily due to SCD is rare in childhood, but other paediatric complications include the following (although there is little good information on the frequency of these problems in childhood):

- nocturnal enuresis
- urinary tract infections – these should be investigated and treated according to NICE guidance[1]
- haematuria – hospital trusts will have their own guidelines for investigating macroscopic haematuria and these should include renal ultrasound, urinary bacterial cultures, electrolytes, and coagulation factors if the bleeding is severe
- renal papillary necrosis, which is one possible cause of haematuria
- microscopic albuminuria – evidence is lacking as to whether screening for this (and other signs of renal disease in childhood) leads to interventions that can prevent problems in later life
- renal medullary carcinoma – this is rare but should be considered if haematuria is persistent.

Hypertension can be a trigger to investigate further for renal disease, although it is not known how blood pressure centiles apply to children with SCD. Because these children normally have low blood pressures, it is thought that further assessment should be carried out if the blood pressure is above the 70th centile.

Recommendations

- Any child with a urinary tract infection should be treated and then investigated according to the NICE guidance. (C)
- Macroscopic haematuria should be fully investigated according to local protocols. (C)
- Blood pressure, urea, creatinine, electrolytes and urine albumin:creatinine ratio should be measured on a yearly basis and renal investigations initiated if hypertension is present, if there are raised creatinine and urea levels, or persistent significant albuminuria. (C)

Lung disease

Acute chest syndrome is a well-characterised complication of SCD in childhood[1]. It is a potentially fatal complication and there is good evidence that recurrent episodes can be prevented by hydroxycarbamide[2]. Asthma can cause very similar signs and symptoms to acute chest syndrome and has been associated with increased episodes of pain. It is not clear however whether asthma in SCD is a distinct entity or whether they are part of the same condition[3].

Chronic lung complications are increasingly recognised, particularly in adults but may occur in older children and adolescents. Three main problems are recognised: chronic sickle lung disease, with a restrictive lung picture; a mixed obstructive restrictive pattern; and pulmonary hypertension.

Anecdotal evidence suggests that, in chronic sickle lung disease, deterioration can be prevented by hydroxycarbamide or regular blood transfusions. It is therefore potentially important to detect the early development of these problems in children.

Low blood-oxygen saturations, as assessed by overnight pulse oximetry, have been linked to both cerebrovascular disease and frequent episodes of acute pain. Referral to a specialist pulmonary hypertension centre with an interest in SCD should be made if there is evidence of pulmonary hypertension[4].

Recommendations

- Children with either two or more episodes of acute chest syndrome in the last 2 years, or one episode requiring ventilatory support, should be offered hydroxycarbamide. (A)
- A systematic and complete evaluation of asthma should be undertaken if the diagnosis is suspected or if there are repeated episodes of acute chest syndrome. (C)
- Oxygen saturations in air should be recorded on an annual basis using pulse oximetry when the patient is well and seen in outpatients. If saturations are <95%, overnight oxygen saturation monitoring should be performed. (C)
- If the mean overnight oxygen saturation is <95%, the child should be investigated for cerebrovascular disease and obstructive sleep apnoea; formal pulmonary function tests and echocardiography should also be arranged. (C)
- If pulmonary function tests suggest chronic sickle lung disease, the child should be monitored with regular pulmonary function tests, plus overnight pulse oximetry and a high-resolution computed tomography (CT) scan of the lungs should be considered; treatment with home oxygen, hydroxycarbamide or regular blood transfusions should be considered in children who show signs of deterioration. (C)
- Echocardiography to assess for pulmonary hypertension should be arranged if there is evidence of chronic sickle lung disease, chronic unexplained hypoxia (oxygen saturations <95%) or other symptoms/signs suggestive of pulmonary hypertension. (C)
- A child with significant pulmonary hypertension should be referred to a specialist pulmonary hypertension centre with an interest in SCD. (C)

Eye complications

Vaso-occlusive events can affect every vascular bed in the eye and may have serious and permanent visual consequences. Detectable retinal disease is very rare in early childhood, being found most commonly between the ages of 15 and 30 years. Patients with HbSC and HbS/β thalassaemia are more likely than those with HbSS to have serious ocular problems[1].

The clinical manifestations are grouped according to whether there is neovascularisation or not. In non-neovascular or 'non-proliferative' cases, there are rarely any visual consequences. In contrast, revascularisation and proliferation may proceed to vitreous haemorrhage and retinal detachment. However, there is a high rate of spontaneous regression or non-progression and the indications for treatment are not clear[2].

Given the uncertainty about the natural history of this complication, there is no evidence to support routine ophthalmologic screening of children, although the NHS recommends a routine eye test every 2 years (more frequently if recommended by an ophthalmic practitioner).

Children and their carers should report any change in vision; if this occurs, they should be referred for an ophthalmologic opinion as a matter of urgency.

Recommendations

- Children and their carers should be made aware of this potential complication. (C)
- Any significant visual symptom should be reported immediately and the child referred urgently for an ophthalmologic opinion. (C)

Hearing impairment

The cochlea is particularly vulnerable to vaso-occlusion because the labyrinthine artery is its sole blood supply. If the labyrinthine artery becomes occluded, ischaemia of the cochlear bed can result, which leads to sudden hearing loss. However, despite this, hearing loss is infrequently reported clinically. It may though be more prevalent than is recognised, possibly because it is often unilateral. Hearing loss is more common in those who have had a prior cerebral infarct or have abnormally high velocities on their TCD scan.

Recent studies have indicated about 10–20% of children with SCD may have hearing impairment[1–4]; this includes children with middle ear disease but there is also a higher incidence of sensorineural hearing loss. There is currently not enough evidence to recommend routine screening for hearing loss in children with SCD.

Regular blood transfusions for the management of cerebrovascular complications, including abnormally high TCD velocities, lead to increased iron

load, which needs to be treated with a chelating agent. Desferrioxamine, deferasirox and deferiprone can all cause sensorineural hearing loss and it is recommended that children on any of these medications should have annual hearing tests[5].

Recommendations

- Parents and carers should be aware of the possibility of acquired hearing problems which may be sudden. (C)
- All children with abnormal TCDs or following a cerebral infarct should have a baseline hearing test. (C)
- All children receiving iron chelating agents should have hearing tests annually. (C)

Leg ulcers

These are relatively uncommon in children in the UK. Nearly all ulcers develop in the ankle region near the malleolus and they are often bilateral. They may be painless or extremely painful. The pathogenesis of this condition is uncertain, but is likely to result from poor microvascular blood flow of abnormal red cells combined with reduced oxygen delivery. Low serum zinc levels have been reported in non-sickle patients with venous leg ulcers; however, low serum zinc levels are found in many patients with SCD and do not correlate specifically with leg ulcers. A controlled study in a small number of patients did however show accelerated healing of leg ulcers in those taking oral zinc sulphate[1].

There has been a randomised double-blind controlled trial using granulocyte-macrophage colony stimulating factor (GM-CSF) in non-sickle patients with chronic venous leg ulcers, which showed acceleration of healing[2]. Another study showed good response using topical GM-CSF in a small number of patients with SCD[3]. Best practice is not clear in this group and neither regular transfusion therapy nor hydroxycarbamide therapy seems to influence outcome.

In the first instance, ulcers should be treated with frequent dressing, support bandages and antibiotics if infected. Physiotherapy to increase ankle mobility and venous return is also likely to be helpful.

Recommendations

- Debridement of the ulcer and antibiotic therapy should be started if infection is present. (C)
- Adequate pain relief should be prescribed. (C)
- Compression bandaging and physiotherapy should be arranged to improve ankle mobility. (C)
- Oral zinc sulphate should be considered in children with persistent leg ulcers. (B)

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Acute complications

Severe pain requiring management in hospital

Pain is the most common cause of acute morbidity in SCD and frequent hospital admission with acute pain has been associated with increased mortality[1,2]. There is also some evidence in adults that painful episodes that are not treated promptly may lead to a higher incidence of chronic pain owing to repeated inflammation[3].

Recurrent painful episodes have a negative psychological impact and the experience of poorly managed episodes in hospital, together with perceived negative attitudes of some staff, are often reported. These attitudes make it more difficult to develop effective long-term pain-coping strategies and may lead to problematic behaviour on the ward[4].

Guidance on pain management in SCD was recently published by NICE[5]. Validated pain assessment tools should be used to measure the child's self-report and behaviour[6]. These should include parental and healthcare professional assessment. Developmentally age-appropriate self-report tools should be used whenever children are able to participate.

Recommendations

- Pain assessment should include the use of a validated pain assessment tool that is developmentally age appropriate. (C)
- There should be a policy in the A&E department regarding triage, pain assessment and length of acceptable time (not exceeding 30 minutes) from arrival to administration of analgesia. (C)
- Children should be managed according to a standard local protocol. This should be developed by collaboration between the LHT and SHT and should include input from a pain control team, paediatric pharmacist and paediatric anaesthetist. The protocol should provide clear guidance on drugs, route of administration, dosage, and monitoring for analgesic effect and side effects. (C)
- Medical and nursing staff involved in treating children for severe acute pain should have regular training in pain management and in the application of the local protocols. (C)
- Children should be monitored regularly for the effectiveness of their analgesia and for signs of adverse effects (e.g. opiate-induced narcosis and hypoventilation and acute sickle chest syndrome, among others). (C)
- The psychological needs of the child and family regarding coping with pain and avoiding painful sickle cell episodes should be addressed during the admission. (C)

Management of the febrile child

All children with SCD are at increased risk of infection, partly because of hyposplenism. In addition, defects in opsonisation and in cell-mediated immunity have been demonstrated. The risk is highest for the those with HbSS and in infants

up to the age of 5 years, a time of particularly high risk for infection with encapsulated bacteria.

In the days before immunisation programmes and prophylactic antibiotics against *H. influenzae* and pneumococcus, infections with these bacteria were common and caused septicaemia, pneumonia and meningitis. Other infections that can occur include:

- salmonella osteomyelitis, the reason for this increased susceptibility is not known[1,2]
- pneumonia due to typical and atypical organisms
- malaria, particularly in children returning from holidays in Africa
- urinary tract infection
- acute cholecystitis
- parvovirus B19, which causes temporary red cell aplasia.

Diagnostic problems can occur. It is common for a child with a simple acute painful episode to present with a fever and no obvious evidence of infection. Some young children present with painful swollen joints or areas of swelling in a long bone. In these cases, it may be difficult to differentiate between acute bone infarction due to sickling and osteomyelitis or septic arthritis.

Blood cultures should always be taken and, if there is a high level of suspicion (e.g. high swinging fever, septic child, localised very tender swelling), imaging with ultrasound to look for a sub-periosteal fluid collection and surgical drainage should be considered before starting antibiotics.

Prophylactic penicillin should always be continued in hospital if a different antibiotic is not prescribed to treat an acute infection.

Empirical antibiotics appropriate for the range of likely infectious agents should be given. An agent active against pneumococcus should always be included. Cover for suspected chest infection should include agents against atypical organisms.

Recommendations

- A protocol for antibiotic treatment of suspected or proven acute infection should be prepared by the SHT in collaboration with the LHT and a designated paediatric microbiologist. (C)
- Cultures of blood, urine and other possible sites of infection should be routinely done on any child presenting with acute pain and fever. (C)
- Malaria films should be sent if there is any suspicion of malaria or if a patient has returned from a malarial region in the previous year. (C)

Acute anaemia

The most common causes of an acute fall in Hb of >30 g/L below the steady-state Hb level are acute splenic sequestration and transient red cell aplasia (TRCA), which is usually due to parvovirus B19 infection[1].

Acute splenic sequestration has been defined as an acute fall of Hb and markedly elevated reticulocyte count, together with an acute increase in spleen size. It is a serious complication of SCD and, if unrecognised, carries significant mortality[2]. Mortality rates can be reduced substantially by parental education, regular palpation of the abdomen at home to detect early signs of splenic enlargement and prompt intervention with transfusion[3,4]. Recurrent splenic sequestration is an indication for splenectomy.

TRCA is characterised by a drop in Hb over a period of about a week, often to levels as low as 30 g/L, with a very low reticulocyte count. It may be associated with fever, headache and abdominal pain. In a young child, it may be difficult to differentiate between TRCA and acute splenic sequestration, as the spleen may still be palpable. In contrast to acute splenic sequestration, the reticulocyte count will be very low or absent and IgM for parvovirus B19 will be present. It usually takes about 7 days for the reticulocyte to return to normal, and a top-up transfusion is often needed until this happens.

Recommendations

- There should be a protocol for recognition and investigation of children presenting with pallor with or without pain in hospital. (C)
- Parents should be taught how to palpate for splenic enlargement and should be aware of the need to bring the child to hospital if they detect pallor and/or an enlarging spleen; they should be aware of the local procedure for emergency assessment. (C)
- Medical staff assessing children with acute sickle cell complications should be made aware of these complications through regular training/education sessions. (C)
- A local protocol for management, including indications for transfusion, should be available. (C)
- Children with two or more episodes of acute splenic sequestration should be considered for splenectomy. (C)

Acute chest syndrome

Acute chest syndrome is characterised by pleuritic chest pain, fever, abnormal chest examination and new pulmonary infiltrates on the chest X-ray. It is an important cause of morbidity and mortality in SCD[1–3]. It is particularly common in early childhood[4], at which age, the clinical features are generally more typical of pneumonia. In later childhood and adulthood, the syndrome can develop during acute pain or after anaesthesia[5].

Early intervention with an effective treatment protocol including analgesia, oxygen, physiotherapy, antibiotics and transfusion can significantly reduce morbidity and mortality. A randomised controlled trial has shown that incentive spirometry performed regularly every 2 hours reduces the risk of acute chest syndrome in patients with chest and back pain[6].

Recommendations

- Parents, patients and carers should be made aware of this complication; they should know how to recognise the symptoms and should be familiar with the local procedure for emergency assessment. (C)
- Children with chest pain, cough, respiratory distress, new chest signs or worsening hypoxia, presenting either in A&E or during the course of a hospital admission, should be carefully assessed and monitored and a chest X-ray organised urgently. (C)
- Incentive spirometry should be used in children with acute chest and or back pain admitted to hospital and requiring opiate analgesia. (A)
- Oxygen saturation monitoring should be used routinely, particularly in those children with respiratory signs and symptoms, acute pain affecting the trunk and girdle regions and those treated with opiates. (C)
- A local protocol should be available for the management of the acute chest syndrome, which should include clear guidance on analgesia, observations, oxygen delivery, antibiotics, intravenous fluids, bronchodilators, physiotherapy, incentive spirometry and nursing observations, as well as the indications for top-up transfusion, exchange transfusion and ventilator support. There should also be a local protocol covering the practical issues of carrying out an exchange transfusion. (C)
- Medical and nursing staff should be made aware of this complication; regular training and education sessions should advise on how to recognise it and provide updates on the local policy for management. (C)
- An agreement should be reached with the local PICU about the indications for transfer, means of communication and the protocol for treatment in the PICU. (C)

Acute neurological complications

(see also management of cerebrovascular disease)

Acute neurological complications are relatively common in children with SCD and are potentially devastating. Cerebrovascular disease, particularly proximal vessel stenosis, predisposes children to acute cerebral infarction. Occasionally older children present with subarachnoid or intracerebral bleeds, which may be related to single or multiple cerebral artery aneurysms. Acute neurological ischaemia is more likely to occur in children with pre-existing cerebrovascular lesions, during acute anaemic events, or with other acute complications.

Other acute neurological complications include behavioural changes, seizures and loss of consciousness. The causes of these complications are not always clear, even after extensive imaging[1].

Symptoms suggestive of meningitis require urgent investigation, including lumbar puncture, blood culture and prompt antibiotic treatment. Acute ischaemic events require urgent investigation with a CT scan and/or MRI/magnetic resonance angiography (MRA) scan to define the event and exclude a haemorrhagic component. This should be followed as soon as possible by exchange transfusion to reduce the risk of progression of the lesion. Intracerebral or subarachnoid bleeds defined by such imaging need to be assessed urgently by a paediatric neurosurgical team.

Although stroke in a child with SCD is likely to be secondary to cerebrovascular pathology, it is important to remember that stroke in childhood can result from alternative pathology, particularly a source of cardiovascular emboli; these should be actively excluded. The RCPCH has published guidelines on the management of all causes of acute stroke in childhood[2].

Recommendations

- Each SHT should have access to a designated paediatric neurologist who can assess and advise on acute neurological complications. (C)
- Each SHT should have a clear plan for access to a neurosurgical unit for managing children and adolescents with cerebral haemorrhage and subarachnoid bleeds. (C)
- RCPCH guidelines on the management of acute stroke should be followed and specific guidelines for acute stroke in SCD should be prepared for the LHT by the SHT. (C)
- Each SHT should have access to neuroimaging facilities including paediatric CT, MRI/MRA and electroencephalogram (EEG). (C)

Fulminant priapism

(see also non-fulminant priapism)

Priapism is a sustained, painful and unwanted erection.

A prolonged attack, lasting >3 hours should be treated as a surgical emergency as, if untreated, cavernosal fibrosis and impotence may ensue. The condition becomes more common in adolescence and minor attacks may go unreported because of a reluctance to tell parents or healthcare professionals[1].

A prospective study of 15 young patients showed that aspiration and irrigation with dilute epinephrine produced immediate detumescence on 37 out of 39 occasions[2]. Etilefrine may also be used[3]. In the event that this is not successful, a glans-corporal shunt may need to be performed. If no relief occurs, the urologists

may need to perform a bilateral non-parallel spongiosum corporal shunt or a corporal-venous shunt[4]. In addition, blood transfusion may be indicated as part of the overall management plan if a shunt needs to be performed.

Recommendations

- A policy for the management of severe fulminant priapism should be agreed with the appropriate paediatric urology team. (C)
- Priapism should be discussed with all boys and their carers at annual review, and written information given, including the need to seek urgent medical attention for prolonged (>2 hours) episodes of priapism. (C)
- Aspiration and irrigation with etilefrine or epinephrine should be the initial treatment of choice. (C)

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Elective surgery and perioperative care

Indications for surgery in children with SCD

As well as needing operative procedures for complications of SCD, such as acute splenic sequestration or gallstones, children may need routine operations for adenoidal hypertrophy, serous otitis media, orchidopexy, dental extractions and other complications that occur in childhood.

Perioperative management plan

All patients with SCD, even without previously severe complications, are at increased risk of complications at the time of surgery. Certain patients are at greater risk of perioperative complications including:

- those with a history of severe sickle-related problems, such as acute chest syndrome, cerebrovascular disease and frequent painful episodes
- those with severe obstructive sleep apnoea.

The perioperative management of patients with SCD requires good communication between surgeons, anaesthetists, haematologists, paediatricians and nursing staff. A clear management plan should be written in the notes prior to surgery.

Preoperative transfusion

The optimal preoperative transfusion policy in SCD is not clear. A randomised controlled trial showed that, in patients with HbSS and HbS/β^0 thalassaemia undergoing low- and moderate-risk surgery, a preoperative top-up transfusion to a target Hb of 100 g/L significantly reduced perioperative complications, particularly acute chest syndrome[1]. An earlier randomised controlled trial showed that a conservative transfusion regimen that raised Hb to 100 g/L was as effective in preventing perioperative complications as an aggressive exchange regimen that reduced HbS to <30%[2].

Major surgery (including cardiovascular surgery and neurosurgery) typically requires transfusion, usually with an exchange transfusion to reduce the HbS level <30%.

The perioperative management of children with HbSC disease, or with a baseline Hb >90 g/L, is less clear, particularly in low- or moderate-risk surgery, and needs to be decided on an individual basis.

Recommendations

- A clear management plan, agreed by all healthcare professionals involved, should be made and recorded before surgery. (C)
- SHTs should have guidelines on perioperative management in patients with SCD to share with local hospitals. (C)

- The transfusion laboratory should know the red cell phenotype/genotype and a recent antibody screen should be available in case blood transfusion becomes necessary before or after the operation. (C)
- Children with HbSS and HbS/β^0 thalassaemia undergoing low- and moderate-risk surgery should have a preoperative transfusion to increase the Hb level to 100 g/L. (A)
- Children with SCD undergoing high-risk surgery, including neurosurgery and cardiovascular operations, should have a preoperative transfusion to reduce HbS to <30%, which will usually involve an exchange transfusion. (C)

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Specific treatments

Hydroxycarbamide

Hydroxycarbamide (previously known as hydroxyurea) promotes HbF synthesis, improves red cell hydration, decreases the neutrophil count and modifies red cell–endothelial cell interactions.

The Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH) showed a reduction in the frequency of painful episodes, incidence of chest syndrome and transfusion requirement without serious short-term side effects[1]. A paediatric study in Belgium showed similar beneficial results[2]. Long-term data from the MSH study has shown a reduction in mortality in the hydroxycarbamide group. More recently, the BABY HUG trial also showed that hydroxycarbamide significantly reduced the frequency of acute pain and other vaso-occlusive complications in very young children, from the age of 9 months[3]. However, the same trial also failed to show that early use of hydroxycarbamide reduced early splenic and renal damage. Hydroxycarbamide has also been shown to be effective in primary stroke prevention in children with abnormal TCD velocities[4].

Hydroxycarbamide has a number of side effects, of which myelosuppression is the most common in the short term. In conditions already predisposed to leukaemia (e.g. polycythaemia rubra vera), there is an increase in the incidence of leukaemia in patients who received hydroxycarbamide treatment. There is no evidence to date from its use in SCD to suggest that children on hydroxy-carbamide are more at risk.

The long-term teratogenic risk is also not known, but sexually active individuals taking hydroxycarbamide should be advised to use contraception. There are concerns about possible effects on fertility, particularly in boys, although there is no good evidence in this area.

Guidelines from the USA suggest that all children with HbSS or HbSβ^0 thalassaemia should be offered hydroxycarbamide at the age of 9 months[5], and recent UK guidelines similarly recommend that children aged 9–42 months should be offered hydroxycarbamide regardless of the clinical severity of their illness[6]. However, it should be noted that hydroxycarbamide is not licensed for children in the UK until the age of 2 years and any offer should only ever follow an in-depth discussion.

There are still some areas which need clarification including: the optimal dose, impact on long-term organ function and effects on fertility.

Recommendations

- Hydroxycarbamide, including its potential benefits and side-effects, should be discussed with all children and parents in the first year of life, and at subsequent annual reviews. (C)

- Hydroxycarbamide should be offered to all children with HbSS and HbS/β^0 thalassaemia aged 9–42 months regardless of the clinical severity of their illness. (A) See Standard 6.
- Hydroxycarbamide should be offered to all children older than 42 months who have recurrent episodes of acute pain or who have had two or more episodes of acute sickle chest syndrome. (A)
- Hydroxycarbamide should be offered to all children older than 42 months whose lives are significantly affected by symptoms of SCD, including those with frequent episodes of pain that disrupt normal activities. (A)
- Hydroxycarbamide should be offered to all children older than 42 months who are at high risk of progressive organ damage caused by SCD, including those with hypoxemia, significant albuminuria, conditional TCD velocities, or significant anaemia (steady state Hb<70 g/L). (B)
- The decision to start hydroxycarbamide should be made in conjunction with the SHT, and agreement should be reached as to which centre will monitor blood counts and maintain the optimal dose, and how these will be communicated between centres. (C)
- The protocol should include information about dose regimen, frequency of blood test monitoring, management of myelosuppression and contraindications for the use of hydroxycarbamide. (C)
- The patient and/or their parents/carer should be given a patient information sheet. Current knowledge about side effects, including subfertility, cytopenias and the possible risk of leukaemia or other malignancies, should be discussed; this discussion should be documented in the patient's notes. (C)
- Boys of the appropriate age should be offered semen storage before starting hydroxycarbamide. (C)

Use of transfusion therapy

(see also sections on lung disease, cerebrovascular disease and perioperative management)

Transfusion is an essential and life-saving therapy for some acute complications of SCD and has been shown to reduce the risk of chronic progressive organ damage in the case of ischaemic stroke[1]. There may be a beneficial effect in preventing other forms of organ damage, but studies are currently lacking.

Transfusion should not be undertaken without careful consideration of the benefits and risks. Informed consent from the parents, or child where appropriate, should always be obtained prior to transfusion.

There is an incidence of about 18% of alloimmunisation following blood transfusion in the sickle population, and two-thirds of antibodies described are in the rhesus (Rh) or Kell systems[2]. However, the risk may be less in those on

chronic exchange transfusion programmes[3,4]. This is in part because the blood donor population and sickle patient population are from different ethnic origins[5]. The risk of alloimmunisation can be reduced by transfusing only if absolutely necessary and using blood that is compatible for Rh and Kell antigens.

There is an incidence of delayed haemolytic transfusion reactions in SCD of between 4% and 22%, which is significantly higher than in other patients[6]. These can mimic episodes of acute sickle pain and clinicians should have a high index of suspicion for investigating for the development of antibodies when painful episodes develop in the post-transfusion period. Once an alloantibody has been identified, antigen-negative blood should be given, other than in the case of anti-M and anti-Kpa, when crossmatch-compatible blood may suffice. More detailed guidance is given in the recent BSH guideline on principles and laboratory aspects of transfusion for SCD[7].

Hyperhaemolysis has also been described post-transfusion without the development of antibodies. This may be due to bystander haemolysis and one study has shown a possible benefit for high-dose steroids and intravenous immunoglobulin[8], with further case reports describing the use of other forms of immunosuppression e.g. rituximab[9].

The viscosity of blood increases with increasing Hb and HbS-containing cells add to that viscosity, so it is important to balance target Hb levels with HbS concentrations. With this in mind, the target of a top-up transfusion for the treatment of acute anaemia is usually no higher than the steady-state Hb level. In monthly top-up transfusions (e.g. for the management of stroke where the HbS is being maintained <30%), the target Hb is usually 120–130 g/L.

Urgent blood transfusion may be beneficial in some acute complications. The aim is usually to correct the anaemia and sometimes to reduce the HbS level to <30% or <50%. Reducing the HbS level to <30% will often require an exchange transfusion, although a top-up transfusion may be adequate if the child is initially very anaemic.

Indications for acute transfusion[10]

Acute transfusion may be indicated in:

- acute anaemia due to
  - parvovirus B19 infection
  - acute splenic or hepatic sequestration
- acute chest syndrome – early top-up transfusion may avoid the need for exchange transfusion
- stroke or acute neurological deficit – exchange transfusion is usually necessary to reduce the HbS to <30%, with a target Hb of 100–110 g/L
- multiorgan failure
- preparation for surgery.

Indications for regular, long-term transfusion[10]

Regular transfusions may be indicated for:

- primary and secondary stroke prevention
- recurrent acute chest syndrome or painful episodes not prevented by hydroxycarbamide
- progressive organ failure.

Iron chelation therapy should be considered in children on regular transfusions according to standard protocols[11]. They should also be offered vaccination against hepatitis A and B, and reviewed regularly with respect to iron and HbS levels.

Recommendations

- At diagnosis or first clinic attendance, all patients should have an extended red cell phenotype performed. As an alternative, a red cell genotype with variant antigen analysis may be obtained. (C)
- All blood transfused should be matched for Rhesus and Kell blood groups. If alloantibodies are identified, further transfusions should be negative for the corresponding antigen. (C)
- Blood group genotyping should be considered in children with SCD who develop alloantibodies or who start a long-term transfusion programme. (C).
- Red cells for transfusion to patients with SCD should be sickle test negative and if possible <7 days old for exchange or <10 days for top-up transfusion. (C)
- Urgent red cell transfusion should be used in children with rapidly progressive acute chest syndrome or acute neurological symptoms or in those who are severely unwell, aiming to achieve an HbS level <30% and an Hb of 100–110 g/L. This will often require an exchange transfusion. (C).
- Long-term transfusion regimens should be used after a cerebrovascular event to prevent recurrence and should be considered if cerebral artery velocities are abnormal on TCD scans. (A)
- Iron chelation should be considered in all children on regular blood transfusions. (C)
- Immunisation against hepatitis A and B should be offered to all those on long-term transfusion programmes. (C)
- Children starting regular blood transfusions should be reviewed initially by a multidisciplinary team (including checks of HbS levels, iron stores and neurological status, as appropriate) and regularly thereafter. (C)

Haemopoietic stem cell transplantation

Hemopoietic stem cell transplantation, which includes bone marrow transplantation (BMT), along with transplantation of stem cells collected from the peripheral blood or umbilical cord blood, is currently the only treatment for SCD that is potentially curative.

Published experience describes a 92–94% survival rate and a 75–84% disease-free survival rate[1–3]. There is no recurrence of clinical vaso-occlusive events in patients with stable engraftment, but 10% of patients experience rejection or recurrent SCD. The majority of patients have an excellent quality of life after stem cell/bone marrow transplantation.

There are however significant risks associated with stem cell transplantation. The most common early complications are acute graft-versus-host disease (GVHD) and neurological events, including intracerebral haemorrhage and seizures. Chronic GVHD is the most common cause of late mortality and morbidity, with an incidence of 5% in the UK. Other late complications include gonadal dysfunction and an increased risk of malignancy.

Unlike thalassaemia major, where the clinical course is fairly predictable, there is a large variation of severity in SCD. In view of this and the high risk of mortality and morbidity from the procedure, stem cell transplantation is not appropriate in every patient.

Since the publication of trials using hydroxycarbamide, some of the recommendations have been modified, as recurrent pain and chest disease are probably now best treated initially with hydroxycarbamide, with stem cell transplantation reserved for those patients who do not respond to hydroxycarbamide.

Recommendations

- All patients or families with a child with SCD should be offered the opportunity to discuss stem cell transplantation as a treatment option; this should not depend on the family having an available donor at the time. (C)
- Haemopoietic stem cell transplantation should be performed in centres experienced in transplants for haemoglobinopathies. Transplants from any donor other than an HLA-identical family member should be undertaken only in exceptional circumstances and as part of a clinical trial. Each SHT should have clear referral links to a suitable transplant centre. (C)

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Standards

Standard 1 (SCT-S08): Sickle cell and thalassaemia screening – reporting newborn screen-positive results to parents

<table>
<tr><td>Description</td><td>Proportion of parents receiving newborn screen-positive results ≤28 days of age</td></tr>
<tr><td>Rationale</td><td>To provide timely results to parents of screen-positive infants in order to give support to parents and carers, emphasise the importance of early penicillin prophylaxis and to ensure prompt referral into treatment (see Informing parents)</td></tr>
<tr><td>Definition</td><td>
<table>
<tr><td>Number of newborn infants with screen-positive results for whom parents receive results ≤28 days of age</td><td rowspan="2">Expressed as a percentage</td></tr>
<tr><td>Number of newborn infants born within the reporting period with screen-positive results</td></tr>
</table>

Specified conditions to be detected in newborn screening are: HbSS, HbSC, HbS/β thalassaemia (S/β^+, S/β^0, HbS/δβ, HbS/γδβ, S/Lepore), HbS/D^{Punjab}, HbS/E, HbS/O^{Arab}, HbS/HPFH, HbS with any other variant and no HbA, and other clinically significant haemoglobinopathies likely to be detected as by-products of newborn screening, including β thalassaemia major, HbE/β thalassaemia and β thalassaemia intermedia
Carrier results need to be followed up but are excluded from this standard</td></tr>
<tr><td>Performance thresholds</td><td>Acceptable: ≥90%
Achievable: ≥95%</td></tr>
<tr><td>Caveats</td><td>Detection of thalassaemia is not part of the programme but we expect β thalassaemia major to be detected as a by-product and the same standards for communicating results to parents and enrolment into care apply</td></tr>
<tr><td>Data collection and reporting</td><td>Reporting focus: haemoglobinopathy centre
Publishing focus: haemoglobinopathy centre
Data source: haemoglobinopathy centre
Responsible for submission: newborn screening outcomes system
Responsible for data quality and completeness: haemoglobinopathy centre</td></tr>
<tr><td>Reporting period</td><td>Annually: 1 April–31 March
Deadline: 30 June</td></tr>
</table>

Standard 2 (SCT-09): Sickle cell and thalassaemia screening – timely follow-up, diagnosis and treatment of newborn infants with a positive screening result

<table>
<tr><td>Description</td><td>Proportion of newborn infants with a positive screening result who are (a) seen at a paediatric clinic or (b) discharged for insignificant results ≤90 days of age</td></tr>
<tr><td>Rationale</td><td>To optimise individual health outcomes, penicillin prophylaxis should start by 90 days of age in children with SCD. Parents of infants with insignificant results must be informed and reassured as early as possible (see Confirmation of diagnosis)</td></tr>
<tr><td>Definition</td><td>
<table>
<tr><td>Number of newborn infants:
a) with clinically significant results who are seen by a paediatrician by ≤90 days of age; and
b) with insignificant results who are discharged by ≤90 days of age</td><td rowspan="2">Expressed as a percentage</td></tr>
<tr><td>Number of newborn infants with a screen-positive result born within the reporting period</td></tr>
</table>

Specified conditions to be detected in newborn screening are: HbSS, HbSC, HbS/β thalassaemia (S/β^{+}, S/β^{0}, HbS/δβ, HbS/γδβ, S/Lepore), HbS/D^{Punjab}, HbS/E, HbS/O^{Arab}, HbS/HPFH, HbS with any other variant and no HbA, and other clinically significant haemoglobinopathies likely to be detected as by-products of newborn screening, including β thalassaemia major, HbE/β thalassaemia and β thalassaemia intermedia

Exclusions include:
– infants born outside of England
– infants who die or move abroad before 90 days of age</td></tr>
<tr><td>Performance thresholds</td><td>Acceptable: ≥90%
Achievable: ≥95%</td></tr>
<tr><td>Caveats</td><td>None</td></tr>
</table>

Reporting	Reporting focus: haemoglobinopathy centre Publishing focus: haemoglobinopathy centre Data source: haemoglobinopathy centre Responsible for submission: newborn screening outcomes system Responsible for data quality and completeness: haemoglobinopathy centre See dashboard HAEM04A Screening to access to specialist care
Reporting period	Annually: 1 April–31March Deadline: 31 July

Standard 3: Timeliness of penicillin prophylaxis

Description	The proportion of infants with HbSS and HbS/β^0 thalassaemia who are offered penicillin (or alternative) prophylaxis by ≤90 days of age
Rationale	To ensure optimum protection against invasive pneumococcal infection before the onset of hyposplenism (see Prevention of infection)
Definition	Number of infants with SCD offered penicillin (or equivalent) prophylaxis ≤90 days / Number of infants born with SCD and eligible* for antibiotic prophylaxis — Expressed as a percentage * Infants with HbSC disease are excluded because the evidence is only available for giving penicillin prophylaxis to children with HbSS and HbS/β^0 thalassaemia. However, most centres will offer penicillin prophylaxis to children with HbSC disease as hyposplenism can develop but at a later age
Performance thresholds	Acceptable: ≥95% Achievable: ≥99%
Caveats	Record parental refusal and reason
Reporting arrangements	Reporting focus: paediatric service Data source: paediatric service responsible for submission to newborn outcomes system

Reporting period	Annually: 1 April–31 March Deadline: 30 September See dashboard HAEM04B Screening to access to specialist care

Standard 4: Coverage of pneumococcal immunisation at 2 years

Description	The proportion of infants with SCD who have been given PPV between 24 and 27 months of age
Rationale	To ensure optimum protection against invasive pneumococcal infection as PPV contains more serotypes than Prevenar 13. PPV is less effective before 2 years of age (see Immunisations)
Definition	Number of children with SCD given PPV at 24–27 months / Number of children born with SCD aged 24–27 months — Expressed as a percentage
Performance thresholds	Acceptable: ≥95% Achievable: ≥99%
Caveats	Record parental decline. The paediatric service is responsible for monitoring coverage wherever the vaccine is given
Reporting arrangements	Reporting focus: paediatric service Data source: to be determined
Reporting period	Annually: 1 April–31 March Deadline: 30 September

Standard 5 Coverage of transcranial Doppler (TCD) scanning

<table>
<tr><td>Description</td><td>(1) The proportion of children with HbSS and HbS/β^0 thalassaemia who have their first TCD at 24–36 months
(2) The proportion of children with HbSS and HbS/β^0 thalassaemia aged 3–16 years who have annual TCD</td></tr>
<tr><td>Rationale</td><td>To ensure timely screening of cerebral blood vessels to determine a child’s potential risk of stroke and to continue to monitor throughout childhood. The incidence of stroke is highest in younger children (see Provision of TCD)</td></tr>
<tr><td>Definition (1)</td><td><table><tr><td>Number of children with HbSS and HbS/β^0 thalassaemia who have their first TCD aged ≥24 and ≤36 months</td><td rowspan="2">Expressed as a percentage</td></tr><tr><td>Number of children with HbSS and HbS/β^0 thalassaemia aged ≥24 and ≤36 months</td></tr></table></td></tr>
<tr><td>Definition (2)</td><td><table><tr><td>Number of children with HbSS and HbS/β^0 thalassaemia aged ≥3 to ≤16 years tested by TCD in the last 12 months</td><td rowspan="2">Expressed as a percentage</td></tr><tr><td>Number of children with HbSS and HbS/β^0 thalassaemia aged ≥3 and ≤16 years</td></tr></table></td></tr>
<tr><td>Performance thresholds</td><td>Acceptable: 99%</td></tr>
<tr><td>Caveats</td><td>Record parental decline
Record other means of surveillance e.g. if technically difficult and child having regular MRI scan</td></tr>
<tr><td>Reporting arrangements</td><td>Reporting focus: paediatric service
Data source: paediatric service</td></tr>
<tr><td>Reporting period</td><td>Annually: 1 April–31 March
Deadline: 30 September
See dashboard HAEM02 Transcranial Doppler (TCD) monitoring</td></tr>
</table>

Standard 6: Coverage of hydroxycarbamide (hydroxyurea) therapy

<table>
<tr><td>Description</td><td>Documented evidence that a discussion has been held with a child’s parents regarding the beneficial effects of hydroxycarbamide
The proportion of children with HbSS and HbS/β^0 thalassaemia who are offered hydroxycarbamide</td></tr>
<tr><td>Rationale</td><td>To optimise long-term clinical outcome in children with HbSS and HbS/β^0 thalassaemia (see Hydroxycarbamide)</td></tr>
<tr><td>Definition</td><td>
<table>
<tr><td>Number of children with HbSS and HbS/β^0 thalassaemia aged ≥9 to ≤42 months where there is documented evidence of a discussion about hydroxycarbamide</td><td rowspan="2">Expressed as a percentage</td></tr>
<tr><td>Number of children with HbSS and HbS/β^0 thalassaemia aged ≥9 to ≤42 months</td></tr>
<tr><td>Number of children with HbSS and HbS/β^0 thalassaemia aged ≥2 to ≤16 years prescribed hydroxycarbamide</td><td rowspan="2">Expressed as a percentage</td></tr>
<tr><td>Number of children with HbSS and HbS/β^0 thalassaemia aged ≥2 to ≤16 years</td></tr>
</table>
</td></tr>
<tr><td>Performance thresholds</td><td>Acceptable (for children aged ≥9 to ≤42 months): ≥99% (see also BSH guideline)
Acceptable (aged ≥2 to ≤16 years): to be determined</td></tr>
<tr><td>Caveats</td><td>Hydroxycarbamide is only licensed for use in children over the age of 2 years</td></tr>
<tr><td>Reporting arrangements</td><td>Reporting focus: paediatric service
Data source: to be determined</td></tr>
<tr><td>Reporting period</td><td>Annually: 1 April–31 March
Deadline: 30 September</td></tr>
</table>

Standard 7: Coverage of children identified through the screening programme subsequently registered on the national haemoglobinopathy registry (NHR)

<table>
<tr><td>Description</td><td>Proportion of children with SCD identified by the newborn screening programme registered on the NHR</td></tr>
<tr><td>Rationale</td><td>Completeness of coverage on the NHR is important to fulfil its central aim of improving patient care. The newborn outcomes system when fully implemented will hold denominator data and record data transfer to the NHR. This will identify variance across networks which can be further explored (see Organisation of follow-up)</td></tr>
<tr><td>Definition</td><td><table>
<tr><td>Number of infants with SCD registered on the newborn outcomes system where data has been pulled through to the NHR</td><td rowspan="2">Expressed as a percentage</td></tr>
<tr><td>Number of infants with SCD registered on the newborn outcomes system</td></tr>
</table></td></tr>
<tr><td>Performance thresholds</td><td>Acceptable: to be determined
Achievable: to be determined</td></tr>
<tr><td>Caveats</td><td>From 2019, all infants identified as having SCD will be referred from the newborn screening laboratory to paediatric care using the newborn outcomes system. Data can be pulled through to the NHR when key data and parental consent are recorded on the newborn outcomes system</td></tr>
<tr><td>Reporting arrangements</td><td>Reporting focus: paediatric service
Data source: paediatric service responsible for submission to newborn outcomes service</td></tr>
<tr><td>Reporting period</td><td>Annually: 1 April–31 March
Deadline: 30 September</td></tr>
</table>

Standard 8: Coverage of children who have had an annual review

<table>
<tr><td>Description</td><td>Proportion of children with SCD that have an annual review</td></tr>
<tr><td>Rationale</td><td>To ensure all children with SCD have the benefit of annual assessment and do not miss out on screening tests and treatment interventions (see Annual review)</td></tr>
<tr><td>Definition</td><td><table><tr><td>Number of children with SCD aged ≥1 to ≤16 years who have started annual review</td><td rowspan="2">Expressed as a percentage</td></tr><tr><td>Number of children with SCD aged ≥1 to ≤16 years</td></tr></table></td></tr>
<tr><td>Performance thresholds</td><td>Acceptable: ≥85%</td></tr>
<tr><td>Caveats</td><td>None</td></tr>
<tr><td>Reporting arrangements</td><td>Reporting focus: paediatric service
Data source: paediatric service</td></tr>
<tr><td>Reporting period</td><td>Annually: 1 April–31 March
Deadline: 30 September
See dashboard HAEM05 Annual review via NHR</td></tr>
</table>

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