



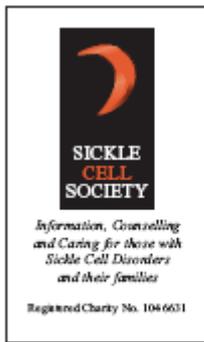
**SICKLE
CELL
SOCIETY**

*Information, Counselling
and Caring for those with
Sickle Cell Disorders
and their families*

Registered Charity No. 1046031

**Standards
for the
Clinical Care of
Adults
with
Sickle Cell Disease
in the UK**

2008



Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK

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Foreword

The Sickle Cell Society believes that every person with sickle cell disease (SCD) has the right to quality care without discrimination between ethnic groups, age, gender or the area of residence of those affected. The reality is that provision of care for adults with SCD can vary significantly between individual professionals as well as health care provision organisations: these standards were born, in some part, from the reality described by service users in a piece of research conducted by the Sickle Cell Society and supported by the Wellcome Trust (see appendix 1)¹. Equal access to services and support in a confidential and sensitive environment can be achieved only if services are organised efficiently and funding made available for service improvement where necessary. This brings new opportunities for evidence-based medicine and practice to flourish across organisational boundaries and among professionals of different backgrounds, working for the higher good of those with SCD.

An organisational model of service delivery for holistic care has been formulated within these standards. Hospital based SCD specialist centres/networks will act as 'expert resources' for local hospitals delivering acute conventional care. Sickle cell and thalassaemia community centres/services, working with local authority and general practice, will underpin access to integrated health and social care in the community. Central to this are patient experts whose experience must be harnessed for the advancement of professional knowledge and in the shaping of services. This model formalises existing networks for some, and maps out care pathways in other areas.

These standards are a tool with which to address inequalities in provision and access to good quality care. They are also an example of excellence in partnering between the medical community, the voluntary sector and the pharmaceutical industry. During their development I have witnessed the deep rooted desire for genuine partnership between these diverse groups in order that these standards could become a reality; they represent the very best vision of good practice available to us at this time. The Sickle Cell Society offers them to the SCD community – service users and professionals – and I urge them to work together towards their implementation.

Dr Lorna Bennett, RGN HV MSc DLSHTM FRSA
Chairperson, Sickle Cell Society

Statements of Support

I am delighted to welcome the publication of the first Standards for the Clinical Care of Adults with Sickle Cell Disease. I know how important these standards will be in ensuring the highest levels of medical care for patients and families who learn to live with sickle cell. I know it is an extraordinary difficult disease to manage. And I know, too, that many patients are helped by the tireless work of the Sickle Cell Society. The Sickle Cell Society celebrates its 30th birthday next year. Over three decades those running the Sickle Cell Society have been both pioneers and carers – and have given advice as well as solace, understanding as well as knowledge. I commend all of you for the work you do in this area. I am particularly pleased that you have collaborated with the NHS to produce these standards, because they will help achieve one of our foremost goals: the lessening of health inequalities in the UK. Thousands of sickle cell patients have benefited from the work you do, and I know they will continue to do so in future.

The Prime Minister, the Rt Hon Gordon Brown MP

The Standards for the Clinical Care of Adults with Sickle Cell Disease is a landmark publication for the care of the thousands of sickle cell patients in the UK. These guidelines are an important step forward in reducing health inequalities faced by ethnic minorities and through the implementation of the standards I look forward to seeing much improved health outcomes for adult sickle cell patients across the UK.

Norman Lamb MP

Liberal Democrat Shadow Secretary of State for Health

Sickle cell is now the most common hereditary disease in the UK, with an increasing number of sickle cell patients of adult age. My involvement with the Sickle Cell Society goes back many years and I am proud that the UK is leading the way globally in producing these Standards for the Clinical Care of Adults with Sickle Cell Disease. We all know that sickle cell disease disproportionately affects black, Asian and minority ethnic communities so I am especially determined to see us tackling the effects of the double and sometimes triple discrimination those with sickle cell can suffer. I encourage the medical and other professionals involved to support the implementation of the standards in order to achieve the potential they have to improve and save the lives of so many.

David Lammy MP

Labour MP for Tottenham, Parliamentary Under-Secretary of State, Department for Innovation, Universities and Skills

The Standards for the Clinical Care of Adults with Sickle Cell Disease represent the hard work of many professionals in the field over several years. I congratulate their dedication and the work of the Sickle Cell Society. I recognise the vital need to improve the health outcomes of adult patients with sickle cell, and welcome the publication of the standards as a hugely significant step in achieving this.

Stephen O'Brien MP

Conservative Shadow Minister for Health

We welcome this publication which sets out clear standards for the delivery of care to adult patients with SCD. The document builds on the considerable expertise of the UK Sickle Cell Society and is a joint venture with specialists as well as the patients themselves. It will act as a suitable tool for driving improvements in clinical care and to help design services in the future.

Prof William Connon, Head of Blood Policy, and Dr Denise O'Shaughnessy, Snr Medical Advisor, Department of Health

The UK Forum on Haemoglobin Disorders welcomes this document. It was written in collaboration between service users and providers. We see the launch of the new adult standards as a landmark in the care of sickle cell disease. They should ensure that the delivery of all aspects of care will be coordinated, equitable and responsive to the needs of every person with SCD. The challenge now is to engage with those commissioning services for patients with these disorders to ensure these standards form the template for service provision in England, and hopefully will also be seen as a valuable resource for the wider health community.

Dr Phil Darbyshire, Chairman, and Dr Baba Inusa, Secretary, UK Forum on Haemoglobin Disorders

Chairman's Introduction

We live in truly exciting times. There continues to be a significant level of evolution in the NHS with many Government initiatives aiming to deliver a patient centred, first class service nearer to home for people with SCD. As a settled immigrant, a SCD service user and a Consultant Haematologist with an interest in haemoglobin disorders, I have been struck by the differences in competency and attitudes of health care workers that have a direct impact on the quality of care provided by hospitals and community based health care providers in the UK. I strongly believe there needs to be a greater emphasis on ownership and accountability by health care providers in order to win back the confidence of service users who fall into ethnic minority groups.

In an attempt to provide equitable care following on from the NHS Sickle Cell and Thalassaemia Screening Programme, the Sickle Cell Disease in Childhood: Standards and Guidelines were launched in 2006. These Adult Standards of Care are a natural progression and will provide a seamless transition from childhood to adulthood with emphasis on preventive rather than reactive programmes. These standards of care aim to provide guidance on the absolute minimum package of care expected for every affected individual residing in the UK as well as developmental goals for the future. Where a standard has been recommended, clear ways of achieving it have been put forward; they have been developed with the utmost professional transparency and must be subjected to continuous evaluation through performance management, audit and reflective practice so as to ensure continuous improvement in care provision.

More than anything, SCD is best managed in the community where care can be delivered as close to home as possible. We must explore innovative ways of commissioning or redesigning services such as chronic pain clinics, community matrons, stroke services, clinical genetics and social services for a group who already feel marginalised and unreachable. My wish is to bear witness to a level of health provision in the UK unparalleled by any country and worthy of emulation; one consistently thought of and delivered immaculately from conception to implementation.

**Dr Ade Olujohungbe Dip. Haem. (Lond).MD FRCP FRCPATH
Consultant Haematologist and Chair of the Adult Standards of Care Working
Group**

Methodology

The Sickle Cell Society invited a multidisciplinary group of professionals and service users (including expert patient programme, psychology, social work, counselling, haematology specialist care and primary care) working within health care and charitable organisations to form a working group. The Sickle Cell Society formulated terms of reference and the working group met to refine and adopt these (see appendix 2). Group members were divided into sub groups, each allocated a specific chapter relating to their area of interest. Where topics fell outside the expertise of these groups (e.g. stroke, obstetrics, urology, etc.) a relevant specialist was recruited to consult on and contribute to that particular section (listed below). An editorial team was formed and met several times to compile, review and edit early drafts, examine evidence, provide consensus and to ensure a seamless, consistent and accessible document. A final draft was opened to a broad and extensive consultation process within the UK SCD community. The completed document was then sent to a predetermined panel of independent reviewers. These reviewers had had no previous sight of, or played any role in the development of the standards content.

A full and complete literature search was conducted in order to highlight any potentially relevant supporting evidence. The search was led by a clinician and a clinical information specialist. Searches of MEDLINE, EMBASE, CINAHL, PsycINFO and The Cochrane Library (incorporating the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews) were carried out. A first phase search filtered 'gold standard' evidence from randomised controlled trials and meta-analyses (see appendix 3 for full criteria). The outputs were reviewed by the editorial team and incorporated where relevant. Sections and topics particularly lacking in evidence base (e.g. HRT, nutrition, etc.) were highlighted and a second phase search was conducted to filter other clinical trials and less robust data, such as observational studies, in order to accumulate as much evidence as possible.

Some areas had an almost complete lack of published data, thus the expert opinion of the working group represents a key driver of best practice throughout the document. As such, recommendations for best practice are graded on AHRQ (1992)² recommendations. In addition, all relevant clinical guidelines and health policies, such as National Service Frameworks, were incorporated where appropriate.

Levels of evidence: grading of recommendations

Levels of evidence are provided within the 'Recommendations for best practice' section in each chapter and are shown as (A), (B) or (C).

(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 User Guide

These standards originate from, and represent, the needs of SCD service users in the UK; they are not a clinical guideline, but aim to document minimum standards of care as well as aid and instruct on how best these standards can be achieved. As a consequence, they must appeal and be accessible to multiple audiences within the SCD community, ranging from service users and carers, commissioners and community health care providers, to specialist care clinicians and those working in the emergency services.

The Sickle Cell Society understands that each audience may have differing needs and requirements of this document and, therefore, it is not intended that the document be read from first page to last. Instead, it is hoped that readers will be able to go directly to the information they require and that is most pertinent to them.

The document is broken into 7 chapters, starting with an overview of SCD aimed primarily at non-clinical readers. Chapter 2 addresses the crucial issue of how best to organise SCD services and recommends models of care as well as methods of commissioning appropriate levels of care.

Clinical chapters 3 and 4 are split into the acute and chronic management of the complications associated with SCD. Consequently, some aspects of the condition, such as priapism or stroke, appear in both settings and readers interested in the management of such complications are encouraged to read both for a comprehensive understanding. Individual chapters have been given to the topics of pregnancy, blood transfusion, and specific therapies/surgery. Similarly, areas of cross-over exist and all topics are cross-referenced where appropriate in order to help sign post the reader to related sections with ease.

With the exception of chapter 1, each chapter begins with a brief introduction and a listed summary of the core standards recommended for each of the topics covered within the body of the chapter (a summary of all core standards is given in appendix 4 for quick reference). The main body of each chapter is given over to 'Recommendations for best practice', where guidance is given on how to go about achieving core standards as well as gold standard levels of care. Recommendations are delivered with supporting levels of evidence (see above) and where a research evidence base has been found, key references are given.

Finally, appendices hold reference information to assist the reader with additional background, as well as useful working tools, such as a shared care communication template and suggested areas for regular clinical review.

Working Group Membership

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Acknowledgements

In addition to all those mentioned above, these standards have benefited from the contributions and support of countless others, far too many to name here. Whether health care professionals, patron or members of sickle cell support groups and sickle cell and thalassaemia centres, the value of their collaboration is immeasurable and greatly appreciated. A special thanks goes to Dr Asa'ah Nkohkwo and Dr Jane Wai-Ogosu who were pivotal in driving project management on behalf of the Sickle Cell Society.

The Sickle Cell Society is also very appreciative to Huntsworth Health for provision of logistical support, and to Novartis Pharmaceuticals (UK) for providing an unrestricted educational grant to help support the development of these standards.

References

¹ Sickle Cell Society. Report on a doctors-patient engagement workshop on managing pain in SCD. 2005.

² Rating Scientific Evidence Strength. Agency for Healthcare Research and Quality. 1992; <http://www.ahrq.gov/clinic/tp/strengthtp.htm> (last accessed Feb 08).

Principal Standards for Best Practice

These principal standards have been selected as the most critical areas for implementation and audit at the time of publication; they should be at the top of any agenda relating to SCD service provision.

Acute pain

People presenting with acute sickle pain should be rapidly assessed, and receive a first dose of effective analgesia within 30 minutes of arrival, with the aim that pain should be controlled within 2 hours. Pain and sedation scores should be recorded systematically and treatment adjusted accordingly.

Acute complications

On emergency presentation, patients should be assessed for acute and potentially life threatening complications including infection, acute chest syndrome, neurological problems, acute renal failure and priapism, and observations for such complications should continue to be recorded regularly, and acted upon, throughout every episode of care. Appropriate senior haematology and other specialist support should be available to manage these complications.

Detecting and managing chronic complications

Patients should be offered regular outpatient follow up, where they will be systematically screened throughout adult life for complications, and treatment started in a timely manner to prevent or slow progression. This includes screening for renal disease, lung disease including pulmonary hypertension, retinopathy, and complications of iron overload in those on long term transfusions. Joint clinical management between the haematology team and the relevant specialist team should be instituted. Management of pregnancy in women with SCD should be in conjunction with a designated obstetrician, with interest and experience in the condition

Networks for care

People with SCD should have access to a range of services depending on their needs, including regular care close to home where appropriate, and complex care at a suitable specialist centre. This is best achieved by close co-operation between local health services, local authority and specialist centre teams. The views of the patient must be included in all care decisions.

Education and training

Education of patients about their condition, and health professionals about necessary care, is centrally important to outcomes. Health care staff should receive relevant, documented, training and competency assessments.

Adequate resources

Services should be commissioned to support highest quality clinical management. Commissioning should be based on evidence, should include measurable quality outcomes, and should promote service improvement and innovation. Leadership by clinical and nursing experts, and patient and public involvement, is key to successful commissioning and mechanisms must be in place to ensure appropriate engagement. Access to necessary high cost interventions should be equitable across the UK.

Sickle Cell Disorders: Overview

1.1 Introduction

This chapter is a brief description of sickle cell disease (SCD). It is not and cannot be a comprehensive review and readers are referred to standard texts for more detailed information. It is intended to inform multiple audiences within healthcare services and introduce many terms used throughout the document.

Haemoglobin (Hb) is the oxygen carrying protein found in the red blood cells of humans and other mammals. In man it comprises four 'globin' (protein) chains, each wrapped around a 'haem' (iron containing) molecule. Newborn babies have a form of haemoglobin, called fetal haemoglobin (HbF), which is largely replaced by adult haemoglobin (HbA) in the first year of life. HbA consists of two alpha (α) globin chains and two beta (β) globin chains.

SCD comprises a group of conditions caused by the 'sickle' mutation. The resulting exchange of valine for glutamine at the 6th position on the β chain leads to the production of a sickle haemoglobin molecule (HbS) which is of low oxygen affinity but with a tendency to polymerise in the presence of hypoxia. These conditions occur when affected genes are inherited from both parents.

1.1.1 Haemoglobin S and other significant variants

SCD comprises a group of conditions caused by the 'sickle' mutation. Individuals who inherit the sickle gene from both parents have homozygous SCD (HbSS), commonly called sickle cell anaemia. Individuals inheriting the sickle gene from one parent, and another specific variant (HbC, HbD_{Punjab}, HbO_{Arab}), or a lack of β chains (β thalassaemia genes) from the other parent, will also be affected by sickling. Together, these comprise the group of genetic conditions which give rise to clinically significant SCD.

1.1.2 Sickle cell carriers

Individuals who inherit only one HbS sickle gene from one parent are sickle cell carriers (HbAS), previously known as sickle cell trait. Sickle cell carriers very rarely have clinical symptoms and often do not know they are carrying the HbS gene unless they have a specific blood test or a child with SCD.

1.1.3 Haemoglobin variants

There are many other variants, both known and unidentified, which will be detected on screening, and which are unlikely to be of clinical significance when found in combination with HbS.

1.2 Epidemiology

Although SCD occurs predominantly in individuals of African descent, these disorders are also prevalent throughout the Mediterranean; Middle East and parts of India; the Caribbean; and South and Central America. The common factor to this distribution is a history of malaria, or migration from a malarial area. Within these regions the HbS gene frequency ranges from 10%-30%. However, due to population migration, SCD is an important part of clinical practice in most countries.

In the UK, SCD affects 1 in 2,400 live births (estimated birth prevalence, all ethnic groups, 2002) and there is now a nationwide screening programme in place. There are currently estimated to be 12,500 individuals living with SCD in England where it is the most common and fastest growing genetic disorder¹.

1.3 Pathophysiology

HbS will polymerise when deoxygenated, making it less soluble. These haemoglobin polymers interact with the red blood cell membrane causing the characteristic sickle shaped blood cell.

The pathological features of SCD relate to the shortened life span of the sickled blood cells (16-20 days in contrast to a lifespan of 120 days in normal red cells) causing a haemolytic anaemia and adhesion of HbS containing cells and white cells to the lining (endothelium) of the microvascular vessels. This process of occlusion in the microvascular circulation produces vascular damage, organ infarcts, painful episodes and other symptoms associated with SCD.

There are two essential pathological processes: haemolysis and vaso-occlusion. Haemolysis results in anaemia. Large vessel damage is caused by repeated endothelial damage by adherent sickle cells, complicated by vasoconstriction and nitric oxide deficiency. This mechanism is likely to be responsible for complications such as pulmonary hypertension and stroke. Small vessel occlusion is caused directly by sickled cells. Vaso-occlusion may cause acute episodes such as painful crisis or more chronic damage such as avascular necrosis of hips and renal failure.

1.3.1 Clinical presentation

SCD is an inherited condition, detectable from birth (e.g. as in neonatal screening programmes). As soon as HbF levels fall and %HbS rises, pathology related to sickling may start to occur. Therefore initial clinical presentation usually occurs in childhood. Some individuals with less severe SCD may develop clinical problems later in life.

The most common clinical manifestations are the painful crises due to blockage of small vessels and tissue infarction. Repeated crises ultimately result in end organ damage and almost any organ can be affected. Other common clinical conditions include splenic sequestration, overwhelming sepsis, acute chest syndrome, priapism, lung disease, recurrent chronic leg ulceration, proliferative retinopathy leading to progressive visual loss and stroke.

1.3.2 Clinical course and survival

In its most severe form SCD has a significant impact on morbidity and mortality. Furthermore, SCD is unpredictable, with random crises of variable severity. This can add to the psychological pressures of living with chronic disease, and may also cause severe social disruption throughout life.

As recently as the 1970s, a person with SCD was not expected to survive to adulthood. Subsequent improvements in patient care and new treatment options have contributed to improved life expectancy. A multi-centre study among individuals with SCD, living in the 1970s and 1980s, reported a median survival of 42 years in men and 48 years in women². Survival estimates in a clinic population in another study suggested survival median for men of 53 years and 58.5 years for women³. A National confidential enquiry into patient deaths in England reported that the most common causes of death in adults with SCD were cerebrovascular accidents, multi-organ failure and acute chest syndrome⁴. The report also called for better evaluation and reporting of cause of death in SCD patients.

1.4 Diagnosis

Opportunities for diagnosis of SCD occur throughout life and may be suspected clinically if an individual presents with a painful crisis or complication. Increasingly, the diagnosis is indicated as a result of testing within a screening programme. The process by which laboratory investigation and confirmatory testing occurs will depend on the mode of presentation, as well as the laboratory facilities. The most common methods used for diagnosis include:

- Full blood count, blood film and reticulocyte count, bilirubin
- Sickle solubility test (e.g. sickledex)
- Hb electrophoresis using cellulose acetate or agar gel
- High performance liquid chromatography (HPLC)
- Isoelectric focussing (IEL)
- Polymerase chain reaction (PCR)
- Supplementary genetic tests

The NHS Sickle Cell and Thalassaemia Screening Programme has produced a laboratory handbook, which outlines policy guidance, laboratory standards, testing algorithms, standardised reporting, referral for DNA analysis and procurement details. It is recommended that all laboratories testing for SCD adhere to the minimum standards outlined in the laboratory handbook for neonatal and antenatal screening⁵.

1.4.1 Neonatal screening

The National Sickle Cell and Thalassaemia Screening Programme has supervised the roll out of universal neonatal screening in England (completed 2004). In this process, the neonatal blood spot test is tested up to 10 days after birth, to screen for major Hb disorders⁶. Extended screening may then lead to the detection of Hb disorders in other family members⁵.

1.4.2 Antenatal screening

The National Antenatal and Newborn Screening Programmes recommend universal antenatal screening. Because of the variation in population HbS carrier frequencies, some areas have been designated 'high prevalence' and both the full blood count and Hb separation tests are carried out in all cases; in 'low prevalence' areas the family origin questionnaire is used to identify women whose blood should be tested for abnormal variants. Whatever the local screening method, fail-safe mechanisms to identify at-risk pregnancies, and targeted neonatal testing, also need to be in place.

1.4.3 Opportunistic screening

Pre-operative screening may need to be carried out in an emergency, sometimes outside normal laboratory hours. In these cases the first test may be the sickle solubility test. However, this will only detect the presence of HbS and further investigation is needed to distinguish sickle trait from significant SCD. HPLC will give a quantitative level of HbS and HbF, as well as demonstrating the presence of HbA, if present, to clarify the diagnosis. Other opportunistic screening requests may come from GP practices, dentists and Family Planning Clinics.

1.4.4 Incidental finding

SCD may be picked up by chance (incidentally) on a routine blood test (eg full blood count, or blood film). HPLC will confirm the diagnosis. In these circumstances, informed consent prior to the test is not possible. Therefore there needs to be a procedure in place, whereby affected individuals are both counselled about their condition, and receive prompt appropriate medical care. Laboratories should have a failsafe

mechanism in place when issuing results, to ensure all appropriate parties are informed of the result.

1.4.5 Predictive factors and variability in phenotype

The level to which SCD clinically manifests itself can vary significantly. Generally, HbSS and HbS/° thalassaemia demonstrate greatest severity. However, even HbSS can display remarkable variation in severity due to both inherited and environmental factors and the interaction between them.

The severity of sickling is proportional to the percentage haemoglobin S present. Genetic factors which may affect the severity of sickling in an individual include:

- A higher than usual HbF level
- Coexisting thalassaemia
- Double heterozygosity (e.g. HbSC)
- Other linked genetic polymorphisms leading to severe, or mild phenotypes

Environmental factors include infection, climate, nutrition, psychosocial factors, socio-economic status, and access to medical care.

Indicators of the severity of SCD may be evident in baseline investigations taken at a time when the individual is asymptomatic, such as baseline haemoglobin, bilirubin, and white cell count. Life threatening events may still arise in 'less severe' SCD.

All individuals with SCD should have a record of baseline parameters against which acute levels can be reviewed during crises, illness or peri-operatively. Such a record may be kept in patient held data, local or national database or case notes. The patient record should also include blood group, rhesus genotype and the need to transfuse rhesus genotype matched, Kell negative, sickle negative blood cells.

1.5 Rationale for therapies

The primary goal of patient management and treatment is to improve survival and reduce the frequency, duration and severity of painful crises and other complications, and improve quality of life, which includes early detection and management of organ damage. Individuals with SCD require ongoing continuity of care, starting in early infancy and developing to a life-long care programme. Much of this document will address the appropriate levels of care required for effective management.

References

¹ NHS Sickle Cell and thalassaemia screening programme. London: NHS 2006.

www.screening.nhs.uk/sickleandthal (accessed Dec07).

² Platt OS, Brambilla DJ, Rosse WF, *et al.* Mortality in SCD. Life expectancy and risk factors for early death. *N Eng J Med.* 1994; 330(23):1639-44.

³ Wierenga KJ, Hambleton IR, Lewis NA. Survival estimates for patients with homozygous sickle cell disease in Jamaica: A clinic based population study. *Lancet.* 2001; 357(9257):680.

⁴ National Confidential Enquiry into Patient Outcome and Death. A sickle crisis? May 2008.

⁵ NHS Antenatal and Newborn Screening Programmes Sickle Cell and Thalassaemia: Handbook for Laboratories 2006.

⁶ NHS antenatal and Newborn Screening Programmes. NHS Sickle Cell and Thalassaemia Screening programme. Standards for the linked antenatal and Newborn Screening Programme. 2006.

Organisation of Care and Commissioning Services

2.1 Introduction

Services for adults with sickle cell disease (SCD) need to take account of the chronic nature of the condition and its effects on further education, work and family life, as well as the variable and unpredictable need for acute hospital care. Service users with a clear understanding of their condition can manage it optimally, and an emphasis on patient education and independent self-care is key. Partnerships between 'expert patients' and professionals enhance care, and patient choice is central to management decisions. Close working between the service user, their multi-disciplinary health care team and social care providers is essential. Specialised commissioning is required to drive service provision and user input should always inform service development and change.

There is wide geographical variation in prevalence of SCD across the UK. Provision of the full range of specialist services for SCD in areas of low prevalence is unrealistic. In order to provide uniform standards of care to all service users, care networks for haemoglobin disorders including SCD and thalassaemia are recommended. The effectiveness of such a service arrangement has already been demonstrated for other chronic conditions such as cystic fibrosis, asthma, diabetes and haemophilia.

Care networks need to be developed across the UK, building on current service provision. In high prevalence areas several large hospital centres may work together to provide specialised services across the network. In low prevalence areas a 'hub and spoke' clinical care model with a SCD specialist clinical centre supervising but sharing care with local hospital units and primary and community care teams may prove more effective. Within this model, specialist supervision oversees local provision, with the patient seen at a specialist centre at diagnosis for initial assessment, for regular clinical reviews, and in between these as necessary for management of acute problems. In low prevalence areas the hub and spoke model for community care will work better with established sickle cell and thalassaemia (SCaT) community centres/services at the hub, supporting community practitioners and care teams working closely with local hospital, primary care and local authority. Centres with specialist expertise provide the opportunity to improve services for people with SCD in areas which do not currently have specialist services. This service arrangement reflects the recommendations of the National Service Framework for Long Term Conditions¹. The roles and responsibilities of SCD specialist centres, local hospitals and community centres/services are outlined in the following sections. It is important that hospital clinicians are enabled to provide clinical leadership for all community teams, in areas where there are no community medical experts in sickle cell to take on this role. Where there are already medical experts fulfilling this role in some areas, there should be close working collaboration between the community and hospital practitioners. Training and development needs of community professionals to improve care in the community should be considered. Clinical supervision arrangements should be available for nurses and other appropriate health care professionals.

The organisation of paediatric services is covered in Sickle Cell Disease in Childhood: standards and guidelines for clinical care². As children with SCD grow through adolescence into adulthood, transition of care from paediatrics to adult services will take place. This is a sensitive time which needs careful planning and support. Transition issues are also covered in the paediatric standards document but for completeness standards are outlined again here.

2.2 Core standards

i) Transition from paediatric to adult services

- There must be a hospital transition policy in place, and preparation and planning should start by age 13-14 years
- A detailed review will be carried out at 15-16 years regarding:
 - knowledge and understanding about SCD
 - self-care and management
 - SCD inheritance and implications for family planning
 - concerns about healthcare in an adult setting and readiness to transfer considered
- A transition or adolescent clinical service will be available to allow the young person to meet the adult sickle cell team and for a formal review and handover to take place. The family carers will also be invited to talk to the adult sickle cell team
- Adult and paediatric protocols for managing complications, in particular painful episodes, will correspond as much as possible

ii) Adult services

Primary care and community services

- Service users will:
 - be registered with a GP
 - be given written information (or materials in other suitable formats as required) regarding approaches to preventing and managing symptoms at home, and what symptoms should make them seek urgent medical advice
 - have a named contact and contact numbers for their local unit and specialist centre as well as the nearest SCaT centre/service
 - have access to support in the community from social services and healthcare services such as community nursing, according to their individual need
 - have appropriate psychological assessment and interventions, including cognitive behavioural therapy
 - be able to access the benefit system to support them financially in a fair and transparent manner that includes help to complete forms if required
 - be supported to access services via the voluntary sector, outreach services or other alternative channels
 - be enabled to achieve independent living through life skills training and support that empowers them to take control of and manage their daily commitments
- Primary Care Trusts (PCTs) will ensure that the Expert Patients Programme (EPP) is available to all service users with SCD and their carers
- Where community practitioners/community teams require specialist community care expertise, support or supervision arrangements to be obtained from an appropriate SCaT centre
- Services will be geared to provide an appropriate level of care in the community, working closely with hospital clinicians and primary care to provide alternatives to hospital care where possible, bringing care closer to patients' homes
- Innovative new models of community care interventions, with the potential to reduce reliance on secondary care, should be given an appropriate level of support
- Community services should receive clinical leadership and support from hospitals until relevant expertise is in place in the community

Hospital services (including emergency services)

- Service users will be invited to attend a specialised clinic on a regular basis and this will vary from monthly to once yearly depending on patient need
- SCD services will be developed into clinical networks including specialised centres and shared-care service providers in local NHS trusts

- In high prevalence areas SCD services may consist of several large centres working together, sharing specialist services and supporting local hospitals, and in low prevalence areas will consist of a specialist centre supporting several local hospitals
- All hospitals will have a mechanism for contacting service users who default from follow-up appointments, and informing the primary care team that they are no longer accessing hospital care
- Out of hours facilities for blood tests, out-patient clinics and day care facilities will be made available so that routine or planned health care does not interfere with education, work or family responsibilities
- There will be designated hospital teams responsible for admission, in-patient care, out-patient care and follow-up, and for ensuring liaison with primary care/community care
- Appropriately skilled staff must be available to guide out of hours assessment and management
- There will be written guidance for teams in local hospitals, written or at least agreed by the local SCD network, covering management of common presentations and indicating clearly under what circumstances, and how the team at the specialist centre should be contacted for advice or patient transfer
- Patients with SCD who need an ambulance to take them to hospital should be taken to their usual hospital if feasible, unless immediate resuscitation is necessary in which case they should be taken to the nearest A&E department. If they become acutely ill out of their own area of residence, they should be taken to the nearest A&E department. Minor injuries or GP led units are not suitable for the assessment and treatment of these patients
- Staff handling patients with SCD need to be aware of the extreme pain they may experience, and transporting and positioning of the person needs to take this into account
- If immediate pain relief is necessary during transfer, Entanox can be used for short periods as long as the baseline oxygen saturation is normal

iii) **Commissioning sickle cell services**

- Services should be commissioned to support highest quality clinical management. Commissioning should be based on evidence; should include measurable quality outcomes; and should promote service improvement and innovation. Leadership by clinical experts, and patient and public involvement, is key to successful commissioning and mechanisms must be in place to ensure appropriate engagement³
- NHS trusts will be required to provide a comprehensive data in support of patient activity to aid service commissioners in specialised commissioning teams (SCTs) and PCTs
- Collection and analysis of appropriate national and local data will help ensure services are accessible to all adults with SCD, regardless of area of residence, relevant to the needs of the local community
- SCD service design will build on existing capacity and infrastructures to maximise use of public resources and reflect local priorities and local needs
- Measures to address health inequalities need to be included in the design of culturally sensitive services, in order to reach those most at risk, and those who may experience difficulties in accessing services. This should include harnessing the experience of generic services which have successfully met the needs of a multi cultural society
- SCD services will be designed and resourced to provide integrated, high quality, holistic care across the whole of the patient journey through primary care, hospital

and community settings applying the principles recommended for chronic conditions

- The training needs of community physicians, nurses, social care and educational professionals should be considered in order to improve care in the community and specialist secondary care centres. The voluntary sector and community care centres should be supported to offer such training
- Explicit measures for engaging service users, the voluntary sector and the public in the design, implementation and monitoring of standards of care will be in place
- SCD services and service users will be best served via a collective specialist commissioning process
- Procurement of activity along the patient pathway in designated specialised centres and other service providers will be resourced under the Payment by Result (PbR) mechanism. In situations where other payment mechanism can procure cost effective high quality services, these mechanisms should be considered
- Access to necessary high cost interventions should be equitable across the UK

2.3 Recommendations for best practice

2.3.1 Overview: networks for care

The appropriate model offers care for the patient as close to home as possible, while allowing access to highly specialist health care when needed for expert assessment or management. Much care can be offered in the home or community setting. Community care should be provided by staff working closely with primary care and local authority. Clinical support from a hospital secondary care specialist should be available as necessary. Routine health checks and acute and ongoing clinical care for some less complex complications should be available in a local hospital setting; clinical management guidelines in local hospitals should be as agreed with, and overseen by, the specialist secondary care centre. However, for major, severe or complex presentations, care should be in a specialised secondary care clinical centre with the appropriately experienced professional team and facilities. All patients should be seen, as a minimum, soon after diagnosis (which is sometimes established for the first time in adults) for regular, usually annual, clinical overview; and at any other times as clinically indicated.

2.3.2 Primary and community care

Service users' understanding of their condition is central. They will continue in adulthood to be offered comprehensive education about it, and how best to minimise the risk of crises and other complications. All should be offered strategies to manage symptoms, including uncomplicated pain, at home and should be provided with a range of suitable analgesics. The benefits of independent self-management wherever possible will be emphasised. The EPP may prove useful for those with SCD (see section 2.3.2.2).

SCD service users and their families should also be clear about which symptoms can indicate serious complications and require them to seek urgent medical assessment, including significant fever, chest pain, breathing difficulties, dehydration, priapism, any unfamiliar pain or other unexpected symptom. People who have co-morbidities may struggle to have their needs met, and every effort must be made to co-ordinate care between different specialties to avoid omission or unnecessary duplication.

Some adults with SCD have little contact with their GP's and may miss general health screening, advice and the possibility of treatment at home in some circumstances in this way. The positive role of the GP and primary care team should be understood and emphasised. Primary health care professionals may play a key role in screening, disease management, patient follow up, and chronic pain management. At a minimum,

GPs need to be aware which of their patients have the condition; they need to work with hospitals in ensuring that all patients are offered an annual review in a specialist centre; they need to understand the infection risk and immunisation needs of patients and the signs and symptoms which require emergency hospital assessment. Prescriptions of antibiotics and/or analgesics and administration of immunisations can be undertaken in primary care; the hospital and primary care teams need to communicate clearly about this, to avoid duplication or omission.

2.3.2.1 Roles and responsibilities of the GP practice

All patients with SCD should be registered with a GP. Although many aspects of care of patients with SCD will be undertaken by specialist services, many patients will also attend GP practices for a variety of services. Therefore:

- GPs should have access to relevant patient records or summaries from the SCD specialist centre, to ensure any interventions or consultations are safe, appropriate and timely
- The primary care team can be responsible for documenting and providing repeat prescriptions for antibiotic prophylaxis, folic acid, and analgesia as well as medications for other co-morbidities. Patients should be reviewed in primary care at least annually to promote compliance and review therapy
- There should be clear communication between the GP and SCD specialist centre about the agreed regime of analgesia to be prescribed for the management of minor painful crises in the community
- GPs should be aware of signs and symptoms which require urgent hospital assessment. They should have access to the designated community or hospital team for training and advice where needed
- The primary care team should document and provide vaccination for the prevention of infection in patients with SCD, because of functional asplenia
- Patients with SCD should always be included in general health screening and advice provided by primary care services

2.3.2.2 The expert patient programme (EPP)

The EPP is a Government initiated, self-management course aimed towards giving people the confidence, skills and knowledge to manage their condition better and feel more in control of their lives. Courses run over 6, weekly, 2.5 hour sessions. The course enables service users to manage fatigue, sleep, pain, anger and depression; manage daily activities; develop their communication skills; interact with the healthcare system; find the health resources they need, and plan for the future. Courses can be specific to SCD or include many different chronic diseases including arthritis, diabetes and asthma, as many of the issues dealt with are common to all chronic disease. SCD specific courses are usually organised in an area with a high local prevalence. However, SCD specific courses are not necessarily the ideal; disease specific and disease generic courses have advantages and disadvantages which should be considered when choosing a course.

2.3.2.3 Multidisciplinary working

Care is best offered by a multidisciplinary team, working across sector and agency boundaries. Health and social care providers should work jointly towards optimising care of the patient at home. According to local provision, there may be specialist nurse counsellors, outreach nursing teams, or use of district nursing services working under specialist guidance. Other professionals such as occupational therapists, dieticians, and dentists should be involved in care as necessary.

Access to dedicated community services will vary between areas. In areas of high prevalence there are frequently SCaT community centres/services run by specialist

nurse counsellors, offering education, advice and support (see www.stacuk.org). All service users should be offered telephone contact with a SCaT centre for discussion and advice. Staff at SCaT centres should be prepared to offer guidance to colleagues in more local community services with whom the patient may have contact.

Appropriately trained nurses/outreach nursing teams may be in place to support the patient managing uncomplicated pain crises at home. This is recommended and much appreciated by service users and families; it is growing practice in some higher prevalence areas. Local arrangements may be made for training and supervision of some non-specialist district nurses to assess and advise service users at home.

Clear communication between community, primary, secondary and tertiary care must be maintained. Clear arrangements should be in place for shared care between primary care, the local hospital and the SCD specialist centre. These will depend on the disposition, size, and staffing levels of the various units, and need to be locally agreed and formalised. The method by which urgent contact can be made by the local hospital to the centre, in and out of normal working hours, should be established and well understood.

Service users must have a named key contact, to phone for advice when necessary. This may be a specialist nurse counsellor, a ward or day-unit based nurse, or a member of the medical team. A patient-held shared care record may be helpful to aid communication between the different providers (see appendix 5).

Family carers often provide key support, and their needs should be considered as well as that of dependents, who may need alternative care during times of illness or hospital admission. In addition, service users should be offered information about the most local Patient Group and national voluntary organisations, such as the Sickle Cell Society.

2.3.2.4 Roles and responsibilities of community services/SCaT centre

In areas where disease prevalence is high, community care centres staffed by specialist nurse counsellors and a variety of other health and social care providers have emerged. For each SCD specialist secondary care clinical centre there should be at least one such community care centre. Financial support for community care centres can be shared between PCTs and Local Authority (LA). All service users, and the wider community, should have access to the services provided from the SCaT centre, including:

- freely available screening and public information
- disease management counselling service
- genetic counselling services and facility for referral for prenatal diagnosis
- educational and health promotional service and materials
- housing and benefits advice
- psycho-social services advice
- facilities for service user/family support groups

Ideally, there should be a 'one-stop shop' available so that a service user can access services in a single visit.

It is usual for the larger SCaT centres to also offer:

- teaching sessions or courses to other health professionals and non-health professionals who work with clients with SCD or thalassaemia
- nurse-led clinics
- some day care pain management facilities^{4,5} and/or a service in which nurses can visit patients in pain at home in order to support self-management there

- integrated psycho-social and health care where a psychologist, social worker and health professional works as an integrated team in the assessment, care and support of patients
- systems to record and share information, and audit care outcomes

All SCaT centres should be working towards offering this broad range of services.

2.3.2.5 The role of social care

The role of social services in supporting people with SCD and their families is in many areas poorly developed, and such agencies may have little understanding about the impact of SCD on an individual or family. Multi-agency involvement has great potential particularly in supporting comprehensive care, and examples of good practice such as 'integrated working' do exist.

Social care and associated agencies should be encouraged to engage with people with SCD to assess social need, providing advice on training and career development, benefits; housing issues; family care advice, guidance and debt counselling and debt avoidance; and provision of occupational, social, cultural and recreational activities.

SCD adults with children can find child care problematic when they require hospital treatment. Even when parents have family support the unpredictability of SCD interrupts and can put a strain on family life. Social care should also assess the needs of carers (including child carers), providing services that support independent living and family cohesion.

2.3.2.6 Education services

Young people (and their parents) describe education services as particularly unresponsive to their needs. Few young people receive what they regard as helpful careers advice at school^{6,7}. Greater employment support and training opportunities for those with SCD should also inform any potential strategy. This could be part of a more general commitment to supporting those with chronic illness or disabilities.

2.3.2.7 Benefits advice

Many people with SCD are in full employment and require no benefit support. However, all should be fully aware of what benefits are available, and able to make informed choices about applying for benefits they may need and be entitled to. Individuals may be entitled to different benefits throughout their lifetime, depending on the severity of their condition and social circumstance.

Some benefits are means tested, so will only be given to individuals with a low income. Others, such as Disability Living Allowance, are available without means testing, but depend on making a clear case of mobility difficulties, extra care needs, or both. The information given in appendix 6 is not exhaustive and is subject to change; up to date information can be acquired via the Department of Work and Pensions website.

It is recommended that individuals regularly check appropriate websites and receive support from welfare rights officers, social workers, Citizens' Advice Bureau (CAB), support group representatives and Jobcentre Plus. Those with access to SCaT centres should be able to access specialist social services advice there. Those living in areas with more limited SCD support may need to contact CAB or try alternative routes to find the information they require.

Financial support for social care and welfare services to improve health outcomes, can be shared between LAs and PCTs.

2.3.2.8 Psychology services

Psychological interventions can also be very helpful for some people in managing their condition. Evidence on the efficacy of cognitive behavioural therapy for helping pain management,⁸ and reports on 'buddying' schemes^{9,10} are encouraging, suggesting such schemes should be considered as part of comprehensive care.

2.3.3 Hospital services: secondary care

Two broad categories of secondary care providers are proposed:

- Local hospitals, which provide services typically for a small to moderate number of SCD service users living locally. Patients would normally attend the local hospital for routine out-patient care and would first be admitted to these units if in-patient care was necessary. In-patient management of uncomplicated pain episodes and infection, for example, would usually be managed in the local unit. Service users on planned regular blood transfusions (e.g. for stroke) should be able to receive these locally
- SCD specialist centres, providing care for a large local population of service users affected by SCD, will have appropriate experience, staffing and facilities to offer comprehensive facilities to their own regular service users as well as for patients who attend networked local hospitals

2.3.3.1 Roles and responsibilities of local hospital unit

All hospitals that care for people with SCD will:

- Liaise with a SCD specialist centre or network regarding routine review, providing sufficient information about clinical events and investigation results to allow informed decision making
- Seek advice from a SCD specialist centre or network about management of complex or life-threatening presentations, arranging urgent transfer of the patient as necessary
- Have a named lead clinician, with deputy, responsible for the care of service users with SCD, leading a designated team which admits service users with SCD. This will usually be the clinical haematology team, but in places may be a nominated acute medical team. Even where there are a small number of service users, this will allow for increasing experience and expertise in management by the designated team
- Liaise with paediatric colleagues in transition of care arrangements leading up to the agreed transfer age (usually 16, sometimes up to 19)
- Keep readily available clinical policies for the management of common presentations, as provided/agreed with the SCD specialist centre
- Provide a clinic for routine out-patient care. Depending on patient numbers, this may be part of a more general clinic, but in every hospital all SCD service users should attend the same clinic, run by the designated lead clinician and multidisciplinary team
- Support and promote routine management and treatment of uncomplicated pain; at home where appropriate
- Offer day unit facilities for planned care such as blood transfusion. Out of hours facilities should be offered wherever possible
- Offer 24 hour access for emergency assessment and admission as necessary
- Manage acute pain, acute anaemia and simple infections, and provide initial care for other complications before transfer to a SCD specialist centre, according to guidelines or protocols shared across the managed care network

2.3.3.2 Roles and responsibilities of SCD specialist centre

SCD specialist centres will form the hub of each clinical network. It is expected that these will be designated by SCTs, with information provided on the specialised health

care management arrangements. High prevalence areas may have several specialist centres working together to provide comprehensive specialist services. These centres will act as reference centres for joint care and provide supervision for local hospital staff as necessary. They will provide the core services for treating people with SCD and, additionally will have facilities to treat more acutely ill and complex SCD patients, and those with advanced complications or co-morbidities. Criteria to define a specialist centre include the level and complexity of the work currently undertaken as well as the throughput of patients accessing its services. SCD specialist clinical centres will:

- Have a designated haematologist, with named deputy, with an interest in red cell disorders
- Have a multidisciplinary team including medical, nursing, and health psychology
- Support and promote management at home where appropriate
- Hold a designated haemoglobinopathy clinic
- Provide 24 hour access for emergency assessment and admission as necessary, under the care of the designated specialist team
- Promptly take over from local hospital units, by in-patient transfer, the care of service users with complicated episodes
- Provide high dependency and intensive care facilities for SCD service users
- Have Clinical Pathology Accreditation (CPA) approved laboratory facilities for accurate haemoglobinopathy diagnoses
- Develop shared care arrangements with local hospitals
- Have in place systems for recording and auditing aspects of service delivery and outcome, for example by use of a clinical database
- Offer specialist input to the care of service users with SCD across the whole network. This will include telephone advice to service users, GP's, or medical/nursing teams at the local hospitals as well as provision of specialist clinical reviews (suggested areas for consideration and investigations to be undertaken at review are given in appendix 7)
- Lead on advising service users and local teams regarding transfusion regimens, including offering exchange transfusion if not available locally, and guidance regarding iron chelation treatment for those receiving regular transfusion
- Lead on writing and establishing guidelines and protocols for the network, agreeing them with lead clinicians from the local hospitals
- Have in place a system of referral to designated social services, housing and benefits advice contacts
- Encourage a patient support group and liaison with existing local and national groups
- Work closely with SCTs and other relevant stakeholders to provide specialised healthcare management

2.4 Commissioning sickle cell services

Commissioning is the strategic activity of assessing needs, resources and current services, and developing a strategy to make best use of available resources to meet identified needs; it involves the determination of priorities, the purchasing of appropriate services and their evaluation. The process of commissioning is outlined in several policy documents^{11,12,13}.

The way in which these services are commissioned will be fundamental to the implementation and quality assurance of standards of care for SCD and thalassaemia. In order to provide equitable and accessible services for people with SCD, it is important that a national commissioning process is in place, and that service delivery is designed appropriately and in accordance with these standards. To commission services for SCD effectively it will be essential to apply current NHS policy drivers for chronic conditions, including:

- practice-based commissioning (PBC)
- payment by results (PBR)
- specialist commissioning
- relevant national service frameworks

2.4.1 Assessing needs and service provision

Often services are characterised by historical patterns of spending and may not have been updated by evidence from local needs assessments or epidemiology. It is important that commissioners of SCD services take active steps to review provision in order to manage increasing demand and the implementation of new technologies effectively.

National and local data must be gathered and utilised to design an appropriate portfolio of services that is generally accessible to all adults with SCD, regardless of area of residence. Work is in progress to develop a national registry of patients with SCD. There must be proper consultation with patients regarding this development as it is imperative that patients are kept informed and are involved in this initiative.

Services must build on existing capacity and infrastructures to maximise on public resources and reflect local priorities and local needs. Gaps and potential for improvements in existing services will be identified using local intelligence and needs assessment. This will include assessing the level, organisation and capacity of existing services. The following are suggested questions to be addressed in this process:

- What is the current service model?
- What services are already in place?
- How well does the current model address the needs of service users at primary care, community care, secondary care, local and specialist levels?
- Are health education and health promotion needs of the public, professionals and patients appropriately addressed?

2.4.2 Deciding priorities and designing sickle services

Strategic plans, based on local data and needs assessment, should be developed at Specialised Commissioning Group (SCG) level, through collaboration of the clinical network, the SCT, local PCTs and the voluntary sector. It is important that service users and the local community as well as local government are involved in the process. Explicit measures to address health inequalities are required in the design of SCD services. The adult SCD standards working group recommends this includes:

- Improved access, improved prevention and early intervention in primary care as central to reducing inequalities in health
- Preventing or minimising common barriers such as services which are intimidating or stigmatising or are difficult to access, inflexible service hours or appointment systems, a lack of interpreters
- Using data on health inequalities to plan services and allow appropriate comparisons to be made between different areas based on ethnicity, socio-economic group, gender, age, etc.

2.4.3 Expected service provision

Commissioners will establish strategies for care and resource utilisation to ensure that patients receive the most appropriate care in the right setting, and ensuring that use of healthcare resource is optimised. Tables 1-3 provide a guide to SCD services, as well as suggested staffing levels, which should be available at a SCD specialist centre, local hospital and in the community¹⁴.

Table 1: Required services

SPECIALIST CENTRES	LOCAL HOSPITAL	COMMUNITY
Services		
A&E	A&E	
Out-patients	Out-patients	Out-patients
Phlebotomy	Phlebotomy	Phlebotomy
In-patient beds supported by full range of specialist input	In-patient beds to manage common uncomplicated presentations	
Day unit (extended hours)	Day unit (extended hours)	Day assessment/day treatment area
Prescribing	Prescribing	Nurse prescribing
Pain management	Pain management	Home care pain service/support for pain management at home
Psychology service	Access to psychology service	Psychology service
Access to genetic counselling services	Access to genetic counselling services	Genetic counselling
Interpreting and advocacy services	Interpreting and advocacy services	Interpreting and advocacy services
Access to social work service	Access to social work service	Social work service
Stroke risk screening/transcranial Doppler		
Stroke care including initial emergency management, specialist diagnostics and initiating transfusion programme	Stroke care including ongoing transfusion and iron chelation	Stroke rehabilitation
Complex surgery	Low risk surgery – in liaison with specialist centre team	
Urological services		
Access to renal services (inc. dialysis and transplant)		
SCD orthopaedic services/surgery		
SCD obstetric care		
High dependency care and ITU		
Access to specialist liver service		
SCD respiratory services		
Pulmonary hypertension screening and access to tertiary centres		
SCD ophthalmology and retinopathy screening		
Erythrocytapheresis and/or facilities for manual red cell exchange		
Full range of diagnostic imaging	Diagnostic imaging including CT/MRI	
Appropriate CPA-accredited laboratory support (diagnostics and transfusion)	Appropriate CPA-accredited laboratory support (diagnostics and transfusion)	
Provision for comprehensive annual clinical reviews		

Table 2: Suggested staffing

SPECIALIST CENTRES	LOCAL HOSPITAL	COMMUNITY
Staff		
Lead haematologist with specialty interest leading multidisciplinary team and named deputy	Designated clinician leading team providing care for SCD service users and named deputy	
Middle-grade cover (SpR/staff grade) available including out of hours	Middle-grade cover (SpR/staff grade) available including out of hours	
Consultant haematologist on-call 24 hours, 7 days a week	Access to advice from consultant haematologist locally, or at Specialist Centre, 24 hours, 7 days a week	
Dedicated specialist nurse(s)	Named lead nurse (maybe as part of broader role)	Specialist nurse manager
		Specialist nurse(s)
Specialist medical teams (see above) with interest and experience in organ-specific sickle cell complications		
Physiotherapist	Physiotherapist	Physiotherapist
Occupational therapist	Occupational therapist	Occupational therapist
Admin and clerical staff to support range of services	Admin and clerical staff to support range of services	Admin and clerical staff to support range of services
Health psychologist with an interest in SCD		Health psychologist with an interest in SCD
		Home care case manager(s)
		Genetic counsellor(s)
		Social worker
		Welfare officer
		Case manager(s)
		Community nurse matron
		Outreach worker(s)

2.4.4 Ensuring high quality services

Commissioners should ensure that they only support services which are being provided to the levels described in the standards. A peer-review process will be established, building on the paediatric services programme. Information from the service review visits can be supplied to commissioners to inform their decisions.

2.4.5 Service user involvement

There must be explicit measures at provider and PCT level for engaging service users and the public, as well as the voluntary sector, in the design, implementation and monitoring of service provision. It is essential that structures for commissioning are established with voluntary sector involvement, ensuring a high level of service user engagement. Where successful, key outcomes of the commissioning process will be responsive to the expressed views and expectations of people with SCD¹⁵.

2.4.6 Specialised commissioning as a possible framework

The adult SCD standards working group recommends, based on the evidence provided in this report, that SCD services and service users are best served via a collective specialised commissioning process. An initial list of resource implications which relates to the standards put forward by this document is given in appendix 8.

Table 3: Additional requirements

SPECIALIST CENTRES	LOCAL HOSPITAL	COMMUNITY
Additional requirements		
Education of professionals	Education of professionals	Education of professionals
Research and audit	Research and audit	Research and audit
Drug funding	Drug funding	Drug funding
Patient information resources	Patient information resources	Patient information resources
Input into national SCD register	Input into national SCD register	Input into national SCD register
User involvement in service provision and development	User involvement in service provision and development	User involvement in service provision and development
		Drop in screening service
		Expert patient programme
		Patient education
		Public information
		Benefits advice
		Liaison with education/employment
		Support for affected individuals and families
		Facilitate/house patient support group

2.4.7 Resourcing community care services

The shift of services for long term conditions, including SCD, into the community has already progressed well in some areas, and this move is much appreciated by service users. It is essential that any transfer of hospital care to the community can be delivered at a high standard, and care in the home or community will need to attract an appropriate tariff. Unbundling of tariffs or new community tariffs for providing care closer to home are likely to be necessary. Innovative new models of community care interventions that have the potential to reduce reliance on secondary care should be given an appropriate level of support.

2.4.8 Resourcing secondary care services

In many areas there are already several centres providing all or most of the specialised care recommended. These centres should co-operate as a network or 'virtual' centre to provide a comprehensive service. In areas where no specialist centre exists at present resources will be needed to develop and support SCD specialist centres which can provide services for local hospitals.

It is essential that commissioners recognise that many district general hospitals with large local populations of SCD patients already provide specialist care, having haematologists with a special interest in haemoglobinopathies and holding specific haemoglobinopathy clinics. This document does not support the concentration of resources into a small number of super-specialist centres at the expense of these hospitals which are currently providing a high quality service to their local population. It is envisaged that any hospital currently providing high quality and comprehensive sickle services will be able to continue to do so, and they will be supported via the commissioning process.

* The funding for current and new drugs is best managed through specialised commissioning to avoid inconsistencies in treatment. Mechanisms must be put in place to alert commissioners to new therapies that require funding.

2.4.9 Other issues

Issues which need systematic consideration in commissioning, developing and refining services include the following¹⁶:

- Some hospital services will need relatively minor adaptation to fit the proposed model, but extra resource will inevitably be required in some hospitals which have not been working to the standards required, or which will take on considerable extra work in supporting an established network. Community centres are scarce and in many areas this aspect of the network is likely to require particular focus. Resources will be required to modernise existing community centres or to set up new sites in the community to deliver community care services. Service users in acute painful crises who prefer to have crises treated in the community, with very few exceptions, cannot do so as this service is under developed
- Many established SCaT centres/services can achieve seamless care by working across organisational boundaries, working closely with local authority and secondary care providers to improve access and provide 'one-stop shop' services for vulnerable patients
- Consideration needs to be given to streamlining job titles. There are a plethora of different terms used by SCD community care staff with a wide variation of roles and responsibilities. Some patients find this confusing, and often do not know if they are seeing the right person
- Several services have a good balance of multidisciplinary professionals, but there is no staffing and caseload weighting consistency across community care organisations
- There is a high level of convergence of medical opinion and collaboration leading to the development of treatment protocols/guidelines (national/international). Community care centres/services have historically developed 'centre' protocols, instead of national community care protocols, endorsed by all centres

2.4.10 Outreach work for people in need

The voluntary sector has significant expertise reaching groups of people who have not traditionally accessed health services. The Sickle Cell Society has an outreach programme supported by over 200 active volunteers. The volunteers are made up primarily from ordinary people from the community. As well as being more cost effective than deploying NHS staff, volunteers may be better received by some 'hard to reach' clients and this is a useful partnership that should be included in commissioning plans.

References

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- ¹ Department of Health. National Service Framework for Long-Term Conditions. 2005.
 - ² NHS Antenatal and Newborn Screening Programmes. Sickle Cell Disease in Childhood: standards and guidelines for clinical care. 2006.
 - ³ Department of Health. World Class Commissioning: Vision Summary. 2007, Dec; NHS.
 - ⁴ Ware MA, Hambleton I, Ochaya I, et al. Day-care management of sickle cell painful crisis in Jamaica: a model applicable elsewhere? *Brit J Haematol.* 1999; 104(1): 93-96.
 - ⁵ Wright J, Bareford D, Wright C, et al. Day case management of sickle pain: 3 years experience in a UK sickle cell unit. *Brit J Haematol.* 2004; 126(6): 878-880.
 - ⁶ Anionwu E, Atkin A. *The Politics of Sickle Cell and Thalassaemia.* 2001; Buckingham, Open University Press.
 - ⁷ Dyson SM, Atkin K, Culley LA et al. The educational experience of young people with sickle cell disease. *Disability and Society.* 2007; 22(6): 581-594.
 - ⁸ Anie KA. *Psychological therapies for sickle cell disease and pain.* Cochrane Review. 2004; The Cochrane Library, Issue 3. Chichester, UK: John Wiley & Sons, Ltd.

⁹ Chernoff RG, Ireys HT, et al. A randomized, controlled trial of a community-based support program for families of children with chronic illness: paediatric outcomes. *Archives of Paediatrics & Adolescent Medicine*. 2002; 156(6): 533-539.

¹⁰ Atkin K, Rodney A, Cheater F, et al. Providing Support for People with SCD and Thalassaemia Disorders and their Families: A Review of the Evidence and Guidance for Good Practice. Report submitted to the Department of Health Policy Research Programme. 2006.

¹¹ Department of Health. Commissioning a Patient-led NHS. 2005; NHS.

¹² Department of Health. Health reform in England: update and commissioning framework. Annex: the commissioning framework. 2006; NHS.

¹³ Department of Health. Our health, our care, our say: a new direction for community services. Government White Paper. 2006; NHS.

¹⁴ Sickle Cell Society. The Regional Support Care Project: an independent evaluation through health and well-being impact assessment. Sickle Cell Society. 2007.

¹⁵ Sickle Cell Society. Report on a doctors-patient engagement workshop on managing pain in SCD. 2005.

¹⁶ Bennett L, Nkohkwo A. An improved future for people with sickle cell disease in England: addressing inequalities in access to community services. Sickle Cell Society. 2006.

Managing Acute Complications

3.1 Introduction

The majority of acute presentations by patients with sickle cell disease (SCD) are due to painful crises. Other acute complications are less common but important as the mortality and morbidity associated with them is high. Early recognition and treatment is essential in their management. This document does not replace local management guidelines, which should be available in every hospital, but highlights core standards of care and suggests which points should be covered in local guidance.

3.2 Core standards

i) Acute painful crisis

- The first dose of an appropriately potent analgesic must be administered within 30 minutes of presentation to a clinical area and should include time spent in triage
- The on call haematologist should be notified of the patient's arrival
- Regular and continuous assessment of pain during an acute episode must be recorded using a standard pain assessment tool for adults. Pain relief from the type of analgesia administered must also be assessed at regular intervals along with vital signs
- Discharge letters should be sent to GP within 10 working days from discharge
- Sufficient analgesia must be provided on discharge. Readmissions within 48 hours of discharge should be audited and a report generated at least annually

ii) Management of the febrile patient

- All patients with a temperature of $>38^{\circ}\text{C}$ should be rapidly investigated in an acute facility and empirical antibiotics started immediately after initial culture samples have been taken
- Chest X-ray, blood and other relevant cultures should be mandatory in patients with temperature of $>38^{\circ}\text{C}$. There should be access to microbiology advice to aid management
- Antibiotic treatment should depend on site of suspected infection and local antibiotic policy

iii) Acute chest syndrome (ACS)

- All patients, carers, medical and nursing staff should be aware of the symptoms of ACS
- Each hospital should have a protocol in place for the management of ACS including the use of transfusion therapy
- Patients with ≥ 2 episodes of ACS within the previous 2 years should be offered hydroxycarbamide (hydroxyurea) therapy

iv) Acute abdomen

- Blood cultures, serum amylase, imaging studies such as abdominal ultrasound scans, abdominal X-ray and where appropriate CT (computer tomography) scans should be performed in patients who present with an acute abdomen
- Sickle cell related causes of acute abdominal pain should in most cases be managed conservatively. The surgical team should be involved early in the management of these patients
- Local policies to include antibiotic cover and indications for endoscopy should be developed in collaboration with gastroenterologists and microbiologists for the management of patients with gallstone related complications

- Symptomatic gallstones should be treated with laparoscopic cholecystectomy because of the shorter hospital stay and fewer immediate surgical complications
- v) Acute anaemia**
- Any patient presenting acutely unwell should have a full blood count and reticulocyte count performed; patients with anaemia and reticulocytopenia should have blood sent for parvovirus serology
 - Clinical examination of a patient presenting with acute anaemia should include an assessment of spleen and liver size
 - Top-up transfusion may be necessary, especially if the anaemia is accompanied by reticulocytopenia. The threshold level for transfusion will depend on the clinical state of the patient
- vi) Acute neurological symptoms**
- Specific guidelines for the management of acute stroke in SCD should be prepared by the SCD specialist centre for the local units, and this should include how and where urgent exchange transfusion is performed
 - Each SCD specialist centre should have access to a designated neurologist who can assess and advise on acute neurological complications (although management should not be delayed until such review); access to a neurosurgical unit for managing patients with cerebral and subarachnoid haemorrhage and intracranial hypertension; and access to neuro-imaging facilities including CT, MRI (magnetic resonance imaging)/MRA (magnetic resonance angiography) and EEG (electroencephalography)
- vii) Suspected acute osteomyelitis**
- The clinician should have a high clinical suspicion for osteomyelitis and blood cultures should be taken early, before antibiotics are started
 - Ultrasound, radioisotope scans and MRIs may be useful diagnostically in expert hands
 - Treatment should be with a prolonged course of appropriate antibiotics
- viii) Acute renal disease**
- Local protocols should be agreed with the renal team for the management of acute renal failure in SCD
- ix) Acute priapism**
- A network policy on management of acute priapism should be agreed between haematology and urology services and the SCD specialist centre (this policy may need to be adapted at local level)
 - Early presentation (<4 hours) is vital to a successful outcome in management of acute attacks. This information should be reinforced continually during clinical visits at least annually

3.3 Recommendations for best practice

3.3.1 Management of painful crisis

A painful crisis is the commonest cause of presentation to hospital for adult patients with homozygous SCD. It accounts for 90% of all hospital episodes.

3.3.1.1 Choice and level of analgesia

Pain severity should be managed according to World Health Organisation (WHO) step ladder of non opioid and opioid analgesia. Patients with moderate pain should be managed with a combination of non-steroidal anti-inflammatory drugs (NSAIDs) unless contraindicated and weak opioids. Patients with severe pain should always be offered opioid analgesia. The efficacy of analgesia should be monitored using a pain score.

Patients who are “opioid naïve” should be offered morphine, diamorphine or equivalent opioid analgesic. Preferences to particular analgesic should be based on history of successful previous exposure, patient’s choice and absence of absolute contraindication(s) or adverse events¹. Pethidine is no longer the analgesic of choice in SCD and should only be used in exceptional circumstances.

The first dose of an appropriately potent analgesic must be administered within 30 minutes¹ of presentation to a clinical area and should include time spent in triage. Regular and continuous assessment of pain and pain relief during an acute episode must be assessed at regular intervals along with vital signs and recorded using a standard pain assessment tool for adults.

Protocols should be in place for the management of complications of opioid treatment such as respiratory depression. Patient information leaflets on the analgesic agents used should be made available when possible.

Use of non pharmacologic and psychological methods of pain management should be encouraged. These methods should be evaluated in a systematic manner to determine their individual benefits.

Hydroxycarbamide has no role in the management of an established acute painful episode.

3.3.1.2 Management protocols

There should be agreed and easily accessible management protocols (available in electronic and paper format if possible) in clinical areas such as the emergency room, day hospitals, and ward areas. If the treatment occurs in a local hospital, the protocol should be agreed with the regional SCD specialist centre/network. Management protocols when individualised should have the input of the patient during “steady state”, as well as that of haematologists and nurse clinicians in charge of the patient’s care, pain control specialists and anaesthetists. This should include preferred analgesics, dosages, route of administration and warning signs of onset of adverse events.

Patients should be instructed about how to access care in the event of an acute painful crises. This may involve local arrangements with ambulance services as to preferred hospital(s) and should include relevant telephone numbers of the designated ward/key personnel in case of need for urgent contact.

3.3.1.3 Management setting

A day care setting should be considered as an alternative to A&E as this has advantages such as individualised patient care and reduced bed occupancy within the hospital. However, if patients access day care treatment repeatedly over a few days, transfer to an in-patient bed should be considered.

Staff involved in management of acute painful crises must be competent in assessing adequacy of pain relief, and recognition and management of side effects (e.g. respiratory depression, nausea, skin itching).

3.3.2 Management of febrile patient

Uncomplicated painful crises are frequently associated with low grade pyrexia $<38^{\circ}\text{C}$ and this is not necessarily indicative of infection unless infection is suspected for other reasons². Such patients need not receive broad spectrum antibiotics, although routine penicillin V (or alternative if penicillin allergic) should be continued.

SCD is associated with an ill defined immune defect in part as a consequence of hyposplenism. Life threatening infections are more common in this population and patients with a temperature $>38^{\circ}\text{C}$ should be rapidly evaluated with clinical examination, blood count, blood/urine/other cultures as indicated by clinical features, and chest X-ray. Empirical antibiotics should be started promptly, pending results of investigations (C).

During assessment of the febrile patient special consideration needs to be given to the more common causes of high fever in SCD³:

- Pneumococcal sepsis
- Gram negative sepsis
- Lower respiratory tract infection
- Urinary tract infections
- Osteomyelitis

Local antibiotic policies should be developed for the management of infections in SCD.

3.3.2.1 Prevention of infection in patients with functional hyposplenism

SCD in all its forms is associated with functional hyposplenism. This is also the case in those patients with compound conditions such as HbS beta thalassaemia. Patients with SCD must be reminded of their increased risk of serious infection, and of measures which may reduce their susceptibility.

There is some debate over use of oral antibiotics and some patients will prefer to choose whether or not to take these as a prophylactic measure. A prophylactic penicillin dose of 250mg bd orally can be used. For penicillin allergic patients, erythromycin, 500mg bd orally, is recommended.

Patients with a temperature of $>38^{\circ}\text{C}$ and/or symptoms of infection should be advised to come to hospital or to seek urgent medical attention as soon as possible.

3.3.2.2 Recommended vaccinations

Current recommendations may need to be reviewed in the light of new vaccines/advice from the Department of Health:

- Pneumococcal C vaccine: adults and children >2 yrs should receive the unconjugated vaccine (Pneumovax II)⁴. Vaccination should be repeated every 5 years
- Conjugated Meningococcal C vaccine: a single dose should be given if not already received as part of primary child immunisation schedule
- People travelling to areas of high risk for meningitis should receive meningococcal ACWY vaccine
- Haemophilus influenzae type b vaccine: a single dose should be given if not already received as part of child immunisation schedule
- An annual influenza vaccination is recommended

3.3.2.3 Malaria chemoprophylaxis

Patients travelling to endemic malaria areas should receive full prophylaxis according to current recommendations for that country.

3.3.2.4 Prevention of blood borne viral infection

All patients should be offered vaccination against hepatitis B. Adults and children should receive Hepatitis B vaccination (3 injections at month 0, 1 and 6). Anti-Hepatitis B surface anti-body levels should be tested 1 month after completion of the vaccination course; a second full course should be offered if the response is poor. Revaccination should be offered 5 years later.

3.3.3 Acute chest syndrome (ACS)

ACS in SCD is a common form of acute lung injury that may lead to acute respiratory distress syndrome and death. Half of all SCD patients will experience at least one episode of ACS during their lives and it is a leading cause of death⁵. It is characterised by respiratory symptoms such as tachypnoea, chest pain, cough or shortness of breath, generally with fever, in the presence of a new infiltrate on chest X-ray. It must be noted that chest X-ray changes often lag behind clinical signs. Such clinical signs or symptoms of chest consolidation in conjunction with worsening hypoxia are sufficient to make a diagnosis of ACS and to require intervention. ACS may be a presenting feature or may develop after a few days of vaso-occlusive crisis and it can be rapidly progressive. The key to successful management of ACS is awareness, anticipation of its development, particularly in high-risk patients, and timely intervention with specific treatments such as oxygen and blood transfusion.

3.3.3.1 Education and out-patient care

All patients and their carers should be taught about ACS and symptoms such as chest pain and shortness of breath which require urgent medical assessment. Medical and nursing staff in the haematology, accident and emergency and acute medical teams should be educated to recognise and manage ACS.

Patients should have steady state oxygen saturations (SaO₂) levels recorded in their notes when they attend clinic.

Hydroxycarbamide has been shown to reduce the frequency of ACS in patients with severe SCD and should be offered to patients with ≥2 episodes of ACS⁶ (A).

3.3.3.2 Early recognition and prevention of ACS

All patients admitted to hospital should be assessed for symptoms and signs of ACS and chest X-ray performed if any of following are present:

- chest pain
- respiratory symptoms
- reduced oxygen saturations (SaO₂) on room air

All patients should be monitored for the development of ACS using regular pulse oximetry measurements and observation of pulse and respiratory rate throughout their hospital admission, in particular if they are on parenteral opiates. SaO₂ measurements should be taken while breathing room air, 6 hourly as long as they are normal; increasing to 1-2 hourly if there is a suspicion of falling levels. If there is suspicion of ACS it is advisable to plan ahead and have blood available for exchange transfusion, even if it is not subsequently used.

Patients undergoing surgery should be evaluated peri-operatively for the risk of ACS which should take into account their previous history and the type of surgery and an individual management plan made which may include blood transfusion therapy.

3.3.3.3 Treatment of ACS

Local protocols for painful crisis should include the features suggestive of ACS with appropriate action to be taken. This protocol should be available in A&E and in paper and electronic formats if possible.

A protocol should be in place for the management of ACS which should include:

- Diagnosis
- Analgesia
- Arterial blood gas measurements
- Nursing observations
- Oxygen and respiratory support
- Incentive spirometry (IS). Randomised clinical trial data have shown IS can prevent the pulmonary complications (atelectasis and infiltrates) associated with ACS in patients with SCD who are hospitalized with chest or back pain above the diaphragm¹⁸ (A).
- Fluid management – this should be done cautiously to avoid excessive hydration and pulmonary oedema
- Bronchodilator therapy should be prescribed for all patients with evidence of wheeze or reversible airways disease, or a history of asthma⁷
- Antibiotics – this should include a macrolide antibiotic or equivalent to cover atypical organisms⁵
- Indications for blood transfusion. Transfusion therapy should be considered at the first signs of hypoxaemia (~5% lower than the patient's steady state level) as acute respiratory failure can intervene rapidly, and exchange transfusion can result in rapid improvement. Initial top-up transfusion should be used for patients with severe anaemia or a significant drop in steady state haemoglobin level. There should be a 24 hour facility for emergency exchange blood transfusion in all hospitals following guidance from the specialist centre
- Indications for transfer to High Dependency Unit (HDU) or Intensive Therapy Units (ITU)

Any patient who is suspected of having ACS should be discussed with a senior haematologist as a matter of urgency and blood transfusion therapy should not be given without haematology input. If the patient is being managed in a local unit setting, the patient should be discussed with the haematology team at the SCD specialist centre.

3.3.4 Acute abdomen

Abdominal pain is a common finding in SCD. Any surgical pathology may occur in SCD, but some conditions that occur more commonly in SCD (listed below) should be considered first:

- Vaso-occlusion
- Constipation
- Cholelithiasis
- Cholangitis
- Mesenteric/colonic ischaemia
- Pulmonary causes (infarction or pneumonia)
- Hepatic infarction/abscess/sequestration
- Intra-abdominal abscess
- Splenic infarction
- Renal or hepatic vein thrombosis

3.3.4.1 Gall-bladder disease

Gallstones are common in SCD; present in up to 30% of children and 70% of adults.

Biliary sludge is a complex mixture of mucus, bilirubin metabolites and cholesterol and may be a precursor to gallstone formation. Gallstones incidentally found during routine abdominal ultrasound do not need intervention in asymptomatic individuals. Complications from gall stones, such as acute cholecystitis, ascending cholangitis, gall-bladder empyema, and acute pancreatitis, may present as an acute abdomen. Pain may be in the right upper quadrant or in the central abdomen, and may be accompanied by fever, rigors, vomiting and worsening jaundice. The management of acute cholecystitis, ascending cholangitis and gall bladder empyema is not different from the general population and consists of broad spectrum antibiotics which should include cover for salmonella species and anaerobic organisms. Elective cholecystectomy, after acute cholecystitis or cholangitis settles, is appropriate. In some instances endoscopy and/or surgery may be required on a more urgent basis. When gallstones are symptomatic and require surgical intervention, cholecystectomy should be done via the laparoscopic route as this is associated with fewer postoperative complications and a shorter stay in hospital⁸ (B).

3.3.4.2 Other abdominal complications

Vaso-occlusion in the mesenteric circulation, often in association with bone pain, can present as abdominal pain with distended loops of bowel on X-ray. The management is supportive.

3.3.5 Acute anaemia

There is a variable degree of anaemia in SCD due to ongoing intravascular and extravascular haemolysis. In the steady state, individuals with SCD are usually able to tolerate this anaemia well. A rapid, significant fall in haemoglobin, usually of at least 2g/dl, may result in the individual becoming symptomatic of anaemia and major reductions may lead to cardiovascular compromise. Acute anaemia in SCD may be due to an increase in haemolysis, bone marrow suppression in particular of erythropoiesis, blood loss as well as sequestration in the spleen and less commonly in the liver.

3.3.5.1 Transient red cell aplasia

Transient red cell aplasia is the result of an arrest in erythropoietic maturation leading to reticulocytopenia and a fall in haemoglobin which can be severe. Transient red cell aplasia in SCD is most commonly due to human parvovirus B19 infection. Associated symptoms may include fever, headache, myalgia, arthralgia, respiratory and gastrointestinal symptoms⁹. Parvovirus B19 infection is usually self-limiting, with the cessation of red cell production lasting on average 4-8 days. Diagnosis is confirmed by the presence of IgM to parvovirus B19 or the presence of parvovirus DNA. Immunity conferred following infection is considered to be life-long.

Blood transfusion is indicated for severe anaemia (see also 6.3.1), particularly for patients who are symptomatic or show signs of imminent or established cardiovascular compromise.

Non-immune close contacts of these patients, often siblings who have SCD, may develop red cell aplasia and should be monitored. In hospital, isolation facilities should be utilised particularly as a precaution for pregnant staff, as infection may result in hydrops fetalis, fetal death or congenital anaemia.

3.3.5.2 Acute splenic and hepatic sequestration

Acute splenic and hepatic sequestration are not common complications in adults with SCD. Acute splenic sequestration occurs when large numbers of red cells are trapped in the spleen resulting in splenomegaly and profound anaemia that develops rapidly, usually within hours. Hypovolaemia and shock may result. Though more common in

children, it is occasionally seen in adults in whom autoinfarction has not occurred, more commonly in HbSC disease. In contrast to transient red cell aplasia, reticulocytosis is seen. Fluid resuscitation is usually required urgently to prevent or treat hypovolemia and often is life saving (see also 6.3.1). Red cell transfusion can follow and should be managed cautiously. It is important to transfuse initially in steps, pausing for fluid equilibration, and eventually only to the patient's baseline haemoglobin as the sequestered red cells gradually return to circulation; over zealous transfusion may result in hypervolaemic shock, or hyperviscosity from too high a haemoglobin level.

Similarly large numbers of red cells can be pooled within the liver resulting in acute hepatic sequestration. Hepatic sequestration is less common than splenic sequestration and presents with abdominal distension, right hypochondrial pain accompanied by acute tender hepatomegaly, a fall in haemoglobin in the absence of blood loss, reticulocytosis, a rise in bilirubin (predominantly conjugated) and mild increase in liver transaminases and alkaline phosphatase. Circulatory collapse is less frequent and sudden than with splenic sequestration. Top-up transfusion and broad spectrum antibiotics may be indicated as there can be an association with infection, in particular salmonella.

3.3.5.3 Other conditions causing acute anaemia

Increased haemolysis can result in a mild increase in anaemia in SCD; this fall in haemoglobin can be more marked in the context of infection, particularly malaria. Delayed haemolytic transfusion reactions can also result in anaemia.

G6PD (glucose-6-phosphate dehydrogenase) deficiency is not uncommon in these patients. Haemolysis may be exacerbated following the use of drugs known to precipitate haemolysis in this inherited red cell enzyme deficiency.

3.3.6 Acute neurological symptoms

Acute stroke is relatively common in SCD, with a prevalence of >5%, and can be ischaemic or haemorrhagic in origin. Acute haemorrhagic strokes are most common between 20-29 years and ischaemic strokes, whilst being most common in children, also have an increasing incidence with increasing age >30 years¹⁰. Patients with prior infarction are at increased risk of haemorrhage as they age¹¹. Intracranial haemorrhage in older patients is commonly related to ruptured aneurysms, typically located at the bifurcations of major vessels, particularly in the vertebrobasilar circulation¹². Subarachnoid and intracerebral haemorrhage occur in the context of acute hypertension and may be associated with corticosteroid use, recent transfusion or bone marrow transplantation. Intraparenchymal bleeding may be associated with large-vessel vasculopathy, especially if moyamoya formation is present. Venous sinus thrombosis and reversible posterior leukoencephalopathy may also be associated with cerebral haemorrhage.

Other neurological complications include behavioural change, seizures, loss of consciousness and migraine and the causes of these are often not clear.

3.3.6.1 Imaging in acute stroke

Acute neurological symptoms such as hemiparesis or aphasia require urgent imaging with CT and/or MRI scan to confirm diagnosis and exclude an intracranial haemorrhage. A normal early CT scan will exclude haemorrhage but not ischaemia, as ischaemic changes may take some time to develop. In this situation MRI scans should be performed, but if this is delayed, and stroke is considered as the likely diagnosis, exchange transfusion should proceed in the meantime. MRA scans should be performed, especially in cases of haemorrhage and will detect large aneurysms and vascular malformations. MRI and MRA may not be adequate to exclude an aneurysm

and conventional contrast angiography may be required. However, there is some concern that certain contrast agents may facilitate sickling and this investigation should be undertaken after consultation with a multidisciplinary team, including an experienced neuroradiologist and a haematologist with an interest in haemoglobinopathies. Conventional contrast cerebral angiography has been performed safely in SCD patients following exchange transfusion to reduce HbS levels to <30%. Magnetic resonance venography (MRV) is indicated when cerebral venous sinus thrombosis is suspected.

3.3.6.2 Clinical management of acute stroke

Patients presenting with clinical evidence of stroke should be clinically stabilised and given careful hydration. Urgent red cell transfusion should be used to correct anaemia and improve tissue perfusion and oxygenation, and to limit tissue damage (C). This may be an initial top-up transfusion (if Hb is ~5-6g/dl) or exchange transfusion if Hb is ≥6g/dl. Urgent exchange transfusion is preferred as it is associated with a lower risk of subsequent stroke compared to top-up transfusion. It is important to avoid hypovolaemia during the procedure and to keep the post-transfusion haemoglobin level <12g/dl. There is no evidence for the role of thrombolysis in patients with SCD and this is not currently recommended.

Haemorrhagic stroke should be treated with liaison with the local neurosurgical centre. Urgent haematology and neurosurgery input should be obtained in view of the wide differential diagnosis and early mortality. There is no known contra-indication to management of haemorrhage as for non-sickle stroke, with general support including intensive care, and evacuation of space-occupying clot. Bleeding aneurysms in patients with SCD have successfully been treated with craniotomy and clipping. Some centres have used embolisation and interventional radiology with coils¹³. There may be a role for exchange transfusion and this is usually performed, although its benefit is not clear. Some cases of moyamoya may be amenable to surgical treatment.

Anticoagulation or thrombolysis may be considered for venous sinus thrombosis which fails to respond to general measures such as rehydration and treatment of infection as treatment appears to reduce mortality in the general adult population¹⁴.

3.3.7 Suspected osteomyelitis

Osteomyelitis occurs in patients with SCD at all ages and in all genotypes and is most commonly caused by salmonella species, staphylococcus aureus and gram negative enteric bacteria. It can be difficult to differentiate between a painful crisis and osteomyelitis as both present with local tenderness, warmth, swelling, fever and a raised white cell count¹⁵. The finding of positive cultures from blood or bone aspiration or biopsy is the most useful diagnostic investigation, however caution should be taken in over zealous bone aspiration as this may introduce infection. It should be remembered that bone pain is 50 times more likely to be due to vaso-occlusion than osteomyelitis, so it is often prudent to treat vaso-occlusion and only investigate for osteomyelitis if pain or fever is persistent.

3.3.7.1 Imaging in suspected osteomyelitis

Plain X-rays show no specific changes in early osteomyelitis, although may show lucent areas later. Ultrasound can be helpful and although the finding of increased subperiosteal fluid is also seen with painful crisis, fluid depths of more than 4mm are highly associated with osteomyelitis¹⁶. Routine bone scans and radiolabelled leucocyte scans will not discriminate between infarction and infection. MRI scans do not differentiate between infection and infarction showing reactive marrow oedema and hyperaemia in both, but gadolinium enhancement may aid diagnosis. MRI is most useful for localising lesions and monitoring response to antibiotic treatment.

3.3.7.2 Treatment of suspected osteomyelitis

If there is a high clinical suspicion whilst awaiting culture results, antibiotic treatment to cover salmonella and staphylococcus should be used. Once culture and sensitivity results are known, antibiotics can be discontinued or changed appropriately. Treatment should continue for 6 weeks. Accumulation of fluid which does not respond to antibiotics should be treated with drainage.

3.3.8 Acute renal disease

There are many structural and functional defects along the nephron in SCD. The hypoxic, hypertonic and acidotic environment of the renal medulla promotes sickling of erythrocytes which leads to vaso-occlusion, ischaemia, infarction and papillary necrosis. Clinically this manifests as hyposthenuria (inability to concentrate urine), which makes patients more susceptible to dehydration (see also 4.3.5.1). Acute renal failure can be precipitated by dehydration, sepsis, drugs or in the context of multi-organ failure and may develop on the background of chronic renal failure.

3.3.9 Acute Priapism

Priapism in SCD can precipitate painful crises and lead to erectile dysfunction in the longer term. Two types exist: a “stuttering” self limiting episode (see 6.3.6.1) and an “acute” attack which requires hospital intervention. A cluster of stuttering attacks may be a warning for a major acute event. Early presentation (<4hrs) is vital and health education is paramount in reinforcing this information.

3.3.9.1 Managing an acute attack

On hospital presentation, intracorporeal diagnostic blood sampling or duplex ultrasonography/MRI may be utilised as long as it does not lead to a delay in therapeutic intervention.

Intracorporeal aspiration of blood with penile irrigation with a selective α 1 adrenergic agonist, such as phenylephrine or etilefrine every 5-10 minutes, can abort an attack and preserve potency for as long as 40 months¹⁷. This can be repeated several times per episode or on subsequent presentations without long term consequences (B). A local policy at the emergency facility incorporating a “rapid access” urological consult with haematological services should be put in place for such a procedure and backup arrangements for red cell exchange transfusion should this fail. The response to exchange transfusion is variable.

Patients should be discharged with an α adrenergic agonist for prophylaxis against further attacks. Patients should be reviewed soon after discharge to ensure that prophylaxis is effective.

3.3.9.2 Operative intervention for an acute attack

Operative intervention in the form of shunts, of varying complexity can be considered if the above modes of treatment fail. However these procedures are almost always associated with erectile dysfunction (ED).

References

- ¹ Rees DC, Olujohungbe AD, Parker NE, et al. Guidelines for the management of the acute painful crisis in SCD. *B J Haem.* 2003; 120(5): 744-752.
- ² Serjeant GR, Ceular CD, Lethbridge R, et al. The painful crisis of homozygous SCD: clinical features. *Brit J Haem.* 1994; 87: 586-91.
- ³ Weirenga KJJ, Hambleton IR, Wilson RM, et al. Significance of fever in Jamaican patients with homozygous SCD. *Arch Dis Child.* 2001; 84: 156-9.
- ⁴ Davies EG, Riddington C, Lottenberg R, Dower N. *Cochrane Database Syst Rev* 2004;(1):CD003885.
- ⁵ Vichinsky EP, Neumayr LD, Earles AN et al. Causes and outcomes of the acute chest syndrome in SCD. *N Eng J Med.* 2000; 342:1855-65.

- ⁶ Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anaemia. *N Eng J Med*. 1995; 332(20): 1317-1322.
- ⁷ Knight-Madden JM, Hambleton IR. Inhaled bronchodilators for acute chest syndrome in people with SCD. *The Cochrane Database of Systematic Reviews*. 2003; Issue 3. Art No. CD 003733. DOI: 10.1002/14651858.
- ⁸ Lujan JA, Parrilla P, Robles R, et al. Laparoscopic cholecystectomy vs open cholecystectomy in the treatment of acute cholecystitis: a prospective study. *Arch Surg*. 1998 Feb;133(2):173-5
- ⁹ Smith-Whitley K, Zhao H, Hodinka RL, et al. Epidemiology of human parvovirus B19 in children with sickle cell disease. *Blood*. 2004 Jan 15;103(2):422-7.
- ¹⁰ Ohene-Frempong K, Weiner SJ, Sleeper LA, et al. Cerebrovascular accidents in SCD: rates and risk factors. *Blood*. 1998; 91: 288-94.
- ¹¹ Powars D, Wilson B, Imbus C, et al. The natural history of stroke in sickle cell disease. *Am J Med* 1978; 65: 461-471.
- ¹² Preul MC, Cendes F, Just N, et al. Intracranial aneurysms and sickle cell anemia: multiplicity and propensity for the vertebrobasilar territory. *Neurosurgery*. 1998; 42: 971-977.
- ¹³ McQuaker IG, Jaspan T, McConachie NS, et al. Coil embolization of cerebral aneurysms in patients with sickling disorders. *Br J Haematol*. 1999; 106: 388-390.
- ¹⁴ Stam J, de Bruijn S, deVeber G. Anticoagulation for cerebral sinus thrombosis. *Stroke*. 2003; 34(4):1054-5
- ¹⁵ Almeida A, Roberts I. Bone involvement in SCD. *Brit J Haem*. 2005; 129: 482-490.
- ¹⁶ Williams RR, Hussein SS, Jeans WD, et al. A prospective study of soft-tissue ultrasonography in SCD with suspected osteomyelitis. *Clin. Radiol*. 2000; 55(4): 255-62
- ¹⁷ Mantadakis E, Ewalt DH, Cavender JD, et al. Out-patient penile aspiration and epinephrine irrigation for young patients with sickle cell anaemia and prolonged priapism. *Blood*. 2000; 95(1): 78-82.
- ¹⁸ Bellet PS, Kalinyak KA, Shukla R, et al. Incentive Spirometry to Prevent Acute Pulmonary Complications in Sickle Cell Diseases. *N Eng J Med*. 1995; 333(11): 699-703.

Managing Chronic Complications

4.1 Introduction

As the survival of patients with SCD continues to improve, the management of chronic complications (table 4) will present a challenge to the medical profession to optimise medical care so that patients can lead a productive life. Managing these chronic complications requires a multidisciplinary approach involving the hospital, primary care teams and community services (see chapter 2). Every effort should be made to manage these complications within the community.

Table 4: Chronic complications of SCD

Organ system	Description
Musculoskeletal	Chronic sickle pain Avascular necrosis (AVN) of the long bones
Genitourinary	Haematuria, priapism, erectile dysfunction
Skin and integuments	Chronic leg ulcers
Ophthalmology	Sickle eye disease
Respiratory	Pulmonary hypertension and chronic sickle lung
Cardiology	Cardiac disease and heart failure
Neurology	Adult stroke
Renal	Chronic renal failure

4.2 Core standards

i) Chronic pain

- The cause of chronic pain should be established as far as possible
- Patients with established avascular necrosis causing chronic pain should be referred for rapid assessment and operation if deemed necessary
- GP and hospital teams should encourage home management of chronic pain as much as possible. The choice of analgesia should be varied and patients should be informed of the side effect profiles
- A multidisciplinary team to treat chronic pain should be established
- Patient advocacy should be encouraged through expert patient programmes, with periodic review of such initiatives

ii) Stroke and other neurological complications

- Patients with arterial stroke in the context of SCD should receive regular blood transfusion, ideally exchange, to keep the sickle percentage below 30% indefinitely
- For those patients on long term transfusion programmes, monitoring of iron overload should be undertaken and appropriate chelation therapy initiated (see chapter 6)
- Patients with moyamoya should be referred to an appropriate centre for consideration of revascularisation
- SCD specialist centres should have access to a designated neurologist with an interest in stroke and the neurological complications of haemoglobinopathies and neuro-imaging facilities including transcranial Doppler (TCD), Duplex scanning of the neck, magnetic resonance imaging (MRI)/magnetic resonance angiography (MRA) and electroencephalography (EEG)

iii) Pulmonary and cardiac disease

- Patients should be screened for chronic sickle lung disease with regular oxygen saturation (SaO₂) monitoring. Patients who are dyspnoeic or have low SaO₂s should be investigated with lung function tests and high resolution CT scans
- Patients with symptoms of disordered sleep breathing should be investigated with overnight SaO₂s and if these are abnormal, they should be referred to a sleep clinic
- Trans-thoracic echocardiography should be used to screen for pulmonary hypertension every 1-2 years
- All specialist sickle centres should have links with the regional pulmonary hypertension services to provide confirmatory testing and to instigate treatment in patients with confirmed significant pulmonary hypertension

iv) Leg ulcers

- A full initial leg ulcer assessment should include Doppler scans, photography or tracings of the ulceration
- Topical antibiotics should be avoided as they can cause sensitisation
- Management of leg ulcers should be by a multidisciplinary team with expertise in leg ulcer management

v) Chronic renal disease

- All patients with haematuria should be referred to urologists for further investigation and management; the former should include ultrasound, computer tomography (CT) or MRI done to exclude renal medullary carcinoma.
- All patients should be screened annually for proteinuria, and a protocol should be in place for further investigation and referral
- Meticulous attention to the control of blood pressure, diabetes and other co-morbidities is necessary

vi) Priapism

- Clear written information on priapism in easily understood language must be available to young men and adults with SCD at first visit to clinic
- Patients should be referred to Urologists for follow-up and preventative management

vii) Eye complications

- All patients with SCD at first contact should be referred to a dedicated sickle retinal clinic for “one stop” assessment/treatment of eye disease attributable to their condition and be followed up as necessary
- Patients presenting with an acute change in vision must be referred immediately to an ophthalmologist for evaluation

viii) Growth and nutritional support

- There should be close co-operation between paediatricians and haematologists as the child approaches the transition to adult care. Any history of growth failure, delayed sexual maturation and nutritional deficiencies must be clearly documented and monitored. If growth failure is identified treatment should be initiated as soon as possible

4.3 Recommendations for best practice

4.3.1 Chronic pain syndrome

Chronic sickle pain is described as an episode of pain of greater than 3-6 months duration. The definition itself is arbitrary and may overlap in individuals with frequently occurring acute episodes. Neuropathic pain (pain originating from nerve damage) such as numb jaw syndrome or “mental nerve neuropathy” or the arthropathic pain of

avascular necrosis of the long bones can be under diagnosed or delayed in their recognition. Hydroxycarbamide (also known as hydroxyurea) has not made an impact on chronic pain.

4.3.1.1 Managing chronic pain

Chronic pain is difficult to eradicate. The emphasis should be on minimising suffering and empowering the patient to cope. Repeat prescriptions of analgesia for affected individuals should be from a named practitioner (i.e. GP, prescribing nurse or hospital specialist). This should include medium to long acting opiates (given orally or transdermally) as frequent short acting opiates are not as effective; adjuvants; and non steroidal to manage their pain. Patients should be conversant with their mode of action and side effect profiles.

NSAID use should be limited to standard doses and defined periods of use. No evidence exists to support the use of one NSAID or route over another. Longer periods of usage require frequent (every 3 months) monitoring of renal function.

Patients should have an alternative analgesia for “breakthrough” pain such as fentanyl (patch or oral lozenge) or oxycodone (oral). Chronic opiate administration can, paradoxically, induce hyperalgesia¹. In the advent of an acute hospitalisation episode, alternatives to drugs used within the community should be considered.

Education

A chance for providing health education, medication review and needs assessment should be done yearly, or more frequently in special cases, for it to be effective and up to date. This should be done within the primary, secondary or community care setting as appropriate for the best outcome. Additionally, the following are also recommended:

- Patients with chronic pain syndromes need their expectations managed as well as the physical component of their pain
- Career/vocational and employment advice should be given to the patient. In some cases, retraining to more conducive jobs may be necessary
- Occupational therapy, psychological therapy with cognitive behavioural therapy may be beneficial
- Weight management advice should be given: high impact exercise/sports should be discouraged as they can exacerbate the damage to AVN
- Education of family members may be beneficial to individuals with SCD, whereby family members with a good understanding of the condition, may act as expert carers in the family, providing support in times of illness

Avascular necrosis (AVN)

Pain caused by AVN should be managed using a multidisciplinary approach led by the physician and the orthopaedic surgeon. Initial investigation should be with a plain X-ray, and if normal, an MRI scan of the affected area. If surgical intervention is contemplated, peri-operative transfusion requirements should be considered. Patients should have thromboprophylaxis instituted peri-operatively as per local policy. Referral to physiotherapist/occupational therapist should be initiated early and a thorough assessment of appropriate exercises and appliances should be made to aid mobility and self-care within the community before discharge.

4.3.2 Managing stroke and other neurological conditions

4.3.2.1 Stroke

Primary stroke prevention

Long term red cell transfusion is the mainstay of primary and secondary stroke prevention in SCD. In children, the stroke prevention (STOP) and STOP2 trials demonstrated that it is possible to prevent stroke in those with intracranial vessel narrowing detected by TCD with regular blood transfusions^{2,3,4}. In adults with SCD velocities >200 cm/sec have not been demonstrated, consistent with the finding that TCD velocities decrease with increasing age⁵. Conditional TCDs >175cm/sec but <200cm/sec are a definite risk factor for stroke. These patients should be monitored closely since many of them convert to >200cm/sec or develop stroke (based on paediatric data)⁶. There are no data on whether a lower cut off (e.g. 170 cm/sec) predicts stroke in adults and this needs further investigation. Hydroxycarbamide also appears to reduce TCD velocities and may prevent stroke⁷.

Patients with SCD who have had TCD velocities >200 cm/sec during childhood screening for which regular blood transfusions is mandated, should continue indefinitely (B). If patients with SCD who have had TCD velocities >200 cm/sec on screening cannot tolerate regular blood transfusion, hydroxycarbamide may be considered but there should be a period of overlap. As TCD velocities >200 cm/sec are rarely documented for the first time in adults, it would be unusual for transfusion to be initiated for this indication in adulthood. The value of TCD screening for stroke prevention purposes in adults with SCD has not been demonstrated and awaits confirmation in future clinical studies.

Adults may have other risk factors for stroke - aneurysms, extracranial stenosis and occlusion, covert or 'silent' infarction on MRI, cardiac compromise and chronic leucocytosis - as well as conventional risk factors such as previous transient ischaemic attack, hypertension (even those considered mild), renal dysfunction, patent foramen ovale, sleep apnoea and nocturnal oxyhaemoglobin desaturation and poor diet. There is no evidence currently that screening for aneurysms, extracranial cerebrovascular disease or cardiac disease leads to stroke prevention and these investigations are unlikely to be cost-effective at present.

Factors that apply to stroke prevention in the general population, such as education about diet (e.g. at least 5 portions of fruit and vegetables per day) and screening for systemic hypertension and poor cardiac function, are likely to be of benefit (C). Patients with SCD have lower mean BP than age and sex matched controls in the general population hence more aggressive management of systemic hypertension in these individuals is indicated on detection⁸.

Patients who report symptoms suggestive of transient ischaemia, or who have a seizure, or other neurological disturbance should have a full work-up including MRI and MRA, Doppler studies of the extra-cranial vessels, and echocardiography (C). Those who are found to have evidence of vasculopathy likely to be due to SCD should be offered regular monthly transfusions aiming to maintain HbS below 30%.

Secondary stroke prevention

Ischaemic stroke

In untreated patients who suffer a first ischaemic stroke the risk of recurrence is 50-92% in patients with sickle cell anaemia (SCA) who receive no treatment⁹. Recurrence is more common if moyamoya collaterals are demonstrated by angiography¹⁰ and in those in whom the stroke occurs outside the context of an acute illness¹¹. The risk of recurrent ischaemic stroke in SCA is reduced to around 10% by regular transfusion (at least 6 weekly) to keep HbS <30%. There appears to be an advantage in terms of

reduced stroke recurrence risk for using exchange rather than simple transfusion¹². Therefore, any adult patient with SCD who has had an ischaemic stroke should be offered long term regular blood transfusion to prevent re-occurrence.

Hydroxycarbamide¹³, bone marrow transplantation¹⁴ and revascularisation for moyamoya¹⁵ are options for some patients, particularly those who cannot tolerate chronic transfusion or experience recurrent events despite reduction of HbS to <30%. However, the risks of neurological complications after bone marrow transplantation are much higher in adults. Further multicentre clinical trials are urgently needed to clarify some of these issues about the optimal way of preventing stroke.

Covert infarction

Clinically covert reinfarction is typical of SCD with an incidence of 7.06/100 patient-years, and also predicts overt stroke¹⁶. There are few data about the prevalence or consequences of covert infarction in adults and there is currently no evidence-based strategy for secondary prevention. Although screening MRI is currently not recommended, individuals who demonstrate evidence of cognitive abnormalities or soft neurologic signs should be evaluated¹⁷.

Haemorrhagic stroke

Aneurysms which have bled in patients with SCD have successfully been treated with interventional neuroradiology (embolisation with coils) or surgery (craniotomy and clipping). Adults with SCD and moyamoya are at risk of recurrent intracranial haemorrhage but the available evidence from non-SCD patients suggests that revascularisation does not prevent recurrent haemorrhage in moyamoya.

4.3.2.2 Epilepsy

Seizures occur in 10%-15% of patients with SCD, 10 times the incidence in the general population¹⁸. They are associated with cerebrovascular disease and covert infarction. Patients with recurrent seizures outside the context of acute events usually respond to anticonvulsants, but finding an effective drug without side effects may take time and patience.

4.3.2.3 Headache

Chronic headache is very common in SCD and may be secondary to migraine, benign intracranial hypertension (perhaps as a consequence of venous sinus thrombosis), hypertension or sleep apnoea as well as tension. Intracranial hypertension is suggested by headaches occurring on waking, particularly if this occurs in the middle of the night. Migraine headaches are often familial, sometimes unilateral, may be preceded by an aura, and often require the patient to lie down in a darkened room because of the severity of the headache and the associated nausea and dizziness. The first episode of acute severe headache, or a significant change in the type of headache, should be evaluated as an emergency in case this is a presentation of intracranial haemorrhage or venous sinus thrombosis.

Patients with migrainous headaches should be treated in accordance with the guidelines for the general population (C). If chronic headaches persist despite the above measures, patients should be referred to a neurologist with interests in headache, stroke and the neurological complications of haemoglobinopathies (C).

4.3.3 Pulmonary and cardiac disease

4.3.3.1 Chronic sickle lung disease

Chronic sickle lung disease has been divided into 4 stages depending on the presence of chest pain, degree of hypoxia, and chest X-ray and lung function test findings¹⁹. It is not clear whether patients inevitably progress through the stages and whether early

intervention is of benefit. It may be associated with a prior history of ACS, but may also occur without such a history, low level pulmonary damage probably occurring during painful episodes.

SaO₂ levels should be monitored regularly in clinic and, if found to be low, the degree of hypoxia should be confirmed with an arterial blood gas. Hypoxic patients should be investigated with lung function tests. Restrictive lung defects are most commonly seen. High resolution CT scans of the chest are more sensitive than chest X-rays and may show evidence of fibrosis, ground glass shadowing, pulmonary interstitial disease and lobar volume loss. The correlation between CT scans and lung function tests is not absolute, but the former is probably more sensitive to detect pulmonary damage. The 6 minute walk test can be used as measure of functional capacity of lung disease and is also a sensitive indicator of pulmonary hypertension²⁰.

If there is evidence of chronic lung disease smoking should cease; vaccinations should be kept up to date and patients should be given evidence on avoiding, or getting early treatment for chest infections (C).

4.3.3.2 Obstructive sleep apnoea

This is common in SCD and may be due to tonsillar hypertrophy or other causes of sleep disordered breathing. It is important to diagnose as, in addition to the symptoms of obstructive sleep apnoea, overnight hypoxia can be associated with increased painful episodes and increased neurological events. Overnight sleep studies should be performed on those who are hypoxic at rest, have symptoms of daytime somnolence, snore or have a high Epworth score. Full polysomnography may be necessary in some cases. Those with abnormal sleep studies should be reviewed by a chest physician with an interest in sleep disorders and/or haemoglobinopathies and they may be considered for a trial of continuous positive airway pressure (CPAP), before or in addition to a tonsillectomy.

4.3.3.3 Pulmonary hypertension

Pulmonary hypertension has been described in 5%-30% of people with SCD. It is thought to be secondary to chronic haemolysis releasing free haemoglobin which leads to nitric oxide deficiency which causes acute and chronic pulmonary vasoconstriction.

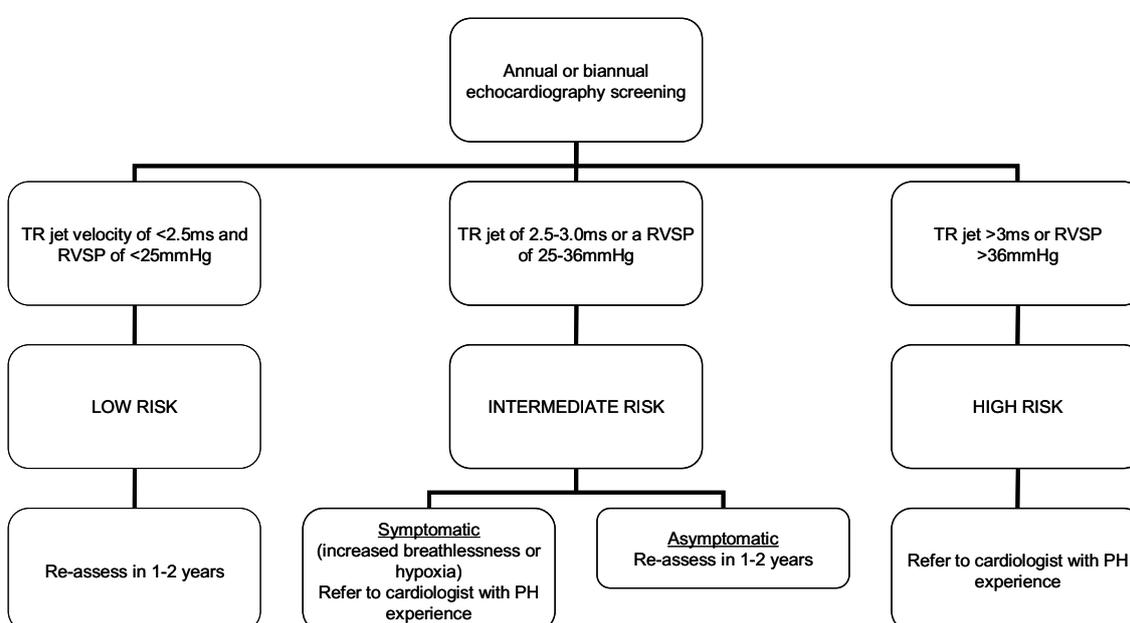
Patients with pulmonary hypertension are often asymptomatic, even with severe disease, and by the time they develop symptoms it may be too late for effective treatment. Idiopathic pulmonary hypertension has a median survival of 2.8 years, but the median survival in patients with SCD and pulmonary hypertension is even less, approximately 2 years. This may be due to the combination of the increased pulmonary pressures and cardiac dysfunction and the anaemia and other chronic organ problems associated with SCD²¹.

Diagnosis of pulmonary hypertension is made by the finding of a raised mean pulmonary artery pressure (MPAP) of >25mmHg at cardiac catheterisation. Patients with SCD tend to have lower pulmonary artery pressures and higher cardiac outputs than patients with primary pulmonary hypertension. The finding of a raised tricuspid regurgitant jet velocity of >2.5ms on Doppler echocardiography has been shown to correlate well with a raised MPAP on cardiac catheterisation and this non-invasive screening tool is being used more frequently. The right ventricular systolic pressure can be measured indirectly from the tricuspid regurgitant velocity. A raised tricuspid jet velocity of >2.5ms has also been associated with an increased risk of death. One suggested screening protocol is shown in figure 1.

Patients with suspected pulmonary hypertension should be referred to the nearest specialist pulmonary hypertension service, as only these services have the ability to prescribe and obtain funding for pulmonary hypertension treatments. The diagnosis of pulmonary hypertension should be confirmed with cardiac catheterisation as not all patients with abnormal echocardiographs will have pulmonary hypertension.

There is no evidence-based treatment for sickle cell patients with proven pulmonary hypertension. It is suggested that they are treated with standard therapy such as oxygen treatment and optimisation of their SCD care with hydroxycarbamide or transfusion therapy. Anticoagulation may be of benefit in selected cases. Targeted pulmonary vascular therapies such as phosphodiesterase 5 inhibitors (sildenafil), prostacyclin analogues, endothelin-1-receptor antagonists (bosentan) and thromboxane inhibitors have been useful in small non-randomised trials. Patients should be enrolled in trials to develop the best screening and treatment pathways.

Figure 1: Screening protocol for pulmonary hypertension



4.3.3.4 Other cardiopulmonary disease

Left sided heart disease and diastolic dysfunction has also been shown in some patients with SCD. Patchy perfusion defects have been seen on VQ scans or CT pulmonary angiograms. These small pulmonary emboli may contribute to pulmonary hypertension and those patients found to have evidence of emboli may benefit from anticoagulation.

4.3.4 Managing chronic leg ulcers

Lower leg ulceration is frequently seen in people with SCD and has a high rate of recurrence. Ulcers affect both males and females and commonly occur during adolescence with a prevalence that increases with age. They can occur in either leg, most frequently over the shin and malleoli. Patients with HbSS are more likely to develop leg ulcers than other genotypes²². The mechanism of ulceration is poorly understood. Leg ulcers can develop either as a result of trauma or spontaneously; patients may complain of pain at the exact spot before the skin ulcerates.

Early intervention is important to minimise progression to a chronic wound, which can have financial implications as well as adversely affect the individual's self-esteem, educational achievement, social integration and relationships.

The treatment of leg ulcers should include the following:

- Leg elevation/bed rest to reduce leg oedema²³
- Topical therapy: emollients or barrier creams can be used on dry or macerated skin; topical antibiotics should be avoided as they can cause sensitisation
- Modern wound dressing which will not cause trauma on removal should be used to create optimum conditions to promote moist wound healing
- Take a wound swab if the ulcer deteriorates, healing is no longer progressing normally or if there is clinical evidence of infection; infections should be treated according to local guidelines
- Graduated compression bandages or hosiery will reduce venous hypertension; a trained practitioner should apply compression therapy and arterial disease must be excluded before compression is used²⁴; in addition, written information should be issued regarding the use of compression, which must include what signs and symptoms to observe for and contact details
- Regular Doppler ultrasonography by suitably trained personnel should be used to measure ankle brachial pressure index²⁴
- If underlying osteomyelitis is suspected, because of fever, bone tenderness, high white count, high CRP, or positive blood cultures, local imaging should be undertaken
- The importance of suitable footwear should be explained especially if the ulcers are on the malleoli
- A healthy balanced diet should be encouraged; correction of zinc deficiency may be of benefit in chronic leg ulcer patients²⁵
- In patients who fail to respond to conservative measures, although formal trials are lacking, blood transfusion may be considered as this has been found to result in healing in individual patients

Services are poorly established and work to establish local expertise should be encouraged.

4.3.5 Chronic renal disease

Kidney disease is an insidious and relatively common manifestation of adult SCD. The spectrum of sickle nephropathy ranges from painless haematuria, proteinuria and progressive loss of function to end stage renal disease (ESRD). The severity of renal insufficiency is associated with a poor survival outcome in patients with SCD. The mechanisms of disease and the impact of treatment options are poorly characterised. An increase in glomerular blood flow, reduction in medullary blood flow from ischemia consequent on sickle haemoglobin and papillary necrosis are all recognised contributors to sickle kidney disease.

4.3.5.1 Hyposthenuria

Renal medullary insufficiency manifests as enuresis which can continue into middle or late teenage years and hyposthenuria, which makes patients more susceptible to dehydration. All patients with SCD should be encouraged to drink a minimum fluid intake of at least 3-4 l/day.

4.3.5.2 Haematuria

Haematuria is a common finding in SCD and can be recurrent. Medullary infarction may lead to renal papillary necrosis which can occur in both patients with SCD and sickle cell carriers, and manifests as haematuria²⁶. Uncommonly the haematuria is

severe with the passage of clots and severe anaemia. Sloughing of the renal papillae can lead to ureteric obstruction and renal failure. The treatment of haematuria is conservative with maintenance of high urinary flow, and when necessary blood transfusion support if blood loss is significant. Desmopressin and antifibrinolytics have been used anecdotally successfully in the treatment of haematuria. In rare instances for life-threatening and prolonged haemorrhage where bleeding is demonstrated from one kidney, surgical intervention may be required.

Renal medullary carcinoma is a rare aggressive neoplasm which occurs almost uniquely in patients with SCD²⁷ or sickle cell carriers²⁸. It manifests as haematuria, flank pain, weight loss, fever, abdominal pain and has usually metastasised at the time of presentation.

4.3.5.3 Proteinuria

Proteinuria can be associated with a very rapid decline in renal function²⁹. Screening for proteinuria should be done at least annually by performing a urinary dipstick test, and if abnormal, a 24 hour urinary protein estimation or equivalent (e.g. protein-creatinine ratio, albumin-creatinine ratio) should be carried out. All patients should have access to a renal physician with an interest in haemoglobinopathies. Patients with proteinuria should be referred to a renal physician for monitoring and consideration for therapy with an angiotensin converting enzyme (ACE) inhibitor or angiotensin-II receptor antagonist such as enalapril or losartan.

Hydroxycarbamide should be considered in patients with microalbuminuria or abnormal renal function who do not respond to treatment with an ACE inhibitor or angiotensin-II receptor antagonist.

4.3.5.4 Monitoring of renal function and renal failure

Renal function should be monitored at least annually. Creatinine levels are often low in people with SCD; any value at the upper limit of the normal range should be identified and discussed with the local renal physician. Rigorous blood pressure control is necessary, with a target of 130/80 for patients with proteinuria. A blood pressure of 140/90 is permissible for dipstick negative patients who have normal renal function. Urinary tract Infections should be promptly treated with suitable antibiotics. G6PD deficiency which may precipitate intravascular haemolysis should be excluded as this may influence choice of antibiotics. Long term use of NSAIDs should be avoided; if unavoidable, regular monitoring of renal function is recommended.

Patients with ESRD and symptomatic anaemia should be considered for erythropoietin therapy (with or without hydroxycarbamide).

Renal replacement therapy, including haemodialysis and transplantation, should be explored in patients with end stage renal disease attributable to SCD. This should be within the context of a clinical study. Survival of patients on haemodialysis for ESRD, age matched for rate, is reduced compared with other causes of ESRD of non diabetic origin. Early referral and consideration for transplantation should be considered.

An increase in frequency of painful crises in individuals with successful kidney engraftment has been noted and hydroxycarbamide may be a useful adjunctive therapy.

4.3.6 Priapism

Priapism in SCD can precipitate painful crises and lead to erectile dysfunction in the longer term. Two types exist: a “stuttering” self limiting episode and an “acute” attack which requires hospital intervention. A cluster of stuttering attacks may be a warning for

a major acute event. Early presentation (<4hrs) is vital and health education is paramount in reinforcing this information (B).

4.3.6.1 Home prevention or management of stuttering attacks

Patients can also be taught self-help strategies by their nurse counsellors or physicians to abort a stuttering attack at its beginning such as aggressive hydration, compound analgesia, warm baths and mild to moderate exercise (C). If this fails, early presentation to hospital should be encouraged.

4.3.6.2 Long term sequelae of priapism/erectile dysfunction (ED)

The use of a phosphodiesterase 5 inhibitor, such as vardenafil, sildenafil or tadalafil, should be reserved for refractory cases of ED ideally within the context of a clinical study³⁰. Access to a clinical psychology service for counselling may help in the emotional issues of ED and opiates may need to be prescribed for chronic pain syndromes due to chronic recurring attacks. Implantation devices may be suitable for some patients who develop ED.

4.3.7 Eye complications

Ocular complications related to SCD may be asymptomatic in the early stages. Consequently, sickle eye disease can remain undetected until visual symptoms occur or unless a formal eye examination is performed by an ophthalmologist. Ocular changes related to SCD can be broadly divided into Non-Proliferative Retinopathy (NPR) and Proliferative Retinopathy (PR) categories, based on the absence or presence of neovascularisation in the eye. This distinction is clinically relevant because the proliferation of new blood vessels (often called 'sea fans') can lead to vitreous haemorrhage and retinal detachment.

NPR manifestations do not normally lead to visual loss and are not indicative of disease progression. However, PR is a serious ocular complication and accounts for 73% of sudden visual loss in SCD³¹. Repeated microvascular occlusion can lead to vascular remodelling and recanalising segments of retinal vessels. Some of these ischaemic changes may result in the growth of new blood vessels. However, in SCD, a high rate of spontaneous regression, or autoinfarction, can be observed.

Panretinal photocoagulation (PRP) laser treatment is the only recognised effective treatment for PR but it is not without its own risks. Given the potential for autoinfarction and the lack of progression of neovascularisation in some eyes, the indications for treatment of retinal neovascularisation are not always clear. In view of this, the benefit of regular ophthalmology screening is not clear and the benefit of early intervention with laser treatment is not proven. It is essential therefore that all patients be taught aware of the risk of ocular complications and have rapid access to the ophthalmology service if they are symptomatic.

Detection of PR is most common in young adults (age 15-29 years)³². The highest prevalence of PR is in the genotypes SS and SC groups (11-45%)³³. However, the progression and complications of PR are more common in SC disease whilst autoinfarction is more prevalent in SS disease.

4.3.8 Growth and nutritional support

Concerns related to delayed growth during childhood and adolescence should be clearly documented during transition to adult services. In the presence of preceding growth failure or sexual and skeletal maturational delay, continued specialist endocrine and nutritional support is indicated.

4.3.8.1 Nutrition

Increased metabolic demands and possible decreased absorption suggest that people with SCD may have a relative deficiency of energy, protein and several micronutrients and thus the RDA for the normal population may not be applicable. In addition, dietary intake can be reduced during painful and febrile episodes in SCD. During follow-up the goal of nutritional counselling is to maintain ideal body weight. Overweight adults have an increased tendency to develop complications such as diabetes and AVN; underweight individuals require further evaluation with the aim of nutritional support if indicated (C).

4.3.8.2 Folic acid

Folic acid supplementation is recommended for all patients with SCD to prevent deficiency caused by increased folate turnover due to chronic haemolysis and thereby reduce the risk of bone marrow aplasia (C). A dose of 1mg orally daily is considered adequate^{34,35}. Every effort should be made to encourage the consumption of leafy vegetables and fruits containing natural sources of folates so that supplements become unnecessary.

There is a small risk that routine folate supplementation may mask the megaloblastic anaemia caused by cobalamin deficiency thereby permitting neurological dysfunction to develop. Superimposed cobalamin deficiency must be considered whenever anaemia worsens or the MCV, LDH or bilirubin level rises in a patient with SCD³⁶.

References

- ¹ Gardell LR, King T, Ossipov MH, et al. Opioid receptor-mediated hyperalgesia and antinociceptive tolerance induced by sustained opiate delivery. *Neurosciences (Let)*. 2005; Dec 9.
- ² Adams RJ, McKie VC, Carl EM, et al. Long-term stroke risk in children with SCD screened with transcranial Doppler. *Ann Neurol* 1997; 42:699-704.
- ³ Adams RJ, McKie VC, Hsu L, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. *N Eng J Med*. 1998; 339: 5-11.
- ⁴ Adams RJ, Brambilla D. Discontinuing prophylactic transfusions used to prevent stroke in SCD. *N Eng J Med*. 2005; 353: 2769-2778.
- ⁵ Valadi N, Silva GS, Bowman LS, et al. Transcranial Doppler ultrasonography in adults with SCD. *Neurology*. 2006; 67: 572-4.
- ⁶ Hankins JS, Fortner GL, McCarville MB, et al. The natural history of conditional transcranial Doppler flow velocities in children with sickle cell anaemia. *Brit J Haematology*. 2008; 142(1): 94-99.
- ⁷ Gulbis B, Haberman D, Dufour D, et al. Hydroxycarbamide for SCD in children and for prevention of cerebrovascular events: the Belgian experience. *Blood*. 2005; 105: 2685-2690.
- ⁸ Karayaylah I, Onal M. Low blood pressure, decreased incident of hypertension, and renal, cardiac and autonomic nervous system functions in patients with sickle cell syndromes. *Nephron*. 2002; 91(3): 535-537.
- ⁹ Pegelow CH, Adams RJ, McKie V, et al. Risk of recurrent stroke in patients with SCD treated with erythrocyte transfusions. *J Pediatr*. 1995; 126: 896-899.
- ¹⁰ Dobson SR, Holden KR, Nietert PJ, et al. Moyamoya syndrome in childhood SCD: a predictive factor for recurrent cerebrovascular events. *Blood*. 2002; 99: 3144-3150.
- ¹¹ Scothorn DJ, Price C, Schwartz D, et al. Risk of recurrent stroke in children with SCD receiving blood transfusion therapy for at least five years after initial stroke. *J Pediatr*. 2002; 140: 348-354.
- ¹² Hulbert ML, Scothorn DJ, Panepinto JA, et al. Exchange blood transfusion compared with simple transfusion for first overt stroke is associated with a lower risk of subsequent stroke: a retrospective cohort study of 137 children with sickle cell anemia. *J Pediatr*. 2006; 149: 710-712.
- ¹³ Ware RE, Zimmerman SA, Sylvestre PB, et al. Prevention of secondary stroke and resolution of transfusional iron overload in children with sickle cell anemia using Hydroxyurea and phlebotomy. *J Pediatr*. 2004; 145:346-352.
- ¹⁴ Walters MC, Storb R, Patience M, et al. Impact of bone marrow transplantation for symptomatic SCD: an interim report. Multicenter investigation of bone marrow transplantation for sickle cell disease. *Blood* 2000; 95: 1918-1924.
- ¹⁵ Fryer RH, Anderson RC, Chiriboga CA, et al. Sickle cell anemia with moyamoya disease: outcomes after EDAS procedure. *Pediatr Neurol*. 2003; 29: 124-130.
- ¹⁶ Pegelow CH, Macklin EA, Moser FG, et al. Longitudinal changes in brain magnetic resonance imaging findings in children with SCD. *Blood*. 2002; 99: 3014-3018.

-
- ¹⁷ Vichinsky E, Gold J. Neuropsychological (NP) dysfunction and Neuroimaging abnormalities in Neurologically intact adult patients with Sickle Cell disease. *Blood (ASH Annual Meeting Abstracts)*. 2007; 110-428.
- ¹⁸ Prengler M, Pavlakis SG, Boyd S, et al. Sickle cell disease: Ischemia and seizures. *Ann Neurol*. 2005; 58: 290-302.
- ¹⁹ Powers D, Weidman JA, Odom - Maryon T, et al. Sickle cell chronic lung disease: prior morbidity and the risk of pulmonary failure. *Medicine*. 1988; 67: 66-76.
- ²⁰ American Thoracic Society. ATS Statement: Guidelines for the Six-Minute Walk Test. *American J Respiratory and Critical Care Medicine*. 2002; 166: 111-117.
- ²¹ Gladwin MT, Sachdev V, Jison ML, et al. Pulmonary Hypertension as a Risk Factor for Death in Patients with Sickle Cell Disease. *New Eng J Med*. 2004; 350(9): 886-895.
- ²² Olujohungbe A, Anionwu EN. Leg Ulcers in Sickle Cell Disorders. In Morrison et al. (EDs). *Leg Ulcers: A problem based learning approach*. 2005. Edinburgh. Elsevier.
- ²³ Clare A, FitzHenley M, Harris J, et al. Chronic leg ulceration in homozygous sickle cell disease: the role of venous incompetence. *Brit J Haem*. 2002; 119: 567-571.
- ²⁴ Clinical practice guidelines. The management of patients with venous leg ulcers. 1998. RCN Institute, centre for Evidence-Based Nursing, University of York; and the School of Nursing, Midwifery and Health Visiting, University of Manchester.
- ²⁵ Serjeant GR, Galloway RE, Gueri MC. Oral zinc sulphate in sickle-cell ulcers. *Lancet*. 1970; 2(7679): 891-892.
- ²⁶ Kincaid-Smith P, Fairley K. The investigation of haematuria. *Semin. Nephrol*. 2005; 25(3): 127-35.
- ²⁷ Wadhwa R, Daf K. Renal medullary carcinoma in sickle cell anaemia. *Indian J Urol*. 2002; 16(2): 92-97.
- ²⁸ Patel K, Livni N, McDondald D. Renal medullary carcinoma: A rare cause of haematuria in sickle cell trait. *Brit J Haem*. 2006. 132(1): 1-1(1).
- ²⁹ Ataga KI, Orringer EP. Renal abnormalities in sickle cell disease. *Am J Haem*. 2000; 63(4): 2005-2011.
- ³⁰ Burnett AL, Bivalacqua TJ, Champion HC, et al. Long-term oral phosphodiesterase 5 inhibitor therapy alleviates recurrent priapism. *Urology*. 2006; 67: 1043-1048.
- ³¹ Moriarty BJ, Acheson RW, Condon PI, et al. Patterns of Visual loss in untreated sickle cell retinopathy. *Eye*. 1988; 2: 330-5.
- ³² Condon PI, Serjeant GR. Behaviour of untreated proliferative sickle retinopathy. *Brit J Ophthalmol*. 1980; 64: 404-411.
- ³³ Clarkson JG. The ocular manifestations of SCD: a prevalence and natural history study. *Trans Am Ophthalmol Soc*. 1992; 90: 481-504.
- ³⁴ Lindenbaum J, Klipstein FA. Folic acid deficiency in sickle-cell anemia. *N Eng J Med*. 1963; 269: 875-882.
- ³⁵ Pearson HA, Cobb WT. Folic acid studies in sickle-cell anemia. *J Lab Clin Med*. 1964; 64: 913-921.
- ³⁶ Dhar M, Bellevue R, Carmel R: Pernicious anemia with neuropsychiatric dysfunction in a patient with sickle cell anaemia treated with folate supplementation. *N Eng J Med*. 2003; 348(22): 2204-7.

Pregnancy, Contraception and Fertility

5.1 Introduction

Pregnancy in sickle cell disease (SCD) has been associated with increased maternal and perinatal mortality due to an increased rate of sickle and pregnancy related complications. Careful management of pregnancy, including prenatal care and access to expertise in SCD aims to minimise complications and result in a successful outcome for most women.

This group are at high risk of having a baby with a major haemoglobin disorder if the baby's father carries a significant haemoglobin disorder and early (ideally pre-conception) and appropriate genetic counselling should be offered by trained practitioners.

In the past, health care professionals tended to advise women with SCD against pregnancy and advice about contraception was sometimes misguided. This is no longer acceptable. Appropriate contraceptive advice is vital to enable women with SCD to make informed choices about their fertility.

Sub-fertility has been described in men with SCD but there is insufficient evidence to make specific recommendations.

5.2 Core standards

i) Pregnancy

- All health professionals dealing with pregnant women with SCD should receive an appropriate level of education about haemoglobin disorders
- Pre-conceptual counselling, including genetic screening and partner testing should be offered to all men and women with SCD
- Hydroxycarbamide (hydroxyurea) should be discontinued in men and women a minimum of 3 months prior to conception
- Chelation therapy should be stopped prior to conception
- If evidence of significant iron overload preconception, pregnancy should be delayed to allow aggressive iron chelation prior to conception
- Pregnancy in women with SCD should be considered as high risk and early booking is recommended. Combined management by a haematologist and obstetrician with experience of managing high risk pregnancy (preferably experience of haemoglobinopathies) is recommended for all pregnant patients with SCD or supervision arrangements must be in place to support patients' booking choice
- Antenatal care should be undertaken at a designated SCD specialist centre and local hospitals should refer to this centre for initial assessment. If care is to continue at the non specialist centre, a joint care plan should be agreed. The choice of maternity unit should be discussed with the woman
- Each woman should have an individualised care plan which takes into account her previous sickle and pregnancy history. Where possible, she should have a named midwife with expertise in caring for women with SCD
- SCD specialist centres should have:
 - arrangements in place for counselling by PEGASUS (Professional Education for Genetic Assessment and Screening) trained health care counselling professionals, with timely access to prenatal diagnosis when required

- a written policy to include antenatal management, labour and delivery and postpartum care
- written guidelines on the management of painful crises during pregnancy and indications for transfusion
- Routine prophylactic transfusion for uncomplicated pregnancy is usually not necessary but should be considered for women with a poor obstetric or medical history
- Timing and route of delivery should be based on obstetric indications, as in women without SCD
- Neonatal capillary samples should be taken when the antenatal screening process has identified a baby with a high risk of a major haemoglobin disorder
- Surgical termination of pregnancy should take place within the acute hospital setting with involvement of the haematology team and appropriate anaesthetic support with all patients having access to bereavement counselling

ii) Contraception

- Each woman should be given contraceptive choice and should be fully informed regarding the potential risks and benefits of the different methods
- Health care professionals should be fully informed about options for contraception in SCD
- Discussion about contraception should take place with male and female adolescents before leaving paediatric care

5.3 Recommendations for best practice

5.3.1 Maternal mortality and morbidity

Early studies of women with SCD have reported worse pregnancy outcomes compared to more recent case series, suggesting that improved medical management has had some impact on outcomes. A number of case series have reported a maternal mortality rate of up to 3%^{1,2}. The Confidential Enquiry into Maternal and Child Health (CEMACH) reported 3 and 2 deaths in women with SCD between 2000-2002 and 2003-2005 respectively, although the total number of pregnancies in women with SCD during that time is unknown^{3,4}. However, it is clear that maternal death rates are higher than for the general population, and it is important not to make simple extrapolations of data from one country to another. Deaths which occur are often related to thrombo-embolic events, which are also a risk for other pregnant populations.

Most case series are retrospective with only one prospective study. The findings between case series are consistent with some, but not others, reporting a higher incidence of pregnancy related complications. Taken together, these series suggest the following observations:

Effects of pregnancy on SCD include:

- Worsening of anaemia
- Increased rates of painful crises and chest syndromes
- Increased rate of infections especially urinary tract infections and postpartum uterine infection

Effects of SCD on pregnancy include:

- Increased rates of miscarriage and stillbirth
- Increased rates of growth restricted babies
- Increased rates of premature labour
- Increased rates of thrombo-embolic disease
- Increased rates of pre-eclampsia

There is no correlation between maternal anaemia and the above complications^{1,5}.

Although these complications are seen more frequently in HbSS than HbSC or HbS/βthal, all sickle cell disorders should receive the same level of care.

5.3.2 Fetal implications of maternal SCD

Perinatal mortality for infants born to SCD mothers is between 4% and 6%² in the UK. Restricted uteroplacental circulation is associated with low birth weight and intrauterine growth restriction (IUGR) in women with SCD. Fetal outcomes do not, however, correlate with maternal anaemia or clinical apparent sickle events and are not improved by transfusion therapy^{5,6}.

5.3.3 Organisation of care

Women should, ideally, be managed by an experienced haematologist and obstetrician (ideally experienced with sickle pregnancy) in a unit able to manage high risk pregnancies. This might be in a combined clinic. Antenatal care should be managed at a SCD specialist centre. If this is not possible for geographical or logistical reasons, the local unit should manage the case in conjunction with the specialist centre utilising an agreed protocol. In accordance with NSF guidance, a woman's personal choice should be taken into consideration⁷.

Where possible a dedicated trained midwife should be part of the team, to help to co-ordinate all aspects of the woman's care through labour, delivery and postpartum period. Consideration should be given to social, psychological and cultural aspects of the woman's care. A specialist PEGASUS trained practitioner, should be responsible for genetic counselling, screening the father of the baby (if not already performed) and arranging prenatal diagnosis (PND).

A local policy should be in place detailing management to include:

- Booking arrangements and procedures
- Partner screening
- Routine antenatal care
- Fetal growth monitoring
- Management of acute crises in pregnancy
- Management of infections
- Indications for transfusion
- Anticoagulation policy
- Management of labour and delivery
- Postpartum management
- Surgical delivery
- Newborn screening
- Contraception

All women should have discussed with her an individualised care plan which should take into account her previous sickle and pregnancy history. This should be documented in the hand held notes.

5.3.4 Pre-pregnancy

Men and women with SCD have a 50% chance of having a baby with a major haemoglobin disorder if their partner carries a significant haemoglobin disorder (see National Screening Programme guidance). Partner screening is recommended pre-conceptually, if their status is unknown. This will enable a couple at high risk of having a baby with major haemoglobinopathy to be counselled either before or at an early stage of pregnancy. Pregnancy should be discussed with male and female patients as part of regular routine review (see chapter 2) and the subject should be introduced into transitional care at the appropriate time.

Hydroxycarbamide (hydroxyurea) is teratogenic in animals and cytogenetic abnormalities have been reported in humans, though the small number of human pregnancies reported with its use have resulted in normal infants⁸. Male and female patients with SCD taking hydroxycarbamide should be advised to discontinue this 3 months prior to conception. If pregnancy is unplanned, the drug should be stopped immediately that pregnancy is recognised and the couple counselled about possible risks.

Women with SCD and their partners contemplating pregnancy should be offered pre-pregnancy assessment at the SCD specialist secondary care centre, or in other suitable community care or primary care environments. Issues to be discussed at this visit should include:

- Family and social care matters
- Partner screening and genetic counselling with information regarding preimplantation genetic diagnosis (PGD) (especially where termination of pregnancy is not an option) and more conventional methods of PND
- Folic acid supplementation, prophylactic penicillin and analgesia requirements
- The risks of pregnancy for the mother and the baby: This will take into account her medical history. Further investigations or clinical opinions will be dictated by this or by local practice
- Discontinuation of hydroxycarbamide and the likely effects on her SCD (if relevant)
- Assessment of iron status if overload suspected, discussion re chelation drugs if being used, timing of pregnancy in relation to iron status, etc.
- Review of Pneumovax status, serology for hepatitis viruses, HIV and to check immunity to rubella

Women with SCD trying to conceive should be advised to report pregnancy as soon as possible.

All women should be advised to take folic acid supplements, even if they were not taking these before. The correct dose for such women is 5mg/day (not the standard 400 micrograms/day dose advised to all women planning pregnancy).

5.3.5 Booking and antenatal care

5.3.5.1 Booking

Maternal blood should be sent for routine obstetric booking investigations plus, haemoglobin electrophoresis and HbS concentration (if not already available), red cell folate, ferritin, urea and electrolyte (U&Es), liver function tests (LFTs), cytomegalovirus (CMV) status, Hepatitis C and HIV (if not done routinely). If not already available, a red cell genotype should also be sent to the blood transfusion laboratory and an extended blood group antibody screen performed.

History should include: frequency and nature of sickle cell crises, acute and chronic complications, transfusion history, infections and routine sickle cell crisis management. The women should have a physical examination and recording of percutaneous oxygen saturations. Further investigations will depend on the clinical findings. An opportunity should be taken to perform an echocardiogram and retinal screening if these have not been done before.

Prophylactic antibiotics should be continued, if already taken. If not, an individual decision whether to start antibiotics can be made after discussion with the woman. A management plan should be made and the woman advised to seek prompt medical attention at the earliest sign of infection or complications relating to SCD.

Routine blood transfusion is not usually necessary for uncomplicated pregnancies, but should be considered for women with a poor obstetric or medical history: each woman will be considered on an individual basis by the haematologist. If the woman has, or has previously had evidence of transfusional iron overload, a cardiac assessment is required to exclude a cardiomyopathy (preferably pre-pregnancy).

Arrangements should be made for genetic counselling and testing of the woman's partner (if not already done) by the specialist practitioner. If the couple are found to be 'at risk' of having a child with a major haemoglobinopathy the option of PND should be discussed and arranged, if appropriate. The woman should be given all the other routine information offered in pregnancy including other antenatal screening tests and advice about nutrition.

5.3.5.2 Subsequent antenatal visits

Care will be individualised for each woman depending on her history and disease severity, but in general:

- The woman should be seen every 4 weeks, or more often as clinically indicated, then every 2 weeks from 28 weeks until 36 weeks, then seen weekly until term
- Full blood count (FBC) and haematocrit should be checked monthly; if concomitant iron deficiency is suspected, confirm by iron studies before prescribing iron medication
- Liver and renal function tests should be checked every 4 weeks (along with clinical assessment)
- Blood pressure should be checked at each visit. Baseline blood pressure is generally lower than in a non sickle population and relatively modest changes may be an early indication of pregnancy induced hypertension. A threshold value of 125/75mmHg has been recommended by some authorities⁹, although diagnosis is more usually dependent on a rise compared with early pregnancy readings
- If significant red cell alloantibodies are detected, serology should be repeated every 2 weeks from 16 weeks gestation, or as directed by the National Blood Service. If indicated, fetal anaemia can be assessed every 2 weeks by middle cerebral artery peak systolic velocities using ultrasound Doppler studies

- Midstream urinalysis should be performed routinely at each visit and midstream urine (MSU) sent to microbiology where indicated. If infection is suspected, treat with a broad-spectrum antibiotic until MSU result confirms significant bacterial growth. Adjust antibiotics according to antibiotic sensitivities if indicated
- Ultrasound scans should be performed as follows:
 - Booking: to confirm gestational age of the fetus and calculate EDD, as well as offering screening for Down's syndrome and other aneuploidies
 - 20 weeks gestation: fetal anatomy survey
 - Consider uterine artery Dopplers at 24 weeks
 - Scans to measure fetal growth at 28, 32 and 36 weeks gestation. If small for dates scan more frequently and perform umbilical artery Dopplers as required

5.3.6 Specific management

5.3.6.1 Infection

SCD is associated with hyposplenism and increased risk of infection. Infection, especially of the urinary tract and respiratory system occurs in 50% of women with SCD during pregnancy⁹. Prophylactic penicillin, where taken, should be continued during pregnancy.

Asymptomatic bacterial urine infections can become symptomatic if left untreated and may contribute to the increased incidence of prematurity and low birth weight. There should be a low threshold for prescribing antibiotics. Any pyrexia associated with or without sickling crisis warrants an infection screen and commencement of broad-spectrum antibiotics. The subsequent result of the infection screen will determine continuation or discontinuation of the antibiotics. If there is clinical concern the woman should be admitted to hospital to maintain hydration, warmth, oxygenation as well as specific therapy.

5.3.6.2 Painful (vaso-occlusive) crisis

Some women may experience more painful crises during pregnancy. If the crisis is severe admit the patient to hospital under joint care of an obstetrician and haematologist. The local policy should indicate choice of ward (i.e. haematology or antenatal) and pain should be managed as normal according to the local pain policy (see also BCSH guideline¹⁰) with the following cautions:

- NSAIDs (e.g. diclofenac) should be used with caution in pregnancy and should not be given in early pregnancy (first trimester) or after 32 weeks gestation (due to the risk of premature closure of the ductus arteriosus)
- Fetal well-being should be assessed regularly with sonicaid/cardiotocography as appropriate

5.3.6.3 Blood transfusion

Although transfusion in pregnancy is well tolerated it carries the risk of alloimmunisation, iron overload and transfusion transmitted infection. A randomised trial of routine transfusion versus emergency transfusion showed no statistically significant reduction in obstetric or perinatal outcomes in the aggressively transfused group. There was a significant reduction in painful crises but not other sickle complications⁶. These results were confirmed in a retrospective review of pregnancies in the UK between 1991-1993¹¹. In the absence of clear evidence to guide practice, it would seem reasonable to conclude that:

- Empiric blood transfusion is not necessary in pregnancy (A)
- Blood transfusion is not routinely required for general anaesthesia or caesarean section

- Indications for transfusion in pregnancy are:
 - Hb falling to <6g/dl
 - Anaemia with cardio or respiratory compromise
 - History of severe SCD related complications (e.g. recurrent Acute Chest Syndromes, stroke, repeated painful crises during pregnancy)
 - Patients on chronic transfusion programmes
 - Twin pregnancies
- If clinically indicated, transfusion should be given under the direction of the haematology team to maintain the HbS level <30%, and a target Hb of 10-11g/dl. Blood may be given by exchange and/or top-up
- Routine guidelines for use of blood products should be maintained including using full Rhesus compatible, Kell negative, CMV negative (in non-immune individuals) red cells
- If the woman is known to have multiple alloantibodies, storage of antigen matched blood may be necessary if complications are anticipated
- Patients on chronic transfusion therapy should be advised to discontinue iron chelating treatment as soon as pregnancy is confirmed. Those with significant iron overload should undergo cardiac and endocrine assessment

5.3.6.4 Prophylactic anticoagulation

SCD is associated with a pro-coagulant state and is considered a risk factor for venous thromboembolism (VTE) in pregnancy¹². Routine anticoagulant prophylaxis is not required. For women with risk factors for VTE, follow Royal College of Obstetricians and Gynaecologists (RCOG) guidelines. This includes any period of reduced mobility e.g. during sickling crisis, and following operative delivery (for up to 6 weeks).

5.3.6.5 Jaundice

Jaundice in SCD is due to an unconjugated hyperbilirubinaemia as a result of haemolysis and may be increased during painful crisis. Any increase in level of jaundice from steady state should be investigated for other causes of hyperbilirubinaemia. There is no risk from maternal haemolytic jaundice to the fetus.

5.3.7 Labour and Delivery

5.3.7.1 Labour

Unless specific complications arise, spontaneous labour and delivery can be anticipated. Dehydration, hypoxia, acidosis, infection and cold can precipitate painful crisis; therefore these should be avoided, especially in labour when there is already increased stress on the body. Paediatricians must be informed if the mother has a history of recent opiate use or dependence.

Placental insufficiency is common, leading to an increased risk of fetal compromise during labour. In view of this the following are recommended:

- IV fluids 3L/24 hours. If PET present, seek consultant advice about fluid replacement
- Oxygen via face mask if partial oxygen percentage (PO₂) <95%
- Continuous electronic fetal monitoring
- Use of standard labour analgesia (e.g. nitrous oxide, opiates or epidural)
- Prophylactic antibiotics to cover labour and puerperium: augmentin or erythromycin (if penicillin allergic)

5.3.7.2 Analgesia

For women receiving prophylactic anticoagulation it is safe to proceed with epidural if >12hrs since the last low molecular weight heparin injection and clotting screen is

normal¹². Advice from a consultant anaesthetist should be requested for women on therapeutic anticoagulation.

5.3.7.3 Caesarean section

For lower segment caesarean section (LSCS), a regional anaesthetic is preferred to a general anaesthetic (GA). GA can be used safely but will need more intensive peri-operative monitoring and increases the risk of postpartum complications.

Post-delivery, all women should be observed closely on the Labour Ward high dependency unit, or equivalent, with 4 hourly observation of vital signs and oxygen saturations on room air (even if on oxygen) until the woman is mobile (see 7.3.1.2). If chest signs and/or symptoms develop, or oxygen saturations fall <92%, a haematologist must be informed as ventilation via continuous positive airway pressure (CPAP) may be necessary (see also below).

Women having a LSCS should have prophylactic anticoagulation until 6 weeks postpartum (C).

5.3.8 Postpartum care and follow up

The mother is still at risk for the first few weeks after delivery. The following are recommended:

- Maintain hydration by intravenous route, monitor and supplement oxygenation if required for at least the first 24 hours after delivery
- Prescribe broad-spectrum antibiotics for 5 days post delivery (e.g. augmentin)
- Mothers should be encouraged to breast feed unless there is a contraindication
- Encourage early ambulation so as to avoid the increased risk of thromboembolism, and consider thromboprophylaxis, if other clinical risk factors exist¹².

If the baby is known to be at high risk of having SCD, as a result of antenatal testing, this should be indicated in the antenatal notes. These babies should have a capillary blood sample taken soon after birth. Arrangements should be in place for the result to be communicated to the mother as soon as possible. The taking of neonatal samples when the antenatal screening process has identified a baby with a high risk of a major haemoglobin disorder is highly recommended. A capillary blood sample should be taken.

Contraception should be discussed with the woman prior to discharge and the choice will depend on the woman's personal preference and ability to take it.

5.3.9 Contraception in SCD

Reproductive decisions present a major dilemma for women with SCD because of the potential risk to the mother and fetus. This is a group that historically has a high incidence of unwanted pregnancy¹³. Contraception should be discussed during transitional care and at regular review and the woman should be fully informed on the advantages and disadvantages of the methods available.

There are very few randomised control trials in this area and no recent studies. A full range of choices can be offered to women with SCD, but some methods may be more suitable than others.

5.3.9.1 Progesterone type contraception

A recent review article into of the use of progestogen-only contraceptives in women with SCD concluded that there were "no clinically or statistically significant adverse

effects associated with progestogen-only contraceptive use among women with SCD¹⁴. Some articles suggested a better outcome for those using progestogen containing contraceptives in terms of symptoms such as painful crises and haematological parameters such as increase in the percentage of HbF. Progestogen contraception is available as a pill or as a depot injection. Relative merits of each type are summarised in table 5.

Table 5: SCD and eligibility for use of reversible contraceptive methods*

Contraceptive Method	Category [†]	Advantages	Disadvantages
Barrier (condom, diaphragm, etc.)	1	<ul style="list-style-type: none"> Neutral effect on symptoms and haematological parameters 	<ul style="list-style-type: none"> Failure rate Allergy to latex (latex condoms)
Combined hormonal contraception (COCC)	2	<ul style="list-style-type: none"> Oral method Widely used Provides effective contraception 	<ul style="list-style-type: none"> Listed as “warning and precaution” Increased risk of thrombosis
Progestogen-only pill (POP)	1	<ul style="list-style-type: none"> May have a beneficial effect on symptoms such as painful crises May improve haematological parameters e.g. HbF 	<ul style="list-style-type: none"> Often causes irregular bleeding or amenorrhoea. Must be taken every day Less reliable than COCP
Depot medroxy-progesterone acetate (DMPA) Norethisterone enanthate (NET-EN)	1	<ul style="list-style-type: none"> As for POP above 	<ul style="list-style-type: none"> May cause irregular bleeding, usually with subsequent amenorrhoea; needs to be repeated 12 weekly (8 weekly for NET-EN)
Implant (progestogen-only) (IMP)	1	<ul style="list-style-type: none"> As for POP above 	<ul style="list-style-type: none"> Requires minor surgical procedure for fitting
Copper intrauterine device (Cu-IUCD)	2	<ul style="list-style-type: none"> Can remain in situ for 5 years 	<ul style="list-style-type: none"> May cause heavy periods Risk of infection
Levonorgestrel releasing intrauterine system (LNG-IUS)	1	<ul style="list-style-type: none"> May lessen menstrual bleeding and/or lead to amenorrhoea 	<ul style="list-style-type: none"> Often causes irregular bleeding when first fitted

5.3.9.2 Combined hormonal contraceptive (COCP)

In the past there has been some concern about prescribing COCPs due to the increased risk of thrombosis, and the product information indicating SCD as a condition requiring “warning and precaution”. However experience with the lower dose pills currently commonly prescribed has shown no additional risk. The WHO recommends that, in the case of COCP, the benefits of contraception outweigh the risks potentially associated with this method¹⁵.

5.3.9.3 Intrauterine device (IUCD)

The main concerns with IUCDs in SCD are the potentially increased risks of menorrhagia and infection. The WHO recommendation is that it can be used if the benefit outweighs the risks associated with this method. Heavy painful periods may

* adapted from WHO and UK guidelines

† CATEGORY: 1. A condition for which there is no restriction on the use of the contraceptive method; 2. A condition where the advantages of using the method generally outweigh the theoretical or proven risk

make the copper IUCD inappropriate for women with SCD. For this reason the levonorgestrel releasing IUD (LNG-IUD) is the preferred choice of IUD in this group.

5.3.9.4 Hormone replacement therapy

In the absence of published information concerning the use of hormone replacement therapy in SCD, the same considerations should apply as in women without SCD. An assessment of bone density after the menopause may be useful in guiding the woman's choices.

5.3.10 Fertility

Fertility in women with SCD does not seem to be impaired when compared to their non sickle counterparts. There are emerging data suggesting that fertility in men may be impaired, particularly if they have had problems with recurrent priapism, testicular infarction or have been on anti-androgen medicines. At this stage it is too early to make any specific recommendations. Men and women who have not conceived after 1 year of regular unprotected sexual intercourse should be offered further clinical investigation.

References

- ¹ Smith JA, Espeland M, Bellevue R, et al. Pregnancy in SCD: experience of the cooperative study of SCD. *Obstet Gynecol.* 1996; 87: 199-203.
- ² Khare M, Bewley S. Management of pregnancy in SCD. *Practical Management of haemoglobinopathies.* Blackwell Publishing. 2004.
- ³ Confidential Enquiry into Maternal and Child Health. *Why Mothers Die. 2000-2002.* RCOG press.
- ⁴ Confidential Enquiry into Maternal and Child Health. *Saving Mother's Lives. 2003-2005.* RCOG press.
- ⁵ Lottenberg R, Hassell KL. An evidence-based approach to the treatment of adults with SCD. *Hematology Am Soc Hematol Educ Program.* 2005; 58-65.
- ⁶ Koshy M, Burd L, Wallace D, et al. Prophylactic red cell transfusion in pregnant patients with SCD. A randomized cooperative study. *N Eng J Med.* 1988; 319: 1447-1452.
- ⁷ National Service Framework for Children, Young People and Maternity Services Standard 11: Maternity Services. 2004. NHS.
- ⁸ Diav-Citrin O, Hunnisett L, Sher G, et al. Hydroxycarbamide use during pregnancy: a case report in SCD and review of the literature. *Am J Hematol* 1999; 60: 148-50.
- ⁹ Hassell K. Pregnancy and SCD. *Hematol Oncol Clin North Am.* 2005;19(5): 903-16, vii-viii.
- ¹⁰ British Committee for Standards in Haematology. Guidelines for the management of the acute painful crisis in SCD. *Brit J of Haematology* 2004; 126: 455-474.
- ¹¹ Howard RJ, Truck SM, Pearson TC. Pregnancy in SCD in the UK: results of a multicentre survey of the effect of prophylactic blood transfusion on maternal and fetal outcome. *Br J Obstet Gynaecol.* 1995; 102: 947-51.
- ¹² Royal College of Obstetrics and Gynaecology. Guideline No 37, Jan 2004.
- ¹³ Howard RJ, Lillis C, Tuck S. Contraceptives, counselling and pregnancy in women with SCD. *BMJ* 1993; 306: 1735-7.
- ¹⁴ Legardy JK, Curtis KM. Progestogen-only contraceptive use among women with sickle cell anemia: a systematic review. *Contraception* 2006; 73(2): 195-204.
- ¹⁵ World Health Organisation. *Medical eligibility criteria for contraceptive use.* 3rd ed. Geneva: World Health Organisation; 2004.

Blood Transfusion

6.1 Introduction

Red cell transfusion may be required in sickle cell disease (SCD) either as an emergency measure or as prevention of the short and long-term complications of SCD. Because red cell alloimmunisation is relatively common among transfused SCD patients, potential benefits must be considered against potential risks. This guidance is aimed at optimising the benefits whilst minimising the risks. However, it should be recognised that some patients may decline blood transfusion for religious or other reasons, even when the potential benefits outweigh the risks; the wishes of these patients should be respected.

6.2 Core standards

i) Transfusion and management protocols

- All hospitals providing care for patients with SCD should have a blood bank that provides a blood transfusion service 24 hours a day, 7 days a week; it should be compliant with UK and EU directives and have regularly updated standard operating procedures for the issue of blood products to people with SCD
- Blood banks should be able to perform ABO grouping, full red cell phenotype (or at a minimum, phenotyping of the Rh and K blood groups), atypical red cell antibody screen and the identification of common atypical red cell antibodies
- All hospitals providing care for SCD patients should have a Hospital Transfusion Committee. There should also be a Transfusion Practitioner whose duties should include the education and training of hospital staff in blood transfusion issues in SCD
- All SCD patients must have their ABO group and full red cell phenotype performed at the first opportunity regardless of the clinical severity of their SCD or their anticipated future blood transfusion requirements
- Red cell units for transfusion to all SCD patients should be ABO compatible and also matched for D, C, E, c, e and Kell to minimise alloimmunisation; donor red cell units should be HbS negative and preferably <2 weeks old
- The blood bank must keep an accurate and detailed transfusion history of every SCD patient that has contact with the hospital. The hospital blood bank must always carry out its own tests on patients who have transferred their care from another hospital if there is any doubt about the validity of the results from the other hospital
- A card bearing details of the full red cell phenotype and all previously detected alloantibodies must be issued to the patient
- All hospitals must have local protocols for the recognition and management of SCD complications requiring emergency red cell transfusion
- A written and up to date protocol for exchange transfusion should be available within the hospital; this can be consulted in the event that a trained nurse is not available to perform this procedure in an emergency
- Hepatitis B vaccination should be routine for patients with SCD, regardless of previous or projected transfusion history (see 3.3.2.4)

ii) Iron overload and chelation therapy

- All patients who have been previously transfused or are currently undergoing regular transfusions, whether top-up or exchange, should have regular quantitative monitoring of liver iron concentration using MRI

- Iron chelation should be considered in all patients on a regular transfusion regimen who have received at least 20 top-up transfusion episodes or have a liver iron concentration of ≥ 7 mg/g dry weight
- All patients receiving iron chelation therapy should be regularly monitored for iron overload; monitoring of response to chelation therapy should be regularly undertaken and appropriate adjustments made
- Monitoring of chelator toxicity should occur regularly and complications clearly documented
- Practical and psychological support should be provided to patients to help improve adherence to chelation therapy

6.3 Recommendations for best practice

Blood transfusion practice in SCD should follow established national guidelines¹. Due consideration must be given to the distinctiveness of this patient group particularly with regard to their tolerance of a low haemoglobin level when in steady state, the speed with which acute complications requiring blood transfusion might develop and the high rate of alloimmunisation. Constant vigilance and effective planning are vital for optimal management of patients requiring either emergency or elective transfusions. Practitioners must take a long-range view when deciding on blood transfusions, even when these are given only occasionally for specific indications. Effective monitoring should be in place for transfusion-transmitted viruses, alloimmunisation and iron overload. Transfusion situations requiring SCD expertise, such as the hyperhaemolysis syndrome are best managed in collaboration with SCD specialist centres or the NBS.

6.3.1 Indications for transfusion

There are 2 main purposes for blood transfusion in SCD:

- To correct anaemia and so improve the oxygen-carrying capacity of blood
- To treat or prevent the occurrence of painful/vaso-occlusive or sequestration complications by lowering %HbS relative to HbA

Although anaemia is a constant feature of SCD, transfusion is rarely justified for chronic anaemia alone as levels are typically between 7-9g/dl, and patients are well adjusted to their steady state haemoglobin level. The evidence-base for the use of blood transfusion in terms of controlled clinical trials is rather limited. Nevertheless, there are certain clinical situations in which it is now accepted as best practice.

The indication for life threatening acute anaemia is self-evident and has understandably not been the subject of therapeutic trials. The early administration of exchange transfusion for acute chest syndrome is accepted as best practice and has been shown to be beneficial in one prospective randomised trial². For other life threatening events, controlled trials are limited. Table 6 shows some of the key sickle acute syndromes in which exchange transfusion may play a role. Further discussion of these can be seen in chapter 3.

Table 6 Transfusion for acute medical emergencies

Top-up transfusion	Exchange transfusion
<ul style="list-style-type: none"> • Transient red cell aplasia • Acute splenic sequestration 	<ul style="list-style-type: none"> • Acute stroke • Acute chest syndrome • Severe sepsis • Acute hepatic sequestration • Acute multi-organ failure • Progressive intrahepatic cholestasis

The indications for red cell transfusion for elective purposes (see table 7) range from conditions in which its efficacy is proven, to others in which the indications have not been formally tested. In the latter group, the use of blood transfusion should be determined on a case-by-case basis after a careful benefit/risk analysis.

Table 7 Possible indications for elective blood transfusions

Level A or B evidence available	Level A and B evidence unavailable
<ul style="list-style-type: none"> • Primary stroke prevention • Secondary stroke prevention • Elective surgery • Painful crises in pregnancy 	<ul style="list-style-type: none"> • Fetal complications in pregnancy • Repeated severe painful crises • Pulmonary hypertension • Leg ulcers

Level (A) evidence refers to evidence from prospective randomised studies. There is level (A) evidence that transfusion reduces the risk of primary stroke³. Overall mortality with elective surgery such as cholecystectomy, head and neck surgery and orthopaedic interventions is about 1%⁴ and a prospective but non-randomised study showed a mortality of 5% in untransfused patients and no mortality in transfused patients⁵. Another randomised study showed equal benefit with both top-up and exchange transfusion and top-up was associated with less alloimmunisation⁶. No randomised studies have examined the risk/benefits of transfusion for minor operations with short durations of anaesthesia. In pregnancy, a prospective randomised study showed that patients randomised to prophylactic transfusion had a significantly lower rate of pain and cumulative complications of SCD⁷. However, in patients randomised to 'no transfusion' there was no difference in the total blood volume received during pregnancy from those randomised to prophylactic transfusion. The study was too small to determine the effect of transfusion on maternal mortality or fetal outcome. Blood transfusion has been used for a variety of other indications where case reports, clinical experience and uncontrolled series have suggested a therapeutic role. These include leg ulcers, progressing avascular hip necrosis and progressive sickle retinopathy. In some of these reports, the benefit of transfusion has appeared to be very dramatic, but specific recommendations must await more extensive data. Blood transfusion in the treatment of pulmonary hypertension seems also theoretically reasonable by decreasing haemolysis and thereby nitric oxide scavenging and consequent pulmonary vasoconstriction. However, evidence from prospective clinical trials is currently lacking.

Further detail on transfusion in primary and secondary stroke as well as elective surgery can be found in chapter 4 and chapter 7 respectively.

6.3.2 Choice of top-up or exchange transfusion

In general, red cell exchange is a better option in situations where a reduction of immediate sickle complications is required, without an undesirable increase in blood viscosity (e.g. acute infarctive stroke, acute chest syndrome). It is also a better option for patients on prophylactic long-term transfusions if iron overload cannot be effectively and safely prevented with chelation therapy. Table 8 shows a summary of advantages and disadvantages for both options.

6.3.2.1 Hyperviscosity

The risk of hyperviscosity is an important consideration in deciding the optimal transfusion regime. HbS containing red cells are hyperviscous in the microcirculation and have poor flow characteristics. This can be exacerbated if the Hb is raised, even though the transfusion is performed with HbA containing red cells. This limits the

amount of top-up units that can be given acutely and it is unwise to exceed a post transfusion Hb of 10-11g/dl particularly if the proportion of HbS cells is >30%.

6.3.2.2 Iron balance

Top-up transfusion will inevitably lead to greater positive iron balance than exchange transfusion. Each unit of blood contains 200mg of iron and simple top-up transfusions lead to rapid accumulation of body iron, reaching 15mg/g dry weight after 21 months of transfusion without chelation with demonstrable liver fibrosis in about 30% of patients^{8,9}. Reductions in net blood requirements and hence iron loading can be achieved with manual or automated exchange transfusions^{10,11}.

Table 8: Top-up vs exchange - summary of advantages and disadvantages

	Advantages	Disadvantages
Exchange	<ul style="list-style-type: none"> Decreased rate of iron accumulation Better control of desired HbS level, especially in patients with relatively high pre-transfusion haematocrit Relatively little risk of hyperviscosity 	<ul style="list-style-type: none"> Venous access can limit applicability Long-term indwelling lines are associated with increased rates of infection and thrombosis More resources required than simple top-up: trained staff, equipment (± apheresis machines, blood warmers) Increased overall donor exposure: higher infection and alloimmunisation risk, blood availability could be a problem in patients with multiple alloantibodies
Top-up	<ul style="list-style-type: none"> Technically easier than exchange transfusion Fewer resources required Reduced exposure to donor blood 	<ul style="list-style-type: none"> Faster rate of iron accumulation Cannot achieve acute target HbS <30% without risk from blood hyperviscosity

6.3.2.3 Alloimmunisation

Steps in donor selection to minimise alloimmunisation to red cells are described below. However, chronic exchange transfusion procedures increase exposure to red cells by at least 2-fold compared with chronic top-up transfusions thereby increasing the risk of alloimmunisation.

6.3.2.4 Venous access issues

The ability to perform an exchange transfusion may be limited by venous access. Although manual exchange can be performed using a single line this is slow and exchange can only be performed isovolaemically using 2 sites of venous access (not in the same arm). In general returning blood to the patient can be achieved with a smaller cannula than required for blood removal and this is usually the limiting factor. In an acute emergency, a central line can be inserted but this may be impractical for long-term exchanges.

Poor venous access is a common problem, often due to the unnecessary insertion of IV cannulae for fluids or medication during repeated in-patient admissions. Indwelling central venous catheters such as Port-a-Caths have an unacceptably high complication rate among SCD patients compared with other patient groups and are therefore best avoided^{12,13}. The complication rate of central lines inserted for short-term therapeutic reasons such as acute exchange transfusion is also high; such lines should not be kept in situ longer than is absolutely necessary. This highlights the need

to avoid unnecessary insertion of cannulae and use of IV fluids when patients are admitted to hospital.

6.3.3 Exchange Transfusion Techniques

A detailed description of how to undertake manual or automated red cell exchanges is beyond the scope of this document: here, some key principles are outlined.

6.3.3.1 Choice of manual or automated exchange

Exchange transfusions can be performed manually¹⁴ or can be automated using a cell separator^{15,16}. Both approaches are suitable for in-patients with acute sickle complications requiring emergency red cell exchange and for out-patients on an elective red cell exchange programme. The proportion of blood exchanged can be varied with either approach as can the intended target final Hb and both approaches can be performed isovolaemically provided venous access is adequate. In practice there has been a very wide variation in what have been referred to as 'exchange' procedures, ranging from little more than a modified 'top-up' to a single procedure aimed at achieving <10% HbS.

Automated apheresis

- Relatively quick: approximately 2 hours to achieve a target HbS <30% in patients with good venous access, using a single continuous flow procedure
- Can be programmed to achieve a target final Hb, %HbS and net fluid balance. If the goal is to achieve the lowest proportion of HbS containing cells as fast as possible this approach will be the quickest where available
- When more than 30-50% of the total blood volume is exchanged, care must be taken to avoid acute hypocalcaemia and dilutional thrombocytopenia
- Use is limited in many parts of the UK by the unavailability of cell separators and/or trained operators

Manual exchange

- Requires less equipment and can be performed in any ward or day care setting without the need for a cell separator or trained cell separator operator (in-patients do not need moving to do the procedure)
- Can be performed with a single vein, or with an indwelling line (although it is done most quickly and isovolaemically using a 2 arm technique)
- Can also be repeated, when required, without the need to book the use of a cell separator or call in a trained operator
- Partial exchange (approximately 30% of the blood volume) can be achieved in 2 hours. This approach is effective on an out-patient basis for maintaining HbS <30% if performed every 4 weeks
- Rapid reversal of chest syndrome can also be achieved effectively with a partial exchange
- Protocols differ from hospital to hospital and will need to be agreed with the SCD specialist centre

6.3.3.2 Organisational practicability of exchange transfusions

Staff trained in automated exchanges may not be available in all units or out of hours. It may also be difficult to arrange for a patient on a high dependency unit to be moved for an automated exchange. Manual exchange may be more practicable under these circumstances and should be achievable in a local unit setting.

6.3.3.3 Volumes to exchange to achieve target HbS values

It is important to understand that the efficiency of exchange decreases as the volume exchanged increases. Exchange becomes very inefficient when the %HbS falls below

10% (because the blood being removed has similar HbA to that being transfused). Acceptable reduction in HbS red cells has been achieved using both a single^{15,16} and a 1.5 red cell volume exchange¹⁷. The greater the acute threat, the larger the exchange volume that may be required (with the lowest final target HbS).

6.3.4 Safety: minimising complications of blood transfusions

Perhaps the most important factor in minimising transfusion risk is the avoidance of unnecessary transfusion in SCD. The main complications of blood transfusions that can have a lasting negative impact on the long-term health of SCD patients are:

- Infection
- Alloimmunisation
- Iron overload (see 6.3.6)

6.3.4.1 Minimising transfusion transmitted infection

- All patients must have their hepatitis B, hepatitis C and HIV status checked and documented when first seen
- Hepatitis B vaccination should be routine for patients with SCD, regardless of previous or projected transfusion history
- Hepatitis B surface antibody levels must be checked annually and boosters given when levels fall below 100mIU/ml
- Regularly transfused patients must be screened annually for hepatitis B, hepatitis C and HIV
- The usual safeguards for blood safety (adequate storage) must be followed in order to prevent bacterial contamination

Despite these precautions there is still a small but significant risk of transfusion transmitted infection. Transfused units contaminated with bacteria are uncommon. Frequently transfused, iron overloaded patients are at risk of *Yersinia enterocolitica* infection. All patients who develop fever post-transfusion should be assessed for possible bacterial infection.

6.3.4.2 Minimising alloimmunisation

Alloimmunisation rate among people with SCD is much higher compared to a non sickle population. The reported alloimmunisation rate of 18-36% is likely to be an underestimate as one third of alloantibodies rapidly become undetectable. The frequency of alloimmunisation increases proportionately with the number of red cell units administered (or exposed to), rising to 57% in patients who have received more than 200 transfusions. Top-up transfusions lead to less donor exposure than exchanges and a lower risk of alloimmunisation. The most frequent alloantibodies are against Kell, C and E; together, these account for 60-98% of detected antibodies in published studies. The risk of alloimmunisation is reduced 10-fold if fully phenotyped matched blood is given and can also be significantly decreased (from about 3% to 0.5% per unit) by phenotypic matching against Kell, C and E antigens¹⁸.

Patients who make Rh and K antibodies are also more likely to form other alloantibodies, thus forming multiple alloantibodies. Over half of alloimmunised SCD patients have more than one alloantibody. There is evidence that alloimmunisation increases the rate of autoantibody formation; prevention is therefore an essential goal.

Recommendations

- An extended serological red cell phenotype should be performed on all patients, ideally before first transfusion, or failing that at earliest opportunity. Molecular typing should be performed on already transfused patients

- Donor blood should be ABO compatible and also matched for D, C, E, c, e and Kell.
- Donor blood should be matched for any other atypical red cell antibodies that are present. In most cases, this will entail ordering in the units from the NBS using the NBS Non-Standard Component Request Form
- Red cell units selected must be sickle negative; the sickle status of the donor unit will be indicated on the pack
- Red cell units should preferably be <10 days old to maximise red cell survival after transfusion. In patients requiring exchange transfusion, units <7 days old should be selected in order to minimise any possible adverse effects of accumulated potassium ions from stored blood. (Occasionally a patient will have multiple antibodies that make it difficult for the NBS to provide fresh SAGM blood. On these occasions use whatever product the NBS are able to provide)
- In an emergency rr units can be given to Ro patients or D+ patients where the Rh phenotype is unknown

Blood may have to be ordered in from the NBS so it is very important to anticipate any requirement for blood early on during the patient's admission, especially in patients presenting with an acute complication that might require blood transfusion.

6.3.4.3 Management of patients with rare blood groups or multiple alloantibodies

Occasionally patients develop a large range of alloantibodies or develop alloantibodies to a rare blood group such as anti-U. Under these circumstances finding donor blood in a timely manner during acute emergencies can be problematic and it is advisable to contact the local or regional transfusion centre to arrange for phenotypically matched donor blood to be frozen specifically for the named patient.

6.3.4.4 Management of hyperhaemolytic transfusion reactions

Hyperhaemolysis is a syndrome in which there is destruction of both donor and recipient red cells following transfusion. There is lysis of both transfused and autologous red cells resulting in severe and occasionally life threatening anaemia associated with reticulocytopenia. This syndrome needs to be differentiated from the more common delayed haemolytic transfusion reaction associated with a positive Coombs test and secondary to development of alloantibodies. In general evidence of red cell antibody-mediated haemolysis is lacking in hyperhaemolysis syndrome. The mechanism of red cell destruction is unclear but may be due to macrophage over activity. Patients may present approximately a week after transfusion often with symptoms suggesting a painful crisis. Continuation of transfusion in this situation may worsen haemolysis. In a patient suspected of hyperhaemolysis the management is problematic but transfusion should be avoided where possible. There have been several reports of response to intravenous immunoglobulin and corticosteroids. In some cases such therapy has allowed successful subsequent transfusion^{19,20}.

6.3.5 Alternatives to blood transfusion

A detailed critique of the alternatives to blood transfusion for all SCD related indications is beyond the scope of this chapter. However some key areas for consideration are highlighted below.

6.3.5.1 Use of incentive spirometry to prevent chest syndrome

There is evidence from a randomised controlled trial that the early use of incentive spirometry in all patients with chest or back pain above the diaphragm can reduce

progression of pulmonary complications by 8 fold²¹ and this should decrease the need of blood transfusions for progressing chest syndrome in a proportion of patients (A).

6.3.5.2 Use of hydroxycarbamide to prevent stroke

There are emerging data that hydroxycarbamide may have a beneficial effect in primary²² or secondary prevention²³ of stroke in children but its role relative to that of blood transfusion has not been defined by prospective trials. Until more data are available, blood transfusion is the modality of choice in treatment and prevention of stroke in SCD.

6.3.5.3 Use of hydroxycarbamide to prevent recurrence or progression of other complications

Hydroxycarbamide can decrease the pain rate, hospital admissions, chest syndrome, number of transfusions and mortality in a high-risk adult population²⁴. When considering a patient for long-term transfusion to reduce the risk of one or more of the above, the alternative use of hydroxycarbamide should be considered first.

6.3.5.4 Use of erythropoietin to correct anaemia

Uses of erythropoietin (epo) in SCD are limited. In most situations the use of epo is likely to increase haemoglobin and sicklecrit, possibly exacerbating the risk of vaso-occlusive complications. There is currently insufficient evidence to recommend the routine use of epo in this patient group. If it is to be used in CRF then this should be done in conjunction with renal physicians.

6.3.6 Iron chelation

Iron overload is frequently not recognised due to the intermittent use of transfusion in many adults. Those patients on regular top-up transfusion regimes are identified earlier and frequently started on chelation therapy but there is often a poor response due to a lack of appropriate infrastructure to help the patients adhere to the treatment.

The aim of chelation is to reduce the risk of complications secondary to iron overload. A large body of evidence has accumulated in thalassaemia patients showing the improved survival in patients who are chelated. There is currently little published data on iron overload in patients with SCD and even less on the treatment of iron overload and consequent reduction in morbidity and mortality. There is some evidence to support worsening clinical outcomes in the presence of severe iron overload. Monitoring of patients is essential and where possible an accurate history should be obtained from the patient on the amount of blood they have received. Patients will develop all the complications associated with iron overload if no chelation is given.

The reduction in co-morbidities related to iron overload in particular the endocrinopathies and cardiac complications would result in a better quality of life and base line health status in patients.

6.3.6.1 When to start

Iron chelation should be considered for patients who have received at least 20 top up transfusion episodes or with liver iron concentrations ≥ 7 mg/g dry weight (C). At this level of iron loading, it is relatively easy to control the body iron burden and the risk of iron-related complications is low. Tissue iron loading becomes difficult to manage once extrahepatic iron deposition has occurred. Although liver iron determination by atomic absorption spectroscopy on a liver biopsy sample is the gold standard for assessing total body iron stores, standardised non-invasive quantitative measurement of liver iron concentration using MRI is now available in the UK for accurate assessment of iron overload, evaluating response to chelation and adjusting dosing of chelation therapy. Serum ferritin may be unreliable for estimating body iron because vaso-occlusive crises

are associated with elevation of serum ferritin¹⁴. However, serial ferritin trends in between quantitative hepatic iron measurements can be useful, provided the serum ferritin tests are always carried out when the patient is in steady state and the results are not used as the sole arbiter of the degree of iron overload or of response to chelation.

6.3.6.2 What to use

There are 3 chelating agents in clinical use but only 2 are licensed for use in sickle cell anaemia.

Desferrioxamine is the agent with which there is most clinical experience. The dose is adjusted according to body weight, age and iron load - and tailored to individual patient needs²⁵. Recommended mean daily doses are 20-50 mg/kg/day. The total dose for the week should be divided over a 5-day period and given over 10-12 hours (the longer the better) usually via a syringe driver pump or balloon infuser, subcutaneously. In children, the dose should not exceed 40mg/kg as effects on growth and bone development are more likely above this dose. More concentrated solutions are associated with more local reactions to desferrioxamine, and if patients have irritating local reactions more dilute solutions are recommended. Hydrocortisone 5-10mg can be added to the infusions to help reduce local skin reactions. The balloon infusers can be made up to 56ml and the additional dilution also helps to reduce the local reactions.

When iron load is low, the risks of toxicity from desferrioxamine such as effects on audiometry (high frequency hearing loss), retinopathy and growth are greater and the dose should be adjusted downwards²⁶. The use of falling ferritin as a guide to dose reduction can be unreliable in SCD as the serum ferritin can be raised for several weeks after a vasocclusive event independently of iron loading¹⁴.

The needles used to provide the infusions are important to help make the infusion more comfortable and the fine 'thumbtack' or 'drawing-pin' style needle introduced at 90 degrees to the skin surface into the subcutaneous tissues has the least skin reactions associated with it. The needle can be inserted into the skin of the abdomen, arms, or legs, wherever it is found most tolerable. Rotations between sites should occur so that scarring in any one place does not occur in order to aid better absorption.

Deferasirox is also licensed as first line treatment in sickle cell anaemia. There are extensive data from clinical trials on short-term (<5years usage) effectiveness but long-term data are not available yet²⁷. The dosage is adjusted according to body weight and the degree of iron overload. The recommended starting dose is 20mg/kg/day and is administered as a once daily drink taken half an hour before food. As patients with sickle cell anaemia are less frequently transfused and are often exchange transfused, a dose of 10mg/kg/day has been found to be effective at maintaining iron balance and 20mg/kg/day at reducing the iron load.

An increase in creatinine while remaining within the normal range is seen in about a third of patients within a few weeks of starting therapy. This has been non-progressive in a clinical trial setting involving over 700 patients for up to 4 years. Outside clinical trials, in over 30,000 patients receiving post marketing surveillance, occasional cases of renal failure have been reported²⁸. It is recommended that two serum creatinine measurements are performed to establish a pre-treatment baseline value prior to the initiation of treatment. Monitoring of the serum creatinine should be undertaken weekly for the first month after commencement of therapy or alteration of dose and monthly thereafter. Dose reduction or interruption should be considered for increases in serum creatinine >33% on 2 consecutive occasions. Measurement for proteinuria is also recommended at baseline and monthly thereafter. It is also advisable to monitor

hepatic function on a monthly basis and dose interruption considered for severe or persistent rises in liver function tests²⁸. Other side effects tend to be minor and include gastrointestinal upset and a rash occurring within 3 weeks of starting. If the rash is mild/moderate deferasirox can be continued but if it is moderately severe therapy should be discontinued and re-initiated at 50% dose once the rash has resolved. Iron overload should be monitored and once this is low the patient should be kept on a maintenance dose if transfusions are ongoing. [Full prescribing and monitoring guidance for deferasirox is included in the Summary of Product Characteristics and can be found at www.emc.medicines.org.uk; doctors are advised to refer to this before prescribing].

The majority of patients who are unable to adhere to desferrioxamine because of the burden of subcutaneous chelation, will adhere to deferasirox and be able to bring their iron overload under control, with an improved quality of life.

All patients treated with desferrioxamine or deferasirox should have annual audiology and ophthalmology assessments (A).

Deferiprone is not licensed for treatment in sickle cell anaemia. If a patient is started on this then the reasons should be clearly documented in the notes and the patient must be made aware of the non-licensed indication. Careful weekly monitoring of the neutrophil count should occur due to the risk of neutropenia and agranulocytosis.

Practical and psychological support should be provided to patients to help improve adherence (C).

References

- ¹ British Committee for Standards in Haematology. Blood Transfusion: Current Guidelines. www.bcshguidelines.com.
- ² Styles LA, Abboud M, Larkin S, et al. Transfusion prevents acute chest syndrome predicted by elevated secretory phospholipase A2 Br J Haematol. 2007; 136: 343-4.
- ³ Adams RJ, McKie VC, Hsu L. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial doppler ultrasonography. N Eng J Med. 1998; 339: 5-11.
- ⁴ Koshy M, Weiner SJ, Miller ST, et al. Surgery and anesthesia in sickle cell disease. Cooperative study of sickle cell diseases. Blood. 1995; 86: 3676-3684.
- ⁵ Haberkern CM, Neumayr LD, Orringer EP. Cholecystectomy in sickle cell anemia patients: Perioperative outcome of 364 cases from the National Preoperative Transfusion Study. Blood. 1997; 89: 1533-1542.
- ⁶ Vichinsky EP, Haberkern CM, Neumayr L, et al. A comparison of conservative and aggressive transfusion regimens in the perioperative management of sickle cell disease. N Eng J Med. 1995; 333: 206-213.
- ⁷ Koshy M, Burd L, Wallace D, et al. Prophylactic red-cell transfusions in pregnant patients with sickle cell disease. A randomized cooperative study. N Engl J Med. 1998; 319: 1447-52.
- ⁸ Harmatz P, Butensky E, Quirolo K, et al. Severity of iron overload in patients with sickle cell disease receiving chronic red blood cell transfusion therapy. Blood. 2000; 96: 76-79.
- ⁹ Olivieri NF. Progression of iron overload in sickle cell disease. Semin Hematol. 2001; 38: 57-62.
- ¹⁰ Porter JB, Huehns ER. Transfusion and exchange transfusion in sickle cell anaemias, with particular reference to iron metabolism. Acta Haematol. 1987; 78: 198-205.
- ¹¹ Adams DM, Schultz WH, Ware RE, et al. Erythrocytapheresis can reduce iron overload and prevent the need for chelation therapy in chronically transfused pediatric patients. J Pediatr Hematol Oncol. 1996; 18: 46-50.
- ¹² McCready CE, Doughty HA, Pearson TC. Experience with the Port-A-Cath in sickle cell disease. Clin Lab Haematol. 1996; 18: 79-82.
- ¹³ Jeng MR, Feusner J, Skibola C, et al. Central venous catheter complications in sickle cell disease. Am J Hematol. 2002; 69: 103-108.
- ¹⁴ Porter JB, Huehns ER. Transfusion and exchange transfusion in sickle cell anaemias, with particular reference to iron metabolism. Acta Haematol. 1987; 78: 198-205.
- ¹⁵ Janes SL, Pocock M, Bishop E, et al. Automated red cell exchange in sickle cell disease. Brit J Haematol. 1997; 97: 256-258.
- ¹⁶ Lawson SE, Oakley S, Smith NA, et al. Red cell exchange in sickle cell disease. Clin Lab Haematol. 1999; 21: 99-102.

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- ¹⁷ Swerdlow PS. Red cell exchange in sickle cell disease. *Hematology Am Soc Hematol Educ Program*. 2006; 48-53.
- ¹⁸ Vichinsky EP, Luban NL, Wright E, et al. Prospective RBC phenotype matching in a stroke-prevention trial in sickle cell anemia: a multicenter transfusion trial. *Transfusion*. 2001; 41: 1086-1092.
- ¹⁹ Cullis JO, Win N, Dudley JM, et al. Post-transfusion hyperhaemolysis in a patient with sickle cell disease: use of steroids and intravenous immunoglobulin to prevent further red cell destruction. *Vox Sang*. 1995; 69: 355-357.
- ²⁰ Win N, Yeghen T, Needs M, et al. Use of intravenous immunoglobulin and intravenous methylprednisolone in hyperhaemolysis syndrome in sickle cell disease. *Hematology*. 2004; 9: 433-436.
- ²¹ Bellet PS, Kalinyak KA, Shukla R, et al. Incentive spirometry to prevent acute pulmonary complications in sickle cell diseases. *N Eng J Med*. 1995; 333: 699-703.
- ²² Gulbis B, Haberman D, Dufour D, et al. Hydroxyurea for sickle cell disease in children and for prevention of cerebrovascular events: the Belgian experience. *Blood*. 2005; 105: 2685-2690.
- ²³ Ware RE, Zimmerman SA, Sylvestre PB, et al. Prevention of secondary stroke and resolution of transfusional iron overload in children with sickle cell anemia using hydroxyurea and phlebotomy. *J Pediatr*. 2004; 145: 346-352.
- ²⁴ Steinberg MH, Barton F, Castro O, et al. Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment. *Jama*. 2003; 289: 1645-1651.
- ²⁵ Porter JB. Practical management of iron overload. *Brit J Haematol*. 2001; 115: 239-252.
- ²⁶ Porter JB, Jaswon MS, Huehns ER, et al. Desferrioxamine ototoxicity: evaluation of risk factors in thalassaemic patients and guidelines for safe dosage. *Brit J Haematol*. 1989; 73: 403-409.
- ²⁷ Vichinsky E, Onyekwere O, Porter J, et al. A Randomized, Controlled Phase II Trial in Sickle Cell Disease Patients with Chronic Iron Overload Demonstrates That the Once-Daily Oral Iron Chelator Deferasirox (Exjade®, ICL670) Is Well Tolerated and Reduces Iron Burden. *Brit J Haematology*. 2007; 136: 501-8.
- ²⁸ Exjade® (deferiasirox) Summary of Product Characteristics. 2007.

Surgery and Specific Therapies

7.1 Introduction

Many people with sickle cell disease (SCD) undergo surgical procedures. There are peri-operative risks associated with SCD, therefore it is important that these episodes are managed optimally. There are now several specific therapies being used in practice; some of these therapies are aimed at treating the complications of the disease and others, such as hydroxycarbamide (also known as hydroxyurea), are aimed at modifying the underlying pathophysiology. This section outlines the evidence for these treatments and their role in patient management. It is becoming clear that the pathophysiology of SCD is complex and the new treatments are aimed at different pathways in its pathogenesis.

7.2 Core standards

i) Surgery

- All hospitals will have a protocol in place for pre-operative screening for SCD
- All hospitals will have a protocol in place for the peri-operative management of patients with SCD

ii) Specific therapies

- Hydroxycarbamide needs to be considered in patients who have:
 - recurrent episodes of acute pain (>3 admissions in the previous 12 months, or are very symptomatic in the community)
 - >2 episodes of acute sickle chest crisis
- All hospitals prescribing hydroxycarbamide for patients with SCD will have a patient information leaflet, and a protocol in place for drug monitoring
- Novel or experimental therapies and participation in trials need to be discussed with the patient as part of their Annual Review. If the local unit is not able to provide these services, there needs to be a clear pathway for provision of care
- Central funding should be sought for a clinical trials network that spans secondary, primary and community settings and includes research nurses and administrative support

7.3 Recommendations for best practice

7.3.1 Surgery

7.3.1.1 Pre-operative testing

All patients with SCD are at increased risk of sickle complications in the peri-operative and post-operative periods with an approximate mortality risk of 1%^{1,2}. This risk is increased more in those with a history of severe sickle-related complications, such as chest crisis or CNS disease and in more complicated surgical procedures. It is therefore important that patients with SCD are identified before the operation (C).

For routine operations, testing for SCD by HPLC or alternative diagnostic method, should be performed at the pre-assessment visit on all patients in the at risk ethnic groups (non-Northern Europeans). In the emergency situation the sickle screen and full blood count should be performed. The majority of cases of homozygous SCD will be picked up in this way. If there is doubt about the diagnosis (for example, in patients with HbSC disease who have a normal haemoglobin), and confirmatory testing cannot be performed rapidly, the haematologist must decide whether the patient should be treated as high risk or not. Examination of the blood film may be of help. For patients with known SCD it is essential to have a full blood count, red cell phenotype and

antibody screen checked pre-operatively. Phenotyped red cells (full Rhesus and Kell typed) should be available for all but the most minor surgery (C).

7.3.1.2. Peri-operative management

There should be collaboration between haematologists, surgeons and anaesthetists to produce an individual pre-operative treatment plan for any patient with SCD undergoing surgery. Routine operations should not take place if the patient is febrile or has a sickle cell crisis. Intravenous fluids should be commenced when oral fluids are stopped and continued until the patient is able to take oral fluids. The patient should be kept normothermic throughout the operation and warming blankets may be required. Ensure there is an oxygen rich environment from pre-medication until the patient is fully awake. Oxygen saturations should be monitored for 24 hours post-surgery. The use of intensive post-operative respiratory monitoring on a High Dependency Unit or the use of respiratory support with Incentive Spirometry or Continuous Positive Airways Pressure (CPAP) should be considered, especially for major surgery or for patients with preceding chronic chest disease. Prophylactic antibiotics should be given, with the choice of antibiotic depending on operation and local preference. Adequate analgesia should be used post-operatively as required (C).

7.3.1.3 Role of transfusion

A Cochrane review found a single randomised clinical trial which looked at pre-operative blood transfusions in SCD³. This trial compared an aggressive transfusion regime, where sickle haemoglobin was decreased to less than 30% by exchange transfusion, with a conservative regime, where a simple top-up transfusion was used to increase the haemoglobin to 10g/dl. There was no difference in peri-operative complications between the 2 groups, implying that top-up transfusion is as effective as exchange transfusion⁴ (A).

An older observational study in the US, however, did show a lower rate of SCD related complication in the group of patients who received pre-operative transfusion². Furthermore a non-randomised, multi-centre study of 364 patients undergoing cholecystectomy found that patients who received no transfusion had a worse outcome (5 fatalities) than patients randomised to either conservative or aggressive transfusion preoperatively (no fatalities). Untransfused patients also had a higher incidence of acute chest syndrome (19% vs 8%) and vaso-occlusive pain (19% vs 5%) than in transfused patients. However the number of patients receiving no transfusion was small (n=34) and larger randomised studies would help to clarify these findings⁵. An international multi-centre trial, the Transfusion Alternatives Pre-operatively in SCD (TAPS), which is funded by the National Blood Service, is being launched to examine this important question and will compare the use of pre-operative transfusion (top-up or partial exchange) with no pre-operative transfusion.

Each local unit should develop a pre-operative protocol in conjunction with the appropriate SCD specialist centre, but this should not replace individual discussion about each patient. It would seem pragmatic to use pre-operative transfusion for those patients having major surgery who have severe SCD, in particular chronic lung damage, and to avoid pre-operative transfusions for patients with mild disease having minor surgery.

7.3.2 Hydroxycarbamide (Hydroxyurea)

Hydroxyurea is now known as hydroxycarbamide. Hydroxycarbamide promotes HbF synthesis, improves red cell hydration, decreases neutrophil count, modifies red cell-endothelial cell interactions and acts as a nitric oxide donor.

7.3.2.1 Who and when

The Multi-centre Study of Hydroxycarbamide in SCD (MSH) was a randomised controlled trial which showed that hydroxycarbamide caused a reduction in the frequency of painful episodes, incidence of chest syndrome and in transfusion requirements⁶. Similar beneficial results were shown by a paediatric randomised controlled trial from Belgium⁷. Recent long term follow up data has shown that survival at 10 years was improved in patients taking hydroxycarbamide⁸.

Absolute indications:

Patients with moderate to severe SCD;

- who have had ≥ 3 painful crises per year over the past 2 years requiring hospital admission
- or have recurrent crises in the community which are severe enough to interfere with their activities of daily living
- or who have had ≥ 2 acute chest syndromes (A)

Possible indications:

Hydroxycarbamide has been used in anecdotal reports or observational studies in the following:

- Patients who have had a previous stroke, but are no longer willing or able to continue a transfusion programme
- Patients with excessive haemolysis causing anaemia or repeated gallstone formation
- Patients with anaemia due to renal disease, especially if they are not willing or able to have blood transfusion
- Priapism
- Leg ulcers (this is controversial as there is also some evidence that leg ulcers are made worse by hydroxycarbamide)
- Pulmonary hypertension

7.3.2.2 Dosage and monitoring

Hydroxycarbamide is an unlicensed medication and should only be commenced after giving the patient written information about the drug, full discussion of its side effects and obtaining signed consent. A dose of 15mg/kg (to the nearest 500mg) should be started in adults and the full blood count should be checked 2 weeks after initiation and after each dose increase. Once stable the full blood count should be checked every 6-8 weeks. It is not clear whether dose escalation to the maximum tolerated dose should be performed routinely; if the patient is still symptomatic, dose escalation should take place, every 4 weeks until the blood count falls. At this point the hydroxycarbamide should be stopped until the full blood count has recovered and restarted at 2.5mg/kg or 500mg lower. This is the maximum tolerated dose. Liver function tests and urea and electrolytes should be checked every 8 weeks. HbF levels should also be checked regularly as this gives a good indication of response as does an increase in Mean Cell Volume (MCV). Haemoglobin levels are expected to rise, but if they rise more than 3g over baseline venesection should be performed (C).

7.3.2.4 Side effects

Myelosuppression is the most common short term side effect and the drug must be monitored with regular blood tests. There is no established evidence of malignancy caused by the use of hydroxycarbamide in SCD, but there have been a small number of cases of leukaemia and lymphoma reported. This needs to be discussed with the patient and balanced against the improvement in symptoms and mortality. There is a risk of teratogenicity, and patients should be warned to use contraception. If a patient wishes to become pregnant, or to father a child, they should stop hydroxycarbamide for

3 months before conceiving. If a woman becomes pregnant whilst on hydroxycarbamide she should stop it immediately and should not recommence until breast feeding has stopped.

Other side effects include hyperpigmentation of nails, nausea and vomiting, skin rash, alopecia and diarrhoea. There was no evidence of an increased incidence of leg ulcers in the MSH study, despite the association of hydroxycarbamide therapy and leg ulcers in myeloproliferative disease.

7.3.3 Novel/experimental therapies

7.3.3.1 Transplantation

Stem cell transplantation is the only potentially curative treatment for SCD. Published evidence shows a 92%-94% survival rate and a 75%-84% disease free survival rate. The vast majority of stem cell transplants in people with SCD have been performed in children, and there is very little experience of them being performed in adults. The British Paediatric Haematology Forum has recommended stem cell transplants only in those <17 years of age, with severe SCD related complications, and who do not respond to hydroxycarbamide. The main indication for stem cell transplant is sickle brain disease as this is a serious complication of SCD where hydroxycarbamide is not indicated. If a clinician feels that a young adult may be a candidate for stem cell transplantation they should be discussed with a specialist centre which is experienced in transplant in haemoglobinopathy and local units should have clear referral links to such a transplant centre.

7.3.3.2 Others

- Gene therapy
- Agents which induce HbF levels: Butyrate, 5-azacytidine, decitabine, immunomodulatory drugs (e.g. lenalidomide)
- Agents which decrease red cell dehydration: ICA 17043, clotrimazole, dipyridamole, zinc, magnesium
- Niprisan
- Anti-adhesion therapies

7.3.3.3 Complementary therapies

There are no randomised controlled trials in the use of complementary therapies in SCD. However, there are several case reports of its use in the management of painful episodes. A recent telephone survey in the US found that over half of the parents of children with SCD surveyed used complementary or alternative medicine therapies. These included (in order of prevalence): bioenergetic therapies such as prayer or spiritual healing; lifestyle therapies such as relaxation techniques and exercise; herbal medicines and massage. There have also been anecdotal reports of benefit with deep tissue and deep pressure massage, self hypnosis, biofeedback and acupuncture. An evaluation of acupuncture in painful crisis showed that pain relief was obtained from needling, but this was the same whether sham sites or acupuncture sites were used.

7.3.3.4 Trials

There are a number of important questions that need to be answered in order that we better manage SCD. A growing understanding of the pathophysiology of SCD has led to a number of newer potential therapies being explored.

The prevention and management of end organ damage and other potentially life threatening complications are important therapeutic goals. Stroke prevention in patients with silent infarction, the management of pulmonary hypertension and the reduction of painful crises are some of the challenges that need addressing. Blood transfusion

remains an important form of treatment and it is expedient that this is used optimally with a good evidence-base.

A number of previous studies have contributed to the current management of SCD such as STOP for stroke prevention and the MSH, demonstrating the clinical efficacy of hydroxycarbamide. There are a number of ongoing clinical trials, which hopefully will answer some important clinical questions. Collaboration between centres in the UK and abroad is on the increase and should be encouraged.

All research activity in the UK is subject to strict research governance. All clinical trials are scrutinised by a multidisciplinary group known as the Central Office for Research Ethics Committee. Only if this group is satisfied that the clinical trial is well designed, safe and is asking an important question, will it be allowed to proceed. Each local centre which is planning to take part in a trial will also have to go through a local ethics committee and a local research and development committee, to show that the trial is relevant for their local population and that they have local expertise to carry the trial out. All trials are carefully monitored and any serious adverse effects seen in the trial are reported to a central committee and may result in a trial being closed down. All trials are subject to rules on 'Good Clinical Practice' and the personnel carrying out the trial will be trained in this.

Whilst it is important that trials are carried out in SCD to help us increase knowledge about the disease and develop new treatments, and that participation in trials is open to all patients with SCD, it is essential that patients are not coerced into entering trials. It must be made clear to any patient entering a trial that they are able to withdraw at any time without influencing any other aspects of their care.

The following are some of the clinical trials actively recruiting or in the process of obtaining regulatory approval in the UK (at the time of writing):

1. ASSET: These phase III studies will assess the safety, efficacy and tolerability of bosentan in patients with pulmonary hypertension
2. PISCES: Priapism in Sickle Cell Study is a randomised double blind placebo controlled looking at 2 different doses of oral ephedrine and etilefrine in the prevention of recurrent (stuttering) attacks of priapism
3. TAPS: Transfusion Alternatives Pre-operatively in SCD study hopes to find out whether there is really a need to give blood transfusions before planned surgery. The study aims to show whether pre-operative transfusion increases or decreases the likelihood of having problems following surgery
4. Walk-PHaSST: Treatment of Pulmonary Hypertension and Sickle Cell Disease with Sildenafil Therapy consists of a screening phase using echocardiography and 6 minute walk tests to identify patients with possible pulmonary hypertension. These patients will be invited to enrol in the main interventional study which will randomise to a 16 week course of sildenafil or placebo.

Throughout this document the lack of grade A clinical evidence to support our current practice is clear. A clinical trials network with funded research nurses and administrative staff to support the clinicians in running trials (in a similar model to that used in oncology) is imperative in order for us to provide the best care possible in the future. Sickle research in the UK is primarily dependent on the good will of clinicians and without the development of a central funding structure for sickle research it is difficult to see how it can continue and grow.

References

- ¹ Serjeant GR. Surgery and anesthesia. In: SCD. Oxford Medical Publications, 1992:455-458.
- ² Koshy M, Weiner SJ, Miller ST, et al. Surgery and anaesthesia in SCD. Cooperative Study of SCDs. *Blood*. 1995; 86: 3676-3684.
- ³ Riddington C, Williamson L. Preoperative blood transfusions for SCD (Cochrane Review). In: The Cochrane Library, Issue 1, 2002. Oxford:Update Software.
- ⁴ Vichinsky EP, Haberkern CM, Neumayr L, et al. A comparison of conservative and aggressive transfusion regimes in the perioperative management of SCD. *New Eng J Med*. 1995; 333(4): 206-207.
- ⁵ Haberkern CM, Neumayr LD, Orringer EP, et al. Cholecystectomy in sickle cell anemia patients: perioperative outcome of 364 cases from the National Preoperative Transfusion Study. Preoperative Transfusion in Sickle Cell Disease Study Group. *Blood*. 1997; 89: 1533-42.
- ⁶ Charache S, Terrin ML, Moore RD, et al. Effect of hydroxycarbamide on the frequency of painful crises in sickle cell anaemia. *N Eng J Med*. 1995; 332: 1317-1322.
- ⁷ Ferster A, Tahriri P, Vermynen C, et al. Five years of experience with hydroxycarbamide in children and young adults with SCD. *Blood*. 2001; 97: 3628-3632.
- ⁸ Steinberg MH, Barton F, Castro O, et al. Effect of hydroxycarbamide on mortality and morbidity on adult sickle cell anaemia: risks and benefits of up to 9 years treatment. *JAMA*. 2003; 289(13): 1645-1651.

Appendices

Appendix 1: Sickle Cell Society review data - key issues raised by service users

Issues raised	Suggested solutions
Day ward opening times vs. out of hours crises occurring (use of unsatisfactory A&E service)	<ul style="list-style-type: none"> • Focus on getting A&E service right • Could have a Day ward sub-unit in A&E ward, but suitable for uncomplicated cases only
Lack of knowledge of Healthcare professionals and other agencies	<ul style="list-style-type: none"> • Haemoglobinopathy input doctors training • Most care from nurses – information days essential part of curriculum • Availability of specialist nurses • Cannot teach compassion but can teach professionalism
Delays and triage causing duplication in A&E	<ul style="list-style-type: none"> • Direct admission to ward is not possible but perhaps direct to haematology ward following doctor's assessment
Variability of care	<ul style="list-style-type: none"> • Standard protocols in place • National guidelines available (2003) • Patient held laminated protocols • Patients should have access to audit of services
No Information regarding side effects of drug and drugs used and why	<ul style="list-style-type: none"> • Providing information regarding side effects and drugs • Information regarding why particular drugs are used or not used
Pressurised to accept particular medication or dose	<ul style="list-style-type: none"> • Medication should not be changed or altered when in crisis. • Oral narcotics may be the answer
Unsuitable Medication (Pethidine)	<ul style="list-style-type: none"> • Degree of flexibility required and discussion re: responsibilities • May need to change doctor if relationship breaks down
Access to analgesia from GPs	<ul style="list-style-type: none"> • Most crises occur out of hours; Doctor is likely to be locum and may not be familiar with SCD. Education required
Complaints	<ul style="list-style-type: none"> • Can be effective way to bring about change • Make sure complaint goes to right person
Hospital at Home	<ul style="list-style-type: none"> • Difficult if complications arise • Not safe
Need for Support Groups	<ul style="list-style-type: none"> • Not to be used for complaints but source of support
Social Services: lack of support, knowledge & understanding	<ul style="list-style-type: none"> • Education and information days

Appendix 2: Terms of reference

1. To act as a body of experts for development of standards of care for adults with sickle cell disease
2. To ensure project funding is subject to robust scrutiny, wholly transparent and open competition
3. To ensure industry partnerships adhere to codes of conduct prescribed by the Health Coalition Initiative and the Association of the British Pharmaceutical Industry
4. To formulate standards of care with demonstrable user representation and consultation so that the views of adults with sickle cell disorders are reflected
5. To take account of key developments that are relevant to the operational context of the standards which include appropriate legislation and other bodies of work
6. To ensure that the role of the Sickle Cell Society is clearly described and acknowledged in the finished document
7. To ensure that the process of resolving differences of opinion is clearly communicated to the whole of the group and agreed

Appendix 3: Literature search strategy

The Cochrane Library, Issue 4, 2006

- #1 MeSH descriptor Anemia, Sickle Cell explode all trees
- #2 MeSH descriptor Hemoglobin, Sickle explode all trees
- #3 MeSH descriptor Hemoglobin SC Disease explode all trees
- #4 "sickle cell":ti,ab,kw
- #5 (#1 OR #2 OR #3 OR #4)
- #6 MeSH descriptor Adult explode all trees
- #7 (adult):ti,ab,kw or (elderly):ti,ab,kw or (aged):ti,ab,kw or (geriatric):ti,ab,kw
- #8 (#6 OR #7)
- #9 (#5 AND #8)

Dialog DataStar MEDLINE 1950 to 2nd November 2006

1. (SICKLE ADJ CELL).TI,AB.
2. ANEMIA-SICKLE-CELL#.DE.
3. HEMOGLOBIN-SC-DISEASE#.DE.
4. HEMOGLOBIN-SICKLE#.DE.
5. 1 OR 2 OR 3 OR 4
6. 5 AND LG=EN AND HUMAN=YES AND ADULT#
7. PT=META-ANALYSIS
8. (SYSTEMATIC ADJ REVIEW).TI,AB.
9. PT=RANDOMIZED-CONTROLLED-TRIAL
10. RANDOM\$7.TI,AB.
11. COCHRANE.SO.
12. 7 OR 8 OR 9 OR 10 OR 11
13. 6 AND 12

Dialog DataStar EMBASE 1974 to 2nd November 2006

1. (SICKLE ADJ CELL).TI,AB.
2. SICKLE-CELL-ANEMIA#.DE.
3. SICKLE-CELL#.DE.
4. HEMOGLOBIN-S#.DE.
5. HEMOGLOBIN-SC-DISEASE#.DE.
6. 1 OR 2 OR 3 OR 4 OR 5
7. 6 AND LG=EN AND HUMAN=YES AND (ADULT# OR AGED.DE.)
8. META-ANALYSIS.DE.
9. (SYSTEMATIC ADJ REVIEW).TI,AB.
10. RANDOM\$7.TI,AB.
11. RANDOMIZED-CONTROLLED-TRIAL#.DE.
12. COCHRANE.SO.
13. 8 OR 9 OR 10 OR 11 OR 12
14. 7 AND 13

Dialog DataStar CINAHL 1982 to 2nd November 2006

1. (SICKLE ADJ CELL).TI,AB.
2. ANEMIA-SICKLE-CELL#.DE.
3. 1 OR 2
4. ADULT.DE. OR MIDDLE-AGE OR AGED.W..DE. OR AGED-80-AND-OVER
5. 3 AND 4
6. PT=SYSTEMATIC-REVIEW
7. META-ANALYSIS#.DE.
8. RANDOM\$7.TI,AB.
9. COCHRANE.SO.

10. 6 OR 7 OR 8 OR 9
11. 5 AND 9

Dialog DataStar PsycINFO 1888 to 2nd November 2006

1. (SICKLE ADJ CELL).TI,AB.
2. SICKLE-CELL-DISEASE#.DE.
3. 1 OR 2
4. 3 AND LG=EN AND ADULTHOOD#
5. RANDOM\$7.TI,AB.
6. (META ADJ ANALYSIS).TI,AB.
7. (SYSTEMATIC ADJ REVIEW).TI,AB.
8. COCHRANE.SO.
9. 5 OR 6 OR 7 OR 8
10. 4 AND 9

Results

Database	No. of citations retrieved
Cochrane Central Register of Controlled Trials	441
Cochrane Database of Systematic Reviews	23
MEDLINE	141
EMBASE	105
CINAHL	17
PSYCINFO	18

Appendix 4: Summary of standards of care

Organisation of Care and Commissioning Services: Core Standards

i) Transition from paediatric to adult services

- There must be a hospital transition policy in place, and preparation and planning should start by age 13-14 years
- A detailed review will be carried out at 15-16 years regarding:
 - knowledge and understanding about SCD
 - self-care and management
 - SCD inheritance and implications for family planning
 - concerns about healthcare in an adult setting and readiness to transfer considered
- A transition or adolescent clinical service will be available to allow the young person to meet the adult sickle cell team and for a formal review and handover to take place. The family carers will also be invited to talk to the adult sickle cell team
- Adult and paediatric protocols for managing complications, in particular painful episodes, will correspond as much as possible

ii) Adult services

Primary care and community services

- Service users will:
 - be registered with a GP
 - be given written information (or materials in other suitable formats as required) regarding approaches to preventing and managing symptoms at home, and what symptoms should make them seek urgent medical advice
 - have a named contact and contact numbers for their local unit and specialist centre as well as the nearest SCaT centre/service
 - have access to support in the community from social services and healthcare services such as community nursing and psychology, according to their individual need
 - be able to access the benefit system to support them financially in a fair and transparent manner that includes help to complete forms if required
 - be supported to access services via the voluntary sector, outreach services or other alternative channels
 - be enabled to achieve independent living through life skills training and support that empowers them to take control of and manage their daily commitments
- Primary Care Trusts (PCTs) will ensure that the Expert Patients Programme (EPP) is available to all service users with SCD and their carers
- Where community practitioners/community teams require specialist community care expertise, support or supervision arrangements to be obtained from an appropriate SCaT centre
- Services will be geared to provide an appropriate level of care in the community, working closely with hospital clinicians and primary care to provide alternatives to hospital care where possible, bringing care closer to patients' homes
- Innovative new models of community care interventions, with the potential to reduce reliance on secondary care, should be given an appropriate level of support
- Community services should receive clinical leadership and support from hospitals until relevant expertise is in place in the community

Hospital services (including emergency services)

- Service users will be invited to attend a specialised clinic on a regular basis and this will vary from monthly to once yearly depending on patient need

- SCD services will be developed into clinical networks including specialised centres and shared-care service providers in local NHS trusts
- In high prevalence areas SCD services may consist of several large centres working together, sharing specialist services and supporting local hospitals, and in low prevalence areas will consist of a specialist centre supporting several local hospitals
- All hospitals will have a mechanism for contacting service users who default from follow-up appointments, and informing the primary care team that they are no longer accessing hospital care
- Out of hours facilities for blood tests, out-patient clinics and day care facilities will be made available so that routine or planned health care does not interfere with education, work or family responsibilities
- There will be designated hospital teams responsible for admission, in-patient care, out-patient care and follow-up, and for ensuring liaison with primary care/community care
- Appropriately skilled staff must be available to guide out of hours assessment and management
- There will be written guidance for teams in local hospitals, written or at least agreed by the local SCD network, covering management of common presentations and indicating clearly under what circumstances, and how the team at the specialist centre should be contacted for advice or patient transfer
- Patients with SCD who need an ambulance to take them to hospital should be taken to their usual hospital if feasible, unless immediate resuscitation is necessary in which case they should be taken to the nearest A&E department. If they become acutely ill out of their own area of residence, they should be taken to the nearest A&E department. Minor injuries or GP led units are not suitable for the assessment and treatment of these patients
- Staff handling patients with SCD need to be aware of the extreme pain they may experience, and transporting and positioning of the person needs to take this into account
- If immediate pain relief is necessary during transfer, Entanox can be used for short periods as long as the baseline oxygen saturation is normal

iii) **Commissioning sickle cell services**

- Services should be commissioned to support highest quality clinical management. Commissioning should be based on evidence; should include measurable quality outcomes; and should promote service improvement and innovation. Leadership by clinical experts, and patient and public involvement, is key to successful commissioning and mechanisms must be in place to ensure appropriate engagementⁱ
- NHS trusts will be required to provide a comprehensive data in support of patient activity to aid service commissioners in specialised commissioning teams (SCTs) and PCTs
- Collection and analysis of appropriate national and local data will help ensure services are accessible to all adults with SCD, regardless of area of residence, relevant to the needs of the local community
- SCD service design will build on existing capacity and infrastructures to maximise use of public resources and reflect local priorities and local needs
- Measures to address health inequalities need to be included in the design of culturally sensitive services, in order to reach those most at risk, and those who may experience difficulties in accessing services. This should include harnessing the experience of generic services which have successfully met the needs of a multi cultural society

- SCD services will be designed and resourced to provide integrated, high quality, holistic care across the whole of the patient journey through primary care, hospital and community settings applying the principles recommended for chronic conditions
- The training needs of community physicians, nurses, social care and educational professionals should be considered in order to improve care in the community and specialist secondary care centres. The voluntary sector and community care centres should be supported to offer such training
- Explicit measures for engaging service users, the voluntary sector and the public in the design, implementation and monitoring of standards of care will be in place
- SCD services and service users will be best served via a collective specialist commissioning process
- Procurement of activity along the patient pathway in designated specialised centres and other service providers will be resourced under the Payment by Result (PbR) mechanism. In situations where other payment mechanism can procure cost effective high quality services, these mechanisms should be considered
- Access to necessary high cost interventions should be equitable across the UK

Managing Acute Complications: Core Standards

i) Acute painful crisis

- The first dose of an appropriately potent analgesic must be administered within 30 minutes of presentation to a clinical area and should include time spent in triage
- The on call haematologist should be notified of the patient's arrival
- Regular and continuous assessment of pain during an acute episode must be recorded using a standard pain assessment tool for adults. Pain relief from the type of analgesia administered must also be assessed at regular intervals along with vital signs
- Discharge letters should be sent to GP within 10 working days from discharge
- Sufficient analgesia must be provided on discharge. Readmissions within 48 hours of discharge should be audited and a report generated at least annually

ii) Management of the febrile patient

- All patients with a temperature of $>38^{\circ}\text{C}$ should be rapidly investigated in an acute facility and empirical antibiotics started immediately after initial culture samples have been taken
- Chest X-ray, blood and other relevant cultures should be mandatory in patients with temperature of $>38^{\circ}\text{C}$. There should be access to microbiology advice to aid management
- Antibiotic treatment should depend on site of suspected infection and local antibiotic policy

iii) Acute chest syndrome (ACS)

- All patients, carers, medical and nursing staff should be aware of the symptoms of ACS
- Each hospital should have a protocol in place for the management of ACS including the use of transfusion therapy
- Patients with ≥ 2 episodes of ACS within the previous 2 years should be offered hydroxycarbamide (hydroxyurea) therapy

iv) Acute abdomen

- Blood cultures, serum amylase, imaging studies such as abdominal ultrasound scans, abdominal X-ray and where appropriate CT (computer tomography) scans should be performed in patients who present with an acute abdomen

- Sickle cell related causes of acute abdominal pain should in most cases be managed conservatively. The surgical team should be involved early in the management of these patients
 - Local policies to include antibiotic cover and indications for endoscopy should be developed in collaboration with gastroenterologists and microbiologists for the management of patients with gallstone related complications
 - Symptomatic gallstones should be treated with laparoscopic cholecystectomy because of the shorter hospital stay and fewer immediate surgical complications
- v) Acute anaemia**
- Any patient presenting acutely unwell should have a full blood count and reticulocyte count performed; patients with anaemia and reticulocytopenia should have blood sent for parvovirus serology
 - Clinical examination of a patient presenting with acute anaemia should include an assessment of spleen and liver size
 - Top-up transfusion may be necessary, especially if the anaemia is accompanied by reticulocytopenia. The threshold level for transfusion will depend on the clinical state of the patient
- vi) Acute neurological symptoms**
- Specific guidelines for the management of acute stroke in SCD should be prepared by the SCD specialist centre for the local units, and this should include how and where urgent exchange transfusion is performed
 - Each SCD specialist centre should have access to a designated neurologist who can assess and advise on acute neurological complications (although management should not be delayed until such review); access to a neurosurgical unit for managing patients with cerebral and subarachnoid haemorrhage and intracranial hypertension; and access to neuro-imaging facilities including CT, MRI (magnetic resonance imaging)/MRA (magnetic resonance angiography) and EEG (electroencephalography)
- vii) Suspected acute osteomyelitis**
- The clinician should have a high clinical suspicion for osteomyelitis and blood cultures should be taken early, before antibiotics are started
 - Ultrasound, radioisotope scans and MRIs may be useful diagnostically in expert hands
 - Treatment should be with a prolonged course of appropriate antibiotics
- viii) Acute renal disease**
- Local protocols should be agreed with the renal team for the management of acute renal failure in SCD
- ix) Acute priapism**
- A network policy on management of acute priapism should be agreed between haematology and urology services and the SCD specialist centre (this policy may need to be adapted at local level)
 - Early presentation (<4 hours) is vital to a successful outcome in management of acute attacks. This information should be reinforced continually during clinical visits at least annually

Managing Chronic Complications: Core Standards

i) Chronic pain

- The cause of chronic pain should be established as far as possible
- Patients with established avascular necrosis causing chronic pain should be referred for rapid assessment and operation if deemed necessary
- GP and hospital teams should encourage home management of chronic pain as much as possible. The choice of analgesia should be varied and patients should be informed of the side effect profiles
- A multidisciplinary team to treat chronic pain should be established
- Patient advocacy should be encouraged through expert patient programmes, with periodic review of such initiatives

ii) Stroke and other neurological complications

- Patients with arterial stroke in the context of SCD should receive regular blood transfusion, ideally exchange, to keep the sickle percentage below 30% indefinitely
- For those patients on long term transfusion programmes, monitoring of iron overload should be undertaken and appropriate chelation therapy initiated (see chapter 6)
- Patients with moyamoya should be referred to an appropriate centre for consideration of revascularisation
- SCD specialist centres should have access to a designated neurologist with an interest in stroke and the neurological complications of haemoglobinopathies and neuro-imaging facilities including transcranial Doppler (TCD), Duplex scanning of the neck, magnetic resonance imaging (MRI)/magnetic resonance angiography (MRA) and electroencephalography (EEG)

iii) Pulmonary and cardiac disease

- Patients should be screened for chronic sickle lung disease with regular oxygen saturation (SaO₂) monitoring. Patients who are dyspnoeic or have low SaO₂s should be investigated with lung function tests and high resolution CT scans
- Patients with symptoms of disordered sleep breathing should be investigated with overnight SaO₂s and if these are abnormal, they should be referred to a sleep clinic
- Trans-thoracic echocardiography should be used to screen for pulmonary hypertension every 1-2 years
- All specialist sickle centres should have links with the regional pulmonary hypertension services to provide confirmatory testing and to instigate treatment in patients with confirmed significant pulmonary hypertension

iv) Leg ulcers

- A full initial leg ulcer assessment should include Doppler scans, photography or tracings of the ulceration
- Topical antibiotics should be avoided as they can cause sensitisation
- Management of leg ulcers should be by a multidisciplinary team with expertise in leg ulcer management

v) Chronic renal disease

- All patients with haematuria should be referred to urologists for further investigation and management; the former should include ultrasound, computer tomography (CT) or MRI done to exclude renal medullary carcinoma.
- All patients should be screened annually for proteinuria, and a protocol should be in place for further investigation and referral
- Meticulous attention to the control of blood pressure, diabetes and other co-morbidities is necessary

vi) Priapism

- Clear written information on priapism in easily understood language must be available to young men and adults with SCD at first visit to clinic
- Patients should be referred to Urologists for follow-up and preventative management

vii) Eye complications

- All patients with SCD at first contact should be referred to a dedicated sickle retinal clinic for “one stop” assessment/treatment of eye disease attributable to their condition and be followed up as necessary
- Patients presenting with an acute change in vision must be referred immediately to an ophthalmologist for evaluation

viii) Growth and nutritional support

- There should be close co-operation between paediatricians and haematologists as the child approaches the transition to adult care. Any history of growth failure, delayed sexual maturation and nutritional deficiencies must be clearly documented and monitored. If growth failure is identified treatment should be initiated as soon as possible

Pregnancy, Contraception and Fertility: Core Standards

i) Pregnancy

- All health professionals dealing with pregnant women with SCD should receive an appropriate level of education about haemoglobin disorders
- Pre-conceptual counselling, including genetic screening and partner testing should be offered to all men and women with SCD
- Hydroxycarbamide (hydroxyurea) should be discontinued in men and women a minimum of 3 months prior to conception
- Chelation therapy should be stopped prior to conception
- If evidence of significant iron overload preconception, pregnancy should be delayed to allow aggressive iron chelation prior to conception
- Pregnancy in women with SCD should be considered as high risk and early booking is recommended. Combined management by a haematologist and obstetrician with experience of managing high risk pregnancy (preferably experience of haemoglobinopathies) is recommended for all pregnant patients with SCD or supervision arrangements must be in place to support patients' booking choice
- Antenatal care should be undertaken at a designated SCD specialist centre and local hospitals should refer to this centre for initial assessment. If care is to continue at the non specialist centre, a joint care plan should be agreed. The choice of maternity unit should be discussed with the woman
- Each woman should have an individualised care plan which takes into account her previous sickle and pregnancy history. Where possible, she should have a named midwife with expertise in caring for women with SCD
- SCD specialist centres should have:
 - arrangements in place for counselling by PEGASUS (Professional Education for Genetic Assessment and Screening) trained health care counselling professionals, with timely access to prenatal diagnosis when required
 - a written policy to include antenatal management, labour and delivery and postpartum care
 - written guidelines on the management of painful crises during pregnancy and indications for transfusion

- Routine prophylactic transfusion for uncomplicated pregnancy is usually not necessary but should be considered for women with a poor obstetric or medical history
- Timing and route of delivery should be based on obstetric indications, as in women without SCD
- Neonatal capillary samples should be taken when the antenatal screening process has identified a baby with a high risk of a major haemoglobin disorder
- Surgical termination of pregnancy should take place within the acute hospital setting with involvement of the haematology team and appropriate anaesthetic support with all patients having access to bereavement counselling

ii) Contraception

- Each woman should be given contraceptive choice and should be fully informed regarding the potential risks and benefits of the different methods
- Health care professionals should be fully informed about options for contraception in SCD
- Discussion about contraception should take place with male and female adolescents before leaving paediatric care

Blood Transfusion: Core Standards

i) Transfusion and management protocols

- All hospitals providing care for patients with SCD should have a blood bank that provides a blood transfusion service 24 hours a day, 7 days a week; it should be compliant with UK and EU directives and have regularly updated standard operating procedures for the issue of blood products to people with SCD
- Blood banks should be able to perform ABO grouping, full red cell phenotype (or at a minimum, phenotyping of the Rh and K blood groups), atypical red cell antibody screen and the identification of common atypical red cell antibodies
- All hospitals providing care for SCD patients should have a Hospital Transfusion Committee. There should also be a Transfusion Practitioner whose duties should include the education and training of hospital staff in blood transfusion issues in SCD
- All SCD patients must have their ABO group and full red cell phenotype performed at the first opportunity regardless of the clinical severity of their SCD or their anticipated future blood transfusion requirements
- Red cell units for transfusion to all SCD patients should be ABO compatible and also matched for D, C, E, c, e and Kell to minimise alloimmunisation; donor red cell units should be HbS negative and preferably <2 weeks old
- The blood bank must keep an accurate and detailed transfusion history of every SCD patient that has contact with the hospital. The hospital blood bank must always carry out its own tests on patients who have transferred their care from another hospital if there is any doubt about the validity of the results from the other hospital
- A card bearing details of the full red cell phenotype and all previously detected alloantibodies must be issued to the patient
- All hospitals must have local protocols for the recognition and management of SCD complications requiring emergency red cell transfusion
- A written and up to date protocol for exchange transfusion should be available within the hospital; this can be consulted in the event that a trained nurse is not available to perform this procedure in an emergency
- Hepatitis B vaccination should be routine for patients with SCD, regardless of previous or projected transfusion history (see 3.3.2.4)

ii) Iron overload and chelation therapy

- All patients who have been previously transfused or are currently undergoing regular transfusions, whether top-up or exchange, should have regular quantitative monitoring of liver iron concentration using MRI
- Iron chelation should be considered in all patients on a regular transfusion regimen who have received at least 20 top-up transfusion episodes or have a liver iron concentration of ≥ 7 mg/g dry weight
- All patients receiving iron chelation therapy should be regularly monitored for iron overload; monitoring of response to chelation therapy should be regularly undertaken and appropriate adjustments made
- Monitoring of chelator toxicity should occur regularly and complications clearly documented
- Practical and psychological support should be provided to patients to help improve adherence to chelation therapy

Surgery and Specific Therapies: Core Standards

i) Surgery

- All hospitals will have a protocol in place for pre-operative screening for SCD
- All hospitals will have a protocol in place for the peri-operative management of patients with SCD

ii) Specific therapies

- Hydroxycarbamide needs to be considered in patients who have:
 - recurrent episodes of acute pain (>3 admissions in the previous 12 months, or are very symptomatic in the community)
 - >2 episodes of acute sickle chest crisis
- All hospitals prescribing hydroxycarbamide for patients with SCD will have a patient information leaflet, and a protocol in place for drug monitoring
- Novel or experimental therapies and participation in trials need to be discussed with the patient as part of their Annual Review. If the local unit is not able to provide these services, there needs to be a clear pathway for provision of care
- Central funding should be sought for a clinical trials network that spans secondary, primary and community settings and includes research nurses and administrative support

Appendix 5: Shared-care communication sheet

Name:	DOB:
Hospital number:	NHS number:
<u>Diagnosis:</u>	

<i>Complications</i>	<i>Regular medication</i>	<i>Preferred analgesia for crisis</i>	<i>Steady state Hb values</i>

Contact	Local Hospital	Specialist Centre	SCaT Centre
Name			
Phone number			
Out of hours contact			

Remember!

Contact the hospital promptly if you have any of the following problems:

- ① **significant fever**
- ① **chest pain**
- ① **breathing difficulties**
- ① **dehydration**
- ① **priapism**
- ① **any unfamiliar pain or other unexpected symptom**

Appendix 6: Benefits in SCD

i) Health Benefits

Disability Living Allowance (DLA)

This is a benefit for those who need help getting around and/or looking after themselves because of their health. Claiming DLA is split into these 2 core elements: 'mobility' (see Vehicles and Transport section for more details) and 'care'. Both have different bandings or levels of allowance based on level of need. You must claim before you reach age 65. It is not means tested or taxable and is paid on top of any other benefits or income which you may be entitled to. DLA is available for children under the age of 16 years if their needs for extra care or supervision are substantially in excess of what is usually required by a child of the same age. The higher rate of the mobility component is available for children aged 3 years and over.

Attendance Allowance (AA)

This is a tax-free benefit for people aged 65 or over who have an illness or disability and need help with personal care.

Incapacity Benefit (IB)

If you can't work because of illness or disability you may be able to get Incapacity Benefit. It is paid weekly at 3 different rates depending on how long you've been unable to work (although certain people under the age of 20 or 25 years may qualify without needing to satisfy National Insurance contributions). If you receive an occupational, personal or public service pension, your incapacity benefit may be reduced, but any other income or savings will not affect your benefit.

Health and independent living

If you have been assessed by your local council as needing care and support services, you may want to choose direct payments. They allow you to buy in and arrange help yourself instead of receiving it directly from Social Services.

Equipment for independent living

You may be entitled to help towards the cost of equipment to enable you to live independently in your own home, or towards the cost of getting standard home equipment adapted so that you can use it.

Health equipment, prescriptions and hospital travel

If you receive Income Support, Income based Jobseekers Allowance or the guarantee of Pension Credit you will automatically qualify for help towards health costs such as free NHS prescriptions, dental care, hospital travel costs, and equipment such as wheelchairs and hearing aids.

Value Added Tax (VAT) relief on equipment and services

Some goods may qualify for VAT 'relief' if the item has been designed, or adapted, solely for a disabled person's use. This includes some medical appliances, certain adjustable beds and hoists and some adapted vehicles. Services that may qualify for relief include: installation of equipment, adaptation of equipment and certain building alterations.

ii) Employment Benefits

Access to work

Access to work is one scheme that can provide you with practical support in work. This includes paying towards special equipment, or a support worker or help with the additional costs of travel to work for you if you are unable to use public transport.

Job grant

You can claim job grant if you take up full-time work (at least 16 hours a week). You must also have been claiming certain benefits for at least 26 weeks before starting your new job; these include IB or severe disablement allowance (you can no longer make new claims for this benefit).

Working Tax Credit (WTC)

If you are working for 16 or more hours per week, you may be able to claim WTC. If you are in work but on low pay, you can apply for WTC to top-up your earnings. You may get extra if someone in your household is registered as disabled. To claim, contact the Inland Revenue as there are varying elements of entitlement depending on your circumstances.

Income support

If you are aged between 16 and 60, on a low income, not working or working on average less than 16 hours a week you can claim income support. Income support is affected by savings. If you are sick and are not getting statutory sick pay, you should claim IB as well as income support.

Housing benefit

Housing benefit is help with paying your rent and some other housing costs. For those on low income it is worked out in a similar way to income support. If your income is low but unable to claim income support, you may still be able to claim housing benefit.

Council Tax Benefit (CTB)

If your income is low CTB helps you to pay your council tax whether you rent or own the property you live in. You need to contact your local authority for more information.

Child Tax Credit (CTC)

CTC is an allowance for parents and carers of children or young people who are still in full-time education. You may get extra if you care for a child registered as disabled.

iii) Vehicles and Transport

Blue badge parking scheme

The blue badge scheme provides a range of parking benefits for people with disabilities with severe walking difficulties who travel either as drivers or as passengers.

The motability scheme

The motability scheme can help you with leasing or buying a car, powered wheelchair or scooter. Your entitlement will be needs-based and dependent on your banding for the mobility component of your DLA. The leasing or hiring of certain equipment and vehicles may also qualify for VAT relief.

Vehicle excise duty (car tax) exemption

You can apply for exemption from paying vehicle tax if you receive the higher rate of the mobility component of DLA or the War Pensioner's Mobility Supplement.

Community and public transport

Your local council may operate dial-a-ride or taxi schemes, for example, using vouchers or tokens. You may also be eligible for a Disabled Persons Rail Card.

iv) Other

Disabled students' allowances

Disabled students' allowances provide help for students in higher education who, because of their disability, have additional costs. Things they help pay for include specialist equipment plus non-medical personal assistance.

Caring for someone?

If you are caring for someone who is disabled, find out about financial and practical help for carers - including carers' assessments and Carers' Allowance - in the 'caring for someone' section of Directgov.uk website.

Winter payments

Winter fuel payments are made by the Government every winter to help some people to pay their fuel bills. People aged over 60 (on or before September 24th, 2006) who normally live in Great Britain or Northern Ireland qualify automatically. However, because people with SCD can be susceptible to the cold your circumstance may mean you can claim (speak to your benefits advisor). Those who qualify should receive £200 per household, while households with someone aged 80 or over may receive a further £100.

Appendix 7: Regular clinical review

Issue	Frequency for discussion/testing	Comment
Discussion: Overall wellbeing, educational/work involvement and how often missed for health reasons. Days in hospital? If so, where?	Each visit	
Any social, family, education, benefit, employment or housing issues?	Each visit	Involve Social Services, housing dept., benefits advice as necessary
Specific discussion about frequency, severity of pain episodes and how managed; steps taken to minimise; possible improvements in management.	Each visit	Concept of 'analgesic ladder' useful
Discussion of any other specific symptoms or problems the patient offers. Check for episodes priapism, neurological disturbance, leg ulcers.	Each visit	
Review infection prophylaxis, ensure supply of antibiotics.	Each visit	
Review immunisation schedule, including when Pneumovax booster due, and if Engerix required.	At least yearly	
Review contraception needs and advice.	At least yearly	Check with specialist centre if uncertainty about best options
Enquire about any plans for pregnancy; whether partner has been checked for Hb disorder. Check understanding of inheritance and risks to offspring.	At first adult clinic attendance, and periodically after	
Consideration of specific therapies if clinical problems warrant (e.g. transfusions/hydroxyurea).	As clinical problems dictate	Further discussion/decision made with specialist centre
Review of specific therapy including appropriateness of dose; review of iron chelation if transfusion iron overload.	At least yearly	Dose adjustment of hydroxyurea according to FBC can be undertaken locally, according to policy provided by centre. Decisions to start/stop therapies should be taken with specialist centre team

Issue	Frequency for discussion/testing	Comment
Examination		
Record weight	Each visit	
Record height	At least yearly	Until maximum height achieved
Clinical examination including BP, heart, lungs, abdomen for liver/spleen enlargement, SaO ₂ by pulse oximeter	At least yearly	Alert GP if blood pressure raised to check and treat if persistently high (risk factor for renal disease)
Specific attention to clinical problems (e.g. leg ulceration)	As needed	May need advice from local tissue viability services or specialist centre
Urinalysis (also see investigations, below)*	At least yearly	More frequently if any suspicion of renal problem (remember urea/creatinine levels are normally low in HbSS; mid-high normal range likely to be abnormal)
MSU if proteinuria		Consider renal referral if proteinuria with no UTI, even if renal function normal
Onward referrals:		
Social Services/benefits advice/housing advice	As needed	Frequently via community centre
Retinopathy clinic	1–2 yearly, more frequently if retinopathy identified	Often at specialist centre if little local expertise
Orthopaedics	As needed	For suspicion of avascular necrosis, according to symptoms and/or imaging
Others	As clinical problems dictate	

Issue	Frequency for discussion/testing	Comment
Investigations		
FBC, U&E, eGFR, LFT including ALT, ferritin	At least yearly or more frequently as needed	Remember ferritin often falsely raised, acute phase reactant, if iron deficiency suspected, transferrin saturation helpful. Patient should be made aware of steady state Hb
Ensure extended red cell phenotyping available	At initial adult clinic attendance	Should be available from paediatric records
Check for microalbuminuria, protein-creatinine ratio where available, 24 hour urine collection for creatinine clearance and protein excretion, and consider renal EDTA excretion if difficulty with collection	Yearly, more frequently if hint of renal impairment	As above *
Echocardiogram (to detect possible pulmonary hypertension)	Every 18 months to 2 years or sooner if symptoms	Should be undertaken by specialist, looking for tricuspid regurgitant jet velocity, refer to pulmonary hypertension clinic if abnormal

Appendix 8: Resources implications and cost benefit

The adult SCD standards working group, after due consideration, recommend that sickle cell services should be under specialist commissioning to ensure that an equitable service is available across the UK. An initial list of resource implications which relates to the standards put forward by this document is listed below. The list is not exhaustive and can evolve over time so will be subject to change.

i) Implications for acute services

The treatment of acute complications of SCD is for the most part covered by standard care, so should not have major resource implications. There are however some issues are outlined below:

Acute pain

- Designation of a ward for admission and allocation of beds for management of patients where significant numbers of patients live locally
- Provision of an adequately staffed day hospital for management of uncomplicated painful crises should be seriously considered. This will have initial start up costs but will lead to decreased hospital admissions, and may have a long-term cost benefit, whilst providing improved quality of care
- Provision of training on pain management and other acute complications for junior medical staff as well as designated clinical nurse specialists, and staff nurses on the wards; training of staff in A&E regularly to reflect throughput/turnover of staff in that clinical area
- Provision of a psychologist skilled in pain management and cognitive behavioural therapy. This may be particularly useful in acute inpatient pain management and lead to decreased length of stay and cost savings
- 24 hour access to personnel to perform exchange blood transfusion, either manual or apheresis
- Hydroxycarbamide and related blood monitoring should be offered to appropriate patients. The costs of the drug and drug monitoring should be outweighed by the decreased hospital admission rates for painful crises and ACS
- Access to specialist services as required, such as neurologist and neurosurgical unit, surgeons and imaging facilities (plain X-rays, ultrasound, CT and MRI)

Pregnancy

- Increased resources will be necessary to run combined obstetric and medical clinics. SCD women will also require an increased number of scans compared to routine standard care. There should be capacity building for increased workload to SCD specialist centres by adequate staffing levels and other financial support

Surgery

- Pre-operative screening for SCD should be part of standard practice and use standard tests provided in the laboratory already. Peri-operative protocols, if not already in place, should not have resource implications. The provision of respiratory support (IS or CPAP) may have cost implications, but these may be balanced by a decreased incidence of post-operative complications. The optimal pre-operative transfusion regimen has not yet been determined, but in view of the very variable practice across the UK at present is likely to be cost-neutral.

ii) Implications for chronic services

Pulmonary and cardiac disease

- Pulmonary hypertension screening by transthoracic echocardiograms should be available to all patients with SCD every 2-3 years
- Availability of lung function, HR CT, overnight sleep studies and sleep clinics should be ensured
- Access to specialist pulmonary hypertension centres for those with abnormal echocardiograms for detailed catheter studies and initiation of complex therapies

Nephropathy

- Longitudinal studies looking at the long term effect of ACE inhibition on preserving renal function are warranted and should be commissioned. This should be seen as an investment in health gain and offset future costs of renal replacement in this patient group
- Erythropoietin therapy for patients with SCD and renal disease should be available if indicated
- Access to renal transplantation unit and renal replacement therapy should be available
- Annual Screening for proteinuria should be funded

Leg ulcers

- Provision of, or access to, a Clinical Nurse Specialist (CNS) in leg ulcer management or tissue viability nurse (TVN) in SCD specialist centres will have implications on resources. Cost benefits will be gained by ensuring patients have the appropriate treatment at the earliest point as well as less time off work, reduced cost of dressings, and improved psychological effects/well-being

Blood transfusion

- The benefits of blood transfusions should be weighed against the cost of providing red cell transfusions, including any additional logistical costs mainly from transporting the red cell units from the NBS, as these units are not normally stocked in the hospital blood bank. This should be supported by partnership working to raise awareness to drive blood donation within minority subgroups for improved blood matching
- The cost of iron chelation therapy is likely to escalate as more patients are put on long-term transfusion programmes. Any cost comparison of price should take into consideration quality of life and adherence issues, or the costs of managing the side effects of iron overload
- Central funding for the use of deferasirox for iron chelation should be available across the UK

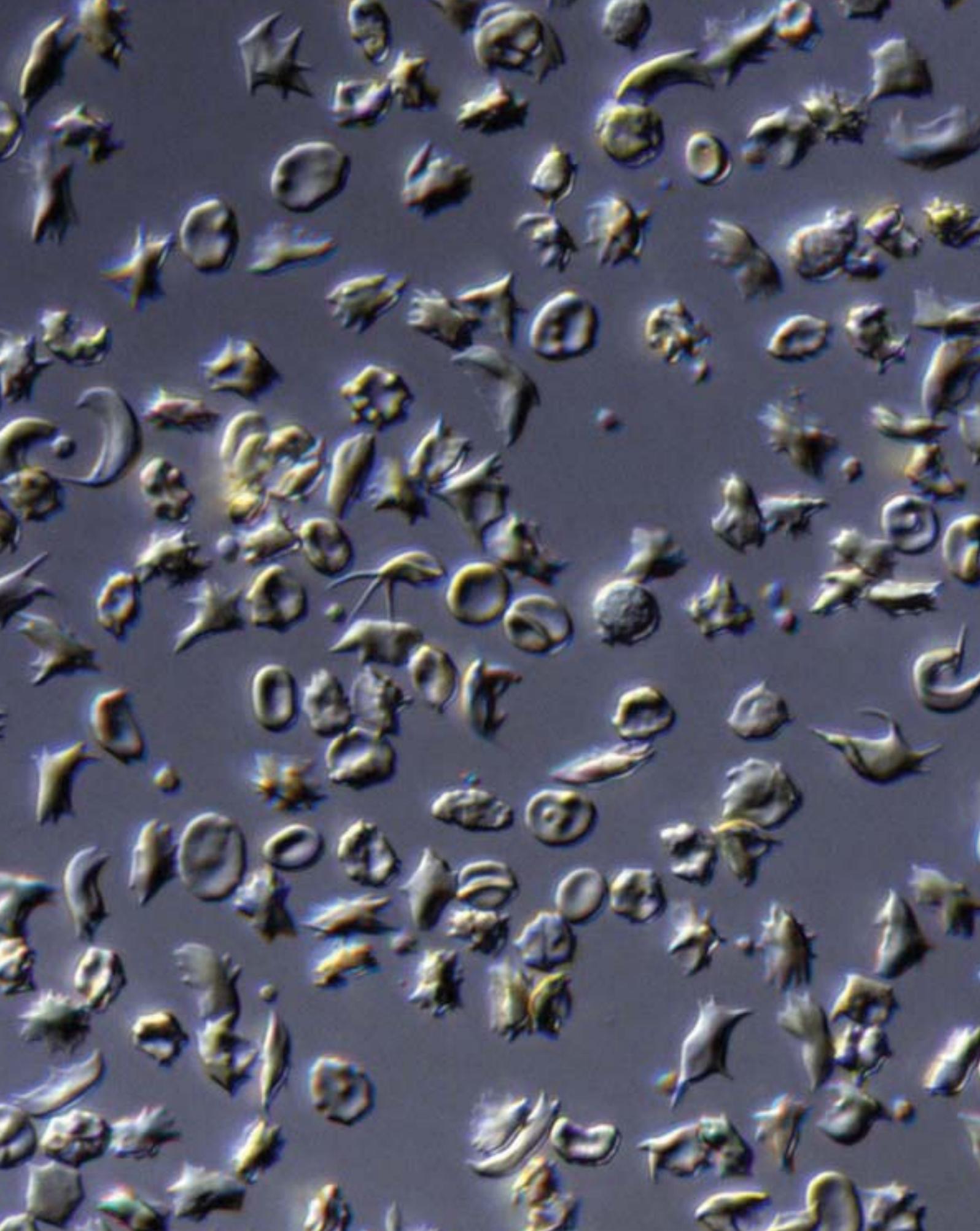
iii) Community services

- There should be development of Sickle Cell and Thalassemia centres/services in areas of high prevalence which offer a wide range of “holistic care” packages such as counselling and genetic testing, provision of information resources to affected individuals, their families and the wider community
- There should be funding allocated to patients and their carers to attend expert patient programmes by their local PCT
- There should be development of the role of community nurse/matron to facilitate patient management of pain within the community

iv) Other

- There should be equitable and transparent access and funding for new treatment strategies and new drugs irrespective of location
- There should be provision of centrally funded clinical research initiatives with adequate administrative support to promote ethically approved translational research across clinical networks and geographical boundaries

ⁱ Department of Health. World Class Commissioning: Vision Summary. 2007, Dec; NHS.



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