SICKLE CELL SOCIETY

2018

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

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

2nd Edition, 2018

Sickle Cell Society
54 Station Road
London NW10 4UA
United Kingdom
Tel.: +44 (0)20 8961 7795
Fax: +44 (0)20 8961 8346
info@sicklecellsociety.org
www.sicklecellsociety.org

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Figure 1: A suggested model of transition, from Musumadi, L., Westerdale, N., & Appleby, H. (2012). An overview of the effects of sickle cell disease in adolescents. Nursing Standard, 26(26), 35-40 [Nursing Standard by Royal College of Nursing (Great Britain)]

Figure 6: Percentage of women experiencing an unintended pregnancy within the first year of use with typical use and perfect use (UKMEC 2016. https://www.fsrh.org/ukmec/)

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Editorial/writing group

Editorial Board

- Dr Jo Howard, Consultant Haematologist/Honorary Reader, Guy's and St Thomas' NHS Foundation Trust, London/King's College London and Chair of the UK Forum on Haemoglobin Disorders (Chair of Editorial/Writing Group)
- Dr Kofi Anie MBE, Consultant Clinical Psychologist/Honorary Clinical Senior Lecturer, Brent Sickle Cell and Thalassaemia Centre, London North West Healthcare NHS Trust/Imperial College London
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- Ms Verna Davis, Service Manager and Lead Haemoglobinopathy Specialist Nurse, Manchester Sickle Cell and Thalassaemia Service
- Mr John James, Chief Executive Officer, Sickle Cell Society
- Ms Natasha Lewis, Lead Nurse Sickle Cell & Thalassaemia, Homerton University Hospital NHS Foundation Trust
- Ms June Okochi, Lead Mentor, Patient representative, Sickle Cell Society
- Dr Shivan Pancham, Consultant Haematologist, Sandwell and West Birmingham Hospitals NHS Trust
- Dr Kate Ryan, Consultant Haematologist, Manchester Royal Infirmary and Chair of the NHS England Clinical Reference Group for Haemoglobinopathies
- Ms Michele Salter, Vice Chair and Treasurer, Sickle Cell Society
- Dr Paul Telfer, Senior Lecturer in Haematology, Queen Mary University of London, Consultant Haematologist Bart's Health NHS Trust
- Dr Anne Yardumian, Consultant Haematologist, North Middlesex University Hospital, London

Contributing Authors

Grateful thanks to the following, who authored or co-authored individual chapters:

- Dr Shubha Allard, Consultant Haematologist/Honorary Clinical Senior Lecturer, NHS Blood and Transplant and Barts Health NHS Trust/ Queen Mary University of London
- Dr Jeremy Anderson, Sickle Cell Team Psychologist, Imperial College Healthcare NHS Trust
- Professor Selim Aractingi, Faculty of Medicine, University of Paris Descartes; Head of Dermatology, Cochin Hospital, Paris
- Dr Glenda Augustine, Consultant in Public Health, City of Wolverhampton Council
- Mr Marcus Bankes, Consultant Orthopaedic Surgeon, Guy's and St Thomas' NHS Foundation Trust
- Dr Martin Besser, Consultant Haematologist, Cambridge University Hospitals NHS Foundation Trust
- Dr Gerry Coghlan, Consultant Cardiologist, Director of Pulmonary Hypertension service, Royal Free London NHS Foundation Trust
- Dr Bernard Davis, Consultant Haematologist, The Whittington Hospital NHS Trust/ University College Hospital London
- Dr Emma Drasar, Consultant Haematologist, The Whittington Hospital, London
- Professor Simon Dyson, Professor of Applied Sociology, De Monfort University
- Professor James Elander, Head of Centre for Psychological Research, University of Derby
- Dr Perla Eleftheriou, Consultant Haematologist, University College London Hospital Foundation Trust
- Dr Kate Gardner, Clinical Research Fellow/Specialist Registrar Haematology, King's College London/King's College Hospital
- Dr Deborah Hay, Consultant Haematologist, Oxford University Hospitals NHS Foundation Trust
- Dr Baba Inusa, Consultant Paediatrician/Honorary Reader, Evelina Hospital London/Guy's and St Thomas' NHS Foundation Trust, London/King's College London
- Dr Banu Kaya, Consultant Haematologist, Bart's Health NHS Trust, London
- Dr Rachel Kesse-Adu, Consultant Haematologist, Guy's and St Thomas' NHS Foundation Trust
- Professor Fenella Kirkham, Professor of Paediatric Neurology, University Hospital Southampton NHS Foundation Trust/University College London/Great Ormond Street Institute of Child Health
- Dr Pavel Kotoucek, Consultant Haematologist, Dartford and Gravesham NHS Trust
- Dr Stella Kotsiopoulou, Consultant Haematologist, Croydon Health Services NHS Trust

- Dr Navdeep Kumar, Consultant in Special Care Dentistry/Honorary Lecturer University College London, Clinical Lead for Oral Medicine, Facial Pain and Special Care Dentistry, Eastman Dental Hospital for Oral Healthcare Sciences
- Dr Usha Kumar, Lead consultant for Reproductive and Sexual Health, Camberwell Sexual Health Centre, King's College Hospital NHS Foundation Trust
- Dr Jane Logan, General Practitioner, FRCGP.
- Dr Jenna Love, Clinical Psychologist, Red Cell Pain Management and Psychology Service, St George's University Hospitals NHS Foundation Trust
- Dr Asad Luqmani, Consultant Haematologist, Imperial College Healthcare NHS Trust
- Ms Claudine Matthews, Social Liaison Officer, Sickle cell and thalassaemia service, Homerton University Hospital NHS Foundation Trust
- Dr Patrick Murphy, Consultant Respiratory Physician/Honorary Senior Lecturer, Guy's and St Thomas' NHS Foundation Trust/King's College London
- Mr Luhanga Musumadi, Advanced Nurse Practitioner Haemoglobinopathies and Lead nurse for Adolescent Transition, Guy's and St Thomas' NHS Foundation Trust
- Dr Douglas Newman, Consultant Ophthalmologist, Cambridge University Hospitals NHS Foundation Trust
- Mr Daniel Nyakutsey, Welfare Support Advisor, Sickle Cell & Thalassaemia Community Services, South East London Sickle and Thalassaemia Centre
- Dr Ruben Nzouakou, Homerton University Hospital NHS Foundation Trust
- Mr Eugene Oteng-Ntim, Consultant Obstetrician, Honorary Reader in Women's Health, Guy's and St Thomas' NHS Foundation Trust/King's College London
- Soorbhi Parekh, Sickle Cell Society
- Dr Elizabeth Rhodes, Consultant Haematologist, St George's University Hospitals NHS Foundation Trust
- Professor Vanderson Rocha, Principal Investigator of Stem Cell Therapies, NHS Blood and Transplant, Oxford University Hospitals NHS Foundation Trust and Professor of Haematology, Transfusion and Cell Therapy, University of Sao Paulo, Brazil
- Nasser Roheemun, Specialist Nurse/Centre Manager, The George Marsh Sickle Cell and Thalassaemia Centre, North Middlesex University Hospital NHS Trust
- Dr Clare Samuelson, Specialist Registrar Haematology, Sheffield Teaching Hospitals NHS Foundation Trust
- Dr Claire Sharpe, Reader in Renal Medicine, King's College London and Honorary Consultant Nephrologist, King's College Hospital NHS Foundation Trust
- Dr Abid Suddle, Consultant Hepatologist, Institute of Liver Studies, King's College Hospital NHS Foundation Trust
- Dr Sara Trompeter, Consultant Haematologist and Paediatric Haematologist, University College Hospital London and Consultant in Transfusion for Haemoglobinopathies, NHS Blood and Transplant

- Mr Nick Watkins, Consultant Haematologist, St George's University Hospitals NHS Foundation Trust
- Dr Josh Wright, Consultant Haematologist, Sheffield Teaching Hospitals NHS Foundation Trust

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- Ms Nkechi Anyanwu, Clinical Nurse Manager, Sickle Cell & Thalassaemia Community Services, South East London Sickle and Thalassaemia Centre
- Professor Barbara Bain, Professor of Diagnostic Haematology, St Mary's Hospital
- Dr Cormac Breen, Consultant Nephrologist, Guy's and St Thomas' NHS Foundation Trust
- Dr Annabel Crowe, General Practitioner, Mental Health Clinical Lead, Governing Body Member for Hounslow CCG
- Dr Yvonne Daniel, Viapath, Specialist Lead Scientist, Haematological Sciences, Special Haematology Lead, Blood Sciences, Guy's Hospital
- Dr Lorna Fraser, Senior Lecturer, Department of Health Sciences, University of York
- Dr Helen Haynes, Research Group Administrator, Department of Health Sciences, University of York
- Dr Quentin Hill, Consultant Haematologist, Leeds Teaching Hospitals NHS Trust
- Dr Paul Holmes, Consultant Neurologist, Guy's and St Thomas' NHS Foundation Trust
- Dr Moin Mohamed, Consultant Ophthalmologist, Guy's and St Thomas' NHS Foundation Trust
- Ms Chengetai Muzah, Specialist Nurse, Sickle Cell and Thalassaemia Centre, East Ham, London
- Dr Lola Oni OBE, Specialist Nurse Consultant/Service Director/Lecturer, Brent Sickle Cell and Thalassaemia Centre, London North West Healthcare NHS Trust
- Dr Sue Robinson, Consultant Haematologist, Guy's and St Thomas' NHS Foundation Trust
- Mr Majed Shabbir, Consultant Urologist, Guy's and St Thomas' NHS Foundation Trust
- Dr Farrukh Shah, Consultant Haematologist, The Whittington Hospital NHS Trust/ University College Hospital London
- Ms Sekayi Tangayi, Service Manager and Specialist Nurse, Sickle Cell and Thalassaemia Centre, East Ham, London
- Mr Neill Westerdale, Advanced Nurse Practitioner Sickle Cell Disease, Guy's and St Thomas' NHS Foundation Trust
- The Haematology team at North Middlesex University Hospital NHS Trust

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Production

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Clinical disclaimer

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

The Sickle Cell Society, UK Registered Charity No. 1046631

The Sickle Cell Society can be contacted at:

Registered address:
54 Station Road
London, NW10 4UA

Telephone: 020 8961 7795
020 8961 8346
email: info@sicklecellsociety.org

Foreword

As Chair and Chief Executive of the Sickle Cell Society we are honoured to serve patients, and their families, and work with the caring professionals in the National Health Service and beyond. Patient Reported Experience Measures by Collaboration for Leadership in Applied Health Research and Care (CLAHRC), National Institute of Health Research (NIHR), Picker Institute and the Sickle Cell Society have revealed significant concerns over the treatment, care, and the quality of service patients receive, which varies according to postcode and provider (Picker Institute Europe, 2015). Research into this condition is increasing however and clinical trials are providing real hope for improving treatments and cures.

If you are reading this foreword we would like to thank you for making a great start, but from this outset, we encourage you to read the 'Standards for Clinical Care of Adults with Sickle Cell Disease' to the end. Learn it, share it, and practice it, until its use is embedded at the heart of treatment and care for people suffering the chronic lifelong medical condition of sickle cell disorder.

These conditions generate enduring effects disproportionately exposing patients to adverse economic and social factors that contribute to health inequalities, (World Health Organization (WHO), 2011). The aim of the *Standards* is to reduce levels of morbidity and mortality and improve the experience of all haemoglobinopathy patients by reducing these inequities and improving timely access to high quality expert care.

The *Standards* comprise the components that characterise sickle cell disorder, and the various practices and people, needed to care for patients. All stakeholders of the condition should make the *Standards* a key reference document; patients, carers, haematologists, commissioners, general practitioners, consultants, junior doctors, nurses, specialist nurses, accident and emergency staff, ambulance staff and paramedics, pathologists, pathophysiologists, psychologists, nutritionists, counsellors, support groups, academics, senior NHS and public health policy makers, researchers and pharmaceutical companies involved in sickle cell research and trials. It is essential they provide consistent best practice services through integrated multidisciplinary teams with systematic approaches and pathways led by the public patient voice. The *Standards* is clear on what to deliver, how to apply and manage delivery, who delivers, and where change and transformation is needed and why.

We commend the *Standards* to all medical professionals especially those working with sickle cell patients. I encourage the NHS and others to take it up and widely disseminate it, supporting training and education around the standard as a requirement for changing the performance of our professionals working in primary, clinical, and social care.

Kye Gbangbola MBA
Chair, Sickle Cell Society

John James
Chief Executive Officer, Sickle Cell Society

Statements of support

The Rt Hon Diane Abbott
Member of Parliament for Hackney North and Stoke Newington
HOUSE OF COMMONS, LONDON SW1A 0AA

24 Answering Service: (020) 7219 3000
Email address: Diane.abbott.office@parliament.uk

Parliamentary Telephone: (020) 7219 4426

23 January 2018

Statement of Endorsement

I am pleased to endorse the new Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK. These new standards play a significant role in improving the care of adults living with sickle cell in the UK. There is still a disparity in the quality of care across the different regions of the UK but these standards are a great step towards ensuring that every sickle cell patient, whatever region they live in, get the same high quality of care.

Diane Abbott

Rt Hon Diane Abbott MP
Shadow Home Secretary
Chair of All-Party Parliamentary Group on Sickle Cell and Thalassaemia
Labour Member of Parliament for Hackney North and Stoke Newington.

Professor Dame Elizabeth N Anionwu DBE CBE FRCN FQNI
Patron: Sickle Cell Society
Emeritus Professor of Nursing: University of West London

10th November 2017

I am delighted to endorse the new *Standards Clinical Care of Adults with Sickle Cell Disease in the UK.*

Whilst management of affected adults with the condition has significantly improved over the years, there are still harrowing accounts of poor clinical care.

This publication will play a major part in ensuring that all individuals, wherever they live in the UK, can expect to receive excellent care from informed health professionals.

Department of Health

From Steve Brine MP
Parliamentary Under Secretary of State for Public Health and Primary Care

39 Victoria Street
London
SW1H 0EU

020 7210 4850

PO-1117368

22 FEB 2013

Mr John James
Chief Executive
Sickle Cell Society
By email to: matthew.neal@sicklecellsociety.org

Dear John,

Thank you for your correspondence of 29 January to Jeremy Hunt about *Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK.*

I would like to thank you for sharing a copy of the revised draft standards, and congratulate the Sickle Cell Society and the UK Forum for Haemoglobin Disorders for their ongoing work to raise the profile of sickle cell disease and to drive the improvement of the services available to those affected by the condition.

Clinical and service standards produced by those involved in advocating for and delivering these services provide the core intelligence that commissioners and providers need. From such standards, commissioners are able to specify, purchase, and monitor services. Providers are helped to understand the standards they must deliver.

Many of your contributors are part of the NHS England Clinical Reference Group for haemoglobinopathies and, as such, will be aware of the service review that NHS England is undertaking in this area. This will include a revision to the service specification and *Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK* will be an important part of that process. The aim of the review, the revision of the specification, and the other commissioning tools that will follow is to ensure that all those in the pathway of care for sickle cell disease are clear about their roles and responsibilities, and how they need to work with others to provide the best possible care for this group of patients.

Thank you again for sharing the draft standards. I hope this reply is helpful.

STEVE BRINE

From the Chief Medical Officer
Professor Dame Sally Davies FRS FMedSci

Department of Health & Social Care

39 Victoria Street
7th Floor
London SW1H 0EU
020 7210 5151
sally.davies@dh.gsi.gov.uk
www.gov.uk

Mr John James
Chief Executive
Sickle Cell Society
54 Station Road
London
NW10 4UA

25th January 2018

Dear John,

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

I commend the updated *Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK* to everyone – clinicians, commissioners, people living with sickle cell and their families. Thank you for sending them over to me.

These guidelines for the care of those with sickle cell disease have been drawn up by an impressive group of professionals and are clearly evidence based, or consensus when evidence is still lacking. They build on earlier standards for care.

I hope everyone in the NHS involved in the care of patients with sickle cell disease translates these new standards into local practice to improve the lives of our patients.

Well done Sickle Cell Society!

Yours ever,

PROFESSOR DAME SALLY C DAVIES FRS FMedSci
CHIEF MEDICAL OFFICER

Chair's introduction

The first edition of the 'Standards for Clinical Care of Adults with Sickle Cell Disease in the UK' (Sickle Cell Society, 2008) has certainly been instrumental in improving care for patients with sickle cell disease (SCD). Haemoglobinopathies have been commissioned as a specialist service by NHS England leading to the development of a service specification and there is an on-going service review at the current time. The services for adults in England underwent peer review against the standards in 2012/13 and this was repeated across the entire UK in 2014/16. The peer review not only defined our baseline of care but the second review saw improvements in many aspects of care across the country and have acted as a catalyst for further service developments. The majority of these standards are applicable for the entire United Kingdom, although commissioning arrangements may differ in the devolved nations so some of the standards around organisation of care may be less relevant.

We have seen a huge amount of clinical and academic research into SCD globally including several key publications on clinical research trials and new insights into pathophysiology. This research continues, with many new drug therapies and potentially curative treatments now on the horizon. It feels as if we are on the cusp of a new era of clinical care for adults with SCD.

Unfortunately these new developments have not always translated into an improvement of care in quality of life or outcomes. Overwhelming feedback from patient surveys shows that many of the issues patients raised in 2008, including timeliness of pain relief, inadequate education of health professionals and inequity of care still exist.

The updating of the Standards document therefore seems timely, if not overdue. Our aims in the production of this document were to engage a broad multi-disciplinary group of health providers, patients and support groups. Whilst these are evidence based, as far as possible where evidence exists, this is not intended to be an academic text and tries to focus on practical management issues. By outlining a minimum expected level of care it aims to reduce inequities in health provision.

We have aimed to retain the key standards from the first edition that are still needed, update those where evidence has changed and add new standards where they are needed. There have been several changes in the document including the development of recommendations and additional appendices to support health care staff. We hope this document will continue to support improvements and excellence in care across the UK.

This document was led and supported by members of the Sickle Cell Society who are working for improvements in clinical care for all those with SCD in this country and worldwide. I would like to thank them for their ceaseless effort and their continued support. They were integrally

involved in the development of these standards at all stages. I would also like to thank the other members of the Editorial Board who have put in many hours of their own time into reviewing evidence and into writing and editing this document. In addition many of the health professionals practicing in the UK have given up their time to author, co-author or review chapters. This is truly a collaborative piece of work.

Finally I would like to acknowledge the work and memory of Ade Olujohungbe, the Chair of the first edition of these standards. He was instrumental in the conception, development and production of the standards and was a valued friend and colleague. Without him these standards would not have been possible.

Dr Jo Howard

Chair of Editorial/Writing group

January 2018

Note on Methodology

The Sickle Cell Society instigated the update of these standards in 2015. The previous editorial board and members of the UK Forum on Haemoglobin Disorders were invited to apply to join the editorial board or to take part as contributing authors or as part of the sounding board. The editorial/writing group met regularly, each oversaw a section of the Standards and were responsible for co-ordinating co-authors, editing their chapters and reviewing the entire document.

The document has been divided into three sections, Section A (General Principles) which includes organisation of care and health and well-being, Section B on the management of acute and chronic complications and Section C which includes other management issues and treatments. In many of the areas discussed, particularly Section A, the guidance is largely practical and organisational with no formal trial or other clear evidence. Even in the clinical chapters there is often a lack of clinical trial evidence and we have relied largely on published retrospective analyses, observational data, expert opinion and the views of patients and families. If a recent systematic review was available its findings were incorporated into the document. If this was not available a literature review was performed and its outcomes summarised.

We have adopted two grades of practical interventions:

Standards

Being that which providers must do to ensure safe and adequate care or where omission could lead to poor clinical outcomes. These include key requirements of any service. Where possible we have tried to ensure these are auditable.

Recommendations

Being those that would be beneficial and that providers should try to follow, but for which there is less evidence or that are less likely to have a direct impact on clinical outcomes.

We note however that there is a lack of research studies for many of these recommendations, especially the non-clinical ones. Practice has evolved over time so we have tried to document what most people do and what is a consensus view of good practice.

The entire document and in particular the standards and recommendations were debated by the editorial panel. A draft document was sent to the Sounding Board in July 2017 and their comments were incorporated into the final draft. Where evidence was lacking a consensus decision was reached by the editorial board.

The patient quotes were collated by the Sickle Cell Society from surveys undertaken with the Picker Institute (Europe); the National Institute for Health Research (NIHR); and Collaboration for Leadership in Applied Health Research and Care (CLAHRC) – North West London. In addition, some quotes were also developed by the Sickle Cell Society's patient lead as part of the peer review process.

Over 700 sickle patients and carers across the U.K participated in the survey and the key themes emerging from the surveys were:

- The poor quality of emergency vs planned care
- Clinical awareness of dealing with SCD across primary and acute care
- Significant variation in care
- The poor management of SCD including coping with pain.

The survey was carried out anonymously and the main objectives of carrying out the survey at this scale were to support the development of this document, to improve the overall quality of sickle cell services across the country by supporting hospitals through the clinical peer reviews and to represent the voices of the patients. The Sickle Cell Society ensured patients were involved in these peer group evaluations engaging with other sickle patients across the country by providing consistent support.

Following from this, the development of this document has also involved patients, carers and the Sickle Cell Society. The objective is to ensure that the voices of sickle cell adult patients are directly represented.

Overarching standards

General principles

OS 1. Adults with sickle cell disease (SCD) should be offered care close to home where possible, but should also have access to highly specialist multidisciplinary care including specialist nursing support.

OS 2. All local hospitals should be linked with a named specialist centre with agreed pathways and protocols for advice and referral for acute and chronic complications.

OS 3. Specialist haemoglobinopathy teams should participate in a quality review programme of haemoglobinopathy services against nationally agreed standards.

OS 4. All consenting patients should be registered on the National Haemoglobinopathy Registry (NHR) and annual review data and adverse events should be reported to the NHR.

OS 5. All patients should have access to specialist psychology support.

OS 6. Core staffing of Specialist Centres for SCD should include a psychologist with a special interest and experience in SCD.

Transition

OS 7. Specialist teams should have a policy and dedicated team for transition, which should include a named transition-lead.

OS 8. Further and higher education institutions, universities and colleges should develop and monitor policies for supporting students with SCD with respect to their education, their health and their careers.

Primary care

OS 9. All adults with SCD should be registered with a general practitioner (GP).

OS 10. Each SCD patient should be offered routine primary health care services at their GP surgery.

OS 11. All adults with SCD should have access to community nursing support.

Acute pain

OS 12. Patients presenting as a medical emergency with an acute painful episode should be offered appropriate analgesia within 30 minutes of presentation to the emergency department.

OS 13. All hospitals with emergency departments should have protocols to guide management of uncomplicated acute presentations of SCD.

Acute complications

OS 14. All hospitals with emergency departments should have protocols to guide management of uncomplicated acute presentations of SCD including when to seek specialist advice.

Chronic complications

OS 15. All patients should be offered regular outpatient review to ensure screening for chronic disease complications and early instigation of treatment according to local protocols and national guidance.

OS 16. All patients with evidence of chronic organ dysfunction should have access to review in multidisciplinary or specialist clinics.

OS 17. Patients with complex pain needs should be referred to a multidisciplinary chronic pain team with experience of SCD, offering both pharmacological and non-pharmacological interventions.

Prevention of infection

OS 18. Specialist and local haemoglobinopathy teams and GPs should ensure that adults with SCD are adequately vaccinated against the following infections according to advice in the Green Book:

- Invasive pneumococcal disease
- Haemophilus influenza type B
- Neisseria meningitis ACWY and B
- Hepatitis B

OS 19. Patients should be periodically warned about the increased risk of invasive pneumococcal disease (IPD) and other forms of sepsis. They should also be educated about symptoms which might indicate infection and to attend for medical assessment if temperature ≥38^{0}C.

Annual review

OS 20. All adults with SCD should be offered comprehensive review from a specialist centre at least annually.

OS 21. A pro forma should be used for the annual review visit to ensure thorough and consistent care and to facilitate data collection.

Pregnancy

OS 22. Pregnant women with SCD should be managed by a multidisciplinary team of obstetricians, midwives and haematologists with an interest in SCD in a unit that manages high risk pregnancy.

OS 23. Units which manage SCD pregnancy should have a clear protocol for patient management.

Hydroxycarbamide (HC)

OS 24. All hospitals looking after adults with SCD should have a prescribing and monitoring protocol for hydroxycarbamide (HC) (also known as hydroxyurea) to maximise benefits and safety.

OS 25. Specialist centres should audit their use of HC to ensure it is discussed with all patients who may benefit from its use.

Transfusion

OS 26. All hospitals that admit SCD patients should have protocols and training in transfusion for SCD including manual exchange procedures.

OS 27. Automated exchange transfusion should be available to all patients with SCD and should be provided by specialist centres.

OS 28. Specialist centres should audit their use of blood transfusion in the acute and chronic setting to ensure its use is consistent with national guidance.

Emerging therapies

OS 29. National Health Service (NHS) England should ensure that all patients have equitable access to high cost interventions.

OS 30. Trials for haematopoietic stem cell transplantation (HSCT) in adults with SCD should be available in the UK.

OS 31. All patients with SCD should have access to information regarding current clinical trials, to enable participation if the patient so chooses.

Section A: General principles

Chapter 1: Overview

Introduction

This chapter is a brief description of sickle cell disease (SCD). It is not a comprehensive review and readers are referred to standard texts for more detailed information.

Haemoglobin is the oxygen carrying protein found in the red blood cells. It comprises four 'globin' protein chains, each wrapped around an iron-containing 'haem' molecule. Newborn babies have a form of haemoglobin called foetal haemoglobin (haemoglobin F). This is largely replaced by adult haemoglobin (haemoglobin A) in the first year of life. Haemoglobin A consists of two alpha (α) globin chains and two beta (β) globin chains.

The sickle mutation is a substitution of C for A at codon 6 of the β globin gene (β^S). The resulting exchange of valine for glutamic acid leads to the production of a sickle haemoglobin molecule (haemoglobin SS). This has a tendency to form aggregates or to polymerise in the deoxygenated state resulting in red cell breakdown and aggregation of red cells in the blood vessels thereby causing blockage.

Haemoglobin S and other significant variants

SCD comprises a group of genetic conditions associated with β^S, which give rise to significant clinical complications. Individuals who inherit β^S from both parents are homozygous and have sickle cell anaemia. Individuals inheriting β^S from one parent, and certain haemoglobin variants (haemoglobin C, haemoglobin D_{Punjab}, haemoglobin O_{Arab}, haemoglobin E, haemoglobin Lepore)or a β thalassaemia gene, from the other parent will also have a variant (compound heterozygote) form of SCD. There are many other variants detected on screening that are of no clinical significance when found in combination with haemoglobin S.

Sickle cell carriers

Individuals who inherit β^S from one parent and the normal β globin gene from the other are referred to as carriers of sickle cell, or as having sickle cell trait. Their red blood cells contain haemoglobin A and haemoglobin S. Sickle cell carriers usually have no clinical symptoms and often do not know they are carrying β^S unless they have a specific blood test.

Epidemiology

Although SCD occurs predominantly in individuals of African descent, these disorders are also prevalent in the Eastern Mediterranean, Middle East, India, the Caribbean and South and Central America. The common factor is a high prevalence of malaria in the area, or migration from a malarial area, because sickle carriers have partial protection from malaria and therefore a survival advantage. In sub-Saharan Africa the gene frequency of β^S ranges from 10% to 30%.

In England, SCD affects about 1 in 2000 live births and there are currently estimated to be around 12,500 – 15,000 individuals living with SCD. It is one of the most common single gene disorders in the UK.

Pathophysiology

Haemoglobin S polymerises when deoxygenated. The accumulation of intracellular haemoglobin polymers results in damage to the red cell membrane causing changes in permeability to cations. The red cell becomes dehydrated, more rigid and less able to negotiate the capillary circulation. The survival of red cells in SCD is significantly reduced resulting in a haemolysis (shortening of red cell life span). However, haemoglobin S releases oxygen to tissues more readily than haemoglobin A, and this may reduce the drive to erythropoiesis. Red and white cells and platelets adhere to the lining (endothelium) of the small vessels of the circulatory system resulting in vascular damage, organ infarcts and progressive ischaemic damage. This complex process of red cell adhesion and aggregation leads to blockage of the blood vessels, known as vaso-occlusion, which impairs blood flow and prevents effective delivery of oxygen to the tissues. This is thought to be the underlying cause of acute episodes such as painful crisis as well as chronic damage such as avascular necrosis of hips and renal failure.

Narrowing and occlusion of larger vessels is thought to be caused by chronic sheer-damage and adhesion of blood cells to the vessel endothelium, complicated by vasoconstriction and nitric oxide deficiency. This mechanism is likely to be responsible for complications such as pulmonary hypertension and stroke.

Clinical presentation

SCD is an inherited condition, which can be diagnosed at birth. The UK has a universal newborn screening programme. Clinical complications do not occur at birth – or in the first few months of life - because the high proportion of intracellular foetal haemoglobin (haemoglobin F) inhibits haemoglobin S polymerisation. During the first year of life, the proportion of haemoglobin F decreases and the proportion of haemoglobin S increases within the red cells. Consequently, pathological effects of sickling start to occur.

The most common clinical manifestations are chronic anaemia and recurrent acute pain episodes, which in adults typically affect the limbs and trunk. Other common clinical conditions include acute complications such as splenic sequestration, overwhelming sepsis, acute chest syndrome, priapism and stroke, and chronic complications such as lung disease, sickle nephropathy, pulmonary hypertension, avascular necrosis of the hips or shoulder joints, recurrent chronic leg ulceration and retinopathy. These are described in more detail in chapters below.

Clinical course and survival

In its most severe form, SCD causes significant morbidity and mortality. However, SCD is variable in severity and the onset of acute and chronic complications is unpredictable. This uncertainty can add to the psychological consequences of living with a life threatening chronic disease. It may also cause severe social disruption throughout the life course.

As recently as the 1970s, a patient was not expected to survive to adulthood. Nowadays, childhood mortality is relatively rare, at least in developed countries, with 99% of children in the UK surviving to adulthood. This is a result of introducing a variety of health care interventions including neonatal screening and enrolment of affected babies in a comprehensive care programme, pneumococcal prophylaxis, and early recognition and better treatment of acute complications in children. Unfortunately, the current outlook for adults is not so encouraging, with estimates of median survival for sickle cell anaemia in the 40s. Single centre data from the UK have shown estimated median survival of 67 years in patients with sickle cell anaemia and higher in patients with sickle cell/haemoglobin C disease (Gardner *et al.*, 2016). Certainly life expectancy is improving but older patients with SCD have an increasing burden of chronic complications and often have complex health needs. A National Confidential Enquiry into Patient Outcome and Death (National Confidential Enquiry into Patient Outcome and Death (NCEPOD), 2008) study in England reported that the most common causes of death in adults with SCD were cerebrovascular accidents, multi-organ failure and acute chest syndrome. The enquiry also called for better evaluation and improved reporting of cause of death in SCD patients.

Diagnosis

SCD may be suspected clinically if a patient from an at-risk ethnic group presents with clinical features suggestive of a painful crisis or an acute complication of SCD. Ethnicity, however, is not always a marker of who might be at risk of SCD. The large majority of new cases are now diagnosed as a result of the neonatal bloodspot screening programme in England.

Laboratory tests used to diagnose SCD:

a) Indirect methods which detect haemoglobin S on the basis of its physical/chemical properties.

- Sickle solubility test (e.g. Sickledex). This test will identify the presence of haemoglobin S if more than 15% of total haemoglobin. It does not differentiate between sickle cell trait, sickle cell anaemia and compound heterozygous states and cannot be used for newborn screening or diagnosis.
- Haemoglobin electrophoresis: cellulose acetate membrane at alkaline pH, acid agarose gel, isoelectric focusing (IEF), capillary electrophoresis.
- High performance liquid chromatography (HPLC).

b) Methods that directly identify haemoglobin S or the underlying mutation:

- Tandem mass spectroscopy
- Direct detection of the β^S mutation. Various methods of DNA analysis may be used.

The NHS Screening Programme for Sickle Cell and Thalassaemia publishes antenatal and neonatal laboratory handbooks (Public Health England, 2017b) which provide detailed guidance on laboratory standards, testing algorithms, standardised reporting formats and indications for referral for DNA analysis. All laboratories testing for SCD should adhere to these standards.

Screening for sickle cell

National screening programme

The plan to establish a linked antenatal and neonatal screening programme for Sickle cell and thalassaemia in the NHS was agreed in 2001 and implemented over the next ten years. It has the following aims:

- To support people to make informed choices before conception and during pregnancy
- To improve infant health through prompt identification of affected babies
- To provide high quality and accessible care throughout the UK
- To promote greater understanding and awareness of the disorders and the value of screening

Neonatal screening

Screening of newborns for SCD is part of the National Newborn Screening Programme in the UK. Testing is done on all babies using a heel prick bloodspot sample taken at 5-7 days of age. The

aim is to identify babies prior to their first clinical presentation. There is compelling evidence from programmes in Jamaica, UK and the United States that early diagnosis can improve clinical outcomes and reduce mortality during childhood. Key interventions include parental education, early initiation of oral penicillin, administration of pneumococcal vaccination and transcranial Doppler risk screening.

Antenatal screening

Antenatal haemoglobinopathy screening is offered to all women in the UK as part of routine antenatal care. In England, testing for sickle cell carrier status is universal in high prevalence areas (more than 1.5 babies per 10,000 births with SCD) and targeted in low prevalence areas, with risk assessed by determining the family origins of baby's mother and father using a validated questionnaire (Public Health England, 2012). Carrier mothers should be offered counselling and fathers invited for testing.

When both parents are carriers, the pregnancy is regarded as 'at risk' (1 in 4 chance of an affected child), and prenatal diagnosis (PND) is offered. Couples found to have an affected foetus require further counselling and are given the option to terminate the affected pregnancy.

Emergency and opportunistic screening

Preoperative 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 haemoglobin S and further investigation is needed to distinguish sickle trait from significant SCD. HPLC will give a quantitative level of haemoglobin S and haemoglobin F, as well as demonstrating the presence of haemoglobin A to clarify the diagnosis. Opportunistic screening requests may come from GP practices, dentists and Family Planning Clinics, and siblings of babies identified through the newborn screening programme should be tested.

Laboratories and clinical services need to ensure that a procedure is in place to allow affected individuals to be counselled about their condition and to 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.

Predictive factors and variability in phenotype

SCD, although the result of a single genetic defect, is variable in clinical severity. Sickle cell anaemia and haemoglobin S/β^0 thalassaemia are regarded as most severe, but there is remarkable variation in clinical phenotype between individuals with these genotypes. We are yet to fully understand the reasons for this. Further, life threatening events can arise in 'less severe' SCD. Genetic and environmental elements have a significant influence on disease severity.

The best characterised genetic factors are:

- Genetic determinants of increased haemoglobin F production
- Coexisting alpha thalassaemia
- Beta globin haplotype
- Linked genetic polymorphisms associated with specific acute and chronic complications
- Environmental factors include infection, climate, nutrition, psychosocial factors, socio-economic status and access to medical care

Rationale for therapies

The goals of management are to improve survival, reduce acute and chronic complications, and improve quality of life. Patients require ongoing continuity of care, starting in early infancy and continuing throughout the life course. This document will describe the appropriate levels of care required to achieve these goals.

Chapter 2: Organisation of care

"We require respect, care, dignity and candour. We require mandated standards that can be challenged by patients when failures occur. Commissioning that reflects need that has parity with other specialised illnesses given SCD is the world's most common genetic condition."

General principles

"We need more nurses, more community services, more adult care support services and a dedicated team to support us with the phases of change we experience as sickle patients."

Introduction

Sickle cell disease (SCD) is a lifelong chronic disease causing complex multi-system medical problems, which can be associated with variable clinical presentations and significant social and psychological challenges. This leads to variable care pathways and the need to work with large numbers of different practitioners. Care therefore needs to be provided by a multi-disciplinary team, working across sector and agency boundaries. This will include health and social care provision, community nursing care, primary health care and secondary/tertiary care in specialist centres as well as third sector organisations.

Services need to take account of the chronic nature of the condition and its impact 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 their disease optimally. An emphasis on patient education and independent self-care is fundamental to successful outcomes, particularly given the uncertainties associated with the condition. Partnership between 'expert patients' and professionals, which enhances care and patient choice, is central to management decisions.

Health professionals need to be aware of the challenges of navigating these complex care pathways and of the importance of consistent and clear communication.

Standards

- Adults with SCD should be offered care as close to home where possible, but should also have access to highly specialist multidisciplinary care including specialist nursing support.
- All patients should have a named key contact and a number to phone if needing advice.
- All hospitals with emergency departments should have protocols to guide management of uncomplicated acute presentations of SCD.

- All local hospitals should be linked with a named specialist centre with agreed pathways and protocols for advice and referral for acute and chronic complications including when to seek specialist advice.
- All adults with SCD should be offered comprehensive review from a specialist centre at least annually. All patients should be offered regular outpatient review to ensure screening for chronic disease complication and early instigation of treatment according to local protocols and national guidance.
- All patients with evidence of chronic organ dysfunction should have access to review in multidisciplinary or specialist clinics.
- All patients should have access to specialist psychology support.

Background evidence

The appropriate model offers care for the patient as close to home as possible whilst offering access to highly specialist health care when needed for expert assessment or management. These requirements are thought to be best addressed by care networks but different models of care have been developed, based on local availability and patient preference, with little evidence about which is best.

Much care can be offered in the home or community setting, with clinical support from the local hospital, which will provide routine health checks and acute and on-going care for less complex complications. Primary and community services are commissioned by Clinical Commissioning Groups (CCGs) and there should be dialogue and seamless service provision between them and the specialist services commissioned by NHS England.

All local hospitals should be linked to a specialist haemoglobinopathy team (SHT). Care should be overseen by the SHT and delivered at linked hospitals. SHTs will generally be linked to hospitals on a geographical basis but arrangements will take into account the prevalence of the conditions and expertise available. The roles and responsibilities for the SHT and their interactions with the linked hospitals should be clearly defined and all patients should be reviewed by the specialist team at diagnosis, for annual review and for major, severe or complex presentations. Clinical management guidelines in local hospitals should be agreed with, and overseen by, the SHT. NHS England is undertaking a service review of specialist haemoglobinopathy services (2017/18) and there may be changes in specialist service provision following completion of this review. It has been suggested that SHTs should work collaboratively to provide a national service providing clinical advice on complex cases and ensuring all patients have access to approved new treatments.

Communication between teams is crucial and may include multidisciplinary meetings and/or patient-held shared care records. Clear arrangements should be in place for shared care. Service users should have a named key contact(s) and be clear about whom to contact for emergency and routine advice.

Key participants in care provision are outlined below.

Family/carers and social network

Friends and family provide essential patient support, including valuable emotional and physical support. They can also act as advocates, particularly when the person with SCD is not well.

Voluntary sector

The Sickle Cell Society (www.sicklecellsociety.org/) is a national organisation supporting patients with SCD and their families. In some areas they offer home visiting services, support groups and other patient/family support. Local voluntary organisations provide similar services in some areas. Other local voluntary organisations also exist, including several regional OSCARs (Organisations for Sickle Cell Relief & Thalassaemia Support).

Education and Employment support

Patients with chronic disease and disability may benefit from additional support within the educational system or in the workplace. These may include student disability services and occupational health services.

Community care

Community support is fundamental to provision of high quality care close to home and all service users should be able to access appropriate community support. Access to dedicated community services will vary between areas. In high prevalence areas there are often Sickle Cell and Thalassaemia (SCaT) community centres run by specialist nurse counsellors offering education, advice and support in the patient home or in the centre. In low prevalence areas, community support may be provided by a community matron or district nursing teams.

Psychological support

Psychological interventions are very important for some people in managing their condition. Psychology staff may offer cognitive behavioural therapy, annual review, one to one intervention or neuropsychological assessment and management. Psychology staff may be based in community centres, in the local hospital or within the specialist centre. All patients with SCD should have access to specialist psychology services.

Primary care

The primary care team has an important role in co-ordinating care for service users with SCD and ensuring that they receive general health care screening and advice. The primary care team will have the responsibility for repeat prescriptions, vaccinations and reproductive care (contraceptive and pre-conceptual care), along with general healthcare unrelated to SCD, but is also important in ensuring the well-being of the patient (e.g. hypertension and cancer screening).

Linked or Local Hospitals

Local hospitals provide services typically for a small to moderate number of SCD services users living locally. The majority of hospitals in the UK will be linked hospitals.

Their role includes:

- Delivery of care, close to a patient's home, in conjunction with SHT according to an agreed care plan
- Having responsibility for care which is delivered locally
- Working with SHT and providing input into multidisciplinary team and governance arrangements

The responsibilities of linked hospitals should be agreed by the SHT and the linked hospital and will depend on local expertise and facilities. However, all hospitals should be able to provide emergency care for painful episodes and other acute complications. They should also be able to undertake simple transfusions and blood monitoring of patients on hydroxycarbamide and iron chelation drugs.

Specialist Haemoglobinopathy Team (SHT)

These are multidisciplinary teams including consultants, trainees, specialist nursing staff (acute), community staff and psychologists with expertise in the management of SCD.

The roles of the SHTs is being re-defined as part of the NHS England service review but the SHT will need to show compliance against the agreed new service specification. The SHT will:

- Be based at a specialist haemoglobinopathy centre (SHC) and will work with named and linked hospital teams (LHT). The SHT may work across several sites, e.g. through outreach clinics or shared posts, in order to ensure they achieve the required standards and oversight of care for each patient whether they attend for his or her care at the SHT or the LHT
- Need to have expertise in the care of people with SCD. For areas of low prevalence the SHT may form partnerships to ensure sufficient patient numbers to develop expertise
- Develop and review each individuals care plan. This should start at birth and be updated as required and at annual review
- Be responsible for governance e.g. audit, mortality reviews, guidelines and protocols
- Provide clinical advice for its linked centres either alone or in collaboration with other SHTs with an agreed rota for cover
- Have access to range of co-dependent services which should include the provision of multi-specialist clinics
- Offer a specialised acute and chronic pain service for sickle cell
- Provide patient information and education

- Provide education and training for staff
- Work with local hospitals to ensure care close to home as possible by offering outreach clinics or by employing new technologies
- Ensure there are mechanisms for ensuring patient participation in service development and quality reviews
- Ensure adequate and comprehensive data sharing flows between LHT and SHT and data entry to the National Haemoglobinopathy Registry

Networks

There is wide geographical variation in the prevalence of SCD across the UK. In order to provide uniform standards of care to all service users, care networks for haemoglobin disorders (SCD and thalassaemia) are recommended so that every patient in the UK can have equitable care, irrespective of where they live, close to home, but with access to a specialist team for management of more severe and complex complications. The effectiveness of such service arrangements have already been demonstrated for other chronic conditions such as cystic fibrosis, asthma, diabetes and haemophilia, although these conditions all have a more consistent distribution around the country.

The model of a network may vary according to prevalence of SCD in the local population, expertise of health professionals and proximity to other services. In high prevalence areas several large hospital centres may work together to provide specialist services across the network. In low prevalence areas a 'hub and spoke' clinical care model with a SCD specialist clinical centre supervising and sharing care with local hospital units and primary and community care teams across a wide area may prove more effective. In very low prevalence areas, it may prove difficult to develop sufficient expertise to provide a specialist service and these networks should link with a larger specialist centre in another network to support them in the management of complex cases and for the development of guidelines, training and audit. This will be defined further in the revised service specification following the service review taking place in 2017/18.

Recommendations

- Service users should be offered information about local patient support groups and voluntary organisations.
- Good communication between community, local and specialist teams is essential and should involve multidisciplinary team meetings. This should include clear instructions for the GP and a care plan. Patient held records may also be helpful.
- Adults with SCD should have access to multi-specialist clinics for management of chronic disease complications.
- The specialist haemoglobinopathy team should have adequate clinical and administrative resources to support all SCD patients in their network.

- The specialist haemoglobinopathy team should supervise a programme for education and training, research and audit and data collection within their network.
- Out of hours facilities for blood tests, outpatient clinics and day facilities should be made available where appropriate for the local population.

Transition services

"As a parent and carer, I know the transition process from child to adult is not effective and non-existent in some areas. We need to crack this issue better."

Introduction

Transition is the process of moving from children's to adults' services. It includes initial planning and offering ongoing support during and after a young person makes this move. The purpose is to help young people and their carers have a positive experience, and to encourage them to adhere to treatment at this time when they can readily default. The process should take into account the broad developmental changes associated with the teenage years and not focus solely on meeting clinical needs. It is important that young people are involved in service design, delivery, and evaluation, and that their experiences are valued.

Standard

- Specialist teams should have a policy and dedicated team for transition, which should include a named transition-lead.

Background evidence

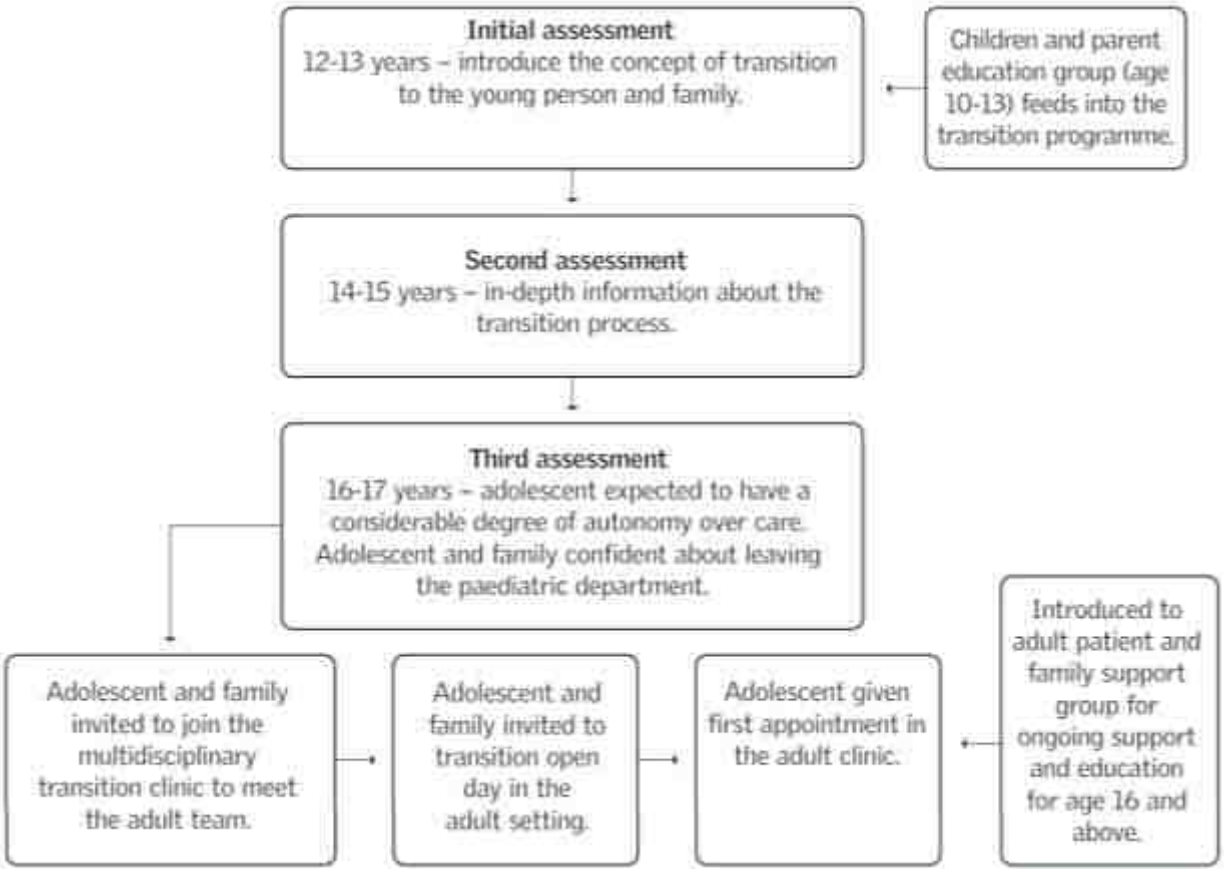
There is a lack of research evaluating the efficacy of transition programmes for young people with haemoglobin disorders in the UK. Most of the evidence is low quality and based on expert opinion, but there are some examples of excellent models of transition programmes for patients with SCD across National Health Service (NHS) institutions (Howard *et al.*, 2010; Inusa *et al.*, 2015; Musumadi *et al.*, 2012). In view of the lack of specific evidence about SCD, many of the recommendations in this chapter are based on the generic Department of Health (DoH) and National Institute for Health and Care Excellence (NICE) recommendations (Department of Health, 2003, 2011; Department of Health Partnerships for Children Families and Maternity / CNO Directorate, 2008; National Institute for Health and Care Excellence, 2016b).

The transition process should take into account the mental and physical developmental stage of the young person and the prevailing circumstances (personal crises, social context and health care service provision). This seamless process should actively begin several years before transfer from paediatric to adult clinic and include assessment of an individual's understanding

of his or her condition, commitment to self-management and the ability of service provision to support the needs of the young person. A jointly created profile or 'passport' document can be developed from discussions between the transition team and the young person. This can then be shared with adults' services. It should be produced early enough to form part of discussions with the young person about planning his or her transition and include information about his or her health condition, education and social care needs, his or her preferences about parent and carer involvement, emergency care plans, history of unplanned admissions, his or her strengths, achievements and future aspirations (Musumadi *et al.*, 2012).

Ideally, there should be a single practitioner acting as the 'named worker' to coordinate transition care, working with the young person to complete the transition planning. Having a single transition lead who works with young people throughout transition until early adulthood has proved effective in ensuring consistent care and has improved the development of relationships with the adult team. It is generally agreed that transfer of patients from paediatric to adult services should be completed by 18 years but transfer can occur earlier in those individuals who are ready for transfer (see Figure 1).

Figure 1: A suggested model of transition (Musumadi et al., 2012)



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Provision of specialist transition teams can be associated with improved concordance, in addition to reduced hospitalisation and emergency care utilisation. This team should identify and utilise the broader psychosocial support available to the young person, which might include family/carers, social services, primary care and colleagues in education (Labore *et al.*, 2017; Williams *et al.*, 2015). Service managers in both adults' and children's services -and across health, social care and education - should proactively identify and plan for young people with sickle cell disease in their locality with transition support needs (Treadwell *et al.*, 2016). Some units have teenage and young adult (TYA) units for inpatient care which can be accessed by patients with SCD and are valued highly where they exist.

It is essential that the young people are treated as equal partners in the transition process and that their views are taken into account. This will support them in making informed decisions and build their confidence to express their preferences for their own care (Noronha *et al.*, 2016; Sobota *et al.*, 2015). The views of young people should also be integral in service planning and development.

The Department of Health quality criteria provides ten generic benchmarks against which all NHS Institutions must measure the quality of their services provision (Department of Health, 2011). These are relevant to SCD and include accessibility, a dedicated transition team, confidentiality and safeguarding, ensuring the environment is young people friendly and staff are appropriately trained. Young people should be involved in monitoring and evaluating patient experience and transition services should include health issues relevant for young people, sexual and reproductive health services and specialist child and adolescent mental health services. It may also be helpful to provide access to peer support during, and in the immediate period after, transition. Transition events or open days where the young people are invited for an introduction to adult service provide a good opportunity for networking and the development of peer support.

Recommendations

- Adult and paediatric sickle services should work together with their local teenage and young person population to ensure they offer accessible and flexible care appropriate to patient need.
- A joint profile or ‘passport’ document can be used to enable the Transition Lead to work with the young person and to assess when they are ready for transition.
- Young people should be offered the opportunity to meet a practitioner from the relevant adult services before they transfer from children's services.
- If a young person does not engage with adult services, health and social care practitioners, working within safeguarding protocols, should try to contact the young person and his or her family and involve other relevant professionals, including the GP.
- Services should work with young people to support them in planning for leaving home to study or work.

- Services should support and encourage access to peer support networks.

Quality improvement

Introduction

Following the production of the first edition of the Standards for Clinical Care of Adults with Sickle Cell Disease in the UK (Sickle Cell Society, 2008) and similar documents on the care of children with SCD and patients with thalassaemia, the haemoglobinopathy community has worked together to meet these standards. The aim is to reduce levels of morbidity and mortality and improve the experience of all haemoglobinopathy patients by reducing inequities and improving timely access to high quality expert care. Haemoglobinopathies have been designated as a specialist service for commissioning by NHS England leading to the development of a service specification. Other initiatives include a rolling programme of peer reviews against quality standards and a national haemoglobinopathy registry.

Suggested medical staffing levels have been given in a review of haemoglobin disorders work force and are summarised in Appendix 2. Similar work on recommended nursing and psychology staffing levels is underway.

Standards

- NHS England (Specialised Commissioning Teams) should ensure that all adults with SCD have access to care from a Specialist Haemoglobinopathy Team.
- NHS England (Specialised Commissioning Teams) should work with Clinical Commissioning Groups in their area to ensure that all adults with SCD have access to community care, local hospital care, social work support and benefits advice.
- NHS England should ensure that all patients have equitable access to high cost interventions.
- SHT should participate in a quality review programme of haemoglobinopathy services against nationally agreed standards.
- All consenting patients should be registered on the National Haemoglobinopathy Registry and annual review data and adverse events should be reported to the National Haemoglobinopathy Registry.
- All centres providing acute care for adults with SCD should participate in an audit of acute pain relief, using the NICE recommendations, at least annually.
- SHT should submit data as required by NHS England for the quality dashboard.

Specialised commissioning

Background evidence

Commissioning is a process by which health needs are identified and services bought to meet those needs. Where possible, an evidence-based approach is used in procuring services and in monitoring their delivery. Specialist services are low volume and high cost or are very complex to deliver.

Services for children and adults with haemoglobinopathies (sickle cell and thalassaemia) and other inherited anaemias were designated as a specialist service for commissioning by NHS England in April 2014 (NHS Specialised Services, 2010). The service specification B-08 (NHS England, 2013) describes the aims and objectives of the service and pathways of care. This recommends care should be delivered by a specialist haemoglobinopathy team (SHT) which by working with linked providers, is expected to deliver a network of care for all patients in the geographical region.

Specialist services are commissioned by Specialised Commissioning Hubs, which are responsible for the Trusts within their geographical region. At the time of this report, network configurations and pathways have not been fully clarified and are the subject of an NHS England service review. This will define the roles and responsibilities of the specialist and linked teams and the commissioning arrangements of the Specialised Commissioning Hubs and the Clinical Commissioning Groups. This must involve consideration of patients' needs and convenience.

Specialised commissioners are supported by Clinical Reference Groups (CRGs) which bring together groups of clinicians, commissioners, public health experts, patients and carers to advise NHS England on the best ways that specialist services should be provided (NHS England, 2016). CRGs lead on the development of clinical commissioning policies, service specifications and quality dashboards. They also provide advice on innovation, conduct horizon scanning, offer advice on service reviews, identify areas of unexplained clinical variation and guide work to reduce variation and deliver value. CRGs, through their Patient and Public Voice (PPV) members, also help ensure that any changes to the commissioning of specialised services are co-produced with and involve patients and the public.

Commissioning of haemoglobinopathy services for patients in Wales and Scotland are devolved locally.

Peer review

Background evidence

Aiming to improve services for patients with haemoglobinopathies, the UK Forum on Haemoglobin Disorders, the Sickle Cell Society, the UK Thalassaemia Society and the NHS Sickle Cell and Thalassaemia Screening Programme have worked with the West Midlands Quality Review Service (WMQRS) to produce Quality Standards and set up a peer review programme of haemoglobinopathy services in the UK.

The first programme of peer review was of services for Children and Young People with Haemoglobin Disorders. This ran between 2010 and 2011. Nineteen centres were reviewed. A review of Adult Services between 2012 and 2013 looked at 32 teams providing haemoglobinopathy services. This was succeeded by programme of joint reviews of children and adult services which ran between 2014 and 2016 and its findings are presented in more detail below. An overview of all of these programmes of peer review and the report from each participating centre are available at www.wmqrs.nhs.uk/publications.

The peer reviews were based on assessment against quality standards, revised before each new programme, and which are consistent with the service specification for haemoglobinopathies. The most recent peer review programme defined standards looking at the following areas:

- Information and support for patients and their families
- Staffing
- Support services
- Facilities and equipment
- Guidelines and protocols
- Service organisation and liaison with other services
- Governance
- Network
- Commissioning

Peer reviewer training was provided for health professionals (doctors, nurses and psychologists), managers, commissioners and patient representatives who were to be part of review teams, before each programme began. All specialist centres and non-specialist centres with a large population of haemoglobinopathy patients were offered the opportunity to take part in the programme and although participation in the programmes was voluntary, all invited centres agreed to be visited. Centres in Wales, Scotland and Republic of Ireland, who requested to be visited, were also included in the most recent programme.

Prior to the visit, centres were asked to complete a self-assessment against the quality standards and also to provide some background information about their service. During the visit the multidisciplinary review team reviewed the evidence provided by the centre, toured

the facilities and interviewed staff members and service users before producing a visit report demonstrating compliance with the quality standards. The programme was overseen by a steering group consisting of multidisciplinary health professionals, members of the WMQRS and patient representatives who met regularly. The steering group reviewed all reports and wrote an overview report. This overview discussed several themes which had become apparent during the visits, and made recommendations.

The peer review report showed marked geographical variation in SCD provision across the UK. Over 80% of service users attended haemoglobinopathy centres in London, with lower attendance reported in other areas particularly the North-East and South West of England. There were unknown numbers of adults with SCD who were cared for by hospital or community teams that did not link to a Specialist centre. Whilst at most of the centres visited, the reviewers identified key staff members who were providing high quality care, they were often working 'singlehanded' and the workload of clinical staff was frequently deemed unreasonably high. This had not improved between successive peer reviews and in several centres there had been problems reappointing into key staff positions following retirement. Doctors in training were often not involved in the routine care of patients with SCD. This exacerbated workforce planning problems. Deficiencies in multidisciplinary care were highlighted and included a lack of psychology support and a shortage of social workers and benefits advisors. Other concerns raised by the peer reviewers included delays in the administration of analgesia for adults presenting with painful sickle cell crisis in emergency departments and the perception that their needs were not being taken into consideration. Many service users requested the provision of routine care, including transfusion and outpatient appointments, outside usual working hours. This, however, was only provided in a minority of centres.

National Haemoglobinopathy Registry (NHR)

Background evidence

The National Haemoglobinopathy Registry (NHR, www.nhr.nhs.uk) was set up in 2009 and is run by an independent group Medical Data Solutions and Services (MDSAS, www.mdsas.com). The NHR aims to improve the quality of data available for patients with haemoglobin disorders in the UK. Initially the registry included numbers of people with SCD, age, geographical location and basic demographic and clinical details. Centres were encouraged to join the NHR and to register their patients using a simple on-line pro forma. The NHR provided a patient information sheet and clinicians were asked to obtain verbal or written consent from patients before entering their details on the registry.

Registrations onto the NHR have gradually increased since it began and over 10,000 patients with SCD from 55 centres registered at the time of publication.

The functions of the NHR have expanded and include the capability to report adverse events including anonymised data for patients who have not given consent for their identifiable details to be registered. This is encouraged as a mechanism for collecting national data for shared learning from these events. This adverse event reporting should be done in addition to usual local mechanisms for reporting mortality and morbidity. A panel of three clinicians reviews clinical events and can raise concerns with the Clinical Reference Group if there are persistent events at a single centre or there are patterns of concerns nationally.

The annual review has been highlighted as a fundamental component of developing specialist care for patients with SCD and all patients with SCD should have an annual review performed by their specialist centre. The NHR has developed a minimum data set for collection at annual review. Use of the NHR annual review template encourages a basic level of data collection on each patient but also allows individual centres to collect more detailed annual information if they wish. Details about the clinical information collected in the annual review are given in Chapter 17: Out-patient management and Appendix 4: Annual review pro-forma.

The annual review can be printed out or transposed into a letter and given to the patient, with copies to his or her GP and any local hospital they attend as an annual summary of care. The annual review function of the NHR needs further work to become fully functional and the peer review programmes highlighted that many centres lacked resources for data input. It is envisaged that information required for the Quality Dashboard currently being developed by the Clinical Reference Group (CRG) should be collected through the NHR annual review screens, allowing centres to rapidly extricate data.

The use of the NHR as a tool for annual review allows collection of up-to-date patient figures at each centre with the ability to track patient numbers over successive years. It has also allowed local or national data to be collated into an annual report (available on the website). Data presented in this report include registrations per centre, genotype, gender, age, ethnicity, adverse events and some specific treatments: transfusion, hydroxycarbamide and iron chelation. These data, plus the adverse events data are also presented at an annual conference.

Additional developments include a patient card and an information service which is available via the website and allows real-time access to the clinical information. This allows filtering of information on a national, regional or trust basis and whilst data are anonymised, it can be exported locally for analysis. This facility ensures that the NHR is a useful resource for stakeholders and it has also provided anonymous information to commissioners and political 'think tanks'.

The NHR is overseen by a steering group of stakeholders from the third sector and community organisations, clinical services and NHS England.

The NHR is a continually evolving resource. It has great potential. Future developments include its use for quality assurance and for epidemiological studies. This is especially valuable given the lack of evidence for the provision of some aspects of clinical care in SCD. The NHR steering

board is also keen to promote greater user interaction, for example, by including patient surveys or by linking to patient information and education websites.

Clinical audit

Background evidence

Clinical audit is a quality improvement activity that seeks to improve patient care and outcomes through the systematic review of care against explicit criteria, and the implementation of change according to available evidence. Defining expected standards of care, which can be used to judge service quality, is fundamental to the process of audit. The editorial board has attempted to ensure that the standards within this document are auditable and can be used as a framework for the development of audit standards.

In addition, there are other areas of care for which audit standards already exist.

There are six quality statements in the NICE Quality standard [QS58], 'Sickle cell disease' (National Institute for Health and Care Excellence, 2014b). These were based on the NICE clinical guideline, 'Sickle cell disease: managing acute painful episodes in hospital' (National Institute for Health and Care Excellence, 2012b). We highlight the first four of the quality statements:

- People who present at hospital with an acute painful sickle cell episode should have a pain assessment, a clinical assessment and appropriate analgesia within 30 minutes of presentation
- People with an acute painful sickle cell episode should have an assessment of pain relief every 30 minutes until satisfactory pain relief has been achieved and then at least every 4 hours
- People with an acute painful sickle cell episode who are taking strong opioids should be monitored for adverse events every hour for the first 6 hours after first administration or step up of pain relief and then at least every 4 hours
- People with an acute painful sickle cell episode should be assessed for acute chest syndrome if they have one or more of the following: abnormal respiratory signs or symptoms, chest pain, fever or hypoxia.

Annual audit of the first of these quality standards is included in the data which specialist haemoglobinopathy centres must collect for the Quality Dashboard.

The British Society of Haematology has produced national guidance on some aspects of sickle cell care and audit templates have been produced for their guidelines. These are available on their website (www.b-s-h.org.uk) and include the following:

- Red Cell Transfusion in Sickle Cell Disease Part 1: Principles and Laboratory Aspects
- Red Cell Transfusion in Sickle Cell Disease Part 2: Indications for Transfusion
- Guideline on the management of acute chest syndrome in sickle cell disease

The quality standards for the recent peer review of haemoglobin disorders (2015-2016) (West Midlands Quality Review Service, 2016a) included a standard on clinical audits. This required that audits covering the following areas should have been undertaken within the last two years:

- Proportion of patients with recommended immunisations up to date
- Proportion of patients on regular penicillin or equivalent or who have a supply for immediate use if required
- Compliance with NICE Clinical Guideline (National Institute for Health and Care Excellence, 2012b) on the management of acute pain, including the proportion of patients attending in acute pain who received first analgesia within 30 minutes of arrival, and achieved adequate pain control within two hours of arrival; and
- Availability of extended red cell phenotype in all patients

It also recommended that services should have a rolling programme of audit including an audit of implementation of clinical guidelines and participation in agreed network-wide audits. Twenty-four per cent of adult centres met this quality standard overall and 30 per cent of adult centres demonstrated evidence of participation in a rolling programme of audit.

In addition to the above audits, centres should be encouraged to develop and participate in other audits relevant to their local populations and local issues.

Recommendations

- NHS England (Specialised Commissioning Teams) should work with Clinical Commissioning Groups to designate Specialist Haemoglobinopathy Teams and the geographical area and local teams for which they are responsible.
- NHS England, CCGs and Hospital Trusts should review the WMQRS peer review reports and work towards implementation of their recommendations.
- Hospital Trusts providing specialist haemoglobinopathy services should review the medical, nursing and psychology staffing levels to ensure they are sufficient to provide an adequate level of care.
- NHS Health Education England should review the workforce plan for specialist medical and nursing staff caring for service users with SCD to ensure there are adequate numbers of trained staff and should ensure that all doctors in haematology training posts gain adequate experience in the care of people with SCD.
- Centres should participate in a rolling programme of audit against their clinical guidelines.

- Lessons learnt from these audits should be incorporated into quality improvements and services should be subsequently re-audited to document these improvements.

The full list of recommendations from the most recent peer review overview reports is available (West Midlands Quality Review Service, 2016b).

Chapter 2: Conclusion

This chapter offered a broad introduction to the organisation of care. Sickle cell disease has clinical, social, economic and psychological consequences for both the individual and his or her family. This presents various challenges requiring a multi-disciplinary response and excellent communication among various stake-holders, alongside a commitment to evidence-based practice and clinical audit.

Chapter 3: Primary care

"The hospital consultants are knowledgeable and always on hand to help or advise. I have minimal contact with my GP with regards to my sickle cell."

"Improved knowledge on the management of sickle cell is required for GPs, specifically when we require medical support."

Introduction

This and the following chapter consider the broader context of care and in doing so introduce a more holistic and discursive account of supporting those with sickle cell disease (SCD) and their families. The scope is necessarily broad, particularly in the use of evidence, which at times is general rather than specific to the experience of SCD. While reasonable to do this, since the experience of those with SCD is likely to share similarities with other long standing chronic conditions, it does identify potential gaps in the research evidence and highlights the need for more research exploring the social experience of SCD. This chapter by focusing on primary care and community nursing highlights their potential for supporting to those with SCD and their families, before considering more specific examples of interventions that can be managed through primary care. Consistent with the broad scope of primary care, this chapter also considers dental care.

Role of the primary care team

Introduction

The family remains the primary caring place for people with acute and chronic ill health. General Practitioners (GPs) and the primary care team have an integral role in supporting the service user with SCD and have a holistic overview of his or her care. The primary care team includes the core team of practice nurses and administrative staff and additional staff which may include midwives, health visitors, district nurses, mental health nurses, social workers and welfare benefits counsellors. Ideally primary care teams represent the first point of contact for patients and families. They can provide continuity and help coordinate care. It is usual for GP registration to take place on birth notification and the 'cradle to the grave' concept of registration promotes a life journey approach.

Standards

- All adults with SCD should be registered with a GP.
- Primary care teams should maintain good communication with the specialist and local haemoglobinopathy teams, enabling two-way exchange of expertise to optimise the care of their mutual patients.
- Each SCD patient should be offered routine primary health care services at their GP surgery.
- Specialist haemoglobinopathy teams should develop locally agreed shared care protocols with GPs defining the roles and responsibilities of each.

Background evidence

An effective primary health care team that includes information sharing, easy communication and agreement on common goals, alongside an understanding of each team member's responsibilities, skills and knowledge, can be of great benefit to someone with SCD and their families. The potential value of primary care, however, is not always realised.

Families are integral to providing health and social care and collaboration is essential in delivering effective primary care. Direct involvement with the patients and their home support and environment can be a particular strength of primary care. There is often a greater awareness of social, economic, family and psychological context and this enables members of the primary care team to become important advocates for the patient, providing valuable advice on welfare, housing and educational issues. While being sensitive to the needs of the individual patient, members of the primary care team can also be well placed to identify and support family carers.

The primary care team also have a role in genetic screening, offering reproductive and health advice, providing routine screening, patient follow-up after emergency admission and co-ordination of care. This might include supporting patients with multiple co-morbidities and managing SCD alongside other unrelated health issues. However, every effort must be made to co-ordinate care between different specialties to avoid omission or unnecessary duplication. This includes developing good working relationships with secondary and tertiary care providers, along with the sharing of information. While not always easy to achieve in practice, it is of great benefit to patients and their families. It also has the potential to reduce health care costs, by ensuring the most appropriate care and treatment.

To facilitate this and ensure continuity of care, a primary care medical record could be problem coded for all known identified patients with a significant haemoglobinopathy. This involves having a system in place for updating patient records as part of the neonatal heel prick, the receipt of new patient registrations and information from other sources, such as hospital discharge summaries. Similarly, results of haemoglobinopathy screening tests, which show 'carrier' status, could be coded on the patient record to prompt the provision of preconception information.

In order to meet their roles and responsibilities, GPs and the primary care team need to have a good understanding of SCD and be aware of patients within their practice. Qualitative studies of patients with SCD and their carers indicate a general lack of 'comprehensive knowledge of SCD' (Al Juburi *et al.*, 2012; Jacob *et al.*, 2016). The outcome of one study was the development of a GP education intervention (Al Juburi *et al.*, 2012) to improve knowledge and management. Whilst this intervention may not be universally available, continuing professional development (CPD) has been available for management in of SCD in the community (Brousse *et al.*, 2014).

Specific responsibilities of the primary care team include (Patel, 2016):

- Early treatment of infections to prevent sepsis
- Prescription of antibiotic prophylaxis
- Ensuring vaccinations are up to date
- Early referral of pregnant women
- Reproductive provision to include contraceptive advice, pre-conceptual counselling and partner testing. They may also be involved in shared antenatal care with the specialist centre
- Referral for psychological support and counselling (including neuropsychological support)
- Encourage treatment compliance
- Patient education and self-management of mildly painful episodes
- Support during transition and the move onto further education

Access to primary care has been highlighted as a barrier to effective treatment; continuity of care and follow-up after discharge from hospital (Al Juburi *et al.*, 2012). Alternative models of care within the community, for instance with specialist service involvement in providing home or day case management have been described (Brousse *et al.*, 2014; Lanzkron *et al.*, 2015; Raphael *et al.*, 2008; Wright *et al.*, 2004).

Recommendations

- SCD specialist teams should provide support and training for GPs and their primary care colleagues.
- The primary care team should be responsible for infection prophylaxis including the prescription of regular antibiotics and vaccination for the prevention of infection due to functional asplenia. Good communication between primary and secondary care is essential to share this information e.g. by using patient held records.
- The primary care team should let the hospital team know if the patient is not collecting prescriptions (e.g. for antibiotics) regularly.

- Hospitals should inform GPs and the primary care team of hospital discharge within seven days and identify any patients who require post-discharge follow-up.
- The primary care team should be responsible for documenting and providing repeat prescriptions for other regular medications including analgesics and there should be clear communication between the GP and SCD specialist centre about the agreed analgesia to be prescribed for management of uncomplicated painful crises in the community.
- GPs should keep records of a person's carrier status and offer timely reproductive advice, when appropriate. They should also offer advice on the implications of being a carrier for the individual and family members.

Community nursing

"More home visits should be encouraged by support workers and nurses"

"My community specialist nurse gave me a card which I carry in my wallet and shows I am on the national haemoglobinopathy registry and has all my medical details at hand in case of an emergency"

Introduction

The provision and easy access to good quality community health care and treatment, with its emphasis on self-management and a family centred approach can support patients with SCD in achieving their goals, including caring for their families and participation in education and the workplace with less disruption than ensues from hospital attendance (see Chapter 4 - Health and well-being). The models of community specialist nursing for sickle cell care vary across the country and there is no nationally agreed model of nursing care. The community nursing role may include social, psychological support and more practical nursing support (e.g. phlebotomy, review of medications, pain management). Community nursing may be provided as a standalone community service, often as part of a community Sickle Cell and Thalassaemia (SCaT) centre, as part of a wider community NHS directive or may be integrated with the acute haemoglobinopathy team. Such nurses often work across primary, community and secondary care. In low prevalence areas community matrons may provide care for patients with SCD as part of a wider brief for chronic disease management although this resource will not be available in all communities. Community teams usually have the responsibility for follow up of screen positive women identified on the national antenatal screening programme and screen positive newborns identified on the national newborn screening programme, both of which are outside the brief of these guidelines which will focus on community nursing for adults with SCD.

Standards

- All adults with SCD should have access to community nursing support.
- The number and case mix of specialist nurses in the community should be regularly evaluated to ensure that services have adequate staffing levels in line with the duties they are undertaking.
- Specialist community nurses should receive appropriate training, supported by certification and competencies to be evaluated as part of their annual professional practice review.
- Clear arrangements for shared care between the community team and local hospital should be in place. This should include multidisciplinary team meetings.

Background evidence

The community specialist nurse has an important role in encouraging self-management and more general health promotion for people of all ages living with SCD (see Chapter 4 - Health and well-being). This role may include:

- Raising community awareness of SCD
- Management of screen positive pregnant women (trait and disease) and their partners including genetic counselling and discussing options for the management of an at risk pregnancy including, where selected, referral for pre-natal genetic diagnosis
- Co-ordination and adoption of a multi-disciplinary team approach, informed by holistic approaches to health care, which can be especially valuable in the management of pain, aiming to avoid omission or unnecessary duplication (Coulter *et al.*, 2013). A patient-held shared care record may be helpful to aid communication between the different care providers.
- Development of personalised care plans, working together with service users and health professionals to agree goals, identify support needs, develop and implement action plans and to monitor progress
- Offering education and enhancing self-management skills of patients and their families to ensure effective self-management within the community setting. This may include mechanisms to minimise risk of crises and other complications, and symptom management, including how to manage uncomplicated pain at home with a range of suitable analgesics and non-pharmaceutical methods (Edwards, 2014)
- Prompt management of painful crises in patients' homes with the aim of avoiding hospital admission and thereby reducing disruption to the patient's life

- Provide education to patients and their families about which symptoms can indicate serious complications and require them to seek urgent medical assessment, including significant fever, chest pain, breathing difficulties, dehydration, priapism, and any unfamiliar pain or other unexpected symptom
- Supporting early discharge from hospital and offer continuing good quality care in a home setting
- Offering advice on a range of subjects including activity and rest; nutrition; prevention and early treatment of infection; general health and well-being; reproductive issues (including pre-conception screening of partners, genetic counselling and prenatal diagnosis if required); and access to benefit and welfare advice
- Facilitating local support groups and forums where patients/carers provide can share their experiences
- Review of community care and specialist standards including collection of data, audit, research and advice at local and national level for improvement of care.

According to local provision, community nursing support may be provided by specialist nurses, specialist nurse counsellors, specialist nurses outreach nursing teams, or use of district nursing services/community matrons working under the specialist guidance of a sickle and thalassaemia community centre or a specialist haemoglobinopathy centre. In areas where disease prevalence is high, community centres staffed by specialist nurses and a variety of other health and social care providers have emerged. These Sickle Cell and Thalassaemia (SCaT) centres are usually based within the local community, but may be within the hospital premises.

In addition to the nursing staff based in the SCaT centre, other specialist service providers may include occupational therapists, dieticians, psychologists, social workers, welfare officers and dentists. There should be access to other social services including housing and benefits advice. Ideally, there should be a 'one-stop shop' available so that a service user can access services in a single visit.

The larger Sickle Cell and Thalassaemia centres may also offer:

- Educational programmes for health and allied professionals who care people with or at risk of SCD and Thalassaemia
- Nurse-led outpatient clinics, treatment adherence clinics and day care pain management services
- Self-management support services in the patient's home

It may be helpful for service users to have a key worker identified within the community service. Certainly service users should have access to telephone contact with a sickle cell and thalassaemia community centre for discussion and advice. Staff at sickle cell and thalassaemia community centres should be prepared to offer guidance to colleagues in local community services that the patient has contact with.

The role of the community nurses in education is very important and this can be done with different methodologies including individual education, supported by written documentation or group education which can be supported by leaflets, posters, DVDs and minutes. The community nurses should also engage in governance work to obtain evidence of service users' views and this can be in the form of service users' group engagement or patient reported experience and outcome measures (PREMS and PROMs) (Department of Health Long-term Conditions NSF Team, 2005).

The Department of Health chronic disease model (2007) suggest three levels of care. This has successfully been employed by some Sickle Cell and Thalassaemia (SCaT) Community Teams. Level one is *self-care support*. This includes organising regular community education for service users and their families/carers, with the focus on living successfully with the condition. These sessions may be topic driven and encourage self-management, whilst raising awareness of acute complications which may need urgent hospital care. Level two is *disease specific case management* and is aimed at those requiring additional community support. The community nurses have a particularly important role in co-ordinating multidisciplinary care, which may include district nurses, physiotherapists, social workers, community psychiatric teams and psychological support. Initial assessment by the community nurse includes history taking and full nursing assessment during home visits or within a community centre. Assessment can be used to evaluate pertinent issues and develop a care plan.

Depending on local practice and available services, facets of the care plan may include:

- Pain management
- Work and Employment issues
- Psychological concerns
- Failure to attend clinics
- Compliance management
- Post-discharge follow up
- Drug monitoring
- Social issues e.g. housing, welfare, employment
- Leg ulcer care
- Chelation therapy monitoring
- Hydroxycarbamide monitoring
- Management of parenteral therapy at home
- Issues impacting on education
- Relationships, sexual health and family planning
- Self-management and advocacy

Level three is *case management of complex sickle cell conditions.* It is for those service users with more complex or high intensity needs. This will usually involve the multidisciplinary team across the community and within secondary services. Examples may include patients with frequent admissions to hospital, with serious chronic complications (e.g. leg ulcers, chronic

pain, and chronic lung disease) or with complex needs due to co-existence of other long term conditions.

Recommendations

- Specialist community nursing guidelines and protocols with measurable outcomes should be developed for the management of this client group.
- Where there is an acute pain service in the community, the nursing team should have protocols for pain management in the community, including nursing assessment tools, care plans and referral pathways (Royal College of Nursing, 2015).

Prevention of infection: immunisations and prophylactic antibiotics

"The penicillin and folic acid helps me. The six monthly clinic at the hospital is usually for blood tests and checks. I have not been in hospital with a crisis for nearly two years."

"I get my pneumococcal vaccines every five years and my flu jabs yearly. I don't tend to have chest infections lately"

Introduction

Patients with SCD are susceptible to a range of bacterial and other infections. Invasive pneumococcal disease (IPD) has generally been considered the most significant cause of infection-related morbidity and mortality, but other bacterial infections, including salmonella and gram-negative urinary tract infections are also important causes of sepsis. The increased susceptibility to IPD is related to a reduction in splenic function which is apparent from an early age. Patients who have been splenectomised are probably at highest risk (Rankine-Mullings & Owusu-Ofori, 2017). Infants and young children are especially vulnerable to infection, but older children and adults are also at increased risk. People with sickle cell/haemoglobin C compound heterozygosity and haemoglobin S/β^+ thalassaemia have a lower incidence of life threatening infection because their spleen function is less damaged. Nonetheless, they should also receive appropriate vaccination.

The Public Health England publication 'The Green Book' (Public Health England, 2014) provides advice on immunisation against infectious disease in the UK as well as additional antibiotic prophylaxis and vaccines. (Frequently updated guidance is available through www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book.) Recommendations for the treatment of suspected or proven infection should be based on local protocols, with relevant antimicrobial resistance patterns taken into consideration.

Standards

- Specialist and local haemoglobinopathy teams and GPs should ensure that adults with SCD are adequately vaccinated against the following infections according to advice in the Green Book:
    - Invasive pneumococcal disease
    - Haemophilus influenza type B
    - Neisseria meningitis ACWY and B
    - Hepatitis B
- Adults who have not previously been immunised with conjugate pneumococcal vaccine should be given a single dose of the current recommended conjugate pneumococcal conjugate vaccine (PCV13). In addition, the pneumococcal polysaccharide vaccine (PPV) should be given at five yearly intervals.
- Influenza vaccine should be offered annually.
- Hepatitis B immunity (HBsAb) should be reviewed annually and a booster offered if levels are <100 mIU/ml.
- Patients should be periodically warned about the increased risk of IPD and other forms of sepsis. They should also be educated about symptoms which might indicate infection and be advised to keep a thermometer at home to check for fever and to attend for medical assessment if ≥ 38°C. Written confirmation of patient education should be provided, either in a clinic letter or as an information sheet.
- Adults with SCD who have had a splenectomy or a history of IPD should continue on lifelong penicillin prophylaxis.
- A discussion of oral antibiotic prophylaxis should be undertaken on transition to adult care and at annual review. Adults with SCD who choose not to continue regular oral prophylaxis should ensure they have received pneumococcal vaccination and should be provided with a supply of appropriate antibiotics for emergency use.

Vaccinations

Vaccinations are usually administered in primary care, but it is useful for hospital teams to remind the staff what is necessary, and check that it has been administered. Advice about vaccinations for adults who are hyposplenic can be found in the Green Book (Public Health England, 2014). Adults with SCD in the UK may not have received all the vaccinations currently recommended for routine childhood immunisation or additional vaccination for hyposplenic children. Therefore the primary care physician and SCD specialist should both ensure that patients receive immunisations in line with the most up to date vaccination advice.

Pneumococcal vaccine

There are two types of pneumococcal vaccine recommended for SCD.

Pneumococcal polysaccharide vaccine (PPV). This was the first vaccine in widespread clinical use for prevention of IPD. The current version contains purified capsular polysaccharide antigen from 23 serotypes of *Streptococcus pneumoniae* (PPV23, Pneumovax). It does not induce a T-cell response, and is not immunogenic in infants. The overall efficacy of PPV in preventing pneumococcal bacteraemia is probably around 50-70% and the 23 types included account for about 96% of the pneumococcal serotypes that cause serious infection in the UK.

Most adult patients develop a good antibody response to PPV by the third week following immunisation but the antibody response may be reduced in those with absent or dysfunctional spleens. The length of protection offered by PPV is not known and may vary between capsular types. Post-immunisation antibody levels usually begin to wane after five years but may decline more rapidly in asplenic patients (Butler *et al.*, 1993). Repeat vaccination of PPV is safe and is usually recommended every five years in patients with SCD because of this declining response. It has been suggested that non responders should perhaps be re-vaccinated more frequently than this, with decisions on re-immunisation being based on antibody levels, but routine laboratories do not measure antibody response to all serotypes and this does not form part of routine practice at present (Cherif *et al.*, 2006; Stanford *et al.*, 2009).

Pneumococcal conjugate vaccines (PCV) have been introduced over the past two decades and are now part of routine childhood immunisation in many countries in the developed and developing world. They consist of a polysaccharide antigen conjugated to an immunogenic protein carrier, and elicit a T cell-dependent immune response which generally produces a durable protective antibody response. The current generation of PCV includes the serotypes responsible for the majority, but not all cases of IPD. Epidemiological and surveillance data suggest a recent serological shift in IPD to serotypes not represented in the current PCV vaccines.

A recent trial of PCV booster doses in older children who had previously received PPV but not PCV provided some evidence for enhanced protective antibody responses.

Recommendations for PCV have recently been revised (Public Health England, 2017a) so that children and adults in a clinical risk group, such as those with asplenia or hypofunction of the spleen, 'including conditions such as homozygous sickle cell disease' should be offered a single dose of 0.5ml of PCV13, although the recommendation is qualified by 'decision based on clinical judgement'.

The majority of adults will not previously been immunised with conjugate pneumococcal vaccine and they should be given a single dose of the current recommended conjugate pneumococcal conjugate vaccine (PCV13) in addition to the previously recommended five yearly PPV.

Health professionals should ensure that adults with SCD should have been offered:

- Pneumococcal polysaccharide vaccination (PPV23) at five yearly intervals; and
- A single 0.5 ml dose of pneumococcal conjugate vaccine (PCV13) which should be given at least six months after PPV.

Meningococcal vaccination

Meningitis B vaccine was added to the childhood vaccine programme in 2015 and is now offered to all patients with an absent or dysfunctional spleen. For adults, two doses not less than one month apart are recommended. It should not be given to pregnant women unless there has been a clear risk of exposure to Meningococcal infection.

In August 2015 a MenACWY conjugate vaccine catch up programme began for all children aged 14-18 years and those <25 years of age and is now recommended for adults with SCD.

Health professionals should ensure that adults with SCD should have been offered:

- One dose of Hib/Men C; *followed by,*
- One dose of MenACWY conjugate vaccine one month later
- Two primary doses of MenB vaccine one month apart [this can be at the same visits as the other vaccinations above].

Haemophilus influenzae type b (Hib) vaccination

There has been a dramatic decrease in the incidence of invasive Hib infections observed in the post-vaccination era in people with sickle cell disease living in high-income countries. Therefore, despite the absence of evidence from randomised controlled trials, it is expected that Haemophilus influenzae type b conjugate vaccines will be useful in children affected with sickle cell disease (Allali *et al.*, 2016). It is included in the childhood vaccination programme in the UK. There is a lack of data on effect of the Hib vaccine in adults but it should be offered to adults with SCD who have not previously been vaccinated in childhood.

Health professionals should ensure that adults with SCD should have been offered:

- One dose of Hib/Men C

Influenza vaccination

Patients with SCD are at higher risk of complications associated with influenza. These can include vaso-occlusive crisis, acute chest syndrome and invasive bacterial infections. Adults with SCD should be offered annual influenza vaccination.

Hepatitis B vaccination

Blood for transfusion is screened for hepatitis B in the UK but patients with SCD have a high lifetime likelihood of receiving emergency blood transfusion and a number may require regular routine blood transfusion.

Adults with SCD should be offered immunisation for hepatitis B if they do not have protective antibody levels (HBsAb >100 mIU/ml). Antibody levels should be checked regularly and vaccination booster offered if HBsAb <100 mIU/ml, unless there is evidence of a previous, cleared infection as indicated by positive HBcAb (Hepatitis B Core Antibody).

Summary of vaccination advice

Please refer to the Green Book for most up to date advice (Public Health England, 2014)

The majority of adults in the UK will not have received primary vaccination according to the current recommendations and specialist teams should communicate with primary care providers to ensure all adults receive appropriate vaccination to prevent infection from *Streptococcus pneumoniae*, *Haemophilus influenza* type B and *Neisseria meningitis* ACWY and B according to the currently recommended vaccination schedule.

Adults with SCD who have not received primary vaccination as part of the national schedule in the UK should be offered:

- One dose of Hib/Men C and one dose of pneumococcal polysaccharide vaccine (PPV23); *followed by,*
- One dose of MenACWY conjugate vaccine *one month later*
- Two primary doses of MenB vaccine one month apart [this can be at the same visits as the other vaccinations above]
- A single 0.5 ml dose of pneumococcal conjugate vaccine (PCV13) which should be given *at least six months after PPV*

Adults with SCD should also be offered:

- Pneumococcal polysaccharide vaccination (PPV23) *at five yearly intervals*
- Annual influenza vaccination
- Hepatitis B vaccine if they have not previously received it and are non-immune (HBsAb <100 mIU/ml)

Salmonella vaccine

Salmonella organisms are a common cause of infection in patients with SCD, and the infection much more commonly becomes invasive, and can lead to sepsis and multi-organ failure. Vaccines have been licensed for use but vaccination has not been implemented at a country-

wide level, in part due to the poor immunogenicity in young children. There is promise of an oral vaccine in the near future. First line antibiotics for sepsis must cover salmonella species.

Antibiotic prophylaxis

The highest risk of pneumococcal infection occurs in children under three years of age. This risk persists despite inclusion of PCV in the routine infant vaccination schedule. The PROPS trial, conducted over 30 years ago, before pneumococcal vaccines were available, showed that regular oral prophylactic penicillin reduced the rate of pneumococcal infections in children with SCD less than five years old and was associated with minimal adverse reactions (Gaston *et al.*, 1986; Rankine-Mullings & Owusu-Ofori, 2017). Evidence is lacking in children with genotypes other than sickle cell anaemia.

National guidelines on prophylaxis for asplenic patients have previously recommended lifelong prophylaxis with oral penicillin. This recommendation was based on expert opinion and case series of IPD in asplenic and hyposplenic adults who mostly had not been advised on any specific measures for prevention of infection. Current opinion on long-term oral penicillin prophylaxis is divided. PROPS 2 attempted to compare the risk of IPD in children age >5 years who continued or stopped oral penicillin, however, the study was not adequately powered and there were insufficient cases of IPD in either group to draw definitive conclusions about lifetime risk (Falletta *et al.*, 1995). As risk of infection decreases with age, there might be a time when preventative antibiotic treatment can be stopped in the fully immunised individual. Those who have had a splenectomy or invasive pneumococcal infections should continue lifelong pneumococcal prophylaxis.

Careful assessment of adherence to treatment will often reveal inconsistent usage. Therefore the clinician should discuss oral antibiotic prophylaxis on transition to adult care and periodically thereafter as part of the annual review. If adults would prefer to continue regular prophylactic antibiotics these should be prescribed. Adults with SCD who are unlikely to adhere to regular oral prophylaxis should consider stopping penicillin prophylaxis *if* they have received adequate pneumococcal vaccination and are aware of the risk of invasive pneumococcal disease. Those who stop regular antibiotic prophylaxis should be provided with a supply of appropriate antibiotics for emergency use. They should be reminded to carry these when they travel abroad. Suitable antibiotics include penicillin V 500mg qds, or amoxicillin 500mg tds or – if penicillin allergic – erythromycin 500mg qds. Patients and their carers should regularly be reminded of the ongoing risk of infection and encouraged to seek medical advice if the patients become febrile (≥38^{0}C) and/or develop symptoms of infection. This can be reinforced with written patient information, either via a clinic letter or a patient information leaflet. The risk of pneumococcal infection increases with increasing age and it may be advisable to restart penicillin prophylaxis over the age of 50 years.

Travel vaccinations and antibiotics

Patients should be encouraged to seek travel advice and to accept all the offered immunisations relevant to the area to which they are travelling; this includes live vaccines such as yellow fever.

There is a common misconception among patients – and some healthcare professionals – that people with sickle cell disease do not get malaria infections; this is incorrect, and malaria infection can be very serious and fatal. Patients with SCD should receive malaria prophylaxis when travelling to malarial areas, in line with general guidance for the area of travel. All chemoprophylactic agents are acceptable in patients with SCD although it should be noted that there is an increase of glucose-6-phosphate-dehydrogenase (G6PD) deficiency in this patient group and in these patients certain agents should be avoided.

Recommendations:

- Patients should be given the relevant and appropriate information to alert health care professionals to the risk of overwhelming infection.
- All patients should be educated regarding the potential risks of travel related infection risks and how to avoid them (in particular malaria and unusual infections, e.g. animal and insect bite infections).
- The patients' primary care team should be responsible for keeping clear records of vaccination and revaccination status for patients with SCD and the status documented at annual review and included in hospital records.

Blood pressure monitoring

"My blood pressure is always monitored when I attend my outpatient appointments. However, this is not very regular."

Introduction

Hypertension is an independent risk factor for stroke, renal disease and pulmonary hypertension. Patients with SCD generally have a lower mean blood pressure (BP) than age and sex matched controls.

Standard

- Check blood pressure at every GP and hospital visit.

Background evidence

In patients with SCD, blood pressure should be monitored at every routine visit to the GP and at each hospital appointment.

In the absence of albuminuria (albumin creatinine ratio (ACR) <3.5mg/mmol), the target blood pressure should be < 140/90. If BP is ≥140/90, treatment should be started in accordance with the NICE / British Hypertension Society algorithm (National Institute for Health and Care Excellence, 2011 updated 2016). This recommends that a calcium channel blocker, e.g. amlodipine, is started as initial management if the patient is African/Caribbean of any age. Diuretics should not be used as first-line treatment in isolated hypertension.

For patients with albuminuria (ACR ≥3.5mg/mmol) target blood pressure should be 130/80. If BP is ≥ 130/80 in the presence of proteinuria initial treatment should be with an ACE inhibitor or angiotensin receptor blocker (ARB) or a calcium channel blocker. Treatment of proteinuria is considered in Chapter 8: Renal and urological complications.

Recommendations

- Hypertension in SCD should be monitored and treated in primary care.
- Patients with hypertension and ACR <3.5 mg/mmol should be treated with a BP target of <140/90 mmHg. Patients with hypertension and ACR ≥3.5 mg/mmol should be treated with a BP target of <130/80 mmHg.
- In the absence of proteinuria initial treatment should be with calcium channel blockers.

Folic acid

"I have been taking folic acid since I was a child, I am now in my 40s"

Introduction

In common with other chronic haemolytic conditions, patients with sickle cell disease are at risk of developing folate deficiency due to increased erythropoiesis and folate turnover.

Standards

- Folate levels should be checked in any patient with worsening anaemia or macrocytosis.
- Co-existing cobalamin deficiency should be considered in any patient taking folic acid supplementation who has neurological signs or symptoms or develops megaloblastic anaemia.

Background evidence

Studies have shown lower levels of folic acid in patients with SCD compared to healthy controls (Liu, 1975) but there are no trials showing the benefit of routine folate supplementation. A recent Cochrane review concluded that a lack of evidence-based research means that while it is possible that folic acid supplementation may increase serum folate levels, the effect of supplementation on anaemia and any symptoms of anaemia remains unclear (Dixit *et al.*, 2016). There are no trials in adults and one randomised double-blind control study of folic acid supplementation in children showed no convincing improvement in anaemia or any other clinical outcome (Rabb *et al.*, 1983). A recent study of discontinuation of folic acid supplementation in young people with SCD showed no differences in haemoglobin, reticulocyte count or folate levels after discontinuation (Nguyen *et al.*, 2016).

Historically many patients have been prescribed daily folic acid but in those who eat a good mixed diet it is probably not necessary. Some patients have a preference to continue folic acid, sometimes only intermittently or when they know their diet may be poor, and there is no reason to discourage this. It may be helpful to take folic acid during periods of ill health and for a short period subsequently. Folate levels should certainly be checked in any patients with increasing mean cell volume or worsening anaemia. Folic acid at a dose of 5mg should be started in women with SCD before conception if possible (see Chapter 18 - Reproductive health.)

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 mean cell volume (MCV), lactate dehydrogenase (LDH) or bilirubin level rises or in the context of any neurological signs or symptoms in a patient on folate supplementation.

Recommendation

- Folic acid supplementation is unlikely to be necessary on a regular basis in adults with SCD with a good mixed diet but could be considered in adults with SCD with a diet which does not contain adequate folic acid or in whom there is proven folate deficiency.

Bone health and vitamin D

"I have been told recently that my Vitamin D is very low and due to lack of sunlight in the UK, it is difficult to receive natural sunlight so my consultant has prescribed Vitamin D supplements and I eat foods high in Vitamin D too"

Introduction

Vitamin D is essential for the normal absorption of calcium and to maintain normal calcium homeostasis and bone mineralisation. Vitamin D deficiency (VDD) can lead to low blood calcium levels and result in bone damage. In adults this can lead to osteomalacia. VDD has been associated with increased fracture risk, musculoskeletal pains, chronic fatigue, cardiovascular disease, asthma and nephropathy. Dietary sources of vitamin D include oily fish and fortified foods but the principal source is biosynthesis from 7-dehydrocholesterol due to the action of ultraviolet (UV) light in the skin. VDD has a high incidence in SCD patients. It has been suggested that osteoporosis may be more common in people with SCD.

Standards

- Vitamin D levels should be measured at least annually in all patients with SCD.
- Patients who have vitamin D insufficiency or deficiency should be started on appropriate vitamin D replacement.
- If there is any evidence of pathological fracture, bone mineral densitometry (BMD) assessment should be carried out.

Background evidence

A systematic review of the prevalence of VDD in SCD identified 15 relevant articles and concluded that suboptimal vitamin D levels were highly prevalent when compared with non-SCD patients or control populations (Nolan *et al.*, 2015). When VDD was defined as vitamin D <20 ng/mL, prevalence estimates in SCD populations ranged from 56.4% to 96.4%. Prevalence of VDD was similar in the general African American population and the SCD population. Rates of VDD in African American patients with and without SCD were both substantially higher than that of Caucasians. The African and African-Caribbean population in the UK is similarly at risk of VDD due to decreased synthesis in pigmented skin, reduced exposure to sunlight due to spending less time outdoors, inadequate dietary intake and compromised intestinal absorption.

VDD is associated with musculoskeletal pains and chronic fatigue in the non-SCD population. These symptoms are common in patients with SCD and it has been suggested that VDD may be contributory. It has also been suggested that VDD may contribute to acute painful episodes (Adegoke *et al.*, 2017; Lee *et al.*, 2015). Many studies have demonstrated an improvement in pain symptoms, bone density markers and overall quality of life in SCD patients treated with high dose Vitamin D supplementation (up to 100,000 IU weekly). A recent Cochrane review

identified only one randomised controlled trial of moderate to low quality (Soe *et al.*, 2017). In this trial 37 people (7-21 years) were treated with vitamin D supplementation or placebo for six months (Osunkwo *et al.*, 2012). Patients taking vitamin D had higher levels of vitamin D in their blood after treatment and significantly fewer pain days, but worse health related quality of life. The Cochrane review concluded that existing evidence was not sufficient to guide clinical practice and that clinicians should consider relevant existing guidelines for vitamin D supplementation and dietary reference intakes for calcium and Vitamin D (Holick *et al.*, 2011; Ross *et al.*, 2011). These advise daily dietary Vitamin D intake of 1500-2000 IU.

Vitamin D is most commonly assessed by measuring 25-hydroxy vitamin D (25-OHD) levels. It may be advisable to assess vitamin D levels regularly in patients with SCD perhaps as part of the annual review. If levels are found to be inadequate or deficient, patients should be offered Vitamin D supplementation according to local guidelines.

Some studies have suggested a raised incidence of osteopenia and osteoporosis in patients with SCD (Almeida & Roberts, 2005; Sarrai *et al.*, 2007). The risk of abnormal bone mineral density may be increased in those with increased bone marrow expansion, decreased haemoglobin and body mass index, suboptimal achievement of peak bone mass and poor calcium and Vitamin D intake. Although it is not routine practice to assess bone mineral densitometry (BMD) in SCD patients, if there is any clinical suspicion of osteoporosis (i.e. pathological fracture) this should be assessed and referral for a specialist opinion for more detailed assessment should be considered.

Recommendation

- Consider measuring bone mineral density in those with low body mass index and haemoglobin.

Dental management of SCD

Introduction

Oral health is an integral and important part of general health and may impact on the general well-being of those with SCD (Fernandes *et al.*, 2016). SCD may be associated with dental problems, including alterations in dental occlusion, which may influence the quality of life of affected individuals. Further, dental infections can lead to an increased likelihood of triggering a sickle cell crisis (Laurence *et al.*, 2013).

Standards

- All patients with SCD should access regular dental care to prevent oral infection and manage the potential orofacial features associated with bone marrow expansion.
- Dentists should be aware of the increased risk of infection in patients with SCD and ensure they prescribe appropriate antibiotics to treat acute infections or to cover dental procedures.

Background evidence

Many orofacial features have been described in SCD but the extent of changes remains variable. SCD may result in compensatory hyperplasia and expansion of the bone marrow including the facial bones which may lead to depression of the nasal bridge, mid-facial overgrowth resulting in maxillary protrusion, and an increase in the vertical dimension (Licciardello *et al.*, 2007). Hypoxia related to SCD has been associated with osteomyelitis of the jaws, particularly the mandible (Javed *et al.*, 2013). Osteomyelitis and/or vaso-occlusive changes may result in painful episodes and/or neuropathies, including 'numb chin syndrome' where the mental nerve is affected (Friedlander *et al.*, 1980).

SCD is a risk factor for moderate to severe malocclusion. Anterior tooth loss, anterior spacing, increased overjet, anterior cross-bite and open-bite have all been described (Costa *et al.*, 2015). Delayed eruption of teeth and dental hypoplasia/ hypo-mineralisation and hypercementosis may also occur. The evidence on susceptibility to dental decay remains contradictory (Fernandes *et al.*, 2015). Data suggest that patients with SCD have increased susceptibility to dental caries, with a higher prevalence of tooth decay and lower prevalence of filled teeth. However, the severity of periodontal disease and inflammatory conditions in patients with SCD is more likely associated with oral hygiene maintenance and other caries risk factors rather than the haematological disorder itself (Al-Alawi *et al.*, 2015; Arowojolu *et al.*, 1996; Javed *et al.*, 2013). This is a reminder about the important of providing good general dental care, irrespective of SCD. Dental pulp necrosis due to infarction/thrombosis of the dental pulp vessels may result in toothache (Cox & Soni, 1984). Diagnosis may be challenging as the tooth may appear otherwise healthy.

There are no randomised trials investigating dental care in patients with SCD and recommendations are based on observational data and expert opinion (Mulimani *et al.*, 2016).

Individuals with SCD may experience additional complications following routine dental treatment and dental care may need to be adapted. In order to reduce the likelihood of triggering a sickle cell crisis, measures should be implemented to reduce stress, such as anxiety management, augmented with inhalational sedation where appropriate (Bryant & Boyle, 2011). It is also important to ensure that the environment is not cold, that the patient is well hydrated and dental infections are managed early. Inhalation sedation is preferable to intravenous sedation but may not be sufficient to enable the delivery of a longer and more complex treatment, particularly when the patient is very anxious.

Recommendations

- Improve awareness of the potential dental and orofacial manifestations of sickle cell disease among patients, their families and the practitioners involved in their care.
- Adults with SCD should receive regular dental care to facilitate preventive measure such as oral hygiene instructions, diet control and fluoride prescription/applications (Smith et al., 1987).
- Dental care should be delivered as a coordinated team approach, with close liaison with the haematologist. If sedation or general anaesthesia is planned, treatment should not be in a community setting, but in a hospital dental department with a sickle cell haematology team on hand, and any pre-procedure interventions must be discussed with them in advance.
- Dentists caring for patients with SCD presenting with acute dental infections/abscesses should receive urgent dental care and antimicrobial therapy as required.

Chapter 3: Conclusion

This chapter considered the role of primary and community health care and although sometimes neglected, such support – as we have seen – has an important role to play in supporting those with SCD. The scope of primary and community health care is necessarily broad. This highlights the importance of coordination, communication and team working between the different stakeholders, including primary and secondary care. This helps ensure patients and their families received seamless care, consistent with the principles of holistic support. The next chapter explores this further, by exploring the role of social and psychological support in the care of those with SCD.

Chapter 4: Health and well-being

Following on from the previous chapter, we now discuss the more general social and psychological support of potential benefit to people with sickle cell disease (SCD) and their families. Once again the focus is broad and at times more theoretical informed, particularly given the lack of evidence specific to the experience of SCD. Nonetheless, the evidence of more general benefit of many of the interventions introduced in this chapter is strong and there is no reason to assume they are not of equal benefit for those with SCD. The chapter also offers a timely reminder of the role of socially orientated provision, which can make an important contribution to improving a person's quality of life.

Public health

Introduction

While there is a strong evidence base for the role of various public health interventions in improving general well-being, there is little if any research that connects it to SCD. Consequently, this is not an especially well established area, although aspects of public health such as nutrition and oral health are beginning to be debated. The general importance of understanding a person's social and economic context and its impact on health and well-being has also been highlighted (Berghs *et al.*, 2016). Public health has an important role to play in advancing the well-being of people with long standing chronic conditions, such as SCD by helping support behavioural change that is sensitive to context (Marmot & Bell, 2012). Interventions that aim to tackle underlying causes of ill-health and reduce health inequalities have the potential to transform lives (HM Government, 2010). To this extent, public health is a natural ally of primary care.

Standard

- Advice on benefits, housing, education and other forms of social care provision should be given when appropriate.

Background evidence

There are marked social gradients in long standing chronic conditions across the life-course; and evidence of enduring effects associated with childhood circumstances (Marmot & Bell, 2012). Further, people with disabilities are disproportionately exposed to the social factors that contribute to health inequalities, (World Health Organization (WHO), 2011) including risk

factors such as lack of physical activity and social isolation alongside broader determinants associated with educational and employment opportunities, poverty and poor housing, and inequitable access to service support (Emerson *et al.*, 2012). These environmental disadvantages are, in turn, disabling and create the potential for social exclusion (World Health Organization (WHO), 2011). There is no evidence to suggest the disabling experience of someone with SCD is any different. It is, therefore, likely that generic public health interventions will improve well-being among those with SCD. This is an important consideration, particularly since such interventions can help maintain and improve quality of life for those with SCD. It remains, however, a neglected area and the potential of public health has yet to be realised.

Previous perceptions of long standing illness are been challenged by a more encompassing understanding of the relationship between 'being ill' and 'being disabled' (Atkin *et al.*, 2010). Disability, although socially patterned, can affect anyone, including those with pre-existing chronic conditions (Marmot & Bell, 2012). Further, international understandings have moved away from a strictly medical definition, where 'disease' and 'disability' are 'caused' by functional deficits (such as physical disability), to one sensitive to environmental determinants and connected to how people experience disability (and illness) as they go about their day-to-day lives (Lollar & Crews, 2003; Oliver & Barnes, 2012). The United Nations Convention on the Rights of Persons with Disabilities (CRPD) reflects these changes. Disability is understood to result 'from the interaction between persons with impairments and attitudinal and environmental barriers that hinders their full and effective participation in society on an equal basis with others' (United Nations, 2007). Human rights and equality frameworks are also increasingly employed to articulate the moral claims and service needs of people with long standing chronic conditions, such as SCD. This has led to a focus on facilitating an enabling environment and emphasising capability, which can support resilience and encourage people to 'flourish' with their condition (Berghs *et al.*, 2016).

Recommendations

- Strategies to address social isolation and lack of social opportunities should be considered, alongside an emphasis on how best to facilitate behavioural change, resilience and empowerment among people with SCD.
- The relationship between socio-economic disadvantage and health needs to be taken into account, when providing support to those with SCD and their families.
- The broader well-being of a person with SCD should be considered during his or her contact with primary and more specialist secondary care provision.
- Appropriate advice should be provided and a person encouraged and supported to take a proactive approach to his or her health.
- An assessment of general health and well-being should occur and advice provided on how best to support a person's quality of life, in a way that facilitates resilience, while being sensitive to his or her socio-economic circumstances.

Psychological interventions

"It is not death or pain that is to be dreaded, but the fear of pain or death." – Epictetus

Introduction

Sickle cell disease (SCD) poses multiple and severe psychological challenges to patients, families, health care professionals and the health care system. As it is present from birth it can interfere with normal adjustment to developmental challenges and achievement of personal goals. This occurs in the context of SCD being a stigmatising medical condition causing considerable socio-economic challenges. On a more individual level, psychosocial issues for people with SCD and their families can result from the impact and disruption due to pain and other symptoms on their daily lives, affecting their quality of life. For example, stress, depression, fear or anxiety may affect pain experience leading to frequent hospital admissions. People with SCD have different levels of health, and variations in their ability to cope from day-to-day. Studies suggest a person's way of coping appears to be a significant predictor of adjustment, independent of the severity of his or her disease.

Psychological interventions should be offered as standard care in the management of SCD adjunctive to medical treatment and nursing care. The specialist multidisciplinary team should include clinical/health or counselling psychologists. The overall goal is to help people build resilience, enhance coping strategies, develop ways to manage symptoms such as anxiety, depression and anger, be able to engage in valued activity and roles and improve their quality of life. These interventions should be available in both hospital and community based settings. Furthermore, cognitive impairment is well recognised as a complication of SCD, both in patients who have had an overt or silent stroke, and in those without magnetic resonance imaging (MRI) evidence of disease. Neuropsychological evaluation can establish the extent of cognitive damage, map this over time and offer treatment strategies.

Standards

- All people with SCD should have access to specialist psychology support.
- Core staffing of Specialist Centres for SCD should include a psychologist with a special interest and experience in SCD.
- Psychological assessments should be carried out when indicated or at least annually, and include the following:
    - Subjective estimates and objective measure of emotional well-being and pain
    - Physical and social function i.e. participation/non-participation or reduction in activities e.g. work, social – subjective estimates and objective measures
    - Objective measures of coping strategies and sources of support.

- Neuropsychological assessments should be carried out as appropriate when neurological complications are indicated.
- Psychological therapies including Cognitive Behavioural Therapy (CBT) should be offered as required, and could be offered in individual or group sessions.
- Psychological support should be offered to patient and carer support groups.

Background evidence

Reviews of psychological studies have shown that people with SCD have a severely compromised health-related quality of life in comparison to the general population and other medical conditions (Anie, 2005; McClish *et al.*, 2005). Moreover, depression, anxiety, and psychological difficulties are prevalent among people with SCD, and predictive of pain experience (Levenson *et al.*, 2008; Sogutlu *et al.*, 2011). There is good evidence to suggest that cognitive behavioural therapy in adults with SCD is beneficial to moderate chronic pain, disability, depression and anxiety associated with SCD (Anie & Green, 2015; Chen *et al.*, 2004; Williams & Tanabe, 2016). This is supported by studies of chronic pain management (in non-SCD samples) with psychological therapies delivered via the internet that were shown to be effective in reducing pain, disability, depression and anxiety in adults, comparable to effectiveness in face-to-face therapies (Eccleston *et al.*, 2014a).

Furthermore, reviews of psychological therapies with children and young people show that these have been effective in reducing pain and perceived disability amongst those with non-headache pain (including sickle cell disease), but only soon after treatment (Eccleston *et al.*, 2014b); and group psychoeducation in families of children and adolescents with SCD has shown improvements in knowledge (Anie & Green, 2015).

Cognitive impairments have been highlighted in adults with SCD who have normal MRIs, suggesting the importance of neuropsychological assessments (Rawle *et al.*, 2015; Vichinsky *et al.*, 2010). Further psychological therapies are outlined in Appendix 2

Recommendations

- Psychologists should be an integral part of multidisciplinary teams for the management of SCD.
- Health professionals should routinely assess a patient's desire for psychological intervention/support by asking questions such as 'How are you feeling/coping?' and should identify patients who would benefit from psychological intervention in order to maximise health related behavioural changes e.g. improving adherence.
- Patients should be encouraged to practice CBT techniques such as relaxation on a regular basis, or seek instruction if needed.

- Patients and their families should be made aware of what psychological support is available within hospital and community settings.
- Patients seeking to make health-related behavioural changes such as quit smoking, should be referred for psychological support in order to maximise success.
- Where serious mental health difficulties or psychiatric problems are identified, referral to a secondary mental health service should be considered and, if possible, discussed with the team psychologist in a timely fashion.
- Specialist staff should be aware of the importance of psychosocial issues in providing care for people with SCD and should have access to training, support, consultation or supervision from a psychologist with a special interest in SCD.

Nutrition and lifestyle

"We could do with some help with food management and what not to eat e.g. foods with iron if you are on an exchange programme."

"I have been fortunate enough to have a research background, so I have researched myself treatments, management and why I need to eat certain foods etc."

Introduction

The importance of nutrition in patients with SCD is largely under-recognised in the UK. Sickle cell patients are not readily referred to dieticians and dietetic involvement in the nutritional care of sickle cell patients is mostly poor. Current nutritional support generally consists of advice on healthy eating and possibly the prescription of a nutritional supplement. An improved strategy for nutritional support should be part of the broader commitment to enhancing the general well-being of people with SCD.

Standards

- Dieticians should be included in the multi-disciplinary team caring for patients with SCD.
- Patients with SCD should be screened for malnutrition/risk of malnutrition by healthcare professionals with appropriate skills and training (National Institute for Health and Care Excellence, 2012a)
- Patients with SCD who have been identified as high risk for malnutrition should be offered nutritional assessment by an appropriately trained dietician and should receive a nutritional management care plan.

Background evidence

Dieticians are qualified health professionals able to assess, diagnose, and treat diet and nutrition problems at an individual and wider public health level and they have a responsibility to comprehensively assess the nutritional needs of all patients and make an accurate nutritional diagnosis. Undernutrition or poor nutrition has been described as a feature of SCD since the 1980s but the specific dietary requirements for this group of patients has not yet been established despite the recommendation for inclusion of nutritional advice into routine care (Hyacinth *et al.*, 2010).

A national cross sectional survey exploring the involvement, knowledge and attitudes of dieticians towards SCD in the UK concluded that dieticians did not understand the nutritional implications of SCD, there were no sickle cell-specific nutritional guidelines, standards and resources to help dieticians, and poor referral rates of sickle cell patients for dietetic input occurred. Dieticians need to comprehensively assess the nutritional needs of sickle cell patient, considering all the factors that affect his or her nutritional intake (European Society for Clinical Nutrition and Metabolism (ESPEN) *et al.*, 2006). These include the wider determinants of health and psychosocial factors, nutritional factors (infection risk, dehydration, frailty and gastrointestinal intolerances) and medical considerations (hydroxycarbamide, transfusion treatment, iron overload) (Matthews, 2015).

NICE guidelines (National Institute for Health and Care Excellence, 2006) recommend that nutrition support should be considered in people who are malnourished or at risk of malnutrition, as defined by any of the following:

- Body mass index (BMI) of less than 18.5 kg/m^2
- Unintentional weight loss greater than 10% within the previous 3–6 months
- BMI of less than 20 kg/m^2 and unintentional weight loss greater than 5% within the previous 3–6 months
- Having eaten little or nothing for more than 5 days and/or are likely to eat little or nothing for the next 5 days or longer
- Have a poor absorptive capacity, and/or have high nutrient losses and/or have increased nutritional needs from causes such as catabolism

Patients with SCD should be evaluated for these risk factors and referred to a dietician for review if appropriate. Effective management of the nutritional needs of patients with SCD could include the development of a 'national nutrition strategy', acknowledging all the key players involved including primary and secondary care practitioners, the dietitian and the patients and their families.

There is little published research in this area but elevated protein turnover and energy expenditure have been reported in adults with SCD, suggesting increased protein and calorie requirements (Badaloo *et al.*, 1989; Hibbert *et al.*, 1992; Jackson *et al.*, 1988) and patients with

SCD often experience anorexia due to general chronic malaise. There is a suggestion that routine dietary supplementation may be of benefit. In a small study, supplementation with Omega (N3) fatty acids resulted in significant reductions in inflammation, oxidative stress, red cell density and pain episodes (Tomer *et al.*, 2001) and several small studies have shown benefit with supplementation of micronutrients (e.g. iron, zinc) but these need further study to establish their efficacy. Prior to iron supplementation it should always be confirmed that the patient is iron deficient.

Recommendations

- The British Dietetic Association should consider development of a sickle cell specific nutritional risk assessment tool to allow consistent dietary assessment.
- Centres could consider offering an annual review with a dietitian to advise on optimal nutrition.
- Health and social care practitioners should be aware of how diet can enhance healthy living and general well-being among patients with SCD.
- Further research into the role of nutritional support for patients in patients with SCD is needed.

Health education

'… the competencies that 'lay' contributors can offer should not be permitted to draw attention away from the need to change professional attitudes and practices, and the value of constructive, 'grown up', professional/patient relationships.'

(Taylor & Bury, 2007)

Introduction

This section covers several aspects of education for adults living with SCD in the community, including how best to think about ongoing education of someone with SCD around his or her illness (what has been called self-management of illness or the 'expert patient'). In doing so, it connects to ideas, such as resilience and empowerment. This section explains why such adult patient education should be a mutual process rather than an issue to be 'managed'; why knowledge and confidence should be the aim rather than the containment of health care utilisation or costs; the danger that some initiatives may be socially exclusive and inadvertently increase disparities in ethnic health; and the importance of recognising the influence of social, economic, political and environmental factors in how people understand and engage with their SCD.

Standard

- Goals for education of adults with SCD should include increased patient involvement, knowledge and confidence.

Background evidence

Much of the literature on patient education for self-management in the UK deals with chronic illnesses in general or chronic illnesses other than SCD specifically. While potentially useful, lessons from studies of other chronic illnesses cannot always be assumed to transfer to a condition such as SCD nor from one ethnic population group to another (Greenhalgh, 2009; Kennedy *et al.*, 2007; Kennedy & Rogers, 2009). Further, evaluation of generic patient education programmes is mixed at best. Such programmes have severe methodological limitations (such as comparing those select few who volunteer with those waiting to enrol on such programmes) and tend to exclude less affluent or so-called lower 'literacy' groups (Greenhalgh, 2009). They also exclude minority ethnic groups (Taylor & Bury, 2007). Available evidence suggests generic education programmes for people with a chronic illness improve knowledge and confidence in the short term, and people enjoy working in groups.

Most, however, do not show improved health outcomes (Greenhalgh, 2009). Nor is there any evidence that such programmes reduce health care utilisation. They may increase it, as knowledgeable people make greater demands of service provision overall (Greenhalgh, 2009). Further, there is no evidence for reduction in long-term health costs (Greenhalgh, 2009; Kennedy *et al.*, 2007; Rogers *et al.*, 2008). A review of four randomised trials of lay-led self-management programmes in the UK showed improved self-efficacy, but three showed no improvement in quality of life and none demonstrated changes in overall health care utilisation (Griffiths *et al.*, 2007). A review of fifteen complex interventions for groups of 'lower literacy' had mixed results, with no differences of the intervention being reported twice as frequently as significant changes across a range of measures; including clinical outcomes, health knowledge, health behaviours, quality of life, and utilisation of health care (Clement *et al.*, 2009).

Patient education programmes have been criticised for three broad reasons. First, for their failure to consider the social determinants of health (poverty, inequality, housing, social security, environment and transport), thereby running the risk of blaming the person living with a chronic illness if change is thought of as a matter for individual behaviour rather than a response to social exclusion (Atkin *et al.*, 2010; Rogers *et al.*, 2008; Taylor & Bury, 2007; Vicarelli & Bronzini, 2009). Second, for drawing attention away from the need to change some professional attitudes and practices; just as people with SCD may not follow health management advice for reasons to do with the context of their lives, so clinicians do not necessarily follow guidelines, for reasons to do with the context of their practice (Ong *et al.*, 2014). Third, the manner in which more aggressively managed systems of care negatively affect people's freedoms and opportunities to cope with the challenges of chronic illness in the ways they find most effective and appropriate (Taylor & Bury, 2007).

Interventions have proved most effective when they (1) involve changes for the health professional as well as the client; (2) look at how people manage and understand their illness in the context of family and social relationships; (3) look at how people manage their illness in the context of material and social resources available to them (Ong *et al.*, 2014). Listening to the stories of people with chronic illness in the context of activist events begins to expose how broader issues of social justice and social inclusion impact on living with the chronic illness (Greenhalgh, 2009).

Some studies have suggested expanding the notion of expert patient to expert family, but note that this can only work if the work situation, home situation and socio-economic situations of the family are taken into account (Vicarelli & Bronzini, 2009). Whilst self-management programmes for African asylum seekers with a chronic illness did not work in improving self-management, because they had other overwhelming social priorities for survival, the course provided a surrogate family and a focus for subsequent campaigning around political and social needs (Kennedy & Rogers, 2009).

Small scale descriptive studies of self-management of adults with SCD suggest that motivational or strength based interviews (focussing on what adults with SCD enjoy doing) can identify the expertise of the person with SCD, enabling them to be educators of health professionals (Campbell *et al.*, 2010); and that adults with SCD can identify key self-management practices they feel work, including keeping journals, body awareness and various forms of lay and professional support (Tanabe *et al.*, 2010). However, social factors making people with SCD vulnerable, including employment status and ability to earn income, are directly related to poor health and were not improved by self-management resources such as communication skills or self-care abilities (Jenerette & Murdaugh, 2008). This connects to the broader evidence, which reminds us that people with disabilities and long term conditions are disproportionately disadvantaged with respect to the social factors that contribute to health inequalities (see above).

Recommendations

- Health education for an adult living with SCD should be regarded as a process that flows in several directions: the person with SCD, his or her family members and professionals can all educate one another.
- There is a need for robust evaluation of the long term effects of inclusive adult education programmes specifically for people with SCD.
- Health and social care practitioners need to be aware of the broader impact of SCD on a person's life and how this impacts on his or her general health well-being.

Support in education and training

Introduction

The section considers how to ensure that educational establishments fulfil their duty of care to students with SCD. This is an especially important consideration as educational qualification can protect against social-economic disadvantage, while also facilitating greater social inclusion.

Standards

- Further and higher education institutions, universities and colleges should develop and monitor policies for supporting students with SCD with respect to their education, their health and their careers.
- Secondary care providers should have a protocol for management of young adults who move away from home to study. This should include transfer of information to their term-time care provider.

Background evidence

There are few studies of adults with SCD in post-compulsory education, that is, in further or higher education colleges or in universities. Most such studies are concerned with general student population knowledge of, and/or attitudes to, reproductive risks of sickle cell carriers, rather than the experiences of adults with SCD themselves. In the absence of specific evidence for adults with SCD, we do know that young people up to age 25 years are not well supported in schools and colleges in the UK, either in terms of catching up any education missed or in being well supported in their health in school (Dyson *et al.*, 2010a). Whether or not staff members know that a person has SCD makes no significant difference to his or her being well-supported or being poorly treated, and young people themselves are sharply divided as to whether or not disclosure of their SCD is beneficial (Dyson *et al.*, 2010b). Changing the social environment of the school/college through the introduction of policy has therefore been proposed as a way forward (Dyson, 2016), though the effectiveness of such policies have yet to be evaluated.

There is even less evidence when assessing the success or otherwise of interventions aimed at supporting students in higher and further education. Some general observations, however, can be made. Students might be unfamiliar or insecure about presenting themselves for treatment at their local hospital, particularly if the student has concerns about the quality of treatment. This could be a specific problem if a student were to move from an area with good experience of managing SCD to another, with perhaps less experience. Anecdotal evidence suggests some students have got on the train back to London whilst in crisis so as to access their known provider. There are several reports of deaths too, where a local hospital has little experience of managing a SCD crisis. Managing this move to further education, therefore, would seem an important part of the process. Some universities have worked with the local sickle cell specialist

nurses to introduce the students with sickle cell to the local team and to the ward where they would be treated should they become ill whilst at university. In other localities, a formal hand-over between health care teams might also be helpful. If the university entry forms ask a question about medical conditions/needs, it might be useful to specify sickle cell as one of the options, particularly since it is one of the most common monogenetic conditions in England. Current questions tend to list asthma, epilepsy or diabetes as examples. This is unlikely to prompt someone with sickle cell.

Finally, universities need to apply flexibility when supporting someone with a long term condition, such as SCD. Does the 'mitigating circumstances' policy take into account the fluctuating nature of the condition and the fact that symptoms can appear at short notice? Is the leave of absence policy sensitive to the needs of someone with SCD? Reports by clinicians in support of mitigation and leave of absence requests can assume particular importance. More generally, are curricula designed in such a way so as a student can catch up weeks/months of missed work? Anecdotal observations suggest that laboratory–based subjects are especially problematic in this regard.

Recommendation

- There is a need for research on the specific challenges facing adults with SCD in education or training, whether in colleges, universities or the workplace.

Welfare and social security benefits

Introduction

Historically, patients with SCD and their families have experienced challenges accessing appropriate welfare support. The undue pressure and stress experience affects their quality of life, health and well-being (as outlined above). Further, financial pressures resulting from current socio-economic factors i.e. austerity and the increasing need to do 'more with less' continues to impact on service provision for sickle cell patients. Most people living with SCD are in full-time employment and therefore may not need to claim welfare benefits support. It is, however, recommended that they are well informed about benefits they could apply for and what the application processes are, should they need to. It is important to note, however, that the benefit system can be difficult to negotiate. This can be off putting and discourage people from making claims. There also remains the long standing difficulty of ensuring that those who administer claims understand the consequences of what it can be like to live with a fluctuating condition, such as SCD, where impairment can be intermittent and often not immediately obvious.

Standard

- Patients raising concerns about social security and welfare entitlements should be referred for specialist advice.

Background evidence

There have been significant changes in benefits and entitlement conditions since the introduction of the Welfare Reform Act 2012 (HM Government, 2012). This Act introduced two major benefits (from 2013): Universal Credit (UC) and Personal Independence Payment (PIP).

UC is the new means-tested benefit being introduced in stages to replace Job Seekers Allowance (JSA); Housing Benefit (HB); Child Tax Credit (CTC); Working Tax Credit (WTC); Employment and Support Allowance (ESA); and Income Support (IS). PIP replaced Disability Living Allowance (DLA) for claimants aged from age 16 to 64 years. Unlike DLA, PIP is a point-based system. The Act also introduced changes ranging from Benefit Capping, the 'Bedroom Tax', Local Housing Allowance (LHA) and Local Welfare Assistance Schemes to the abolition of Council Tax Benefits (CTB). (Additional information on the different benefits mentioned can be found in Appendix 3.)

One of the aims of UC was to simplify the benefits system but claiming benefits remains complex. Those with SCD and their families are not always aware of their entitlements, how they can claim these entitlements and how to appeal. Financial support can be fundamental to general health and well-being and benefits can play an important role in facilitating this. There is a more general lack of coordination of welfare support, which can include housing and other social care needs, in addition to benefits.

Greater joint-working (and to include those working in health care), support for the role of third sector organisations, along with making accessible information and advice available to those with SCD and their families, would be an important way forward. The fluctuating nature of SCD, however, makes it difficult to assess. Moreover, assessors within the benefits and social care agencies can seem poorly informed and lack insight into the consequences of SCD, which make it difficult to make reasoned and evidence-based care assessments and may lead to conflict with patients.

It has been suggested that the creation of a single multi-agency body in areas of high SCD prevalence, consisting of all key stakeholders (including primary and secondary care agencies, social services, housing departments, Department for Work and Pensions representatives, welfare support advisors), similar to the current multi-disciplinary team (MDT), but including a broader range of disciplines, could help solve current difficulties. Alternatively the employment of specialist community benefit or welfare advisors may improve patient access and support.

Recommendations

- Those assessing such claims should have sufficient knowledge of the consequences of SCD and its impact on a person's life. Specialist training should be considered to facilitate this.
- The production of detailed welfare benefits application guides, specifically addressing how sickle cell patients need to complete forms, by third sector (voluntary) organisations in partnership with statutory providers would be useful in decreasing benefit rejections.
- The provision of welfare support advisors or volunteers with the expertise to assist with benefits applications should be considered.
- Benefits and welfare advice should be offered to patients during transition because of specific changes in benefits at 16 years, whereby patients entitled to DLA must apply for PIP.

Patient voice, support groups and peer support

'Patient engagement can deliver more appropriate care and improved outcomes'

(The King's Fund, 2012)

Introduction

Voluntary and community organisations (non-government organisations), often in partnership with National Health Service (NHS) practitioners, have played an instrumental role in ensuring the visibility of sickle cell in UK (Anionwu & Atkin, 2001). Research reminds us how such organisations not only have the trust of local communities, but act as mediators and guarantors of good practice by operating as a bridge between local communities and health care providers (Berghs *et al.*, 2015). Funding, however, remains a problem and many voluntary and community organisations have to continually bid for grants, which are often short-term, to ensure their sustainability. This creates vulnerability and has the potential to threaten the important support and advocacy role played by voluntary and community organisations.

The Sickle Cell Society is the national charity for SCD in the U.K. It provides a range of services to individuals living with SCD and their families including provision of information and advice, direct support services such as a helpline service, training and education and a peer mentoring programme and activities for children and young people. There are also large numbers of small geographical based sickle cell patient and families support groups across the country with whom the Sickle Cell Society works in partnership, as part of its core objective to support individuals to achieve their full potential.

The Sickle Cell Society enables engagement and involvement of patients and their families in peer reviews of all sickle cell services in England with clinicians and NHS England, as well as involvement in research and clinical trials and the development and/or improvement of sickle cell services at individual hospital and community sites. For example, the Society worked closely with the Picker Institute (Europe) and the Collaboration for Leadership in Applied Health Research and Care (CLAHRC) to carry out the biggest survey of SCD patients in England to support service improvement and outcomes for patients and their families (Picker Institute Europe, 2015).

Standard

- Statutory agencies should develop partnerships with voluntary and community organisations aiming to improve access to patient and family voices, while delivering more social orientated provision.

Background evidence

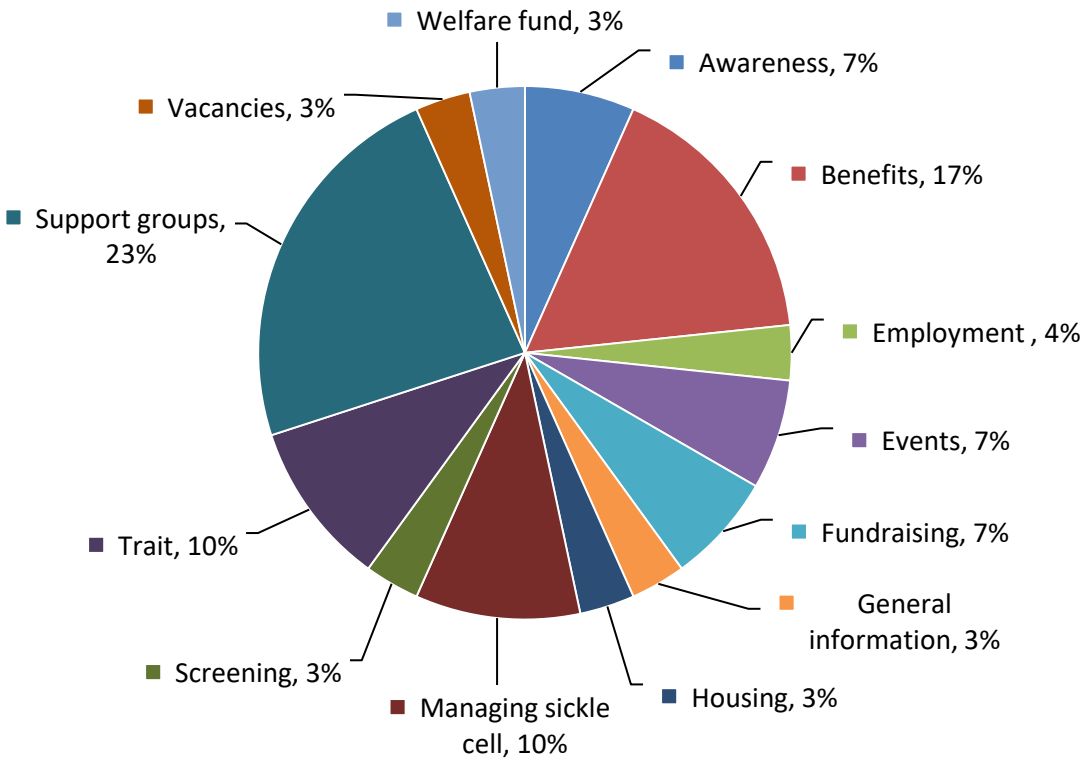
Experience of care, clinical effectiveness and patient safety are the key components of quality in the NHS (NHS England, 2014). Care for patients with SCD can be inconsistent. Service provision can also vary depending on where you live in the country. These factors together with the varied prevalence of SCD pose a challenge for patients when accessing appropriate specialist care, particularly in low prevalence areas (West Midlands Quality Review Service, 2016a).

In 2015, the National Institute for Health Research (NIHR) collaboration for Leadership in Applied Health Research and Care for North West London, the Picker Institute Europe and the Sickle Cell Society (SCS) collaborated on a project to better understand the experiences of people living with SCD of the health care they receive for their conditions.

As a consequence of this collaboration, the SCS analysed the main issues they are contacted about (see Figure 2). This monitoring data revealed that 23% of calls to the SCS helpline were by individuals seeking information regarding their nearest support group, so that they may link with other people with SCD and share relevant issues, ideas, information, and experiences. Many individuals also required support and advice on benefits, as they were concerned about how the recent changes had affected their entitlement and financial situation (see above). Ten per cent of individuals with SCD were seeking advice and information about managing their condition, often relating to temperature changes, employment, and recent stressors, and another 10% enquired about sickle cell trait.

[Figure 2 shown overleaf]

Figure 2: The main issues about which Sickle Cell Society are contacted



NHS clinicians and care providers can form bridges with local communities by linking with organisations involving patients, families, support groups and the SCS to shape and improve local health and health care services. This can facilitate trust and confidence in formal health and social care support.

The key principles of NHS/SCD working include:

- Voluntary and community organisations can provide a channel for the views of patients/families directly and/or indirectly
- Such organisations can facilitate the involvement and support of patients in NHS matters
- They can ensure patients/families affected by service issues are supported and/or consulted/involved in any decision making processes
- Voluntary and community organisations can facilitate and involve patients/families in any appropriate training for clinical/non-clinical NHS staff
- Staff members from voluntary organisations often serve on advisory groups to input the patient perspective as well as other expertise. This may include research steering committees, review bodies (e.g. National Institute of Health and Care Excellence, NHS Sickle Cell and Thalassemia Screening Programme) and guideline production.

Patients with SCD and their families, often seek professional help, advice and support beyond doctors and nurses. They also rely on support from family members, peers and charities. This led to charities such as the SCS and the various branches of the Organisation for Sickle Cell Relief & Thalassaemia Support (OSCAR) by parents, clinicians and people living with SCD in the 1970s. Over the years other local peer support groups have been established, most operating under the national umbrella of the Sickle Cell Society or OSCAR usually covering small geographical areas.

These support groups mainly offer information and advice to local people with SCD and their families. They vary in size, leadership, capacity and resources, to the extent that some groups have not been able to continue their operation over the years. The Sickle Cell Society has over 15 affiliated peer support groups across the country (www.sicklecellsociety.org).

There is good evidence to show that external help, advice and support beyond the clinical treatment of patients by doctors, nurses and other health professionals can optimise health outcomes (Berkman & Glass, 2000; Cohen *et al.*, 2000). Voluntary and community organisations are in an excellent position to offer this care and support as they work within the communities they help, which helps engender trust and legitimacy. These organisations are especially helpful in engaging with the social determinants of health and the disadvantages faced by those with SCD and their families. They can also provide sickle cell patients with vital information regarding their rights and entitlements, offer advocacy services and represent their psychosocial and financial needs. Good partnerships with statutory health and social care agencies remain fundamental in facilitating the role of voluntary and community organisations. Adequate funding is required to ensure continuation of their work as funding for voluntary and community organisations is often difficult to obtain and can be short-term. This creates problems of continuity and sustainability.

Recommendations

- Central and local government should work with NHS commissioners and providers to consider how best to fund the work of third sector organisations, especially given the important role these organisations can have in facilitating patient voice and community involvement.
- Health and social care agencies should explore ways of developing the capacity of voluntary and community organisations as a means of ensuring the maximum opportunities for offering accessible and appropriate provision for those with SCD and their families.
- Ways of ensuring mutual respect and understanding between third sector organisations and statutory provision should be negotiated and established. Good practice should be disseminated as widely as possible.

- Sustaining the support provided to the SCS as the national charity representing people with sickle cell in the UK.
- Co-production and continued involvement with patients and their families in peer reviews, research, clinical development and trials.

Chapter 4: Conclusion

The chapter connects to the previous chapter, by considering the broader aspects of care. In doing so, it offers a reminder about the importance of understanding individual and family context, alongside the need to support people to take responsibility for their health and well-being. Sensitivity to the social and economic circumstances in which people and their families experience SCD underpins this emphasis; as does a consideration of the broader determinants of health when considering well-being and quality of life. This highlights the role of a diverse range of provision, while also underlining the value of resilience and empowerment. This in turn is consistent with broader debates about disability and human rights, which are increasingly being employed to facilitate an enabling environment, in which people can flourish and fulfil their full potential. Such debates have not had a great deal of impact on our current understanding of SCD, but their influence could open up different ways of thinking about the disabling consequences of the condition.

Section B: Management of acute and chronic complications

Chapter 5: Acute and chronic pain

The acute painful episode, or crisis, is the characteristic presentation of sickle cell disease (SCD). These episodes can occur unpredictably, often without clear precipitating factors. Pain can fluctuate in intensity and duration, ranging from mild to severe and debilitating. The acute painful episode is the most frequent cause of hospitalisation, accounting for more than 90% of hospital episodes but the majority of acute painful episodes are managed within the community.

Chronic pain is usually defined as persistent pain lasting for more than three months. In patients with SCD, this needs to be distinguished from a long lasting or repetitive acute pain crisis. The mechanisms of chronic pain are not fully understood and the incidence is almost certainly underreported. There is little evidence about management strategies specific for patients with SCD.

Acute pain

'I insist upon compassionate care, adequate pain control and respectful communication'

"Some doctors at A&E are very prompt in responding to my pain crisis and some not."

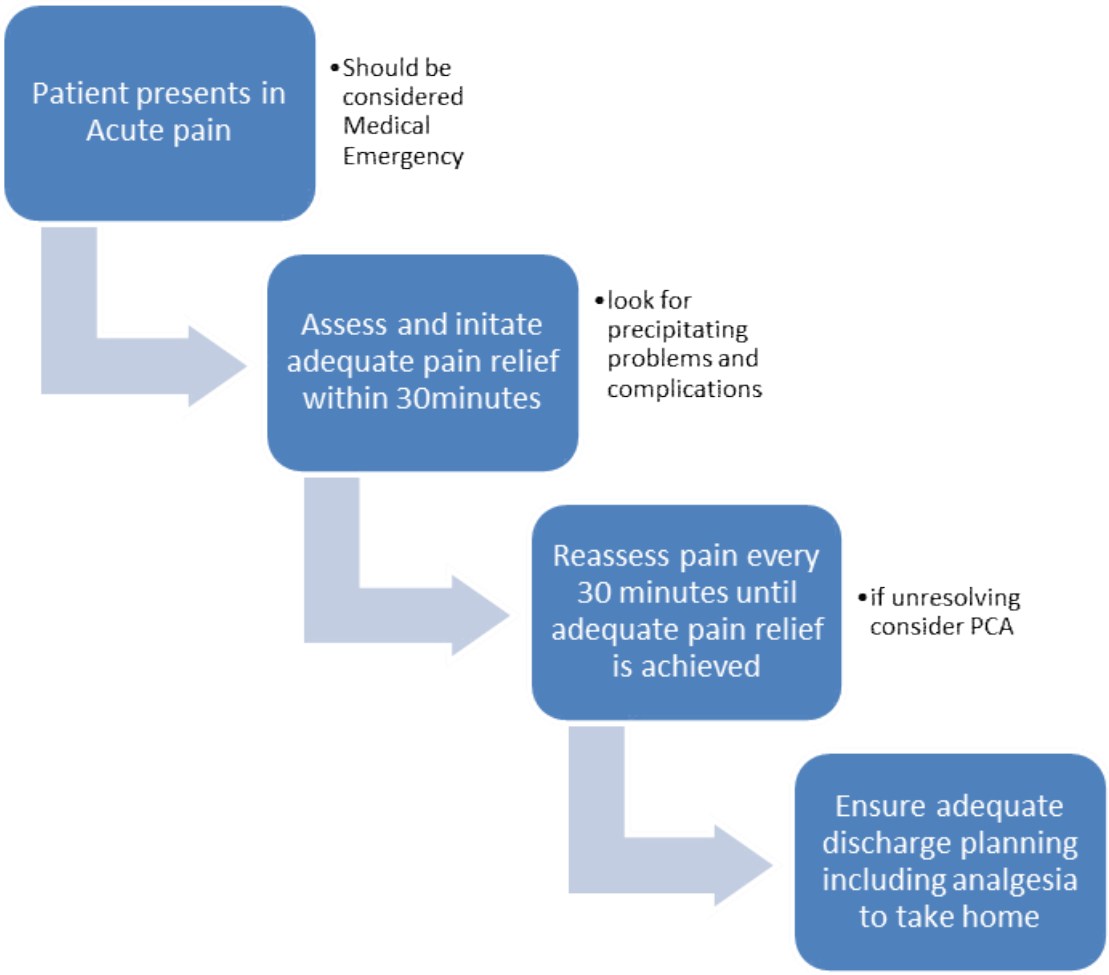
*"…At *** Hospital, no matter how serious the pain, you are not seen immediately you arrive. Even though I have a care plan, it takes the nurses and doctors ages to get it and implement it. In the meantime, you are just screaming in agony, and the staff will actually shut the "door" of your cubicle/room and ignore you. There can be a delay of anything between 40 minutes, over an hour or two, before you are given medication. To get adequate and timely treatment in A&E feels like a struggle."*

Standards

Based on: (National Institute for Health and Care Excellence, 2012b)

- Patients presenting as a medical emergency with an acute painful episode should be offered appropriate analgesia within 30 minutes of presentation to the emergency department.
- All hospitals should have a protocol for management of acute pain crisis which is consistent with (National Institute for Health and Care and Excellence (NICE) standards and compliance with this protocol should be audited at least annually (see Figure 3, overleaf).

Figure 3: Acute Pain Quick Reference



(PCA: Patient controlled analgesia)

Background evidence

The pathophysiological events driving the manifestation of the acute sickle painful episode include vaso-occlusion by sickled red cells, tissue ischaemia and inflammation and nociception (Ballas *et al.*, 2012).

The patient presenting with acute sickle pain should be treated as an medical emergency and offered analgesia within 30 minutes from time of booking (National Institute for Health and Care Excellence, 2012b). Assessment of pain with a pain-scoring tool and history of analgesic use can inform the choice of an appropriate initial analgesic. The choice of drug, dose and administration route should be tailored to pain and severity using the WHO analgesic ladder for pain relief (World Health Organization, 1986). Patients with moderate pain that have not had any prior analgesia at home can initially receive a non-steroidal anti-inflammatory drug

(NSAID) and weak opioids whereas patients presenting with severe pain or moderate pain persisting after prior analgesia should be offered a strong opioid up front (National Institute for Health and Care Excellence, 2012b). Either an oral or a parenteral route of administration of the strong opioid may be appropriate, depending on clinical situation and patient choice. The subcutaneous route is preferred to intra-muscular due to the risks of muscle scarring and poor absorption with the latter.

Patients' experiences of treatment in the Accident and Emergency Department (A&E) are sometimes negative and underlined by a perceived lack of staff training and experience; lack of understanding; and break down of trust (Elander *et al.*, 2011; Telfer *et al.*, 2014). Interventions aiming at increasing patient-healthcare provider trust and respect may improve quality of care (Elander *et al.*, 2011).

Reassessment and ongoing management

The effectiveness of pain relief should be assessed every 30 minutes from initial analgesic administration until satisfactory pain relief is achieved and four hourly thereafter (National Institute for Health and Care Excellence, 2012b). If the patient has severe pain on reassessment a second bolus dose of a strong opioid can be offered (or a first bolus dose if they have not yet received a strong opioid).

If pain persists in spite of repeated doses of bolus strong analgesics, then patient controlled analgesia (PCA) should be considered (National Institute for Health and Care Excellence, 2012b). PCA has been shown to be efficacious in achieving pain relief, with smaller total doses of opioid analgesics compared to continuous infusion, thereby having the potential for fewer adverse effects (van Beers *et al.*, 2007). Further, repeated bolus opioid doses do not achieve smooth and sustained analgesic effect (Telfer *et al.*, 2014). PCA should, therefore, be considered for analgesia in patients who are admitted to hospital with painful crises. PCA can be initiated either in the A&E department or on the ward, following admission (National Heart Lung and Blood Institute, 2014).

Pethidine, although offering effective pain relief, has significant neurological adverse effects (convulsions) and therefore it is not recommended for use in the acute sickle painful episode setting (National Heart Lung and Blood Institute, 2014; National Institute for Health and Care Excellence, 2012b). Corticosteroids are also not recommended for treatment of the acute painful episode.

Supportive treatment: As an adjunct to opioid treatment, patients should receive regular paracetamol and NSAIDs, unless contra-indicated (National Institute for Health and Care Excellence, 2012b). Moreover, opioid medication has frequent adverse effects, thus regular laxatives – and if needed, anti-emetics and antipruritics – are recommended for patients who are on opioid treatment (National Institute for Health and Care Excellence, 2012b). Intravenous

hydration is recommended for patients who are unable to take fluids orally (National Heart Lung and Blood Institute, 2014). Oxygen therapy should be offered to patients who have a reduction in measured oxygen saturation 95% or below (National Institute for Health and Care Excellence, 2012b). Some patients find supplementary oxygen helpful even if their saturations are normal.

Prevention of complications: Incentive spirometry has been shown to reduce the incidence of acute chest syndrome (ACS) in children and young adults (2-18 years) with acute sickle pain in the chest and back. Incentive spirometry should be considered in adults admitted with chest or back pain (National Heart Lung and Blood Institute, 2014).

Blood transfusion during the acute sickle painful episode: Red cell transfusions are not recommended for the treatment of the uncomplicated sickle painful episode. They may be needed if there are additional indications for blood transfusion (Davis *et al.*, 2017a, 2017b) (see Chapter 21 - Blood transfusion).

Non-pharmacological interventions: Although trials have not demonstrated a clear benefit from the use of non-pharmacological interventions for the management of the acute sickle painful episode, such interventions (including relaxation/behavioural techniques and local heat application) could be used on a case-by-case basis to support pain management (National Heart Lung and Blood Institute, 2014; National Institute for Health and Care Excellence, 2012b).

Monitoring

Close monitoring is essential to ensure optimal analgesic effect and to identify:

- the presence of adverse effects from analgesic treatment
- any indicators of underlying or additional complications such as infection, falling oxygen saturations etc.

Detailed clinical assessment (pain score, sedation score, respiratory rate, oxygen saturations on air) should be performed, especially in patients on strong opioids, every hour for the initial six hours and after any dose escalation and four hourly thereafter (National Institute for Health and Care Excellence, 2012b). This will help detect and manage any adverse effects from analgesia. If the patient does not respond to standard treatment for an acute painful sickle cell episode, he or she should be reassessed for the possibility of an alternative diagnosis.

Discharge

As the painful sickle episode resolves, there should be a gradual withdrawal of opioid analgesia (National Heart Lung and Blood Institute, 2014). Prior to discharge, patients should be offered adequate information on the management of their painful symptoms at home, access to specialist advice and care, and how to obtain repeat prescriptions and adequate supplies of

analgesics (National Institute for Health and Care Excellence, 2012b). This is necessary, as many patients with sickle cell disease experience pain in between acute painful episodes (Ballas *et al.*, 2012). Good discharge planning enables smooth transfer of patient care to the community and should aid in reducing readmissions.

Recommendations

Based on (National Institute for Health and Care Excellence, 2012b)

- All units should be able to offer patient controlled analgesia (PCA) for when pain does not settle with initial intermittent opiate dosing.
- Trusts should consider treating patients presenting *frequently* with uncomplicated pain in a day unit setting. However, for patients who present *infrequently,* overnight admission should be preferred.
- Staff (nursing and medical) involved in the care of patients with acute painful sickle episodes should have training in pain monitoring and management and should have access to local management protocols and specialist support.

Chronic pain

"Can do with more appointments that aren't rushed. Further investigation into chronic pain in one area of the body should be looked at. More information about NHS trials for treatments."

Introduction

The Pain in Sickle Cell Epidemiology Study (PiSCES) concluded that pain in SCD was far more prevalent and severe than previously thought with most patients managing their pain at home. Adult patients in this American single site study reported experiencing pain on 54.5% of the surveyed days; with 29% of patients experiencing pain on more than 95% of the days (Smith *et al.*, 2015). Whilst this study did not distinguish between acute and chronic pain it does suggest that a large number of patients experience pain on most days. Another American study of adult patients with SCD reported 92% of patients experienced pain lasting from 6 months to 2 years with 90% taking pain medication on a daily basis for a period of 6 months (Thompson & Eriator, 2014)

There is little robust evidence about the management of SCD chronic pain, so most of the following is derived from general guidance on the management of chronic pain, and prescribing in non-cancer chronic pain. Alongside medication-directed management, there is increasing support and recommendation for working within a multidisciplinary team (MDT) in managing chronic pain, including therapeutic interventions such as psychology and specialist pain

physiotherapy, rather than depending on pharmacological therapy alone. Through engagement with the MDT, people living with SCD can be supported in acquiring and developing skills in pain management, including managing unhelpful or difficult thoughts, managing difficult emotions including anxiety, stress and worry, pacing activities, moving and exercising in the presence of SCD and mindfulness and relaxation strategies.

Standards

- Patients should be asked about whether they experience chronic pain as part of their annual review.
- Use of opioids should be regularly reviewed at clinic visits, including at annual review.
- An underlying cause of chronic pain should be sought and treated if appropriate.
- Patients with complex pain needs should be referred to a multidisciplinary chronic pain team, with experience of SCD, offering both pharmacological and non-pharmacological interventions.

Background evidence

Chronic pain in patients with SCD may result from obvious tissue damage such as avascular necrosis of a joint or an on-going leg ulcer. In these situations treatment of the underlying cause is paramount. In other situations the pathological basis is less clear, but the pain may be due to slow to resolve acute painful episodes or chronic pain syndromes associated with previous tissue injury, central sensitisation and neuropathic pain.

Central sensitisation is the result of excessive nociceptive signals acting on the central nervous system causing changes within the brain and spinal cord. The consequence is continuous and increased pain sensations (Ballas *et al.*, 2012). Central sensitisation has been described in many chronic pain syndromes and in SCD there is some evidence that patients with higher levels of central sensitisation have more pain and experience more vaso-occlusive crises. Hyperalgesia is an exaggerated pain response to normally mild stimuli and is associated with central sensitisation syndrome and excessive opioid usage.

Neuropathic pain (pain often described as numb, tingling, shooting or like pins and needles) is increasingly recognised as an element of acute or chronic SCD pain (Brandow *et al.*, 2014). It is a result of nerve injury or dysfunction secondary to a blockage of blood supply or persistent inflammation.

Patients with SCD may also describe pain transforming from acute to chronic. As patients get older, pain patterns are seen to change and older patients with a history of highly painful episodes do appear to transition into a chronic pain state (Hollins *et al.*, 2012).

Management

Management of chronic pain is aimed at improved function and quality of life and needs a multidisciplinary approach (Niscola *et al.*, 2009) including medical and psychological interventions (Howard *et al.*, 2009). Patients should be asked whether they suffer from chronic pain (which they may describe as 'every day' pain, background pain or on-going pain they experience at home) including frequency, site, duration and triggers, as a minimum, as part of their annual review. Patients should be helped to understand the differences between acute and chronic pain, that chronic pain is not necessarily an indication of tissue injury or damage, and that different management approaches may be necessary and more helpful than those used for acute crisis pain.

Pain syndromes have historically been managed pharmacologically, often using opiates. Pharmacological management should be specific to the patient, and use of an individual care plan with patient involvement will aid successful treatment (Ballas *et al.*, 2012). Medication choices need to take into account the risk of short and long-term side effects. There is no specific guidance to management of chronic pain in SCD and so good practice guidelines can be derived from evidence for prescribing in non-cancer chronic pain (Chou *et al.*, 2009; Franklin, 2014). Atypical analgesics (e.g. gabapentin, amitriptyline, pregabalin, duloxetine) are useful for the management of neuropathic pain.

There is increasing awareness and concern about prescription opioids in the management of chronic pain. At doses of more than 120 mg oral morphine equivalent a day there is increased risk of harm, with no increased benefit and the likelihood that opioid-based medication is not working (BMA board of science, 2017). The prescriber must be aware of these cautions, while also recognising the difference between physical dependence (which is to be expected and should not automatically raise concerns) and addiction (which is more problematic) (Savage *et al.*, 2003). There have been reports of patients with SCD being vulnerable to pseudo-addiction due to ongoing under-treatment of pain and subsequent stigmatisation as addicts (Elander *et al.*, 2004). Understanding the balance between giving sufficient pain relief and the risk of side effects is important, particularly since for many patients the levels of pain experienced will be difficult for them to manage.

Cognitive behavioural therapies (CBT) have been used alongside conventional medical treatment for the management of sickle cell pain, with some preliminary positive results (Thomas *et al.*, 1999). CBT has also been incorporated into treatment manuals (Anie *et al.*, 2002). There has been relatively little exploration of the application of other psychological treatments, such as acceptance-based approaches, in patients with SCD (Masuda *et al.*, 2011). In other conditions, pain management programmes (PMPs) based on CBT and more recently acceptance-based principles are the treatment of choice for people with persistent pain. These techniques are particularly useful when the pain adversely affects quality of life and where there is significant impact on physical, psychological and social function (British Pain Society,

2013). The aim is to help patients learn self-management strategies to reduce the impact pain has on their mood, quality of life and daily activities. These approaches could be beneficial to people living with chronic SCD pain but need further evaluation.

Recommendations

- Patients with neuropathic pain should be offered appropriate analgesic medication.
- Individual care plans should be considered for patients with complex care needs.
- Long-term opioid use should be regularly reviewed. A care plan should be devised to avoid an escalating regime of opioids. Clear prescribing guidance should be developed in conjunction with the chronic pain team and GPs to ensure a single prescriber.
- All health care professionals involved in caring for the patient, including primary care, should be aware of prescribing plans for opioids and who the key prescriber is.
- Self-management techniques such as pain management programmes and complementary therapies need further evaluation in patients with SCD.

Chapter 6: Neurological complications

"I have had migraines for the last 10 years and get them twice a month. I haven't been given any pain killers that help them. My consultant sent me to have an MRI and found nothing and advised that migraines are not curable and therefore I need to manage the triggers".

Introduction

Central nervous system (CNS) complications in adults with sickle cell disease (SCD) cause significant morbidity and mortality. Acute presentations can include headache, seizures, focal neurological signs, visual impairment, altered consciousness and acute deterioration in cognition; aetiologies include stroke and infection. Early recognition of acute neurological complications is vital, alongside rapid diagnosis and appropriate management. Adults with SCD are at risk of both acute ischaemic and haemorrhagic stroke with the risk of acute ischaemic stroke increasing with older age (Ohene-Frempong *et al.*, 1998; Strouse *et al.*, 2009).

Strokes have long-term effects including neurocognitive and neuropsychological dysfunction. There is very little evidence or commentary focused on the assessment and management of these conditions in adults. Most guidance and treatment strategies are extrapolated from paediatric data and expert consensus. Consequently, there are key questions that remain unanswered.

Acute stroke

Standards

- Patients presenting with suspected transient ischaemic attack (TIA) or stroke should have urgent neuroimaging.
- Adults presenting with TIA or stroke should be managed within a hyperacute stroke unit with access to multidisciplinary support from a haemoglobinopathy specialist centre, vascular interventional neuroradiology, neurology and neurosurgery.
- Urgent red cell exchange is recommended for patients with a sickle related acute ischaemic stroke.
- Thrombolysis should be considered for patients with acute ischaemic stroke who meet current UK national recommendations for stroke treatment if there are no contra-indications.

Incidence and aetiology

Observational studies have reported high rates of acute ischaemic stroke in adults with SCD of 11% by the age of 20 and 24% by the age of 45 years (Ohene-Frempong *et al.*, 1998; Strouse *et al.*, 2006). There are many fewer data on *de novo* and recurrent stroke rates in adults following the introduction of childhood stroke screening or with increasing use of hydroxycarbamide.

Cerebral vasculopathy is the most common cause of stroke in children with SCD but is found to be a cause of stroke in only 41% of cases in adults (Calvet *et al.*, 2015). Older patients may have other co-morbidities including hypertension, diabetes, hyperlipidaemia, renal dysfunction, impaired cardiac systolic function and atrial fibrillation which are all recognised cardiovascular risk factors in adults without SCD. Other contributory factors are relative and acute anaemia, and multi-organ dysfunction (Powars *et al.*, 1978).

Acute haemorrhagic strokes are reported at increased rates in adults with SCD. Hypertension and multi-organ failure are risk factors for cerebral haemorrhage. Aneurysms, which are reported in 10.8 per cent of adults with SCD, (Nabavizadeh *et al.*, 2016) can rupture, typically leading to subarachnoid haemorrhage, most commonly in young adults. Low steady state haemoglobin concentration, high steady state white cell count and transfusion within the previous 14 days have been identified as risk factors for haemorrhagic stroke (Ohene-Frempong *et al.*, 1998; Strouse *et al.*, 2006).

Extradural and subdural haemorrhage is also recognised and may occur in the absence of head trauma.

Investigation of patient presenting with symptoms of stroke

All adult SCD patients presenting with acute stroke should be carefully assessed by a multidisciplinary team which includes an experienced haematologist, neurologist and stroke physician. Early liaison and transfer to specialist centres with access to appropriate services is recommended.

Patients presenting with acute symptoms of TIA or stroke should have urgent neuroimaging. UK stroke management standards dictate all patients presenting with stroke symptoms should have neuroimaging within one hour of presentation. This must also apply to patients with sickle cell disease. Whilst this is being organised, preparations for exchange transfusion including provision of appropriately selected blood and line insertion if necessary should be planned. Non-contrast computed tomography (CT) of the head can help to exclude acute haemorrhage. Magnetic resonance imaging (MRI) of the head and magnetic resonance angiography (MRA) of head and neck with diffusion weighted imaging will help to identify acute ischaemic events, vasculopathy and other pathology. Magnetic resonance venography may be necessary in some cases to exclude cerebral sinus venous thrombosis (CSVT).

Management of acute ischaemic stroke

Exchange transfusion: retrospective review of children presenting with acute stroke showed better outcomes after initial treatment with exchange transfusion compared to simple transfusions (Hulbert *et al.*, 2006) and whilst there are no specific comparable data in adults, there seems no reason why findings should differ. Furthermore there is a high recurrence rate of stroke without therapeutic intervention (Powars *et al.*, 1978). Urgent exchange transfusion, therefore, is necessary in the context of acute stroke.

Thrombolysis: limited data on use of thrombolysis in patients with SCD are available. The UK National Clinical Guidelines for Stroke (Royal College of Physicians, 2016) and NICE guidelines (National Institute for Health and Care Excellence, 2017) for the management of acute stroke in adults over the age of 16 years without SCD which promote thrombolytic and antiplatelet therapy include little evidence for these therapies in the management of adults with SCD. A recent publication looked at the safety and outcome of thrombolytic therapy in acute ischaemic stroke in patients with SCD (Adams *et al.*, 2017). Comparison of outcomes in 832 SCD and 3328 non-SCD controls found no significant differences found in the fraction receiving thrombolytic therapy or experiencing symptomatic intracranial haemorrhage.

Therefore there is no evidence of increased intracranial haemorrhage in adults with SCD with acute stroke who have received thrombolytic therapy and the authors concluded that adults with SCD and acute ischaemic stroke should be treated with thrombolysis if patients otherwise qualify.

Both the SCD and traditional stroke risk factors are likely to contribute to the aetiology of acute ischaemic stroke in adults with SCD. Current evidence suggests that adults with SCD with acute ischaemic stroke may benefit from both acute exchange transfusion and from thrombolysis. Management will therefore need careful collaboration between the hyperacute stroke team and haematologists to decide whether to offer exchange transfusion, thrombolysis or both and to ensure that both can be done in a timely fashion. This decision will need to consider patient age, genotype, phenotype, MRI findings and traditional risk factors. If patients need both thrombolysis and exchange transfusion and require central line insertion for the exchange transfusion, this will need to be completed prior to thrombolysis.

Use of anticoagulant therapy in sickle-related stroke has not been well studied although there are case reports of use in carotid dissection, cerebral sinus vein thrombosis (CVST) and cardio-embolic stroke.

A negative MRI scan does not exclude acute ischaemic stroke and in patients with clear neurological signs but initial normal MRI, exchange transfusion should still be considered, with early repeat of MRI.

Management of acute haemorrhagic stroke

There is lack of formal evidence promoting management of acute intracranial haemorrhage (ICH) in adults with SCD but European Stroke Organisation guidelines (Steiner *et al.*, 2014) for generic management of adults without SCD are available. These are likely to apply to patients with SCD. The role of transfusion therapy particularly in this context has not been fully evaluated. Adults presenting with ICH require management within a multidisciplinary team which includes neurosurgery, vascular interventional neuroradiology, specialist haematology, neurology and acute stroke services. Early liaison and transfer to specialist centres with access to these services is recommended. Standard management for haemorrhagic stroke should be followed and patients cared for within a high dependency unit. Exchange transfusion should be considered prior to neurosurgical intervention unless it will delay surgery when it should be performed post-surgery. Careful attention should be paid to fluid balance and blood pressure monitoring. Standard operative optimisation should be followed for emergency craniotomy and clipping.

Recommendation

- In adults with SCD presenting with acute stroke, causes of stroke seen in adults without SCD should also be considered (such as thrombophilia, CNS infection, illicit drug use, arterial dissection and congenital heart disease).

Stroke prevention

Standards

- Adult patients who experience an acute ischaemic stroke attributed to sickle cell disease should be offered long term transfusion therapy.
- Patients who have been started on chronic transfusion therapy for primary prevention during childhood should be assessed by an expert in SCD at transition to adult care to discuss the risks and benefits of ongoing transfusion. They should be offered continuation of transfusion therapy or hydroxycarbamide if they have had a previous abnormal transcranial Doppler (TCD) that has normalised and there is no evidence of vasculopathy.
- Patients who have been started on chronic transfusion therapy for secondary stroke prevention during childhood should be offered continuation of transfusion therapy.
- Patients who have been started on hydroxycarbamide for primary stroke prevention during childhood should be offered ongoing hydroxycarbamide therapy after transition to the adult service.

- Anti-platelet therapy should be considered in patients with acute ischaemic stroke as per national stroke guidelines unless there are any contra-indications.

Primary stroke prevention

Systematic review of the literature did not identify any randomised controlled trials (RCTs) specifically addressing the management of primary stroke prevention in adults with SCD (Estcourt *et al.*, 2017).

The benefit of transfusion therapy for primary stroke prevention in children is well documented (Abboud *et al.*, 2011; Adams *et al.*, 1998; DeBaun *et al.*, 2014). Hydroxycarbamide is effective in preventing strokes in children at high risk (Ware *et al.*, 2016). There is little evidence to guide optimal management once patients who have been started in childhood on a primary stroke prevention programme reach adulthood. This group of patients should be offered life-long transfusions or hydroxycarbamide if appropriate (consistent with the TWiTCH findings (Ware *et al.*, 2016)). The risks and benefits of treatment, including the risks of withdrawal of transfusion therapy should be fully discussed with the patient on transition to the adult service, and thereafter at least annually. Long-term transfusion should be strongly recommended if there is progressive ischaemia, vasculopathy, or recurrent TIA. If adult patients on transfusion for primary stroke prevention opt to stop transfusion it may be appropriate to offer interval TCD and/or MRI scanning although there is little evidence for this.

Unlike in the paediatric population, there are currently no verified imaging techniques to identify adults at risk of stroke. Adult patients studied with TCD have not been found to have the increased velocities seen in at-risk children (Silva, 2009) and there is no supporting evidence in adults for routine regular neuroimaging by either MRI or CT modalities (NIH, 2014)

Systematic review found no evidence to guide the management of *de novo* silent infarction in adults (Estcourt *et al.*, 2017), but in adults with an incidental finding of silent infarction on MRI it may be appropriate to offer interval MRI scanning and consider intervention if there is progressive ischaemia.

Stroke prevention strategies used for the general population are also relevant for adults with SCD, including treatment of hypertension, use of antiplatelet therapy for those with vascular risk factors, treatment of hyperlipidaemia and consideration of anticoagulation in the presence of atrial fibrillation (Strouse *et al.*, 2011).

Secondary stroke prevention

Systematic review of the literature did not identify any randomised controlled trials (RCTs) specifically addressing secondary stroke prevention in adults with SCD (Estcourt *et al.*, 2017) but there are observational data supporting the role of transfusion therapy in secondary stroke prevention. In 1978 Powars et al., looked at the natural history of stroke in sickle cell disease and reported that 50% of patients with SCD and an overt stroke had a second stroke within two

years and 66% within ten years (Powars *et al.*, 1978). The highest risk appeared to be early after the first stroke with 80% of the second strokes being seen within 36 months of the first stroke. Long-term or chronic transfusion programmes have been shown in children to reduce the risk of recurrent strokes (DeBaun, 2011; Lusher *et al.*, 1976; Sarnaik *et al.*, 1979). The improvement in recurrent stroke rates means that a chronic transfusion programme aiming to keep haemoglobin S at less than 30% is now a standard of care in children for secondary stroke prevention. Following these studies, chronic transfusion therapy with the same goals is used in adults for secondary stroke prevention. However transfusion therapy alone is not a guarantee of stroke prevention and there are reported cases of children having overt strokes or developing silent infarcts on imaging despite long term transfusion maintaining a low haemoglobin S percentage (Hulbert *et al.*, 2011; Scothorn *et al.*, 2002). Conversely, it may be possible to relax the target haemoglobin S percentage after 5-10 years post-stroke (Cohen *et al.*, 1992).

Uncertainty exists about the duration of the chronic transfusion programme and in particular, when it is safe to stop. Studies in children have reported both success in stopping transfusions and cases of further stroke on stopping transfusions. These studies include a case series from Rana et al., who reported on nine consecutive patients with sickle cell disease and stroke whose long-term transfusion therapy was discontinued and in whom no ischaemic strokes developed during 80.75 patient years of follow-up (Rana *et al.*, 1997). However, Wang et al. reported a high risk of stroke recurrence after discontinuation of 5-12 years of transfusion therapy (Wang *et al.*, 1991). They saw five recurrent cerebrovascular events in the ten patients studied. There are no robust studies done in adult patients to help determine the length of transfusion therapy required. Further, the role of neuroimaging to help guide this decision is not clear. The risks and benefits of continuing long-term transfusion should be discussed with the patient. In patients on long term transfusion for secondary stroke prevention, neuroimaging (usually MRI/MRA done as regular intervals) may be reassuring to show a lack of progression of neurological damage over time and may encourage adherence to therapy. Where chronic transfusion therapy is undertaken in adults this should be done by exchange transfusion rather than regular top up transfusions where possible and preferably by automated exchange rather than manual so as to avoid iron loading and maintain a stable haemoglobin concentration (NICE guidance, 2016).

Consideration should be given to management of risk factors for stroke including both SCD-related stroke (hypertension, anaemia, chronic lung disease, avascular necrosis, retinopathy, sickle nephropathy and renal failure) and ischaemic stroke not related to SCD (diabetes mellitus, atrial fibrillation, hyperlipidaemia and renal disease)

Other treatments for consideration in secondary prevention include hydroxycarbamide and haematopoietic stem cell transplantation (HSCT) (see Chapter 23 - Haematopoietic stem cell transplantation). Evidence from children has shown that hydroxycarbamide is not equal to transfusion in terms of efficacy for recurrent stroke prevention but may be viable for consideration where transfusion is not possible or not acceptable to patients (Bortolusso Ali *et al.*, 2011; Kassim *et al.*, 2015). History of a previous stroke is one of the indications for HSCT in SCD, but this potentially curative option is not currently available for adults in the UK.

Recommendations

- There is inadequate evidence to recommend routine screening by TCD or MRI to predict stroke risk in adults.
- Hydroxycarbamide should be considered for prevention of recurrent stroke where transfusion is not possible or acceptable.

Other neurological complications

Standard

- Cognitive impairment should be considered in adults with SCD and they should have access to cognitive assessment and rehabilitation.

Cerebral sinus venous thrombosis should be considered in patients with focal neurological abnormality and negative MRI/MRA scans. Cases of posterior reversible leucoencephalopathy syndrome (PRES) are most commonly seen in hospitalised patients although the risk factors for this clinico-radiological syndrome are poorly understood. Pneumococcal meningitis and recurrent seizures are more common in SCD than the general population.

Neurocognitive impairment

Neurocognitive impairment in adults is poorly researched but gradual neurocognitive decline is recognised in SCD and in some cases may be related to silent cerebral ischaemia and small vessel vasculopathy. A study of neurocognitive function assessment in neurologically intact adults with sickle cell anaemia found that participants showed poorer performance on neurocognitive tests, when compared to non-sickle cell peers; anaemia was associated with the age related decline in cognitive performance; and MRI findings did not explain the differences. Study participants were asymptomatic and had no end organ failure (Vichinsky *et al.*, 2010). Evidence from this study also suggests that early identification of patients suffering from neurocognitive impairment allows them to benefit from accessing cognitive rehabilitation programmes (Vichinsky *et al.*, 2010). Further research would help identify other potential interventional therapies.

Headaches

Headache is a common symptom in patients with SCD and although in most cases not indicative of significant CNS pathology, the possibility of intracranial haemorrhage, cerebral sinus venous thrombosis, CNS infection and ischaemic stroke should be considered. Studies are predominantly paediatric with one study showing that one third of children had headaches and 15% had migraines (Dowling *et al.*, 2014). Neither headaches nor migraines were found to be associated with silent infarcts but have been associated with cerebral vessel stenosis on MRA

(Niebanck *et al.*, 2007) and higher rate of painful crises requiring admission to hospital (Dowling *et al.*, 2014).

There is no evidence base for the management of chronic headaches or migraines in adult patients with SCD and referral to a neurologist may be needed. Headaches do seem to be more frequent than in the general population (DeBaun & Kirkham, 2016). For the diagnosis of migraine, family history is often an important factor with patients experiencing acute severe and often incapacitating headaches. These are typically throbbing in nature and may be associated with photophobia or phonophobia more commonly than with aura. Triggers include stress, red wine, some foodstuffs, menstruation and missing meals. The duration of acute migrainous symptoms may be reduced by early anti-emetics and analgesia. Triptans (serotonin receptor agonists) are often effective and should be offered. Prophylaxis with propranolol or other agents may be required if migraine frequency is greater than four per month.

Recommendations

- Review by neurologist should be considered for patients with chronic headaches and migraines.
- Migraines should be treated with standard migraine treatment

Chapter 7: Cardiorespiratory complications

Acute chest syndrome

"I use to have yearly acute chest syndromes (ACSs) which had subsequently led to pneumonias so I was asked by my consultant to consider hydroxycarbamide which has completely stopped the ACSs and I haven't had any since I started the treatment."

"Being taught how to use my spirometer has been really helpful to aid my breathing."

Introduction

Acute chest syndrome (ACS) is an acute illness characterised by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on chest X-ray. The presence of hypoxia is not included in the definition, but in clinical practice, hypoxia is a useful predictor of severity and outcome (Vichinsky *et al.*, 2000).

ACS can be a severe life-threatening condition and early recognition of progression to acute respiratory failure is vital. Patients with SCD can present with ACS, or it may develop some time after onset of severe pain. Vigilance for this complication should be maintained for the duration of the hospital admission. ACS is the third leading cause of death in adult patients with SCD in and may result in longer term morbidity such as chronic lung disease and pulmonary vascular disease.

Standards

- All hospitals should have a treatment pathway for ACS.
- Antibiotics, with cover for both *Streptococcus pneumoniae* and atypical organisms, should be prescribed for patients with ACS even if blood cultures and sputum cultures are negative. Anti-viral agents should be used if there is clinical suspicion of influenza A.
- Early simple ('top-up') transfusion should be considered early in the hypoxic patient but exchange transfusion is necessary if there are severe clinical features or evidence of progression despite initial simple transfusion.
- Hydroxycarbamide should be recommended for prevention of recurrent ACS.

Background evidence

The clinical features of ACS, management and outcome have been well described in large case series studies (Vichinsky *et al.*, 2000). The clinical features of ACS are non-specific and vary depending on age. In adults common presenting symptoms are dyspnoea, chest pain and cough. Clinical signs include fever, tachycardia, tachypnoea, hypoxia and pulmonary infiltration as evidenced by reduced air entry, crepitations, pleural rub, bronchial breath sounds and/or pleural effusions. Clinical signs often precede chest X-ray findings, although in some cases the chest examination may be normal.

Chest X-ray changes include segmental, lobar and multilobar consolidation usually of the lower lobes, and/or pleural effusions. The commonest finding on CT is pulmonary consolidation; the finding of small vessel occlusion should be interpreted with caution as this can be part of the pathophysiological process of acute chest syndrome (Mekontso Dessap *et al.*, 2014).

The laboratory findings in ACS are non-specific but may include an acute fall in haemoglobin concentration and platelet count, which are markers of disease severity. In patients with low oxygen saturations SpO_2 ≤94% on air (or >3% below patients baseline), arterial blood gas (ABG) measurements are useful to support clinical decisions such as respiratory support and transfusions and a Pa O2 of below 9kPa implies severe disease that may need transfusion (Howard *et al.*, 2015).

The severity of ACS is variable but there may be marked hypoxia and Type 1 respiratory failure. Respiratory support with invasive and non-invasive ventilation may be required. There have been several observational studies describing the benefit of supportive therapies for ACS such as antibiotics, oxygen and respiratory support, including continuous positive airways pressure (CPAP), bronchodilators and incentive spirometry (Fartoukh *et al.*, 2010; Padman & Henry, 2004). Overall the quality of evidence for these interventions is low (Knight-Madden & Hambleton, 2016; Martí-Carvajal *et al.*, 2015). There are no data indicating benefit of specific antibiotic therapy in ACS but common organisms include *Chlamydophila pneumonia, Mycoplasma pneumonia, Streptococcus pneumonia, Staphylococcus aureus and Haemophilus influenza* and therefore antibiotic choice should reflect this and local resistance profiles (Martí-Carvajal *et al.*, 2015). There is increasing evidence of the benefit of high flow humidified oxygen in the treatment of non-hypercapnic hypoxaemic respiratory failure. Whilst no specific data exist regarding the efficacy of high flow humidified oxygen in patients with SCD and ACS, consideration should be given to its use in an attempt to reduce the need for invasive ventilation and its complications. There is also inadequate evidence to support other interventions such as inhaled nitric oxide or steroids.

A Cochrane review (Dastgiri & Dolatkhah, 2016) found one very small randomised trial of using blood transfusion to prevent ACS. The majority of patients in this multicentre trial were recruited to an observational arm and only ten participants met the inclusion criteria for randomisation of whom four were randomised to the transfusion arm and received a simple transfusion. None of these four participants developed ACS whereas 2/6 participants in

standard care arm developed ACS (Styles *et al.*, 2012). The review concluded this was insufficient evidence to make a reliable conclusion about the role of transfusion.

The benefit of both top-up and exchange transfusions has been described in case series and observational studies (Vichinsky *et al.*, 2000). A pragmatic approach is to consider simple transfusions for selected patients with milder degrees of hypoxia whose haemoglobin concentration is low enough to allow for this, and exchange transfusions for more severe cases of ACS.

Hydroxycarbamide has been shown to reduce the incidence of ACS in patients with recurrent painful vaso-occlusive crises (Charache *et al.*, 1995) and is recommended for patients who have had a single life threatening or recurrent episodes of ACS. Long term transfusion may be considered in those patients for whom hydroxycarbamide is ineffective; the incidence of ACS is reduced in patients receiving long term transfusion for other indications. Pre-operative transfusion reduces the incidence of post-operative ACS and is recommended for patients with sickle cell anaemia and sickle cell/β^0 thalassaemia prior to surgery (Howard *et al.*, 2013).

The following recommendations have been published in national UK guidelines (Howard *et al.*, 2015).

Recommendations

- Essential investigations for the diagnosis and management of ACS are chest X-ray, full blood count, basic biochemistry tests (creatinine and liver function tests) and blood group and screen (or cross match). Blood cultures, sputum for microscopy and culture and sputum and nasopharyngeal aspirate for viral testing including influenza A (and H1N1 subtype) should also be performed if clinically indicated.
- Pulmonary embolism, fluid overload, opiate narcosis and hypoventilation may cause or trigger ACS and should be considered when a diagnosis of ACS is made as these conditions may require additional treatment.
- Patients should be monitored for predictors of severity, which include worsening hypoxia, increasing respiratory rate, decreasing platelet count, decreasing haemoglobin concentration, multilobar involvement on chest X-ray and neurological complications.
- Patients should be treated aggressively irrespective of their sickle genotype.
- Incentive spirometry should be offered to patients with chest or rib pain to prevent ACS and may be of benefit in patients with ACS.
- Bronchodilators should be used if there is a history of asthma or evidence of acute bronchospasm.
- Consider chronic transfusion for prevention of recurrent ACS if hydroxycarbamide therapy is not effective.

Chronic respiratory complications

Chronic respiratory pathology is common among individuals with sickle cell disease. Chronic lung disease in adult patients includes a range of interstitial and pulmonary vascular abnormalities which can lead to impaired pulmonary function including restrictive and obstructive lung defects and impaired gas transfer. Sleep disordered breathing is also common.

Standards

- Assess all patients for respiratory symptoms and with respiratory examination at each annual review.
- Monitor oxygen saturation SpO2 at least annually.
- Patients with respiratory symptoms or chronic hypoxia should be investigated with:
    - Spirometry with transfer factor
    - High resolution computerised tomography (CT) of the lung
- A sleep study should be recommended in all patients with:
    - self reports of disturbed sleep
    - excessive daytime sleepiness (Epworth sleep score >10)
    - oxygen saturations awake <95%
    - a history of snoring, priapism or early morning headaches.
- Patients with suspected chronic lung disease or abnormal sleep studies should be referred to a respiratory physician for review and consideration of therapy.

Background evidence

Chronic lung disease

Mild restrictive lung defects are described in up to 70% of adults with SCD and ventilatory defects are more common than in ethnically-matched controls. Some studies have shown that the degree of reduction in lung function correlates to previous number of ACS episodes (Knight-Madden *et al.*, 2010). Chronic sickle lung disease (CSLD) describes an interstitial abnormality of lung parenchyma characterised by progressively worsening restrictive lung disease, pulmonary hypertension, hypoxaemia, and chest pain (Knight-Madden *et al.*, 2010); and with fibrotic changes on CT scan. It is reported to affect approximately 5% of patients with SCD with an average age of onset of CSLD at 25 to 33 years (Powars *et al.*, 1988). CSLD may develop as a result of repetitive damage to lung parenchyma by recurrent episodes of ACS, although this is not always the case and it may be seen in adults with no history of ACS.

Sleep disordered breathing

Sleep disordered breathing (SDB) is a group of conditions characterised by complete or partial cessation of normal respiration during sleep resulting in nocturnal hypoxia or obstructive sleep apnoea (OSA). Nocturnal hypoxia and intermittent nocturnal desaturation/OSA are both common in SCD (Rogers *et al.*, 2010; Samuels *et al.*, 1992) and have been correlated with morbidity including frequent painful vaso-occlusive crisis (Hargrave *et al.*, 2003), risk of future central nervous system (CNS) event (Hollocks *et al.*, 2011) and priapism (Roizenblatt *et al.*, 2012). Up to 40% of children and adolescents have nocturnal hypoxia, and OSA has been reported in up to 60% of adults with SCD. Nocturnal hypoxia and OSA may co-exist.

Respiratory investigations

Pulmonary function tests (PFTs) objectively assess the function of the respiratory system, and multiple studies have reported on the abnormalities found in SCD patients. The Cooperative Study of Sickle Cell Disease (Klings *et al.*, 2006) reported that 90% of 310 adult patients were found to have abnormal PFTs. The most common abnormality was a mild restrictive defect, in 74% of the patients. Obstructive disease, either alone or mixed with restrictive disease, was relatively uncommon in this study, occurring in only 3% of the patients. Other studies report lower rates of restrictive change within this patient group of 22–36% with mixed restrictive/obstructive change seen in 6–12 % (Sylvester *et al.*, 2006). Fields et al also reported a significant rate of decline in FEV1 in SCD adults over time after the age of 20 years (Field *et al.*, 2008) compared to the general population (Fletcher & Peto, 1977).

The utility of PFTs is not established and there are no randomised controlled studies comparing screening versus non-screening approaches, nor are there randomised trials reported on what management approaches should be undertaken in SCD patients with abnormal results. There is little to be gained from screening asymptomatic patients but if symptomatic they are useful to explain symptoms and to quantify abnormalities.

Imaging studies have also reported that between 40-90% of sickle patients (Aquino *et al.*, 1994; Sylvester *et al.*, 2006) have abnormal results on high resolution CT (HRCT) chest scans. Sylvester et al reported a reticular pattern to be the most prevalent finding, and positively correlated to the presence of linear bands and subpleural curvilinear lines, with the main abnormality being scattered foci of lung fibrosis predominantly in the lung bases.

The diagnosis of nocturnal hypoxia or OSA is made with overnight oximetry or formal polysomnography (sleep study). In the general population, nocturnal hypoxia is diagnosed when the time with SpO2 <90% is >30% of total sleep time. OSA is diagnosed if there are more than ten episodes of significant oxygen desaturation per hour (over 4% from baseline) overnight. This is known as the 4% Overnight Desaturation Index (ODI). However, the cut off for nocturnal hypoxia and OSA have not been validated in SCD, and the figures are extrapolated from other respiratory conditions.

Treatment

A review of the Cochrane database in May 2016 found no randomised studies looking at the role of long-term transfusion in managing chronic sickle lung disease (Estcourt *et al.*, 2016a). One study reported significantly improved oxygen saturations in patients on hydroxycarbamide compared to patients not on this therapy, with significantly higher median SpO2 when awake, asleep and at nadir.

There is little evidence to guide treatment options for SCD patients with nocturnal hypoxia or OSA, although long-term low flow nocturnal oxygen has been reported in small cohorts to be safe, with no detrimental effect on erythropoiesis. Current practice is based on evidence from non-sickle patients. Treatment options offered include continuous overnight oxygen via a concentrator, CPAP or mandibular advancement devices. There are no reported trials looking at these therapies in sickle patients and where chronic sickle lung disease is suspected or diagnosed, involvement of a specialist respiratory physician to guide therapy is recommended.

The Prevention Of Morbidity in Sickle cell disease trial, POMS 2b (Kirkham, 2015), comparing standard treatment with auto-adjusting continuous positive airways pressure (APAP), will address some of these questions.

Recommendation

- Routine pulmonary function tests (PFTs) in asymptomatic adult patients are *not* recommended.

Cardiac complications

Cardiovascular manifestations are associated with premature mortality and are becoming more evident with increasing longevity in adults with SCD. Pulmonary hypertension (PH), left ventricular diastolic dysfunction, dysrhythmias and sudden cardiac death are all recognised complications of SCD.

Standards

- Assess all patients for cardiac symptoms (dyspnoea, dizziness, chest pain, ankle swelling) and perform cardiac examination that includes assessment for signs of right heart strain at each annual review.
- Patients with cardiorespiratory symptoms and signs should be evaluated with electrocardiography (ECG) and echocardiography.

- In patients with sickle cell disease echocardiography should be performed at initial presentation to adult service and at least once every three to five years even in asymptomatic patients (or earlier if patients are symptomatic or hypoxic).
- Echocardiography should be repeated annually in patients with previously elevated tricuspid regurgitant jet velocity (TRV) who have not had right heart catheterisation (RHC).
- Patients should be referred to a pulmonary hypertension specialist centre for consideration of RHC if:
    - TRV >290 cm/sec
    - TRV 250-290 cm/s and symptoms suggestive of pulmonary hypertension.

Background evidence

Pulmonary hypertension

Pulmonary hypertension (PH) is diagnosed by right heart catheterisation showing a mean pulmonary artery pressure (mPAP) at rest of 25 mmHg or greater. This has been reported in 6 to 11% of adults with SCD (Fonseca *et al.*, 2011; Gladwin *et al.*, 2004; Mehari *et al.*, 2012; Parent *et al.*, 2011). The pathogenesis of pulmonary hypertension in SCD appears to be multifactorial (Simonneau et al., 2013). The causes of PH in adults with SCD include left sided heart disease, chronic lung disease, chronic thromboembolic disease and pulmonary vascular disease. One study showed features of precapillary pulmonary hypertension in 40% of patients but postcapillary pulmonary hypertension (defined by pulmonary capillary wedge pressure >15 mm Hg) in the other 60% (Parent *et al.*, 2011). Further, pulmonary pressures can rise acutely during painful vaso-occlusive crises and acute chest syndrome.

Multiple mechanisms are postulated to contribute to the development of PH including chronic intravascular haemolysis leading to reduced nitric oxide scavenging, thrombosis, hypoxaemia, oxidant stress and asplenia. PH in SCD is associated with increased age, poor functional capacity, prior history of cutaneous leg ulceration, anaemia, higher N-terminal pro–brain natriuretic peptide (NT-proBNP) levels, renal insufficiency and markers of haemolysis (Fonseca *et al.*, 2011; Mehari *et al.*, 2012; Parent *et al.*, 2011).

Symptoms of PH may be nonspecific in nature. Patients may experience fatigue; limited exercise tolerance; progressive evidence of dyspnoea on exertion (particularly worsening on walking up an incline or climbing stairs); chest pain, light-headedness; and syncope. Physical examination should include review of signs of right heart strain including right ventricular heave, ankle swelling and raised jugular venous pressure (JVP). PH is associated with increased mortality despite modest elevations of mPAP (Castro *et al.*, 2003; Mehari *et al.*, 2013; Mehari *et al.*, 2012; Parent *et al.*, 2011).

Screening and diagnosis

Doppler echocardiography is a useful non-invasive tool for the initial evaluation of suspected cases of PH and for screening. The prevalence of TRV ≥ 250 cm/s in adults is approximately 30%. This threshold is associated with impaired functional status and increased mortality and helps identify patients at greater risk of PH (Caughey *et al.*, 2015; De Castro *et al.*, 2008; Fonseca *et al.*, 2011; Gladwin *et al.*, 2004; Parent *et al.*, 2011). TRV ≥300 cm/s is present in 11% adults and associated with at least ten fold increased risk of death (Gladwin *et al.*, 2014; Gladwin & Vichinsky 2008).

Raised TRV alone is not a good predictor of PH. In one study, the positive predictive value of TRV of 250 cm/s to detect the presence of PH was 25% although this was increased with a higher TRV threshold of 290 cm/s (Parent et al. 2011). Meta-analysis of pooled data from four studies that performed RHC on the majority of patients with TRV 250 cm/s demonstrated that only 53 out of 173 (31%) had PH confirmed (Niss *et al.*, 2016).

The impact of screening for PH on patient outcomes is not established and a universal strategy on screening for PH has not been adopted. Recommendations vary from screening with echocardiography every one to three years to screening only if there are clinical and laboratory findings associated with increased risk of PH and the USA expert panel was unable to make a specific recommendation for or against screening for PH due to insufficient evidence (Gordeuk *et al.*, 2016; Klings *et al.*, 2014; National Heart Lung and Blood Institute, 2014).

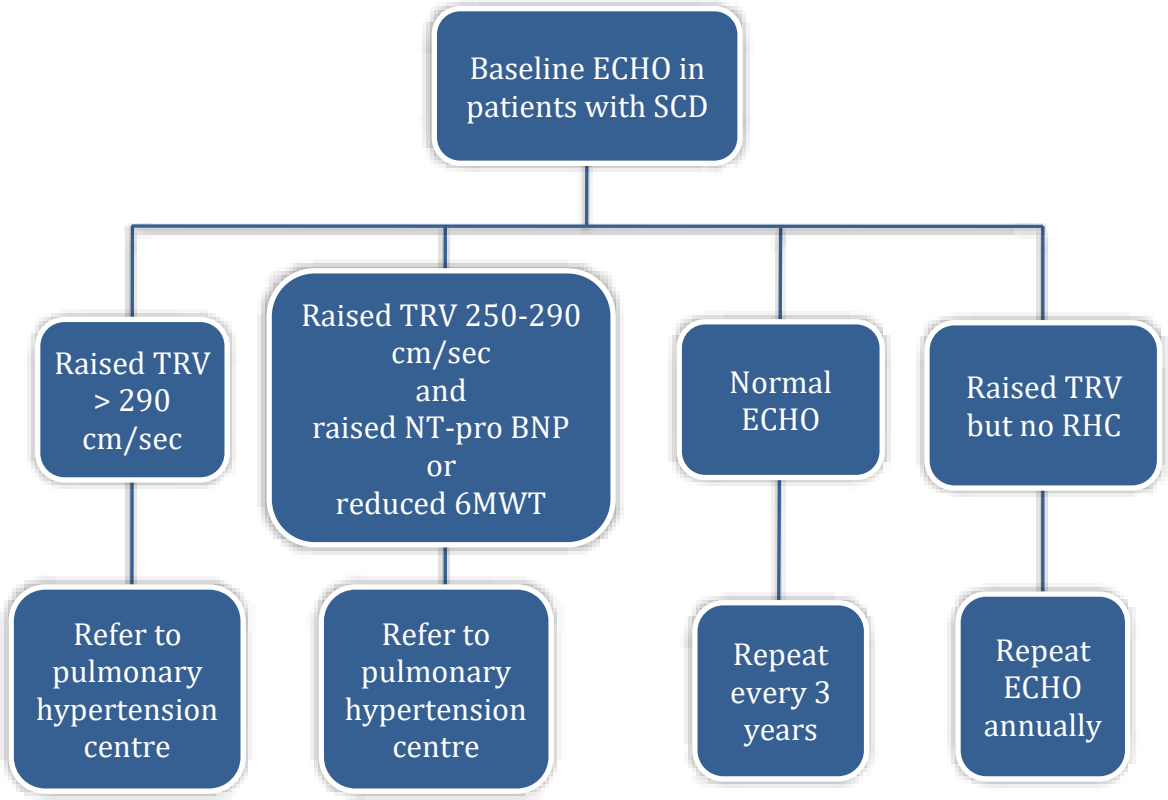
Screening with Doppler echocardiography should ideally be performed when patients are clinically stable in the non-crisis state, preferably at least four weeks after an episode of acute chest syndrome and two weeks after an acute painful episode.

N-terminal pro-brain natriuretic peptide and six minute walk (6MW) test may also be useful for assessment of PH and if used in combination with echocardiography they increase its positive predictive value (Parent et al. 2011). The 6MW may be challenging for patients with SCD and chronic pain or other chronic health problems.

Apart from TRV, as per European Society of Cardiology/European Respiratory Society guidelines, other features should be considered, in particular right ventricular or right atrial dilation, pulmonary acceleration time, inferior vena cava (IVC) dilation and septal flattening. Abnormalities in these measures provide supportive evidence that pulmonary pressures are raised. However, invasive haemodynamic assessment (with right heart catheterisation) is required to diagnose PH and guide treatment decisions.

In the investigation of PH it is also important to consider additional causes such as connective tissue disease, portal hypertension and human immunodeficiency virus (HIV) infection. The evaluation of PH should include autoimmune screen, pulmonary function tests and sleep study. Ventilation perfusion scan is recommended as initial investigation for detecting thromboembolic disease and pulmonary CT angiography may subsequently be required (see Figure 4 overleaf).

Figure 4: Algorithm for pulmonary hypertension screening



ECHO = echocardiography
TRV = tricuspid regurgitant jet velocity
NT pro-BNP = N-terminal pro-brain natriuretic peptide
6MWT = 6 minute walk test
RHC = right heart catheterisation

Management: There have been no completed randomised controlled trials to guide treatment for PH in SCD. Targeted PH therapies such as endothelin receptor antagonists, phosphodiesterase-5 inhibitors and prostacyclin agonists have been tried (Machado et al., 2005; Minniti et al. 2009). Bosentan appeared well tolerated in a placebo controlled trial but the study closed early due to poor recruitment and it was not possible to determine efficacy due to limited sample sizes (Barst *et al.*, 2010). The use of sildenafil in the Walk PHaSST study resulted in increase in hospitalisation for vaso-occlusive events (Gladwin et al., 2014). There have been no clinical trials examining the efficacy of hydroxycarbamide or blood transfusion in PH. The American Thoracic Society committee recommends hydroxycarbamide as first-line disease modifying therapy for this high-risk population with PH (Klings *et al.*, 2014). Management of postcapillary PH involves treatment of fluid overload and systemic hypertension.

Other cardiac abnormalities

Diastolic dysfunction is common in SCD. The prevalence rates reported in multiple studies vary depending on the criteria assessed to define diastolic dysfunction (Niss *et al.*, 2016). In one study diastolic dysfunction was reported in 18% of adults and present in combination with elevated TRV in 11% of patients (Sachdev *et al.*, 2007). The combination of diastolic dysfunction with elevated TRV was associated with additional increased mortality risk. Risk factors for diastolic dysfunction included increasing age, higher systolic and diastolic blood pressure, lower haemoglobin concentration and increasing creatinine (Sachdev et al. 2007). A recent study has shown diffuse myocardial fibrosis is associated with diastolic dysfunction in SCD (Niss *et al.*, 2017).

Echocardiographic abnormalities are common in SCD and heart chamber dilatation is often seen. Left ventricular ejection fraction is normal in the majority of patients. The opinion of a cardiologist should be sought for significant abnormal or unexplained findings.

In addition to the usefulness of TRV in the evaluation of PH, elevated TRV itself is associated with increased mortality risk. Disease modifying therapy has been recommended for patients with elevated TRV due to associated mortality risk (Klings *et al.*, 2014).

Cardiac iron overload

Cardiac iron deposition secondary to multiple transfusions is uncommon in SCD. The pathophysiology of SCD may modulate iron distribution and myocardial iron loading is much less common and non-transferrin bound iron levels are lower in SCD compared to thalassaemia. Cardiac toxicity may manifest with conduction abnormalities, left ventricular dysfunction and cardiac failure. Magnetic resonance imaging with cardiac T2* is used to evaluate cardiac iron status. The frequency of assessment of iron overload and monitoring on chelation treatment should follow specific guidance (see Chapter 22 - Iron chelation).

Recommendations

- Patients with PH should be evaluated for thromboembolic disease, chronic lung disease, hypoxaemia, sleep-disordered breathing, HIV infection and autoimmune disease.
- Evaluation for risk factors of PH should include assessment of renal function, liver function and systemic hypertension.
- Disease modifying therapy with hydroxycarbamide or blood transfusion should be considered in patients with pulmonary hypertension.
- Consideration should be given to the use of vasodilator therapy for select patients with precapillary PH under the supervision of a pulmonary hypertension specialist.

Chapter 8: Renal and urological complications

Introduction

Renal complications (sickle cell nephropathy, SCN) occur in approximately 60% of patients with the more severe forms of SCD (sickle cell anaemia and S/β^0 thalassaemia) at some point during their lives, although these figures are halved in individuals with compound heterozygosity for haemoglobins S and C. In most cases, SCN develops slowly and insidiously over time, starting in the very young with glomerular hyperfiltration and leading to microalbuminuria in late childhood or early adulthood. The majority of patients do not progress further, but a number will gradually develop unselective proteinuria and slowly progressive chronic kidney disease (CKD) leading to decreased renal reserve. These patients are at increased risk of acute kidney injury (AKI) complicating vaso-occlusive crises or other interim illnesses, events that often precipitate a further decline in their baseline renal function following recovery from the acute episode. End stage kidney disease (ESKD) is an uncommon complication, though its incidence is on the rise.

The mechanisms of disease and the impact of treatment options are poorly characterised but an increase in glomerular blood flow, reduction in medullary blood flow from ischemia, papillary necrosis, and use of non-steroidal anti-inflammatory drugs are all recognised contributors to sickle nephropathy.

Not all renal disease in patients with SCD is due to SCN. Urinary tract infections are common, and these patients may have other conditions such as lupus nephritis, or glomerulonephritis secondary to blood-borne viruses and so microscopic haematuria, proteinuria and renal dysfunction should always be investigated with this in mind.

Renal disease

Standards

- Patients with acute renal failure or with evidence of declining renal function should be managed jointly with a renal physician.
- Patients should be monitored at least annually for symptoms or signs of renal disease (urinary tract infection, haematuria), for hypertension and for the presence/progression of albuminuria, proteinuria and declining renal function.
- New-onset haematuria should be investigated, regardless of age, to exclude malignancy.

- Patients with proteinuria (urinary protein to creatinine ratio (uPCR) >50 mg/mmol) should be offered treatment with ACE inhibitors or angiotensin receptor blockers (ARBs) and considered for Hydroxycarbamide therapy.
- Patients with end-stage kidney disease (ESKD) should be considered for renal replacement therapy including transplantation.

Background evidence

Hyposthenuria

Hyposthenuria (the inability to concentrate urine >450 mOsm/kg under water-deprived conditions) is a universal finding in patients with SCD. This is not the same as sickle cell nephropathy. In children, hyposthenuria is usually reversible by blood transfusion, but with age, the condition becomes irreversible and it becomes a permanent feature (Statius Van Eps *et al.*, 1970; Stevens & Levin, 2013). This may manifest as nocturnal enuresis and predisposes patients to dehydration when unwell. All patients with SCD should be encouraged to have a minimum fluid intake of at least 3-4 litres/day. The only randomised controlled trial conducted in this field was the BABY HUG trial which demonstrated that 24 months of treatment with hydroxycarbamide was associated with better urinary concentrating ability in children (Alvarez *et al.*, 2012).

Haematuria

Renal papillary necrosis, caused by vaso-occlusion of the vasa recta, manifests as haematuria in patients with SCD and sickle trait (Alhwiesh, 2014). The clinical manifestations depend on the degree of infarction and range from asymptomatic to frank haematuria. In rare cases, the haematuria is severe with the passage of clots and severe pain (renal colic). Sloughing of the renal papillae can lead to ureteric obstruction and hydronephrosis. Renal ultrasonography (US) can be used to show the renal abnormalities but computed tomography (CT) urography may be needed to confirm the diagnosis. The treatment of haematuria is conservative with maintenance of a high urinary flow with intravenous saline and when necessary, blood transfusion support if blood loss is significant. Urologists should be involved at an early stage to offer advice on bladder irrigation. Radiological or surgical intervention may be required in severe cases with prolonged haemorrhage.

Patients with renal medullary carcinoma may also present with haematuria, sometimes with additional abdominal or back pain and weight loss. This rare and aggressive cancer is virtually restricted to those with the sickle gene, particularly sickle trait, sickle cell/haemoglobin C disease and occasionally sickle cell anaemia. It has usually metastasised at the time of presentation and has a very poor prognosis with median survival of less than one year from diagnosis (Davis *et al.*, 1995).

Haematuria may also be a sign of the more common renal cell carcinomas, renal calculi or non-sickle related glomerular disease. For this reason new onset haematuria should always be investigated (regardless of age) and patients should be referred to a urologist or nephrologist if appropriate (Alvarez *et al.*, 2015; Sharpe & Thein, 2014).

Acute kidney injury (AKI)

AKI can occur in as much as two to ten per cent of patients admitted with SCD (Sklar *et al.*, 1990) and is more frequent in those with acute chest syndrome (Audard *et al.*, 2010). AKI can be precipitated by dehydration, sepsis, drugs (e.g. non-steroidal anti-inflammatory drugs (NSAIDs), intravenous contrast media); it can occur in the context of multi-organ failure or develop on the background of chronic renal failure (either from sickle-related nephropathy or other aetiologies). The management of acute renal injury should follow similar principles to those applied in other patient groups.

Proteinuria

The appearance of albumin in the urine (albumin to creatinine ratio (ACR)) persistently >3.5 mg/mmol (30 mg/g) can be detected in 20% of children with SCD. This prevalence increases with age to >60% in those 46 years of age or older (Sharpe & Thein, 2014). In a subset of patients, microalbuminuria progresses to unselective proteinuria, occasionally becoming nephrotic in range after many years; and is associated with increased mortality (Drawz *et al.*, 2015). Patients with an ACR persistently >30 mg/mmol should be monitored using the unselective protein to creatinine ratio (PCR) as this will more accurately reflect their total protein loss. Full nephrotic syndrome (heavy proteinuria, hypoalbuminaemia and peripheral oedema) is uncommon at approximately 4%, but when it does occur, it is associated with a very poor outcome (Bakir *et al.*, 1987). A recognised trigger for nephrotic syndrome is a recent infection with human parvovirus B19. All patients with nephrotic syndrome should be referred to a nephrologist.

Proteinuria is associated with rapid progression of CKD, and reducing this proteinuria with inhibitors of the renin angiotensin system (either angiotensin-converting enzyme inhibitors [ACEi] or angiotensin receptor blockers [ARBs]) slows this progression in patients with either diabetic or non-diabetic proteinuric renal disease (Chaturvedi & The EUCLID study group, 1997; Jafar *et al.*, 2001). Although a recent systematic review found insufficient evidence to offer recommendations on treatment of proteinuria in SCD, observational data have shown responses in patients with SCN and proteinuria treated with ACEi. (Aoki & Saad, 1995; Falk *et al.*, 1992). Based on the evidence available for other causes of proteinuric renal disease and international guidelines for the management of proteinuric CKD (Stevens & Levin, 2013), ACEi or ARB treatment should be considered when the uPCR is >50 mg/mmol (500 mg/g). These drugs must be introduced cautiously, because many patients have a low/normal blood pressure and so moderate doses can cause postural hypotension. Patients with SCN are prone to hyperkalaemia, which can be exacerbated by ACEi and ARB treatment and patients and other care-givers should

be informed that the medication should be temporarily stopped during episodes of acute kidney injury or other acute illnesses associated with dehydration.

Based on evidence from a number of prospective and retrospective cohort studies and case reports, hydroxycarbamide should also be considered for patients with microalbuminuria or abnormal renal function alongside treatment with an ACE inhibitor or angiotensin-II receptor antagonist, or in those intolerant of this treatment (Sharpe & Thein, 2014; Silva Junior *et al.*, 2014).

Monitoring renal function

Renal function should be monitored at least annually. Creatinine levels are often low in people with sickle cell anaemia and sickle cell/β^0 thalassaemia due to hyperfiltration and increased proximal tubular excretion, resulting in a high estimated glomerular filtration rate (eGFR). Increased rate of change of creatinine may, therefore indicate declining renal function before the value moves out of the normal range. Anyone with an eGFR which is declining by >5 ml/min/year or an absolute value <60 ml/min should be identified and discussed with a nephrologist. Rigorous blood pressure (BP) control is recommended, as higher BP is associated with worse renal function in patients with SCD as in other causes of CKD (Gordeuk *et al.*, 2008). A blood pressure of 140/90 is permissible for dipstick negative patients or those with an ACR <3.5 mg/mmol but a target of 130/80 should be used for those with an ACR >3.5 mg/mmol (Stevens & Levin, 2013). Urinary tract infections should be promptly treated with suitable antibiotics. Long-term use of NSAIDs should be avoided in patients with an eGFR <60 m/min; if unavoidable, regular monitoring of renal function is recommended (Nderitu *et al.*, 2013).

End stage kidney disease

Patients with CKD and symptomatic anaemia may benefit from erythropoietin therapy, with or without hydroxycarbamide, although high doses are often required (Sharpe & Thein, 2014). Renal replacement therapy, including haemodialysis and transplantation, should be explored in patients with end stage kidney disease (ESKD), in conjunction with the local nephrologist (McClellan *et al.*, 2012). Survival of patients with SCD on haemodialysis is reduced compared with other causes of ESKD of non-diabetic origin. Early referral and consideration for transplantation should be considered (Huang *et al.*, 2013) Delayed graft function and increase in frequency of painful crises in individuals post-renal transplantation has been noted and exchange blood transfusion (EBT) +/-hydroxycarbamide should be considered in patients on the transplant waiting list and with functioning grafts (Sharpe & Thein, 2014).

Recommendations

- Patients with SCD who develop acute renal failure should have close monitoring of their renal function. These patients should have adequate hydration and fluid balance; nephrotoxic drugs should be avoided.
- All patients with SCD should be encouraged to have a minimum fluid intake of at least 3 l/day.
- NSAIDs should be avoided in patients with stage 3-5 CKD not on renal replacement therapy (eGFR <60 ml/min).
- Patients with hypertension and ACR <3.5 mg/mmol should be treated with a BP target of <140/90 mmHg. Patients with hypertension and ACR >3.5 g/mmol should be treated with a target of <130/80 mmHg.

Chapter 9: Priapism

"I am in my 40s and have never suffered priapism, however, there are people I know who struggle with the embarrassing moment of going into A&E to treat this and sometimes, they just don't go"

Priapism is defined as a persistent, prolonged and painful penile erection unrelated to sexual stimulation. Stuttering priapism describes short episodes of recurrent or intermittent ischaemic priapism. These are self-limiting and typically occur at night. It can lead to a more sustained or fulminant episode (Adeyoju *et al.*, 2002). This acute/fulminant priapism requires emergency treatment to avoid long-term erectile dysfunction.

Standards

- All men should be educated about priapism and should be asked about both stuttering and fulminant priapism as part of their annual review.
- Patients should have access to a multidisciplinary team including an urologist with a specialist interest in SCD-related priapism.
- Each haemoglobinopathy unit should have an emergency pathway and access to emergency urology services for cases of fulminant priapism.

Background information

Priapism has a lifetime incidence of up to 35-90% in male patients with SCD with the majority of first episodes occurring before the age of 20 years. The initial presentation may be with stuttering priapism or with fulminant priapism. It is a complication that causes significant embarrassment and discomfort. It is often poorly discussed with patients (Olujohungbe & Burnett, 2013). Patient education and discussion of management options is vital as delays in treatment and exposure to repeated episodes risks permanent erectile dysfunction. Several studies have described poor understanding and education about priapism with one case series showing that only 5% of men with sickle cell disease presenting with an acute episode of priapism recalled learning about priapism and the connection with SCD (Adeyoju *et al.*, 2002; Bennett & Mulhall, 2008). Patient education should focus on conservative management of priapism (such as gentle exercise, trying to urinate and keeping warm) and simple steps of trying to prevent episodes such as keeping hydrated at bedtime. It is also important that patients know when to seek emergency treatment if prolonged priapism develops.

Opinion suggests that these patients should be managed in conjunction with an urologist who has a specialist interest in SCD- related priapism (Kato, 2012).

Priapism is categorised as either ischaemic (low flow) or arterial (high flow) in origin. Priapism in SCD is of the low-flow ischaemic type and presents with rigid painful corpora but the glans penis is soft. The low O_2 tension caused by stasis of blood within the corporeal tissues predisposes red blood cells to sickle, leading to obstruction of penile vessels ((Olujohungbe *et al.*, 2011). The priapism perpetuates local ischaemia leading to penile fibrosis and erectile dysfunction (Levey *et al.*, 2012).

Acute priapism

Patients with a painful, rigid, priapic episode of more than one hour should be encouraged to attend hospital where initial management should include adequate treatment of their crisis with pain relief, hydration, adequate oxygenation and an alpha adrenergic agent (usually etilefrine) if not already taken at home. Patients should be encouraged to urinate and should only be catheterised if they have a full bladder and are unable to void.

History taking during an initial assessment should include the duration of the episode, the presence of pain, previous episodes of priapism and their treatment (both stuttering and fulminant), any trauma, medications including analgesic and recreational drugs, and other complications and current treatments of SCD. An understanding of the patients' baseline normal erectile function should also be sought and recorded.

Patients should be referred for urgent urological review. The longer the ischaemic priapism has persisted, the greater the need for surgical intervention. Recent British Association of Urological Surgeons (BAUS) genital emergencies guidelines have separated ischaemic priapism into 3 categories by time since onset:

- <48 hours
- 48-72 hours
- >72 hours

The recommended treatment for priapism that does not settle with conservative treatment presenting at <48 hours is penile aspiration of the stagnant ischaemic blood to decompress the corpora cavernosum. This is best performed with a 19 gauge needle through the glans or laterally from the penile shaft. It can be performed under local anaesthetic in the Emergency Department after a penile block. Blood aspirated from the corpora is dark with a low pO_2, pH and glucose. The diagnosis of a low flow ischaemic priapism can be confirmed by sending of a sample of the aspirated blood for blood gas analysis. Aspiration is combined with injection of an alpha adrenergic agents directly into the corpus cavernosa. This is recommended to assist with maintaining detumescence. Phenylephrine can be given intracavernosally in 200 µg aliquots up to a maximum of 1000µg and this can achieve a higher rate of detumescence but must be done with continuous blood pressure and pulse monitoring in a controlled setting (Broderick, 2012; Mantadakis *et al.*, 2000; Montague *et al.*, 2003). If this fails surgical intervention should be considered with a distal shunt procedure (Montague *et al.*, 2003). The simplest of distal shunts involves placing a wide bore cannula through the glans and into the corpora (Winter shunt).

If these measures have been ineffective, or if the patients presents at 48-72hrs, a more definitive distal shunt procedure by a specialist urologist may be required (T-shunt). While this may achieve successful detumescence, the impact of larger distal shunts on erectile function is more significant. Reported rates of successful detumescence with presentation times >48hrs is only 30%, with severe erectile dysfunction in up to 100% (Zacharakis *et al.*, 2014).

For those presenting at >72hrs, the BAUS emergencies guidelines recommend referral of the patient to a specialist unit to consider a primary penile implant. Placement of a malleable prosthesis is effective at treating both the low flow priapism and the subsequent erectile dysfunction that will inevitably occur in cases, which present so late. An early insertion in the acute setting is technically easier to do, with lower rates of complication and allows maximal preservation of the penile length. However it can be difficult for patients to accept the insertion of a permanent device at the time of an acute presentation, and careful discussion and counselling is required.

There is no randomised trial evidence for either simple or exchange transfusion in acute priapism and variable responses are described in the literature. Patients who require shunt procedures under general anaesthesia may require simple transfusion prior to anaesthesia if they have haemoglobin concentration (Hb) below 90 g/l (see Chapter 19 - Surgery). If shunt procedures are not effective in relieving the priapism, exchange transfusion could be considered prior to the definitive shunt procedure, which is major surgery. There are anecdotal reports of high rates of neurological complications in patients with priapism receiving exchange transfusion, but these were associated with high post-transfusion Hb, which may in turn be associated with increased viscosity.

Patients with recurrent episodes of acute priapism will usually employ self-management techniques at home including exercise, hydration and urination and they will usually be prescribed an alpha adrenergic agent.

Stuttering priapism

The aim of treatment of stuttering priapism is to prevent further episodes and reduce long-term sequelae but a paucity of large-scale studies make clear recommendations difficult. The involvement of an urologist with an interest in priapism and SCD is important and Doppler ultrasound may have some role in diagnosis and therapeutic monitoring to identify reduction of changing smooth muscle tone (Patel *et al.*, 2015).

In the UK alpha-adrenergic agonists and anti-androgens are most commonly used with oral alpha-adrenergic agonists (e.g. etilefrine) having efficacy of up to 72% (Okpala *et al.*, 2002). These should be considered as first line therapy. Patients often take their treatment at bedtime due to the prevalence of episodes of stuttering priapism occurring overnight. In the UK long acting etilefrine is not currently available and short acting preparations are used. Starting dose

is usually 5 mg at bedtime, increasing up to a maximum of 25 mg (or 10 mg repeated after 4 hours) if required, although there is little clear guidance. Given the short acting nature of etilefrine, combined with the more frequent occurrence of stuttering priapism in the second half of the night, patients on short acting drugs often benefit from setting an alarm to take a second dose half way through the night. There is a risk of palpitations and hypertension at the higher doses. Ephedrine at 15-30mg has also been used and appears to be effective.

Hormonal treatments (anti-androgens, gonadotropin-releasing hormone agonists or antagonists and oestrogens) have been used to reduce testosterone levels, inhibiting the action of androgens on erections (Salonia *et al.*, 2014). In adults cyproterone is usually favoured as the anti-androgen if alpha-adrenergic agents are not effective. It should be added to current therapy rather than replacing it, unless the alpha adrenergic agonist is not tolerated. Patients should have potential side effects discussed with them, including hot flushes, gynaecomastia, impaired erectile function, and reduced libido. There are also concerns about fertility as it can affect spermatogenesis. Hormonal treatments should be avoided if possible in teenage children or others who have not achieved puberty or sexual maturity.

SCD is reported as a contra-indication to the use of cyproterone due to the potential increased thromboembolic risk. Therefore this treatment should be discussed thoroughly with the patient and the discussion documented. Further, the dose should be kept low (150 mg or less in divided doses per day) and reduced gradually to 50 mg a day.

Studies have looked at the role of oral phosphodiesterase type 5 (PDE5) inhibitors proposing that PDE5 inhibitors would increase the PDE5 levels, increase NO availability, regulate cGMP expression and prevent priapism (Burnett *et al.*, 2014; Burnett *et al.*, 2006a, 2006b). A randomised trial of sildenafil versus placebo showed no difference in the treatment arms but some benefit of sildenafil in the open label phase of the study (Burnett *et al.*, 2014). The side effects of long term sildenafil in sickle cell disease also need to be considered (Lane & Deveras, 2011).

Many other medications (digoxin, ketoconazole, baclofen, gabapentin and 5-alpha reductase inhibitors such as finasteride) have been described in historical small studies with some benefits but all need further clinical trials to establish their role in the prevention of stuttering priapism (Abern & Levine, 2009; Levey *et al.*, 2012).

None of these agents are licensed for use in SCD related priapism and patients should be counselled accordingly.

There is limited evidence for the efficacy of SCD disease modifying therapy. One small trial of five patients (Saad *et al.*, 2004) reported improvement in stuttering priapism in four patients whilst receiving treatment with hydroxycarbamide but further reviews of the management of priapism in SCD do not recommend routine use of hydroxycarbamide (Olujohungbe & Burnett, 2013). Transfused patients in the silent cerebral infarct transfusion (SIT) trial showed

significantly decreased rates of priapism (0.8 vs 6.7 adverse events per patient year, p=0.02) but observational data of the effect of long term transfusion on the rates of priapism have shown opposing results, with some studies showing a benefit of transfusion and others showing no benefit (Ballas & Lyon, 2016; Driss *et al.*, 2011). Further research into pharmacological therapies for priapism and into the benefit of SCD-directed therapies are required. The long-term benefit of these treatment options on sexual function should also be recorded.

Recommendations

- Treatment options including alpha agonists and anti-androgens should be considered in patients with stuttering priapism. If these are not successful, other drug therapies or anti-sickling therapies can be considered.
- Blood transfusion should be considered when acute priapism does not settle with conservative measures and prior to surgery.

Chapter 10: Fever and sepsis

Introduction

People with sickle cell disease (SCD) remain at risk of severe infections, in particular due to encapsulated organisms such as *Streptococcus pneumonia* associated with hypo-and asplenism (see Chapter 3 - Primary care). Defects in complement activation also contribute to risk of morbidity and mortality from sepsis, along with localised ischaemia of bowel or bone, allowing entry of enteric organisms into the circulation and predisposing an individual to both Gram-negative bacteraemia and septic shock/disseminated intravascular coagulation (DIC) and osteomyelitis. Indwelling vascular access devices, where present, further increase this risk. Sepsis remains an important cause of mortality in adults with SCD (National Confidential Enquiry into Patient Outcome and Death (NCEPOD), 2008; Yanni *et al.*, 2009), related not only to the increased risk of severe sepsis, but also due to the precipitation of sickling crises by fever and infection (Booth *et al.*, 2010). While risk is highest in sickle cell anaemia, other genotypes are also at significant risk of serious infection (Leikin *et al.*, 1989).

Standards

- Patients with sickle cell disease presenting with a fever ≥ 38.0°C require a full clinical review, including cultures of blood, urine and any other potential sites of infection.
- Patients with sickle cell disease presenting with a fever ≥ 38.0°C should have broad-spectrum antibiotics administered, to include coverage for pneumococcus as well as Gram-negative organisms including salmonella.
- Where chest signs or symptoms are present, a chest X-ray should be requested and acute chest syndrome considered (see Chapter 7 - Cardiorespiratory complications).

Background evidence

There is a paucity of good-quality, prospectively-collected evidence to guide recommendations. Data are predominantly paediatric and observational.

Rates of serious bacterial sepsis have reduced significantly with the introduction of universal penicillin prophylaxis from infancy and improved immunisation schedules for pneumococcus. Sepsis, however, still remains an important cause of mortality in both children and adults with sickle cell disease in the UK (National Confidential Enquiry into Patient Outcome and Death (NCEPOD), 2008). Reported rates of bacteraemia in febrile children with sickle cell disease are low (around 1 per cent) but *Streptococcus pneumoniae* (particularly non-vaccine serotypes) continues to cause serious infection. Penicillin resistant strains are also resistant to other

augmented penicillins e.g. co-amoxiclav, piperacillin/tazobactam, so if resistance is suspected alternative antibiotics should be given. Other organisms such as salmonella also contribute significantly to the burden of cases (Bansil *et al.*, 2013; Baskin *et al.*, 2013; McCavit *et al.*, 2011; Narang *et al.*, 2012; Rogovik *et al.*, 2010; Savlov *et al.*, 2014; Wright *et al.*, 1997).

For all patients with SCD presenting with fever above 38.0°C comprehensive review needs to include:

- Full examination
- Cultures of blood, urine and any other potential site of infection, such as throat;
- Full blood count with differential and reticulocyte count
- Chest X-ray in all patients with respiratory symptoms or signs

Broad-spectrum parenteral antibiotics should be administered to include coverage for pneumococcus as well as Gram-negative organisms including salmonella. Antibiotic choice should be consistent with local microbiological advice. If the focus of infection is evident then antibiotic therapy can be directed appropriately. Cover for atypical organisms should be included in those with suspected acute chest syndrome (Booth *et al.*, 2010). A diagnosis of malaria should be considered if patients have a history of travel to an endemic region. Where blood cultures are positive for *Staphylococcus aureus* or salmonella, even in the absence of focal signs, a diagnosis of osteomyelitis (see Chapter 11 - Orthopaedic complications) should be considered (Norris *et al.*, 2003; Sadat-Ali, 1998).

Where a patient's clinical condition suggests severe sepsis, or where deterioration is suspected, early consideration should be given to the need for intensive care unit support. In overwhelming sepsis with multi-organ failure, exchange transfusion should be considered.

Outpatient management of febrile children with SCD has been shown to be safe and effective in prospective US studies (Wilimas *et al.*, 1993; Williams *et al.*, 1996) and these findings are confirmed by a large retrospective review (Baskin *et al.*, 2013). Although there are no comparable studies in adults, these data support the safety of managing certain patients with fever alone, without additional risk factors, as outpatients, after initial investigations and after cultures have been taken. Patients and their family/carers must understand the importance of the need to return in the case of any deterioration. If blood cultures become positive the patient should be admitted for ongoing care including parenteral antibiotic therapy.

Patients should however be admitted for ongoing care and observation if they: have symptoms or signs of acute chest syndrome (including hypoxia), tachycardia, dehydration, vomiting; require supportive care such as intravenous (IV) fluid or oxygen; are 'ill-looking'; have a history of sepsis or a central venous access device in situ; have abnormal investigations (decreased haemoglobin concentration or platelet count); do not have a reliable contact telephone number and a reliable care-giver who can observe at home; or have a history of poor compliance.

In an effort to contribute further to the available evidence, data on patient outcomes after presentation with fever or infection should be collected prospectively and any episode of proven bacterial sepsis should be recorded as an adverse event on the National Haemoglobinopathy Registry.

Recommendations

- Patients presenting with fever alone who are otherwise well, and in whom no other risk factors are present may be considered for outpatient management with appropriate antibiotics after appropriate review and blood cultures have been taken.
- Comprehensive patient education regarding the risks, and the early signs, of infection, is an important part of ongoing care of patients with sickle cell disease.
- While the recommendations above relate to patients presenting with fever ≥38.0°C, the same measures should be considered in any patient who is unwell or who presents with signs or symptoms suggestive of infection.

Chapter 11: Orthopaedic complications

"I suffered AVN and had a hip replacement after waiting for 4 years on a waiting list. It was a terrible 4 years of agony. I would suggest that people do not make assumptions about any unusual pain you may be having. Get it diagnosed and treated ASAP"

Osteomyelitis

Introduction

Osteomyelitis occurs at all ages in patients with sickle cell disease (SCD) and the prevalence is higher in patients with the more severe haplotypes (Almeida & Roberts, 2005). Osteomyelitis can be difficult to distinguish from vaso-occlusion. Both can present with pain, localised tenderness, warmth, swelling, fever and leucocytosis. The commonest sites are the femur, tibia and humerus. Bone pain is much more likely to be due to vaso-occlusion than osteomyelitis. It is prudent to treat initially for the former and investigate for infection if pain persists or is atypical and fever continues.

Standards

- Blood cultures should be taken in patients with ongoing bone pain and/or fever where a clinical diagnosis of osteomyelitis is suspected. In selected cases radiological examination or bone biopsy/aspiration should be considered to confirm the diagnosis.
- Treatment of osteomyelitis should be with a prolonged course of an antibiotic appropriate to cover the organism isolated.

Background evidence

Salmonella (especially the serotypes: *Salmonella typhimurium*; *Salmonella enteritidis*; *Salmonella choleraesuis*; and *Salmonella paratyphi B*), *Staphylococcus aureus* and other gram-negative enteric bacilli are the most common causes of osteomyelitis (Atkins *et al.*, 1997; Burnett *et al.*, 1998), perhaps due to bowel micro-infarcts facilitating the egress of these organisms. Tuberculosis has also been reported to cause osteomyelitis in SCD.

In practice the diagnosis is usually based on clinical findings and positive blood cultures. Positive cultures from bone aspiration or biopsy will confirm the diagnosis of osteomyelitis but bone aspiration should be limited to specific cases bearing in mind the potential risk of introducing infection.

Imaging

Plain X-rays show no specific changes in early osteomyelitis and should be reserved for cases with persistent pain and high clinical suspicion and not be performed routinely in patients with fever and bony pain. Lucent areas are seen much later in the course of infection. Ultrasound changes such as subperiosteal fluid can be seen with vaso-occlusion but fluid depths >4 mm are strongly associated with a diagnosis of osteomyelitis (William *et al.*, 2000). Routine bone scans and radiolabelled leucocyte scans do not reliably distinguish between infection and vaso-occlusion. Magnetic resonance imaging (MRI) scans similarly are not discriminatory showing reactive bone marrow oedema and hyperaemia. MRI is most useful for localising lesions and monitoring the response to treatment.

Treatment

Initial therapy in patients suspected of having osteomyelitis should be broad spectrum to cover salmonella and staphylococcus pending culture results. There are no relevant trials on the efficacy and safety of the antibiotic treatment approaches for patients with SCD suffering from osteomyelitis (Martí-Carvajal & Agreda-Pérez, 2016). Once an organism has been isolated, antibiotic therapy can be tailored; a prolonged course is recommended, often up to six weeks, although duration will depend on local microbiological advice and response. Drainage is recommended for fluid accumulation that does not respond to antibiotic therapy.

Avascular necrosis

Avascular necrosis (AVN) – also referred to as osteonecrosis – results from bone death due to loss of blood supply. It can result in chronic pain as well as impairment and disability. It is most common in the head of the femur but can occur in other bones. The treatment for AVN is dependent on the grade of joint involvement.

Standards

- AVN in SCD patients should be managed using a multidisciplinary team (MDT) approach involving the haematologist and a specialist orthopaedic surgeon.
- AVN should be considered in SCD patients presenting with either sudden onset or progressive joint pain especially in the hip or shoulder joints and initial investigation should begin with plain X-ray, MRI should considered if the plain X-ray is normal.
- Analgesia and physiotherapy should be offered in the early stages of AVN
- Total hip replacement is indicated in patients with persistent, intractable hip pain and disability affecting daily activities who have failed non-operative management.
- Major joint arthroplasty surgery should be carried out in centres experienced in managing patients with SCD.

Background evidence

Presentation and diagnosis

Avascular necrosis may affect up to 50% of patients with sickle cell disease (Martí-Carvajal *et al.*, 2016) and most commonly affects the femoral head (Issa *et al.*, 2013) and the humeral head although it has also been reported to affect multiple other joints including the knees, feet and back. It commonly affects multiple joints. AVN may be asymptomatic in the early stages but the majority of patients present with intermittent, progressive or acute pain. Patients with hip AVN commonly present with groin pain, but may also present with pain in the buttock, knee or with diffuse lower limb pain.

Diagnosis of AVN is primarily based upon imaging findings. Plain radiographs are the most appropriate initial investigation of hip pain, but have low sensitivity for early stage disease. If the plain X-ray is normal, and symptoms are persistent, MRI should be considered as it has the highest sensitivity and specificity for AVN compared to other modalities (Choi *et al.*, 2015).

AVN of the femoral head is a progressive disease leading to eventual collapse of the femoral head and over 80% of hips with early disease, seen only on MRI, will progress to collapse within 8 years (Poignard *et al.*, 2012). The prognosis of AVN is related to the location and size of the osteonecrotic lesion as well as the presence or absence of collapse of the necrotic segment. Whilst it can be helpful to stage hip AVN to quantify the disease and help guide treatment there is no universally agreed classification system for hip AVN and the most widely used are shown in Figure 5 (Choi *et al.*, 2015).

[Figure 5 shown overleaf]

Figure 5: Ficat and Steinberg classification systems (Choi et al., 2015)

Stage	Radiographic signs	
	Ficat + Arlet	**Steinberg**
0	Inconspicuous/normal findings	Radiographs and MRI scan are normal
I	Inconspicuous findings or minor changes (slight patchy osteoporosis, blurring of trabecular pattern, subtle loss of clarity)	Radiographs are nondiagnostic; MRI is abnormal
IIA	Diffuse/ focal radiological changes (osteoporosis, sclerosis, cysts)	
IIB	Subchondral fracture ("crescent sign") segmental flattening of femoral head ("out-of-round appearance")	Radiographs demonstrate abnormalities consistent with osteonecrosis; head is round
III	Broken contour of femoral head, bone sequestrum, joint space normal	Radiographs reveal crescent sign
IV	Flattened contour of femoral head, decreased joint space, collapse of femoral head, acetabular osteoarthritic changes	Flattening of the femoral head
V		Acetabular involvement and narrowing of joint space
VI		Loss of joint space; advanced arthritic changes

MRI: magnetic resonance imaging

Treatment

The Cochrane systematic review on treatment of AVN in SCD concludes there is inadequate evidence to guide practice (Martí-Carvajal *et al.*, 2016) and notes that AVN is a complex condition and should be managed with an MDT approach involving a specialist orthopaedic surgeon and haematologist.

Treatment is broadly divided into conservative and surgical approaches with non-surgical management largely the preserve of early stage disease.

Conservative or non-surgical management

Management approaches useful in patients with early stage disease include: physiotherapy; pain management approaches, including injection of local anaesthetic into the joint; activity modification; and walking aids. Although helpful, conservative treatment of AVN alone does not provide prolonged symptomatic relief and does not prevent disease progression.

Surgical management

Core decompression

This surgical approach is based on the theory that avascular necrosis is similar to a compartment syndrome of bone. Hence decompression will promote revascularisation and healing. Its use as treatment of AVN of the hip is controversial. Well-controlled prospective trials are lacking and the most recent Cochrane review in 2016, identified only one randomised clinical trial (Neumayr *et al.*, 2006), which reported no additional benefit of core decompression over physiotherapy for symptom improvement. They note that this conclusion is based on one trial with high attrition rates and further trials are needed to evaluate hip core decompression.

Some studies, mostly small case series have reported positively on this therapy option in early stage disease only. (Kamath *et al.*, 2015; Mukisi-Mukaza *et al.*, 2009; Styles & Vichinsky, 1996). It remains in use in clinical practice and may have a role in selected younger patients with early stage disease that produces significant pain.

Results of core decompression for shoulder AVN in sickle patients is similar to that for hip AVN, with some studies reporting good outcomes (LaPorte *et al.*, 1998), although these were retrospective studies with broad aetiology for shoulder AVN not just SCD. Kennon et al reported 100% of SCD patients with stage I/II AVN of the shoulder progress to collapse despite decompression, compared to 50% of chronic steroid induced AVN patients who did not experience disease progression (Kennon *et al.*, 2016).

Joint replacement surgery

Essentially when there is collapse, the prognosis is poor and treatments other than total hip replacement (THR) are unlikely to be effective. In patients who have intractable pain and are medically fit to undergo the procedure it has the potential to dramatically improve function and relieve pain. Hip arthroplasty in sickle patients can be technically difficult due to the narrowing of the medullary canal within the bone, sclerosis and associated deformities. Early studies reported high failure rates with over 59% failures at five years, alongside high associated infection rates. However, more recently reported case series have shown marked improvement in patient outcomes – with reduced infection rates and with a low revision rate (13.5%) at 13 years – when the surgery is undertaken in a centre with experience of managing sickle cell patients and adequate precautions are taken against infection (Clarke *et al.*, 1989; Hernigou *et al.*, 2008).

The three most recently published studies on total hip replacement surgery in sickle cell patients have reported markedly improved results (Gulati *et al.*, 2015; Issa *et al.*, 2013; Jack *et al.*, 2016) and advocate the use of cementless ceramic prosthetic devices over cemented ones and pre-surgical optimisation. They report improved outcomes with low rates of sickle complication rates if preoperative exchange transfusion is used (6% reported by Jack et al) as well as low infection rates of 0-9% (Gulati *et al.*, 2015; Jack *et al.*, 2016).

There are fewer studies reported for shoulder surgery in sickle patients. However good outcomes have been reported with regard to both arthroplasty and resurfacing surgery in sickle patients with AVN, with 81% satisfaction and significant clinical score improvements post operatively (Kennon *et al.*, 2016)

The decision to proceed to joint replacement surgery should be taken in the specialist multidisciplinary setting with involvement of the orthopaedic surgeon, a haematologist, the patient and if appropriate the anaesthetist and pain management team. Pre-surgical management of the patient should focus on optimisation of SCD with preoperative transfusion and medical management of co-morbidities and post-operative management should include infection prevention, thromboprophylaxis and appropriate rehabilitation. Major joint arthroplasty surgery should only be carried out in centres experienced in managing patients with SCD and should not be performed as occasional cases in smaller units.

Recommendations

- The anaesthetic and pain management team should be involved in preoperative management of patients with SCD prior to joint replacement surgery.
- Core decompression can be considered in selected cases of non-collapsed femoral head in the young patient.
- The use of cementless prosthetic devices is preferred for hip replacement surgery in SCD.
- Post-operative infection prophylaxis and thromboprophylaxis are recommended unless contra-indicated.

Chapter 12: Gastroenterological and hepatobiliary complications

Introduction

Abdominal pain is common in sickle cell disease (SCD) and may be due to complications of SCD or to other causes of abdominal pain, as in other patients. The differential diagnosis of abdominal pain includes sequestration syndromes, mesenteric syndrome, constipation, gall stone complications, infective aetiologies (e.g. pyelonephritis, intra-abdominal abscesses and diverticulitis) and dysmenorrhoea. Hepatobiliary complications in SCD are common and have a multifactorial aetiology. They may be caused by the sickling process itself; by hypoxic injury due to vaso-occlusion; or by iron overload secondary to multiple blood transfusions. In addition, patients with SCD may develop coexistent liver disease such as viral hepatitis and autoimmune liver disease. Mild abnormalities in liver function tests are common and may be seen in uncomplicated vaso-occlusive crises, but some patients develop progressive liver disease and end-stage liver disease. Biliary tract complications are common in patients with SCD, especially in those with sickle cell anaemia, primarily due to the development of gallstones.

Depending on the nature of the problem, referral to a specialist centre with expertise in sickle hepatopathy may be appropriate. In progressive liver disease, treatment may include an exchange transfusion programme and liver transplantation can be considered for highly selected patients with end stage liver disease.

Standards

- Liver function (liver enzymes and bilirubin) should be monitored at least annually.
- Symptomatic gallbladder stones should be treated with laparoscopic cholecystectomy because of the shorter hospital stay and fewer immediate surgical complications.
- Exchange transfusion should be considered early in the presentation of patients with intrahepatic cholestasis.
- Simple transfusion to baseline haemoglobin can be considered for patients with acute hepatic sequestration associated with anaemia.
- Liver biopsy should only be considered in cases of genuine diagnostic dilemma and should be done via the trans-jugular route to minimise bleeding risk.

Background evidence

Splenic complications

There is a paucity of data relating to splenic complications in adult patients with SCD; most reports are in paediatric patients due to the higher prevalence of splenic complications in children. Case reports and observational studies in adult patients describe complications such as splenic sequestration, hypersplenism and splenic infarction. Splenic enlargement in SCD in adulthood may imply a lesser disease severity (Asnani *et al.*, 2013). Splenic sequestration in adults may develop insidiously often with abdominal pain. Patients with chronic splenomegaly can develop hypersplenism and may be predisposed to acute splenic sequestration (Subbannan *et al.*, 2009). The largest case series of splenic complications in 124 adults with sickle cell/haemoglobin C compound heterozygosity reported a splenectomy rate of 9.6 per cent for infarction, sequestration, hypersplenism and subcapsular bleeding (Subbannan *et al.*, 2009). The patients who required splenectomy had lower haemoglobin concentration and a more severe clinical course. Splenectomy was well tolerated in most reports. Other therapies described were supportive care and blood transfusions (Koduri & Nathan, 2006).

Mesenteric syndrome

The mesenteric or girdle syndrome is a rare complication of SCD that manifests as acute bowel pseudo-obstruction. Patients present with an ileus, a distended abdomen without localising signs or rebound, and distended bowel loops or fluid levels on X-ray. Preceding pain in back, abdomen or limbs maybe reported. Patients can have a degree of hepatomegaly and there is often associated bi-basal lung consolidation.

There are few case reports to guide optimal treatment. Other surgical pathologies should be excluded. The management is largely conservative (intravenous hydration, analgesia, nasogastric aspiration if vomiting). There is a potential for progression to bowel complications (Qureshi *et al.*, 2006) and acute chest syndrome; exchange transfusion should be considered early in management of these patients.

Monitoring liver function and investigating liver disease

Liver function should be monitored at least annually and testing should include liver enzymes as well as total and conjugated bilirubin. Unconjugated bilirubin is almost always raised in people with sickle cell anaemia and sickle cell/β^0 thalassaemia, due to haemolysis; conjugated bilirubin and ALT give a better indication of liver problems. Mild derangement of liver enzymes is common and is not independently associated with mortality (Gardner *et al.*, 2016).

Further investigation of liver dysfunction should be prompted by clinical signs of liver disease or persistent abnormalities in liver function testing. Drug and alcohol history may be relevant and non-SCD causes of hepatic disease should be excluded: autoimmune studies and viral

hepatitis serology must be performed. Ultrasound is accurate in the assessment of cirrhosis, ascites, portal vein anatomy, and the biliary system. Magnetic resonance cholangiopancreatography (MRCP) is the imaging technique of choice in the diagnosis of cholangiopathy. Iron status can be monitored with ferritin but is best assessed with magnetic resonance imaging (MRI) scanning such as FerriScan® R2. Liver biopsy should be avoided in the acute setting, due to an increased risk of bleeding and liver rupture (Zakaria *et al.*, 2003). In rare cases of diagnostic dilemma after specialist hepatology assessment, if a liver biopsy is conducted, a trans-jugular route minimises bleeding risk. The role of non-invasive markers of liver fibrosis with transient elastography and enhanced liver fibrosis score has yet to be elucidated in this patient group (Drasar *et al.*, 2017).

Jaundice

Most patients with SCD have a baseline degree of hyperbilirubinaemia. Elevations in bilirubin levels can be due to:

- Haemolysis which may be exacerbated in a vaso-occlusive crisis, delayed transfusion reaction and hyperhaemolysis
- Obstructive causes such as gallstones or biliary sludge
- Intrahepatic cholestasis
- Progressive liver disease

Management depends on the underlying cause.

Gallstones

Gallstones are a common occurrence in SCD present in up to 30% of children and 70% of adults (McCall *et al.*, 1977). They are more common in sickle cell anaemia than in other genotypes. They are usually asymptomatic and are often detected incidentally on routine imaging. Gall stone complications may develop due to infection and inflammation of the gall bladder and biliary duct (acute cholecystitis, gallbladder empyema, ascending cholangitis) or due to obstruction of the biliary ducts and acute pancreatitis. Despite the high prevalence of gallstones, symptomatic biliary tract disease occurs in around 20% of patients with SCD (Amoako *et al.*, 2013) and symptoms include jaundice and acute abdominal pain. The management of acute cholecystitis, ascending cholangitis and gall bladder empyema is no different from that in the general population (National Institute for Health and Care Excellence, 2014a). Antibiotics should be instituted early in view of the risks of infection and should be broad spectrum including cover for Salmonella species and anaerobic organisms.

Asymptomatic gallstones do not require treatment but patients should be informed of possible complications.

Elective cholecystectomy is appropriate after acute complications such as cholecystitis or pancreatitis settle. 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, following preoperative transfusion, as this is associated with fewer postoperative complications and a shorter stay in hospital (Al-Mulhim & Al-Mulhim, 2009; Howard *et al.*, 2013).

Hepatic sequestration

Acute hepatic sequestration refers to liver enlargement caused by intrahepatic trapping of red cells accompanied by acute anaemia. Patients can present with right hypochondrial pain accompanied by an enlarging, tense liver (compared to baseline) due to stretching of the liver capsule. The laboratory features are acute anaemia, reticulocytosis, a mild to moderate hyperbilirubinaemia and normal transaminases levels. Circulatory collapse is less frequent and sudden than with splenic sequestration. The management is supportive. Transfusion may be indicated for symptomatic anaemia. Episodes may be recurrent. There are small numbers of case reports and no published studies on hepatic sequestration.

Acute intrahepatic cholestasis

Intrahepatic cholestasis is an uncommon but severe form of acute sickle hepatopathy. The clinical picture consists of severe right upper quadrant pain, acute hepatomegaly, coagulopathy, extreme hyperbilirubinaemia (mainly conjugated) but moderately elevated liver enzymes. Some patients progress to acute hepatic failure. The pathophysiology is due to intrasinusoidal sickling leading to vascular stasis causing hypoxic injury and swelling of hepatocytes which leads to intracanalicular cholestasis. Assessment should include exclusion of other causes of liver dysfunction and imaging of the biliary tract by ultrasound and/or MRCP to look for other causes of cholestasis. Liver biopsy is relatively contraindicated due to the risk of bleeding and other complications. Supportive management should include hydration, adequate pain relief and treatment of co-existent infection.

There are no randomised trials to assess interventions for patients with intrahepatic cholestasis but there is a suggestion that early exchange transfusion can improve outcomes and reduce mortality (Ahn *et al.*, 2005; Brunetta *et al.*, 2011; Gardner *et al.*, 2014; Sheehy *et al.*, 1980).

Chronic sickle hepatopathy

Chronic sickle hepatopathy includes a spectrum of presentations, with varying degrees of severity: some patients manifest with modest derangements in liver function and hepatomegaly but a subset will develop progressive liver disease and cirrhosis. These patients may progress over months to years towards end stage liver disease. Recurrent episodes of extreme conjugated hyperbilirubinaemia are sometimes a prognostic feature. The natural history of liver disease and predictive factors for those who will develop end stage liver disease

are poorly characterised. A variety of pathologies are described including biliary type cirrhosis and sclerosing cholangitis.

For those with sickle-related liver disease, referral to a specialist centre with expertise in sickle hepatopathy is appropriate. Hepatic dysfunction is not an indication for starting hydroxycarbamide therapy.

In patients with chronically progressive liver disease, there are case reports supporting the use of an exchange red cell transfusion programme (Altintaş *et al.*, 2003; Blinder *et al.*, 2013; Gardner *et al.*, 2014; O'Callaghan *et al.*, 1995).

Cholestasis in the non-SCD setting has been treated successfully with the bile salt ursodeoxycholic acid for over 20 years (Cotting *et al.*, 1990) but its efficacy has not been assessed in the context of SCD. However, it seems a reasonable inference to use ursodeoxycholic acid in SCD patients with chronic cholestasis.

Viral hepatitis

Hepatitis B and C infection may arise due to transfusion therapy, although the incidence is low. The course of acute hepatitis is similar to the general population. The indications for treatment of chronic viral hepatitis should be similar to other patient groups. Viral hepatitis should be managed by hepatologists. The majority of patients are now treated with highly effective and well tolerated anti-viral therapy. Careful monitoring of the haemoglobin concentration is recommended when ribavirin is used, as it causes haemolytic anaemia.

It is also possible to transmit Hepatitis E through transfusion or through contact with contaminated food products. Blood products are now screened for Hepatitis E in the UK, but there is a small persistent risk of transmission.

Iron overload

Iron overload can contribute secondary insult to the liver in patients with hepatic dysfunction. In these patients, particular attention must be paid to iron overload monitoring and management. Iron overload should be treated with iron chelation and therapy should be considered appropriate when liver iron concentration exceeds 5-7 mg Fe/g dry weight (DW).

Liver transplantation

There are very limited data on the use of liver transplantation for end stage liver disease due to sickle hepatopathy. Initial transplantation results were poor, but experience is slowly accruing, with at least 22 cases reported in the literature (Gardner *et al.*, 2014). Results are improving as a result of better patient selection and perioperative management of sickle cell disease. The role of transplantation has yet to be fully defined but it can be considered in patients who have no significant end organ damage aside from the liver *which could increase their perioperative risk*.

Recommendations

- Patients with sickle-related liver disease should be managed by a multi-disciplinary team including haematologists and specialist hepatologists.
- Patients with liver dysfunction should be investigated for other causes of liver disease including autoantibody screen, viral hepatitis serology and hepatobiliary imaging.
- The investigation and management of patients with acute complications of gallstones should follow general treatment guidelines for these conditions.
- Patients with progressive liver disease should be considered for exchange transfusion programmes under the supervision of a specialist sickle/liver service.
- Patients with chronic cholestasis may be treated with ursodeoxycholic acid.
- Liver transplantation in SCD should be considered in highly selected patients, and in specialist centres with dual expertise in sickle cell disease and hepatology.

Chapter 13: Ophthalmological complications

"I have sickle cell retinopathy, it would be good to see someone in the same hospital instead of going somewhere else because when that happens there is often communication breakdown and I suffer for it."

"I started to get blurred vision. It was sickle retinopathy. I advise others not to wait until their next consultant appointment before going to an eye specialist or A&E."

Introduction

The most important ophthalmic complication of sickle cell disease (SCD) is sickle retinopathy, which can cause significant visual impairment. Patients with sickle cell/haemoglobin C compound heterozygosity have a higher risk of sickle retinopathy than patients with sickle cell anaemia.

Standards

- All patients with SCD should be informed about the risk of ophthalmic complications and asked about visual symptoms at their annual review.
- All patients with SCD should have baseline retinopathy screening.
- Patients should be educated about acute symptoms (including trauma) and how to access help.
- Patients with visual symptoms should be referred for ophthalmic review.
- Patients with a history of retinopathy should have regular ophthalmic review.
- Laser photocoagulation therapy should be considered for patients with proliferative sickle retinopathy.

Background evidence

Sickle retinopathy is the most common ophthalmic complication of SCD and is classified into non-proliferative and proliferative forms. It is an occlusive vascular condition, with a predilection for the peripheral retinal vasculature, leading to retinal ischaemia and infarction. The pathophysiology involves mechanical obstruction of retinal capillaries by sickled erythrocytes, though direct endothelial damage may also occur (Elagouz *et al.*, 2010).

Non-proliferative sickle retinopathy (NPSR) does not normally lead to visual loss unless the vaso-occlusive process involves the macula, which can be detected on OCT scanning ('foveal splaying') or on angiography (fluorescein or OCT angiography) with evidence of macular ischaemia and loss of the capillary bed. Other NPSR features include salmon patch haemorrhages (pinkish-red superficial retinal haemorrhages), which resolve to leave iridescent

spots (intraretinal deposits of haemosiderin) or black sunbursts (patches of retinal pigment epithelial hyperplasia).

Retinal venous tortuosity is a common finding, caused by peripheral arteriovenous shunting. Retinal arteriolar occlusion may occur, typically involving the peripheral retina if the major branches are involved and can cause acute loss of vision. Other findings in NPSR include dark, dilated capillaries on the optic disc and angioid streaks. These, however, rarely cause visual problems.

The chronic peripheral retinal ischaemia leads to the release of angiogenic factors (such as VEGF) and subsequent development of neovascular fronds at the border of perfused and non-perfused retina. Proliferative sickle retinopathy (PSR) is characterised by the development of peripheral retinal neovascularisation (termed 'sea fans'). PSR is the more severe form of sickle retinopathy due to the risk of visual loss from vitreous haemorrhage and/or retinal detachment (Moriarty *et al.*, 1988).

The incidence and severity of PSR is greater in sickle cell/haemoglobin C disease than in sickle cell anaemia. The peak prevalence is around 20 - 35 years, with PSR developing earlier in sickle cell/haemoglobin C disease than sickle cell anaemia (Elagouz *et al.*, 2010). In one natural history study, PSR had developed in 14% per cent of sickle cell anaemia subjects and 43% of sickle cell/haemoglobin C subjects by their mid-twenties (Downes *et al.*, 2005). Spontaneous regression of PSR occurred in 32% of affected eyes. Visual loss was more common in patients with a history of vitreous haemorrhage or visual loss in the contra-lateral eye.

The ophthalmic complications of SCD are generally asymptomatic in the early stages. PSR usually develops insidiously with no symptoms until vitreous haemorrhage or retinal detachment occurs. This leads to visual loss which can be treated by vitreoretinal surgery with restoration of useful vision in selected cases (Williamson *et al.*, 2008). Surgery can be challenging due to the presence of peripheral vitreoretinal pathology.

PSR, and the subsequent risk of visual loss, therefore remain undetected until visual symptoms occur or an eye examination is performed by an optometrist or ophthalmologist. The question arises whether patients should have regular ophthalmic screening to identify those at risk of visual loss, but screening is only of value if there is an effective intervention that would prevent visual loss.

Laser photocoagulation therapy has been suggested as treatment for PSR, involving ablation of peripheral ischaemic retina leading to regression of retinal neovascularisation (Farber *et al.*, 1991) aiming to prevent visual loss due to vitreous haemorrhage and/or retinal detachment. This trial indicated that laser treatment did prevent the occurrence of vitreous haemorrhage but there was no difference in the incidence of retinal detachment, complete regression of PSR or development of new PSR between eyes treated with laser photocoagulation therapy and those not treated.

Despite limited evidence regarding the benefit of this intervention, a recent systematic review

concluded that laser photocoagulation therapy for eyes with PSR may prevent visual loss and vitreous haemorrhage and should be considered as a therapeutic intervention for patients with PSR (Myint *et al.*, 2015). There is insufficient evidence to suggest that laser photocoagulation therapy will prevent the development of new proliferative lesions. No intervention is required for small, asymptomatic neovascular fronds but some centres would consider treatment for large elevated sea fans, rapid growth of retinal neovascularisation, or vitreous haemorrhage, although outcomes without treatment are unclear.

The role and frequency of regular ophthalmic screening is therefore uncertain (Myint *et al.*, 2015) and there may be a benefit of targeted screening for those patients who are most likely to develop visual loss (sickle cell/haemoglobin C disease and patients with previous episodes of visual loss or vitreous haemorrhage). One pragmatic approach is that all patients should have a baseline review, with repeat screening at two-three years if they have no evidence of retinopathy and remain asymptomatic, although there is limited evidence of benefit from this approach. Patients with evidence of retinopathy should have more frequent review, at least annually but more frequent if severity and extent of changes suggest this is necessary. All patients with SCD should, however, be informed about the risk of ophthalmic complications and asked to report visual symptoms. Patients presenting with acute visual symptoms must be referred on an urgent basis to an ophthalmologist with expertise in the management of sickle retinopathy.

SCD can also affect the anterior segment of the eye. Anterior segment involvement includes conjunctival vascular lesions (corkscrew and comma-shaped vessels), sectoral iris atrophy and pupillary abnormalities. Hyphaema following trauma is a sight-threatening emergency in patients with SCD because sickled erythrocytes can clog the trabecular meshwork leading to elevated intraocular pressure with the risk of optic nerve damage.

Central and peripheral retinal arterial occlusion have been reported with a possible improvement of symptoms with exchange transfusion.

Another potential cause of visual loss in SCD is drug-induced retinopathy due to iron chelating agents (such as desferrioxamine). Patients with SCD requiring iron chelating agents because of repeated blood transfusions should be monitored for visual problems, particularly since early detection of retinal toxicity may prevent long-term visual sequelae (Haimovici *et al.*, 2002). There are no studies to guide the frequency of review.

Recommendations

- Patients with SCD should be treated by ophthalmologists with sub-specialty expertise in retinal disorders and SCD.
- Patients on desferrioxamine or deferasirox should also be monitored for visual problems due to the development of drug-induced retinopathy.
- The role of routine ophthalmic screening in asymptomatic patients is not clear but could be considered in patients with sickle cell/haemoglobin C disease.

Chapter 14: Anaemia

Introduction

Patients with sickle cell disease (SCD) have a variable degree of anaemia due to ongoing intravascular and extravascular haemolysis. In the steady state, individuals with sickle cell anaemia and sickle cell/β^0 thalassaemia will usually have a haemoglobin concentration (Hb) of 60-90 g/l and those with sickle cell/haemoglobin C disease and sickle cell/β^+ thalassaemia will usually have a higher Hb. A patient's baseline Hb should be determined by successive values in the steady state. Traditionally patients with SCD have been thought to tolerate significant anaemia and have not been offered treatment for stable chronic anaemia. Fatigue is increasingly being described as a significant symptom for patients with SCD and may be associated with chronic anaemia, even if this is stable. Furthermore, patients may tolerate their anaemia for many years but with increasing age and co-morbidities (e.g. cardiac or respiratory disease) may develop symptomatic anaemia despite a stable Hb.

A rapid, significant fall in Hb, usually of at least 20 g/l, may result in the individual becoming symptomatic and major reductions may lead to cardiovascular compromise. Acute anaemia in SCD may be due to an increase in haemolysis, e.g. due to a transfusion reaction, infection or glucose-6-phosphate dehydrogenase (G6PD) deficiency, reduction in erythropoiesis, blood loss and sequestration, in the spleen and less commonly in the liver.

Standards

- Any patient presenting acutely unwell should have a full blood count and reticulocyte count performed to assess for acute anaemia.
- A diagnosis of parvovirus infection should be considered in patients with anaemia and reticulocytopenia.
- Clinical examination of a patient presenting with acute anaemia should include an assessment of spleen and liver size.
- Simple ('top-up') transfusion, aiming for the patient's baseline Hb, may be necessary for patients with acute anaemia. The threshold level for transfusion will depend on the clinical state of the patient.
- Patients with progressive anaemia should be evaluated for both sickle-related aetiologies (most importantly renal impairment) and non-sickle related pathologies.

Background evidence

Transient red cell aplasia

Transient red cell aplasia (TRCA) in SCD is most commonly due to human parvovirus B19 infection, which causes an arrest in erythropoietic maturation. This results in anaemia, which can be severe, accompanied by reticulocytopenia. Associated symptoms may include fever, headache, myalgia, arthralgia and respiratory and gastrointestinal symptoms. Other complications include acute chest syndrome, acute splenic sequestration, acute hepatic sequestration, kidney injury, neutropenia, thrombocytopenia and neurological complications (Smith-Whitley *et al.*, 2003).

Parvovirus B19 infection is usually self-limiting, with the cessation of red cell production lasting on average four to eight days. Diagnosis is confirmed by the presence of immunoglobulin (Ig)M 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, particularly for patients who are symptomatic or show signs of imminent or established cardiovascular compromise. Non-immune close contacts of these patients 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, foetal death or congenital anaemia.

Splenic sequestration

Acute splenic sequestration occurs when large numbers of red cells are trapped in the spleen. This results in splenomegaly and profound anaemia. This can develop rapidly, usually within hours. Though more common in children, it is occasionally seen in adults in whom autoinfarction has not occurred, usually in the milder forms of SCD (sickle cell/haemoglobin C disease, sickle cell/β^+ thalassaemia) (Asnani *et al.*, 2013). In contrast to TRCA, the acute anaemia is accompanied by reticulocytosis, circulating nucleated red blood cells (NRBCs) and thrombocytopenia due to trapping of red cells and platelets in the spleen.

The management of acute splenic sequestration is fluid resuscitation followed by cautious red cell transfusion to the patient's baseline Hb. Overzealous transfusion may result in hyperviscosity from too high an Hb as the sequestered red cells gradually return to the circulation. Recurrent episodes of acute splenic sequestration may warrant splenectomy.

Other causes of acute anaemia

A mild fall in haemoglobin may occur in an uncomplicated vaso-occlusive crisis. Acute haemolysis may be due to transfusion reactions, infections and G6PD deficiency. Patients with

SCD may develop anaemia due to any of the causes seen in the general population including iron deficiency which may be due to use of non-steroidal anti-inflammatory drugs. Megaloblastic anaemia due to excessive nitrous oxide use has been described.

Chronic anaemia

Patients with SCD may develop gradually progressive anaemia. This should be fully investigated. Important causes of anaemia to consider are renal impairment, haematinic deficiency, hypersplenism (patients with genotypes other than sickle cell anaemia) and chronic infection or inflammation. Non-sickle aetiologies (primary haematological disorders, bleeding) should also be considered.

A progressive anaemia may be seen with increasing age and older patients with SCD have been demonstrated to have lower Hbs, absolute reticulocyte count and indirect bilirubin levels when compared to their younger peers (McKerrell *et al.*, 2004). Possible explanations for the fall in Hb are reduced haemopoiesis as the platelet count has also been shown to be reduced in older patients. Deteriorating renal function, which is common with increasing age, is also an important cause of progressive anaemia, and a decrease in Hb has been correlated with worsening creatinine clearance in older patients. This may be in part due to decreased erythropoietic drive as serum erythropoietin levels are lower than expected for the degree of anaemia in patients with SCD and decrease further as the renal function deteriorates (Ataga & Orringer, 2000).

For patients with significant fatigue or other symptoms of anaemia, intervention may be appropriate. Hydroxycarbamide has been shown to significantly increase Hb (Charache *et al.*, 1995; Keikhaei *et al.*, 2016; Wong *et al.*, 2014), and reduces transfusion requirements in some instances (see Chapter 20 - Hydroxycarbamide). Erythropoietic stimulating agents (ESAs) may be appropriate in patients with decreased creatinine clearance. Occasionally intermittent simple transfusion may be required to treat symptomatic anaemia, although this carries the attendant risk of iron overload.

Recommendation

- Baseline haemoglobin (Hb) should be included in clinic letters (or annual review) to GPs to enable them to diagnose worsening anaemia.

Chapter 15: Leg ulceration

Introduction

Leg ulceration is a frequent and disabling complication of sickle cell disease (SCD). Once they occur they may persist for months or years and are associated with severe chronic pain; recurrence is frequent. There is little evidence about best management but a multidisciplinary approach is necessary and treatment may include both local wound care and systemic treatments.

Standards

- Annual review should include questioning about leg ulceration and inspection of the lower extremities for active or healed leg ulcers.
- Patients with leg ulceration should be treated by a multidisciplinary team which includes wound care experts.
- Patients with sickle-related leg ulcers should be assessed for venous insufficiency with venous reflux studies.
- Multi-component compression bandaging should be offered, particularly in patients with evidence of venous insufficiency.
- Zinc levels should be measured in patients with leg ulcers and supplements should be offered to those with deficiency.

Background information

The frequency of leg ulceration shows marked variation in different populations with quoted incidences varying from 75% in Jamaica to 25% in United States and close to zero in Saudi Arabia (Alsultan *et al.*, 2012; Koshy *et al.*, 1989; Serjeant, 1974). Leg ulceration is less common below 20 years of age and is more frequent in males and in sickle cell anaemia (Alavi & Kirsner, 2015; Koshy *et al.*, 1989; Minniti *et al.*, 2010). They most commonly occur on the ankles and may occur secondary to trauma or insect bites. They are prolonged in duration, may take several years to heal and are often recurrent. Even after healing they may be associated with local discolouration and scarring.

The pathophysiology of leg ulceration is not fully understood but they are more common in patients with higher levels of haemolysis. In addition, mechanical obstruction, high blood viscosity, venous incompetence, hypercoagulability and thrombosis may also play a role in the development of ulcers (Bartolucci *et al.*, 2012; Connes *et al.*, 2013). These factors place patients at higher risk of developing ischaemia and once tissue damage occurs the cycle repeats leading to further tissue damage with fluid retention and inflammation encouraging ulcer formation and limiting healing.

Treatment

Once diagnosed, treatment of leg ulcers should be multidisciplinary and should include haematologists, dermatologists, vascular/plastic surgeons, and wound care teams. Specialist pain team input may be required as leg ulcers can be extremely painful and psychology support is often helpful.

Topical treatments and wound care

Wound care is an important element of ulcer care (Minniti & Kato, 2016). Effective debridement is important to remove non-viable tissue and to encourage healing. A moist wound surface should be encouraged and whilst randomised controlled trials (RCTs) have not shown a benefit of particular dressings a simple moist wound-healing approach does seem to be as effective as advanced medical and surgical treatments.

Guidelines for the treatment of non-SCD related venous ulceration recommend compression therapy to increase venous leg ulcer healing and to decrease the risk of ulcer recurrence. The use of multi-component compression bandages is also recommended in preference to the use of single component bandaging (O'Donnell *et al.*, 2014); in the absence of sickle-specific advice, these recommendations should be used for treatment of SCD ulcers particularly where venous disease is present.

Infection should be identified and treated early. In patients with deep ulcers or ulcers associated with bony pain or systemic evidence of infection, osteomyelitis should be considered and magnetic resonance imaging (MRI) performed.

The 2014 Cochrane Review reported six randomised controlled trials of topical treatments but reported that only one trial achieved noticeable benefit (Martí-Carvajal *et al.*, 2014). This trial used an arginine-glycine-aspartic acid matrix (RGD peptide matrix) and found a decrease in ulcer surface area, but the Cochrane review noted a high risk of bias in this study and recommended further trials. Case reports and phase 1 studies of topical sodium nitrate, granulocyte-macrophage colony-stimulating factors, a bi-layered epidermis/dermis construct, a collagen matrix, an autologous platelet gel and a synthetic bioengineered heparan sulphate solution have all suggested benefit, but need further systematic study (Altman 2015). Case reports of energy-based modalities (low frequency ultrasound or low level laser therapy) have been published, but again these need confirmatory study.

Systemic treatments

Zinc supplementation is used in patients with chronic wounds who have zinc deficiency. There is only one small study of oral zinc supplementation in SCD ulcers; this was suggestive of benefit but did not provide statistical analysis of results (Serjeant *et al.*, 1970). Despite the lack of evidence it may be appropriate to measure zinc levels in patients with leg ulcers and consider zinc replacement in deficient individuals.

Pentoxifylline improves red cell and white cell deformability, inhibits platelet aggregation and thrombus formation and improves microcirculation flow. It has been used extensively in the treatment of venous leg ulcers and is recommended for long-standing or large venous leg ulcers. There is only a case report of its use in SCD, but it has been suggested that pentoxifylline could be used as an adjunct in SCD patients where there is venous insufficiency (Altman *et al.*, 2016). Other systemic therapies that have been used in the treatment of SCD ulcers include L-carnitine, arginine butyrate and bosentan, but none have conclusive evidence of efficacy.

Hydroxycarbamide is commonly used for treatment of SCD (see Chapter 20 - Hydroxycarbamide), but its role in leg ulcers is not clear. Hydroxycarbamide has been shown to be associated with leg ulceration in patients with myeloproliferative neoplasms, but this association has not been seen in multicentre studies in SCD. There is insufficient evidence to interrupt hydroxycarbamide treatment in patients with SCD and leg ulceration.

There are no RCTs investigating the role of blood transfusion in the treatment of SCD ulcers. Case reports have reported efficacy of simple transfusion, aiming to increase Hb and improve oxygen delivery, and of exchange transfusion which will also decrease haemoglobin S percentage. The lack of evidence and complications associated with blood transfusion means it is difficult to recommend routine transfusion in patients with leg ulcers, or to recommend a particular modality of transfusion. However a trial of transfusion may be appropriate in a patient with intractable leg ulcers, particularly if they are significantly anaemic.

Surgical treatments

Surgical treatments of leg ulceration in SCD include microsurgical free flap transfers and skin grafting but have been associated with high rates of failure and ulcer recurrence. Surgical intervention may be appropriate for some intractable ulcers. However further investigation is needed before a surgical approach can be recommended as part of routine care.

Other treatments

Bed rest is often recommended but is generally impractical. It may work by reducing ankle oedema and venous pressure.

Sickle leg ulcers are usually associated with severe pain and adequate pain relief should be prescribed; this may require the involvement of chronic pain teams. Regional nerve blocks may be of benefit.

Prevention

Patient education is a vital part of ulcer management and advice should include:

- Eating a nutritious and well balanced diet;
- Avoiding injury, especially to your feet, ankles and legs;
- Avoiding dry skin by using local moisturisers;
- Wearing socks and well-fitting shoes;
- Using insect repellents and protection against insect bites;
- Treating minor trauma around the ankles quickly;
- Avoiding blood tests or intravenous line insertion in the lower limbs; and
- Considering wearing compression stockings to reduce oedema.

Recommendations

- Education about the prevention and management of leg ulcers should be offered to all patients with SCD.
- Patients with SCD-related leg ulcers should be offered appropriate analgesia and may require support from a specialist pain team.
- Hydroxycarbamide should not be withheld from patient with leg ulceration.
- A trial of blood transfusion therapy should be considered in patients with intractable leg ulcers.

Chapter 16: Other complications

Acute multisystem organ failure

Multisystem organ failure (MSOF) is a clinical syndrome of severe life threatening acquired physiological dysfunction in at least two organs usually associated with a vaso-occlusive crisis and/or sepsis. The complications that most commonly occur are failure of the lungs, liver and/or kidneys (Hassell *et al.*, 1994; Hiran, 2005).

Standards

- Patients with MSOF should be transferred to the intensive care setting for supportive therapy.
- Patients with MSOF should be transfused early as this can reduce further organ damage and improve survival.

Background evidence

MSOF may occur after several days of hospitalisation and treatment for an unusually severe vaso-occlusive crisis. Some cases result from fat embolism syndrome. In most cases, patients do not have a prior history of chronic organ failure. Clinical deterioration is rapid with the onset of fever, a fall in haemoglobin concentration (Hb) and platelet count, and respiratory distress. Acute respiratory failure is usually associated with development of acute chest syndrome (ACS). Hepatic failure is associated with marked elevations in total and direct bilirubin and transaminases, and deranged coagulation. Acute renal failure is associated with a rapid elevation of serum creatinine, with or without the presence of oliguria and hyperkalaemia. Rapid diagnosis and treatment of MSOF is necessary to prevent death and will involve early transfer to an Intensive Care Unit for consideration of haemofiltration and ventilation and other organ support.

Section C: Treatment and additional management issues

Chapter 17: Out-patient management

"I get a quarterly outpatient appointment with my haematologist and have had this for most of my adult life. We discuss any changes or issues with my sickle"

Introduction

The aims of outpatient management of adults with sickle cell disease (SCD) are to promote health maintenance and to recognise and manage emerging disease complications in a multidisciplinary setting. Patients and their families should be fully informed about the sickle condition, kept up to date about changes to their therapy and be made aware of new and evolving therapy options including clinical trials.

Standards

- All adults with SCD should be offered comprehensive review from a specialist centre at least annually.
- A pro forma should be used for the annual review visit to ensure thorough and consistent care and to facilitate data collection.
- A written summary of outpatient appointments (including the annual review) should be shared with the patient, his or her general practitioner and the local hospital team.

Background information

The specialist service specification for haemoglobinopathies (NHS England, 2013) stated that all patients with sickle cell disease should receive comprehensive assessment by a healthcare professional with a specialist interest in SCD at least annually either in a specialist centre or as part of an outreach clinic by a team from a specialist centre.

The aim of this specialist annual review is to improve equity in patient care and ensure access to specialist investigations, such as magnetic resonance imaging (MRI) for liver and cardiac iron assessment, and to multidisciplinary specialist and supra-specialist teams.

The annual comprehensive review provided by the specialist haemoglobinopathy team (SHT) or its delegate should aim to cover all aspects of care including:

- Education around the condition and lifestyle factors that may affect health
- Discussion or confirmation of the personalised analgesia plan for pain crisis and review of the analgesia plan upon acute presentation to the Accident and Emergency unit
- Review of chronic pain and prescriptions used to treat this

- Discussion of therapeutic options currently available and new information including ongoing trials open to the patient
- Review of adherence to drug therapy including such as ACE inhibitors
- Review of immunisation status and prophylaxis against infection
- Review of disease complications encountered over the previous year and previously
- Assessment of any new or ongoing symptoms
- Referral for specific investigations e.g. MRI hip and specialist clinics (ideally joint clinics where possible) if appropriate (e.g. orthopaedic, respiratory and renal)
- Assessment of emotional and psychosocial well-being with referral onto to psychology teams if required
- Ensuring patient has a named contact within the service
- Discuss/consent for National Haemoglobinopathy Registry (NHR)
- Discussion about contraception, fertility, pregnancy and (where appropriate) genetic information (see Chapter 18 - Reproductive health)
- Documentation of clinical observations including oxygen saturations and clinical examination

It should also include review of appropriate screening investigations (echocardiography, respiratory investigations, ophthalmology review, renal function and proteinuria, liver function).

A suggested pro forma for the annual review is outlined in *Appendix 4: Annual review pro-forma*.

In addition to the annual review, routine or steady state reviews should be provided local to the patient's home. This may be at a local trust, or may be with the SHT if this is the patient's nearest hospital. These reviews will aim to review clinical progress and manage issues arising since the previous review. This visit should include discussion of acute pain episodes and hospital admissions since the previous appointment and discussion of other sickle-related complications and other medical issues. Medications and immunisation history should be reviewed, examination findings (including vital signs) and investigations (including full blood count and renal profile) should be documented. The patient's understanding and adherence to prescribed therapy should be discussed at each visit and referral on to specialist teams or clinics including psychology considered as required. The frequency of these reviews will depend on the severity of the patient's sickle cell phenotype with some patients likely to require review as often as two monthly whilst others may only be seen at the annual review.

For patients managed with hydroxycarbamide, additional attention must be given to the efficacy of the current dose as well as the patient's adherence to the medication. Patients must be made aware of the requirement for contraception and any side effects and concerns should be addressed.

Patients on long term transfusion programmes should, during their comprehensive annual review, have additional attention given to ensuring that they understand the rationale for transfusions and the associated risks. They should also be asked to provide annual consent to continue transfusions. The rationale for long term transfusion should be reviewed in light of any new clinical evidence at least annually and transfusion targets should also be reviewed to ensure they are being met. Patients on regular transfusions must additionally have their iron status monitored and have their hepatitis B serological status checked annually. It may also be helpful to review Hepatitis C and HIV status annually. Patients on chelation therapy should have their current therapy reviewed including adherence and medication efficacy. Investigations for assessment of iron load must be requested at least annually for iron loaded patients or those suspected to be developing iron overload.

A written summary with results of relevant investigations, highlighting any changes and making clear recommendations should be sent to the patient, the general practitioner (GP) and the local hospital team if the patient has one. This summary should include recent blood results (e.g. full blood count and renal profile). A suggested letter pro forma is given in Appendix 5.

Chapter 18: Reproductive health

Contraception

Introduction

The unmet need for contraception in women with sickle cell disease (SCD) remains high (O'Brien *et al.*, 2011; Whaley *et al.*, 2015) due in part to confusion among health care providers about the safety of various options (Haddad *et al.*, 2012; Smith-Whitley, 2014). Evidence based guidelines on the safety of various contraceptive methods in chronic medical conditions, including SCD, were consulted in preparation of this chapter (Faculty of Sexual and Reproductive Healthcare (FSRH), 2016; National Heart Lung and Blood Institute, 2014; National Institute for Health and Care Excellence (NICE), 2005 updated 2014; World Health Organization (WHO), 2015).

Standards

- Each woman, man or couple affected by SCD should be encouraged to have a reproductive life plan.
- All women of childbearing age and all men with SCD should receive contraceptive counselling to prevent unintended pregnancy at least as part of annual review.

Background evidence

A systematic review of nine studies examining the safety of hormonal and intrauterine contraceptive use among women with SCD concluded that, although the evidence was of fair to poor quality, progestogen-only and combined hormonal contraceptive methods did not increase the frequency or severity of sickle cell crises and were not associated with an increased risk of adverse clinical events (Haddad *et al.*, 2012). There was a lack of evidence on the risk of venous thrombo-embolism (VTE) among combined hormonal users with sickle cell disease and on intrauterine contraceptive device (IUD) use among women with SCD. Another systematic review of progestogen-only contraceptive use among women with SCD did not identify any adverse events or clinically or statistically significant adverse changes in haematological or biochemical parameters associated with use of progestogen-only methods (Legardy & Curtis, 2006). Some studies have suggested that progestogen-only contraceptive users experienced a decrease in symptoms and less frequent and severe painful crises compared with non-users and improvement in biochemical & haematological parameters (de Abood *et al.*, 1997; De Ceulaer *et al.*, 1982) but systematic review of the data found insufficient evidence to recommend progestogen-only contraception above other contraceptive options (Haddad *et al.*, 2012).

A Cochrane review on steroid hormones for contraception in women with SCD (Manchikanti Gomez *et al.*, 2007) reported on one randomised controlled trial (RCT) (De Ceulaer *et al.*, 1982) which compared use of three monthly depot medroxyprogesterone acetate (DMPA) versus intramuscular saline placebo in 25 patients in a crossover study design with a six month wash out period. During DMPA use, there was a non-significant trend towards reduced painful sickle episodes (OR 0.23; 95% CI 0.05 to 1.02), however, because of the short crossover period results may be biased.

Contraception choices and effectiveness of contraceptive methods

A wide range of contraceptive methods is available with varying effectiveness, particularly for the methods that require consistent and correct use (Figure 6).

The following table compares the percentage of women experiencing an unintended pregnancy during the first year of contraceptive use when the method is used "typically" (which includes both incorrect and inconsistent use) or "perfectly" (correct and consistent use). Methods considered as long-acting reversible contraception (LARC) are highlighted in Figure 6. Use of LARC methods such as injectables, implants and intrauterine devices are more effective in preventing pregnancies than user-dependant methods such as oral contraceptive pills (NICE guideline, 2005).

[Figure 6 shown overleaf]

Figure 6: Percentage of women experiencing an unintended pregnancy within the first year of use with typical use and perfect use (Faculty of Sexual and Reproductive Healthcare (FSRH), 2016). Modified from (Trussell, 2011).

Method	**Typical use (%)**	**Perfect use (%)**
No method	85	85
Fertility awareness-based methods	24	0.4-5
Female diaphragm	12	6
Male condom	18	2
Combined hormonal contraception (includes combined oral contraception, transdermal patch and vaginal rings)	9	0.3
Progestogen-only pill	9	0.3
Progestogen-only injectable (DMPA)	6	0.2
Copper-bearing intrauterine device	0.8	0.6
Levonorgestrel-releasing intrauterine system	0.2	0.2
Progestogen-only implant	0.05	0.05
Female sterilisation	0.5	0.5
Vasectomy	0.15	0.1

From *UKMEC 2016.* https://www.fsrh.org/ukmec/ (Faculty of Sexual and Reproductive Healthcare (FSRH), 2016). Reproduced under licence from FSRH. Copyright © Faculty of Sexual and Reproductive Healthcare *2006 to 2016.*

Patient information on contraception can be found on the Family Planning Association website (www.fpa.org.uk).

The UK Medical Eligibility Criteria for contraceptive use (UKMEC) (Faculty of Sexual and Reproductive Healthcare (FSRH), 2016) adapted from WHO guidelines (WHOMEC) (World Health Organization (WHO), 2015) offers guidance to providers of contraception for individuals in the UK with certain health conditions or characteristics. The UKMEC has provided guidance on the use of following types of contraceptive methods in women with SCD:

Progestogen-only contraception is classified as UKMEC 1, meaning these agents can be used without restrictions. Progestogen-only contraception includes the following methods:

- Progestogen-only subdermal implant (single-rod implant containing 68 mg etonogestrel licensed for 3 years of use in the UK)
- Progestogen-only injectable: depot medroxyprogesterone acetate (DMPA) (given intramuscularly or subcutaneously at 13 week intervals)
- Progestogen (levonorgestrel)-releasing intrauterine system (LNG-IUS) (licensed for 3 or 5 years of use)
- Progestogen-only pills (POP) (containing norethisterone 350 µg, levonorgestrel 30 µg or desogestrel 75 µg, currently available in the UK). Theoretically, the desogestrel pill may be expected to be more effective than norethisterone or levonorgestrel POP, especially with typical use, because ovulation is suppressed more consistently and it has a longer missed-pill window.

Progestogen-only contraceptives are a good choice in women with SCD due to a lower risk of thromboembolism compared to combined hormonal contraception (CHC) and possible reduction in acute painful events (Smith-Whitley, 2014). Unpredictable vaginal bleeding is a known side-effect which can affect user-acceptability.

Combined hormonal contraceptives are classified as UKMEC 2, meaning that "the advantages of using the method generally outweigh the theoretical or proven risks".

Combined Hormonal Contraception includes the following methods:

- Combined oral contraception
- Combined contraception transdermal patches
- Combined contraception vaginal rings

The recommendations in the UKMEC refer to low-dose combined oral contraception (COC) containing ≤ 35 µg ethinylestradiol combined with progestogen. Recommendations are the same for all COC formulations, irrespective of their progestogen content. Recommendations for COC are also applicable to the combined contraceptive patch and ring.

Combined hormonal contraceptive users have additional benefits of predictable bleeding pattern with reduced menstrual flow and pain.

There is an increased risk of venous thromboembolism (VTE) in users of CHC with an increased relative risk of about 2 compared with non-users, translating to a low absolute risk of about 9-10 events per 10,000 users per year (Reid *et al.*, 2010). Studies have found differences in risk of VTE associated with COC containing different progestogens with evidence suggesting that COC with levonorgestrel, norethisterone and norgestimate are associated with lowest risk (Faculty of Sexual and Reproductive Healthcare (FSRH), 2014). Individuals with SCD have been shown to have a chronically activated coagulation system and have an increase in risk of VTE compared with healthy controls; however, the exact risk is unclear (Haddad *et al.*, 2012). Given the increased risk for VTE among healthy individuals on combined hormonal contraceptives and the potential for increased VTE with SCD, there is a theoretical concern that the interaction will lead to further increased risk for VTE for SCD patients who use CHC (Haddad *et al.*, 2012). The systematic review by Haddad et al. did not identify any studies that specifically examined the risk of arterial and venous thromboembolism in CHC users with SCD which represents a major gap in literature.

When assessing safety of combined hormonal contraception in women with SCD, any co-existing medical conditions which may contra-indicate use of the method must be taken into consideration; For example, history of stroke is a contraindication to combined hormonal contraception (National Heart Lung and Blood Institute, 2014).

The copper intrauterine device (Cu-IUD) is classified as UKMEC 2, meaning that "the advantages of using the method generally outweigh the theoretical or proven risks". Only one small cross-sectional study has been reported examining the use of IUDs among women with SCD. This did not report any serious adverse events but nor did it provide any comparative statistics to a non-IUD group or to a non-sickle cell group. There is, therefore, insufficient evidence to comment on the safety of this method for this population (Howard *et al.*, 1993). However, theoretical concerns about IUD use in this population are few, and there is no current evidence to support limiting IUD use among women with SCD (Haddad *et al.*, 2012).

There is concern about an increased risk of menstrual blood loss with Cu-IUD and an intrauterine system (IUS) which is generally associated with reduced blood loss may be preferable in women with SCD.

Emergency contraception. Advice to women with SCD about emergency contraception (EC) options as a means of preventing unintended pregnancy following any unprotected sexual intercourse (UPSI) should not differ to advice given to the general population. Methods of emergency contraception currently include the Cu-IUD (the most effective form of EC, for use between 0 and 120 hours of UPSI or within 5 days of expected ovulation), and two methods of oral EC – ulipristal acetate 30 mg (licensed for use within 120 hours of UPSI) and levonorgestrel 1.5 mg (licensed for use up to 72 hours after UPSI).

Recommendations

- Progestogen-only contraceptives (pills, injections and implants), progestogen-releasing intrauterine systems and barrier methods have no restrictions for use in women with SCD.
- The advantages of using low-dose combined hormonal contraceptives (pills, patches and rings) and intrauterine devices generally outweigh the theoretical or proven risks in women with SCD.
- Women should be informed that in the general population the risk of venous thromboembolism with use of combined hormonal contraception is approximately doubled compared to non-users, but that the absolute risk remains low. There is lack of evidence on whether this risk increases further due to their sickle cell disease.
- When assessing safety of contraceptive methods in women with SCD, any co-existing medical conditions that may contra-indicate use of the method must be taken into consideration.
- Use of long acting reversible contraceptive methods such as injectables, implants and intrauterine devices are more effective in preventing pregnancies than user-dependant methods such as oral contraceptive pills and barrier methods.
- Due to the significant health risk during pregnancy in women with SCD, women should be advised to consider LARC methods, which are highly reliable and effective. The sole use of barrier methods and user-dependent methods of contraception (e.g. oral contraception) may not be the most appropriate choice for these women given their relatively higher typical use failure rates.
- Due to the potential teratogenic effects of hydroxycarbamide, sexually active couples should use contraception if one person is using hydroxycarbamide. Hydroxycarbamide should be stopped prior to conception.
- Health care professionals should have access to specialist advice about appropriate contraception for people with SCD when required.

Pre-conceptual advice

Introduction

The wish to have children is a realistic expectation for adults with SCD and they should be supported in this. Discussions about conception should, therefore, be part of routine care. Pre-conceptual advice may be given in an *ad hoc* fashion in response to patient enquiry but should also be part of the routine care offered by the general practitioner, community nursing team, hospital specialist and other health care professionals. This discussion will include advice about optimisation of health prior to conception, partner screening, folic acid supplementation, pre-implantation genetic diagnosis (PIGD) and antenatal diagnosis.

Standards

- Adults of reproductive age with SCD should be counselled about their reproductive choices as part of their annual review. This should include discussion of partner screening and medications that may affect conception.
- Adults with SCD who have a partner who is a carrier of a haemoglobin variant that puts them at risk of a child with sickle cell disease should be given information about pre-natal or pre-implantation genetic diagnostic options.

Background evidence

Discussion of conception should be embedded into routine care and (as a minimum) should be part of the annual review from young adulthood onwards. Women who are planning pregnancy should be reviewed to optimise their underlying SCD prior to conception and to ensure the chronic complications of SCD are under control. This includes ensuring she is up to date with immunisations, is offered penicillin (or equivalent) prophylaxis and is taking regular folic acid. Medications that are contraindicated in pregnancy, such as hydroxycarbamide, angiotensin-converting enzyme (ACE) inhibitors and chelation therapy, should also be stopped prior to conception (Byrd *et al.*, 1999; Diav-Citrin *et al.*, 1999). Consideration should also be given to screening for end organ damage including baseline proteinuria, echocardiography screening for pulmonary hypertension and ophthalmological review.

Male patients should be advised to stop hydroxycarbamide for at least three months prior to conception.

All adults with SCD should be encouraged to engage with partner screening before embarking on pregnancy. If the partner of a patient with sickle cell anaemia is found to be a carrier of a relevant β globin variant (e.g. haemoglobin S, haemoglobin C) or β thalassaemia there will be 50% chance of the child having a SCD. It is important that anyone who is at risk of having an affected infant (i.e. partner is a carrier or is affected by haemoglobinopathy) is aware of this and receives appropriate counselling, which will include discussion of the reproductive options: non-intervention, pre-natal diagnosis once pregnancy is achieved or pre-implantation genetic diagnosis. Further information can be accessed at the NHS Sickle Cell and Thalassaemia screening programme website (www.gov.uk/topic/population-screening-programmes/sickle-cell-thalassaemia).

Pre-implantation/prenatal diagnosis should be offered to couples at risk of having a foetus affected by a haemoglobinopathy. Counselling should be given by appropriately trained professionals and pre-natal diagnosis should be offered as early as possible in pregnancy. Current Public Health guidance is that patients are booked within 10 weeks of conception to ensure access to termination of an affected pregnancy if required as soon as practicable, but it is clear that this is often not offered in a timely fashion. PIGD is a technique designed to help couples at risk of having a child with a serious genetic condition. It involves using *in vitro*

fertilisation (IVF) to create embryos in the laboratory from the eggs/sperm of the couple. Each embryo is tested for SCD by an embryo biopsy and one or two unaffected (or trait) embryos are transferred back to the woman. This is a complicated and lengthy technique, requiring numerous hospital appointments and only approximately 1 in 5 couples who start PIGD treatment will have a baby. Couples who request this intervention will need to be referred to one of the few centres that provide this service. Currently the majority of patients (approximately 75%) will receive funding for their treatment from their Primary Care Trust, the others self-fund, but this is subject to change due to commissioning and political priorities. Treatment will currently only be funded by the NHS if the couple do not have a living healthy child.

Pregnancy

"I am currently pregnant and the care I am receiving is excellent."

"I know a specialist hospital that has a haematologist obstetrician which should be encouraged. However, with my current pregnancy, I get a multi-disciplinary team with my haematologist, specialist midwife and obstetrician attend my visit with me".

Introduction

Pregnant women with SCD are at high risk of complications with an increased risk of maternal and foetal perinatal mortality and morbidity (Oteng-Ntim *et al.*, 2015a; Oteng-Ntim *et al.*, 2015b). A Royal College of Obstetricians and Gynaecology (RCOG) green-top guideline is available to guide management (Royal College of Obstetrics and Gynaecology, 2011).

Standards

- Pregnant women with SCD should be managed by a multidisciplinary team of obstetricians, midwives and haematologists with an interest in SCD in a unit that manages high risk pregnancy.
- Units which manage SCD pregnancy should have a clear protocol for patient management.
- Pregnant women with SCD should be prescribed low-dose aspirin 75 mg once daily from presentation to reduce the risk of developing pre-eclampsia, providing there is no contraindication.
- Routine prophylactic transfusion is not recommended during pregnancy for women with SCD but is indicated in certain situations.

Background evidence

SCD is associated with a high incidence of foetal and maternal complications (Oteng-Ntim *et al.*, 2015b) with highest rates found in patients with sickle cell anaemia and in lower income countries. Maternal complications include increased maternal mortality, increased sickle complications (acute pain crisis, acute chest syndrome and infection, particularly urinary tract infection) and increased pregnancy complications (pre-eclampsia, pregnancy-induced hypertension, thromboembolism and caesarean rate). Rates of hospital admission and admission to the high dependency unit during pregnancy are higher with women with SCD than in the general population. Foetal complications include increased rates of miscarriage, still birth and perinatal mortality and an increased risk of premature labour and foetal growth restriction. This morbidity is thought to be secondary to an increased tendency towards vascular stasis, a pro-coagulant state and increased metabolic demand. There are difficulties surrounding trials in pregnancy, particularly those involving an intervention, and therefore evidence in this area is limited and mainly observational. The published data are derived predominantly from women with sickle cell anaemia; whilst such women are more likely to experience complications during pregnancy, these complications can also affect women with sickle cell/haemoglobin C and other sickle genotypes. Consequently these recommendations apply to all genotypes.

All women with SCD (regardless of genotype) should be made aware of the potential morbidity and mortality that are associated with pregnancy, ideally prior to conception (Howard & Oteng-Ntim, 2012; Oteng-Ntim *et al.*, 2015b).

Antenatal period

Women with SCD should be encouraged to let their haematologist know as soon as they are pregnant. This will allow early referral to a multidisciplinary high-risk pregnancy team. Screening for chronic complications and partner screening (if not already on record) should be completed early and medication history should be reviewed. If women have not undergone a preconception review they should be advised to take daily folic acid and the need for prophylactic antibiotics should be reviewed. Drugs that are unsafe in pregnancy (e.g. ACE inhibitors, iron chelators) should be stopped immediately (Royal College of Obstetrics and Gynaecology, 2011). Women receiving hydroxycarbamide should have been specifically counselled not to become pregnant but if a woman does conceive whilst taking it she should be counselled about possible risks, it should be stopped immediately and she should be offered a detailed anomaly scan at 20 weeks gestation (see Chapter 20 - Hydroxycarbamide).

Women should be encouraged to attend antenatal and haematology clinics (or joint obstetric-sickle clinics) regularly. At a minimum, women should be reviewed in clinic monthly to 24 weeks, fortnightly to 34 weeks and weekly thereafter, although some women need more frequent review. Regular monitoring should include blood pressure monitoring and urinalysis. Careful monitoring of foetal growth is recommended due to risks of foetal growth restriction. A viability scan should be offered at 7-9 weeks gestation with a routine first-trimester scan (11-14

weeks) and a detailed anomaly scan at 20 weeks gestation. Growth scans should be performed every 4 weeks from 24 weeks of gestation. These enable early detection of foetal growth restriction and allow appropriate delivery planning (Royal College of Obstetrics and Gynaecology, 2013).

A VTE assessment should be performed at 12/40 weeks gestation and the assessment should be repeated throughout pregnancy as per the Green Top Guidelines for reducing the risk of venous thromboembolism during pregnancy and the puerperium (Royal College of Obstetrics and Gynaecology, 2015). This document rates women with SCD as intermediate risk for thromboprophylaxis and recommends that thromboprophylaxis with low molecular weight heparin (LMWH) is considered from 28 weeks gestation. A number of studies have indicated that women with SCD have an increased risk of pre-eclampsia and pregnancy-induced hypertension (Chakravarty *et al.*, 2008; Oteng-Ntim *et al.*, 2015a; Oteng-Ntim *et al.*, 2015b; Villers *et al.*, 2008) and although there is no specific evidence for the role of aspirin in SCD, it has been shown to decrease the risk of pre-eclampsia in high risk pregnancies and should be offered to all women unless there are contra-indications to its use.

The evidence is conflicting regarding transfusion in pregnancy although a decrease of acute pain crises in women on prophylactic transfusion was shown in a randomised controlled trial (Koshy *et al.*, 1988). A Cochrane review (Okusanya & Oladapo, 2016) found the data available to be biased and of low quality. It concluded that there was no clear evidence of benefit of prophylactic transfusion over selective transfusion (current standard of care). In contrast a recent meta-analysis (Malinowski *et al.*, 2015) demonstrated an association with prophylactic transfusion and reduction in maternal mortality and sickle-specific and neonatal complications, including acute pain crises, pulmonary complications, pyelonephritis, perinatal mortality, neonatal death and pre-term birth. They concluded however that the evidence resulted from a small number of studies - many with methodology limitations - and that a randomised trial is required to fully assess the balance of risks and benefits.

On current evidence prophylactic transfusion is not recommended routinely in pregnant women with SCD. The need for prophylactic transfusion should be discussed prenatally or in the antenatal clinic and should be considered in women with twin pregnancies, women with significant complications during previous or current pregnancy (e.g. acute chest syndrome, multiple admissions with painful episodes) and in women who are established on long-term transfusion programmes (Davis *et al.*, 2017a; Royal College of Obstetrics and Gynaecology, 2011). In the acute setting transfusion may be required for the management of anaemia – consider treatment if the haemoglobin concentration (Hb) is <70 g/l or there is symptomatic anaemia – or for the treatment of acute complications such as acute chest syndrome. In the latter situation the woman should be offered ongoing transfusion therapy for the rest of her pregnancy.

Acute pain is common during pregnancy, occurring in up to 50% of women and therefore centres should have guidelines to aid management. These usually mirror management outside pregnancy but non-steroidal anti-inflammatory agents should be avoided before 12 weeks and

after 28 weeks of gestation. In addition, patients and their carers, as well as medical and nursing staff should be aware of the presentation of complications of sickle cell disease, including acute chest syndrome, acute stroke and acute anaemia. A low threshold for admission should be in place particularly for patients presenting with fever, an acute fall in Hb or lower oxygen saturations. Patients should be aware of where to present for care during their pregnancy including out of hours and arrangements should be made for the multidisciplinary team to be contacted in an emergency. Women with SCD should be advised to receive prophylactic LMWH during antenatal hospital admissions.

Delivery

Timing and mode of delivery should be guided by obstetric indications and if there are no contra-indications women should be encouraged to continue to term, anticipating spontaneous labour and normal vaginal delivery. There appears to be an increase in painful episodes and acute chest syndrome in the intrapartum period in SCD (Oteng-Ntim *et al.*, 2015a), which increases if the labour is prolonged. Women in labour and post-delivery should be managed with input from the specialist haematology team. Sickle cell disease is not a contraindication for a standard vaginal delivery but continuous foetal heart monitoring is recommended due to an increased rate of still birth and other complications. Women with SCD should be offered anaesthetic assessment in the third trimester of pregnancy with regional analgesia being recommended for caesarean section. Routine transfusion is not recommended prior to caesarean section but should be considered if Hb is <70g/l or if the Hb falls more than 20 g/l below baseline.

Post-partum

Pregnant women with SCD should have a clear postnatal care plan to ensure good transition of care to the haematology and community teams. The increased risk of pain crises continues into the postnatal period, as does the increased risk of VTE. Women should be aware of these risks and appropriate post-partum thromboprophylaxis should be given as per 'Green top' Guideline no. 37a (Royal College of Obstetrics and Gynaecology, 2015). This document rates women with SCD as intermediate risk and recommends that they all receive 10 days post-partum thromboprophylaxis with LMWH. In addition, it recommends that any woman who received antenatal LMWH should receive six weeks of post-partum thromboprophylaxis. As most women will receive antenatal thromboprophylaxis from 28 weeks gestation, they will also receive six weeks post-partum treatment. There is no contra-indication to breastfeeding and this should be encouraged. Women who were taking hydroxycarbamide prior to conception should not recommence this until they stop breastfeeding.

Chapter 19: Surgery

Introduction

Many people with sickle cell disease (SCD) undergo surgical procedures. There are perioperative risks associated with SCD, such as acute chest syndrome and acute painful crisis. It is therefore important that these episodes are managed optimally. Recent national guidance on the use of transfusion on SCD should improve practice in this area and the relevant standards are based on that guidance (Davis *et al.*, 2017a).

Standards

- All hospitals should have a protocol in place for preoperative screening for SCD.
- All hospitals should have a protocol in place for the perioperative management of patients with SCD, which will include recommendations for oxygenation, hydration, warmth and surgical and anaesthetic techniques.
- Preoperative transfusion (simple transfusion to Hb 100 g/l if Hb <90 g/l or partial exchange if Hb >90g/l) is recommended for patients with SCA undergoing low and medium risk surgery.
- Exchange transfusion is recommended for all patients with SCD undergoing high risk surgery.
- Preoperative transfusion should be considered for patients with non-SCA genotypes undergoing low and moderate risk surgery taking into account previous history and complexity of surgery.

Background evidence

Because of the risk of perioperative and post-operative complications, patients with SCD should be identified prior to surgery. Koshy et al. found that overall mortality during a 6-year follow up period of SCD patients was 0.3% (Koshy *et al.*, 1995). This compared to an overall mortality rate of 1.1% in a 30-day post-operative period in those patients who had undergone surgery. Post-operative complications increased with age and varied with the type of surgery. The risk was thought to be secondary to acute tissue injury and chronic organ damage from vaso-occlusion.

Preoperative testing

For routine operations SCD testing should be performed with diagnostic tests, such as high performance liquid chromatography (HPLC), isoelectric focussing or mass spectrometry, at the pre-assessment visit in all non-Northern Europeans. In emergencies the majority of cases of

sickle cell anaemia can be identified by a positive sickle solubility test and full blood count showing anaemia. If there is doubt about the diagnosis, and confirmatory testing cannot be performed rapidly, the haematologist must decide whether or not the patient is high risk. Examination of the blood film may be helpful.

For patients with known SCD it is essential to have a full blood count, red cell phenotype and antibody screen checked preoperatively. Phenotyped red cells (full Rh and Kell typed) should be available for all but the most minor surgery.

Perioperative management

There should be collaboration between haematologists, surgeons and anaesthetists to produce an individual preoperative 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 because of the increased risk of complications. Perioperative hydration, oxygenation and warmth should all be managed expectantly. In patients who are 'nil by mouth' for more than 4-6 hours, the use of intravenous fluids should be considered and should be 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.

Oxygen supplementation should be considered from pre-medication until the patient is fully awake and oxygen saturations should be monitored. Intensive post-operative monitoring on a High Dependency Unit should be considered for those patients with a severe disease phenotype or with chronic respiratory disease. Respiratory support with incentive spirometry (Ahmad *et al.*, 2011) or continuous positive airways pressure (CPAP) (Leff *et al.*, 2007) post-operatively is not proven but could be considered. In view of the increased risk of infection in patients with SCD, the use of prophylactic antibiotics should be considered. Patients should receive an assessment of risk for venous thromboembolism and should receive appropriate thromboprophylaxis as per local or national guidance. Adequate analgesia should be provided post-operatively. Patients who require frequent opiate analgesia at home may have a higher than expected post-operative analgesia requirement. It may be helpful to involve the acute pain team preoperatively to develop an analgesia plan.

Local anaesthesia or regional anaesthesia should be encouraged where feasible. The use of tourniquets may be associated with an increased risk of sickling complications and should be avoided.

Role of transfusion

The role of preoperative transfusion in SCD has recently been reviewed by the British Society of Haematology (Davis *et al.*, 2017a) and data are summarised below. Vichinsky et al. randomly assigned patients to one of two transfusion arms: either an aggressive regimen of transfusions to maintain a preoperative Hb of 100 g/l and a haemoglobin S of 30% or less or a conservative

transfusion regimen to maintain the Hb at 100 g/l, regardless of the percentage of haemoglobin S (Vichinsky *et al.*, 1995). The conservative approach was as effective as the aggressive approach in preventing complications and was associated with fewer short-term complications of blood transfusion.

Haberkern et al. looked further at the subjects from the same study who had cholecystectomy and transfusion (Haberkern *et al.*, 1997). These randomised subjects were compared to those who were eligible for study registry but not randomised. The number of patients receiving no transfusion was small but they had a worse outcome (five 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 transfused patients.

Transfusion had a negative impact when studied by Al-Jaouni et al. who randomised sickle cell anaemia patients into two groups: Group I (n=181), received no preoperative transfusion and Group II (n=188) received simple or partial exchange transfusion preoperatively (Al-Jaouni *et al.*, 2006). Within the preoperative transfusion group, 14% developed postoperative complications versus 7% in the non-transfused group (p=0.002). These investigators considered avoidance of preoperative transfusion is a safe practice in properly selected steady state sickle cell patients. Unfortunately the article was very brief and it is difficult to assess the validity of these conclusions.

A significantly more detailed report than that of Al-Jaouni et al. was provided by the Transfusion Alternatives Preoperatively in SCD (TAPS) study investigators, although fewer patients were randomised (Howard *et al.*, 2013). This was an international multi-centre trial where patients with sickle cell anaemia or sickle cell/β^0 thalassaemia scheduled for low-risk or medium-risk elective operations (under general or regional anaesthesia) were randomised to no transfusion or transfusion within 10 days before surgery (Howard *et al.*, 2013). For the transfusion arm if the patient had an Hb of lower than 90 g/l then a top up transfusion was given (target Hb 100 g/l) but a partial exchange transfusion was used if the Hb was greater than this threshold (with an aim to achieve a haemoglobin S <60%). A significant increase in clinically important complications (39% vs 15%) and serious adverse events (30% vs 3%) were seen in the non-transfused arm and this was predominantly due to an increase in acute chest syndrome in the non-transfused arm (27% vs 3%). The study closed early because of the excess of serious adverse events in the non-transfused arm. Subgroup analysis of low risk operations was not possible because of the small numbers. Consequently, the finding of reduced acute chest syndrome applies mainly to medium risk operations. The study acknowledged the use of preoperative transfusion in sickle cell/haemoglobin C disease (which constitutes up to 30% of patients with SCD) requires a similar study.

The Cochrane review concluded there was low quality evidence that preoperative blood transfusion may prevent development of acute chest syndrome and insufficient evidence from randomised trials to determine whether conservative preoperative blood transfusion was as

effective as aggressive preoperative blood transfusion in preventing sickle related or surgery related complications in sickle cell anaemia. The review did not comment on management of people with sickle cell/haemoglobin C disease or sickle cell/β^+ thalassaemia or for those with a high baseline Hb. (Estcourt *et al.*, 2016b).

Sickle cell anaemia and sickle cell/β^0 thalassaemia patients having medium risk surgery under general anaesthesia should have preoperative transfusion. A simple transfusion will usually be appropriate for patients with Hb <90g/l but an exchange transfusion may be indicated for patients with Hb >90g/l or a very severe disease phenotype. The benefits in low risk surgery for sickle cell anaemia and sickle cell/β^0 thalassaemia are less clear, but a simple transfusion should be considered for patients with Hb <90g/l. In high risk surgery (e.g. cardiac or neurosurgery) most clinicians would recommend exchange transfusion in all disease genotypes. In a non-high risk situation transfusion in sickle cell/haemoglobin C disease and other milder phenotypes needs to be considered on a case by case basis, depending on preoperative Hb, type of surgery and disease phenotype.

There is little evidence to support the role of preoperative transfusion in the emergency situation. In a patient with Hb <90 g/l having medium or low risk surgery a simple transfusion should be considered if time allows; if not blood should be cross-matched for perioperative or post-operative transfusion. For patients with Hb >90g/l, type of surgery, urgency of surgery and disease phenotype should be considered. If surgery is urgent it should proceed with exchange transfusion being carried out post-operatively if required.

Recommendations

- The decision for preoperative transfusion and methodology for transfusion in other situations will depend on genotype, phenotype, preoperative Hb and type of surgery.
- Preoperative transfusion prior to emergency surgery will depend on genotype, phenotype, type and urgency of surgery and preoperative Hb.

Chapter 20: Hydroxycarbamide

"I currently attend the Hydroxycarbamide monitoring clinic at the Medical Day Unit at my hospital on a monthly basis. The clinic is run by the senior specialist nurse and the care I receive is efficient. I am listened to and all my needs are addressed. She is an excellent nurse and brings a lot of value to the sickle clinics".

"I have had fears about my levels of fertility and that is why I haven't taken this medication"

Introduction

Over the last 30 years, sustained evidence has accumulated regarding the efficacy, experience and safety of hydroxycarbamide (HC) (also known as hydroxyurea) in SCD in adults. Until recently it has been the only drug licenced by the Food and Drug Administration (FDA) (granted 1998) and the European Medicines Agency (EMA) (granted 2007) for use in SCD. Given as a once daily oral medication, it is effective in reducing the frequency of vaso-occlusive crises (VOC), acute chest syndrome (ACS) and the need for transfusions and hospitalisation in adults with sickle cell anaemia (SCA) (Charache *et al.*, 1995). There is good evidence for its efficacy and safety, with clinical benefit in the majority of patients, potentially modifying the natural history of SCA including the onset or progression of end organ damage.

Unfortunately for a number of reasons, HC is underutilised in patients with SCA who might otherwise benefit from its use. Recent national guidance should improve consistency of use (Qureshi *et al.*, 2017 (in press)). Further studies evaluating the optimal dosing, role in preventing organ damage as well as the benefit in other sickle cell disease (SCD) genotypes are warranted to advance the understanding of its benefits.

Standards

Adapted from (Qureshi et al., 2017 (in press))

- In adults with SCA and sickle cell/β^0 thalassaemia with three or more moderate to severe pain crises in a 12 month period, recommend treatment with HC.
- In adults with SCA and sickle cell/β^0 thalassaemia who have a history of severe and/or recurrent ACS, recommend treatment with HC.
- HC should be offered to adults with SCA and sickle cell/β^0 thalassaemia and sickle associated pain or severe symptomatic anaemia that interferes with quality of life (QOL) or activities of daily living (ADL).

- HC should be discussed with adults with sickle cell/β^+ thalassemia or sickle cell/haemoglobin C disease who have three or more moderate to severe VOC in a 12 month period, a history of severe/recurrent ACS or recurrent pain that interferes with QOL or ADL.
- All hospitals looking after adults with SCD should have a prescribing and monitoring protocol for HC to maximise benefits and safety.
- Male adult patients should be offered sperm analysis and cryopreservation before commencing HC.
- Specialist centres should audit their use of HC to ensure it is discussed with all patients who may benefit from its use.

Background evidence

Mechanism of action

There are several potential mechanisms for the action of HC that are relevant for patients with SCD including haemoglobin F induction. HC most importantly inhibits ribonucleotide reductase (RR), an enzyme critical in the transformation of ribonucleotides into deoxyribonucleotides, leading to inhibition of DNA synthesis and eventual cellular cytotoxicity (Elford, 1968). The *in vivo* effects of HC on RR are predictably transient leading to intermittent cytotoxic suppression of erythroid progenitors and cell stress signalling. This affects erythropoietic kinetics and physiology, culminating in a gradual increase of haemoglobin F.

In addition, HC reduces surface expression of adhesion receptors as well as bone marrow production of neutrophils and reticulocytes both of which promote vaso-occlusion via vascular adhesion (Ware, 2010). Further observations include improved cellular deformability and rheology of red blood cells with increased blood flow and a decrease in haemolysis. Finally donation of a nitric oxide (NO) moiety by HC has beneficial effects on vascular endothelium including local vasodilation (Gladwin *et al.*, 2002). This compensation for haemolysis-induced NO consumption (Reiter *et al.*, 2002) might explain the clinical improvement some patients feel soon after HC initiation before maximal haemoglobin F induction.

Clinical efficacy

A recent Cochrane review concluded that HC was effective in decreasing the frequency of pain episodes and other acute complications in adults with SCA and sickle cell/β^0 thalassaemia (Nevitt *et al.*, 2017). However it concluded that there was insufficient evidence on its long-term benefits for the prevention of chronic complications or for a role in sickle cell/haemoglobin C disease. The Multicentre Study of Hydroxyurea in Patients with Sickle Cell Anaemia (MSH), a placebo-controlled randomised controlled trial, was the first trial to confirm the efficacy and tolerability of HC. The trial enrolled 299 adults with a mean age of 30.5 years. Patients in the

study received the maximum tolerated dose (MTD) or a maximum dose of 35mg/kg/day. The primary end point was reduction in frequency of painful crises and the trial was terminated early due to clinical benefit (Charache *et al.*, 1995). Significant findings from MSH trial include:

- Lower annual rates of pain crises (median 2.5 crises per year vs. 4.5 crises per year)
- Longer time to a first crisis on study (3.0 months vs. 1.5 months) and longer time to a second crisis (8.8 months vs. 4.6 months)
- Lower incidence of ACS (25 patients vs. 51 patients)
- Reduced need for blood transfusion (48 patients vs. 73 patients)
- Increased total Hb and haemoglobin F

More recently, extension of follow-up analysis to 17.5 years for nonrandomised adults indicated continued safety and benefit of HC, including reduced mortality (Steinberg *et al.*, 2010) related to haemoglobin F levels and frequency of VOC. Long term follow up of a prospective non-randomised study from Greece which enrolled individuals >16 years with SCA, sickle cell/β^0 thalassemia and sickle cell/β^+ thalassemia also showed benefits in survival for those who received HC (Voskaridou *et al.*, 2010). In addition, two paediatric cohort studies have demonstrated that children with severe SCA who received HC had higher survival rates than children with less severe complications not on HC (Lê *et al.*, 2015; Lopes de Castro Lobo *et al.*, 2013).

Further supporting evidence arises from more than 20 observational studies enrolling >3000 adults followed up for 2-8 years consistently showed a reduction in VOC and hospitalisation and an increase in haemoglobin F (National Heart Lung and Blood Institute, 2014).

Patient selection

Initial clinical trials restricted enrolment to individuals with substantial clinical severity and certainly HC should be offered to any individual with recurrent hospital admissions for acute pain or ACS. Consideration should be given to use beyond eligibility criteria used in the MSH trial, to recurrent acute and chronic pain as well as symptomatic chronic anaemia affecting the ability of adults with SCD to participate in desired daily activities (Platt *et al.*, 1994). The BABY-HUG study showed that HC was effective in decreasing recurrent pain, ACS and hospital admission in unselected children with SCA, leading to recommendations that all young children with SCA are offered HC therapy. These results are not necessarily generalisable to adults, but certainly adults with SCA should be made aware of the results of the BABY-HUG study and should be given information about the drug to allow them to make informed choices about its use.

Prospective multicentre randomised trials are assessing the role of HC in preventing organ dysfunction in SCA based on encouraging but uncontrolled single institution reports suggesting efficacy of HC for children and adults with sickle-related end organ damage (Fitzhugh *et al.*, 2015).

HC administration

The optimal dose of HC for an individual patient is still a source of debate and the Cochrane review found insufficient evidence to recommend a standard dose or dose escalation to MTD (Nevitt *et al.*, 2017). The initial phase 1/2 trial using HC demonstrated a near linear dose response, with treatment dose (mg/kg/day) correlating with percentage haemoglobin F response (Charache *et al.*, 1995). This observation coupled with a greater treatment response demonstrated the feasibility of a stepwise escalation of dose towards the MTD. The MTD is defined as a stable once daily dose that leads to the greatest benefits without causing side effects or toxicities (Ware *et al.*, 2016).

The MSH trial enrolled patients at a starting dose of 15 mg/Kg/day escalated to a MTD. Doses were increased in 5mg/kg/day increments at eight week intervals until myelosuppression was caused, at which point the dose was reduced to the previous dose increment; this was designated the MTD. Studies across multiple age ranges have shown that impressive laboratory and clinical benefits occur when HC is used at the MTD which typically averages 25 mg/kg/day (Kinney *et al.*, 1999; Thornburg *et al.*, 2009; Ware *et al.*, 2011; Ware & Helms, 2012). Several studies have used a 'clinically or minimally effective dose (MED)' of 15 to 20 mg/kg/day with good clinical outcomes or a standard dose of 10-20 mg/kg/day (de Montalembert *et al.*, 1997; Ferster *et al.*, 1996; Wang *et al.*, 2011a; Wang *et al.*, 2011b). The maximum dose used in these studies was 30-35mg/kg (Wong *et al.*, 2014).

Studies utilising HC at MTD typically achieve higher haemoglobin F percentages than the MED, typically 15-20 mg/kg/day defined operationally as the dose whereby patients improve clinically and feel better. Treatment at the MTD generally yielded better laboratory values with Hb >90 g/l, MCV >110 and haemoglobin F >20% (Ware *et al.*, 2016). A prospective multicentre clinical trial comparing low-dose HC with MTD is warranted.

A starting dose of 15mg/kg/mg in adults is usually well tolerated, with dose reductions for those with chronic kidney disease. The target of treatment should be an increase in HbF, a neutrophil count of 1.5 – 2.0 × 10^9/l and absolute reticulocyte count of 100-200 × 10^9/l.

In view of the risk of myelosuppression a full blood count and reticulocyte count should be checked two weeks after commencement and after every dose increment and should be checked every 8-12 weeks throughout treatment. Treatment should be halted if the neutrophil count is </= 1 x10^9/l, platelet count is <= 80 x10^9/l, Hb <45g/l or >20% decrease or reticulocyte count < 80 x10^9/l.

Most patients will achieve MTD within 12 months; maximum laboratory effects are also reached within the time-frame (Bridges *et al.*, 1996).

Use of a treatment protocol

Every centre treating patients with HC should have a treatment protocol to enable appropriate dosing and monitoring to maximise safety and benefits of therapy.

Toxicity

Most frequently recorded side effects of HC include leukopenia, neutropenia and thrombocytopenia. These tend to be mild and reversible with dose reduction or discontinuation. Less commonly reported side effects include gastrointestinal disturbances (Charache *et al.*, 1995), skin and nail changes, and leg ulcers. There is no definitive evidence that HC is causative of the latter (Voskaridou *et al.*, 2010).

There have been concerns about the long term toxicity of HC, particularly with regard to carcinogenesis, teratogenicity and fertility. Studies in cohorts with over 17 years of exposure to HC show no increase in stroke, myelodysplastic syndrome, leukaemia or cancer (Steinberg *et al.*, 2010). Long term follow-up from the MSH trial reported 94 pregnancies in enrolled male and female subjects regardless of their HC exposure. Of 16 pregnancy outcomes in female subjects with known HC exposure at conception or during gestation or male subjects exposed to HC at the time of conception, 8 live births, 5 elective and 3 spontaneous abortions were reported. Of the live births, no birth defects were reported, consistent with other studies reporting pregnancy outcomes (Ballas *et al.*, 2009; Gilmore *et al.*, 2011).

HC and abnormal spermatogenesis

Sperm abnormalities, such as oligospermia, azoospermia, decreased motility, and increased morphological abnormalities, occur in males with SCD receiving HC (Garozzo *et al.*, 2000; Grigg, 2007). Baseline sperm abnormalities are frequent in males with SCD, with rates as high as 91% (Berthaut *et al.*, 2008; Nahoum *et al.*, 1980) but are increased in patients with SCD treated with HC (Berthaut *et al.*, 2017; Sahoo *et al.*, 2016).

The published literature is limited on the risk of developing sperm abnormalities or infertility on exposure to HC with inconsistencies in the age of initiation, length of exposure and follow-up studies once HC is discontinued. One small study compared serial sperm counts and morphology before, during and after HC treatment and showed decreased sperm counts in five patients after starting HC with azoospermia in one patient (Berthaut *et al.*, 2008). Another paper has shown 4% of azoospermia prior to HC treatment, 10% whilst on treatment with 73% reversion to normality after stopping hydroxycarbamide for 3 months (Sahoo *et al.*, 2016). However it is difficult to determine if fertility was impaired in these cohorts.

There is therefore limited information regarding the reversibility of azoospermia or oligospermia which makes counselling patients starting HC challenging. Sperm banking should be offered prior to commencing HC.

Evidence of effectiveness in adults with genotypes other than sickle cell anaemia or haemoglobin S/β^0 thalassaemia.

For SCD individuals with genotypes other than SCA or haemoglobin S/β^0 thalassaemia there have been no phase 3 trials of HC. The non-randomised study from Greece enrolled 165 subjects with haemoglobin S/β^+-thalassemia, 44 of whom received HC. The 10-year survival for the subset of patients with haemoglobin S/β^+ thalassaemia receiving HC was not significantly different from those receiving conventional therapy (Voskaridou *et al.*, 2010). Some phase 2 and retrospective studies have suggested a beneficial effect of HC on laboratory and clinical parameters in patients with sickle cell/haemoglobin C disease but the Cochrane review concluded that evidence was limited for this genotype (Luchtman-Jones *et al.*, 2016; Nevitt *et al.*, 2017; Wang *et al.*, 2011a; Wang *et al.*, 2011b).

Recommendations

- Consider HC in adults with SCA and sickle cell/β^0 thalassaemia with symptomatic chronic anaemia or proteinuria unresponsive to ACEi or angiotenisn receptor blocker treatment.
- Adults with SCA should be aware of the evidence of efficacy of HC and be given information about the drug to enable joint decision making about its use.
- Females of childbearing age should be counselled regarding the need for contraception while taking HC. HC should be discontinued if pregnancy is planned, immediately an unplanned pregnancy is recognised and during breast-feeding.
- Males should be counselled regarding the need for effective contraception while taking HC.

Chapter 21: Blood transfusion

"The last blood transfusion I had resulted in hyperhaemolysis with ITU admitting me for several weeks as my body rejected the newly transfused blood. It would be interesting to know how others cope"

Introduction

The use of transfusion in patients with sickle cell disease (SCD) is increasing but there is marked variation in rates of - and indications for - transfusion between different hospitals. In part this is due to a lack of evidence and clear guidelines for use, but a recent national audit demonstrated that transfusion modality choice is often based on availability (NHS Blood and Transplant, 2016). Recent national guidance should improve consistency (Davis *et al.*, 2017a, 2017b). Red cell transfusion may be required as an emergency life-saving measure for the treatment of acute complications while regular red cell transfusion may be used for the prevention of long-term complications. Modality of transfusion includes simple transfusion and exchange transfusion; the latter may be performed as a manual or automated procedure. The choice of volume and modality of transfusion can be complicated and it is advisable that emergency cases are always discussed with an expert in the field. Patients should be provided with information on transfusion and any alternatives if clinically appropriate.

Standards

Based on (Davis *et al.*, 2017a, 2017b)

- Automated exchange should be available to all patients with SCD and should be provided by all specialist centres.
- All hospitals that admit SCD patients should have protocols and training in transfusion for SCD including manual exchange procedures.
- SCD patients needing transfusion must be given ABO Rh (CcDEe) and Kell compatible units. Blood should be antigen negative for clinically significant antibodies that are currently or have previously been detected.
- All patients should have a red cell genotype/phenotype available. A genotype that offers analysis of Rh variants may be preferable as these are common in this patient group.
- Adverse events involving transfusions should be reported using the local hospital adverse events reporting system, to the National Haemoglobinopathy Registry, and to Serious Hazards of Transfusion/Serious Adverse Blood Transfusion Reactions and Events (SHOT/SABRE).

- Simple transfusion to steady state haemoglobin concentration (Hb) may be indicated for patients with acute exacerbation of anaemia due to aplastic crisis or sequestration crisis.
- Transfusion is not recommended in uncomplicated vaso-occlusive crisis.
- Urgent red cell exchange is recommended for patients with a sickle-related acute ischaemic stroke.
- Adult patients who have experienced an ischaemic stroke should continue on long term transfusion therapy.
- Simple ('top-up') transfusion should be considered early in the hypoxic patient with acute chest syndrome (ACS), but exchange transfusion is necessary if there are severe clinical features or evidence of progression despite initial simple transfusion.
- Chronic transfusion should be considered for prevention of recurrent ACS if hydroxycarbamide therapy is not effective.
- Exchange transfusion should be considered early in the presentation of patients with intrahepatic cholestasis and/or multi-organ failure.
- Specialist centres should audit their use of blood transfusion in the acute and chronic setting to ensure its use is consistent with national guidance.

Aim of transfusion therapy and choice of modalities

The aim of transfusion therapy in patients with SCD is both to increase the Hb and therefore improve oxygen carrying capacity and to decrease the haemoglobin S percentage, which will decrease vaso-occlusion. Transfusion therapy may be administered as simple or 'top-up' transfusion or as an exchange transfusion which involves venesection and transfusion. Exchange transfusions can be performed manually or may be automated. A summary of the characteristics of each method is summarised in Figure 7. Transfusions may be required as an isolated procedure in the acute setting for treatment of an acute complication or may be required in the long term for prevention of acute or chronic complications.

Simple transfusion is effective in increasing Hb and in improving oxygen carrying capacity and is the best option when the primary reason for acute transfusion is severe anaemia. The patient's baseline Hb should be used as a post-transfusion Hb target, which should not exceed 110 g/l because of the risk of hyperviscosity with transfusion to higher Hbs. The change in haemoglobin should be considered carefully when deciding transfusion volumes as a rapid change in Hb leads to a change in viscosity and can result in a stroke or other large vessel occlusion. A change of 40g/l in 24 hours is usually the maximum recommended. Simple transfusion is not as effective as exchange transfusion in reducing haemoglobin S percentage in the acute situation, unless the starting Hb is very low.

Exchange transfusion offers an advantage in the acute situation if a rapid reduction of haemoglobin S percentage is required to reverse an acute sickle complication (e.g. ACS or stroke). Targets for pre- and post- transfusion Hb are usually similar and targets for post-transfusion haemoglobin S percentage is usually <30%, depending on the indication for

transfusion. Exchange transfusion may be a time critical, life-saving intervention and the procedure for manual exchange should be included in education programmes for advanced trainees in paediatrics and haematology, with appropriate support from consultant haematologists and specialist nurses (Royal College of Nursing, 2011; West Midlands Quality Review Service, 2016a).

When choosing a modality for a long term transfusion programme, the considerations will be availability of procedure, venous access, iron loading/need for chelation and frequency of procedures. Simple transfusions are easy to administer but iron loading can occur rapidly and transfusion will be required every 3-4 weeks. In this context a low haemoglobin S percentage can be maintained. Manual exchanges need to be administered as often but iron load less quickly.

Long term automated exchange transfusion programmes offer good control of haemoglobin S percentage. They rarely result in iron overloading and whilst they involve increased blood use and thus donor exposure, paradoxically have been shown to decrease alloimmunisation in retrospective cohort data (Michot *et al.*, 2015). The increased costs of staff and equipment may be offset by fewer hospital visits and less iron loading and need for chelation. Exchange transfusion has been shown to be cost effective and is the recommended modality for long term transfusion therapy (National Institute for Health and Care Excellence, 2016a).

Obtaining robust venous access can be a problem in patients with SCD but ultrasound guidance may facilitate intravenous access (Putensen, 2015). Some patients may require intermittent central venous access or indwelling venous access, although the latter has been associated with high rates of infection and thrombosis in patients with SCD.

[Figure 7 shown overleaf]

Figure 7: Comparison of different transfusion modalities (all times approximate)

	MODALITY		
FEATURE	**Top-up transfusion**	**Manual exchange**	**Automated exchange**
Staffing and training	Basic	Moderate	High
Frequency	3-4 weekly	3-4 weekly	4-8 weekly
Length of procedure	4-6 hours	2-4 hours (up to 4-8 h if acute exchange in a previously untransfused patient)	2 hours
Units of red cells	2-3	3-6	8-10
Volume shifts	Large	Minimal / Moderate	Minimal
Ability to predict % haemoglobin S and Hb post-transfusion	Moderate	Moderate	Very accurate
Iron loading (long term use only)	High	Moderate	Minimal

Selection of blood and communication with transfusion laboratory

Poor communication may contribute to the failure to meet special transfusion requirements. Emergency transfusions for SCD patients may happen out of hours when their usual medical teams are not available, or at hospitals where the previous transfusion history is unknown.

Compatibility testing

This should be undertaken according to the British Society for Haematology compatibility guidelines (British Committee for Standards in Haematology *et al.*, 2013; Bruce *et al.*, 1999). Fully automated systems should be used for ABO typing to reduce the risks of interpretation and transcription error. Antibody screening should always be undertaken as part of pre-transfusion testing. If an alloantibody is detected its specificity should be determined. If the patient has a known red cell alloantibody, each new sample should be fully tested to exclude further alloantibodies. Samples should be sent to a red cell reference laboratory if there is difficulty in antibody identification.

Extended red cell phenotype/genotype

An extended phenotype (or genotype) including C, c, E, e, K, k, Jka, Jkb, Fya, Fyb, M, N, S and s should be performed at baseline. If the patient is S- s-, then U typing should be performed. If the patient has not been transfused within three months then testing can be undertaken serologically, otherwise genotyping is needed. Extended phenotype matching for additional red cell antigens is not performed routinely and even with this strategy the formation of allo-antibodies is not completely abolished (Chou *et al.*, 2013; O'Suoji *et al.*, 2013). High resolution Rh genotyping using DNA-based testing has showed high rates of variant or altered Rh alleles in patients with SCD and this explained the occurrence of some of the cases of alloimmunisation from Rh antigens despite using phenotypically matched blood (Chou *et al.*, 2013). The accuracy of red cell matching may be enhanced with DNA based testing and this is now provided by NHS Blood and Transplant (NHSBT), although it is not clear if this should be routinely offered to all patients and what impact this will have on provision of blood for transfusion.

Blood product selection

As a minimum, red cells should be ABO Rh (D, C, c, E, e) and Kell compatible (British Committee for Standards in Haematology, 2004; Royal College of Obstetrics and Gynaecology, 2011; Sickle Cell Society, 2008) and haemoglobin S negative (British Committee for Standards in Haematology, 2004; Sickle Cell Society, 2008). If there are clinically significant red cell antibodies (current or historical) then the red cells selected should be negative for the corresponding antigens. If possible, red cells should be less than 10 days old for simple transfusion and < 7 days old for exchange transfusion. This may not be possible in individuals with multiple alloantibodies or in a true emergency when the freshest units available should be used. Alloimmunisation increases clinical risk through delays in securing compatible units and

because of potential delayed haemolytic transfusion reactions. Careful planning and communication between all teams is essential; this includes liaising with NHSBT.

Adverse transfusion reactions

Patients should be counselled regarding possible adverse reactions to transfusions. Transfusion adverse events should be identified and monitored according to local guidelines and should be reported using the local hospital adverse events reporting system, the National Haemoglobinopathy Registry, and SHOT/SABRE.

Iron overload is discussed in Chapter 22 - Iron chelation. Rates of transfusion-transmitted infection are very low in the UK. Virology testing (hepatitis B, C and human immunodeficiency virus) should be undertaken at first presentation and then yearly in those receiving transfusions. Hepatitis B vaccination should be given to all SCD patients and boosters given when antibodies to hepatitis B surface antigen fall below 100 mIU/ml.

Alloimmunisation is more common in SCD than in the general population, in part due to ethnic differences between recipient and donor population. Rates of alloimmunisation have been decreased by routine extended phenotypic red cell matching for Rh and Kell typing (Vichinsky *et al.*, 2001) but the role of further extending phenotyping or genotyping blood provided to SCD patients is not currently clear. Red cell alloimmunisation may result in delayed haemolytic transfusion reactions (DHTR) or subsequent haemolytic disease of the new born and can lead to difficulties in obtaining compatible blood for transfusion.

DHTR typically presents 5-15 days following red cell transfusion and varies in severity. More severe presentations may include pain, rapid decrease in Hb, cola-coloured urine and renal dysfunction accompanied by increased haemolytic markers and a new allo-antibody. There is observational evidence of response to methylprednisolone and high dose intravenous immunoglobulins in addition to erythroid stimulating agents. Rituximab or eculizumab have been used in cases resistant to these therapies (de Montalembert *et al.*, 2011; Noizat-Pirenne *et al.*, 2015; Vidler *et al.*, 2015).

Hyperhaemolysis in which both transfused red cells and the patient's own red cells are destroyed has also been described. It is characterised by a rapid decrease in Hb below the pre-transfusion level and destruction of both transfused and the patient's own red cells. While it may be triggered by a new red cell antibody there is frequently no evidence of an allo-antibody. Treatment with methylprednisolone and high dose intravenous immunoglobulins can be effective in slowing and halting the red cell destruction and is recommended (Danaee *et al.*, 2015; Win, 2009). There will be evidence of both HbS and HbA in the urine during the episode.

Both DHTR and hyperhaemolysis may recur with subsequent transfusions and there are case reports of pre-transfusion immunosuppression being used to reduce recurrence. Expert advice from the Specialist Haematology Team (SHT) and from NHSBT should be sought if these complications are suspected.

Indications for transfusion

Adapted from (Davis et al., 2017a, 2017b)

The evidence regarding the indications for blood transfusion has recently been reviewed thoroughly by the British Society for Haematology and these standards have used the review's conclusions (Davis *et al.*, 2017a, 2017b).

Acute anaemia: Simple transfusion should be used in the situation of acute anaemia where the primary goal of transfusion is to correct this anaemia and improve oxygen carrying capacity (see Figure 8). There is insufficient evidence to recommend transfusion for the treatment of acute painful crisis but simple transfusion should be considered if there is worsening anaemia or haemodynamic compromise. Transfusion should be avoided if the acute anaemia is due to a delayed haemolytic transfusion reaction unless the anaemia is severe or life-threatening.

Figure 8: Indications where primary goal is to correct acute anaemia

Indication	**Grade**
Aplastic crisis	1B
Acute splenic sequestration	1B
Acute hepatic sequestration	1B

Other acute complications (see also Section B - Management of acute and chronic complications): In patients experiencing other acute sickle complications the primary goal of transfusion is usually to reduce the haemoglobin S concentration in relation to haemoglobin A. This will usually be best achieved by an exchange transfusion. In ACS simple transfusion may be effective in patients with mild or moderate symptoms, but an exchange transfusion will be required for patients with evidence of severe disease or in those who baseline Hb is high (Chapter 7 - Cardiorespiratory complications). For acute ischaemic stroke there is some observational evidence that initial exchange transfusion is more effective in reducing the risk of stroke recurrence (Hulbert *et al.*, 2006), so exchange transfusion is recommended unless the patient is significantly anaemic, when they will require a simple transfusion followed by an exchange transfusion (Chapter 6 - Neurological complications). Exchange transfusion is recommended for patients with acute life threatening complications of SCD including acute multi-organ failure, severe sepsis, mesenteric (girdle) syndrome and acute intrahepatic cholestasis. The role of transfusion in acute priapism is discussed in Chapter 9 - Priapism.

Indications for chronic transfusion

See also: Section B - Management of acute and chronic complications

The use of chronic transfusion programmes for primary stroke prevention for children with raised transcranial Doppler (TCD) measurements or silent infarcts is well supported by high quality evidence. There is no such evidence to guide practice in adults, but similar principles may apply in adults. Children who have commenced transfusion for these indications in childhood should be reviewed during transition to adult care and continuation of the transfusion programme considered. Following the TWiTCH study that showed non-inferiority of hydroxycarbamide versus transfusion in patients with raised TCDs with normal brain imaging, there will be some patients who can be offered hydroxycarbamide. This should be done after appropriate imaging, consultation and discussion with the specialist centre.

Whilst data on secondary stroke prevention in adults are limited, current recommendations are that adults who have a sickle-related stroke should continue on long term transfusion therapy. Similarly adults who have had a stroke in childhood and have been commenced on transfusion therapy should be reviewed on transition and should be continued on long term transfusion therapy (see Chapter 6 - Neurological complications).

Both transfusion therapy and hydroxycarbamide are effective in reducing recurrent pain and recurrent ACS. Patients with these complications should be initially treated with hydroxycarbamide and offered blood transfusion therapy only if treatment with hydroxycarbamide fails (see Chapter 20 - Hydroxycarbamide).

There is limited evidence for the use of chronic transfusion in other indications but its use has been reported in the treatment of renal disease, pulmonary hypertension, leg ulcers and recurrent priapism.

The role of transfusion in pregnancy and for preoperative management is discussed in chapters 18 and 19.

Recommendations

- A transfusion history should be obtained in all SCD patients requiring transfusion whether elective or emergency. Additional information on red cell genotype/phenotype and antibody history may be available from other hospitals and from NHSBT.
- Close communication is essential between clinical and laboratory teams so that appropriate blood is given.
- Centres should consider transfusion reactions in patients presenting unwell following a transfusion and should contact specialist teams for advice in management.
- Patients with a history of red cell allo-antibodies or haemolytic transfusion reaction should be given an alert card.

Chapter 22: Iron chelation

"I am currently on the exchange programme so I haven't had to worry about iron overload and chelation therapy as I did previously, although when I travel outside London, the machine isn't available"

Introduction

The aim of chelation is to reduce the risk of complications of iron overload, which may develop with intermittent or regular blood transfusions. A large body of evidence has accumulated in thalassaemia patients showing the improved survival in patients who are chelated, but there are relatively few published data sets on iron overload in patients with sickle cell disease (SCD). Whilst iron overload related complications tend to be less frequently encountered in sickle patients, MRI evidence does support iron deposition in extrahepatic organs (Wood *et al.*, 2016). The clinical relevance of this iron deposition remains unclear however post mortem data identifies iron overload related complications such as liver cirrhosis and cardiac failure as causes of death (Darbari *et al.*, 2006). Iron tends to accumulate in the liver rather than the heart in patients with SCD in contrast to thalassaemia and other iron loading conditions. Thus iron overload in SCD is associated with liver damage, fibrosis, cirrhosis and sometimes even liver failure.

Standards

- All patients with serum ferritin persistently raised >1000 µg/l who have been previously transfused should have quantitative monitoring of liver iron concentration using magnetic resonance imaging (MRI).
- Iron chelation is recommended in patients who have a liver iron concentration of > 7mg/g dry weight on MRI scanning.
- Patients receiving long term blood transfusion should have regular monitoring for iron overload and appropriate iron chelation therapy according to their iron burden.
- All patients receiving iron chelation therapy should be regularly monitored for therapeutic effect and chelator toxicity.
- Support should be provided to patients to help improve adherence to chelation therapy.

Background evidence

Iron monitoring

Serum ferritin remains a convenient, cheap and widely used way of assessing body iron but levels can be very variable, probably due to inflammatory processes related to crises. Studies of iron chelation in patients with SCD have shown variable responses of ferritin measurements (Cappellini *et al.*, 2010; Vichinsky *et al.*, 2011). 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 other methods are used to assess iron overload and response to chelation.

Liver biopsy, which was historically used for monitoring iron overload, has been superseded by MRI technology and MRI monitoring of liver iron concentration is now available in the UK and should be part of standard of care. Assessment of iron load in SCD is extrapolated from other diseases. Liver iron concentration (LIC) <7 mg/g is not associated with obvious hepatic pathology while >15 mg/g is consistently associated with liver fibrosis (Bassett *et al.*, 1986). Liver MRI can accurately assess response to chelation. MRI methods routinely used in the UK are R2 Liver (FerriScan®), T2* (cardiac and liver iron) and R2* for liver. The methods are not interchangeable and therefore consistently the same method should be used to monitor the trend in liver iron.

Although serum ferritin correlates less well with MRI LIC in patients with SCD when compared with patients with thalassaemia, a ferritin persistently raised >1000 µg/l, on at least two occasions in the steady state, should be an indication for MRI monitoring of iron overload (Adamkiewicz *et al.*, 2009; Smith *et al.*, 2014). This is approximately equivalent to transfusion of 20 units of packed red blood cells (PRBC).

The role of iron chelation in SCD according to transfusion strategy

Previously or currently on intermittent transfusions for acute complications.

Patients receiving intermittent/occasional simple transfusions over many years can accumulate considerable amounts of iron. Ferritin should be assessed regularly, at least at annual review, and appropriate MRI monitoring undertaken if the ferritin is persistently >1000µg/l. Iron chelation should be offered to all patients with liver iron values above 7mg/g/dw and considered for those with liver iron concentration of 5-7mg/g/dw dependant on co-existing morbidity in the heart or liver.

Patients on regular simple transfusions

These patients should be offered iron chelation therapy once 10-20 units of blood have been administered or the ferritin is above 1000µg/l. Iron chelation should be continued for as long as the patient remains on transfusions with the aim to keep liver iron <5mg/g/dw and cardiac T2*>20ms.

Patients on regular exchange transfusions

Many patients on long-term transfusion therapy will receive automated exchange transfusions. These are less likely to cause iron loading than long term simple transfusion and are recommended by the National Institute of Health and Clinical Excellence (NICE). Some patients may still gain iron, particularly if the post-exchange haemoglobin is higher than that pre-exchange. Patients receiving manual exchange transfusions can gain iron, albeit at a slower rate than with simple transfusions.

MRI scanning is indicated if there is a raised or increasing ferritin level (>1000 µg/l). Patients who are iron loaded (LIC >7mg/g) when they embark on long-term automated transfusion therapy should be treated with iron chelation therapy and be monitored for iron overload with serial serum ferritin and MRI LIC. Iron chelation can be stopped once the ferritin is <500µg/l or liver iron <5mg/g/dw.

Iron chelation

Deferasirox and desferrioxamine are both licensed as iron chelators in SCD and lead to similar dose-dependent liver iron concentration (LIC) reductions in transfused SCD patients (Vichinsky *et al.*, 2007). Deferiprone is not licensed for SCD but there is evidence that it is as effective as desferrioxamine. (Calvaruso *et al.*, 2014).

Desferrioxamine

Desferrioxamine (DFO) is usually given as a subcutaneous infusion, most often 8-12 hours overnight but can also be given as a continuous intravenous infusion in heavily iron-loaded patients. Patients are usually treated between four and seven days per week depending on the degree of iron overload (electronic Medicines Compendium (eMC), 2017a). DFO can also be given by continuous intravenous infusion to reverse cardiac dysfunction, but this is rarely needed in patients with SCD.

DFO is now usually given via portable, light-weight, pre-filled infusion pumps rather than battery operated infusers, which has improved ease of use and adherence. Fine 'thumbtack' or 'drawing-pin' style needles introduced at 90 degrees to the skin into the subcutaneous tissues have the fewest reactions. The skin of the abdomen, arms or legs can be used in rotation to reduce scarring that can affect absorption.

The usual daily dose is 20-40 mg/kg/day.

Oral vitamin C (maximum 200 mg daily, in divided doses) may enhance iron excretion when on regular desferrioxamine. Vitamin C should not be administered within the first month of desferrioxamine therapy.

The most frequent side effect is local effects at infusion sites. Hydrocortisone can be added to the infusion fluid if this is a problem. Optic nerve damage and sensorineural hearing loss are

serious adverse effects, occurring more commonly with high doses. They can be reduced by keeping the ratio of the mean daily dose (mg/kg of desferrioxamine) divided by the serum ferritin (µg/l) below 0.025. Retinal examination and audiometry should be done prior to starting treatment and then annually.

Desferrioxamine promotes infections such as by *Yersinia enterocolitica* or Klebsiella spp. (Adamkiewicz *et al.*, 1998). Patients should be advised that if they develop fever with pharyngitis, diffuse abdominal pain or enteritis/enterocolitis, they should stop desferrioxamine therapy and seek urgent medical advice so that appropriate antibiotic treatment can be instituted.

Deferasirox

Deferasirox (DFX) is an orally active iron chelator, given once daily. It was previously given as a dissolvable tablet but this has now been replaced by a film coated tablet.

The starting dose of the film coated tablet is 14 mg/kg/day.

Serum ferritin should be monitored monthly and the dose adjusted every 3 to 6 months, if required. In patients whose serum ferritin level has reached the target (usually between 500 and 1,000 µg/l), dose reductions in steps of 5 to 10 mg/kg should be considered. Interruption of DFX should be considered if ferritin is persistently < 500 µg/l.

Serum creatinine, creatinine clearance (estimated with the Cockcroft-Gault or MDRD formula in adults) and/or plasma cystatin C levels should be monitored prior to therapy, weekly in the first month after initiation or modification of therapy with deferasirox and monthly thereafter. During clinical trials, increases in serum creatinine of more than 33% on at least two consecutive occasions, sometimes above the upper limit of the normal range, occurred in about 36% of patients. This should lead to dose reduction and interruption of treatment, if persistent. Cases of acute renal failure have been reported following post-marketing use of deferasirox (electronic Medicines Compendium (eMC), 2017b).

Serum transaminases, bilirubin and alkaline phosphatase should be checked before the initiation of treatment, every two weeks during the first month and monthly thereafter. Deferasirox may be a contributing or aggravating factor for hepatic failure, but the most common cause of liver dysfunction and failure in the iron loaded patients is the iron itself.

If there is a persistent and progressive increase in serum transaminase levels that cannot be attributed to other causes, deferasirox should be interrupted. Once the cause of the liver function test abnormalities has been clarified or after return to normal levels, cautious re-initiation of treatment at a lower dose followed by gradual dose escalation may be considered. Deferasirox is not recommended in patients with severe hepatic impairment (Child-Pugh Class C).

The Summary of Product Characteristics should be consulted regarding dose adjustments in relation to renal or liver changes (electronic Medicines Compendium (eMC), 2017b).

Long term safety data was provided by Vichinsky et al. who followed transfusion-dependent SCD patients for five years, but only 33.5% completed the study (Vichinsky *et al.*, 2011). Deferasirox adverse events were predominantly gastrointestinal (including nausea and diarrhoea), mild-to-moderate and transient in nature. Creatinine clearance remained within the normal range throughout the study. Serum ferritin levels in patients with 4 or more years of deferasirox exposure significantly decreased by, on average, 591 µg/l. Gastrointestinal haemorrhage, gastric ulcer (including multiple ulcers), duodenal ulcer and gastritis occur but are uncommon.

Another side effect is skin rash which resolves spontaneously in most cases. When interruption of treatment is necessary, treatment may be reintroduced after resolution of the rash, at a lower dose followed by gradual dose escalation.

Deferiprone

Deferiprone is an oral iron chelator, given three times a day. It is not licensed for use in SCD. Consequently, patients should be made aware of this and the reasons for its use should be clearly documented in the notes. Adverse effects include agranulocytosis, neutropenia and arthropathy, as well as gastro-intestinal disturbance, intermittent elevation in alanine transaminase (ALT) and zinc deficiency. Agranulocytosis (neutrophil count < 0.5×10^9/l) has been described in up to 1.5% of patients, at a median of 162 days after starting treatment, and is the most severe side effect of this drug. Weekly full blood count monitoring is recommended whilst on this treatment. Deferiprone therapy has been given in combination with desferrioxamine in patients with significant iron overload and it is thought to have a particular benefit in those with cardiac iron overload. Combination therapy should only be instigated after discussion with a specialist centre.

Chapter 23: Haematopoietic stem cell transplantation

"Is stem cell transplant a safe cure for sickle cell and what are the risks if any"?

Introduction

Haematopoietic stem cell transplantation (HSCT) is a potentially curative option for sickle cell disease (SCD) albeit one which is not without risk. Most HSCTs for SCD have utilised matched siblings as donors and are performed in children and adolescents and currently the National Health Service (NHS) only funds HSCT those up to age 19 with SCD.

Adults have only recently been regarded as acceptable transplant candidates, given the unpredictable prognosis and cumulative organ damage from SCD, coupled with an increased risk of dying from transplantation with increasing age due to toxicity of the conditioning regimen. In recent years, 'reduced intensity' or 'non-myeloablative' preparative regimens prior to HSCT in adults with SCD have emerged as feasible options for HSCT in adults. In addition the encouraging results of using alternative donor HSCT such as haplo-identical donors have led a worldwide interest in establishing clinical trials of transplantation of adults with SCD

Standards

- Adults with SCD who are being considered for HSCT should be discussed at a multidisciplinary team (MDT) meeting with appropriate expertise which must include the specialist haemoglobinopathy team.
- Trials for haematopoietic stem cell transplantation (HSCT) in adults with SCD should be available in the UK.

Background evidence

Systematic review has found no randomised controlled trials assessing the risks or benefits of HSCT in adults with reports limited to observational studies (Oringanje *et al.*, 2016). Reports in the literature on the outcomes of HSCT in adults with SCD include small series of patients transplanted with different types of conditioning regimens and most frequently from HLA-identical siblings and in selected patients.

One report of 15 young adults receiving HLA-identical sibling donor stem cells with a myeloablative conditioning regimen showed relatively high rates of graft-versus-host disease (GVHD) but with a median follow-up of 3.4 years (range 1-16.1), overall disease-free survival

was 93% (Kuentz *et al.*, 2011). All survivors currently enjoy a normal quality of life without immunosuppression. Chimaerism at 1 year was full-donor in 12 patients and mixed but >75% donor in 2 patients.

Prospective evaluation of 10 adults, aged 16 to 45 years, undergoing a non-myeloablative transplant (consisting of alemtuzumab, total-body irradiation and sirolimus) from a matched sibling donor (MSD) found that all patients were alive at a median of 30 months after transplantation. Eligibility was irreversible vasculopathy or unmanageable symptoms from SCD. Nine patients had long-term, stable donor engraftment, at levels sufficient to reverse the SCD phenotype (Hsieh *et al.*, 2009). In a later update on 30 patients aged 16-65 years with severe disease enrolled in this non-myeloablative transplant study 29 patients survived a median of 3.4 years (range 1-8.6), with no non-relapse mortality (Hsieh *et al.*, 2014). These results, while encouraging, are applicable to the, at best, approximately 10-20% of patients with SCD who have a matched sibling donor.

Bolanos-Meade and colleagues reported on 17 patients, 14 from HLA haplo-identical and 3 HLA-matched sibling donors, transplanted with a reduced-intensity conditioning regimen (fludarabine, cyclophosphamide and total body irradiation). All received bone marrow grafts. With a median follow-up of 711 days (minimal follow up 224 days), 11 patients engrafted durably. Graft failure was observed in 43% of haplo-identical pairs but overall survival (OS) was 100% due to the high rates of graft-failure disease-free survival (Bolaños-Meade *et al.*, 2012).

In a recent series of 1000 patients with SCD, transplanted from an HLA-identical sibling, 154 patients were adults or young adults (>16 years old) (Gluckman *et al.*, 2017). Seventy-one adults were transplanted in Europe and 83 in North America. Median age at HSCT was 19 years (16-54). All received bone marrow or peripheral blood stem cells (PBSC) from an HLA-identical sibling. Conditioning regimen was reduced intensity in 40 patients and myeloablative in 114. The 5 year overall survival (OS) was 95% and 81% for patients younger than 16 years compared with those 16 years and over. The 5 year probability of GVHD-free survival was 86% and 77% for patients younger than 16 years compared with those 16 years and over.

Results from these studies indicate that non-myeloablative HSCT in adult patients with severe SCD is safe and has curative potential. Patients with significant transfusion requirements and sickle cell-related complications can achieve stable donor chimaerism with associated stabilisation of end organ dysfunction, donor-derived haematopoiesis and decrease in health care utilisation. Barriers yet to be overcome include: advanced disease precluding transplantation; conditioning-related early and late toxicities; Graft versus host disease (GVHD); lack of related donors; high graft rejection rates; lack of full-donor chimaerism; and long-term use of immunosuppression.

Given recent advancements in HSCT for adults with SCD, several investigators have suggested that transplantation should be offered to patients with severe disease, in whom the risk of transplant-related morbidity and mortality is judged similar to the risk of long-term SCD-related morbidity and mortality. At the time of these standards HSCT is not available for adults

and there are no clinical trials open for adults in the UK. The decision for HSCT is complex and should be made in a multi-disciplinary forum. Suggested patient selection criteria are given in appendix 6.

Recommendation

- Protocols for HSCT in adult patients with SCD should be agreed nationally.
- There needs to be ongoing discussion with commissioners around funding for stem cell transplants in adults.

Chapter 24: Emerging therapies

"I have been advised by my consultant that I meet the criteria for a new clinical trial, but I am unsure what the side effects are".

"The NHS still do not fund any emerging therapies for the sickle population. More and more people are travelling abroad to receive curative treatments for sickle"

Introduction

Outside of hydroxycarbamide, blood transfusion and haematopoietic stem cell transplantation there are no agents in routine use that are of proven clinical benefit in SCD. Treatment therefore remains supportive and reactive. A growing appreciation of the underlying pathophysiological mechanisms in SCD, is leading to an expansion of potential therapeutic targets. This section reviews these targets and the rationale underlying their further exploration. A collaborative approach nationally and internationally is required to set priorities for sickle cell clinical research and to ensure optimal trial design.

Standard

- All patients with SCD should have access to information regarding current clinical trials, to enable participation if the patient so chooses.

Drugs currently under evaluation

The Clinical Trials databases of the United States National Institutes of Health (NIH) and the UK clinical trials gateway have a number of agents under active investigation at the time of writing (see www.clinicaltrials.gov and www.utctg.nihr.ac.uk). Most remain in early phase, although some agents are showing considerable promise as a means for altering the underlying pathophysiology associated with sickling (Ataga, 2009; Conran, 2015; Kato, 2016).

Reducing vascular endothelial adhesion and cell-cell interactions

'Anti-adhesive therapies' are drugs that, through diverse mechanisms, disrupt the interactions between blood cells and the vascular endothelium that are critical for the development of vaso-occlusive crises. Upregulated expression of selectins, the adhesion molecules present on blood cells and on the vascular endothelial surface, is associated with severity of phenotype in sickle cell disease (SCD) and contributes directly to vaso-occlusion (Okpala, 2015). The inhibition of selectin binding is therefore a rational target for drug development in SCD and is the focus of agents in advanced phase assessment.

Amongst these, rivipansel is a pan-selectin inhibitor that has demonstrated the capacity to reduce requirements for parenteral opiates in patients suffering acute vaso-occlusive crises (though the duration of painful crises was not reduced by a statistically significant margin in phase II studies). A phase III multicentre randomised placebo-controlled trial of rivipansel (Rivipansel: Evaluating Safety, Efficacy and Time to Discharge (RESET) trial) is currently enrolling.

Results from a multicentre randomised phase II trial (the SUSTAIN trial) using crizanlizumab, an antibody against P-selectin, have shown a significant decrease in median number of crises per year and in median time to first and second crisis (Ataga *et al.*, 2017).

Other agents under active assessment as a consequence of recognised impact on selectins include the low molecular weight heparin, tinzaparin. This was included in a recent Cochrane review of the effectiveness of low molecular weight heparins for the reduction of painful crises. Despite superficially promising results in phase II trials, the Cochrane team downgraded the evidence as a result of poor trial design leading to serious risk of bias (van Zuuren & Fedorowicz, 2015).

Selectin inhibition is not the only mechanism by which cellular adhesion to the endothelium may be subverted. Vepoloxamer (MST-188) is an amphipathic triblock copolymer, which is thought to adhere to hydrophobic domains on cell membranes, reducing cell adhesion and blood viscosity. A phase III trial (Evaluation of Purified Poloxamer 188 in subjects in crisis – EPIC trial) assessing its efficacy in reducing the duration of painful episode failed to meet the primary endpoint.

Closely allied to the issues of cellular adhesion and endothelial activation is platelet recruitment and activation. However, the 'Determining Effects of Platelet Inhibition on Vaso-Occlusive Events (DOVE) trial, a paediatric phase III trial of the $P2Y_{12}$ inhibitor prasugrel, which reduces platelet aggregation, failed to show a statistically significant impact on the frequency of painful crises (Heeney *et al.*, 2016). Importantly, even a negative result for this trial was afforded high impact publication, in large part due to its careful design and broad geographical reach. In this regard, the DOVE trial clearly demonstrates that high quality, patient-focused, multinational clinical research in SCD is achievable.

The (non-significant) trend toward a reduction in crisis frequency in older children treated with prasugrel may prompt further study of this agent in young adults and older patients with SCD. Meanwhile, phase II trials assessing the potential impact of antiplatelet agents on the duration of painful episodes continue with the alternative ADP receptor blocker ticagrelor.

Modifying nitric oxide signalling

A second major group of investigational drug targets in sickle cell disease focuses on the modification of nitric oxide signalling. Haemolysis has a multifaceted effect in decreasing nitric oxide availability, via free haemoglobin scavenging, release of arginase, and inhibition of nitric oxide synthase (Kato, 2015).

Trials to replenish arginine, the substrate for nitric oxide synthase, include a single centre, randomised controlled study assessing its impact in the setting of children admitted with acute pain episodes. Although the primary endpoint of length of stay was not statistically significantly different between control and test arms, there was an encouraging impact on pain scores and opiate use which would support ongoing phase III studies. L-citrulline, an arginine precursor, is in early phase trials under the same rationale.

Since the effects of nitric oxide are largely mediated by cGMP, phosphodiesterase inhibition would also be expected to promote nitric oxide signalling. Early phase trials are in place as a presage to investigating the effect of PDE9 inhibition on the frequency of painful crises (PDE9 is expressed predominantly in haematopoietic cells, by contrast the ubiquitous/smooth muscle distribution of PDE5, inhibition of which has been associated with an increase in painful crises). Direct stimulation of guanylate cyclase (e.g. by the experimental agent riociguat, for which phase II studies are currently in preparation) would be expected to give similar potential benefits in sickle cell disease.

Preclinical and observational studies highlight the diverse mechanisms that support further investigation of nitric oxide modulation. For example, PDE9 inhibition and arginine supplementation both diminish adhesion of leucocytes and red cells to the vascular endothelium, as well as inhibiting platelet activation. The observation that oral hydroxycarbamide also acts as a nitric oxide donor raises the possibility of using these investigational agents in a combinatorial or adjuvant setting; a concept not explored to date in the management of SCD.

Reducing inflammation/oxidative stress

Inflammation and dysregulation of the innate immune system are also thought to be central to the pathophysiology of SCD. Statins have broad anti-inflammatory, vaso-active and cell adhesion effects, and are the subject of phase II trials. The anti-oxidant *N*-acetylcysteine (NAC) has also been shown to have vasoactive and anti-inflammatory effects (Nur *et al.*, 2012). A phase III trial assessing the potential impact of NAC on the frequency of sickle-related pain, including the frequency and duration of hospital admissions did not show any clinical benefit over placebo, but findings were confounded by poor compliance. In an adherent subset there was evidence of reduction of days with painful crises and a trend to reduction in other pain related endpoints in the NAC treatment arm (Sins *et al.*, 2017). A phase 3 trial with L-Glutamine, another anti-oxidant, has shown a reduction sickle cell crisis (3 events vs 4 events) and in median incidence of hospitalisation (2 events vs 3 events) in the treated versus the untreated group. This drug was licensed for use in the US in 2017 (Niihara *et al.*, 2014; Sins *et al.*, 2017).

Allosteric effectors of haemoglobin

The agents discussed above all focus on the consequences of SCD in terms of vaso-occlusion, endothelial dysfunction, inflammation and ischaemia. However, the proximal pathophysiological mechanism, namely the polymerisation of sickle haemoglobin, may also be targeted. The investigational drugs GBT440 and Aes-103 stabilise the R-state of haemoglobin, increasing its oxygen affinity and directly impeding polymerisation. GBT-440 is now in a phase III trial and has promise as a drug that acts at the onset of the sickling process.

Reducing red blood cell dehydration

Although there is some scientific rationale for drugs which limit red blood cell dehydration, a recent Cochrane review failed to find evidence to support a role for the agent senicapoc, a Gardos channel inhibitor which has been widely studied in the context of sickle cell disease (Nagalla & Ballas, 2016).

Reactivating foetal haemoglobin

This remains an appealing target for investigational drugs, not least since it appears to be one of the key mechanisms of action of hydroxycarbamide. Alternative inducers of foetal haemoglobin that continue to attract attention in clinical trials include the histone deacetylase inhibitors, panobinostat and vorinostat, as well as the immunomodulator agent, pomalidomide, though these remain in early phase trials (Okam & Ebert, 2012; Okam *et al.*, 2015).

Gene therapy

Gene therapy involves autologous haematopoietic stem cell transplantation, using HSCs that have been modified *ex vivo* either to correct or to circumvent the sickle mutation (Hoban *et al.*, 2016). Although expensive and technically challenging, this is a technique of curative potential that would not be expected to hold the immunological complications (and possibly the higher procedure-related mortality) of allogeneic transplantation, currently the only other curative strategy in sickle cell disease.

Additive gene therapy

Major advances in the understanding of the mechanics of globin gene expression, plus critical technological breakthroughs, have made gene therapy a more practical future option for the treatment and potential cure of SCD. Either normal or modified anti-sickling β globin variants have been used in lentiviral vectors, driven by the β globin promoter and regulatory regions to ensure high level, erythroid-specific expression once incorporated into the cell. Since permanent incorporation of the target gene into the patient's haematopoietic cell genome is needed, the development of small, effective insulators has been important in enabling a reduction in off-target effects on the expression of nearby genes.

Trials of gene therapy for SCD are now active in Europe and North America, though with limited patient outcome data reported at the time of writing. Data on the first patient treated on the HGB-205 gene therapy study at 12 months post-drug infusion confirm a therapeutic benefit with anti-sickling haemoglobin accounting for 51 per cent of all haemoglobin production which is above the minimum 30 per cent threshold required to have a therapeutic benefit (Cavazzana *et al.*, 2015; Ribeil *et al.*, 2017).

Genome engineering

The development of targeted nucleases has given researchers the capacity to make small and precise changes to the sequence of genes (known as gene editing) without the requirement for the permanent insertion of viral DNA vectors. For conditions arising as consequence of a recognised point mutation, of which sickle cell anaemia is a prime example, these gene editing techniques provide the potential scope to make corrective genetic changes.

Although significant technical hurdles remain in the precise editing of haematopoietic stem cells with long term repopulating potential for autologous transplantation, this remains an area of active study. Expanding appreciation of the detailed mechanisms of normal expression of the transcription factor BCL11a, critical for silencing gamma globin expression, also means that tissue-specific disruption of this gene (with resultant therapeutic increases in haemoglobin F levels) can also be achieved in sickle cell models. While gene editing is not yet available clinically, significant steps forward have been made in the last decade in securing a proof of principle.

Chapter 24: Conclusion

There have been genuine advances in the last decade in highlighting potential new targets for drug treatment of sickle cell disease, with the focus broadening from gamma globin de-repression to include a variety of anti-inflammatory, vaso-active and anti-adhesive agents. It is especially encouraging that several agents (including rivipansel, MST-188 and N-acetylcysteine) have progressed to phase III studies. Supporting a trials-active culture in the field of major haemoglobinopathies and ensuring all patients have access to trials will be essential for ongoing progress.

Chapter 25: Overall conclusion

Section A of this document outlines general principles of care for adults with sickle cell disease (SCD). The acute and chronic complications of SCD are outlined in section B so can either be read in its entirety or used by clinicians faced with a particular complication. Section C provides information on more general topics, including reproductive health, and outlines currently available treatments and briefly introduces possible future treatment options. Additional resources have been provided in the appendices including an annual review pro forma and guidance on staffing levels.

The editorial team have spent the past two years updating this edition of the standards but they will become out of date and we advise readers to use additional sources of information where indicated. Where clinical trials are available we have incorporated them into the standards but we have been faced with a lack of high-grade evidence in many areas and have relied on consensus opinion from the editorial team to provide pragmatic and practical advice.

There is a lack of effective treatment of SCD at present but there are many ongoing clinical trials involving new pharmaceutical agents and therapeutic advances and we hope these will be available when the next edition of the standards is published.

Appendices

Appendix 1: Medical staffing recommendations

A workforce survey was led by Dr K. Ryan on behalf of the UK Forum on Haemoglobin Disorders and can be found at www.haemoglobin.org.uk/library/. The recommendations are summarised below.

A suggested programmed activity (PA) allocation for lead consultants at Specialist Haemoglobinopathy Centres (SHCs) is 1.5 programmed activities (Pas) for every 50 patients for direct clinical duties, made up as:

- Clinics including specialist annual review (2.0 hours /week);
- Ward rounds (1.5 hours/week);
- Day unit attendance and ad hoc consultations, on call (1.0 hour per week); and
- Clinical administration and multidisciplinary team (MDT) meetings (1.5 hours/week).

Other PAs

- 0.25 PA for every 50 patients for supporting activities, National Haemoglobinopathy Registry (NHR) and data collection, audit, teaching, patient liaison, network participation;
- 0.25 PA continuing professional development (CPD) per consultant; and
- 1PA for geographical area clinical lead.

Additional programmed activities are also likely to be required for other activities including specialist training; laboratory work; research; and outreach clinics.

Appendix 2: Psychological therapies

Psychological Therapies

Cognitive Behavioural Therapy

Cognitive Behavioural Therapy (CBT) is a gold standard psychological intervention and comprises two approaches i.e. cognitive and behavioural techniques.

Psychoeducation

Psychoeducational interventions primarily focus on improving knowledge and understanding of patients about their illness while at the same time providing psychological support.

Other Psychological Therapies

There are other established and emerging psychological therapies, which should also be considered for people with sickle cell disease (SCD) based on evidence in other conditions.

a. Mindfulness-Based Cognitive Therapy (MBCT) specifically helps people with recurring depression or chronic pain, by combining mindfulness techniques including meditation, breathing exercises and stretching, with elements from cognitive therapy to help break negative thought patterns.

b. Acceptance and Commitment Therapy (ACT) uses acceptance and mindfulness strategies, together with commitment and behavioural change schemes to help people accept difficulties that come with their lives to build resilience.

c. Motivational Interviewing is an evidence-based treatment that addresses ambivalence to behavioural change. This helps to motivate people to stop habits such as smoking and engage in valued activities, for instance, adhere to medication.

Appendix 3: Benefits advice

An individual's entitlement to benefits is likely to change, along with how benefits are structured. The information below is correct at the beginning of 2018. The Citizens Advice is an excellent resource, providing up-to-date information (www.citizensadvice.org.uk/benefits/). Government information is available from: www.gov.uk/browse/benefits

Personal Independence Payment (PIP)

PIP is the new benefit which replaced Disability Living Allowance (DLA) for those aged 16 to 64 years, who have illnesses, disabilities and mental health conditions and need financial support in order to pay for the extra help or support they need with everyday activities. It consists of two components, daily living activities and mobility component. Each component is paid at either a standard or enhanced rate; depending on the total number of points awarded by a Department for Work and Pensions (DWP)-appointed Independent Health Professional (IHP), at a PIP consultation, based on their (the IHP's) view of the impact an illness, disability or mental health condition has on the claimant's ability to do simple daily activities.

Claimants need to answer a total of twelve questions; ten for daily living activities and two for mobility. They also need to score 8 points in order to get standard rate or 12 points for enhanced. The IHP awards the points based on a criteria referred to as 'PIP descriptors'. Further details about the entire application process, which is in three stages, are available on gov.uk and Citizens Advice Bureau (CAB) websites. It is highly recommended that all claimants familiarise themselves with this benefit or seek assistance from a welfare advisor before they start the application process.

Employment and Support Allowance (ESA)

ESA is a benefit for people who have difficulties working due to an illness, disability or health condition. Current incapacity benefit claimants are being assessed for a switch over to ESA. Also note that income-related ESA is being replaced with universal credit (UC) soon, as part of the welfare reform programme. There are two types of ESA; contribution-based ESA and income-related ESA. Claimants should, where possible seek advice from CAB, a social worker or a welfare support advisor before applying for ESA due to its complexity. Those who are not able to work due to their health and have not made enough national insurance contribution may qualify for the income-related ESA.

ESA application process is in three stages. A simple mistake with the application process could lose you benefits. Patients should therefore seek assistance from CAB, social workers or welfare support workers for step by step guidance through the application process.

Statutory Sick Pay (SSP)

If you are employed but unable to work due to illness, you can get SSP for 28 weeks. This is paid by your employer, who may also pay additional sick pay, depending on your contract.

Attendance Allowance (AA)

AA is a benefit for people who are disabled or have care needs, aged 65 or over and are not in receipt of DLA or PIP. It is paid at two rates. You can get the lower rate if you need frequent care during the *day **or** night*. You get the higher rate if you need frequent care during the *day **and** night*. It is highly advisable that you contact the CAB or an experienced welfare support officer if you want to apply for AA. The gov.uk and CAB websites publish detail information about this benefit.

Direct Payment (DP)

This is funding you can access through your local social services to enable you pay for care and services yourself. This is subject to an assessment by social services of your care needs. NHS choices publish further information about this. Contact your local social service team for advice on how to access care through direct payment

Universal credit (UC)

Universal credit is the new benefit introduced to replace 6 existing benefits. It will be a single monthly payment for people in or out of work. It is being introduced gradually so it is important for claimants to check when it is going live in their area. The following means-tested benefits are being replaced by UC:

- Income Support
- Income-based Jobseeker's Allowance
- Income-related Employment and Support Allowance
- Housing Benefit
- Working Tax Credit
- Child Tax Credit

www.moneyadviceservice.org.uk/en/articles/universal-credit-an-introduction (09/03/2016)

Free NHS Prescription or prepayment prescription certificate

Free prescriptions are generally only available to those on income-based benefits such as income support, and those suffering from specific health conditions of which sickle cell disease (SCD) is not one. However, low income patients can apply for exemption from prescription

charges on the basis of their income. Anyone who is not able to get free prescriptions could apply for a prepayment certificate which reduces the prescription charge considerably. Link below for further information on exception.

See www.nhs.uk/NHSEngland/Healthcosts/Pages/Prescriptioncosts.aspx

Local Welfare Assistance Scheme (LWAS)

Crisis loan and community care grant were replaced with LWAS in April 2013. This new system of emergency support is administered by local authorities who are able to apply qualifying rules at their discretion. Patients with SCD are able to apply for local welfare assistance scheme for emergencies through their local authority.

Benefits Cap

Since 2013, if you are aged between16 to 64 years, the total amount of benefits you can get per week is limited to £350 for a single person and £500 for a couple or lone parent. These figures could be reduced further in the near future. You can check the money advice service website for the list of benefits that are included in the cap and for any change in the above amounts.

Local Housing Allowance

This can be claimed by private sector tenants who need assistance with their rent. There are limits on how much you can claim so check with your local authority for details.

Council Tax Reduction

Council Tax Benefit was abolished in April 2013. This has been replaced by council tax reduction schemes. It is no longer subject to standard rules across the country. The reduction you get is now dependent on local rules, set by your council.

Additional benefits

- Equipment for independent living
- Health equipment and hospital travel
- Value added tax (VAT) relief on equipment and services
- Access to work
- Community and public transport
- Disabled Students' Allowance
- Caring for someone
- Winter fuel payment
- Pension credit

Sources of further information

- Department for Work and Pensions
- UK Government: www.gov.uk
- UK Legislation: www.legislation.gov.uk
- Citizens Advice Bureau: www.citizensadvice.org.uk/
- Money Advice Service: www.moneyadviceservice.org.uk/
- Child Poverty Action Group: www.cpag.org.uk/
- Turn2us : www.turn2us.org.uk
- NHS Choices: www.nhs.uk/
- NHS England: www.england.nhs.uk/
- Age UK: www.ageuk.org.uk/
- Independent Age: www.independentage.org/
- Disability Rights UK: www.disabilityrightsuk.org/

Appendix 4: Annual review pro-forma

Annual Review Pro forma

Date of current review: ……/……/…….
Date of last review: ……/……/……. Name of Reviewer: ……
Diagnosis: ……
Height: _____ m Weight: _____ Kg Spleen size: _____ cm
BP / mmHg SaO_2 %

AFFIX PATIENT LABEL

Centre changed in this review period: Y ☐ N ☐ Local Hospital Team: ……
Number of emergency (A&E or urgent day care) attendances *(IN LAST 12 MONTHS)*:……
Does the patient have an **emergency care plan**? Y ☐ N ☐
Has the patient had any **Red Cell Antibodies**? Y ☐ N ☐ Unknown ☐

Has the patient **conceived a child** in this review period? Y ☐ N ☐
If Yes, outcome: C Section ☐ C Section / Live Birth ☐ Live Birth ☐ ND ☐
Preterm baby less than 36 weeks ☐ Spontaneous Miscarriage ☐
Therapeutic Abortion ☐

COMPLICATIONS *(past 12 months):*		**DESCRIPTION**	**DATE**
Acute chest syndrome	☐	……	……/……/……
Bone Problem	☐	……	……/……/……
(i.e. AVN, Osteopenia, Osteoporosis, Other (specify)			
Gallstones	☐	……	……/……/……
Chronic Hepatitis B, C, HIV	☐	……	……/……/……
Hepatic or Splenic sequestration	☐	……	……/……/……
Hyperhaemolysis	☐	……	……/……/……
Leg ulcers	☐	……	……/……/……
Multi organ failure	☐	……	……/……/……
Neurological: Stroke/TIA	☐	……	……/……/……
Osteomyelitis	☐	……	……/……/……
Other Bacteraemia	☐	……	……/……/……
Pneumococcal Infection	☐	……	……/……/……
Parvovirus	☐	……	……/……/……
Priapism	☐	……	……/……/……
Pulmonary Hypertension	☐	……	……/……/……
Renal Failure	☐	……	……/……/……
Sickle Retinopathy	☐	……	……/……/……
Sickle Hepatopathy	☐	……	……/……/……

TRANSFUSION: Has the patient had regular transfusions in this review? Y ☐ N ☐
Indication for transfusion: ……
Type of transfusion: EBT: Long term EBT ☐ Urgent/one off ☐ Auto/Manual ☐
Top up: Long term Top up ☐ Urgent/one off ☐ New Allo-antibody ☐ *(document on NHR)*

INVESTIGATIONS IN THIS REVIEW PERIOD:

Mandatory	Others	Transfused Patients
ACR	ECG	Audiology
Bilirubin	Echo	Bone Profile (Ca)
Creatinine	MRI/MRA	FSH/LH
Ferritin	Ophthalmology	GTT
Hb	Other Radiology	Thyroid
LFT	Pulmonary function	Testosterone
Microalbuminuria	Sleep study	Virology
Vitamin D		

Annual Review Pro forma

VACCINATIONS IN THIS REVIEW PERIOD:

Influenza	☐	Date given: ……/……/…….
Haemophilus	☐	Date given: ……/……/…….
Pneumovax	☐	Date given: ……/……/…….
Hep B	☐	Date given: ……/……/…….
Meningitis C	☐	Date given: ……/……/…….
Meningitis B	☐	Date given: ……/……/…….
Men ACWY	☐	Date given: ……/……/…….
Meningitis+Hib (Menitorix)	☐	Date given: ……/……/…….
Prevenar	☐	Date given: ……/……/…….
Other:		Date given: ……/……/…….

SPECIALIST IMAGING:

Cardiac T2*(ms) result: Date given: ……/……/…….

……

Liver T2* (ms) result: Date given: ……/……/…….

……

Liver R2 FerriScan® result: Date given: ……/……/…….

……

IRON CHELATION IN THIS REVIEW PERIOD:

Iron Chelation type:

Deferasirox ☐ Deferiprone ☐ Desferrioxamine ☐

Combined Desferrioxamine+Deferiprone ☐

MEDICATIONS IN THIS REVIEW PERIOD:

Penicillin V	☐	Date given: ……/……/…….
Folic Acid	☐	Date given: ……/……/…….
		Date given: ……/……/…….
ACE Inhibitor	☐	Date given: ……/……/…….
Hydroxycarbamide	☐	Date given: ……/……/…….
Vitamin D	☐	Date given: ……/……/…….
Biphosphonates	☐	Date given: ……/……/…….
Other	☐	Date given: ……/……/…….

OPERATIONS IN THIS REVIEW PERIOD:

Adenotonsillectomy	☐	Hip replacement	☐
Cholecystectomy	☐	Orthopaedic	☐
Retinal Surgery	☐	Splenectomy	☐

Other

……

Date of operation:

EXAMINATION:

Respiratory symptoms and examination

Symptoms of sleep disordered breathing ……

Cardiac symptoms and examination ……

Leg ulcers and inspection of lower extremities ……

Annual Review Pro forma

DISCUSSION CHECKLIST ***(tick all that apply and document)***

Acute care plan: Emergency department:

Home pain plan:

Chronic pain review: Opiate use

Referral to pain management:

Adherence to medications:

Discussion of infection prevention and need for early treatment:

Review of visual symptoms:

Referral to other specialist services:

Fertility/contraception. Pre-pregnancy counselling:

Priapism:

Discussion of therapeutic options currently available and new information including ongoing trials. Is the patient eligible for a clinical trial?

Emotional and psychosocial well-being; is psychology referral needed?

Holistic assessment – lifestyle, education, work or welfare issues. Consideration of referral to community services.

Offer additional information: Include key contact details, NHR information, local patient support groups, relevant patient information.

Offer patient satisfaction survey (optional)

Any other comments:

Referral for MDT (local or network) discussion if needed.

Management Plan: (Insert acute pain plan action points from consultation)

Date:

Appendix 5: GP outpatient letter

To include:

Active problems:

- Active painful episodes:
- Number of hospital admissions, number of A&E, day unit admissions, number of days of pain at home in last 12 months
- Emergency care plan:
- Chronic pain: Site, severity, review of analgesia
- Pregnancy in last 12/12
- Surgical procedures in last 12/12

Other health concerns:

- Chest pain
- Shortness of breath (at rest or exertion)
- Symptoms of sleep apnoea
- History of urinary tract infections or haematuria
- Leg ulcers
- Visual symptoms
- Priapism

Transfusion history in previous 12/12

Vaccination history

Medications

- If on hydroxycarbamide – dose, is the patient on maximum tolerated dose, when was last increase, what is HbF%

Examination and Observations:

- Bp and oxygen saturations
- Cardiorespiratory examination, review of lower legs for ulceration, abdominal examination

Investigations (to include)

- Full blood count, renal function, liver function tests, Vitamin D
- Others as appropriate

Referrals (may include)

- Psychology
- Benefits officer
- Ophthalmology
- Discussion
- Fertility and contraception
- New treatments and trials

Example of GP letter

Dear […]

[X] was reviewed in the sickle clinic for their annual review today.

Active problems:

Active painful episodes: [X] has had two hospital admission in the past year, in April and August 2017. Both lasted three days and were for acute pain. They have pain severe enough to interfere with activities of daily living approximately twice a month requiring bed rest and analgesia.

Emergency care plan:

Morphine 5mg sc given 2-4 hourly

Chronic pain:

[X] has had chronic pain in the left hip for over six months. There is pain in the groin on movement and on examination. X-ray was normal and MRI has been ordered today. They will be reviewed in the orthopaedic clinic.

No pregnancy in last 12/12

Surgical procedures in last 12/12: Laparoscopic cholecystectomy in Jan 2017. Uncomplicated procedure.

Other health concerns:

No chest pain, shortness of breath or sleep apnoea. No urinary or visual symptoms.

Leg ulcer in left leg previously but this is now healed.

Floaters in left eye for past three months – to be referred to ophthalmology.

Transfusion history in previous 12/12:

2 units simple transfusion prior to surgery in January 2017

Vaccination history:

Hib/Men C, PCV13, Men B, MenACWY given in primary vaccination schedule

Pneumovax (PPV23) given 2015 (due 2020)

Influenza – given Oct 2017-11-11

Hepatitis B – immune October 2017 (HBsAb 120mIU/ml)

Continued…

Medications:

Folic acid 5mg od (taken 2-3 times per week)

Penicillin V 250mg bd

Analgesia. Paracetamol, Ibuprofen, Dihydrocodeine, taken as required (approx. once a fortnight)

Hydroxycarbamide: Commenced June 2012. 1g daily, maximum tolerated dose. HbF 13%.
Aware of need for contraception

Examination and Observations:

Bp 124/72, Oxygen saturations 99% on air

Cardiorespiratory examination, review of lower legs for ulceration, abdominal examination - normal

Investigations (to include):

Full blood count, renal function, liver function tests, Vitamin D results

Referrals:

Referred to psychology team for review.

Referred to ophthalmology

Referred to orthopaedic clinic

Discussion:

[X] continues on the Mirena® coil with no plans for pregnancy at present.

Current trials discussed.

Next appointment:

[--/---/----]

Yours sincerely

Cc: Patient; General Practitioner; and local hospital (if appropriate)

Continued...

Please also read the following general information about the condition which we hope will be helpful for you and your team, in managing this patient.

Risk from infection in people with sickle cell.

People with these conditions are more at risk from some infections, in particular bacterial infections, as spleen function is poor. Pneumococcus and Salmonella species are especially dangerous but any bacterial infection will affect a person with sickle cell more severely than other people. **Steps to reduce the risk are**:

1] Having available at all times a supply of Penicillin V. This can be taken EITHER at a dose of 250 mg [one tablet] twice daily every day OR not taken every day but the patient should know to start taking a treatment dose – 500 mg [2 tablets] FOUR times a day at the first hint of infection, fever, sore throat, cough, shivers etc. Even if they take it at a preventing, lower dose they should increase to this larger treatment dose if they develop symptoms. Penicillin allergic patients should have a supply of Erythromycin 500 mg bd.

We recommend that, if they are not feeling better within 24 hours, they see you or us for further assessment and consideration of broader spectrum antibiotics. If symptoms are not responding to usual antibiotics, please refer to us **urgently via the Emergency Department** especially if there is any possibility of sepsis.

2] Appropriate vaccination.

Adults with SCD who have not received primary vaccination as part of the national schedule in the UK should be offered:

- One dose of Hib/Men C and one dose of pneumococcal polysaccharide vaccine (PPV23); followed by
- One dose of MenACWY conjugate vaccine one month later
- Two primary doses of MenB vaccine one month apart [this can be at the same visits as the other vaccinations above]
- A single 0.5 ml dose of pneumococcal conjugate vaccine (PCV13) which should be given at least six months after PPV

Adults with SCD should also be offered

- Pneumococcal polysaccharide vaccination (PPV23) at five yearly intervals
- Annual influenza vaccination.
- Hepatitis B vaccine if they have not previously received it and are non-immune (HBsAb <100 mIU/ml)

ALSO

3] If there is any suspicion of **food poisoning**, please refer to us for assessment, stool culture

Continued…

etc. Salmonella infection must be treated, even if symptoms are mild, or symptoms have settled but stool culture is positive, as it can become rapidly invasive and very serious.

4] Please advise **antimalarial** prophylaxis if you are aware s/he is travelling to a malarious area. People often think that if they have sickle cell disease they are protected against malaria – this is far from correct, and malaria can be especially dangerous in in these patients.

Managing pain in sickle cell.

Pain is common, but not universal, in people with HbSS and $S\beta^0$ thalassaemia. It is less common but still sometimes occurs in those with SC or $S\beta^+$ thalassaemia. It can be of varying severity. Many uncomplicated pain episodes can be managed safety at home, taking oral paracetamol and ibuprofen, and plentiful fluid. Patients who have significant pain crises will usually have a supply of graded stronger analgesia: co-codamol, dihydrocodeine, tramadol and / or oral morphine.

'Red flag' symptoms : significant fever, marked pallor, sleepiness, vomiting/diarrhoea so unable to keep up positive fluid balance, chest pain, breathing problems, any suggestion of limb weakness, anything UNUSUAL other than familiar limb or back pains. If these occur, with or without pain, the person must be assessed here at the hospital, and will often need admission for care of complicated episodes.

Watching for less common complications.

Sickle cell can cause a host of complications, the range getting wider as the person gets older. Patients will have a comprehensive 'annual review' screening for some of the longer term problems, as well as managing any current symptoms or problems.

****** N.B. Omit if female ***:*** [However, an acute complication to be watchful for from the start is **priapism.** This is a painful penile erection, lasting longer than normal. It can be 'stuttering' – coming and going, sometimes a couple of times a night, or can be 'fulminant' – an attack which starts and will not spontaneously resolve. If your patient has stuttering priapism, please let us know for an early clinic review. If he has a fulminant attack he should be directed immediately to the Emergency Department for possible aspiration.]

You and your team in primary care can help by:

a] Repeat prescribing Penicillin V 250 mg bd for those who take it regularly, and 500 mg qds [give a two week supply] for those who take if only for signs of infection. Please give Erythromycin 500 mg bd for people who are penicillin allergic.

b] Prescribing oral Paracetamol and ibuprofen when requested, and any other medications including stronger analgesia, as indicated from clinic letters.

c] Remembering that symptoms which may be trivial in others [e.g. sore throat, fever of 38.0°C or higher] may warn of significant bacterial infection in those with sickle cell disease: please

Continued...

give broad spectrum antibiotics early, and refer to us promptly via ED if there is any possibility of sepsis.

d] Being aware of the side effects of some of the medications he / she may require in the future: for example ***hydroxycarbamide*** [given as a disease modifier as it reduces the frequency and severity of pain crises] can cause neutropenia and ***deferiprone***, sometimes used to reduce iron levels in patients on regular transfusions, can cause agranulocytosis, SO anyone on these medications should be **referred immediately to hospital if febrile**. ***Deferasirox*** is also used to reduce iron levels in transfused patients, and it can cause indigestion, even upper GI bleeding, rash, and kidney and liver function abnormalities. If people on ***desferrioxamine*** develop acute abdominal pain we will need to assess them in case of Yersinia bowel infection. **Please contact us immediately if you have any concerns about anyone on these medications.**

e] Encouraging / giving annual 'flu vaccine and other vaccinations as needed

Contact numbers:

[*01234 567890*]

Appendix 6: Indications for haematopoietic stem cell transplantation (HSCT) in adults with sickle cell disease

Patient Selection

Adapted from (Angelucci et al., 2014)

Indications

- Patients with sickle cell disease (SCD) at high risk for disease-related morbidity or mortality defined by
- Overt stroke
- Pulmonary hypertension as defined by cardiac catheterisation
- Patients requiring long-term transfusion therapy for other sickle-related complications
- Patients with potentially reversible complications not ameliorated by HC
- Vaso-occlusive crises and/or acute chest syndrome (≥3 hospital admission per year while on maximal tolerated dose of HC)
- Patients unable to receive transfusion therapy due to alloimmunisation or hyperhaemolysis

Inclusion criteria

- Aged between 18 and 65 years of age
- Availability of fully HLA-matched or haplo-identical family donor
- Negative B-HCG within 7 days of commencing conditioning
- ECOG score ≤ 2
- Ability to comprehend and sign informed consent

Donors

- 6/6 HLA identical family donor
- Haplo-identical donor in the absence of 6/6 family donor
- Fit to receive granulocyte colony-stimulating factor (G-CSF) and give peripheral blood stem cells as assessed by an independent physician experienced in the medical assessment of HSCT donors
- Ability to comprehend and willing to sign an informed consent

Exclusion Criteria

Patients

- DLCO (diffusing capacity of lung for carbon monoxide) <45% predicted
- LVEF (left ventricular ejection fraction) <40% estimated by ECHO
- Uncontrolled bacterial, fungal or viral infections within one month of HSCT
- Active lower limb ulcers
- Active hepatitis B or C or human immunodeficiency virus (HIV) infection
- Liver cirrhosis or organ failure incompatible with survival following HSCT
- Major ABO mismatch if high titre antibodies present
- Failure to comply with adequate iron chelation pre-HSCT
- Pregnant or lactating
- Where haplo-identical donor is the only option available, presence of anti-bodies to donor HLA antigens

Donors

- Pregnant or lactating
- HIV positive
- Sickle cell disease (SCD)

Appendix 7: Frequently asked questions

General questions

I have the sickle cell trait, but can I experience symptoms associated with sickle cell disorder?

Sickle cell trait means you carry one copy of the sickle cell gene (S) and one copy of the normal haemoglobin gene (A) so sickle cell trait may be referred to as 'AS'. Because most of the haemoglobin in your body is normal, the majority of people do not have symptoms.

There's a slightly higher rate of complications during surgery if you have the trait. However, if your anaesthetist knows, he or she can make sure you have extra oxygen, which reduces the changes of complications. Lack of oxygen is one of the known causes of complications in people with sickle cell trait. So be careful if you're at a high altitude (e.g. at the top of a mountain, long-haul flights). Other known triggers are high atmospheric pressure environments (such as scuba diving) and dehydration, so make sure you drink lots of water if you have the trait. Exercise is also a trigger. If you exercise, let your teacher/coach know you have the trait, and stay hydrated throughout.

The majority of people with sickle cell trait have no complications associated with this. For people with trait are often told they can't do sport, and they can't be at altitude, but that's not true, you just need to take a little extra care.

What is the difference between sickle cell disease and sickle cell anaemia?

Sickle cell disease is an umbrella term that describes a group of inherited major blood disorders that are characterised by abnormal haemoglobin molecules called haemoglobin S. Sickle cell anaemia is the commonest and most severe sub-type of sickle cell disease abbreviated as HbSS. Other sub-types of sickle cell disease include HbS β^0 thalassaemia, HbS β^+ thalassaemia, HbSC, Hb SD Punjab, HbSE and HbSO. The other forms of sickle cell disease are usually milder and vary in terms of the spectrum of the problems they might cause with some patients not being aware of the diagnosis until it is picked up incidentally on routine testing.

What is the difference between SS and SC genotype?

In the SS genotype an individual inherits two copies of the abnormal haemoglobin S but in the SC genotype the individual inherits one copy of haemoglobin S and one copy of haemoglobin C from each parent. The SC genotype tends to be milder although individuals are prone to all the complications that can occur in the SS genotype. The SC genotype tends to have less frequent crisis and a higher haemoglobin level with overall milder disease behaviour.

What's the general life expectancy for people with sickle cell disease?

The general life expectancy for people with sickle cell disease is dependent on a number factors including the natural behaviour of the disease in a particular individual, other medical problems unrelated to sickle cell disease as well as the quality and access to appropriate healthcare facilities and professionals. Historically, early studies from the United States suggested that the median life expectancy for men and women with the more severe form of sickle cell disease i.e. sickle cell anaemia was between 42 and 48 years. Interventions such as regular penicillin, vaccinations, blood transfusion and Hydroxycarbamide as well as availability and access to specialist care have improved life expectancy. Bone marrow transplantation is potentially curative. A recent study from London suggested that the median survival for patients with sickle cell anaemia was closer to 70 years although this cannot be immediately be extrapolated to an individual's life expectancy due to the number of factors previously discussed.

Primary care

What is the role for GPs in sickle cell disease care?

It is very important for people with sickle cell disease to maintain their health. General practitioners (GPs) can help them stay healthy and prevent sickle cell crises. GPs prescribe penicillin prophylaxis and give immunisations in their surgeries to prevent infections. They can recommend vitamin supplements such as folic acid, and appropriate analgesia for pain. GPs can also reinforce self-management of sickle cell disease such as fluid intake and keeping warm, provide advice about healthy lifestyles including smoking cessation, and travel information including countries where malaria is prevalent and prophylaxis is needed.

How can my GP help me when I have sickle cell pain?

Many people with sickle cell disease have pain at home and do not go to the hospital. Your GP can help you manage your pain at home, and advise you of when to go to the hospital. Your GP can review your analgesia (medication for pain) with you regularly and recommend changes if necessary, or complementary (additional) therapies including physiotherapy and massage. It is important to talk to your GP about your pain management even if you are admitted to hospital.

Why should sickle cell patients have all these vaccinations?

Patients with sickle cell disease are more prone to infections for a number of reasons, an important one being the gradual reduction in size and the function of the spleen. Particular strains of some bacteria are potentially life threatening due to the risk of complications such as severe pneumonia, acute chest syndrome and sepsis. A number of vaccinations are available and although they do not provide universal protection, they reduce the risk of specific infections. The recommendations as to which vaccinations are most appropriate potentially change over time. Patients should be advised by their haematologist as to the required vaccinations; these

are either administered in the hospital outpatients or via the GP. Vaccinations are also given to protect against potential infection transmission in the course of treatment. An example is vaccination against hepatitis B due to the very small risk of contracting this infection from a blood transfusion.

What are the long-term effects of these vaccinations on my immune system?

Vaccinations work by stimulating the immune system to produce antibodies that fight infections and therefore have a protective role. Apart from stimulating the immune system to produce antibodies, there should be no long-term effects on the immune system.

How can sickle cell disease affect my teeth?

Patients with sickle cell disease are prone to all the problems that other individuals have as regards their teeth and dental care. There are a number of oral hygiene and dental problems that occur more frequently in patients with sickle cell disease. These include pain and yellow discolouration of the tissue of the mouth, delayed tooth growth as well as abnormalities of the covering of the teeth, poor alignment and sometimes increased dental infections. Some of these problems are due solely to having sickle cell disease but others relate to dental hygiene as a whole. Therefore good dental hygiene and regular brushing reduces dental problems, but importantly early attendance at a dental clinic if any problems arise is highly recommended.

Does all dental treatment have to be done in the hospital?

By no means does all dental treatment have to take place in the hospital. Your dentist should regularly assess your dental hygiene and early warning signs of any abnormalities of the teeth or gums. Most non-invasive dental care can be undertaken by a dentist. For more complex dental work, a discussion is usually had between the dentist and hospital maxillofacial surgeon as to the suitability, safety and appropriateness of undergoing dental treatment either in the community or in the hospital, especially if a general anaesthetic is required. Sometimes special precautions are required to reduce the risk of developing complications after a dental procedure which will require discussion with your haematologist.

Health and well-being

What is the benefit of going to the outpatient clinic when I am well?

It is very important for people with sickle cell disease to maintain their health.

Sickle cell disease affects people differently, and it is important to look out for early signs of problems with your spleen, lung, heart, kidneys, liver, eyes and other body organs. This is done in the clinic, and you may be asked to go to other clinics for additional tests or examinations to prevent complications later. Also, some patients are on long-term treatment for their sickle cell

disease such as hydroxycarbamide (previously known as hydroxyurea) or transfusion and require regular blood tests and monitoring.

What is a psychologist?

A psychologist working in healthcare has professional training and clinical skills to help people learn and cope much better with life issues and emotional problems. There are many kinds of psychologists working in healthcare; however they all help by using a variety of methods based on the best available research, and consider each person's unique values, characteristics, goals and circumstances.

Why would a psychologist be needed for sickle cell disease?

Sickle cell disease affects people differently; some do well by their own means, and others need help. Even those who do well sometimes need some support. Psychologists help people with sickle cell disease to recognise their daily situations including health problems, stress, and what they do about their pain and other symptoms. They help to find practical and realistic solutions to these problems, and better coping methods to live with sickle cell disease.

How can psychology help to deal with sickle cell pain?

There is good research to show that a kind of therapy called cognitive behavioural therapy (CBT), which includes certain things like relaxation can reduce the frequency, duration and intensity of pain. There are other methods you can learn to change the way you think about pain that can help lessen the distress of being in pain.

How can I find a psychologist to help me with sickle cell disease?

That depends. Your hospital and sickle cell team may have a psychologist(s) working with them. If your hospital does not have a psychologist as part of its sickle cell team, they will be able to refer you or ask your GP to find a psychologist through, for example, Improving Access to Psychological Therapies (IAPT) or other psychological services near you.

Do I need to be an inpatient to see a psychologist?

No. In all likelihood, if your hospital has a psychologist available, you will be able to have support as an outpatient. Most psychologists work with carers and families too; you do not even need to be a patient in order to find some help, so long as the concern is related to sickle cell disease. You could also be referred to see a psychologist by your GP.

How else might a psychologist help me with sickle cell disease?

Sometimes people want to make health-related changes that are not directly related to sickle cell disease, but are helpful nonetheless. For instance, if you want to quit smoking, psychologists have strategies to help you quit. Although this is not directly related to sickle cell disease, we know smoking is especially harmful in sickle cell disease because it increases the chance of getting a chest crisis, so making a change here will help. Psychologists also work together with patients, carers and their families in order to improve the experience of the healthcare system. They can help people deal with disagreements, conflict, and other challenging scenarios that can arise between patients, families and providers.

What are the main nutritional problems associated with sickle cell disease?

There are many nutritional consequences associated with the main clinical features of sickle cell disease namely, chronic haemolysis, vaso-occlusion, chronic inflammation and impaired immune function. Research conducted investigating the role of nutrition in sickle cell disease provides convincing evidence that sickle cell patients have a high resting energy expenditure with associated increased cardiac output, high protein turnover, appetite suppression, low body mass index (BMI) and exercise tolerance and are at risk of 'protein/ energy-like malnutrition'. Many complications associated with sickle cell disease therefore have a nutritional underpinning with under-nutrition identified as a critical feature and a serious complication of the disease.

Why is good nutrition important in the management of sickle cell disease?

Good nutrition is associated with good clinical outcomes and improved quality of life which is observed in many people living with long term conditions such as chronic obstructive lung disease (COPD) and diabetes and it is no different for people living with sickle cell disease. Without good nutrition, sickle cell patients are at high risk of disease-related malnutrition resulting from poor appetite and weight loss, frailty, increased risk of infection, weakness, immobility and muscle loss as well as developing complications of sickle cell disease itself. Good nutrition is associated with increased recovery from illness, reduced length of hospital stay and improved functional status in individuals. Timely referral to a dietician can help improve the overall nutritional intake and nutritional status of sickle cell patients at risk of disease-related malnutrition.

What is the best nutritional management for patients with sickle cell disease?

Educating sickle cell patients about their condition and the associated nutritional risks is paramount to supporting the effective nutritional management of the condition. Dehydration, impaired immune functioning, inflammation, chronic anaemia and fatigue, constipation and low BMI are the common nutritional problems facing a sickle cell patient so the best nutritional management would be tailored to effectively management and reduce the incidence and effects

of these problems. Following the national healthy eating guidelines such as the Eat Well Guide are helpful adjuncts to managing the nutritional status of sickle cell patients

Can we get more information on how diet can improve sickle cell crisis?

A healthy and balanced diet is important as part of the overall care of patients with sickle cell disease. There are no specific dietary interventions that affect sickle cell crisis, but adequate nutrition both in terms of quantity and timing of eating might reduce the propensity to develop a sickle cell crisis. Information on diet in sickle cell disease is available in most clinics where patients are looked after. In addition, a patient can request a consultation with a dietician either via the local hospital clinic or via his or her general practitioner. There is a significant amount of reading material related to diet in sickle cell disease online, but it is important that information accessed by this means is validated by healthcare professionals who look after patients with sickle cell disease. This information is usually best accessed from sickle cell disease specific websites.

Should I take multivitamins or a blood tonic for my anaemia?

Multivitamins and blood tonics are supplements, and their constituents are variable. These are supposed to be nutritional supplements that help you produce more red blood cells and reduce your anaemia; however there may be side effects that can be detrimental to your health. It is very important to show any supplements you intend to take to your doctor for the correct advice. Do not rely solely on the information provided by people selling these supplements.

Does sickle cell cause my insomnia?

Insomnia is difficulty getting to sleep or staying asleep for long enough to feel refreshed the next morning. People with sickle cell disease may have hypoxia (low oxygen levels in their blood). This has something to do with sickle cells that do not carry enough oxygen, and breathing problems that make it difficult for you to have a good night's sleep, resulting in insomnia. Furthermore, when people have sickle cell pain it usually affects their sleep. Some people have to live with frequent pain and even though it may not affect their daily activities as much, it may interfere with their sleep. Also, some people worry about their sickle cell disease and this may disturb their sleep.

Where can I get further information about living with sickle cell disease?

There are many sources of information about living with sickle cell disease. The Sickle Cell Society, other voluntary organisations, and support groups produce information. Your GP can provide you with information, and there are NHS websites. You can also ask health professionals at the hospital where you attend, and community based sickle cell centres.

Who can I speak to about daily health issues related to my sickle cell disease?

You can speak to health professionals about issues related to you sickle cell disease. Speak to your GP, specialist doctors or nurses. If you are not feeling well contact these health professionals immediately to make an appointment, do not wait for your scheduled clinic appointment, which may be weeks or months away. It is important that health issues related to sickle cell disease are addressed early to avoid subsequent complications.

How do the voluntary organisations and charities help people with sickle cell disease?

Voluntary organisations and charities support and represent people with sickle cell disease. Advocacy is very important, and these organisations and charities facilitate this. They can direct and assist people with sickle cell disease to access services such as social support, welfare benefits, and housing. In addition, these organisations may provide small grants to help with the finances of people with sickle cell disease.

Why am I not entitled to free medication and why is access to any form of welfare for sickle cell in the UK extremely difficult?

Some groups of people are automatically entitled to free NHS prescriptions, some are not. You can get free NHS prescriptions if you are: aged 60 years or over; under 16 years; 16-18 years and in full-time education; pregnant or have had a baby in the previous 12 months and have a valid maternity exemption certificate. You will not automatically qualify unless you fall into these groups, or are in receipt of welfare benefits, or medication given in hospital when you are an inpatient. The system around welfare benefits is complex and can be difficult to understand, you may be entitlement to some benefits but it is better to seek advice to ensure that you can claim appropriately.

How should I communicate my medical needs to my employer and what are my rights?

You are under no obligation to tell your employer about your sickle cell disease if you do not want to, unless your condition may affect your health and safety in the workplace, you work in the armed forces or you drive for work. If you do decide to disclose, having an ongoing dialogue about your condition and medical needs may help to manage the work environment and your workload, and if you ever need time off for hospital appointments.

Even if you don't need any support, you may still want to tell them so they're aware in case things change in the future. This can help to avoid any misunderstanding if any of your symptoms – particularly if hidden symptoms such as fatigue start to affect you at work. Consider arranging an informal chat with your employer, and it always helps to prepare what you are going to say e.g. the medical treatment you are currently receiving, any support or

reasonable adjustments you may need and a reassurance that you are committed to your job – having sickle cell disease doesn't change your skills or experience. It may also be beneficial to bring in some literature about the condition to raise awareness.

Under the Equality Act 2010 (UK Government, 2010), your employer is required to take 'reasonable adjustments' to allow you to continue working. For example, providing a warm, draught-free work environment, access to drinking water and toilet facilities, and good accessibility in and around the building will help you continue working without exacerbating your condition. Further reasonable adjustments include making informed decisions about tasks you can and cannot do, providing supervision/support to reduce stress, altering your hours of work or allowing you additional time off.

To find out more about disability and employment you can contact your local job centre and ask to speak to the Disability Employment Adviser.

Or contact the Disability Rights Commission on **08457 622 633**, or **08457 622 644** for the textphone, or write to them: Freepost, MID02164, Stratford-Upon-Avon CV37 9BR.

If you feel you have been a victim of disability discrimination in the workplace, please contact: the Equality Advice Support Service discrimination helpline on **0808 800 0082**. They can help you by:

- explaining what the law says and how this applies to you
- explaining how a situation could be resolved
- supporting you to try and resolve issues informally
- if the issues can't be resolved informally, referring you to a conciliation or mediation service
- if you need or want to seek a legal solution, helping you work out if you're eligible for civil legal aid or what to do if you plan to represent yourself

Pain management

What is the maximum waiting time for analgesia in A&E departments and why is there variation?

It is recommended that analgesia is given within 30 minutes of arrival in the Accident and Emergency (A&E) department. Unfortunately A&E departments are often very busy and this is not always achieved. If you are having to wait more than 30 minutes for analgesia please make sure your local sickle team are aware so they can make sure you have a clear care plan and they can support A&E to meet the national standard.

Why has my opioid dose been reduced recently?

Opioids have lots of side effects and doctors try to give the smallest effective dose for the minimum amount of time. There are lots of reasons why your dose has been reduced and you should discuss this with your doctor or nurse specialist. You may have developed side effects (e.g. sleepiness or low oxygen levels) on your previous dose, your doctors may be trying to gradually decrease your dose of opioid, or they may have introduced a different pain killer.

Why do I not get IV fluids when I am on the wards?

If you are able to take fluids orally then you will not be given intravenous (IV) fluids. You will be prescribed IV fluids if you are not able to drink, for example if you are vomiting.

Why is my doctor recommending gabapentin?

Gabapentin is used for the treatment of neuropathic (nerve-related) pain, and may be offered if your pain is sharp, burning or shooting. It is usually used together with opiates.

Why are analgesic patches used?

Transdermal patches such as fentanyl can be used for both acute and chronic pain control and they slowly releases a small, regular amount of pain killer. Some patients find that lidocaine patches, used in addition to other therapy, can provide effective analgesia where pain is very localised.

Disease complications

When do I know I am having an asthmatic attack and an acute chest syndrome?

It can sometimes be quite difficult for an individual patient to distinguish the two conditions, an asthma attack can range from mild to life-threatening while an acute chest syndrome is also potentially life-threatening and requires immediate medical attention. They both have some symptoms in common including shortness of breath. It is important that a patient recognises that they are unwell and immediately seeks urgent medical attention with the team managing his or her sickle cell disease.

Is priapism caused by sexual activity?

Priapism is a prolonged, painful erection lasting more than a few hours and essentially is a form of sickle cell crisis that is localised to the penis. Although in most cases this is not associated with normal sexual function or desire, occasionally patients do report that priapism develops during sex. Having sex can be physically demanding and this might trigger a sickle cell crisis including an episode of priapism.

Why am I at risk of fevers and blood infections (sepsis)?

Patients with sickle cell disease have an increased propensity to infections, most importantly due to the reduction in the size and function of the spleen therefore compromising its function in fighting certain types of bacteria and as part of the immune system. This reduced capacity of the spleen predisposes to infections which sometimes can be life threatening especially in cases of severe pneumonia or sepsis. It is for this reason that patients are routinely vaccinated on a regular basis as well as prescribed oral antibiotics to take as a preventive measure, although none of the interventions completely remove the risk of severe infection.

What should I do if I have a fever?

It is important to seek prompt medical care if you notice a high fever. It is always helpful to document the exact temperature using a thermometer. Subsequently this should be followed by direct contact with your local haematology team depending on the access arrangements during and outside working ours. If there is any difficulty or delay in accessing your local haematology team, then it is advisable to attend the Accident and Emergency Department of your local hospital where further investigations and in most cases appropriate antibiotics will be commenced and possible admission, which might also reduce the risk of developing a crises.

What should I do if I notice blurred vision or something floating across my vision?

It is advisable to seek medical help as soon as possible. This would ideally be at an eye casualty otherwise reporting to your local Accident and Emergency Department will prompt a referral either to an eye casualty, or ophthalmology clinic dependant on the severity of the symptoms and findings on the initial examination.

There is not enough information being given about sickle retinopathy. Why?

Sickle related eye disease is complex and needs input by eye specialists who are able to recognise and advise and undertake appropriate management. For patients, it is important that they have regular optician reviews as the first signs of sickle retinopathy might well be picked up at this stage. It is also important that should a patient develop blurring of vision or any other significant visual abnormalities, they should report to the nearest emergency eye unit or his or her local team responsible for his or her sickle cell disease. Sickle retinopathy tends to be a slowly developing process with most patients who are not monitored carefully being unaware until a major complication of the retinopathy occurs. The advice is to have regular optician reviews or attend clinics arranged by the local sickle cell disease team.

How do I prevent avascular necrosis and how do I manage it?

Avascular necrosis (AVN) which most commonly affects the hips but can affect the knees, the ankles, the shoulders or elbows is a chronic degenerative condition related to sickle cell disease. It is somewhat similar to a chronic form of arthritis. The measures that are put in place to manage and prevent progression of arthritis are also helpful in this condition. Maintaining good posture, regular exercise and an optimal body mass index are very helpful in reducing the onset and slowing down the progression of AVN. In terms of its management appropriate pain relief is usually the first line, but sometimes differing from that used in managing an acute sickle cell crisis. Appropriate advice should be sought from a patient's GP and local sickle cell disease team who might refer the patient to an orthopaedic surgeon. Sometimes in addition to the above measures, physiotherapy is recommended; a proportion of patients will need some form of surgical intervention to manage the AVN.

Surgery

Why do I need to have a transfusion before surgery if I never needed one before?

Surgery confers a number of risks on patients with sickle cell disease, including an increased risk of a sickle cell crisis either during surgery or afterwards. Not only is it important for a surgeon to discuss your condition with your haematologist prior to undertaking any form of surgery, but in certain cases a transfusion might be recommended to allow surgery to proceed safely. This transfusion can either be in the form of a top-up or in some cases an exchange blood transfusion. In many cases, simply increasing the haemoglobin with a transfusion reduces the risk of sickling and developing a crisis around the time of surgery. Overall outcomes following surgery have been shown to improve following a transfusion; protocols and guidance are provided dependant on how severely the patient is affected by sickle cell disease and the nature and potential risks associated with the surgery.

Should I insist the surgeon contacts a haematologist before my operation?

Yes, as appropriate advice and potential intervention will reduce the risks of surgery in patients with sickle cell disease.

Treatment

Does hydroxycarbamide cause leukaemia?

Hydroxycarbamide has been used in sickle cell disease for over 20 years and a careful follow-up of patients over many years has shown that there is no increased risk of leukaemia in patients with sickle cell disease taking hydroxycarbamide as part of their treatment. Hydroxycarbamide is used in a number of other blood conditions some of which are forms of leukaemia while

others are pre-leukaemic blood disorders. In those with pre-leukaemic blood disorders, as there is already a propensity to develop leukaemia, a proportion of patients on hydroxycarbamide for these conditions will go on to develop leukaemia while on hydroxycarbamide. This is definitely not the case when hydroxycarbamide is used in sickle cell disease; there are several thousands of patients followed up over many years to support this finding.

Will hydroxycarbamide make me infertile?

In general for men, hydroxycarbamide does not prevent a man from making a woman pregnant or fathering children. Sperm count and function might be reduced while taking hydroxycarbamide. In most cases these abnormalities are corrected after hydroxycarbamide has been stopped for 2-3 months. In a few cases, the sperm count and function has not returned to normal after this period. It is recommended that a sperm sample is taken and stored before commencing hydroxycarbamide. It is strongly recommended that contraception is used when taking hydroxycarbamide because the drug can potentially be harmful to a developing foetus.

In women pregnancy should be avoided when a woman or her partner is taking hydroxycarbamide due to the potential risk of foetal abnormalities. The drug should also be stopped immediately if you become pregnant.

What is the risk of contracting HIV or hepatitis from a transfusion?

It is extremely rare for someone to develop a viral infection from a blood transfusion in the UK, as the blood services undertake strict testing processes to detect contaminated blood. For example it is estimated that;

1. The risk of getting hepatitis B is about 1 in 1.3 million
2. The risk of getting hepatitis C is about 1 in 28 million
3. The risk of getting HIV is about 1 in 6.5 million

It is reassuring to know that there has been no recorded case of an individual developing any of the viral infections above from a transfusion since 2005.

Will a blood transfusion start a sickle cell crisis?

Blood transfusions are very safe procedures with a very low risk of side effects. They do not directly start a sickle cell crisis, although a rare reaction to a transfusion could precipitate a sickle cell crisis.

What will happen if I don't take my iron chelation?

Excess iron from transfusions accumulates in a number of organs including the liver, pancreas, joints and heart. Unfortunately the body does not have the capacity to excrete the excess iron

that is absorbed. Iron chelating drugs act efficiently to remove excess iron form the body either due to an inherent tendency to absorb iron or that which accumulates through blood transfusions. The ultimate outcome of failure to adhere to iron chelation therapy is progressive damage to vital organs due to the accumulation of iron, which in some cases is irreversible. This can lead to liver disease, diabetes, arthritis, infertility and heart disease including the risk of early death.

Can I have a transplant if I have a sibling as a donor?

Yes, if a sibling is a compatible match with you. At the time of preparation of these standards of care, bone marrow transplantation for adults with sickle cell disease is not routinely commissioned or funded by NHS England, although this might change in the future.

What is a bone marrow/stem cell transplant and would I be eligible for the procedure?

In an individual with a sickle cell disease (SCD), the bone marrow produces red blood cells that contain haemoglobin S, which leads to the complications of SCD. The transplant process involves eradicating the patient's stem cells, the patient's immune system, using strong medicines like chemotherapy. The stem cells are then replaced with a matched donor's stem cells using a transfusion through an IV tube. The new bone marrow then produces red blood cells that are healthy as they do not contain haemoglobin S.

In the UK, funding for stem cell transplants is available where it can be shown that the potential benefits outweigh the risks. Patients are at higher risk of catching life-threatening infections due to chemotherapy and the immunosuppressants taken to avoid risk of graft-versus-host-disease (GVHD), which is when the donor cells attack the host cells. GVHD that does not respond to treatment can lead to organ damage or even death. A further risk is graft failure (when the donated bone marrow fails to take). Each risk has a 5-10% chance of occurring. Transplants are generally safer in children than in adults because their immune systems and other body tissues are better able to regenerate and recover quickly from toxic treatments.

To be considered for the treatment, the following criteria must be met:

- The recipient must be healthy enough to survive the process, and not have severe organ damage.
- There must be a matched donor. The donor will ideally be a healthy sibling who is a cell/tissue match. There is about a 1 in 4 chance that a sibling will have matching tissue and be a suitable donor.

Research into a cure for SCD is ongoing in the UK and abroad. For example, there is a new type of stem cell transplant being developed, whereby chemotherapy is not needed, reducing the risks involved. However, recipients still require immunosuppressants.

If you would like to find out more about the treatments available to you in line with your medical need and history, please speak to your consultant.

I have heard of new drugs in other countries, why are these not available in the UK?

As at the time of preparing these standards, a number of new drugs have shown encouraging results in the context of well-designed clinical trials. These new drugs are likely to be used on their own or with hydroxycarbamide. Drug trial results are validated and published, then assessed by the various licensing and funding regulatory bodies, including the European Medicines Agency (EMA), the National Institute for Health and Care Excellence (NICE) and NHS England. Once approved for use and funded, they will be available to patients in the UK.

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Sickle Cell Society
54 Station Road
London NW10 4UA
United Kingdom
Tel.: +44 (0)20 8961 7795
Fax: +44 (0)20 8961 8346
info@sicklecellsociety.org
www.sicklecellsociety.org