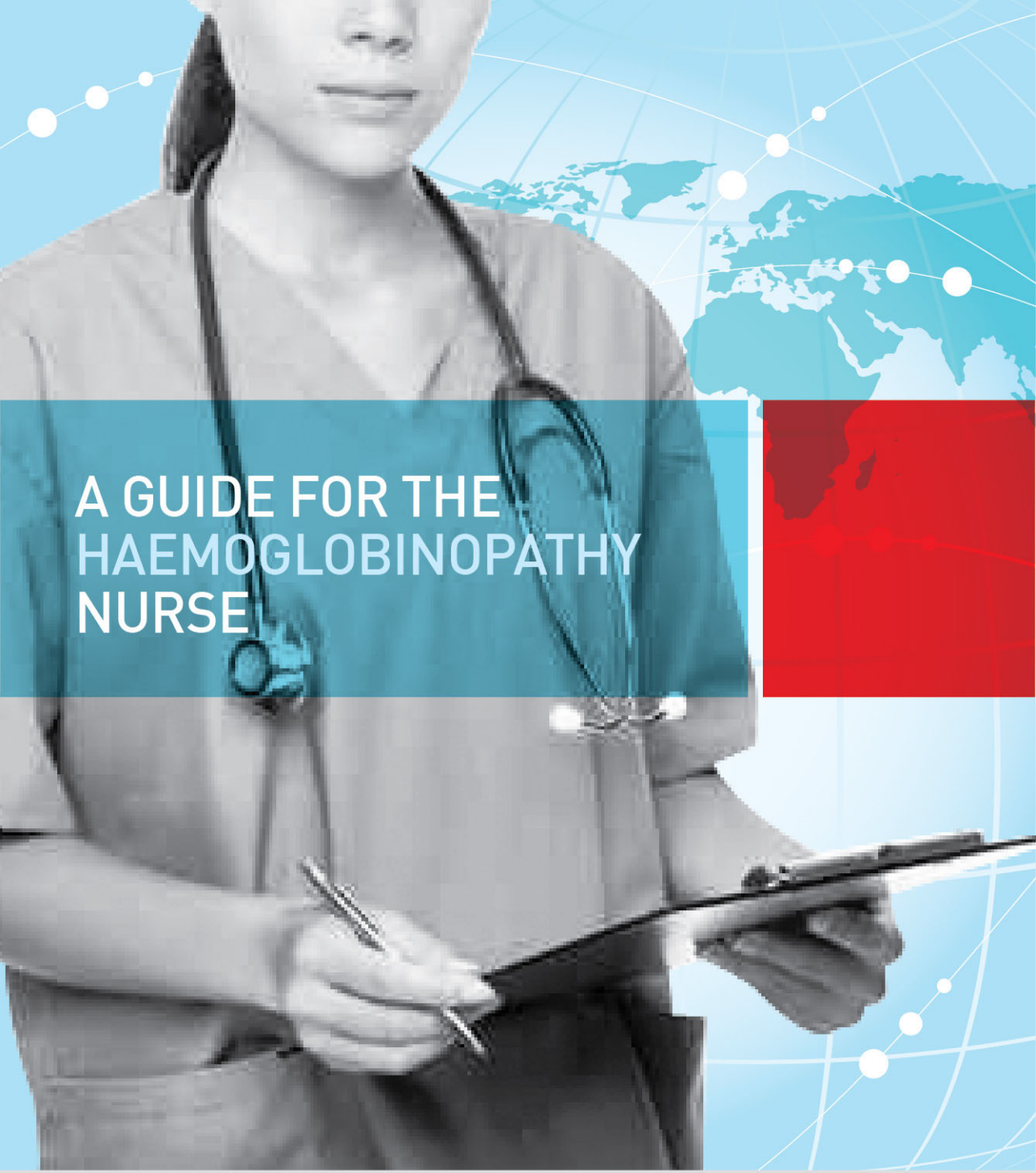

A GUIDE FOR THE HAEMOGLOBINOPATHY NURSE

THALASSAEMIA INTERNATIONAL FEDERATION

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A GUIDE FOR THE HAEMOGLOBINOPATHY NURSE

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ABOUT THALASSAEMIA INTERNATIONAL FEDERATION (TIF)

The Thalassaemia International Federation (TIF) is a non-profit, non-governmental organisation founded in 1987 by a small group of patients and parents representing mainly National Thalassaemia Associations in Cyprus, Greece, UK, USA and Italy – countries where thalassaemia was first recognised as an important public health issue and where the first programmes for its control, including prevention and clinical management have started to be promoted and implemented. TIF works in official relations with the World Health Organisation (WHO) since 1996 and with a number of other official health bodies and patient oriented organizations (www.thalassaemia.org.cy)

MISSION

The development of National Control Programmes, including both components of prevention and management and the promotion of their establishment across 'affected' countries.

VISION

Establishment of equal access to quality health care for every patient with thalassaemia wherever he or she may live.

OBJECTIVES

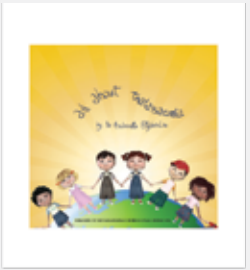
The objectives of the Federation in addressing effectively the needs of the world thalassaemia family have since its establishment remained the same and include:

- The establishment of new and promotion of existing National Thalassaemia Patient/Parents Associations
- Encouraging, motivating and supporting studies and research for further improving prevention strategies, clinical care and for achieving the long-awaited final cure and
- Extending the knowledge and experiences gained from countries with successful control programmes to those in need.

TODATE

TIF has developed into an umbrella federation with 102 member associations, from 60 countries of the world, safeguarding the rights of patients for quality health care.

Its educational programme, focused on the needs of patients/parents, medical health professionals and the community at large, has been, and still is, amongst its strongest tools towards achieving its objectives.
TIF since 1990 has organised 60 national/local, 6 regional workshops and 14 international conferences and has prepared, published, translated and distributed more than 15 books todate in more than 50 countries worldwide.



JOIN US, become a member of our world thalassaemia family

“Knowledge is our power”
“Unity is our strength”

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PREFACE
FROM THE PRESIDENT AND THE EXECUTIVE DIRECTOR OF THALASSAEMIA INTERNATIONAL FEDERATION (TIF)

The Thalassaemia International Federation (TIF) is dedicated to ensuring that patients everywhere have access to quality health care. By focusing on the role of the nurse in the care of patients with haemoglobin (Hb) disorders, it is hoped that this Guide will play a key part in meeting that goal.

This book is the first of its kind to be published by TIF, and we are greatly indebted to the expert panel of nurses who wrote it. They have shown exceptional commitment and generosity of spirit, sharing valuable knowledge and experience to complete a challenging and time-consuming task. We are confident that their work will be of great benefit to other nurses, particularly those in developing countries where Hb disorders are most prevalent, and where health infrastructure and services for chronic diseases, including nursing care, are in urgent need of reinforcement and reform. We are also aware that advances in medicine and science are running and some of the information contained in this book may need updating. TIF is committed to do so regularly and indeed the ongoing collaboration of expert nurses including the authors of this book is invaluable.

The nurse plays a critical role in any team of healthcare professionals involved in the care of patients with chronic diseases including Hb disorders such as thalassaemia and sickle dell disease. These are extremely challenging diseases that are fatal if left untreated. However, by sharing expert knowledge on their prevention and treatment, these conditions can be effectively managed.

TIF places great importance on nursing as a valued part of patient care well beyond the medical component. We hope that this Guide will help and motivate more nurses across the world to become involved in the care of patients with this group of diseases.

The authors welcome any comments, suggestions or insights, with a view to further improving care in the haemoglobinopathies.

Panos Englezos, President, Thalassaemia International Federation
Androulla Eleftheriou, PhD, Executive Director, Thalassaemia International Federation,

FORWARD
FROM EDITH AIMIUWU

The nurse plays a vital role in the care of patients with sickle cell and thalassaemia. There is hardly an intervention, treatment or care programme in which the nurse does not play a significant part. It is therefore of the utmost importance to have a nursing service that is integrated, seamless and suitable for patients in both the acute and community setting, irrespective of what part of the world they are in.

This book is the first of its kind-guidelines for the care of patients with sickle cell or thalassaemia, written by and for nurses. The information provided here has been carefully compiled by specialist nurses experienced in the care of patients with haemoglobinopathies, including blood transfusion, iron overload, screening, pain management and counselling. It is the aim of this book to help nurses everywhere to ensure the provision of quality care for all their patients with sickle cell or thalassaemia.

These guidelines have been produced under the auspices of the Thalassaemia International Federation (TIF), which works to promote awareness of the haemoglobinopathies, particularly thalassaemia, and to give prominence to the views of patients and their families. TIF's goal is to ensure the equal rights of all patients everywhere to high quality care, by disseminating the knowledge, experience and expertise gained from countries with successful control and treatment programmes to areas where it is most needed.

Haemoglobinopathies such as sickle cell and thalassaemia affect patients' lives and the lives of their families in different ways. In addition to physical symptoms, they must cope with feelings of anxiety, guilt and fear of the unknown. Nurses play a vital role in helping patients and their families manage all these aspects of disease.

Nurses are also essential in helping patients to become experts in their own condition, teaching effective techniques for self-management, the prevention of complications and the transition of paediatric patients to the adult team of healthcare specialists, as well as in genetic counselling.

I am confident that these guidelines will assist nurses all over the world in providing safe and effective services to patients with sickle cell and thalassaemia, enabling nurses to make the most of their unique skills and abilities in patient care.

FORWARD
FROM ALDINE THOMAS

Sickle cell and thalassaemia are autosomal recessive disorders that affect people from many parts of the world. However, the quality of care patients receive is to a great extent determined by the level of economic development of the country they live in. By sharing expertise in the management and prevention of sickle cell and thalassaemia, these guidelines for nurses aim to ensure that patients everywhere receive the best treatment possible.

These guidelines are the result of an initiative by the Thalassaemia International Federation (TIF). The project began with a meeting of seven specialist nurses from Lebanon, Cyprus and England in February 2011, for a brainstorming session to outline the sort of information that would help a first-time nurse treating a haemoglobinopathy patient.

Topics were assigned with the help of Dr Androulla Eleftheriou and Dr Michael Angastiniotis.

Therese Khairallah, who works at the Chronic Care Centre in Lebanon, wrote the overview of thalassaemia, including the definition, symptoms and types, and the general management and complications of the disease.

Najat Ajami, who also works at the Chronic Care Centre, was tasked a discussion of the care of the adolescent patient-a particularly difficult time for patients, who must follow a regimen of regular transfusions and medication that sets them apart from their peers at an age when everyone fears being different. Adolescence is also the time when the patient transfers from a familiar group of child healthcare providers to adult services.

Therese and Najat worked together on routine tests in thalassaemia, including blood tests, and specialist tests including T2*.

Antonia Georgiou works at the Cyprus Thalassaemia Centre, and was responsible for documenting the role of the nurse in the management of a person with thalassaemia, including social and psychological support-an important means of ensuring the patient is able to verbalise issues, helping to reduce the risk of low self-esteem and depression. Christina Papadopoulou also works at the Cyprus Thalassaemia Centre, and wrote the section on chelation, documenting the three types of chelation therapy currently available, how to use them, side effects and observations.

Christina and Antonia also wrote the section on infection control, including HIV and hepatitis C.

Nasser Roheemun works as a Specialist Community Nurse at the George Marsh Centre in North London. He wrote the section about genetic counselling, including preimplantation diagnosis, and support for families with an affected child. He also wrote about hydroxycarbamide, describing what it is and how it is given, plus monitoring and advice. Elizabeth Aimiuwu is a Paediatric Nurse Specialist in Haemoglobinopathies at the Whittington Hospital in London. She was responsible for the section on blood transfusion in sickle cell and thalassaemia, including exchange transfusions and information about blood groups, reactions and monitoring.

Aldine Thomas, Clinical Nurse Specialist in Haemoglobinopathies (Adult) at the Royal London Hospital (part of Barts and The London NHS Trust) wrote about sickle cell, including a disease overview and details regarding screening, testing, side effects and complications in the organs and systems of the body.

This book is intended for the use of nurses caring for people with sickle cell and thalassaemia, including their role in supporting the client group and their families. I hope it is helpful.

FORWARD FROM PANAYIOTA PANAYIOTOU

The provision of high quality care to the sufferers of thalassaemia and sickle cell anaemia is of great importance and value, both to patients and their families.

This book giving all the necessary information about the disease, treatment and guidelines of care, will enhance the ability of nurses in all countries to provide thus high quality nursing care needed.

Nurse S.R.N. SCM BA Cuvationis Nursing Education and Nursing Administration

KEY MESSAGE*
THE ROLE OF NURSING IN THE HEALTH CARE SYSTEM OUTCOMES

"Models of proactive, targeted nurse-led care that focus on preventive patient self-management for people with chronic disease are either more effective and equally or less costly or are equally effective and less costly than the usual model of care".

"Additional key components of more effective and efficient health care models involve community-based nurse led models of care with an interdisciplinary team that includes the primary care physician. Such complex intervention requires specifically trained or advanced practice nurses who supplement the care provided by physicians and other healthcare professionals. The proactive, comprehensive, co-coordinated model of community care is patient and family dwelling individuals with complex chronic conditions and social circumstances".

"Nurses-led models of care can be financed by costs advertised from hospitals and emergency departments to home or community care. For example, after managing the current hospital caseload of patients awaiting alternative levels of care, the number of hospital beds could be reduced to free up funds, for this reallocation of funding".

" In Ontario alone, representing 37% of the Canadian population, independent reports estimate that millions of dollars could be saved in direct health care costs within one year by:

- having nurses provide leading practices in home care;
- integrating nurse-led models of care to reduce high hospital readmissions by 10% for those with chronic conditions
- providing proactive community care and patient self-management for those with congestive heart failure and other chronic diseases"

"Addressing the source of and reasons for excessive and growing health expenditure would include:

- providing nurse-led proactive, comprehensive and preventative care for those with chronic illness
- financing by reducing resources of current acute hospital care and
- having physicians and nurse practitioners continue to practice acute and episodic care ".

* Extracts taken from Canadian Health Services Research Foundation (Dr Gina Browne, Ph.D., Reg. No, June 2012), Better care: An Analysis of Nursing and Healthcare System outcomes, Paper 2

*"We've come a long way since 1979 when I was appointed as the first ever Sickle Cell & Thalassaemia specialist nurse in England. We have a national screening programme for sickle cell and thalassaemia; we've built up clinical services for people living with these debilitating conditions; and we've established national standards for training and practice. Specialist nurses have played a pivotal role in this success story - but they still have a lot to do. Every patient deserves the highest quality of care, and specialist nurses are best placed to deliver it" Professor Elizabeth Anionwu, CBE, FRCN, Emeritus Professor of nursing, University of West London**

*Understanding the contribution of sickle cell and thalassaemia specialist nurses: a summary report, May 2012, Professor Elizabeth Anionwu & Dr Alison Leary

COMMENTS FROM PATIENTS

"I dread the moment I have to entrust my veins to a non-specialist nurse in an Emergency Department or other surgery who does not know my story, history and value of keeping healthy veins" (Patient)

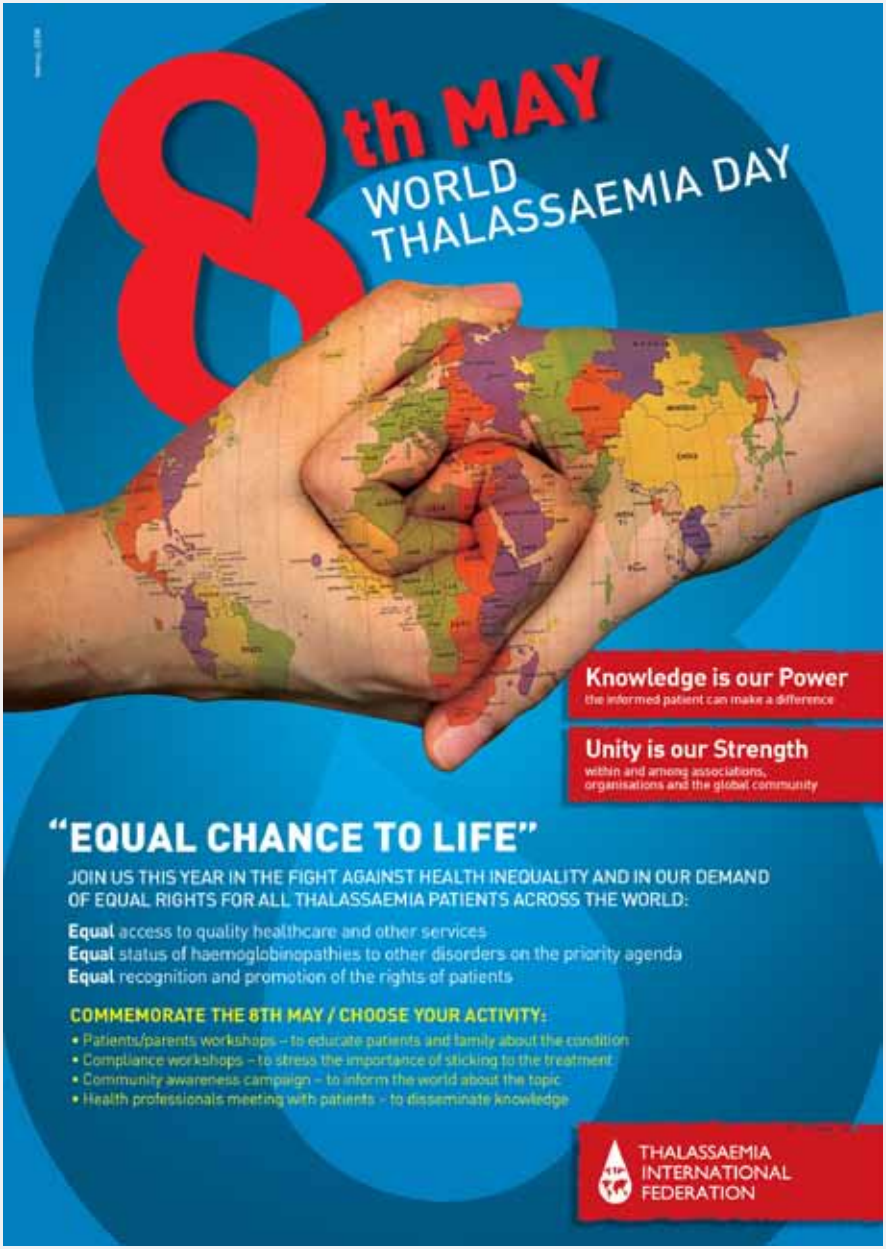
"What I have shared with my specialist nurse, I have never shared with anyone" (Patient)

"A great part of my gratefulness to my doctors and government who provided me with appropriate medical care, free of charge but an equally great part of my greafulness goes to my specialist nurse who helped me through many and difficult years of my life to apply correctly and keep the to the treatment" (Patient)

"The hemoglobinopathy nurse expert, provided through the position of an Advanced Nurse Practitioner(ANP), a Nurse Coordinator, or a Medical Day Unit staff nurse, is an essential resource and a strong asset to both the allied health team and the medical team. Much of the responsibilities of the clinic, and coordinating multy-discipline care rests on the shoulders of the hemoglobiopthaies nurse. This position role has a direct and critical impact on patient care. From a patient perspective the hemoglobinopathy nurse expert is a trusted medical expert who understands the complexities of the concerns and challenges facing thalassemia patients or parents. The nurse is a professional and a sincere friend who provides practical advice and assists in determining solutions for critical situations related to health matters. Hence, a vital partner for the patient on the care management plan." (Riyad Elbard, Treaurer of TIF Board of Directors, Patient)

"Caring is the essence of nursing"
(Mr Loizos Perikleous, Secretary of TIF Board of Directors, Patient)

"The nurse specialist is an essential element in the successful management of thalassaemia. As well as expert medical care, nurse specialists provide experienced, skilled support and encouragement throughout an often arduous treatment regime. A specialist nurse who knows the patient, family and their social situation intimately is uniquely placed to provide an indispensable link between the haematologist, the patient and other health professionals and essential services. In the view of the UK Thalassaemia Society, the haematologist, the specialist nurse and the patient working in partnership together is the best way to provide an optimum level of care; and any service which does not include the support of a specialist nurse cannot be considered to be a specialist centre for treatment of the haemoglobinopathies" (Gabriel Theophanous, President, UK Thalassaemia Society)


8th MAY
WORLD
THALASSAEMIA DAY
Knowledge is our Power
the informed patient can make a difference
Unity is our Strength
within and among associations, organisations and the global community
"EQUAL CHANCE TO LIFE"
JOIN US THIS YEAR IN THE FIGHT AGAINST HEALTH INEQUALITY AND IN OUR DEMAND OF EQUAL RIGHTS FOR ALL THALASSAEMIA PATIENTS ACROSS THE WORLD:
Equal access to quality healthcare and other services
Equal status of haemoglobinopathies to other disorders on the priority agenda
Equal recognition and promotion of the rights of patients
COMMEMORATE THE 8TH MAY / CHOOSE YOUR ACTIVITY:
• Patients/parents workshops – to educate patients and family about the condition
• Compliance workshops – to stress the importance of sticking to the treatment
• Community awareness campaign – to inform the world about the topic
• Health professionals meeting with patients – to disseminate knowledge
THALASSAEMIA INTERNATIONAL FEDERATION

DEFINING NURSING*

"Nursing is the science that observes, classifies, and relates the processes by which persons positively affect their health status, and the practice discipline that uses this particular scientific knowledge in providing a service to people. (Roy, 1984)"

"The goal of nursing is that individuals achieve their maximum health potential through maintenance and promotion of health, prevention of disease, nursing diagnosis, intervention and rehabilitation. (Rogers, 1970)".

"Nursing is deliberate action to bring about humanely desirable conditions in persons and their environments. (Orem, 1985)".

"In Nursing in Action (Salvage, 1993), nursing is functionally defined as: to help individuals, families and groups to determine and achieve their physical, mental and social potential, and to do so within the challenging context of the environment in which they live and work. This requires nurses to develop and perform functions that promote and maintain health as well as prevent ill health. Nursing also includes the planning and giving of care during illness and rehabilitation, and encompasses the physical, mental and social aspects of life as they affect health, illness, disability and dying".

"Nurses ensure the active involvement of the individual and his or her family, friends, social group and community as appropriate in all aspects of health care, thus encouraging self-reliance and self-determination. Nurses also work as partners with members of other professions and occupations involved in providing health and related services".

"Nursing is both an art and a science that requires the understanding and application of the knowledge and skills specific to the discipline. It draws on knowledge and techniques derived from the humanities and the physical, social, medical and biological sciences".

"The nurse accepts responsibility for and exercises the requisite authority in the direct provision of nursing care, She is an autonomous practitioner accountable for the care she provides".

Benner (1984) recognized that much of the knowledge base required for nursing was embedded in practice and acquired not only through theories learned, but also by learning how to be an effective practitioner. In other words, a way of constructing a theory of nursing is to watch what it is that nurses do, and to ask them to reflect on their practice, and then to define, from the practice-based information, the nature of nursing.

*Extracts from WHO/HDP/HUR-MID/97.5, Nursing practice around the world.

Building on Benner's work, Brykczynski (1989) described, through observational research, the nature of nursing practiced in primary health care settings in the USA. She identified six domains of nursing practice in this setting, and these are adapted, compared and combined with data from the regional papers to offer a framework for the consideration of the nature of nursing.

MANAGEMENT OF HEALTH AND ILLNESS STATUS

This domain includes assessing, monitoring, coordinating and managing health status over time. The nurse detects acute and chronic disease, instigates and interprets investigations, selects and monitors appropriate therapeutic interventions and does this within a supportive and caring relationship, so that she can also attend to the experience of illness with the patient.

MONITORING AND ENSURING THE QUALITY OF HEALTH CARE PRACTICES

Within this domain fall the responsibilities associated with professional practice, such as self-monitoring and seeking consultation with others as appropriate. The nurse, as an autonomous professional practitioner, ensures not only that she is a safe and effective practitioner, but also that her colleagues, including physicians, are too (exactly as physicians do for nursing). This domain also covers the mastery of problem solving skills which nurses demonstrate: for example, nurses are capable of assessing what could be added to, or omitted from, medical orders. Nurses feel able to give constructive feedback to others on the quality of their practice.

ORGANIZATIONAL AND WORK ROLE COMPETENCIES

The competencies within this domain are about self-management and management of the health care system. Included is the setting of priorities with individuals, families and communities to ensure that multiple needs are met in a timely fashion; coping with staff shortages; dealing with bureaucracies; building and maintaining a therapeutic team; and obtaining specialist care for patients as necessary. The nurse works intersectorally in a range of settings, including community clinics, hospitals, schools and workplaces. Nurses can influence health policies at a strategic level, locally, regionally or nationally, through setting priorities, being actively involved in health programme planning and the allocation of resources, and through preparing and submitting reports at all levels.

THE HELPING FUNCTION

In this important domain lie the characteristics of caring in nursing. It includes the ability to establish a climate for healing, providing comfort, being with a patient, whether individual, family or community, in distress, and being committed to a healing relation-

*Extracts from WHO/HDP/HUR-MID/97.5, Nursing practice around the world.

ship within nursing care. The helping role should ensure that the individual, family and community has maximum participation in all health care planning, treatment and care giving. On an individual level, pain management is an important part of this domain, with the nurse helping to interpret pain and, with the patient, select appropriate strategies for management.

In working with families and groups, the nurse can facilitate the development of a healthy community or family, through helping to set appropriate goals, teaching (see below too), and by providing emotional and informational support, especially in helping patients and carers to understand disease processes and symptoms.

THE TEACHING-COACHING FUNCTION

Within this domain are included competencies in teaching for health. In order to motivate people to change, the nurse has to capture readiness to learn, and to provide information in an appropriate way. In addition, the nurse should teach for self-care. To do this, the nurse has to demonstrate a readiness to understand the person's or group's interpretation of health and illness, the realities of their social and economic situations, and the nature of their environment.

EFFECTIVE MANAGEMENT OF RAPIDLY CHANGING SITUATIONS

Not only must nurses be skilled in everyday "ordinary" situations, they must also know how to deal with emergencies. To do this they have to be able to understand the problem, and sometimes institute immediate treatment. They should also be able to manage a crisis situation in health care through appropriate allocation of resources to meet rapidly changing demands. For nurses in some countries it may be war or natural disasters which cause the situation changes, and response may be needed on a large scale; one example is the organization of health care services to meet the needs of a sudden immigration of refugees.

Other rapid changes may be directly related to health and illness. In epidemic situations, for example, there will be a need for emergency planning and allocation of nursing resources. For individuals and families, nurses must be a resource to help them cope with a changing illness/health trajectory.

Together, these six domains provide a helpful description of nursing practice, because they can be appropriately applied to a number of settings. The domains of practice were generated by observing nursing work, and therefore, not surprisingly, describe the role of the nurse in direct care giving, health promotive activities, educational work, disease

*Extracts from WHO/HDP/HUR-MID/97.5, Nursing practice around the world.

prevention and in offering these skills within a relationship characterized by a commitment to caring, and to a partnership with the person or group who is the recipient of nursing care.

In addition, the domain of practice can be linked to levels of competency. For example, a novice practitioner, or a health care assistant with a limited knowledge base for practice, would need some support and direction in implementing practice, which might vary from actual clinical supervision, to protocols to guide practice. An expert, on the other hand, who is practising from a broad and deep knowledge base in nursing, and has integrated nursing theory with practice, could be creative and innovative, would be able to deal with uncertainty in clinical and societal situations, and able to research and develop nursing practice, within the context of working with others. These differences in levels of practice may be echoed in educational qualifications.

The uniqueness of nursing practice lies in the ability of the nurse to integrate all the domains of nursing practice in a way which is responsive to the needs of individuals, families and groups, and which will therefore be different for each situation. The truly expert nurse will be able to use a wide range of competencies within each domain. Expert nursing practice is built knowledge experience and the ability to reflect on, and research, practice.

Nursing practice today is at different stages of development in different countries. Solutions to problems have to suit the needs of each country and must be arrived at through the collaboration of nurses, nurse educators, nursing managers, other health care workers, and representatives of the communities with whom nurses work. Yen all countries, strategies to carry out the recommendations of the Expert Committee will go far toward overcoming the factors constraining nursing practice and enabling nurses around the world to achieve their Potential and\assure health for all.

*Extracts from WHO/HDP/HUR-MID/97.5, Nursing practice around the world.

THE ROLE OF NURSES* IN THE MANAGEMENT OF HAEMOGLOBIN DISORDERS

Nurses had always a fundamental role to play in the patient care. They are the ones that:

- Provide empathy and understanding and work with the patients and their family
- Are responsive to the needs of patients or families/carers
- Are patient-centered and compassionate
  - they listen,
  - are understanding,
  - welcoming,
  - non-judgmental,
  - are open to receiving feedback,
  - confidential,
  - accountable,
  - they build relationship with peers
  - they share ideas
  - facilitate involvement of stakeholders
  - inform appropriately at all stages
- Investigate patients current life styles, hopes and expectations
- Takes into account cultural, ethnic, religious, linguistic differences/beliefs
- Evaluate adherence to medical and other care to reach joint decisions on how to address the problem(s).
- Have knowledge and are fully updated on all aspects of treatment and other care according to practiced national (or hospital) Guidelines.
- Know how to work within the patient's and families' level of competence
- Develop and maintain a self-managed plan that achieves the potential of the individual while at the same time focuses on maintaining their motivation and confidence.

*RCN Competencies, Royal College of Nursing, Caring for people with sickle cell disease and thalassaemia syndromes

CHAPTER 1
INTRODUCTION

THE ROLE OF THE NURSE

The role of the nurse is critical to the management of chronic disorders such as thalassaemia or sickle cell disease (SCD). One of the most important aspects of that role is to support patients in playing an active part in their own care.

The nurse has frequent, even daily, contact with a patient over the course of many years. As such, the nurse enjoys a particularly close relationship with the patient one that affords considerable influence in the effort to help patients take care of themselves.

In a chronic care setting, the nurse must continually develop her knowledge of the condition/s she manages as a member of a team of healthcare professionals. **The nurse must be expert in the nursing procedures involved.**

However, nursing is both an emotional and an intellectual endeavour that requires a natural and sincere commitment to meet the needs of each patient, not just in terms of medical care but also their psychological well-being.

COMMUNICATION

The nurse must learn the social skills of communication that daily contact with patients demand.

The nurse is the first member of a healthcare team that a patient visiting a haemoglobinopathy day care centre will meet, talk to and confide in. Every patient has concerns about their condition and its treatment, causing feelings of stress, fear, uncertainty, desperation and depression. However, they are often reluctant to discuss these with the doctor, whom they may regard as 'busy and must not be disturbed'. In such situations, it is the nurse that a patient will turn to-a person perceived as understanding and friendly.

The nurse must offer the patient her attention and be sensitive to 'hidden' messages. Patients may communicate their feelings in a non-verbal manner, as well as by means of open expression and queries. The nurse should be a **good listener**, even if she does not always have a ready answer.

Being 'too busy' can be an excuse for avoidance: the nurse must make time for the patient as much as possible. Avoidance is common among health professionals, including doctors, who feel uncomfortable dealing with patients' emotional ups and downs.

The empathy and sensitivity of a nurse is an essential element in the care of patients with chronic diseases. Patients spend many hours on a ward or in a day care centre, waiting for blood units to be delivered from the blood bank, undergoing a transfusion, having a venipuncture-times when they may have something to discuss, or perhaps just want to chat. The nurse is the one to listen and give feedback.

SUPPORT

The role of the nurse is to give the patient time to express feelings and fears-to 'be there' for the patient, to support and encourage, to reassure and to calm. Haemoglobinopathy patients have a lifelong experience of suffering, both physical and emotional. Pain and uncertainty of what tomorrow may bring give rise to chronic anxiety and discomfort, which are not always directly expressed. The essential element of caring provided by the nurse is to enable a patient to come to terms with the problems and disappointments that the illness creates.

The psychosocial component of nursing is not a simple task, requiring intelligence and insight into a patient's behaviour, in addition to a caring attitude. Every patient is a person with a unique character. Each will have developed mechanisms of coping with their condition, some of which may not always be helpful. The developmental stage of a patient is important, with different issues emerging as the individual matures, especially during adolescence. The nurse must take all of these factors into account when soothing an anxious patient.

NURSES' BEHAVIOUR

The nurse must show empathy and sensitivity, but must also acknowledge her limitations and set boundaries in her interaction with patients. It requires great strength of character to remain supportive in a strained environment, where empathy must be balanced with objectivity.

The nurse's demeanour sends a message to patients. Looking happy as much as possible will make the nurse more approachable and may be an advantage in a clinical setting, bearing in mind that every action or attitude may be misinterpreted by an anxious patient.

Just as patients vary in their outlook, so, too, do nurses. And just as patients interpret the nurse's demeanour, so do nurses interpret the patients'. One trap that the nurse may fall into is to discriminate between patients who are 'cooperative' and those who 'are not'. The nurse should also be alert that when patients complain or apportion blame, they are resorting to coping mechanisms, which should be recognised as such and not taken personally or regarded as offensive.

Upsetting events are signals for dialogue. They may also require the intervention of other members of the multidisciplinary group providing care to the patient, including a psychologist or social worker. The mood of a patient with a chronic illness may change very easily, especially with the appearance of a new complication to which the patient must adapt, or additional treatment that the patient must follow. Such situations call for discussion-a proper communication between friends, who are supportive of one another.

ADHERENCE

Adherence to prescribed treatment is a major issue in chronic disease, especially Hb disorders, the management of which is associated with chronic pain and/or painful procedures. A number of factors can induce patients to neglect or even stop therapy, including fatigue, burnout and fears about the side-effects of drugs, as well as disappointing life events. The main therapy that is often neglected by thalassaemia patients is iron chelation, which addresses the excess iron load caused by the pathophysiology of the disease and the blood transfusions that are part of its treatment.

The issue was particularly prevalent in the past, when the only available iron chelation therapy involved the daily, subcutaneous infusion of Desferrioxamine over a period of several hours-a painful and inconvenient procedure that interfered with other aspects of life. The availability of orally-administered chelation agents has improved patient adherence to treatment. However, the daily routine can still be difficult to keep up.

Many studies have shown that patients receiving psychological and social support as part of their care more easily accept and adhere to treatment. Where a patient faces difficulties in following a treatment regimen, it is often the nurse who is first to notice.

The nurse is also the person best placed to offer the patient initial support and encouragement.

Non-adherence is a very serious matter, which may lead to serious or fatal complications. It is therefore imperative that signs of non-adherence are reported to the doctor overseeing the patient, to be investigated by the whole team.

TRUST

Trust plays a pivotal role in both the clinical management and the nursing care of a patient, and should be carefully fostered. A patient with a severe Hb disorder must feel secure in the relationship with the nurse, whether they are communicating face-to-face in a clinical environment or over the phone from home. During adolescence, trust is still more important in the development of healthy social and psychological behaviour.

A sense of trust that the nurse is sincerely trying to help motivates a patient to do what is best for his or her health, in terms both of adhering to treatment and developing self-management skills.

INFORMATION

The exchange of information between the medical team and the patient is a key part of building trust. **It is critical to ensure that the doctor-nurse team follows an agreed protocol, so as not to contradict or disagree with each other on any aspect(s) of medical care.**

A major role of the nurse is to complement the doctor in sharing information with the

patient. Many patients leave the doctor's office with questions to clarify or confirm with the nurse. **The nurse must therefore be well versed in the disease, its prevention and management and, importantly, on the protocols used in the hospital or clinic concerned. The nurse uses simple language and takes enough time to ensure that a patient understands the information they need and want.**

QUALITY OF LIFE

The aim is no longer simply survival, but survival with a good quality of life. Advances in the management of chronic diseases such as thalassaemia mean that patients receiving good quality care can expect to live long and full lives. Patients today can get an education, have a job, be in a relationship, get married and have a family. In addition to improved treatment, greater knowledge about prevention means that a large number of patients with Hb disorders today are adults. The goal of any treatment protocol should therefore be to enable patients to accept their condition and focus on achieving fulfilment in life.

The nurse plays a critical role in preparing the patient to successfully negotiate life challenges. One aspect of that role is to encourage patients to follow a treatment regimen correctly and consistently, without gaps. This will help ensure that unnecessary complications are avoided and a better quality of life is maintained for the longer-term. A second aspect of preparing the patient for life challenges is to enable patients to follow a treatment regimen as easily as possible. This means providing treatment at convenient times, minimising interference with the demands of school or work.

Patients who feel socially or professionally isolated, who do not feel integrated or recognised as valuable members of society, become frustrated and demoralised, losing their motivation to keep up with the demands of managing their disease. Such feelings are particularly likely to emerge in late adolescence and adulthood, around issues of sexual relationships, career development and financial (in)dependence. The nurse has an important role in this context as a patient advocate, informing teachers and employers about the part treatment plays in improving patient quality of life. The nurse may also advocate for patient interests with health authorities and society in general, helping to combat ignorance that leads to discrimination.

FAMILY SUPPORT

The nurse offers invaluable support to the family of a patient, especially when the patient is young. This support begins with emphasising the need to maintain regular treatment or preventative care, without interruption or delay, as well as guidance and reassurance

about practical aspects of patient care. For example, parents may find it emotionally difficult to insert a needle into a child. The nurse offers advice about the importance of regular treatment, and the least painful way to insert a needle, using local anaesthetic creams or pre-puncture freezing sprays. The nurse also teaches patients and parents about the need for cleanliness, and how to detect and report serious symptoms, such as fever or pain.

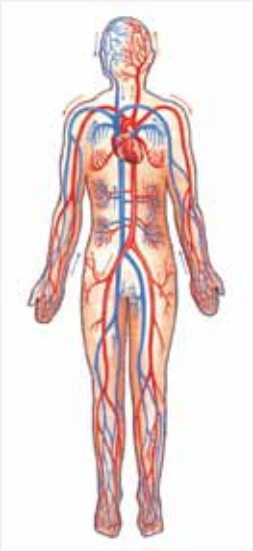
The treatment of patients with Hb disorders involves many tasks that family and patients must learn to do by themselves. The nurse plays a critical role in helping families achieve independence from the centre or hospital, educating patients and parents and liaising as needed with other health professionals, such as psychologists.

MULTIDISCIPLINARY CARE

The nurse plays a central part in offering support to patients and parents as part of a team of specialists in Hb disorders. This team will include a haematologist, an endocrinologist, a cardiologist and an orthopaedic surgeon and a psychologist which are the main specialties. The psychologists professional expertise is available to patients as well as the nurses and doctors, who may themselves require support in the course of an emotionally demanding job. The team is usually coordinated by a doctor, and meets regularly to discuss individual patients or patients as a group, as well as any adjustments to agreed policies and protocols.

CHAPTER 2
BLOOD AND RED BLOOD CELLS (RBCS)

Hb disorders belong to a family of genetic, non-malignant haematological diseases that affect the haemoglobin molecule of red blood cells (RBCs). The following chapters offer an overview of these disorders, including their inheritance, prevention, pathophysiology, clinical outcome and management, as well as a brief 'refresher' of core concepts.



RED: oxygenated blood
BLUE: deoxygenated blood

BLOOD - "THE RIVER OF LIFE"

Blood is a vital fluid that brings nourishment to the body's organs and tissues and carries away waste substances. A healthy adult has about 5 to 6 litres of blood – roughly 7-8% of total body weight.

Blood is moved around the body by the heart, which pumps blood through a network of pipes-the blood vessels. These vessels are the arteries, veins and capillaries, each of which has a different size and function. Together, they make up the circulatory system of the body.

THE ROLE OF BLOOD

Blood performs many important functions:

- Transport of oxygen: Blood collects oxygen from the lungs, and distributes this essential nutrient around the body.
- Removal of waste products. Blood carries carbon dioxide, a gas formed by cells, to the lungs to be released from the body. Waste products such as urea and uric acid are carried to the kidneys and liver, to be removed from the body in urine and stools.
- Transport of hormones. Blood carries substances that regulate the function of important systems of the body, such as the endocrine, sexual and reproductive systems.
- Carries nutrients. Blood delivers to the body the proteins, fats and carbohydrates produced from food broken down by the digestive system.
- Fights infection. Blood helps the body fight infection and disease through cells that form part of its defence system, the immune system.

WHOLE BLOOD

Whole blood is made up of two parts:

- Non-cellular - the part that contains no cells, and
- Cellular - the part that contains cells.

The non-cellular part of blood is a yellowish liquid called plasma, which makes up 55% of whole blood and is composed of water and salts, as well as important proteins.

Cellular blood is composed as follows:

- Red blood cells (RBCs) or erythrocytes. The body contains around 4,500,000-5,000,000/mm3 of RBCs-almost 45% of total blood volume. RBCs have the longest average lifespan of any of the cellular elements of blood, at 100-120 days.

  The primary function of RBCs is to deliver oxygen to every cell in the body, which it carries bound to a compound called haemoglobin. Red blood cells contain as many as 300 million molecules of haemoglobin. The iron these contain give blood its red colour. In fact, RBCs are so packed with haemoglobin that they do not contain some of the parts found in other cells, such as a nucleus.

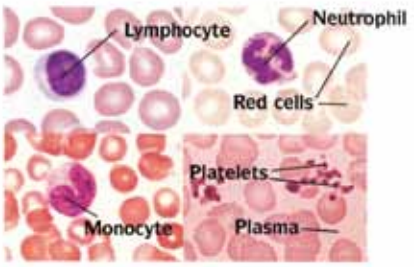
  The membrane or outer layer of a red blood cell is very flexible, like a soap bubble. This allows the cell to bend and compress without breaking as it passes through the tiniest blood vessels (the capillaries) to deliver oxygen wherever it is needed.

  RBCs also contain substantial amounts of an enzyme known as carbonic anhydrase, which plays an important part in transporting carbon dioxide from the tissues to the lungs.

- White blood cells or leucocytes make up just 1% of blood. They play a vital role, working as the body's first line of defence against invading infectious agents.

  White blood cells are bigger than red blood cells but they are much fewer in number-about 7,000/mm3 of blood-and their lifespan is much shorter at just 18-36 hours.

- Platelets play a single, crucial role in the blood: they begin the process of coagulation (forming the blood into a clot) to prevent the body losing blood from a damaged vessel. Platelets are the smallest blood cells in the body. There are around 200,000 platelets/mm3 blood, with a lifespan of 97-100 days.



Composition of blood

BLOOD TYPES/GROUPS

There are four major blood groups, A, B, AB and O, identified by the type of protein (also known as the marker or antigen) carried on the surface of the red blood cells. Each person's blood falls into one of these four main categories-i.e. each person has red blood cells of just one of these groups.

- Blood group A - red blood cells carry a marker A on their surface.
- Blood group B - red blood cells carry a marker B on their surface.
- Blood group AB - red blood cells carry both A and B markers on their surface.
- Blood group O - red blood cells carry neither A nor B markers on their surface.

Red blood cells can also contain another antigen, unrelated to blood group-the Rhesus (Rh) antigen. Blood containing the Rh marker is described as Rh positive, while blood without the Rh marker is described as Rh negative.

More than 20 other red blood cell types have been discovered, but the above are the most important and most commonly known.

There are several reasons why a person may need to know his/her blood type. The most important is where an individual needs to receive blood from another person, i.e. when a blood transfusion is needed. In a blood transfusion, the blood of the donor (the individual who gives blood) and the blood of the recipient (the individual who receives blood) must be carefully matched so that the recipient's body does not reject the donor's blood. The process of matching a donor's blood group and Rhesus antigen with a recipient usually takes place in the laboratory of a blood bank, and is referred to as cross-matching or compatibility testing. If the blood group and Rhesus factor are not identical, the recipient's body will identify the donated blood as an intruder and will try to destroy it. The body's effort to fight the 'foreign', unmatched blood can result in severe illness and even death if not promptly diagnosed and treated. The table below details the compatibility of blood groups between donor and recipient.

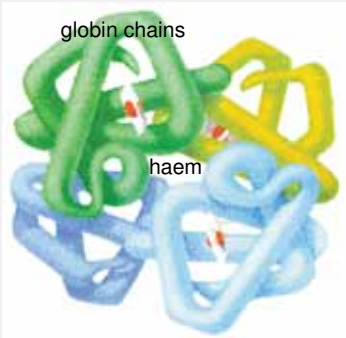
GROUP	CAN DONATE TO	CAN RECEIVE FROM
A	A and B	A and O
B	B and A	B and O
AB	AB	all groups
O	all groups	O

Patients who receive regular blood transfusions require special care in matching the donor blood and a whole chapter is devoted to the process of blood transfusion later in this book.

HAEMOGLOBIN AND IRON

Haemoglobin is a specialised type of compound molecule-a protein-found in red blood cells. It has two parts:

- A protein, called globin, made up of four protein chains arranged in matching pairs. There are several types of chains-the α-chains, α2, and the non-α· chains, β2, γ2 ,δ2 ,ζ2 ,ε2 matched in pairs as α2γ2 , α2β2, α2δ2 , α2ζ2 , and α2ε2.
- Haem-a ring structure synthesised in the cell's mitochondrion and cytosol. An iron molecule contained in the haem, haem-iron, enables the transport of oxygen around the body. Iron easily binds with and releases oxygen, making it the perfect means of delivering oxygen to the tissues and cells.



Normal adults have 4g of iron in their body, 75% of which-i.e. about 3g-is used to synthesise haemoglobin.

The production and synthesis of haemoglobin (Hb) is controlled by a number of genes: the α-globin genes on chromosome 16 and the β-, γ- and δ-globin genes on chromosome 11. There are four genes that code for α-chains and two genes that code for β-chains. Irrespective of the number of genes responsible for controlling the synthesis of α- and β-chains, these two chains are produced in exactly equal amounts.

Different types of haemoglobin result from combining the different chains and different types of haemoglobin produced at each stage of life, as shown below:

"α" chain	"non-α" chain	Hb	Name of haemoglobin	Stage of life produced
ζ	ε	ζ2ε2	Gower 1	First eight weeks of gestation
α	ε	α2ε2	Gower 2	First eight weeks of gestation
ζ	γ	ζ2γ2	Hb Portland	First weeks of gestation and in hydrops foetalis due to homozygous α-thalassaemia
α	γ	α2γ2	HbF	Dominant Hb from 6 weeks gestation to term. <1% in normal adult
α	β	α2β2	HbA	Up to 10% in normal foetus froma at least 8 weeks gestation. Dominant Hb in normal adult.
α	δ	α2δ2	HbA2	Minor Hb produced at 1/30th of level of HbA and associated with it. <3% in normal adult.

Table 1 From TIF's Guidelines For the Clinical Management of Thalassaemia (2008)

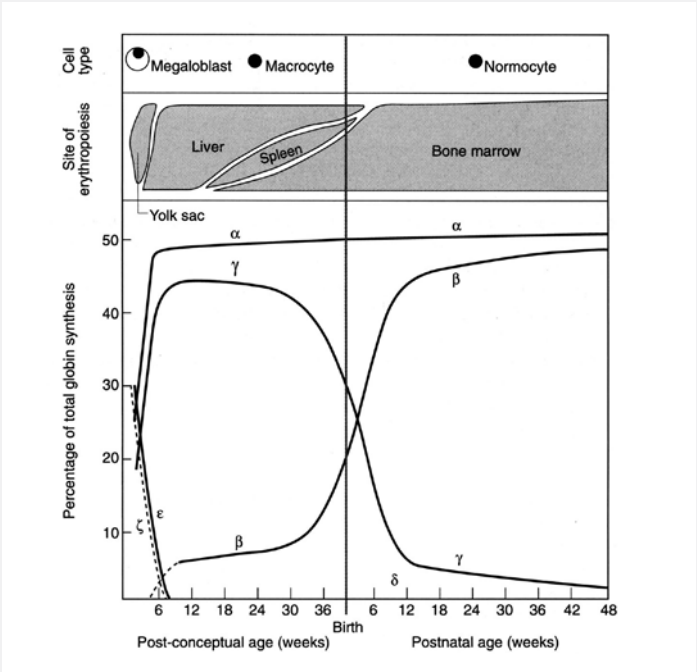


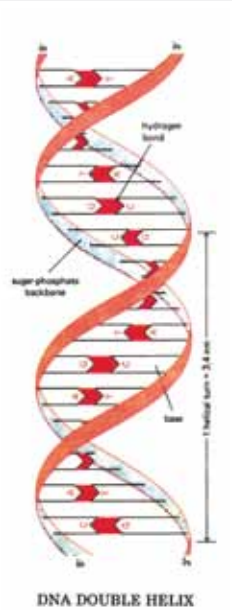
Table 1 From TIF's Guidelines For the Clinical Management of Thalassaemia (2008)

BASIC GENETICS OF BLOOD FORMATION

The protein components of blood, described above, are inherited and passed from parents to children through the genes.

Genes are biological units of inheritance-the unique blueprints for an individual organism, providing all the biological information needed to control growth and development. The key part of each gene is a chemical substance called deoxyribonucleic acid, or DNA.

DNA is a ladder-like shape, with two parallel structures supporting a series of rungs. Each rung is made of two chemicals, called bases, paired together. Each base is represented by a different letter: C, G, A, T-C for cytosine, G for guanine, A for adenine, T for thymine. These four bases always pair up as follows: A with T, and C with G (2a). The order in which bases are laid along the 'ladder' provides an organism's genetic code. Taken together, an organism's DNA is referred to as the 'genome' (2b). The human genome contains thousands of genes.



DNA DOUBLE HELIX

DNA

Chromosomes

A great number of genes are needed to carry out the many and complicated biological functions of the human organism. These genes are kept linked together in the cell on extremely long pieces of DNA, called chromosomes. Each human cell (except sperm/egg cells) has two copies of each chromosome, one from the mother and one from the father.

Different kinds of organisms have different numbers of chromosomes. Humans have 23 pairs of chromosomes, or 46 in all (2c). Twenty-two pairs, or a total of 44, are the same in both males and females, and are called autosomes. The remaining pair, the two sex chromosomes, decides the gender.

After years of research, it has been possible to identify numerous genes that, when affected, are responsible for different illnesses. These illnesses are called genetic disorders.

Genetic disorders can be separated into four categories:

- Chromosome abnormalities-these result when entire chromosomes or large segments are missing, duplicated or altered.
- Single-gene disorders-these are caused when a change or mutation at the level of the gene causes changes or prevents the synthesis of the product of a single gene.
- Multifactorial disorders which result from changes (mutations) in multiple genes, often coupled with environmental causes (i.e. several factors must come together before a pathological condition is produced).
- Mitochondrial-disorders caused by changes (mutations) in non-chromosomal DNA, located within small structures in the cytoplasm of the cell, known as the mitochondria-the cell's energy station (2d).

Thalassaemia and sickle cell disease (SCD) are known as single-gene disorders. Single-gene disorders are passed from parents to child through one of four basic patterns, first described by Gregor Mendel, a monk, in 1865. The four patterns are:

- autosomal dominant
- autosomal recessive
- x-linked dominant and
- x-linked recessive

These terms are used in genetics to describe whether the clinical outcome (phenotype) resulting from the gene abnormality (genotype) can be inherited from (i) just one parent (autosomal dominant), or from (ii) the contribution of both parents (autosomal recessive), or only through (iii) an abnormality in the sex-determining chromosome from one parent (x-linked dominant), or as a result of (iv) the sex-deciding chromosomes of both parents (x-linked recessive).

Thalassaemia and SCD are examples of single-gene disorders that are passed from parents to child by (ii)-the autosomal recessive pattern of inheritance.

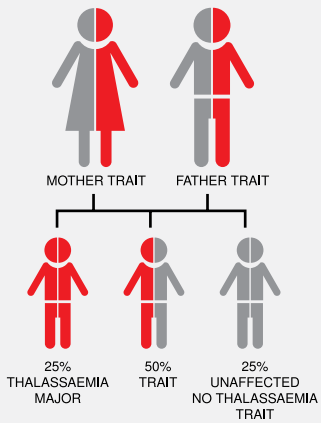
An 'autosomal' disease can affect males and females alike, since the abnormality is on one of the autosomes-i.e. not on the chromosomes responsible for determining the sex of a child.

'Recessive' means that the child needs to inherit the defective gene from both the father and the mother in order to develop the severe clinical condition of thalassaemia major.

Individuals who inherit a defective gene from both their mother and father are described

as homozygotes-in the case of β-thalassaemia, they are described as patients with homozygous β-thalassaemia. They may also be referred to as having thalassaemia major, Mediterranean Anaemia or Cooley's Anemia. These patients will develop all the symptoms associated with the disease.

Those who inherit a normal gene from one parent and a defective gene from the other are referred to as heterozygotes, for example in thalassaemia, as heterozygous for thalassaemia. Other terms used include being **a carrier of the thalassaemia** trait or **an individual with thalassaemia minor**. Such individuals will not develop symptoms of the disease, however, they could pass the defective gene on to their children. If both parents are carriers, then there is a 25% (1:4) chance in each pregnancy that the child will be a homozygote-i.e. a 1 in 4 chance that the child will inherit a defective (thalassaemia) gene from both parents as seen in the example in the figure opposite.



Autosomal recessive inheritance

It is possible to inherit a different mutation from each parent e.g thalassaemia & sickle cell.

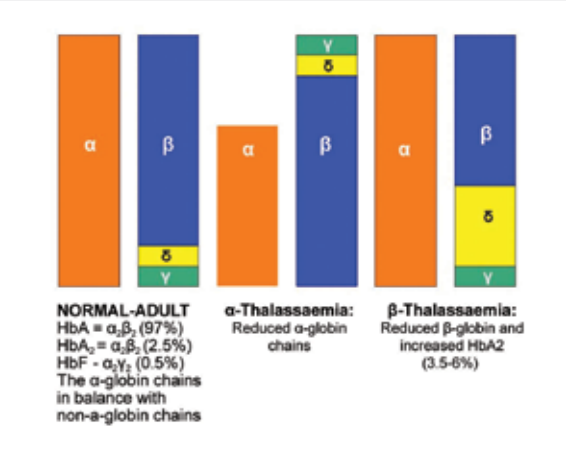
The major haemoglobin disorders are classified as to whether the α- or β-globin chains are affected (see table below).

α-globin chain disorders	β-globin chain disorders
α-thalassaemias HbH disease α-thalassaemia hydrops foetalis (= Hb Bart's hydrops foetalis)	sickle cell disorders sickle cell anaemia (HbSS) HbS/β-thalassaemia HbSC disease HbSD disease other rare sickling
	β-thalassaemias β-thalassaemia major β-thalassaemia intermedia HβE/β-thalassaemia other rare thalassaemias

THE HAEMOGLOBIN MOLECULES IN HAEMOGLOBINOPATHIES

Thalassaemia is an inherited disease of the blood, passed from parents to children through the genes. This hereditary disorder occurs as a result of mutations affecting the synthesis of the haemoglobin molecule, found in the red blood cells (RBCs). In 'normal' or adult haemoglobin (HbA), a protein is formed consisting of two alpha (α) and two beta (β) chains. In thalassaemia, there is a reduction in the production of either the α- or the β-chains in the haemoglobin molecule.

- In α-thalassaemia, there is a decrease or lack of α-chains. The genes responsible for the production of α-chains are the α-globin genes, located on chromosome 16 (schematically shown below).
- In β-thalassaemia, there is a decrease or lack of β-chains. The genes responsible for the production of β-chains are the β-globin genes, located on chromosome 11 schematically shown below.



Other Hb disorders referred to as 'abnormal', or structural variants include sickle cell disease (SCD), HbE, HbC, HbD and combinations of these with β-thalassaemia such as SCD/β-thal and HbE/β-thal. These will be described later in this Guide.

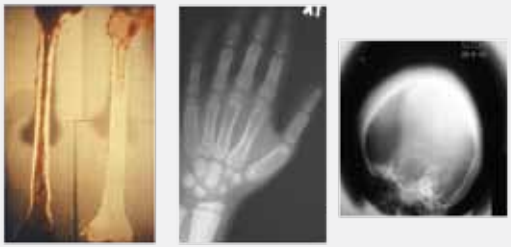
CHAPTER 3
THALASSAEMIA OVERVIEW

The β-homozygote state has a wide range of clinical severity, divided into two broad categories. Patients in the first category, thalassaemia major, cannot survive for long without regular blood transfusions. Patients in the second category, thalassaemia intermedia, may survive with occasional or no transfusions, or with chronic transfusions initiated at an older age.

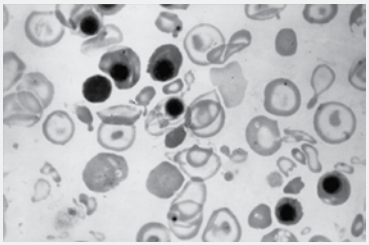
Differences in the severity of thalassaemia are usually due to genetic factors, such as mutations that result in the production of more β-globin chains, or the co-inheritance of α-thalassaemia and/or other genetic factors, each of which contribute different mechanisms in ameliorating the pathology and clinical outcome of the disease. For example, a given factor may allow for the production of some foetal haemoglobin (HbF), leading to the partial correction of the imbalance occurring between the α- and β-chains, which is the single most important cause of the pathophysiology of thalassaemia.

The major clinical consequences of the pathophysiology of thalassaemia are severe, life-threatening anaemia and severe bone marrow hyperactivity. These result in:

- Fatigue
- Severe pallor
- Growth failure
- Bone deformities, especially of the skull
- In the absence of treatment, falling haemoglobin levels lead to heart failure, severe complications involving other vital organs and death in the first decade of life.



Bone Disease



Blood morphology
(β-thalassaemia major)

An example of the sequence of events from the identification to the diagnosis of a patient with β-thalassaemia major is shown below.

Patient presents with pallor, severe anaemia, jaundice, and hepatosplenomegaly

Recommended evaluations

- History and physical examination
- Complete blood count and platelets
- Examination of peripheral blood smear

Diagnosis of thalassaemia major based on Hb evaluation

- Serum Hb (<7 g/dL)
- Hb electrophoresis

The optimal treatment of thalassaemia should be based on established guidelines, such as those published by the Thalassaemia International Federation (TIF), available at www.thalassaemia.org.cy.

Key aspects of patient care include:

- Blood transfusions to maintain pre-transfusion Hb at 9.5 to 10g/dl. Patients require regular (every two to four weeks) transfusions of packed red blood cells, filtered prior to storage, to remove donor white cells which may cause adverse reactions.
- Iron chelation therapy to prevent or reduce excess iron deposits in the body, which result mainly from the breakdown of transfused RBCs in the case of β-major, and from GI absorption in the case of β-intermedia (although transfusion therapy is also now used in the treatment of β-intermedia).
- Splenectomy, although this procedure has become more rare with the improved provision of appropriate treatment.

Some major indications regarding splenectomy are:

- Oversized spleen > 6cm below the costal margin and causing discomfort.
- Transfusion requirement over 200-220mL/Kg/yr.
- Other signs of an overactive spleen, such as low white blood cell count and low platelet count.

After splenectomy complications include a pre-disposition to infection and an increased platelet count. Prophylaxis from these complications is discussed in chapter 7.

Splenectomised patients and their families should be well educated to recognise early signs of febrile episodes and consult with their physician.

THALASSAEMIA INTERMEDIA (β-THALASSAEMIA)

Beta-thalassaemia intermedia is β-homozygous thalassaemia, with a milder clinical outcome. Consequently diagnosis is usually confirmed at a later age than is the case in severe β-thalassaemia major.

Many patients maintain a haemoglobin level of 6-9g/dL without regular blood transfusions, although these may become necessary during intercurrent infections or if complications develop. As the management of the severe, β-thalassaemia major, form has improved over recent years, there has been increased focus on the better management of the intermedia form, including blood transfusion and iron chelation.

CLINICAL COURSE (β-THALASSAEMIA INTERMEDIA)

Patients may have a very mild clinical course, showing no significant symptoms and so may go undiagnosed for a long time. Others are more serious but still maintain a good Hb level after the age of 2-3 years. Later in life, regular transfusions may become necessary due to complications, which include weak bones with deformities and fractures, thrombophilia and pulmonary hypertension.

SYMPTOMS (β-THALASSAEMIA INTERMEDIA)

In moderate cases one observes:

- Slight pallor
- Slight yellowish discoloration of the sclerae
- Enlarged abdomen and spleen

In more severe forms, the patient may experience:

- Malaise
- Pallor

- Fatigue
- Bone deformities
- Fractures

TREATMENT

- **Splenectomy** may be indicated because of a massive enlargement of the spleen, leucopenia, thrombocytopenia, increased transfusion requirements or symptomatic splenomegaly.
- **Transfusion therapy** may be needed in cases of severe anaemia, with symptoms including a rapidly falling haemoglobin level, failure of growth and development, severe bone deformities and other complications. Later in life complications such as thrombophilia, pulmonary hypertension, leg ulcers and priapism may also necessitate regular transfusions. Pregnancy in a thalassaemia intermedia woman is most likely to require transfusion support.
- **Iron chelation therapy** may also be needed, as a result of iron overload due to periodic or regular transfusions, or the increased absorption of iron from the intestine that is consequent to chronic anaemia.

  Whatever the cause of iron load in thalassaemia intermedia, such patients will accumulate iron at a much slower rate than multitransfused patients. Nevertheless, iron levels in the body should be monitored from an early age. Serum ferritin is an unreliable measure in this form of thalassaemia, the assessment of liver iron should be undertaken every 1-2 years, through MRI-based technologies or liver biopsy. If iron accumulation is detected, a chelating drug should be prescribed.

  The latest research indicates that iron chelation should be implemented in thalassaemia intermedia if LIC exceeds 5 mg/g dry weight*. However, chelation regimens in thalassaemia intermedia remain a point of discussion today amongst experts, with debate including the level at which liver iron must be maintained to reduce or prevent associated complications in the liver and endocrine system, until more data and evidence based information is compiled.

- **Modulation of foetal haemoglobin production** to partially correct the α- to β-chain imbalance may also help to maintain better oxygenation and prevent complications in a significant number of thalassaemia intermedia patients.

* 1. Musallam KM, Cappellini MD, Wood JC, Motta I, Graziadei G, Tamim H, Taher AT. Elevated liver iron concentration is a marker of increased morbidity in patients with β thalassaemia intermedia. Haematologica. 2011; 96(11): 1605-12
2. Musallam KM, Taher AT, Rachmilievitz EA. β – Thalassaemia interrmedia: a clinical prespective. Cold Spring Harbor Perspectives in Medicine. 2012; 2a013482.

Hydroxyurea is the most commonly used drug in this regard. However, observed benefits in thalassaemia intermedia have been limited, and are less than those seen in sickle cell disease. Other drugs have been tried, such as short chain fatty acids and erythropoietin, and have shown variable benefit in thalassaemia intermedia,while some substances are still under trial.

β-thalassaemia/HbE is a condition, in which an individual inherits HbE (an abnormal haemoglobin) from one parent and beta thalassaemia from the other. The disorder resembles β-thalassaemia intermedia, and may vary in severity from a mild form of thalassaemia intermedia to a severe, transfusion-dependent form. It is most prevalent in SE Asia and the West Pacific region, and in countries with immigrant populations from these regions.

β-thalassaemia/HbE is broadly classified into three types:

- Mild β-thalassaemia/HbE, in which Hb levels remain at 9-12g/dl
  - Does not require treatment
  - Rarely develops clinical problems
- Moderately severe β-thalassaemia/HbE-clinical symptoms of similar severity to thalassaemia intermedia, in which Hb ranges from 6-7g/dl
  - Iron overload may occur
  - No regular blood transfusion required unless there is a complication such as infection
  - Hepatosplenomegaly and bone changes occur in varying degrees
- Severe β-thalassaemia/HbE-clinical severity of thalassaemia major, in which Hb may be as low as 4-5g/dl and patients are managed as thalassaemia major patients.

COMPLICATIONS OF THALASSAEMIA (MAJOR AND INTERMEDIA)

Although certain complications are more common in β-thalassaemia major than in β-thalassaemia intermedia and vice versa, a number of complications (as seen below) are common to both forms and are mainly due to iron overload, even though they occur later in life in thalassaemia intermedia.

Endocrine problems

- Delayed puberty, growth retardation
- Diabetes mellitus
- Hypothyroidism
- Hypoparathyroidism
- Hypogonadism
- Osteoporosis

Cardiac abnormalities

- Pericarditis
- Arrhythmias
- Biventricular failure
- Congestive heart failure
- Pulmonary hypertension (more common in thalassaemia intermedia)

Hepatic abnormalities

- Cirrhosis (especially if HCV and or HBV co-exist with iron overload)
- Liver failure

Splenic enlargement with possible hypersplenism

Table comparing the frequency of complications in thalassaemia major and intermedia.

COMPLICATIONS IN THALASSAEMIA		
	T. Major (n=60)	T. Intermedia (n=63)
Age	26	32
Splenectomy	83	67
Cholecystectomy	7	68
Gallstones	23	63
Cardiopathy	25	5
HCV infection	98	33
Liver disease	68	22
DM	10	2
Hypothyroidism	11	2
Hypogonadism	93	3
Extramedullary haematopoiesis	0	24
Thrombotic events	0	22
Leg Ulcers	0	33

Capellini M et al. Haematological, 2002, 2509

CHAPTER 4
BLOOD TRANSFUSION

Regular blood transfusion is the most effective means of alleviating anaemia in patients with thalassaemia major, and may also become necessary in the treatment of thalassaemia intermedia and sickle cell anaemia (as will be described later).

If not properly treated, anaemia can result in failure to thrive, tissue anoxia, congestive heart failure and early death. Blood transfusion therapy corrects anaemia, suppresses the production of defective red blood cells in the bone marrow (ineffective erythropoiesis), avoids liver and spleen enlargement and prevents other complications related to severe anaemia, such as infection and bone deformity.

The decision to commence blood transfusion is determined by the medical specialist following careful monitoring of the infant's haemoglobin, and usually starts when Hb levels fall below 7g/dl. Transfusions may begin above this level if the patient experiences fatigue, poor feeding, developmental delay, failing growth or signs of cardiac failure. Other symptoms, such as increasing splenomegaly, evidence of bone expansion or changes in facial appearance could also prompt a decision to commence blood transfusion therapy.

WHOM TO TRANSFUSE

Thalassaemia Major

- Confirmed Laboratory Diagnosis
- Hb < 7g/dl on 2 occasions, > 2 weeks apart
- Hb > 7g/dl with:
  - Facial changes
  - Poor growth
  - Fractures
  - Extramedullary hematopoiesis

Several investigations should be carried out prior to the first transfusion, including:

- Serial Hb measurements
- Full red cell phenotype (see below)
- Liver function test and baseline ferritin level
- Hepatitis B surface antigen or other serological markers if vaccinated (anti-HBs)
- Hepatitis C antibody (and HCV-RNA if positive)
- HIV antibody (and HIV Ag and/or HIV-RNA if positive)
- Co-existence of G6PD deficiency (tested by qualitative and quantitative tests)

BLOOD GROUPS

There are more than 20 blood group systems, including 600 different antigens. It is advisable that patients be transfused with blood that is ABO and RhD compatible and, if possible, compatible for the full Rh type, Kell, Kidd and Duffy. As many blood group systems as possible should be aimed for and, where possible, identified before initiation of transfusion since, these proteins can stimulate antibody production.

Following the first transfusion, patients should ideally be tested for the presence of **new** antibodies to RBCs before each successive transfusion and the results carefully reported. In addition, it is important to avoid transfusion of blood from first-degree relatives (haploidentical donors), as this can increase the risk of developing a serious fatal complication known as transfusion-associated graft-versus-host disease (TA-GVHD*). This risk is higher in countries that do not have national, voluntary, non-remunerated blood donation policies, where patients must provide their own blood donor very often a family member. In this situation, the blood should be irradiated to eliminate the risk of TA-GVHD*.

FILTERING, AGE AND STORAGE OF BLOOD

The blood to be transferred to patients who need regular transfusions, should be filtered prior to storage to avoid white blood cell (WBC) interactions, and should be as fresh as possible, preferably not more than 10 days old. Storage temperature (4°C) and transfusion of blood temperatures should be very closely monitored and checked at all times.

PRE-TRANSFUSION MANAGEMENT - THE NURSE'S ROLE

The patient and family should be involved in the decision to initiate blood transfusions and adequate information and explanation should be provided. The patient should be given simple and clear information explaining the risks and benefits of transfusion, and what to expect. This should also include written information in the form of leaflets.

Blood transfusions should be carried out in a familiar location, such as a day-care unit or thalassaemia centre, or in a designated area within the hospital, by experienced nursing staff competent in the administration and supervision of the process.

Once a decision to commence transfusion has been reached, relevant protocols should be followed to ensure that the procedure is safe and effective. Where such protocols have not been established, the haemoglobinopathy unit should aim to do so as soon as possible. A wealth of information, knowledge and experience is available from relevant websites as required.

* Transfusion - Associated Graft versus Host Disease

The nurse's role in ensuring the safety and effectiveness of blood transfusion includes responsibility for patient identification, documentation and communication. Other aspects relating to blood screening and processing, as well as arranging transfusion regimens, are the responsibility of medical experts in transfusion and haematology.

PATIENT IDENTIFICATION

The patient for blood transfusion must be accurately identified and clearly noted. This is the responsibility of the nurse, who must establish the patient's:

- Last name
- First name
- Date of birth
- Hospital/unit number

This identification process is vital to the process of blood sampling, collection of blood from storage and delivery to the clinical area, as well as for administrative purposes. The health care professional should ask the patient during sampling and administration of blood to state their full name and date of birth, which should correspond with the hospital number. Where patients cannot identify themselves, as in the case of a very young or unconscious patient, identification should be obtained from the parent or carer.

When collecting a blood specimen from the patient for compatibility testing, the nurse should:

- Deal with one patient at a time, to avoid distractions
- Identify the patient and ensure that the name, date of birth and hospital number correspond with the information on the request form
- Take at least 6-7mls blood into the cross match tube
- Accurately label the bottle with the patient's details
- Sign the form and specimen bottle before sending to the blood transfusion laboratory
- Collect blood sample for cross matching a maximum of 2-3 days before a planned transfusion, or as soon as possible if urgent.

DOCUMENTATION

Blood transfusion documentation should include pre-transfusion information, administrative data and observations.

During transfusion, the patient's clinical file should be available and should include:

- Management plan
- Blood test results (full blood count, ferritin biochemistry, etc.)
- Date for transfusion

The prescription should include:

- Patient's details
- Type of blood component to be administered
- Any special requirements
- Date
- Volume and/or number of units to be transfused (in paediatrics, this should be clearly written in millilitres)
- Rate or duration of the blood transfusion (according to the medical specialist/treating physicians' instructions)

COMMUNICATION

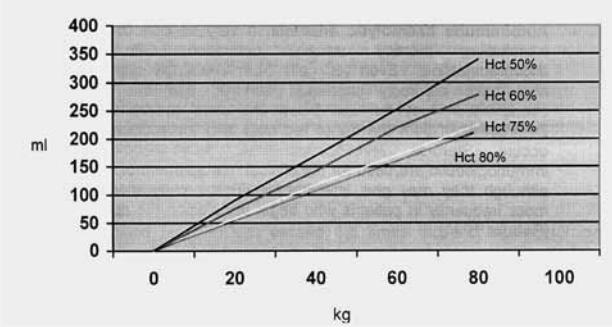
Effective communication is needed between all staff involved in the blood transfusion process for thalassaemia patients, including medical and nursing staff, laboratory staff and support staff. Insofar as possible, the timing of a blood transfusion should be planned to suit the patient and family, minimising disruption to their work and school life. It is important that policies and guidelines are in place to reduce the errors that could result from any miscommunication between staff, patient and family.

TRANSFUSION REGIME

The amount of blood to be transfused depends on several factors, including the targeted increase in haemoglobin and the weight of the patient. According to international guidelines (see TIF Guidelines for the Clinical Management of Thalassaemia 2008), pre-transfusion haemoglobin should not fall below **9.5g/dl-10g/dl**, with post-transfusion haemoglobin of **13-14g/dl**.

The volume of blood to be transfused can be calculated as shown in the two tables below:

Amount of donor blood, depending on haematocrit, required to raise the patient's haemoglobin by 1 g/dl (depending on weight in kg).



From TIF's "Guidelines for the Clinical Managment of Thalassaemia"

Target Increase in Haemoglobin Level	Haematocrit of Donor Red Cells 50%	60%	75%	80%
1 g/dl	4.2 ml/kg	3.5 ml/kg	2.8 ml/kg	2.6 ml/kg
2 g/dl	8.4 ml/kg	7.0 ml/kg	5.6 ml/kg	5.2 ml/kg
3 g/dl	12.6 ml/kg	10.5 ml/kg	8.4 ml/kg	7.8 ml/kg
4 g/dl	16.8 ml/kg	14.0 ml/kg	11.2 ml/kg	10.4 ml/kg

Guidelines for choosing how much blood to transfuse

EXAMPLE:
As an example, to raise the haemoglobin level by 4g/dl in a patient weighing 40kg and receiving blood with a haematocrit of 60% would require 14.0 x 40, 560ml. This calculation assumes a blood volume of 70ml/kg of body weight.

The blood transfusion regime described above, carried out every two to five weeks, helps to prevent complications such as growth impairment, bone deformities and organ damage. It also allows improved quality of life, enabling the patient to engage in normal activity.

The total blood transfused should be recorded. A record of the transfusion should be maintained in the form of a chart, to ensure evaluation of the transfusion therapy. This evaluation should include pre- and post-transfusion haemoglobin levels, the interval between transfusions and the total transfused blood per kilogram per year. This will also provide an indication of the iron load received.

Where the amount of transfused blood required to maintain desired Hb levels is greater than 200-220mls/kg per year, a splenectomy may be indicated, depending on other symptoms. However, as noted above, a splenectomy is not advisable before the age of five, as the patient is more susceptible to infection.

ADMINISTRATION OF BLOOD - THE NURSE'S ROLE

A blood transfusion should be carried out when **there is enough staff available to observe the patient and monitor for any transfusion reactions**. Depending on hospital policy, one or two registered health care professionals competent in blood administration should carry out final checks, as described in the previous section. In addition, the nurse should check that the **unit to be transfused is within the expiry date**, record the volume and ensure there is no leak, clot, etc.

In situations where there is no pre-storage leucodepletion of blood components, a **bedside leucodepletion filter** may be used and in this case, the nurse is needed to have sufficient knowledge to assist efficiently in the setting up and monitoring of this additional procedure.

Transfusion of the red blood cell unit should be commenced **no more than 30 minutes of collection** from storage, which is at a specified controlled temperature, and **completed within 4 hours**. A unit can safely be administered over 90-120 minutes, at an average of 3-5mls/kg/hr. **This can be longer in patients with cardiac involvement** (see TIF's Guidelines-http://www.thalassaemia.org.cy).

The iron chelator **desferrioxamine** (described in following chapters) can be co-administered with red blood cells through a y-connection, **but must not be added to the blood**. However, this practice is in decline as there is **doubt about the efficacy of administering desferrioxamine intravenously with blood transfusion**.

COMPLICATIONS IN RED BLOOD CELL TRANSFUSION

Despite the huge benefits, health professionals need to be well versed with the potential risks of blood transfusion therapy. In particular those involved in the case of multiply transfused thalassaemia patients who in fact constitute the largest patient group of regular blood receivers.

Reactions to blood transfusion fall into two categories:
A. Immune-mediated transfusion reactions, in which the patient's immune system responds to the transfused blood.

B. Non-immune mediated transfusion reactions, in which reactions are not the result of the patient's immune system.
Both categories of reaction can occur during or just after a transfusion (acute reactions)- after just a few millilitres of blood have been introduced, during the course of the transfusion, or after it has finished. Alternatively, a reaction may be delayed, occurring several days or weeks after a transfusion, or even over the longer term.

Tables 1 and 2 indicate the types of category A and B reactions that can occur and Table 3 indicates the transfusion related pathogens and infections.

Table 1

IMMUNE MEDIATED TRANSFUSION REACTIONS	
ACUTE	DELAYED
Haemolytic (intravascular)	Alloimmune
Anaphylactic	Haemolytic (extravascular)
Febrile non-haemolytic	Platelet refractoriness
Allergic (urticarial)	Graft vs Host Disease (GVHD)
Transfusion Related Acute Lung Injury (TRALI)	

About Thalassaemia, Eleftheriou A (TIF Publication 2007)

Table 2

NON-IMMUNE MEDIATED TRANSFUSION REACTIONS		
ACUTE	FREQUENCY	DELAYED
Haemolytic (in vitro)		Metabolic iron overload
Metabolic:		Infectious:
Coagulopathy		1. Bacterial
Hypothermia	rare	Gram negative
Citrate toxicity	rare	Gram negative
Hypocalcaemia	rare	2. Viral*
Hyperkalaemia	rare	HBV
		HCV
		HIV 18<2
		HTLV 18<2
		CMV
		E-B
		B19
		3. Prions: Creutzfeld Jakob
		4. Parasitic** (eg malaria)
Embolic	rare	
Circulatory overload	1/10,000	

About Thalassaemia, Eleftheriou A (TIF Publication 2007)

Table 3

TRANSFUSION-TRANSMITTED INFECTIOUS AGENTS AND DISEASES		
VIRAL	PARASITIC	OTHER AGENTS
HAV	Malaria	HGV
HBV-HDV	Microfilariasis	TTV
HCV	Trypanosoma cruzii	SEN-V
CMV	Toxoplasmosis	CJD???
EBV	Babeosis	TREPONEMAL
HPV B-19	Visceral leishmaniasis	Syphilis
HIV 1+2	Chagas disease	BACTERIAL
HTLV 1+2		Yersinia enterocolitica
Coxsackie B		Multiple organisms

The frequency of viral or bacterial contamination varies widely among countries, depending on the quality of public health and blood transfusion services, and on the local prevalence of these pathogens.

The risk of parasitic transmission is greater in developing countries, depending on local prevalence and preventative measures taken at the national level.

In most European countries, North America and some other countries outside these regions, the residual risk of transmission of HCV, HBV and HIV is indeed negligible today due to extensive efforts in strengthening the whole chain of events from blood donor education, selection and management to donor screening, quality assured blood processing, provision of transfusion to the patient and monitoring of adverse or unwanted events (short and long term) to accurate and prompt reporting. In these countries patients with thalassaemia infected with HCV for example are older patients transfused before the 1990s. On the contrary, in other countries where such measures have not or have been suboptimal taken, transmission of pathogens including hepatitis viruses, still occurs (table 4).

Table 4

RATE OF CHRONIC VIRAL INFECTIONS IN THALASSAEMIA MAJOR	
VIRUS	%
HCV	10% - 75%
HBV	1% - 35%
HIV	< 2%
HBV and HCV	5% - 10%
HCV and HIV	0.5% - 1.5%
HBV and HIV	1% - 1.8%
HBV + HCV + HIV	0.6% - 0.8%

TIF's survey, 25, countries 2008

TREATING TRANSFUSION REACTIONS

The prognosis for a transfusion-related reaction depends on its severity. An outline of how some of these reactions may be treated follows:

Serious complications

- **Acute Haemolytic Transfusion Reaction** (AHTR), anaphylactic, sepsis (bacterial contamination) and air embolism-stop the transfusion. Fluids may be administered intravenously and various medications used to treat or prevent associated medical conditions, such as disseminated intravascular coagulopathy (DIC), renal failure and shock.
- **Overload of the circulatory system** may be treated by administering oxygen and diuretics, to increase fluid loss, as well as slowing or stopping the transfusion.
- **Transfusion-Related Acute Lung Injury** (TRALI) may be resolved by appropriate respiratory support.
  The effects of delayed haemolytic anamnestic response and alloimmunisation may be reduced with corticosteroids.
- **Graft-versus-host disease** (GVHD) requires appropriate support therapy.
- **Viral contamination** should be treated according to the virus concerned.

Benign complications

- **Febrile non-haemolytic transfusion reaction** (FNHTR) may be addressed with antipyretics.
- **Rash and itching** (urticaria) may be reduced with antihistamines.

PREVENTING TRANSFUSION REACTIONS (TR) - THE NURSE'S ROLE/CONTRIBUTION

Incorrect patient (and consequently incorrect blood group) identification is by far the most commonly reported error in transfusion-related fatalities. Transfusion services and other relevant departments must therefore implement rigorous policies to ensure that optimal transfusion procedures are always followed, and medical staff must strictly adhere to established transfusion standards and protocols to protect the health and safety of patients.

The nurse plays a key role in the prevention and early identification of signs of transfusion reaction (TR). Important aspects of that role include ensuring that:

- Samples for blood typing and compatibility testing are clearly identified. The patient's full name and date of birth are clearly noted on the tube label before a sample is drawn, and the data on the Transfusion Application Form checked carefully.

- A medical officer verifies that any infusion equipment is being used according to the manufacturer's recommendations.
- A medical officer carries out a visual check of the blood unit for evidence of contamination before it is attached to equipment-e.g. colour change to dark purple, clots or haemolysis-and verify that the unit has not expired.
- Compatibility between the patient and the blood unit are verified, by checking the certificate of the patient's blood group against the blood group as shown on the blood unit label.
- Identification details of the blood unit(s) transfused are noted in the patient's record, so that donor(s) may be traced, if necessary.
- The patient is carefully observed over the course of the transfusion, particularly in the early stages when a transfusion reaction (TR) is more likely to occur.
- Blood components are transfused within the recommended time, to avoid compromising clinical effectiveness, safety and ease of administration.
- **NOTE-rapid transfusion of cold blood may be dangerous. Frozen units must be handled with great care, as the containers may be brittle and may easily crack at low temperatures.**
- Appropriate pre- and post-transfusion parameters are recorded, to determine the efficacy of the transfusion.
- Observed reactions are noted and reported. All serious complications should be investigated. (Draw a post-transfusion sample and send it with the unused blood product and its administration set to the blood bank for serological incompatibility investigation and bacterial culture test.)
- In case of repeated TR, investigation for the presence of irregular antibodies outside the ABO and Rh systems is recommended. When repeated FNHTR occurs, leukocyte-poor components should be used.
- It is important to bear in mind that some complications may be delayed, such as the onset of disease transmitted by blood transfusion. Where a donor is found to have seroconverted, patients that have received their blood must receive a medical follow-up.

Many hospitals in Europe and the US have Blood Transfusion Committees that include representatives of the blood transfusion service and of main clinical units with significant transfusion activity. Such committees can further enhance the efficacy of transfusion practice, by:

- Defining blood transfusion policies adapted to local clinical activities.
- Conducting regular evaluations of blood transfusion practices.
- Analysing any undesirable event linked to a blood transfusion, and taking any corrective measures necessary.

The nurse practitioner should closely monitor all patients on blood transfusion for any symptoms/signs such as:

- **Fever or Raised temperature - 1.5°C above base line**
- **Chills and rigors**
- **Tachycardia**
- **Hypertension**
- **Collapse**
- **Flushing**
- **Bone, muscle, chest and/or abdominal pain**
- **Shortness of breath**
- **Nausea**
- **Generally feeling unwell**
- **Respiratory distress**
- **Urticaria rash**

The table below relates the type of reactions and their causes with the most commonly observed symptoms and with the timing of these occurrences.

TYPE OF REACTION	TIMING	CAUSE	SYMPTOMS
acute haemolytic	after infusion of a few mls of blood	ABO incompatibility	dyspnea, chest constriction, fever, chills, lumbar pain, hypotension shock, renal failure
anaphylactic	-	congenital deficiency in IgA	skin flushing, hives, itching, dyspnea, vomiting, diarrhoea, chest pain, hypertension, loss of consciousness, shock
air embolism	-	air entering the system	cough, dyspnea, chest pain and shock
bacterial contamination (sepsis)	towards the end or after completion of transfusion	transmission of bacteria through transfused blood	fever, chills, vomiting, diarrhoea, hypotension, shock, renal failure, DIC
circulatory overload	-	transfusion proceeding too quickly	dyspnea, cyanois, increased systolic pressure
TRALI (Tansfusion Related Acute Lung Injury)	-	reaction between transfused anti-leucocyte antibodies and patient's granulocytes	dyspnea, cyanosis, cough, hypotension
FNHTR (Febrile Non-Haemolytic Transfusion Reaction)	-	reactions between leucocyte antigens in transfused blood and anti-leucocyte antibodies in the patient's blood-- some reactions believed to be due to tranfusion of proteins called cytokines, produced by leucocytes during blood storage	increase in patient's temperature by 1°C or more without any other medical explanation
allergic (urticaria)	-	results from foreign allergens in the donor's blood reacting with patient's antibodies or antibodies in the donor's blood reacting with patient's allergens	urticaria (hives), rash, localised oedema

About Thalassaemia, Eleftheriou A (TIF Publication 2007)

IF A TRANSFUSION REACTION IS SUSPECTED - THE NURSE'S ROLE/CONTRIBUTION

The nurse in collaboration with the head nurse and/or the medical specialist proceed to:

- **Stop the transfusion.**
- **Maintain venous access.**
- **Monitor vital signs (temperature, pulse respiration and oxygen saturation.**
- **Where needed, resuscitate the patient with normal saline or crystalloid fluid at a slow rate. If the hypotension is prolonged, the patient may require inotropes.**
- **Inform patient's clinicians.**
- **Recheck the Identity of the patient against the unit.**
- **Monitor urine output. The first urine passed should be sent to the laboratory to monitor for free haemoglobin.**
- **Send blood specimen to the lab for repeat cross-match, full blood count, urea, electrolyte and liver function tests.**
- **The unit of blood should be retuned to the laboratory with the giving set for further investigations.**

DISCUSS WITH CLINICAL HAEMATOLOGIST and obtain guidance on patient management

CHAPTER 5
INFECTIONS IN THALASSAEMIA

Patients with thalassaemia major have a higher risk of infection because of:

- **Anaemia**
- **Splenectomy**
- **Iron overload**
- **Blood transfusions**
- **Use of desferrioxamine**

ANAEMIA

Where patients receive insufficient blood transfusions or no transfusions at all, anaemia is the most important cause of serious infections such as pneumonia. Although this is rarely a problem in the West, where adequate blood is more easily available, insufficient transfusion is a frequent problem in some countries of the developing world and such infections may therefore still occur.

SPLENECTOMY

Patients who have had their spleen removed, especially if removed at a very young age, face a significant risk of developing serious infections such as Streptococcus pneumonia, Haemophilus influenza and Neisseria meningitides, caused by encapsulated bacteria. Other bacteria, viruses and parasites may also cause serious infections in these patients. This is because the spleen, as mentioned earlier, is involved protecting the body against infections. (More detailed information on splenectomy is provided in Chapter 3: Thalassaemia Overview)

IRON LOAD

Patients who are well transfused but inappropriately chelated-either because of difficulties procuring iron chelators or because of a low level of compliance-may also have an increased risk of developing severe infections. This is because some infectious agents thrive on iron: the higher the level of iron in the body, the more quickly such agents may grow and multiply, causing very serious infections. The best-documented infection is caused by a bacterium called Yersinia enterocolitica-a peculiar infectious agent that, unlike other bacteria, does not have a mechanism of its own for collecting and using iron from its own environment. In healthy individuals, these bacteria are harmless and of little or no clinical importance. However, in thalassaemia major, where there is excess iron in the body either free or bound to the desferrioxamine molecule, Yersinia grows and multiplies rapidly, causing serious, life-threatening infections.

A great deal of work has been carried out on the role of iron in bacterial infections. However, there has also been considerable research into the role of iron in viral infec-

tions (such as hepatitis and AIDS), examining how iron may affect the progression of these infections and their response to treatment with recommended drugs. The results of these investigations indicate that in thalassaemia, iron overload may be related to a worse prognosis for chronic viral hepatitis B and C and a poorer response to the treatment of chronic viral hepatitis. The effectiveness of iron chelation therapy thus seems to play an important role in the prognosis of chronic viral hepatitis in these patients. It has also been demonstrated that HIV infection in patients with thalassaemia major becomes more severe when their chelation regime includes less than 40mg/kg body weight of desferrioxamine, or when serum ferritin levels are above 1935ng/L.

In summary, iron may play an important role in increasing the severity of infections in thalassaemia major, because iron may:

- serve as a nutrient for the growth of pathogens;
- serve as a nutrient for proteins called enzymes that support the multiplication of infectious organisms;
- remove important chemicals called antioxidants that protect the body's cells against inflammation;
- damage certain types of cells that play an important role in the body's defence against infection.

BLOOD TRANSFUSION

There is a wide range of bacteria and parasites that may be transmitted through blood, some more clinically significant than others and some more frequent in some parts of the world than others due to higher local prevalence. Inappropriate or suboptimal quality of blood (safety) is still a fact in many countries and this puts a large population of patients at risk. (see table below and also table 3, page 50)

PREVALENCE OF HBsAg-POSITIVE AND ANTI-HCV-POSITIVE THALASSAEMIA PATIENTS

GEOGRAPHIC AREA	SCREENED SUBJECTS, NO.	$HBsAg^+$ %	$ANTI\text{-}HCV^+$ %
Iran	732	1.5	10.3
Turkey	300	0.8	4.4
Thailand	104	2	21.2
Lebanon	305	0.3	14
India	104	3.8	21
Malaysia	85	2.4	22.4
Malaysia	72	1	13
Indi	70	5.7	ND
Iraq	550	ND	67.3
Pakistan	35	ND	60
Italy	1481	ND	85.2
Bhrain	242	ND	20.5
Brazil	32	ND	48.8
Hong Kong	00	ND	34
UK	73	ND	23.3

Blood, 21 October 2010, Volume 116, Number 16

CHAPTER 6
IRON OVERLOAD AND IRON CHELATION

Thalassaemia causes iron to accumulate in the body from the destroyed red cells and increased absorption of iron from the gut. However, another important cause of iron accumulation in thalassaemia is the basic treatment for the disease-blood transfusion therapy.

Each millilitre (ml) of red blood cells contains about 1.16mg of iron. An average unit of blood contains about 250ml of packed red cells-i.e. 250 x 1.16 or between 200-290mg of iron. The iron released from the breakdown of these red blood cells is the major source of the iron that accumulates in the bodies of patients receiving lifelong blood transfusions. For example, a patient receiving 30 units of blood per year will have an excess of around 6g of iron a year (200 x 30 = 6,000 mg = 6g), or about 15-16mg/day. The body is unable to excrete such a large amount of extra iron, and so it piles up in the tissues and organs of the body. If this iron is not removed by medical intervention, it can be extremely harmful, causing some of the most serious complications in thalassaemia major.

The clinical symptoms of iron overload generally appear around the age of 10, although evidence of the toxic effects of iron has been found in the liver of much younger children. Injury to the liver-known as fibrosis-begins within two years of the start of transfusions. Serious liver injury (cirrhosis) can develop before the age of 10 if there has not been treatment to remove the excess iron, particularly where the patient has hepatitis B and/or C. Heart disease-one of the most frequent causes of death in thalassaemia major-has also been reported within 10 years of the start of a transfusion regime, although heart failure does not usually occur until after 15 years or more. Iron loading is also the most important cause of delayed sexual maturation in patients with thalassaemia, affecting about half of both male and female patients. In addition, iron loading can cause difficulties in women trying to conceive (around 25% of cases), and is frequently a cause in the development of diabetes mellitus. Over the long term, excess iron causes bone complications and damage to other important organs, such as the thyroid and parathyroid. Therefore patients must receive treatment to remove excess iron, which will otherwise accumulate in the body with serious effects on the patient's quality and length of life.

HOW EXCESS IRON DAMAGES THE BODY

As iron accumulates in the body-either as a result of thalassaemia itself, or of blood transfusion therapy, or both-the main iron-carrying protein in the blood, transferrin, gets filled up (saturated) with iron. Without any iron-free transferrin available, unbound iron-which is very harmful to the body-begins to circulate in the blood. Iron also accumulates

in the tissues, bound to protein storage molecules called ferritin and haemosiderin. Iron stored in these proteins is less harmful than unbound iron. However, these storage proteins become saturated and the body constantly breaks them down and they release unbound iron. Iron can also be released from storage proteins when the patient is ill, particularly with an infection. Non-transferrin bound iron-the iron left over in the system when there is no more transferrin to bind to it-is unstable. That means it can easily gain or lose a negative charge, called an electron. When iron gains an electron, it changes from having three positive charges (a type of iron known as 3^+ or ferric iron) to having two positive charges (a type of iron known as 2^+ or ferrous iron). As iron moves between the 2+ and the 3+ states, it produces harmful substances called free radicals, which can cause extensive damage to the body's tissues.

The best-known process by which free radicals are produced is called the Fenton reaction-a chemical reaction that is simplified as follows:

Hydroxyl radical (HO) generation

$$O_2 + Fe^{3+} \rightarrow O_2 + Fe^{2+}$$
$$H2O_2 + Fe^{2+} \rightarrow OH^- + HO^- + Fe^{3+}$$

The only way to remove excess iron is to use drugs called iron chelators, which combine with iron to form a compound that can be excreted from the body through the urine and/or stools. These drugs are used to control the level of iron in the body and to prevent damage to vital organs. There are three iron chelating drugs currently in use: desferrioxamine, deferiprone and deferasirox.

DESFERRIOXAMINE (DFO)

Desferrioxamine (DFO) was the first iron-chelation drug to be manufactured. Developed in the 1960s, DFO was introduced to the market in the early 1970s for the treatment of thalassaemia major. DFO works in two ways. The first is a slow process in which DFO binds iron to form a substance called ferrioxamine, which is then excreted from the body. The second role of DFO is to decrease the toxicity of iron in the body by absorbing free radicals.

Patients with thalassaemia start using this drug when they begin regular blood transfusion therapy, after the first 10-20 transfusions or when their ferritin level reaches 1000µg/l.

HOW TO USE DFO

DFO is administered **subcutaneously or intravenously** via a specially designed pump that infuses the drug over a period of 8-12 hours. DFO must be delivered slowly because it has a short half-life. That is, it is rapidly eliminated from the blood-in 20-30 minutes. A long period of infusion allows a steady concentration of DFO to be maintained in the blood, giving the drug maximum time to absorb excess iron.

Most children need to start using DFO by the age of 2 or 3 years. As this is a lifelong, daily treatment, it is impractical for it to be administered at the treatment centre or hospital. It is therefore necessary to teach first the parents, and later the patient, how to carry out the procedure at home. This is where the nurse has a major part to play. The doctor may have explained the need for the procedure and even outlined how it is done, but the nurse must undertake the task of teaching and demonstrating the use of DFO in practice. This is not an easy task.

Neither parents nor patients are likely to have come across any of the procedures involved. In addition, parents usually suffer feelings of guilt and fear at subjecting their child to such treatment. To stick a needle in their own child, to cause it pain, is a source of great distress. The role of the nurse therefore begins with offering support and reassurance. There is no magic formula or psychological technique for approaching the task. But an important start is for the nurse to show genuine feelings of caring and to avoid being in a hurry or busy with other things.

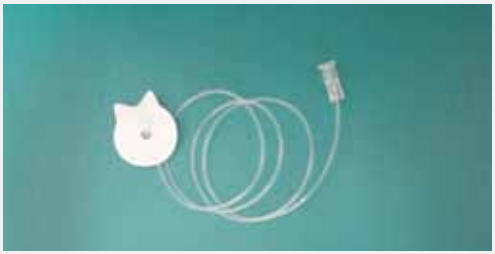
Encouragement should be given without being judgmental. Most parents will be responsive and efficient in helping their child. Others will struggle more, requiring greater resources of nursing care. The nurse should report her experiences with the family to the team headed by the treating physician. Parents who have difficulties in coping that cannot be overcome through the support of doctors and nurses may be referred to a psychologist, who should also be a member of the team. The psychologist may choose to see the family, or may give advice to the nurse on how to proceed. It is also extremely helpful to refer families to local patient associations for support, where such organisations exist. As the child grows older, the nurse's relationship will be less with the parents and more with the adolescent or adult patient.

Once a trusting relationship has been established, parents must learn how to use DFO appropriately and safely, including how to store, dissolve and administer the drug. DFO should be stored undissolved at room temperature or, if dissolved, refrigerated at 4° C. The correct solution for administration is 10%. This means that a 500mg vial is dis-

solved in 5ml sterile water. A new 21G needle is inserted through the rubber cap, which has been previously sterilized by alcohol, and the water injected. The powder will dissolve after some shaking of the vial. In some countries with advanced care of thalassaemia, the solution may be prepared by the hospital, under sterile conditions.

The types of subcutaneous needles used to administer the drug to the patient should be well demonstrated.

NEEDLE BUTTERFLY



THUMBTACK

Patients may try different types of needle, to establish which is best suited to their lifestyle. Many prefer the butterfly needle, which is inserted at an angle of about 45° to the skin surface. Other patients prefer small thumbtack needles that are inserted vertically through the skin and fixed with a special tape.

REPLACEMENT

SITE

SIDE

HYGIENE AND GENERAL INFORMATION

Issues of cleanliness and hygiene are critical to the safe administration of DFO. Parents must be instructed in the importance of hand and skin cleansing and antisepsis. In addition, medical staff must be aware of conditions at the patient's home, where cleanliness, antisepsis and personal hygiene may be neglected or less than ideal, constituting a serious risk of infection-related complications. If necessary, the home should be viewed at first hand by a social worker or a health visitor.

The nurse must indicate sites for subcutaneous infusions (see picture), emphasising the need to rotate between sites. The nurse can also demonstrate the application of topical anaesthetic, such as EMLA cream, to the injection site, which will help to reduce the pain associated with the administration of DFO.

There are two types of infusion pumps, mechanical and balloon. Balloon pumps are generally smaller, lighter and quieter, and more convenient for patients. The various types of infusion pump must be demonstrated and the patient (or the family, in the case of a child) should choose the one that suits them best, depending, of course, on availability. The use of the pump should be clearly demonstrated, with special emphasis on the importance of the time control. If the drug is given too fast, there may be local or other reactions.

BALOON PUMPS

MECHANICAL PUMPS

(About Thalassaemia (2007), Eleftheriou A. (TIF Publication 2007)

DOSE

The average dose of DFO for adults is 30-60 mg/kg body weight and for children 20-40 mg/kg body weight.

The exact dose for each patient is calculated on the basis of age, body iron load and clinical condition.

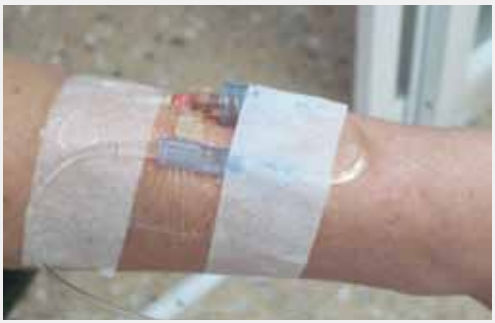
Giving vitamin C with each infusion improves the efficiency of chelation by increasing the amount of iron excreted. However, vitamin C can affect the heart, so patients must only be given it on days of infusion and in a limited dose of 2-3mg/kg/day.

OTHER WAYS OF ADMINISTERING DFO

- **Continuous 24-hour intravenous infusion**
  This method involves administering DFO through a vein via an indwelling catheter. This technique may save the lives of patients who are suffering from severe iron loading and associated cardiac complications. However, this method should be adopted where patients have access to experienced surgical support in hospital settings as this is associated with a considerable high risk of infection and/or blood clots. It is very rarely used today and only in exceptional cases, such as severe iron overload with heart complications or female patients who are planning a pregnancy and have significant iron overload and have no access to, or are unable to take their intensive chelation regimens. (e.g. combined DFOX/DEP treatment)

  Patients with an indwelling catheter may need to take special drugs called anticoagulants to help prevent clotting. They must also keep the skin around the catheter clean in order to prevent infections, immediately seeking medical advice if they notice any soreness or redness of the skin, or if they develop a fever. It is the duty of the nurse to teach the patient, who is usually an adult, how to keep the skin clean and to be proactive in case of infection, which can easily escalate to a septicaemia. In addition, the nurse will assist the doctor in inspecting the insertion site and changing catheters.

- **Intravenous 8-12 hour infusion**
  This method is used in patients who have difficulties with subcutaneous infusion. However, it is not as effective as 24-hour continuous intravenous infusion in cases of severe iron loading, and should not be considered as an alternative to 24-hour infusion for intense chelation treatment. In addition, this method should be used with caution as it may cause damage to the veins that are essential for blood transfusion therapy.



COMPLICATIONS ASSOCIATED WITH DFO

Infection with Yersinia enterocolitica is a severe infection that occurs mainly in patients taking DFO. It should be suspected in all patients who develop fever, especially if accompanied by abdominal pain and diarrhoea or vomiting. Joint pains and skin rashes may occur, and it may also progress to septicaemia. The condition may be confused with appendicitis. If a patient on DFO presents with these symptoms DFO must be immediately discontinued and intensive antibiotic treatment begun, even before confirming the presence of Yersinia. The organism may be cultured in stool or blood and specific antibodies may be detected in a blood sample.

Local reactions at the infusion site associated with DFO include redness, soreness, itching, swelling and lumps, pain and general discomfort. To reduce these reactions the patient must:

- Avoid inserting the needle near important blood vessels or nerves, minimising the risk of damage or bleeding.
- Change the site for injection frequently, using different parts of the body.
- Local pain may be reduced by applying topical anaesthetic creams such as EMLA.
- Swelling may be reduced by applying a warm compress on the affected area after DFO administration.
- For redness, soreness, itching or swelling, the use of heparin cream or an antibiotic plus cortisone ointment may be recommended.
- The rate of infusion should also be checked, as swelling can occur when DFO is administered too quickly.

Other adverse reactions, particularly associated with high doses of DFO, include:

- **Hearing problems:** high-frequency deafness may occur if the drug is given in high doses, especially in children who are not heavily iron loaded. Hearing should moni-

tored annually in patients taking DFO.

- **Eyesight problems:** associated with very high doses of DFO, and also with the presence of diabetes. These include reduced acuity, impaired colour vision and night blindness.
- **Slowed growth and skeletal changes** are also related to high doses of DFO, especially in young children. For this reason it is recommended to start young children on a low dose of 20mg/kg/day and not to increase this beyond 40mg/kg/day until growth has been completed. The characteristic short trunk and short upper arm of some thalassaemia patients are due to the effects of DFO on the bone growth plate (metaphysis), as is knock-knees.

In summary, specific laboratory and clinical tests, in addition to routine biochemical and haematological follow-ups, must be conducted on all patients on DFO (as per TIF Guidelines). These include monitoring of ferritin levels (3-6 monthly), audio-visual checks (at least once a year) and six-monthly monitoring of growth and skeletal changes.

DEFERIPRONE

Deferiprone or very commonly known as L1 is another chelator, or drug used to remove excess iron from the body. An important aspect of this drug s for any other oral medication, is that it is taken orally, which means patients are likely to find it easier to adhere to treatment over the long term. However, the support, understanding and vigilance of the nurse and team are still very much needed.

USE OF DEFERIPRONE

Patients are prescribed 75mg/kg body weight per day. Like DFO, the drug has a short half-life (3-4 hours). It is therefore taken **in three doses** over the course of the day. It is used by many patients across the world as a monotherapy but it is also used in intensive chelation in combination with desferrioxamine

In the late 1990s clinicians started using DFO in combination with L1 as an intense treatment to increase the quantity of iron excreted from the body. Research indicates that each drug may remove iron from different parts of the body. Combined treatment has been found to be particularly useful in adult patients with accumulated iron especially in the heart.

The effectiveness of combination treatment in iron-loaded patients has been shown through magnetic resonance imaging (MRI-the T2* method), which enables the quan-

tification of iron in the heart. This technology has made it possible to accurately and regularly test patients for the appearance of significant amounts of iron on the heart, long before the function of the heart is compromised. It has also been shown that even if heart function is already compromised, combination therapy can reverse this and function may be restored.

Despite the practical difficulties of combined treatment, the associated fall in ferritin levels and clearing of iron, particularly from the heart, has made it acceptable to most patients. For best results, the two drugs are initially administered on the same day. As the iron load is reduced, DFO injections may become less frequent and adjusted according to the medical specialists' recommendations taking into account the needs or clinical condition/past history of each patient.

There are currently no established guidelines on the combined use of DFO and L1, whether simultaneously or sequentially, or on related side effects. Each medical specialist must therefore develop his/her own protocol, based mainly on individual patients' needs.

SIDE EFFECTS OF DEFERIPRONE

The most serious side effect of L1 is a reduction in the level of neutrophils (part of the white blood cells), known as neutropenia. In more severe cases, the neutrophils may disappear altogether-a condition known as agranulocytosis. This loss of white cells, which are responsible for the body's defences against infection, puts the patient in danger of serious, possibly life-threatening infection.

This side effect happens rarely (neutropenia in 1-4% and agranulocytosis in 0.5-1.5%). However, it is essential that any patient taking deferiprone should initially have a blood count **every week** (subsequently reduced to every two weeks) to detect any drop in white cells early. In this event, the drug should be stopped. The nurse should be fully aware of this issue, and warn patients taking the drug to immediately report any signs of infection, such as a fever or even a cough or runny nose, so that a blood count and a doctor's examination can be arranged.

Patients using L1 may experience pain and swelling of the joints, usually in the knees, ankles, elbows, hips and lower back. Sometimes the pain in the knees is so severe that the medicine must be discontinued. Other complications include:

- Gastrointestinal problems such as nausea, dizziness, vomiting, diarrhoea and abdominal pain.

- Zinc deficiency. Zinc should be measured in the course of routine biochemistry tests. If low, zinc supplements may be given.

In summary, the specific laboratory tests required for a patient taking deferiprone, in addition to routine biochemical and haematological follow-up (as per TIF Guidelines), include:

- **Ferritin levels (3-6 months)**
- **Full blood count (weekly, or at least every 2 weeks)**
- **Biochemical analysis for liver function (3-monthly)**
- **Zinc levels (3-monthly)**

The frequency of such tests may vary, according to the treatment protocols adopted by each clinic.

DEFERASIROX/EXJADE

Deferasirox is the newest iron chelator, and is also taken orally. Deferasirox has been keenly awaited by the many patients hoping to move towards more 'personalised' care, tailored to individual need. The drug has been approved by European and US regulatory bodies (the EMA and the FDA), for use by children over 2 years of age, according to the EMA, and over 6 years of age, according to the FDA.

An important advantage of deferasirox is that it remains at high levels in the blood for a sufficiently long period of time (12-18 hours) and the daily dose can be taken all at once.

The nurse as for the other drugs, must explain the proper use of deferasirox when it is first prescribed by the doctor.

- Deferasirox should be taken at about the same time each day, on an empty stomach.
- After taking it the patient should wait at least 30 minutes before eating.
- The tablets are dissolved by stirring in a glass of water, apple juice or orange juice (not in fizzy drinks). Dissolve in half a cup if taking less than 1000 mg/day. The tablets are not chewed or crushed or swallowed whole.
- After drinking the solution, a little additional water (or juice) is poured into the glass and drunk, to ensure that any remaining medicine is consumed.
- A missed dose should be taken as soon as possible.
- Tablets may be stored at room temperature but away from excess heat.

The use of deferasirox can be adjusted according to patient's need, in a treatment regimen tailored to an individual patient's iron load. **The starting dose may be 20mg**/

kg/day. However, the doctor familiar with the patient's iron level and general clinical status may increase this to 30 or 40mg/kg/day, as needed.

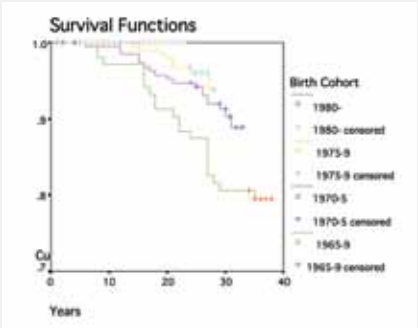
SIDE EFFECTS OF DEFERASIROX

- Gastro-intestinal side effects such as nausea, vomiting, diarrhoea, abdominal pain, constipation and indigestion (relatively common)
- Skin reactions such as rashes (common but not usually severe)
- Increase of blood creatinine (more frequent). In most cases, does not progress to abnormally high levels of clinical significance. However, patients with reduced or compromised kidney function may be unable to take this medication.
- Problems with hearing and eyesight (rare). Check annually.

CONCLUSION

The availability of three iron-chelating agents means that the treatment of thalassaemia can be tailored to the needs of individual patients. This is a major medical advance that has contributed to the increased survival of thalassaemia patients-where such treatment choices are available and accessible to patients.

The survival curve opposite demonstrates the dramatic improvement in survival, with patients being born during years of improved medical and other care.



Survival of thalassaemia patients in Cyprus by birth cohort

There is currently greater knowledge and experience of the role of iron chelation in β thalassaemia major. However, research has shown that patients with thalassaemia intermedia and sickle cell anaemia, may also require iron chelation later in life, even if they are infrequently or never transfused, due to the excess iron that will have accumulate over the years due as a result of increased absorption from the gut. An improved understanding of the pathophysiology and medical complications involved in thalassaemia intermedia has also led, in more recent years, to the identification of a number of criteria for the initiation of chronic transfusions in these syndromes, requiring thus the accurate and frequent monitoring of iron load and consequently the initiation of iron chelation treatment.

CHAPTER 7
LABORATORY AND CLINICAL ASSESSMENT AND MONITORING FOR THE THALASSAEMIA PATIENT

Each centre and multidisciplinary team develops its own testing, monitoring and assessment protocol for thalassaemia, including the frequency and type of tests conducted However, some general points, as outlined in TIF's Guidelines, are highlighted below.

1. **General Tests**

   CBC (Complete Blood Count): routinely performed every 1-3 months, or weekly (at least every 2 weeks) in patients taking deferiprone.

   Biochemical tests include liver function tests (ALT, AST, γ-GT) and kidney function tests (e.g. urea, creatinine, creatinine clearance), particularly for patients taking deferasirox where it may be necessary to check creatinine levels monthly.

   Viral serology tests (HBV, HIV, HCV,): every 6-12 months and

   DNA-based viral tests, according to the serological findings and antiviral treatment regimens used in the case of patients infected with HBV and/or HCV and or HIV.

2. **Iron Overload Assessment and Monitoring in heart and liver**

   The protocol below is taken from a UK, NHS Haemoglobinopathy reference centre.

CONDITION	S. FERRITIN	MYOCARDIAL T2*MRI	FERRISCAN Measures Liver Iron Content (LIC)	LIVER
Beta thalassaemia major or other transfusion dependent anaemia	Every 3 months	From age 8: every 2 years if T2*>20ms. If 10-20ms every year. If <10ms, or EF reduced test every 6 months	From age 8 annually	Only if indicated for histology or if laparotomy
Thalassaemia Intermedia, NTDT* or iron loading anemias	Every 6 months Target value of equal or below 800 mg/< is recommended as reflecting a LIC of equal or less than 5mg F/g dw	Every 5 years after age 10 but increase if iron load detected	From age 10 annually LIC range /Clinical relevance	Only if indicated for histology or if laparotomy

Each centre develops its own protocol based on its resources, facilities and needs.

Ferritin

A ferritin level consistently below 2500 μg/L has been shown to reduce the risk of cardiac complications but a target value of approximately 1000 μg/L or less is recom-

*NTDT: Non Transfusion Dependent Thalassaemias

mended. As factors such as inflammation, ascorbate status, and hepatitis can affect the serum ferritin level, results should be interpreted with caution. Day-to-day variations are particularly marked with high degrees of iron loading and interpatient variability is considered to be largely due to changes in inflammatory status.

In patients with thalassaemia major, current practice is to initiate chelation after 10-20 blood transfusions or when the ferritin level rises above 1000 µg/L. Ferritin should ideally be monitored at least **every 3 months**. (in β-thalassaemia major)

Research is ongoing to identify complementary markers, such as labile plasma iron, that can be used in combination with serum ferittin levels to predict body iron load. Below the positive and negative issues with regards to the use of this test are tabulated.

MEASURING AND INTERPRETING SERUM FERRITIN	
ADVANTAGES • Easy to asses • Inexpensive • Repeat measures are useful for monitoring chelation therapy • Positive correlation with morbidity and mortality	DISADVANTAGES • Indirect measurement of iron burden • Fluctuates in response to inflammation, abnormal liver function, metabolic deficiencies • Serial measurement required

Liver Iron Concentration/Content (LIC)

This is most commonly assessed by liver biopsy and Magnetic Resonance Imaging (MRI) methods. Its clinical significance as evaluated using MRI based methods through many years of studies and observations as well as positive and negative issues of its use are described in the two tables (1+2) below:

Table 1

LIVER IRON CONCENTRATION THRESHOLDS IN TRANSFUSIONAL IRON OVERLOAD	
LIC RANGE	CLINICAL RELEVANCE
0.17-1.8 mg Fe/g dw	Normal range in the healthy population
3.2-7.0 mg Fe/g dw	Suggested optimal range of LIC foe chelation therapy in transfusional iron loading
7.0-15.0 mg Fe/g dw	Increased risk of complications
>15.0 mg Fe/g dw	Greatly increased risk of cardiac disease and early death in patients with transfusional iron overload

Extract from Olivieri et al, Blood 1997; 89, 739-61

Table 2

MRI ASSESSMENT OF LIC	
ADVANTAGES	DISADVANTAGES
• Assesses iron content throughout the liver • Potentially widely available • Pathological status of liver and heart can be assessed in parallel	• Indirect measurement of LIC • Requires MRI imager with dedicated imaging method

The use of liver biopsy is today very limited for the purpose of assessing liver iron content. Its disadvantages as seen on the table below outweigh its advantages which mainly focus on the better evaluation of the liver histology.

ASSESEMENT OF IRON LEVELS BY LIVER BIOPSY	
PROS	CONS
• Validated reference standard • Direct measurement that generally provides reliable information • Allows concomitant histological/pathological assessment • Allows for measurement of non-heme storage iron	• Invasive: associated risk of bleeding infection, and pain • Requires skilled physicians and standardized laboratory techniques • Sample size is small relative to size of liver - measurement may not be representative of general iron distribution • Certain liver diseases can result in spurious measurements

Cardiac Iron

Cardiac iron can be rapidly and effectively assessed in millisconds (ms) using a gradient echo MRI technique known as T2*, which has become the standard method.

ASSESEMENT OF CARDIAC IRON BY MRI T2*	
Normal	20+ ms
Moderate overload	10 - 20ms
Severe overload	less than 10ms

Total body iron stores is another important parameter for medical specialists to draw conclusions and support their decision on how to move forward with each individual patient and this is calculated as below:

Total Body Iron stores can be calculated from LIC as shown below:

10.6 x LIC (mg/g dry weight)*

*Angelucci E., Giovagnoni, A., et at: Limitations of magnetic resonance imaging in measurement of hepatic iron. Blood, 1997, 90, 4736-4742)

IMMUNOPROPHYLAXIS

- Pneumococcal vaccine should be given at least two weeks in advance of splenectomy, and again 3-5 years later. Children vaccinated under the age of 2 should be re-vaccinated at the age of 2 years (response is poor in children <2 years). A booster vaccine should be given 5 years after the first dose.
- Haemophilus influenza vaccine should be given to patients before and after splenectomy.
- Meningococcal polysaccharide vaccine should be given to patients undergoing splenectomy, and to non-immunised splenectomised patients from 2 years of age, including adolescents and adults. A booster vaccine should be given 5 years after the first dose.
- Hepatitis B vaccine should be given to activate immunisation against HBV infection. It should also be given to all splenectomised and non-splenectomised patients with Hb disorders. The first dose is given by the first month of birth, the second dose 2 months after the first and the third dose 6 months after the first dose. A booster vaccine is administered 5 years later.
- Influenza virus vaccination is recommended annually, to prevent or reduce the risk of febrile illness.

CHEMOPROPHYLAXIS

- Splenectomised patients should be given oral penicillin to prevent any risk of infection.
- 125mg b.i.d for children <2yrs
- 250mg b.i.d for children >2yrs
- Alternative antibiotics may be prescribed if the patient cannot take penicillin (e.g. cotrimoxazole, erythromycin)

ENDOCRINE TESTS

- Thyroid function (FT4, TSH4) from the age of 12 years on an annual basis.
- Gonadal function, assessed mainly by the FSH, LH and testosterone levels.
- Glucose tolerance test (for patients over 10 years of age) is recommended annually.
- If fasting blood sugar (FBS) > 126mg/dl then an oral glucose tolerance test (OGTT) should be performed.
- Growth hormone deficiency test (if recommended by endocrinologist).
- Bone mineral density (DEXA), measured in the area of the spine and the hip. The World Health Organisation (WHO) defines osteopenia as occurring when bone density is reduced to a T-score of -1 to 2.5 below normal. Osteoporosis is described as a bone mass of below -2.5, where normal is above -1. Although these definitions may

not apply to thalassaemia patients, they should be used until more appropriate definitions are established. DEXA is performed if bone pain or fractures occur, and at least annually as patients grow to young adults.
- Bone age, describing the degree of maturation of child's bones (x-ray of fingers, wrist and hand).
- 25-OH vitamin D3, PTH, calcium, phosphate (on endocrinologist's advice).

CARDIAC TESTS

- Full cardiological assessment to be performed annually, or more frequently if problems occur.
- Chest x-ray to check heart size and lungs to be performed annually, or more frequently according to clinical indications.
- Electrocardiogram (ECG), to show any tendency to arrhythmia, poor functioning of the heart chambers (ventricles).
- 24-hour ECG (to record rhythm that may be missed in standard ECG).
- Echocardiogram, indicating size of heart chambers and heart function.
- MRI T2* to establish measurement of heart tissue.

AUDIO-VISUAL TESTING

All thalassaemia patients should have an ophthalmic examination once a year from the age of 4 years, especially those taking desferrioxamine (DFO), to monitor for drug and iron load side effects. There may be need to modify the dose of the chelating drug

MONITORING OF GROWTH

Growth is affected in most patients with thalassaemia. In poorly transfused patients, growth failure may occur in childhood. In well-transfused patients, growth is usually normal until puberty, when a retardation of growth velocity results in failure to achieve the growth 'spurt' associated with the age. Such patients will exhibit short stature, which in most cases is not proportional but rather the result of shortness of the trunk.

The nurse, who is usually responsible for measuring the patient, must therefore include both the sitting and standing height of the patient. This is best done using a stadiometer (Figs. 1 and 2). All measurements must be carefully recorded on a growth chart (Fig. 3), which should always be included in patient records. Special charts are also available for charting growth velocity, which is a comparison of the present height with that of 6-12 months previously (see Fig. 4).

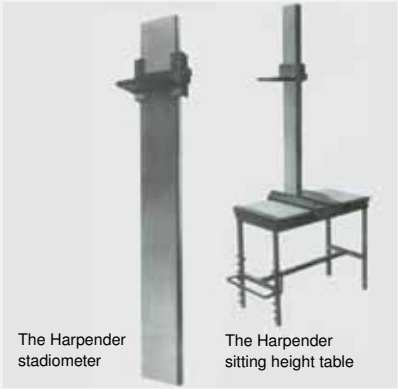


Fig. 1
The stadiometer

Fig. 2
A wall stadiometer

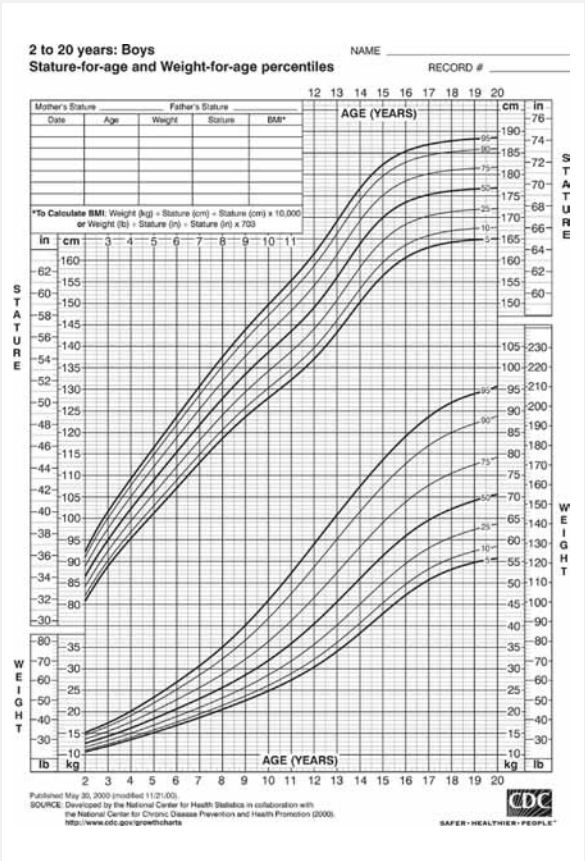


Fig. 3
Example of a growth chart

MONITORING SEXUAL DEVELOPMENT

Even well-treated thalassaemia patients frequently have damage to the endocrine glands, which results in disturbances in the development of puberty. There may be delayed onset of puberty, which means lack of breast development in girls by the age of 13 years, and lack of testicular enlargement in boys by the age of 14 years. There may also be arrested puberty, which is a lack of pubertal progression for more than 12 months with reduced growth velocity. The stages of normal pubertal development are

described in Tanner charts, which are useful points of comparison in assessing patients (Figs. 4 and 5).

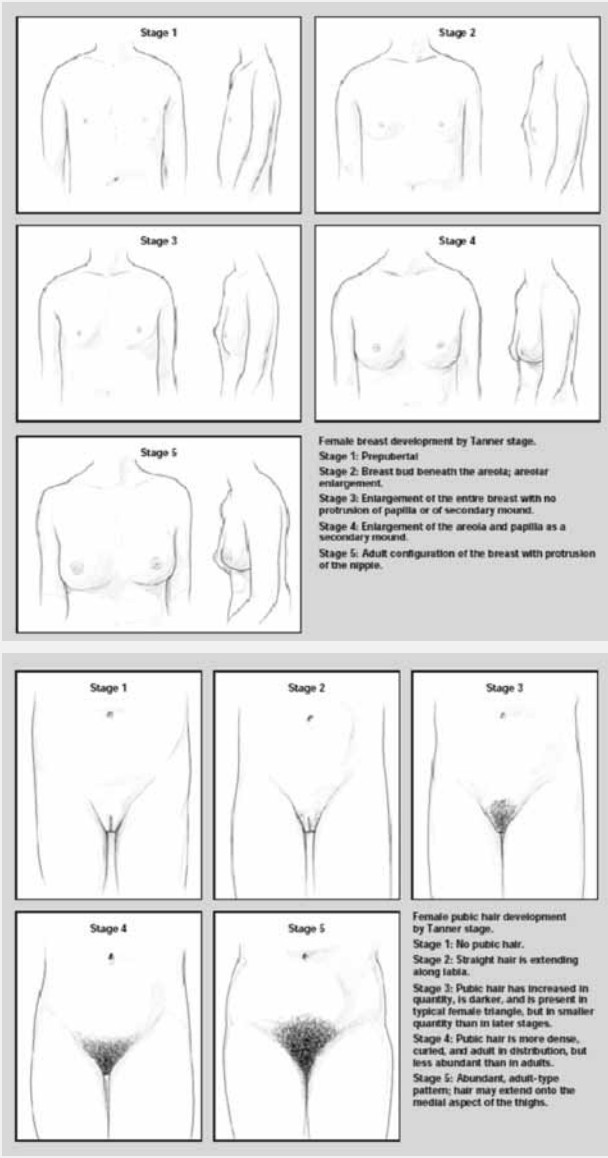


Fig. 4
Tanner staging in girls

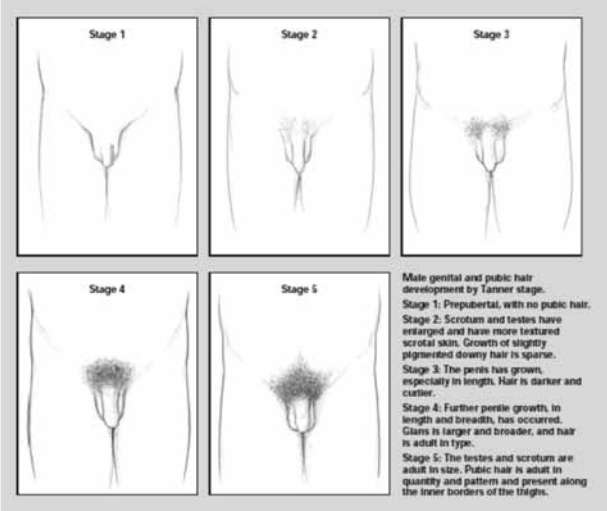


Fig. 5
Tanner staging in boys

The prader orchidometer is used for determination of testicular size.

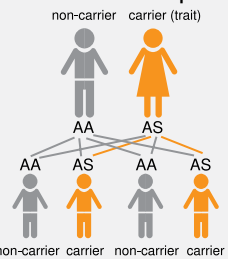
CHAPTER 8
OVERVIEW OF SICKLE CELL DISORDERS (SCD)

Sickle cell disease (SCD) is a disorder with an autosomal recessive pattern of inheritance, as is β-thalassaemia. That is to say, it is inherited from both parents through their genes, and affects male and female equally. SCD occurs as a result of a mutation in the gene regulating the production of the haemoglobin molecule, causing a structural change in the molecule that affects its functionality.

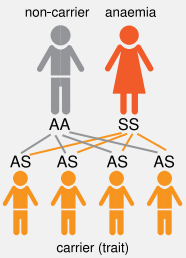
The change in the structure of the haemoglobin molecule in SCD affects the shape of the red blood cells. Normal red blood cells are smooth and flexible, able to move through the smallest blood vessel with ease. In SCD they are inflexible and more viscous. The abnormal haemoglobin produced in SCD, called sickle haemoglobin, causes the red blood cells to become stiff with curved shapes, like crescent moons-or sickles. These cells die prematurely, resulting in anaemia. They also pile up, sticking together to form plugs in small vessels that slow or block the flow of blood and the transfer of oxygen to the various organs and tissues of the body. This results in pain and tissue damage, and can lead to the serious complications that are characteristic of sickle cell anaemia.

INHERITANCE SCENARIOS

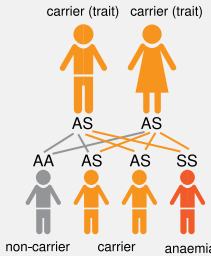
The sickle cell gene is passed from generation to generation, in the same pattern of inheritance described for β-thalassaemia.



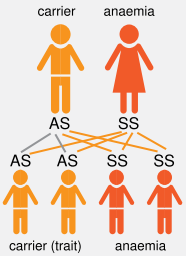
When one parent has sickle cell trait and the other is a non-carrier, they have 50% chance of having a baby carrier of the sickle cell trait



When one parent has sickle cell anaemia and the other is a non-carrier, all their children will have sickle cell trait



When both parents have sickle cell trait, they have a 25% (1 in 4) chance of having a baby with sickle cell disease



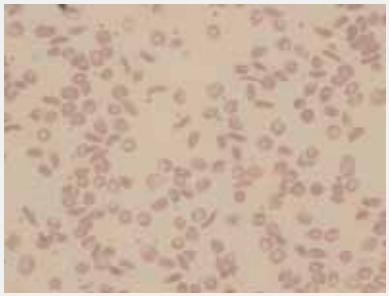
When one parent has sickle cell anaemia and the other has sickle cell trait, 50% of their children will have sickle cell anaemia and 50% sickle cell trait

non- carrier AA carrier (trait) AS sickle cell anaemia SS

DIAGNOSIS

There are several tests to diagnose sickle cell, the commonest and most reliable being haemoglobin electrophoresis, isoelectric focusing, electrophoresis, high performance liquid chromatography (HPLC) and capillary electrophoresis. These methods allow determination of the type and quantity of the different haemoglobins.

In addition, very simple tests such as the solubility test or the blood smear, examined under a microscope, can reveal the presence of sickled red cells.



Sickled red cells

Below is a table of possible combinations of genes (genotypes) with their associated clinical outcome (phenotypeS).

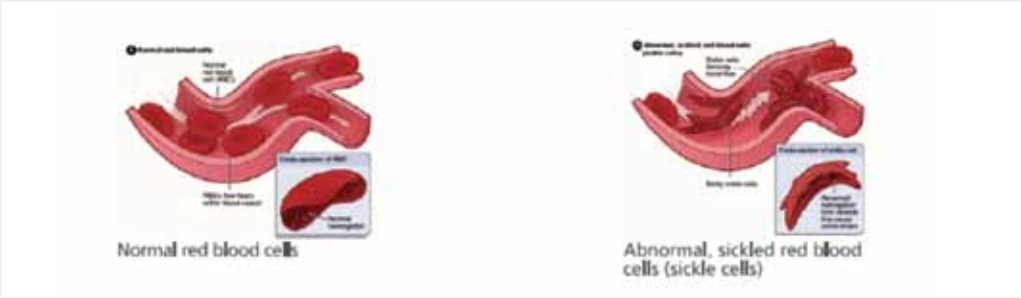
Genotypes and phenotypes associated with the HbS mutation

	β genotype	Hb electrophoresis		Phenotype
Sickle cell trait (HbAS)	β^A/β^S	HbS HbA_2 Rest HbA	Approx. 40% Normal	Clinically asymptomatic
Sickle cell disease (HbSS)	β^S/β^S	HbS HbF HbA HbA_2	Approx. 80–98% 0–20% None Normal	Most severe of the genotypes
Sickle cell disease (HbSC)	β^S/β^C	HbS HbC Minimal HbA_2	50% 50%	Less severe than HbSS but retinopathy more common
Sickle cell disease (S/β° thalassemia)	β^S/β° thalassemia	HbA HbA_2 HbF Rest HbS	None 4–6% 0–25%	As severe as HbSS
Sickle cell disease (S/β^+ thalassemia)	β^S/β^+ thalassemia	HbA HbA_2 HbF Rest HbS	Up to 35% 4–6% 0–20% (>50%)	Mild to moderate phenotype

PATHOPHYSIOLOGY OF SICKLE CELL

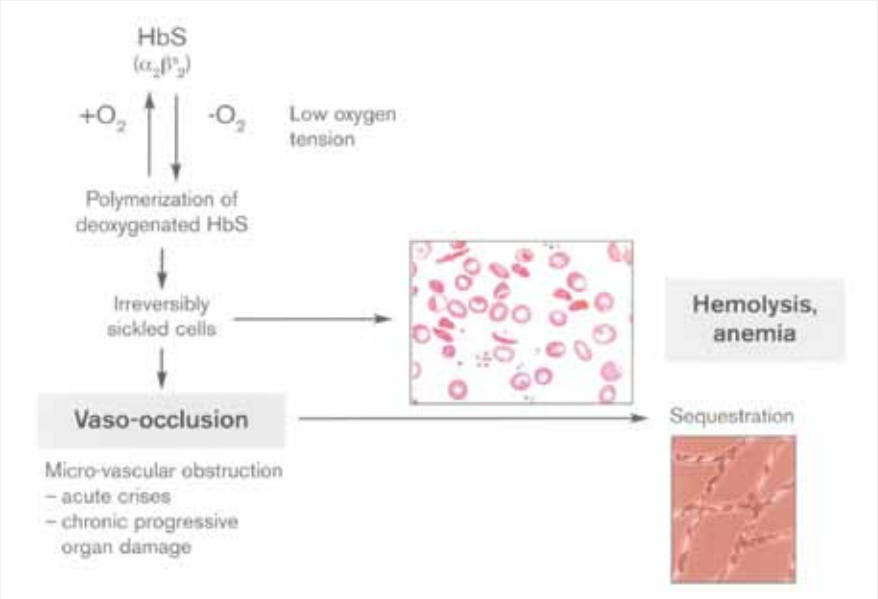
The haemoglobin molecule picks up oxygen in the lungs and releases it when the red cells reach peripheral tissue. The haemoglobin molecule in the red cell exists as a single unit. However, when the sickle cell releases oxygen in the peripheral circulation to the tissues, the molecules clump together to form polymers. When the red cell returns to the lungs and picks up oxygen, the haemoglobin molecules become single units again.

A red cell will travel around the circulatory system of the body four times in one minute, during which the sickle haemoglobin undergoes repeated episodes of polymerisation and depolymerisation. Polymerised sickle haemoglobin molecules group together in long bundles of 14 strands, in a braid-like formation that distorts the cell.



The polymerisation and depolymerisation causes changes within the red cell membrane that damage both the lipid and protein components of the red cell membrane, resulting in membrane stiffness. In addition, the damaged proteins tend to clump together to form abnormal clusters in the red cell membrane, while antibodies develop to these protein clusters leading to more red cell destruction (haemolysis).

The average life of a normal red blood cell is 120 days. In sickle cell disease, a red blood cell lasts about 20 days. The bone marrow attempts to compensate for the resulting anaemia by increasing dramatically to produce more red blood cells, but is unable to do so. The degree of anaemia varies between the various forms of sickle cell disease. The main pathological processes in SCD is simplified in the diagram below:



Pathophysiology of Sickle Cell Disease

TYPES OF SICKLE CELL DISEASE

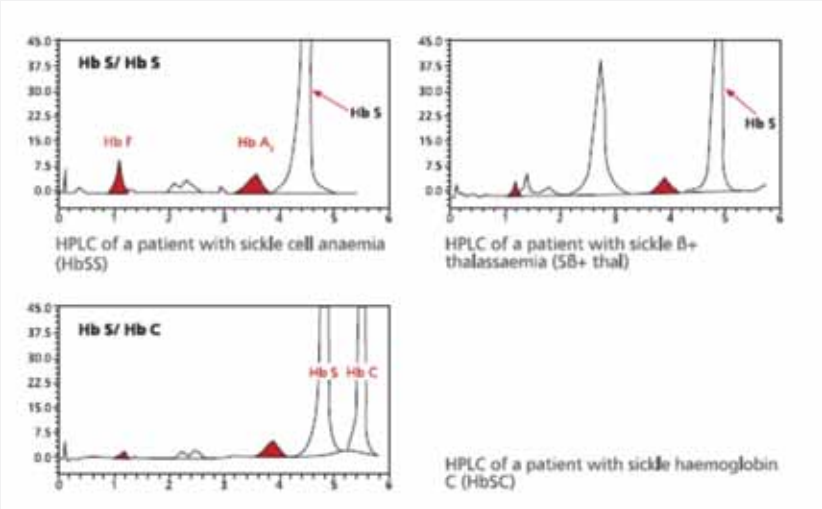
The three commonest types of sickle cell disease are: **haemoglobin SS** (Hb SS or sickle cell anaemia), **haemoglobin SC** (Hb SC) and **haemoglobin sickle beta thalassaemia** (HbS/βthal). Each of these types can cause sickle pain episodes and complications, but there is a wide range of severity.

The name 'sickle cell anaemia' is commonly used interchangeably with 'sickle cell disease', but they are not the same. Sickle cell anaemia is the commonest and most severe type of sickle cell disease, where the gene for sickle haemoglobin is inherited from both parents and results in the production of only abnormal sickle haemoglobin.

In haemoglobin SC disease, one parent passes down the sickle gene, while the other parent contributes the C gene type of haemoglobin. This form is less severe than sickle cell anaemia.

Similarly, a child with haemoglobin sickle beta thalassaemia (HbS/βthal) inherits one

sickle cell and one beta thalassaemia gene, which produces either a decreased amount of β-chains or none at all. If no β-chains are produced, the condition is called $S\beta^0$ thalassaemia, and the clinical picture is similar to sickle cell anaemia. If the amount of β-chains produced is decreased but not absent, the condition is called $S\beta^+$ thalassaemia and is usually less severe than sickle cell anaemia. Sickle beta thalassaemia has a high prevalence in the Mediterranean region and has a clinical presentation that is similar to sickle cell anaemia and different from beta thalassaemia.



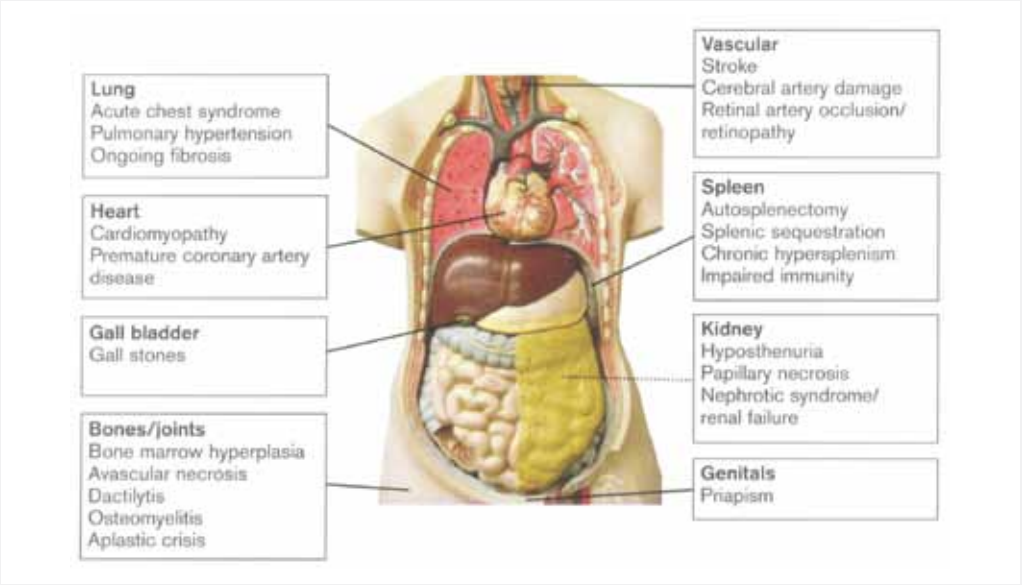
People with HbSS tend to have a steady state Hb of between 5-10g/dl
HbS/β0 between 6-11g/dl
HbSC between 10-15g/dl
HbS/β+ between 9-14g/dl

The haematocrit of a person with sickle cell (SC) is about half the normal value of people without the disease-about 25% compared to 40-45%. People with SC have a higher haematocrit than those with SS.

Although the sickling disorders occur predominantly in individuals of African descent, the disease is also prevalent throughout the Mediterranean, the Middle East and parts of India, the Caribbean and South and Central America, where falciparum malaria was endemic. Within these regions, the HbS gene frequency ranges from 10-30%. However,

due to population movements through the years, SCS is an important part of clinical practice in all countries. Approximately 250,000 children are born with homozygous SCD around the world each year. In the USA, SCD affects approximately 72,000 African-Americans and 1 in 375 African-American newborns. In the UK, it affects 1 in 2,400 live births (all ethnic groups) with 12,500 individuals living with SCD. In many countries, including the UK, SCD is the most common and fastest growing genetic disorder.

COMPLICATIONS OF SICKLE CELL



Clinical Manifestations of Sickle Cell Disease

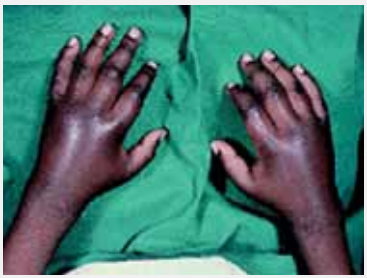
The most frequent complications include:

1. **Pain**

   'Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage' (Stevens,1987)

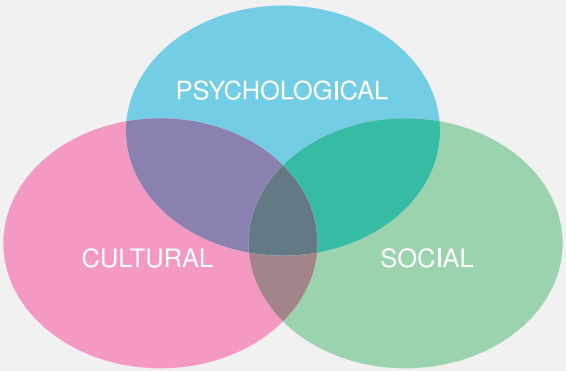
   'Pain is what the experiencing person says it is and exists whenever he or she says it does' (McCaffery,1992)

Pain is the most common manifestation of SCD (also referred to as a vaso-occlusive event), accounting for 96% of hospital admissions of affected patients. Repeated hospital admissions with pain are associated with a higher mortality rate. Pain in sickle patients is highly variable and unpredictable, with severity differing from one patient to the next-a fact that could be attributed to genetic and/or physiological features. Although pain is not itself directly life-threatening, inappropriate treatment can lead to unnecessary suffering and potential complications.



Pain is usually the first symptom experienced. In children from the age of 6 months to 2 years pain mostly affects the fingers and toes and is referred to dactylitis (hand & foot syndrome)-a swelling of the soft tissues of the hands and feet due to blockage of the capillaries.

As well as being unpredictable, the occurrence of pain in sickle cell disease is debilitating and dehumanising. The intensity varies from crisis to crisis and from patient to patient. Some patients describe the pain as deep, aching and tiring. Sickle cell disease pain can affect any part of the body, however individual patients can identify their typically affected areas e.g. the lower back, the extremities, the abdomen, etc. Psychosocial factors play a big part in pain perception and behaviour. Social and cultural aspects influence the way an individual experiences pain and could be intertwined with the pain itself.



Factors that can influence sickle cell disease pain

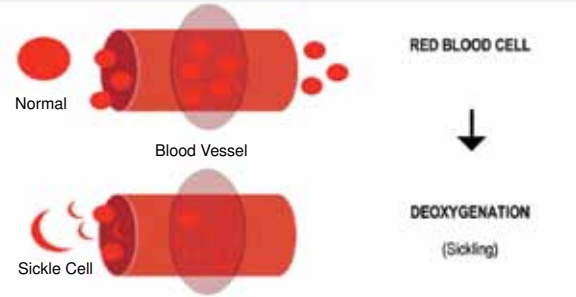
Physiology

Two essential pathological processes occur during a sickle cell crisis:

- Haemolysis-causes anaemia and vascular endothelial damage.
- Vaso-occlusion-results in acute and chronic ischemia, bone infarction with subsequent release of inflammatory mediators and activation of afferent nerve fibres, which in turn causes pain.

Sickle cell pain occurs as sickle red blood cells form clusters and cause vascular obstruction as seen in sketches below. The rigid red blood cells damage the wall of the blood vessels and cause the release of cytokines and chemokines, which trigger the release of inflammatory chemicals such as bradykinin, ATP and prostaglandins, resulting in stimulation of nociceptors:

Vaso-occlusion → Tissue Damage → Nociception → Transduction → Release of Chemicals (hyper-haemolysis, increased WBC count and decreased platelet count)



Causes of pain in SCD

In the below table, the major cause of pain are tabulated:

Acute pain	Chronic pain
Acute vaso-occlusive episode	Avascular necrosis
Acute abdominal crisis	Leg ulcers
Acute priapism	Degenerative joint disease
Acute cholecystitis	Chronic osteomyelitis
Acute osteomyelitis	Cerebrovascular disease

Pain Assessment

It is imperative to carry out adequate assessment using a reliable and valid pain assessment tool, which can facilitate and help evaluate pain management and serve as a reliable basis for medication protocols, as well as being useful in predicting the length of hospitalisation.

Studies have found that sickle cell pain is often not effectively managed due to poor assessment. The World Health Organisation (WHO, 1988) recommended that pain should be assessed according to the age and development of the patient. In addition, frequent pain assessment can improve the quality of communication between sickle cell patients and family, and nursing and medical staff.

Pain can be described as mild, moderate or severe, and should be assessed and the score documented at least every four hours or more frequently if necessary.

Specific behaviours that might be exhibited in young children include:

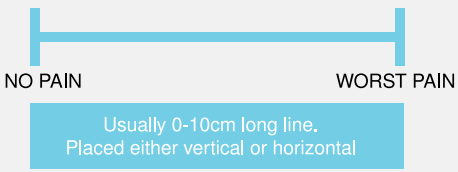
- Pulling ears
- Rolling head from side to side
- Unable to distract
- Crying, moaning, screaming, etc
- Irritable, restless, unsettled
- Abnormally still
- Guarding, defensive of painful area
- Lying on side with legs flexed on abdomen
- Refusing to move a body part

Pain Assessment Tools

Pain assessment tools that can be used include:

- **Self reporting**
  The patient's 'self report' of the amount of pain being experienced is the most reliable indicator of pain and the best method of assessment. However, this might not be possible in the very young or in cognitively impaired patients, such as those with impaired speech as a result of stroke, etc. In such situations a behavioural/physiological tool should be employed.

- **Visual-Analogue Scale**
  Usually this is a 0-10 cm-long line, placed either vertically or horizontally, with 0 being no pain and 10 being worst pain.



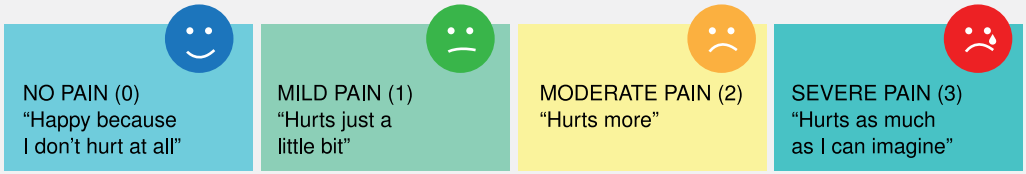
- **Numerical scale**
  A score of 0, representing no pain and 10, being the maximum possible (severe).

- **Oucher scale (Beyer)**
  The patient points to the face that best describes how they feel (from a crying to a happy face). This is very suitable for young children.

- **Pain diary**
  This can be maintained and brought in by the patient, providing the medical team with adequate knowledge of the frequency, intensity and duration of pain, especially in the case of chronic pain.

- **The pain assessment chart** as used in some of London's (UK) Heamoglobinopathy reference centres (Whittington Hospital (UK) are shown below:

Oucher scale (Beyer)



2. **Anaemia**
   Healthy red blood cells have an average life span of about 120 days, after which they die and need to be replaced. However, sickle red blood cells are fragile and die prematurely after only 10 to 20 days, resulting in anaemia. People with sickle cell disease can also get worsening anaemia due to blood becoming entrapped in a suddenly-enlarging spleen (acute splenic sequestration) and/or a stop in the formation of new blood cell (aplastic episode) due to certain infections and/or excessive breakdown of red blood cells (hyper-haemolytic crisis). Symptoms of anaemia include pallor, jaundice, (yellow skin colour), getting tired easily, irritability, loss of appetite and poor growth.

3. **Acute splenic sequestration**
Sickle cells can block the blood vessels of the spleen, just as they can any other organ. With repetitive blockage, the spleen undergoes infarction and subsequent damage, and usually stops functioning (automosplenectomy) in most affected people by the age of 5, except in the case of some Mediterranean patients, where big spleens persist until a relatively old age.

In most children with sickle cell disease, the spleen stays enlarged for several years and in some cases can rapidly entrap red blood cells, resulting in the sudden onset of severe anaemia and a state similar to internal bleeding. This condition is called acute splenic sequestration. By 6 years of age acute splenic sequestration becomes infrequent, because the spleen of children with sickle cell anaemia usually becomes small due to scarring from recurrent sickling. However, in the Mediterranean area where sickle cell anaemia is characterised by persistent big spleen beyond 6 years, and in children with SC disease and S-βthal disease, it is common to see acute splenic sequestration at an older age, and sometimes in adulthood.

Acute splenic sequestration is a leading cause of death in children with sickle cell disease. It is a medical emergency and can be fatal within a few hours. The child becomes very pale and lethargic, and develops rapid breathing, a thumping (palpable) heartbeat and a bloating abdomen (abdominal distension) due to huge spleen. If any of these signs and symptoms appears, you need to take your child to the emergency room immediately. It is important that parents are taught about signs and symptoms of severe anaemia, as well as how to palpate the child's spleen.

4. **Frequent infections**
Infants and young children with sickle cell disease are extremely vulnerable to life-threatening infections in the lungs (pneumonia), blood (sepsis), lining of the brain (meningitis) and bone (osteomyelitis). Children under the age of 5 are at highest risk for these infections. The most worrisome infections are caused by a few types of bacteria, including **Streptococcus pneumoniae (pneumococcus)**, **Haemophilus influenzae type b (Hib)**, **Neisseria meningitidis (meningococcus)** and **Salmonella**. Other infections that children with sickle cell disease are vulnerable to are those caused by flu viruses. Because their immune systems-particularly the spleen-do not work normally, these children develop infections caused by the same germs that afflict other children, but they get these infections more frequently, become very ill faster, and are more likely to develop severe complications, or even die. Adolescents and adults can fight such infections much better than young children, because their immune system is stronger.

The spleen, which is located in the upper-left part of the abdomen, functions as part of the body's defence against infection by filtering bacteria from the bloodstream. A damaged spleen, like an absent spleen or absent lymph nodes, makes a child more vulnerable to serious and sometimes fatal infections.

Infections are treatable and complete recovery possible only if they are recognised and treated early enough.

Death from infections declines dramatically where affected children are identified early in the newborn period, receiving prompt medical care to help prevent complications, including antibiotic penicillin and vaccines to protect against serious infections (described in the following table).

Infections and causative agents

TYPES OF INFECTION	COMMON ORGANISMS
Meningitis	Streptococcus pneumoniae Haemophilus influenza Nesseria meningitidis
Acute Chest Syndrome	Streptococcus pneumoniae Mycoplasma pneumoniae Chlamydia pneumoniae Legionella Respiratory Syncytial Virus (RSV)
Osteomyelytis/Septic Arthritis	Salmonella Staphylococcus aureus Streptococcus pneumoniae
Urinary Tract Infection (UTI)	Escherichia Coli (E.Coli) and other gram-negative bacteria
Infection of unknown origin	Streptococcus pneumoniae Haemophilus influenza, Salmonella Gram-negative bacteria
Influenza infection	Viral influenza
Transient Red Cell Aplasia	Parvovirus B 19

Patients with sickle cell disease with infection can present with the following symptoms:

- Fever.
- Ill appearance. A child who has lethargy or poor skin colour or looks sick can have a serious infection, even in the absence of fever and must be treated immediately.
- Dehydration, poor fluid intake, poor perfusion.
- Low haemoglobin (less than 5gm/dl).
- Chest symptoms, such as cough and dyspnoea, due to chest infection or pulmonary infiltrate.
- Blood tests could indicate raised white blood cell count, raised C-reactive protein, elevation of neutrophils.
- Acute pain.

Patients with SCD that present with a fever above 38.5 degrees centigrade and other signs of infection should be rapidly assessed and laboratory investigations carried out, including chest X-ray, blood, urine and throat culture and oxygen saturation before commencing antibiotics. However, patients presenting with a fever above 40 degrees centigrade or toxic-looking children should be treated promptly with antibiotics before laboratory results are available.

Febrile or sick-looking children with sickle cell disease must seek immediate medical attention and receive intensive and rapid treatment, including empiric antibiotic administration. Acetaminophen (eg. Panadol®, Tylenol®, Tempra®) can be given for temperatures above 101° F, after calling the healthcare provider. Ibuprofen (eg. Motrin®, Advil®, Profinal®, Pediafen®) can also be given, particularly for stubborn fever, provided the child does not have a bleeding disorder or a stomach or kidney problems. Aspirin should not be given to children, as its use has been associated with a dangerous syndrome affecting the liver and the brain called Reye's syndrome.

The incidence of complications can be reduced in this group of patients by simple preventive measures such as prophylactic administration of penicillin. There is good evidence that penicillin protects against encapsulated bacteria, which cause septicaemia and/or meningitis, provided it is taken regularly. It is essential that all children, especially those under 5 years of age, should take penicillin (or clarithromycin or erythromycin, if penicillin sensitive, depending on local protocol) twice daily continuously, starting by the age 3 of months.

Children with sickle cell disease should be vaccinated as per the national vaccination schedule, which specifically protects them from several severe types of encapsulated bacteria infections, which include Meningococcal C, Haemophilus influenzae type B and pneumococcal conjugated vaccine. These are part of the routine immunisation schedule for all infants. Pneumovax 11 injection is given to children with sickle cell disease at 2 years of age and every 5 years thereafter. Extra travel immunisation should be given, and this is to include meningitis ACWY when travelling to countries where other strains of meningitis are prevalent, and hepatitis B, especially for those on chronic blood transfusion.

5. **Stroke**

Stroke is one of the most catastrophic and frequent medical problems encountered in sickle cell disease. It is seen mostly in sickle cell anaemia and in young children. It can occur if sickle cells block blood flow to an area in the brain, resulting in decreased oxygen delivery and brain injury. Less frequently and more so in adults, stroke can be due to bleeding in the brain. A stroke can be overt with clear symptoms, or silent and detected only on special imaging studies such as MRI.

The best way to know if a child is at high risk of stroke is to conduct a special test called the transcranial Doppler (TCD), which measures the velocity of blood flow to the brain. Researchers have recently shown that when this test is abnormal, a child is at high risk of a stroke, and immediate preventive treatment must be given. Unfortunately, this test is available in only a few centres worldwide.

The signs and symptoms of a stroke include any of the following, alone or in combination: severe headache, fainting, seizure, sudden weakness or numbness of an arm or leg or the whole body, abnormal eye movement, asymmetric facial movement, change in the level of consciousness and abnormal speech. A child exhibiting any of these signs must be taken to hospital as soon as possible. A stroke can be fatal, or can result in significant unfavourable conditions (sequelae).

6. **Acute chest syndrome**

This life-threatening complication is the second commonest cause of death in sickle cell disease patients, after infection. It is more frequent in children than in adults, and in sickle cell anaemia compared to other forms of sickle cell disease. Acute chest syndrome is characterised by chest pain, fever, cough, difficulty in breathing, with an image or chest x-ray similar to pneumonia. The symptoms and signs of this condition are similar to those of a lung infection (pneumonia). Acute chest syndrome is caused

by trapped sickle cells in the blood vessels of the lungs or by an infection. Recurrent attacks can damage the lungs. This condition requires immediate hospitalisation and medical treatment.

7. **Pulmonary hypertension**
   This is a condition in which the blood pressure in the pulmonary arteries is abnormally high. This results in the right side of the heart having to work harder to push the blood through the arteries to the lungs. Patients exhibit shortness of breath and reduced exercise tolerance. Over time, the right ventricle becomes thickened and enlarged resulting in heart failure.

8. **Avascular necrosis**
   This condition is a result of poor blood flow to the bones, which is slowed or obstructed by sickle cells. Without blood supply, the area of bone tissue dies (necrosis), causing the bone to collapse. This leads to bone destruction, pain and loss of joint function. The condition is common in the hip (femoral head) but happens in other bones including the shoulder (humeral head).

   Avascular necrosis usually occurs between the ages of 30 and 50, and is not seen frequently in children. When the hipbone is involved, a painful limp is usual. With walking, more pressure and damage ensue and the condition becomes chronic.

   Methods to prevent or minimise the risk of developing avascular necrosis include gentle and controlled exercise of the shoulders and hips, doing leg-lifts in a sitting position and lifting light weights. Jogging should be avoided.

   Treatment of this condition depends on the patient's age and the degree of severity. Crutches are used for a period of a few months to take the weight off the joint. Children below the age of 12 seem to heal well with analgesia, NSAIDs and careful, limited weight bearing. In late adolescents and adults, conservative treatment often meets with failure or partial success. Joint-preserving surgery and transfusion are often reported in such age groups, in order to stop joint-deformity. If an affected child has grown to final size and cannot walk without severe pain, hip-replacement is required.

9. **Kidney and bladder problems**
   Renal abnormalities are common in sickle cell disease. Beginning in childhood, patients develop a urinary concentration defect, resulting in a predisposition to noctur-

nal enuresis (bed-wetting). In addition, kidney and bladder infections are frequent in these patients. Haematuria may result from the rupture of renal vessels damaged by scarring or venous engorgement.

Chronic sickling results in the destruction of the renal medulla, which induces production of renal vasodilating substances that feedback to the glomerulus, causing hyperfiltration. The glomerular filtration rate (GFR) then begins to decrease.

The course of sickle nephropathy is unpredictable; however proteinuria is a sign of progressive sickle nephropathy so this should be screened for at regular clinic visits.

Medication can help in the early stages but in the latter stages patients become reliant on peritoneal dialysis or haemodialysis, or may require kidney transplant.

There are several ways a child can be helped to stop wetting his/her bed. Limit the amount of fluids he/she drinks in the evening. If he/she has had large amounts to drink during the day, wake him/her to urinate twice during the night, setting an alarm clock in the middle of the night to wake him/her to go to the bathroom.

In case of kidney bleeding it is very important to get plenty of fluids, sometimes through an IV in the hospital, and to rest in bed. After sending urine for analysis and culture, kidney infections need to be treated with antibiotics administered intravenously for at least 10 days, and bladder infections with antibiotics given by mouth for 10 days.

10. **Sickle retinopathy/eye problems**

Sickle cell disease can cause eye damage and, rarely, blindness. The sickled cells cause blockages in the tiny vessels at the back of the eye, leading to ischaemia, hypoxia, tissue necrosis and bleeding. New vessels then grow (neovascularisation), which may result in retinal infarction or detachment.

The sickle retinopathy goes through 5 stages:

- peripheral arteriolar occlusions
- peripheral arterio-venular anastomosis
- neovascularisation
- vitreous haemorrhage
- retinal detachment

Regular examinations by an ophthalmologist will help to recognise the problem early, when it can be treated. In the early stages, there are no symptoms and only an eye-doctor (ophthalmologist) with special equipment can see the bleeding or scarring. At this stage, the eye damage can be treated. Without treatment, however, these early changes can lead to loss of vision.
By the time a teenager complains of poor vision, changes may have gone too far to be treated. A child must therefore be checked by an ophthalmologist once a year.

11. **Priapism and impotence**
Priapism is a prolonged, painful erection of the penis in men that is not related to sexual stimulation. The blood pools in the cavernous tissues due to the sickling process and the high cavernous pressure prevents arterial inflow of blood. Prolonged anoxia results in smooth muscle necrosis and fibrosis, which can lead to permanent erectile dysfunction.

Priapism may improve spontanuosly or with measures such as a warm bath or shower or medication. If not, it is important to seek medical help. Priapism must be treated appropriately: if left untreated over time, it can result in impotence.

For episodes lasting for a few minutes, no treatment is necessary except for reassurance and follow-up. But for episodes lasting for a few hours, immediate blood transfusion should be administered. In a few selected cases, surgical intervention may be needed.

12. **Aplastic crisis**
In an aplastic crisis the bone marrow stops functioning for a period of time and the haemoglobin quickly drops to as low as 2-4g/dl. The reticulocyte count is 0% but starts to rise as the patient starts to recover. Aplastic crisis is usually consequent to Parvovirus infection (HPV B-19). The condition is life-threatening and requires support from blood transfusions and hospital care to address it effectively.

13. **Stunted growth**
Red blood cells provide the body with the oxygen and nutrients needed for growth. A shortage of healthy red blood cells can slow growth in infants and children and delay puberty in adolescents. As they become adults, most children with sickle cell disease reach full size. If a child is smaller than his/her cohort and/or has delayed puberty, reassure him/her that he/she will most likely catch up in a few years.

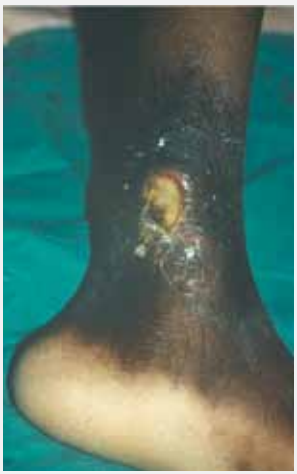
14. **Gallstones/cholelithiasis/biliary sludge**

The rapid breakdown of the red blood cells leads to an increased released of a pigment (bilirubin), which is responsible for the yellowish colour of the skin and eyes (jaundice or icterus). This may then result in acute or chronic cholecystitis, a life-threatening infection of the gallbladder.

Gallstones can often result in infection in the gallbladder (cholecystitis) and sometimes in the blood (sepsis). If a child develops signs and symptoms of gallbladder infection (fever with increasing jaundice, associated with right-sided upper abdominal pain radiating to the shoulder), urgent hospitalisation and treatment with intravenous antibiotics and fluids is indicated. This is usually followed by removal of the gallbladder (cholycystectomy). The purpose of removing the gallbladder is to avoid serious and sometimes fatal complications. Taking out the gallbladder does not cause serious problems. However, without a gallbladder, people may have trouble after eating fatty foods.

15. **Leg ulcers**

These painful lesions are seen in 10-20% of sickle cell anaemia patients, and usually appear between 10 and 50 years of age. They are more common in males than in females, and are aggravated by hot climate, trauma, infection and severe anaemia. Typically, they are open elevated sores with surrounding skin redness and thinning, located within patches of skin that are darker than the normal surrounding skin (hyperpigmentation). They are mostly seen on ankles and can be single or multiple. Some heal rapidly, while others become chronic or recurrent. If present, seek medical attention promptly.



CHAPTER 9
MANAGEMENT OF SICKLE CELL DISEASE

PAIN MANAGEMENT IN SCD

Sickle cell pain should be managed aggressively. Pain relief should be based on assessment and the analgesia ladder used accordingly. The treatment plan for each patient is individualised, chartered and monitored by using assesment tools as described previously (page 84-85). Management of sickle cell disease pain should include rest, hydration and pharmacological and non-pharmacological methods of pain relief.

- **Hydration**

  Fluid management is a very important aspect of management of sickle cell pain, as dehydration is known to precipitate a crisis. In addition, patients with sickle cell disease do not concentrate urine very well, which can lead to increased frequency of passing urine resulting in reduced fluid in both the vascular and tissue compartments, which in turn increases the problem of intracellular dehydration and increased plasma viscosity.

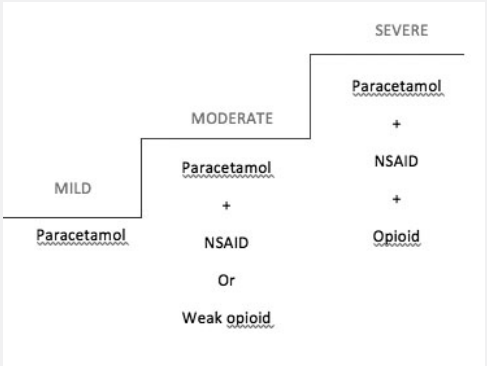
  Patients with vaso-occlusive crisis should be well-hydrated, through the oral or intravenous route. Venous access can often prove difficult in patients and great care should be taken in canulation. The oral route should be encouraged when possible. When patients have abdominal symptoms or are unable to tolerate oral fluids, the intravenous route should be used but discontinued once the patient is stable and the pain controlled.

  Patients with sickle cell disease often require 1.5 times the normal fluid requirement (2-3 litres over 24hours in adult patients), except when contra-indicated. However, fluid overload must be avoided as it can complicate an acute chest crisis, if present.

  The nurse should ensure that the patient has access to fluids at the bedside and document signs of dehydration such as dryness of the skin, cracked lips, sunken eyes, increased jaundice, particularly of the eyes, and increased or decreased urine output. An adequate fluid balance chart should be maintained, as this will guide the medical team in the management of the patient.

- **Pharmacological management**

  Analgesia should be tailored according to the needs of the individual patient, following a successful pain assessment, and should consist of opiates, non-opiates and adjuvant medication, which can be used singly or in combination to achieve adequate pain relief. The WHO guideline for analgesia drug therapy (shown below) suggests the administration of analgesia by the ladder, by the clock and by the appropriate route.



WHO Analgesic ladder

Analgesia

Entonox (nitrous oxide gas) - can be used for a short period of time in the ambulance/first 30-60mins in hospital (holding measure).

Paracetamol - this could be oral, by the intravenous route, or the rectal route (20mg/kg/ dose start, then 15-20mg/kg every 4-6hours in children. (It is essential to follow the manufacturer's guidelines.)

NSAIDs* - Ibuprofen or Diclofenac. (Caution in renal or liver impairment.)

Opiiods

- Intra-nasal Diamorphine-0.1mg/kg (max 6mg) given within first 5 minutes (one dose only, in children over 10kg).
- Codeine phosphate for oral use-available as a syrup 0.5-1mg/kg in children under 12 years and tablets 30-60mg above 12 years. Should be used with caution if the patient has decreased kidney or liver function.
- Dihydrocodeine tablets-30mg every 4-6 hours. Not recommended for children under 12 years.
- Morphine sulphate (oral, rectal, subcutaneous, intramuscular or intravenous route)-examples of available preparations are liquid Oromorph, tablet Sevredol, modified-release (MST). The oral dose for adults is 10-20mg every 4 hours (may go up to 50mg in severe pain). In children, 5-10mg according to age and severity of pain. The MST continuous release suspension or tablets are given every 12 hours. Parenteral forms SC, IM and IV are given in severe pain in adults, usually from 2.5-10mg to a maximum of 20mg, and in children from 1-12 years 200mcg/kg to a maximum of 2.5mg.

*NSAIDs : Nonsteroidal Antiinflammatory Drugs

- Other opioid base drugs are available, such as tramadol, oxycodone and fentanyl.
- Intravenous patient-controlled analgesia (PCA)/nurse-controlled analgesia (NCA), through an electronic infusion pump.

The advantages of PCA are
- Quicker onset of analgesia
- Patient controlled
- Smaller amount of total morphine used
- Potentially fewer side effects
- Safe

Disadvantages of PCA include
- Side effects
- Not suitable for all
- IV access required
- Attached to a machine
- Equipment malfunction

The possibility of complications increase when adding a continuous infusion
- Proxy use
- Patient risk factors
- Lack of training
- Where the chest syndrome is an opioid side-effect or because it is too painful to take deep breaths
- PCA used by the patient over sedation should not be a problem. (?)

When should PCA be stopped?
- When patient's condition improves
- When other, less invasive methods are available
- When side-effects are greater than pain relief

- **Non-pharmacological methods**
  Non-pharmacological methods of pain control are useful in alleviating stress, as well as increasing the ability to cope with acute and chronic pain and thereby improving sense of well-being.

  They include:
- Massage, which can relax the tension in muscle tissue around the joints and decrease muscle pain

- Warm bath
- Application of heat pads/tiger balm
- Positioning
- Diversionary therapy e.g. play, video, TV, etc.
- Input of psychologists to improve positive thoughts (see below)
- Involve play specialist
- Use of Tens machine (transcutaneous electrical nerve stimulation), which can improve blood circulation with subsequent vasodilatation and reduction in vaso-occlusion, as well as suppression of the transmission of painful stimuli via the A and C fibres.

Psychological intervention

- Key to helping the patient to self-manage the disease and its symptoms
- Not usually undertaken during the acute episode
- Helpful in:
  - Stress management
  - Distracting techniques
  - Treating clinical depression
  - Improving self-esteem, etc.

The tables A, B and C below provide guidance on the use of some pain management schemes (as described in the book: Sickle Cell Disease, by Adlette Inati-Khoriaty MD 2008).

Table A

ACETAMINOPHEN DOSAGE ACCORDING TO AGE AND APPROXIMATE WEIGHT					
		DOSAGE			
AGE	APPROXIMATE WEIGHT RANGE	ORAL DROPS	SYRUP	CHEWABLES 80 mg	CHEWABLES 100 mg
under 3 months	Under 4.55 kg	1/2 dropper	1/4 tsp.	-	-
3 to 9 months	8.18 - 10.45 kg	1 1/2 droppers	3/4 tsp.	-	-
2 to 3 years	10.9 - 15.9 kg	2 droppers	1 tsp.	2 tablets	-
4 to 5 years	16.36 - 21.36 kg	3 droppers	1 1/2 tsp.	3 tablets	1 1/2 tablets
6 to 8 years	21.8 - 26.8 kg	-	2 tsp.	4 - 5 tablets	2 - 2 1/2 tablets
9 to 10 years	27.27 - 32.27 kg	-	2 1/2 tsp.	6 tablets	3 tablets
11 years	32.7 - 43.18 kg	-	3 tsp.	6 tablets	3 tablets
12 years & over	43.64 kg & over	-	3 - 4 tsp.	6 - 8 tablets	3 - 4 tablets

How supplied:
Drops: Each 0.8-m1 dropper contains 80-mg acetaminophen.
Syrup: Each 5-ml teaspoon contains 160-mg acetaminophen.
Chewables: Regular tablets contain 80-mg acetaminophen each. Double strength tablets contain 160-mg acetaminophen each.
Dosage may be given every 4 hours as needed but not more than 5 times daily.
Adapted from http://www.drelizabethdickey.com/condition.aspx?condition_id=53

Table B

IBUPROFEN DOSAGE ACCORDING TO AGE AND APPROXIMATE BODY WEIGHT					
		DOSAGE			
AGE	APPROXIMATE WEIGHT RANGE	ORAL DROPS	SYRUP	CHEWABLES 80 mg	CHEWABLES 100 mg
5 - 11 months	4.55 - 7.73 kg	1 dropper	1/2 tsp.	-	-
12 - 23 months	8.18 - 10.45 kg	1 1/2 droppers	3/4 tsp.	1 1/2 tablets	1/2 tablet
2 to 3 years	10.9 - 15.9 kg	2 droppers	1 tsp.	2 tablets	1 tablet
4 to 5 years	16.36 - 21.36 kg	-	1 1/2 tsp.	3 tablets	1 1/2 tablets
6 to 8 years	21.8 - 26.8 kg	-	2 tsp.	4 tablets	2 tablets
9 to 10 years	27.27 - 32.27 kg	-	2 1/2 tsp.	5 tablets	2 1/2 tablets
11 years	32.7 - 40.45 kg	-	3 tsp.	6 tablets	3 tablets
12 years & over	40.9 kg & over	-	3 - 4 tsp.	8 tablets	4 tablets

Adapted from http://www.drelizabethdickey.com/condition.aspx?condition_id=53

Table C

QUANTITY OF FLUIDS NEEDED FOR A PERSON WITH SICKLE CELL DISEASE*			
BODY WEIGHT (kg)	LITRES (recommended range per day)	BODY WEIGHT (kg)	LITRES (recommended range per day)
5	0.5 to 0.7	35	1.8 to 2.7
10	1.0 to 1.4	45	2.0 to 3.0
15	1.2 to 1.8	55	2.3 to 3.4
20	1.4 to 2.2	65	2.5 to 3.8
25	1.5 to 2.3	75	2.8 to 4.1
30	1.7 to 2.5		

* May need more with fever, pain, exercise and hot water

New scientific data, information and use of drugs and combinations should certainly be taken into consideration when a clinic or unit develops its protocols and algorithms and all the tables above constitute only examples.

ORGANISATION OF CARE

The tables below (A & B) provide an example of the possible organisation of the care that can be delivered by the GP or the medical specialist in a SCD reference centre (from Sickle Cell Disease, by Adlette Inati-Khoriaty MD 2008).

Table A

REGULAR HEALTHCARE PLAN BY PAEDIATRICIAN/INTERNIST OR FAMILY DOCTOR		
AGE	FREQUENCY OF VISITS	EVALUATION
Birth - 6 months	Every month	Physical exam (PE) and developmental assessment, vaccines, monthly CBC and when needed
6 months - 1 year	Every 2 months	PE and developmental assessment, vaccines, PPD and urinalysis at one year, CBC every 2 months and when needed
1 year - 5 years	Every 4 to 6 months	PE and developmental assesssment, vaccines, CBC every 6 months and when needed, yearly PPD, yearly eye check-up > 3 years
6 - 18 years	Every 6 - 12 months	PE, vaccines, CBC every 6-12 months and when needed, yearly PPD, yearly eye check-up
Over 18 years	Every year	PE, CBC every year and when needed, other tests as advised by doctor

Table B

CARE PLAN IN A COMPREHENSIVE SICKLE CELL DISEASE CENTRE	
EVALUATION	INTERVAL
Physical Exam • Birth - 6 years • 6 - 18 years • Over 18 years	 Every 2 - 4 months Every 4 - 6 months Every 6 - 12 months
Family genetics	At diagnosis
Genetic Counselling and education	At diagnosis and 1 - 2 times per year
Social Worker visits (home,school and work site)	At diagnosis and once a year
Laboratory tests: Blood (CBC, Kidney, liver tests and iron test) and urine (urinalysis)	Every 6 - 12 months
Other special laboratory and x ray studies	When needed
Abdominal echo (to look for gallstones and spleen/liver size)	Every 2 years (>6 years) and when needed
TCD (to study stroke risk)	Once a year > 2 years and more if indicated
Cardiac echo (studies heart function)	Once a year > 10 years
Evaluation (eyes, lungs, neurological)	Once a year and when needed
Psychological/Family/Therapy Consultation	Once a year and when needed
Physical Therapy Assesment (for joint problems and after surgery)	When needed
Developmental Screen	Once a year and when needed
Dietician	Once a year and when needed
Adolescent Centre Evaluation	At least once/year and when needed

MONITORING AND NURSING CARE

Nurses play a vital role in the management of sickle cell patients in pain. Continuous assessment and close monitoring are essential. Specific measures include:

- Close monitoring of observations, temperature, pulse, respiration, blood pressure and oxygen saturation.
- Give oxygen if below 95% in air.
- Document pain, sedation and nausea scores 1-2 hourly if on opiates.
- Monitor for drug side effects, such as constipation, pruritus, over-sedation, respiratory depression (if on opioids), nausea and vomiting, and ensure adequate treatment is given.
- Use of incentive spirometry in patients above 6 years, if pain is in the chest or the abdomen, or in the back above the diaphragm.
- Adequate education of the patient on home management and coping mechanisms.
- Seek multidisciplinary approach for complicated cases.
- Use hydroxyurea and blood transfusion therapy where patient quality of life is affected by frequent painful episodes.

TREATMENT OF SICKLE CELL DISEASE COMPLICATIONS

Sickle cell disease (SCD) is a chronic, life-long disease. However, with early diagnosis and treatment, together with parental education and involvement, affected people can survive into middle and late adulthood.

Treatment for SCD is usually aimed at avoiding crises, relieving symptoms and preventing complications. A major part of the care of sickle cell disease can be handled at home by parents. Responsible, dedicated and knowledgeable parents make a great difference to a child's survival and quality of life. The nurse plays a critical part in enabling and supporting parents in that role.

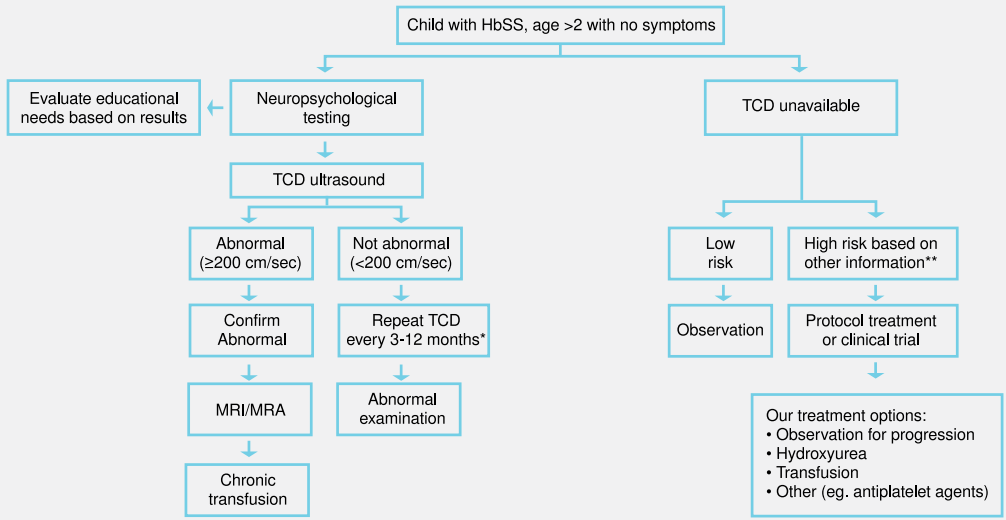
Once a child has been diagnosed with sickle cell disease, parents should be advised where possible to enrol at a specialised (comprehensive) sickle cell disease centre, where a team of experienced health professionals can oversee the child's care. Such teams include doctors of multiple specialities, nurse practitioners, genetic counsellors, nurses, social workers, play and occupational therapists, psychologists and dieticians. Adolescents and adults with sickle cell disease also benefit greatly from enrolment in comprehensive sickle cell disease centres, where regular screening for possible complications can be carried out, and new treatments and recent research discussed.

Stroke

Children who have had a stroke and those whose tests (TCDs) show they are at high risk for developing a stroke need to be treated with monthly blood transfusions for at least 5 years (if not indefinitely, as indicated by recent studies). These transfusions help prevent more strokes. Treatment for minor strokes is often the same as treatment for other strokes.

At the end of the treatment period, the patient will undergo special tests to determine if the risk of developing a stroke in the future is still present. If this risk is still present, then transfusion needs to be continued. If not, transfusion will be stopped and the child will be monitored very carefully. The doctor can explain the benefits of transfusion therapy in stroke and the treatment of transfusional iron overload, with the added support of the nurse.

A child that has had a stroke is best treated in a comprehensive sickle cell disease centre, under the supervision of an expert multidisciplinary team, able to offer neuropsychological testing and rehabilitation, in addition to advice about iron overload and chelation. A serious outcome of sickle cell strokes and other brain problems is the development of learning problems in some affected children. To identify these learning problems early, all children should be screened with routine exams, starting at 6 years (as shown in the below algorithm). If there are learning problems, these need to be managed from the outset.



*Optimal frequency of rescreening not established. Younger children with velocity closer to 200 cm/sec should be rescreened more frequently
** Prior transient ischemic attack, low steady-state Hb, rate and recency of acute chest syndrome, elevated systolic blood pressure

Identification and management of stroke risk in children with sickle cell disease. http://www.nhlbi.nih.gov/health/prof/bloods/sickle/sc-mngt.pdf 2004.

Acute chest syndrome
This extremely common complication requires hospitalisation and urgent treatment. Any delay in treatment will expose a child to unfavourable consequences. The treatment of acute chest syndrome consists of broad spectrum antibiotics intravenously and by mouth, in addition to medication to open up the airways (bronchodilators). Early transfusion has been shown to improve recovery and shorten hospital stay. Administration of oxygen, medications to control fever and pain and incentive spirometry to prevent lung collapse (atelectasis) are important parts of treatment. Over-hydration can be dangerous and should be avoided.

Acute splenic sequestration
Acute splenic sequestration is a medical emergency. Failure to recognise the symptoms and signs of this dangerous condition can result in death within a few hours. The treatment of acute splenic sequestration is an immediate blood transfusion. Acute splenic sequestration can recur in a high percentage of patients and there are various treatment options for this condition, including chronic transfusion and complete or partial removal of the spleen (splenectomy). The doctor can outline treatment options for parents, explaining their pros and cons, with the support of the nurse.

Hand-foot syndrome
This early sign of sickle cell disease in children is a self-limiting condition without adverse resulting conditions (sequalae). Its treatment consists of hydration, analgesics such as acetaminophen or ibuprofen, and observation. If the pain is severe and non-responsive to the usual analgesics and/or if there is fever, the child's treating physician should be alerted. In such cases the patient may need hospitalisation for administration of stronger analgesics and intravenous hydration.

Surgery
People with sickle cell disease may need various types of surgery. The three commonest types are removal of the spleen (splenectomy) and removal of the gall bladder (cholecystectomy), and orthopedic surgery for problems like osteomyelitis, and avascular necrosis. The spleen is removed when it starts trapping blood suddenly, resulting in life-threatening anaemia (acute splenic sequestration). The commonest reason for removing the gallbladder is for gallstones. It is advised that transfusion be given prior to surgery to decrease the percentage of sickle cells (see below). This will improve oxygenation and may minimise complications. During surgery, the patient needs to be kept warm and must receive adequate hydration. Following surgery, blowing into a small mouthpiece (spirometry) will help decrease lung collapse and lung infection, which are the two commonest complications of surgery in sickle cell disease. Early mobilisation is essential and helpful to recovery.

BLOOD TRANSFUSION

This is not a lifelong component of treatment in SCD, as it is in β-thalassaemia major. However, it is indicated in SCD in some situations, including:

- **Severe anaemia**
- **Prevention and treatment of stroke**
- **Prolonged, painful erection of the penis (priapism)**
- **Lung infarction or pneumonia (acute chest syndrome)**
- **Surgery**
- **Frequent and severe painful episodes**

Below is a table describing in more detail the indication for transfusion therapy in SCD.

Indications for transfusion therapy in sickle cell disease[7,24]

Acute/episodic	■ Anemia ■ Splenic sequestration ■ Severe or long-lasting aplastic crises ■ Stroke ■ Acute chest syndrome ■ Multiple-organ failure syndrome ■ Pre-operative (in select cases) ■ Malaria-associated severe hemolytic anemia with impending cardiac decompensation
Chronic	■ Heart failure ■ Prophylaxis against recurrent stroke ■ Stroke prevention when transcranial doppler velocities are abnormal ■ Chronic pulmonary hypertension (unresponsive to other approaches) ■ Refractory congestive heart failure ■ Severe recurrent vaso-occlusive crises ■ Previous splenic sequestration in a child aged 2–3 years (in anticipation of later splenectomy) ■ Chronic pain

Stuart MJ, Nagel RL. Sickle-cell disease. Lancet 2004;364:1343-1360
24:Vichinsky E. Consensus document for transfusion-related iron overload. Semin Hematol 2001;38:2-4

In sickle cell disease, blood transfusions increase the number of normal red blood cells in circulation and decrease the number of rigid sickle cells, thus helping to relieve anaemia and improve blood flow to tissues. In children with sickle cell anaemia at high risk of stroke, regular blood transfusions can decrease the risk of stroke. If used appropriately

transfusion therapy can prevent or minimise organ damage in many people with sickle cell disease.

There are two types of transfusions a patient may receive: simple or exchange. Below is a table describing the various approaches to transfusion therapy.

APPROACHES TO TRANSFUSION THERAPY			
APPROACH	APPLICATIONS	ADVANTAGES	DISADVANTAGES
Simple transfusion Patients are given additional units of blood without removal of sickle cell blood	Severely anemic patient Hb levels 5-6 g/dl	• Simple and effective • Widely available	• Iron Loading
Automated exchange transfusion (erythrocytapheresis) Sickle cells are removed and replaced with normal red cells	Prefered when rapid alteration of Hb is required	• Rapid • Little net iron gain • Decreases HbS while leaving haematocrit and whole blood viscocity unchanged	• Increased red cell utilization • Increased rate of donor exposure, therefore, increased risk of infection or alloimmunisation
Rapid exchange transfusion Whole blood removed from one arm while donor cells are transfused in the other	Widely appropriate	• Little net iron gain	• Somewhat slower • Careful control of blood removed versus blood infused required

A simple transfusion involves the transfusion of a set amount of blood into the patient. An exchange transfusion involves giving a certain amount of blood while removing the same amount. This type of transfusion is used mostly in sickle cell disease in order to replace sickle cells with normal cells. It will also increase the haemoglobin level without increasing blood viscosity, and may result in less iron accumulation than regular (simple) transfusions.

Before any transfusion, the donor blood as in every case of transfusion is fully matched with that of the recipient, taking all precautions to eliminate contaminants. The blood for transfusion as for β-thalassaemia major, is filtered and leukodepleted and pre-warmed to body temperature.

In an exchange transfusion, the patient's blood is withdrawn 5-20ml at a time (according to the patient's size), discarded and replaced by donor blood. In sickle cell anaemia this means that sickled cells will be replaced by healthy red cells, which have a normal level of haemoglobin, thus correcting the anaemia. In addition, the increase in haemoglobin will suppress the bone marrow's production of more sickle cells.

The exchange may be carried out through a single vein using a three-way tap, with manual removal and replacement. Another technique is to remove whole blood from one arm and at the same time to transfuse the donor blood through the other arm, at the same rate of flow. Automated systems for exchange transfusions are also available.

The total volume of blood exchanged depends on the patient's weight and haematocrit. In children the volume is 50-60ml/kg. In adults 6-8 units of blood are usually needed.
All transfusions carry the risk of transmission of bacterial or viral agents and more frequent than in β-thalassaemia major the risk of allo-immunisation. In the case of exchange transfusions, there are a number of additional risks that must be considered:

- Volume overload, if the amount transfused is greater than the amount removed. This is especially dangerous in patients with pre-existing heart complications, in whom heart failure can easily be precipitated.
- Conversely, inadequate replacement of blood may lead to hypotension and shock. Increasing the haemoglobin level above 12g/dl may lead to hyperviscocity, which may precipitate a vaso-occlusive crisis and stroke.
- Blood clots may disturb the acid base balance. Hypoglycaemia and other metabolic disturbances are also a danger, mainly in children.

Complications of Transfusion Therapy

While transfusion therapy provides considerable clinical advantages, it also presents a number of challenges, some of which are greater in patients with SCD than other populations:

- Volume overload - can result in congestive heart failure and pulmonary oedema in patients with cardiac dysfunction.
- Iron overload - iron loading and subsequent accumulation is potentially toxic and debilitating, unless effective iron chelation therapy is administered.
- Alloimmunisation and delayed haemolytic transfusion reactions - 20-30% of patients with SCD who receive transfusion therapy become alloimmunised. The delayed transfusion reaction occurs 5-20 days after transfusion and can cause severe anaemia, painful crisis or death.
- Viral infection - hepatitis and other viral infections are particularly problematic in patients with SCD, due to pre-existing organ damage. Bacterial infections are rare.

Below is a table that provides recommendations based on UK, NHS on the protocol to be used for assessing and monitoring iron overload.

IRON OVERLOAD ASSESSMENT AND MONITORING PROTOCOL				
CONDITION	S. FERRITIN	MYOCARDIAL T2*MRI	FERRISCAN Measures Liver Iron Content (LIC)	LIVER
SCD on regular top-up/exchange transfusion	Before staring transfusion and then every 3 months	Every 5 years after starting transfusion	1 year after staring transfusion then annually unless 20mg/g dw when every 6 months	Only if indicated for histology or if laparotomy

TREATMENT OF LEG ULCERS

It is important to treat ulcers at any early stage, when they are small and not infected. This treatment is difficult and entails good compliance from the patient and family. It consists of: leg-elevation, cleaning and covering the ulcer, wearing comfortable flat shoes and clean white cotton socks until the ulcer heals. If the ulcer is surrounded by red, painful skin and there is pus oozing from it or its surroundings, indicating that it is infected, you must consult a doctor for antibiotics. If in 2 or 3 weeks after the above treatment the ulcer is getting larger or has not shown signs of healing, hospitalisation is required for intensive ulcer care, strict bed rest and transfusion. Transfusion brings more oxygen to the tissues and may aid healing. If, despite this, treatment the ulcer still doesn't heal, then a skin graft will be used to cover the ulcer. Sometimes, more than one skin graft is needed. Care of ankle ulcerations in haemoglobinopathy patients can be divided into topical measures, in which the nurse plays an active role, and systemic measures, which depend on medical decisions and are related to the failure of local measures to heal the ulcer over time.

- Dressings are usually applied to keep the ulcer clean and allow healing. The affected area is cleaned with warm water or normal saline, removing dead tissue (debridement) and then applying a dressing. There are several types of dressing but there does not seem to be an advantage of one over the others. A simple non-sticky dressing is sufficient for most cases. Dressings are changed weekly.
- Elastic compression bandages may help with oedema and venous congestion.
  If there are signs of infection such as pus, then antibiotic ointments will help. Occasionally systemic antibiotics are necessary.
- Surgical interventions may be necessary, such as debridement and autologous skin grafting.

ADDITIONAL ROLES OF THE NURSE

Other aspects of the care of SCD patients in which the nurse may play a significant role are quite similar to those of the care of thalassaemia patients and include:

- Integration into society
- Issues related to school/university
- Pregnancy

Integration into society

Adolescents and adults with sickle cell disease may experience difficulties integrating with their peers and wider society, sensing a feeling of rejection and marginalisation. Instilling self-confidence and independence in patients is extremely important. Support groups are a very effective tool for enhancing patients' life-skills. Programmes aimed at educating society about sickle cell disease and the rights of affected people to a happy, healthy and fulfilled life are also important. Patients with sickle cell disease often have fears of dying, while their parents live in constant fear of losing their child. The nurse should encourage patients and parents to share these fears with a healthcare provider, a social worker or a close friend. The message must always be that talking can help patients and parents to contain and live with their fears, so that death does not dominate the life of parents or child.

Issues related to school/university

Children and adolescents with sickle cell disease may often be absent from school/university days due to recurrent health problems. This, combined with poor self-esteem and difficulty coping, can result in poor academic achievement and a further sense of depression and hopelessness, particularly in adolescence.

The nurse can support the patient and/or parents, ensuring that teachers are fully informed about sickle cell disease and patient needs, and encouraging open discussion between patient and parents about difficulties faced at school/university. It is important to support parents in insisting that their child stays in school, and setting goals and plans for a fulfilling career in the future. At the same time, it may also be necessary to consult a specialist for a possible learning disorder.

Pregnancy

Women with sickle cell disease can get pregnant and deliver healthy babies. However, it is important to ensure that a patient with SCD visits a genetic counsellor, who will clarify the chances of having a child with sickle cell disease and the various options available for having healthy children.

Prior to pregnancy and during pregnancy and labour, a pregnant woman with SCD will need close monitoring to minimise and prevent complications for both her and her baby. Early and regular prenatal care is important. Routine pregnancy care includes a healthy diet, vitamin and folic acid supplements, increased fluid intake, stopping alcohol, smoking and medicines that can be harmful for the baby, in addition to foetal growth and heart rate testing.

A fall in oxygen saturation is common in any woman in labour. If the mother has sickle cell disease this can precipitate a vaso-occlusive crisis, thromboembolism and acute chest syndrome. Apart from close monitoring of oxygen saturation there should be readiness to resuscitate and provide intensive care.

During labour, intravenous (IV) fluids, oxygen and close foetal monitoring are needed. Close monitoring by a team of medical specialists, including an obstetrician trained in high risk and sickle cell disease pregnancies, can help early detection and treatment of complications, resulting in a better pregnancy outcome. Complications for the mother include high blood pressure, urinary and lung infections, gallbladder problems, heart failure. Other risks include poor baby growth, premature birth, miscarriage or newborn death. Blood transfusion, which helps the blood carry more oxygen, is indicated for hypertension, severe anaemia, increased frequency of pain crisis and previous foetal loss.

CHAPTER 10
NUTRITIONAL AND LIFESTYLE ISSUES IN HAEMOGLOBIN DISORDERS

Hereditary haemoglobin disorders are not nutritional anaemias. However, they are influenced by nutritional and environmental factors that must not be overlooked. The production of red cells is dependent on the presence of factors that the body acquires from the environment, including minerals such as iron and cobalt, vitamins such as B12, B6, C, E, riboflavin and folic acid.

IRON

Iron is essential for the formation of blood, and is normally absorbed from food. In haemoglobinopathy patients, however, excess iron can accumulate, becoming toxic to various tissues. It is therefore important to understand the way the body deals with iron. Most of the iron in the human body, up to 60-70%, is found in the haemoglobin molecules of red blood cells, with lesser amounts found in muscle tissue and in enzymes. Around 20-30% is in storage proteins such as ferritin and haemosiderin, and the carrier proteins (transferrin) that transport iron through the blood stream. Iron is absorbed from food in the small intestine, with the help of acids such as hydrochloric acid found in the stomach and ascorbic acid (vitamin C).

The body absorbs more iron according to levels in haemoglobin-the protein with the highest concentration of iron. When levels of iron in haemoglobin are low, the body absorbs more iron, with rates of absorption from the gut increasing by 20-30%. An anaemic patient that is overloaded with iron because of repeated transfusions will therefore absorb more iron than the body needs.

For this reason, the iron content of food should be considered in deciding the ideal diet of multi-transfused patients. Meat and liver are rich sources of organic iron (ferric iron), which is more easily absorbed. Non-organic, ferrous iron, mostly from vegetable sources and eggs, is less easily absorbed. It is also important to note that more iron is absorbed during the accelerated growth periods of infancy and childhood.

The presence of vitamins C favours both the absorption and the metabolism of iron, since it plays a role in the release of iron from storage proteins. On the other hand, phenolic acids, present in red wine, and flavinoids such as tannins from black tea, reduce iron absorption. Drinking tea during a meal may reduce the absorption of iron by as much as 50%, and coffee reduces the absorption of non-organic iron. Calcium also reduces absorption.

The diet of a patient on regular blood transfusions should contain foods that do not favour iron absorption-that is, more vegetables, tea and coffee and less red meats.

VITAMINS

Vitamin B12 (cobalamine) is an important element in haemopoiesis and should therefore be included in the diets of patients with thalassaemia or sickle cell disease. Food rich in B12 includes eggs, some fishes and seafoods, milk, cheese and soya. (It is also rich in liver and kidneys, which are to be avoided).

Vitamin B6 (pyridoxine) is also needed for haemopoiesis. It is available from fish and chicken as well as brown bread, eggs, vegetables, peanuts and milk (as well as red meats, which must avoided).

Vitamin E is required for haemopoiesis and is also an antioxidant, which supports the body's immune response and which may help iron-loaded patients. Vegetable oils such as olive oil, sunflower oil and soya oil are all sources of this vitamin, as are eggs, nuts and meat.

Vitamin C increases the absorption of iron and so must be taken with caution in thalassaemia, since the likelihood of toxicity will also increase. However, in the case of iron overload vitamin C is oxidised at an increased rate, which may give rise to a deficiency of vitamin C with consequent adverse effects. In addition, by increasing the availability of labile iron, vitamin C makes iron more easily available to desferrioxamine. Therefore vitamin C supplements may improve the efficiency of this chelator (this is not true of oral iron chelators).

The pros and cons of vitamin C are balanced in the following way: a limited supplement (2-3mg/kg/day) of vitamin C is given to patients taking desferrioxamine, at the time of the subcutaneous infusion. All other patients are recommended to take a diet rich in fruits and vegetables.

Riboflavin also plays a role in haemopoiesis, and is found along with other vitamin B complexes, such as thiamine, in green vegetables, fish, chicken, eggs, nuts, legumes and wholemeal bread.

Folic acid is a component in the production of the DNA molecule. A deficiency may occur where there is a massive destruction of cells and nuclei, as is the case of ineffective erythropoiesis in untreated thalassaemia. A deficiency of this vitamin will result in difficulty producing healthy red cells and a megaloblastic anaemia may result. These complications are seen in thalassaemia patients who are poorly transfused or those for whom regular transfusions are regarded as unnecessary, as in thalassaemia intermedia

and some cases of HbH disease. In such cases, supplements of 1mg/day of folic acid are prescribed.

In regularly transfused cases of thalassaemia major, the bone marrow production of red cells is suppressed and marrow expansion reduced. It is therefore not necessary to give supplements in such cases. When supplements are not needed, a dietary intake rich in folates is an advantage in haemoglobin disorders. Such a diet includes meat, chicken, green vegetables, wholemeal bread and bran.

Calcium and vitamin D are also dietary factors that must be regulated in haemoglobin disorders. Several factors disturb the metabolism of calcium, including damage to the endocrine organs, particularly the parathyroid glands. Reduced supply of calcium is a factor contributing to osteoporosis, which is very common in thalassaemia. In such cases supplements are given of calcium and vitamin D. Such supplements are not to be taken at the same time as the bisphosphonate group of drugs, which are also used to treat osteoporosis (calcium and vitamin D supplements are taken in the evening, while bisphosphonates are taken in the morning).

Calcium and vitamin D supplements are not routinely given in thalassaemia, since dietary intake should be sufficient and supplementary amounts may lead to the formation of kidney stones. However, where vitamin D is deficient, a diet rich in fish oils (such as cod liver oil), eggs and cereals as well as exposure to sunlight will help boost levels without supplementation. Foods rich in calcium include milk and dairy products (cheeses and yogurt), nuts and fish.

Zinc is an element that may be reduced in patients with iron overload, and may be depleted by the use of certain iron chelators. The doctor will decide which patients will be regularly monitored for levels of zinc. If found deficient, supplements must be prescribed since deficiency may affect growth.

DIABETES IN THALASSAEMIA

Many patients with thalassaemia develop diabetes as they grow beyond puberty. In such cases, diet becomes an even more important issue and usually a clinical dietician is called upon to help. However, the nurse must be aware of key issues surrounding diet and be ready to advise the patient and the family.

In diabetes, the patient's calorie needs are estimated according to age, sex, size (estimation of body mass index (BMI) = kg/height^2) and activity level. If overweight, the

patient is advised to lose some weight. Having estimated the required calorie intake, the diet is planned such that less than 50% of calories come from carbohydrates, with monounsaturated fatty acids (avoiding saturated fatty acids) providing 30% of energy intake. Complex carbohydrates are preferred to sugars since they are absorbed at a slower rate, avoiding fluctuations in the level of glucose in the blood. Around 10-20% of calories should come from proteins-less in cases of renal involvement due to diabetes. Dietary fibres, especially soluble fibres from fruit and vegetables, will reduce blood sugar levels following a meal and so reduce the need for insulin. A diabetic diet should include an intake of 20-30g of fibre per day.

The calorie intake of a diabetic patient should be divided into 4-5 meals per day, to minimise fluctuations in blood sugar. Three major meals and two snacks are recommended. Regular monitoring of blood glucose is necessary and regular exercise must not be neglected.

EXERCISE IN HAEMOGLOBIN DISORDERS

Patients with these haematological disorders can exercise as much as any non-affected individual. Each patient's endurance will depend on state of health and any complications that may have developed due to the disorder, such as of the heart or liver. Patients should therefore seek medical advice regarding the type of exercise they wish to pursue, and should interrupt an exercise if they feel too tired.

SMOKING

Haemoglobinopathy patients should be absolutely discouraged from smoking. One reason is that smoking tobacco produces free radicals, which cause oxidative damage and may add to the oxidative stress already present due to free iron radicals. Smoking is also a serious danger to the respiratory system and will contribute to the development of chronic bronchitis. The increase in insulin resistance caused by smoking is particularly dangerous in diabetic patients. In sickle cell anaemia, the risks are even greater since smoking increases the danger of endothelial damage to blood vessels, strokes and other complications of vascular origin. Furthermore, cigarette smoking may affect bone metabolism and bone remodelling. An additional, albeit comparatively minor, issue is the staining of teeth in patients whose teeth are already in poor condition because of poor calcium metabolism.

ALCOHOL CONSUMPTION

Excess consumption of alcohol increases the possibility of developing osteoporosis. In addition, alcohol is an irritant to the gut and the pancreas, which may already be

affected by iron overload. Alcohol also causes changes in fat metabolism in the liver, increasing oxidative damage and so worsening the effects of iron overload and also of hepatitis B and C, which are common in thalassaemia. This will accelerate progression to cirrhosis and hepatocellular carcinoma. Alcohol may also interact with other medications. However, moderate consumption of red wine with meals in thalassaemia intermedia may reduce iron absorption.

In sickle cell disease, alcohol is particularly damaging in the short term, after one binge, as well as in chronic consumption. This is partly due to its diuretic effect and the reduced ability to concentrate urine, since alcohol inhibits the anti-diuretic hormone (ADH). The increased excretion of dilute urine leads to dehydration, which leads to increased blood viscosity. The danger of inducing a vaso-occlusive crisis is very high with all possible consequences, including stroke, pulmonary thrombosis and sudden death.

OTHER SUBSTANCES

Substance abuse is dangerous in all people. Peer pressure puts adolescents at increased risk, especially in societies where substance abuse is common. The dangers of adding this factor to an already chronic disorder affecting many vital organs of the body cannot be over-emphasised. It is possible that some patients with a chronic disease may see joining the group and being 'in' with peers as a compensatory mechanism, making them 'normal'. Studies have shown that patients with chronic disease do take such risks, but no more than their otherwise healthy peers.

One danger is that during a period of experimentation, the patient may neglect or adhere poorly to prescribed treatment, especially iron chelation, with additional consequences to health. The healthcare team should be sensitive to symptoms and signs of substance abuse and to the signals and cries for help that the patient may be sending. Good communication and trust between patients and carers is essential, both in bringing these issues into the open and in their subsequent management.

CHAPTER 11
GENERAL INFORMATION FOR THALASSAEMIA AND SCD

COMMON QUESTIONS AND CONCERNS

The nurse more than any other health professional may need to respond reliably and accurately to the following:

- **Are carriers healthy?**
  Yes. In the case of sickle cell disease (SCD), carriers usually don't experience symptoms unless they are in an area with low oxygen, such as at high altitude, where they may experience pain episodes or problems with their spleen. They have a higher-than-normal risk of developing urinary tract infections and may have intermittent bleeding in their urine. These problems are infrequent and do not pose any major health problem.

- **Can people with a trait develop the disease at any time in their life?**
  No. This can never happen, because those who have the sickle cell trait have inherited only one sickle gene, whereas those with the disease have inherited two sickle genes. Genes are inherited from parents and are determined at conception, and thus can never be acquired in one's lifetime. Therefore, a haemoglobinopathy trait can never transform into sickle cell disease or thalassaemia.

- **Can people with the trait donate blood?**
  Yes, if their haemoglobin is within normal range, which is the usual situation.

- **How can my partner and I be tested for the thalassaemia or sickle cell trait?**
  You can be tested by a complete blood count (CBC) and by either haemoglobin electrophoresis (HbE) or high performance liquid chromatography (HPLC). These tests can be ordered by your doctor and are simple and inexpensive.

- **What options are usually given to two carriers who want to be marriage partners?**
  These two persons need to be informed about the 1 in 4 chance in each pregnancy of having a child affected by the disease. They will then be given various options appropriate to the couple's situation, cultural and social orientations. Some options include: (i) to reconsider and perhaps end their relationship, (ii) to opt not to have children and consider adopting a child, (iii) to accept having prenatal diagnosis in each pregnancy and opt for termination of pregnancy if the foetus has the disease or to do preimplantation diagnosis (PGD) through which a healthy baby could be expected. These and other options that may become available in future have their pros and cons, costs, and availability issues in a country (e.g. PGD).

- **If we are both carriers of the sickle or thalassamia trait, can we test our baby before it is born?**
  Yes. Prenatal testing can be done using one of two methods, chorionic villus sampling (CVS) or amniocentesis.

- **Why does my child have yellow eyes? (mainly in SCD)**
  Your child has yellow eyes due to a pigment called bilirubin, which is released from broken-down red blood cells. Under normal conditions, the liver gets rid of this bilirubin and the eyes are not yellow. But in sickle cell disease the red cells are broken down much faster than usual and the liver cannot get rid of all of the excess bilirubin, which goes to the eyes, giving them a yellow colour-a condition called scleral icterus. Drinking more water can help the body get rid of bilirubin in the urine and subsequently diminishes some of the yellow colour, but this can never be completely eradicated. Taking folic acid daily slightly reduces the rate at which red blood cells break down, but the yellow colour does not completely disappear.

- **At what age do people with sickle cell disease or thalassaemia die?**
  It is a common misconception among many people, and even some healthcare providers, that these patients have a very short life. The truth is that people with haemoglobin disorders can lead long and productive lives and some can survive into their 70s and 80s in countries where patients have full access to appropriate management and other care. You can find a more detailed answer to this question in an article about sickle cell anaemia on the Centres for Disease Control and Prevention (CDC) website, at http://www.cdc.gov/ncbddd/sicklecell/ and in TIF's publication at http://www.thalassaemia.org.cy

- **Is there a developmental delay in children with sickle cell disease?**
  Developmental delay is not characteristic of these disorders except in cases of stroke and chronic severe anaemia in SCD. However, children with sickle cell disease or thalassaemia can develop other medical problems just like other children, such as brain tumour, other genetic defects, birth/prenatal hypoxia (decrease in oxygen), etc., which can result in developmental delay. On the other hand, there are many adults with sickle cell disease or thalassaemia who are intellectually brilliant, highly successful professionals in a range of fields.

- **Can people with sickle cell disease travel by air?**
  People with sickle cell disease generally tolerate air travel, but they can develop some potential problems on an occasional basis, such as pain, fatigue and dehy-

dration. The higher the altitude and the longer the trip, the more sickle cell-related problems will develop. In order to prevent these potential problems, passenger cabins must be pressurised and have the facilities to provide supplemental oxygen at all times. In addition, extra fluids must be consumed during air travel.

SUGGESTIONS FOR STAYING HEALTHY FOR ALL AGE GROUPS WITH SCD

- Take folic acid supplements daily, and eat a balanced diet.
- Drink plenty of water
- Avoid temperature extremes and high altitudes
- Avoid stress
- Exercise regularly, but don't overdo it
- Fly on commercial airplanes with pressurized passenger cabins

CHAPTER 12
OTHER APPROACHES TO TREATMENT/CURE

A great deal of research has been carried out in the field of sickle cell disease over the past two decades, resulting in new and effective treatments that have significantly improved the outlook for patients with sickle cell disease.

Agents which increase foetal haemoglobin (Hb)

- **Hydroxyurea (Droxia®, Hydrea®, Cytodrox®)**

The most promising and widely-used of these agents has been the drug hydroxyurea. This drug seems to work by stimulating production of foetal haemoglobin-a type of haemoglobin found in newborns that helps prevent the formation of sickle cells. This drug, usually used to treat cancer, has been proven to be very helpful for adults and children with severe disease. Taken daily, hydroxyurea raises the haemoglobin and improves the well-being of patients, decreasing the frequency of painful crises and possibly reducing the need for blood transfusions. However, there is some concern about the possibility that one-term use of this drug may cause tumours or leukaemia in certain people.

- **Butyric acid & othe fatty acids**

Some studies have shown that this commonly used food additive may increase the amount of foetal haemoglobin in the blood.

Bone marrow transplant

To date, bone marrow transplant offers the only potential cure for sickle cell disease and thalassaemia. The younger the child is at the time of the transplant, the higher the cure rate and the lower the risk of complications. This procedure involves the intravenous transfer into the patient of healthy bone marrow from a donor who does not have sickle cell disease and who is immunologically compatible with the patient. This healthy marrow replaces the bone marrow and sickle cells of the patient and, after some time, starts producing normal blood cells. Prior to the procedure, the patient's bone marrow is destroyed using chemotherapy or radiation. Post-transplant, the patient is given drugs to help prevent rejection of the donated marrow. In some cases the transplant does not work or the patient's body rejects the new marrow.

Bone marrow transplant carries some risks, requires a lengthy hospital stay and is quite costly. It is also difficult to find matched donors. The procedure is currently only recommended for people who have significant symptoms and problems resulting from sickle cell anaemia, such as stroke or severe pain, and those who are unresponsive to all types of treatment.

Experimental treatments/investigational approaches are summarised in the table below:

Investigational approaches to the management of sickle cell disease

Therapeutic approach	Clinical effect
Nitric oxide	Has the potential to downregulate endothelial cell activation and inhibit adhesion, and prevent polymerization by increasing the affinity of HbS for oxygen[15]
5-deoxyazacytidine (decitabine)	Low doses can elevate HbF with acceptable toxicity[16,17]
Butyric acid compounds	Increases HbF production in erythroid cells and inhibits the proliferation of other cell types, including erythroid cells[18]
Clotrimazole	Inhibits cation transport channels in erythrocyte membranes, thereby reducing cellular dehydration. May have value as an adjunct to hydroxyurea therapy[19,20]
Anti-adhesion therapy	Potential to modulate cellular interaction in patients with SCD; little clinical evidence to date
Gene therapy	Early promise demonstrated in a transgenic mouse model, but clinical evidence is not yet available[21]

Gene therapy

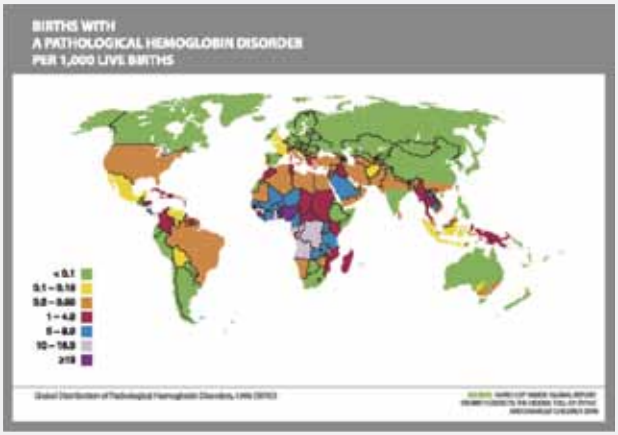
Because sickle cell anaemia s caused by a defective gene, researchers are studying whether correcting this gene and reinserting it into the bone marrow of people with sickle cell anaemia will result in normal haemoglobin formation. Scientists are also exploring the possibility of 'turning off' the defective gene while 'turning on' another gene, responsible for the production of foetal haemoglobin-a type of haemoglobin that prevents sickle cells from forming. This is based on the observation that patients with sickle cell disease and high foetal haemoglobin tend to have a milder course and a lower risk of complications than those with low foetal haemoglobin.

CHAPTER 13
PREVENTION AND GENETIC COUNSELLING IN HAEMOGLOBIN DISORDERS

Haemoglobinopathies are a major public health problem around the world, with hundreds of thousands of affected children born annually.

Unfortunately updated and upgraded epidemiological data is still absent from many regions of the world, making all available figures' including those described below, perhaps grossly underestimated. According to currently available data:

- It is estimated that 7% of the global population is a carrier of a pathological Hb gene;
- Between 300,000 - 500,000 children are born annually with a severe Hbpathy
- About 80% of affected children are born in middle and low income countries
- About 70% are born with SCD and the rest with thalassaemia disorders
- 50-80% of children with sickle cell anaemia and 50,000-100,000 children with β-thalassaemia major die each year in low and middle income countries (World Bank 2006, report of a joint WHO-March of Dimes meeting in 2006)



An essential component of the control of haemoglobin disorders, in addition to case management is prevention. A successful prevention strategy must include the following elements:

- Community awareness
- Genetic counselling
- Screening
- Obstetric services
- Prenatal diagnosis

Another technique to support prevention and overcome issues related to pregnancy

termination choices following prenatal diagnosis (see later for more information) is pre-implantation genetic diagnosis (PGD). And although this approach may not be culturally suited to all population groups it does offer another alternative to have a child free of a severe Hb disorder. It is however a very costly and technologically demanding technique and these limit significantly its widespread use. Other approaches currently under development focus on the diagnosis of at-risk embryos through an examination of the peripheral blood of the pregnant women.

It is important that all patients, as well as pregnant women and their husbands/partners, are given as much and as reliable and updated information as possible to assist them in their choices, including explanations of the inheritance patterns and management of these conditions; essential, to support them in making informed decisions about pregnancy.

Prevention programmes provide genetic screening to establish whether both partners are carriers of a haemoglobinopathy and so at risk of having an affected child. Such screening is carried out before or early in a pregnancy, or even before marriage. At-risk couples expecting a child can be offered prenatal diagnosis, to find out if the baby is affected. The couple can then choose how to proceed.

Thalassaemia International Federation (TIF) works in official relations with and supports the World Health Organisation's (WHO) resolutions* and recommendations in encouraging member states to develop and implement nationally integrated strategies for the control of haemoglobinopathies.

COUNSELLING

Counselling is usually the responsibility of a genetic counsellor, a medical specialist or a haemoglobinopathy nurse who is knowledgeable about the disease and who has been trained in providing comprehensive, confidential counselling in a non-directive manner. Counselling should include an explanation of the inheritance pattern of sickle cell disease or thalassaemia and the implications for the planned baby, allowing the individual or couple the freedom to make an informed choice. The screening of partners should only be carried out with consent, unless compulsory screening is part of a national prevention programme.

COUPLES NOT AT RISK

Couples who are not at risk should be informed as soon as possible, in order to alleviate fear and anxiety.

* WHO 118th Session Agenda Item 5.2, May 2006, Thalassaemia and other Haemoglobinopathies, 59th WHA, agenda Item 11.4 WHO59.20, May 2006, Sickle-Cell Anaemia, WHA document A61/8 (April 2008) Action Plan for the Global Strategy for the Prevention and Control of the Noncommunicable Diseases.

AT-RISK COUPLES - FOR 'ABNORMAL' HAEMOGLOBIN.

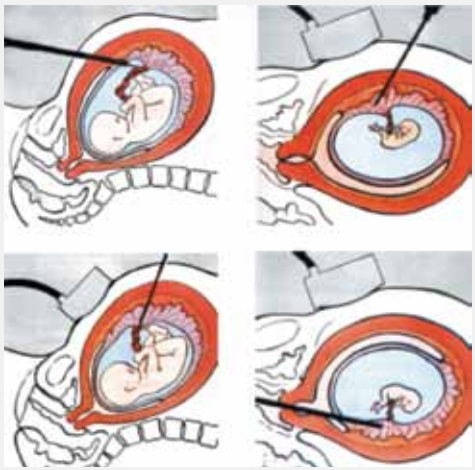
In the same way as for β-thalassemia major and SCD counselling should be offered to carriers for "abnormal" haemoglobins or otherwise referred to as structural variants.

When both partners in a couple are carriers of an abnormal haemoglobin the couple is at-risk (25% chance) of having a baby with a major haemoglobinopathy. The couple must be contacted and an early appointment arranged to see a genetic counsellor, who may be a doctor or a nurse. Further counselling should be offered if necessary, to ensure both partners are aware of the implications for their baby if the combination of abnormal haemoglobins is one that could result in a clinically significant disorder. (e.g. HbE/β thal, β thal/SCD etc). This should include a discussion of how the disorder is managed in their country and elsewhere, and the option of prenatal diagnosis (PND). Again, such information must be shared in a non-directive manner.

PRENATAL DIAGNOSIS (PND)

Prenatal diagnosis is a test carried out during pregnancy, to establish whether the baby has inherited a particular haemoglobinopathy.

Prenatal diagnosis should be considered if both partners are carriers of β-thalassaemia or SCD or carry an abnormal haemoglobin gene (as described above). In these cases there is a one-in-four chance in each pregnancy that the baby will have a severe type of anaemia. If the pregnant woman wants to consider prenatal diagnosis and her partner is unavailable for testing, the advice of a specialist haematologist should first be sought.



An affected baby can be detected from as early as 10 or 11 weeks of pregnancy. Counselling on prenatal diagnosis should be offered to at-risk couples. However, the couple's decision as to whether or not to have prenatal diagnosis must be respected and supported. Further counselling should be offered before the test is carried out.

It may be necessary to have blood samples from other family members, in order to minimise errors and confirm the embryo's diagnosis. Results should be made available as early as possible, in order to alleviate fears and anxiety. and should be provided by

the counsellor, doctor or nurse, in an appropriate manner.

There are three ways to carry out prenatal testing:

Foetal blood sampling

- This test can be done between 10 and 20 weeks of pregnancy. A sample of blood is taken from the umbilical cord via a needle inserted through the mother's abdominal wall. A local anaesthetic is given beforehand and an ultrasound scan used so that the doctor can see exactly where to direct the needle.

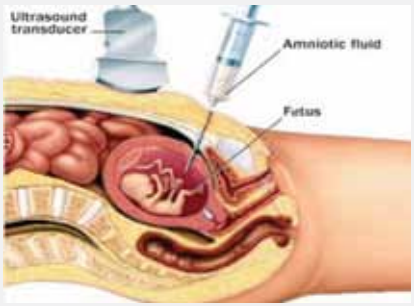
Chorionic villus sampling (CVS)

- This test is most commonly used, and can be done from the 11th week of pregnancy. The test involves obtaining a sample from the chorionic villi, which contains copies of the genes the baby has inherited. The test can be done either through the vagina and cervix, or by putting a needle through the abdominal wall after the injection of a local anaesthetic. An ultrasound scan is also used so that the doctor can see exactly where to direct the needle.

Amniocentesis

- This test is done up to 20 weeks of pregnancy. It is used very occasionally, when CVS or foetal blood sampling cannot be carried out for some reasons.

  In the CVS a small needle is inserted into the womb to remove a sample of the fluid surrounding the baby. The fluid is then tested to reveal the genes the baby has inherited. An ultrasound scan is usually used so that the doctor who should be expert in this technique can see more accurately where to direct the needle.



ACCURACY & SAFETY OF PRENATAL DIAGNOSIS (PND)

Prenatal diagnosis involves practically no risk to the mother but anything which interferes with a pregnancy carries a risk of miscarriage for some women.

In addition, a small margin of error is associated with every medical test. However, in most cases the chance of a mistake is very small.

RESULTS OF THE TEST

The results of PND should be made available as soon as possible, and should be conveyed to the couple (or pregnant woman if partner is not available) in an appropriate, informative way. If the baby is found to be affected, the parents should be offered further counselling to allow them to decide the next step forward and depending on local/national legislation and cultural/religious beliefs: Parents should be allowed to make their own decision and be assured that, whatever they decide, health professionals will respect their wishes and continue to offer maximum support.

PRE-IMPLANTATION DIAGNOSIS (PGD)

This is a procedure of in-vitro fertilisation that improves the chances of parents who are carriers of a haemoglobinopathy having a healthy child. Eggs are taken from the mother and sperm from the father, to be fertilised in a laboratory. The fertilised eggs are then tested for the presence of the thalassaemia or sickle cell gene. Fertilised eggs free of the haemoglobinopathy gene are then implanted into the mother for normal development. There are pros and cons for this technology as well.

Advantages

PGD will benefit couples who have had repeated terminations from previous prenatal tests and those who have moral or religious objections to termination or need to find an HLA compatible donor for an affected child. It is also recommended in infertile couples.

Disadvantages

Disadvantages include the need for technological expertise, the need for repeated attempts before a healthy baby is actually born, and the high cost of the procedure.

SUPPORT FOR AN AFFECTED CHILD

Although women and their partners should be offered antenatal screening and counselling and should be fully informed of any risks of an affected pregnancy, this may not always be the case. Equally, parents may have chosen to go ahead with a pregnancy, but still be shocked at a positive diagnosis. It is therefore important to refer the parents of an affected child to a specialist counsellor/healthcare professional early on.

At the same time early referral (at 2-3 months of age) to a doctor specialised in haematology or to a haemoglobinopathy nurse is extremely important, in order to ensure timely access to care, including prophylactic treatment (as in SCD) and a disease management plan (as in thalassaemia major).

The continuous education of parents and patients, including in recognising and managing early signs and symptoms of illness, is essential. From this moment on, the nurse plays a critical role, providing patients and parents with a lifetime of support, assistance and monitoring.

FURTHER READING SUGGESTED

TIF PUBLICATIONS - www.thalassaemia.org.cy

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- Synodinos J, Petrou M, Galanello R, Angastiniotis M (eds.)
- Prevention of Thalassaemias and Other Haemoglobin Disorders Vol.1 (2003), Galanello R,
- Eleftheriou A, Trager-Synodinos J, Old J, Petrou M, Angastiniotis M (eds.)
- Compliance to Iron Chelation Therapy with Desferrioxamine,
- DVD with all publications
- Conferences Proceedings (www.thalassaemia.org.cy)

Please visit http://www.ukts.org/nurse.html?i5s3

- Royal College of Nursing Competences
- Caring for people with sickle cell disease and thalassaemia syndromes
- Understanding the contribution of sickle cell and thalassaemia specialist nurses

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