

* CHAPTER 13

Sickle cell disease: a short guide to management

Frédéric Galactéros

1. Introduction

Sickle cell diseases are defined as genetic conditions in which at least one β globin gene allele carries the β^S (6V) mutation, associated with characteristic vascular occlusion accidents and correspondingly accelerated haemolysis (Table 1). Sickle cell diseases (SCD) can arise from either homozygosity for the β^S (6V) mutation (sickle cell anaemia), or from coexistence of the β^S (6V) mutation with other β gene variants or β thalassaemia.

Table 1: Definition of sickle cell syndromes

At least one β globin gene allele carrying the β 6 V mutation (HbS)
Vaso-occlusive events leading to ischaemia can be demonstrated in the tissues at sea level oxygenation
Abnormal haemolytic rate accompanies vaso-occlusion

Table 2 lists the approximate incidences of annual new cases of SCD. Sub-Saharan Africa is the area of highest incidence as around 2% of the newborns in this area are affected. Prevalences are much less easy to determine due to the absence of registries in most places where SCD is common. There are probably more than 75,000 SCD individuals in the USA and between 15 and 25,000 in Western Europe. The prevalence in countries like UK, Belgium or France is rapidly increasing. We have no idea of the global survival rate in Africa, but if only 10% patients reach adulthood, then there would be a minimum of one million individuals with SCD in this area.

Table 2: Approximate worldwide annual incidences of SCD in newborns

North America	4 to 5,000
South America	5 to 10,000
Central America	1 to 2,000
Western Europe	1 to 2,000
North Africa	1 to 2,000
Central Africa	200 to 400,000
Middle East	1 to 2,000
South Asia	10 to 20,000
TOTAL	220 to 440,000

2. Pathophysiology and modifying factors (1)

In SCD, the sickle haemoglobin (HbS) has acquired the capacity to polymerize by hydrophobic interaction at low oxygen concentration and at a minimal protein (HbS) concentration, conditions which can both occur in the normally functioning red cell (2).

Polymerisation of Hb within the red cells is the primary and necessary condition for vaso-occlusion, which is the main specific manifestation of SCD and which differentiates SCD from other haemolytic anaemias.

Cycles of oxygenation and deoxygenation of red blood cells (RBC) produce repeated sickling and unsickling, leading to RBC damage, increased rate of red cell breakdown and the formation of very short-lived but continuously formed sub-populations of very high density irreversibly sickled RBC (ISC).

The kinetics of ISC formation appear to be very heterogeneous, some reticulocytes becoming ISC almost immediately while others behave quite normally (3-5). The major factors which affect the survival of individual RBC are the HbF content, which seems to be randomly distributed in native RBCs, and the kinetics of dehydration.

2.1 HbF level

Any increment in RBC HbF content has a beneficial effect on the primary cause of sickling: polymerisation. Neither the HbF tetramer ($\alpha_2\gamma_2$) nor the hybrid $\alpha_2\gamma\beta^S$ takes part in the polymerisation of HbS (6). HbF has a demonstrated anti-sickling effect, and polymerisation in physiological conditions is almost abolished if the RBC HbF fraction is over 20%.

Any erythropoietic stress tends to stimulate HbF synthesis. In SCD, the sustained haemolytic rate leads to HbF over-expression in the reticulocytes and after that there is a selective enrichment of HbF-containing RBC since they have a lower haemolytic rate.

In SCD, the fall in HbF level after birth is delayed and is only fully stabilised at 5-6 years of age. There is a large range of individual residual HbF expression, between 0.1 to 25%, mainly depending on gender, β globin cluster haplotype and the lowering of α -globin synthesis by coexistent α -thalassaemia (7, 8). Most adult patients have 5 to 8% HbF as determined by chromatographic analysis of their lysed RBC. Attempts to maximise HbF production in SCD by the use of drugs have proven to be clinically effective (see below).

2.2 Cellular hydration

The hydration state of an RBC is the only means of modifying the intracellular Hb concentration during the life of the cell. During the circulatory cycle there are both

tissue-specific and general physiologic changes in RBC hydration. In SCD the interesting thing is that desoxy-HbS polymer initiation is kinetically highly dependent on cellular protein concentration changes.

Any small elevation of RBC HbS concentration resulting from dehydration has a drastic clinical effect by reducing the delay after which massive polymerisation takes place. To simplify, there is a race between the RBC transit time in the microcirculation where deoxygenation happens and sickling delay which, if it is short enough, will favour the trapping of the polymer-containing RBC and vaso-occlusion.

The way in which RBCs gain or lose water depends on exchanges which, by osmotic forces, influence water movements. Table 3 describes the four pathways that have been implicated in the dehydration of SCD RBC (9-12).

Besides the prominent role of ion exchange channels in RBC water regulation and the effects of drugs, it must be emphasized that adequate cell hydration is primarily dependent on sufficient and regular oral water intake.

Table 3: Pathways involved in SCD RBC dehydration

Pathway	RBC Expression	Inducers	Potentially useful in inhibiting agents
Anion permeability	All RBC	Physiological	Cl ⁻ conductance blockers
Gardos channel	Reticulocytes++	Ca ⁺⁺	Clotrimazole ICA 17043 Endothelin 1 receptor inhibitors
K-Cl cotransport	Reticulocytes++	Acidic pH Oxidative conditions	Magnesium (pidolate)
Deoxygenation induced	Depends on RBC sickling propensity	Low PO ₂	HbF inducing drugs dipyridamole

2.3 The vascular environment

The vascular environment in which SCD RBC circulate is not a passive bystander (13-15). There is a complex network of interactions between sickle RBC and the vasculature in which the endothelial cells play a major role. Leucocytes and platelets also contribute to vaso-occlusion but in even less well-defined ways.

Sickle cells not only have abnormal rheological behaviour, leading to perturbed blood flow and elevating the shear stress on endothelial surfaces, but also have properties of adherence to endothelium. In addition, intravascular haemolysis has systemic effects on vascular reactivity through plasma haemoglobin and plasma arginase, and possibly other RBC components (16).

- Endothelial cells and sickle RBC (particularly the youngest RBC) can both be activated by inflammation, stress hormones, endothelin 1 and ischaemia. Such effectors promote the activity of a network of complementary adhesion molecules (17). Sickle RBC adhesion to endothelium is probably one of the main mechanisms leading to vaso-occlusive episodes (18, 19).
- Plasma haemoglobin and haem are NO scavengers, the proposed means by which intravascular haemolysis can induce vasospasm. A state of NO resistance seems to characterise the endothelium in SCD. Not only does NO synthase not react normally, but the endothelium itself seems to be resistant to NO donors. Endothelin 1 production is increased during the clinical steady state and even more so during vaso-occlusive crises (VOC) (20). Endothelin 1 promotes RBC dehydration by activating the Gardos channel (21, 22).
- Arginase catalyses the synthesis of urea with arginine as substrate, hence its presence in the plasma may reduce substrate availability to NO synthases (23).
- Neutrophil counts have been shown to be associated with the overall severity of vaso-occlusive episodes and with death risk. Neutrophils may play a direct role in initiating VOC. Even in the SCD steady state neutrophils have stimulated adhesive properties and are further activated by inflammation (24, 25).

2.4 Genetic heterogeneity

Sickle cell disease is genetically heterogeneous (26) (Table 4).

A number of β globin alleles, other than the normal β gene, can interact with HbS and promote polymerisation. Two mechanisms have been demonstrated: first, increase of relative HbS proportion within RBC when the interacting allele has lowered expression; second, enhancement of polymer formation (D Punjab-0 Arab-S Antilles).

Table 4 gives the features of the most common genetic conditions leading to SCD.

2.5 Other factors

A number of other factors, genetic or acquired, are recognized as severity modulators (27-30).

Besides the major role of HbF synthesis level, α -globin gene expression is clearly a potent modulator of the clinical profile (Table 5). This remains true in both the developed country health care environment and in Africa.

In Central Africa almost 70% of SCD individuals are carriers at birth of one or two α^+ thalassaemia genes. In many regions like West Africa or in African-American populations the corresponding incidence is around 35%.

Table 5 summarises the main settings that worsen the SCD phenotype.

Table 4: Sickle cell disease - main genotype to phenotype relationship

Genotype	Severity trend	Optimized life expectancy (2005)	Haemolytic rate
SS	High severity in 20 to 30%	45 to 65 years	Hb: 6 to 11 g/dl; R**: 5 to 25%
S/ β^+ thal* or S/(low A) β^+ thal S β^+ thal (10 to 25% HbA)	"	"	"
SC	Low severity in 80%	>65 years	Hb: 9 to 14 g/dl; R: 3 to 10%
SD Punjab SO Arab	"	"	Hb: 10 to 15 g/dl; R: 3 to 10%
SE S Lepore	Severe	35 to 65 years	Hb: 6 to 11 g/dl; R: 5 to 25%
S/HPFH	Very low severity	>65 years	Hb: 9 to 14 g/dl; R: 3 to 10%
AS Antilles	No	Normal	Normal
AS	Very low severity	Normal	Hb: 10 to 14 g/dl; R: 3 to 5%
AS	No	Normal	Normal

* *Thalassaemia* - ** *Reticulocytes*

Table 5: Factors aggravating the (SS or S β^0 thal) SCD phenotype

Predictive factors	Trends
Low HbF production	Earlier splenic dysfunction Earlier onset of clinical symptoms Earlier death Increased risk of VOC, ACS and LU
Hb below 7 g/dl	Earlier death Increased risk of stroke, LU and cardiac dysfunction
Hb over 9 g/dl	More VOC, ACS and EAN
No α thalassaemia	More strokes
α thalassaemia (mostly ++ α^+ / α^+)	More VOC and EAN
Higher leukocyte value (>12x10 ⁹ /l)	Earlier death More strokes
High VOC rate	Earlier adult death
Pulmonary hypertension	Earlier adult death
Nocturnal hypoxemia	More strokes

VOC: vaso-occlusive crises; ACS: acute chest syndrome; LU: leg ulcer

3. General health management

General health management (31, 32) must begin with neonatal (or prenatal) diagnosis so that parents can be informed and the disease explained to them, and the necessary collaborative network set up, including the parents and other carers (33-35).

Disease management must take into account the familial and genetic dimensions of the disease (36, 37) (Table 6).

Table 6: General health maintenance organisation

<p>1. Environmental</p> <ul style="list-style-type: none"> • Altitude: less than 1500 m • Avoid body cold exposure • Avoid hot weather exposure 	<p>4. Education</p> <ul style="list-style-type: none"> • Health education for the patient and relatives • Information on symptoms requiring medical advice • Genetic counseling • Appropriate use of analgesia at home
<p>2. Way of life</p> <ul style="list-style-type: none"> • Regular hydration • Avoidance of alcoholic beverages • Suppression of active (or passive) tobacco use • No cannabis or other illegal drugs • Avoidance of strenuous exercise • Adoption of a quiet way life 	<p>5. Psycho-social management</p> <ul style="list-style-type: none"> • Implementation of care pathways • Easy access to social workers • Open access to psychologist • Avoidance of stress
<p>3. Nutrition</p> <ul style="list-style-type: none"> • Folic acid supplementation 5 mg/d, 10 d/month • Zinc 10 mg/d (1 to 2 month/y) until puberty 	<p>6. Occupational orientation</p> <ul style="list-style-type: none"> • Avoid physically tiring jobs • Avoid occupations with cold exposure

3.1 Health education

This is of particular importance, and must provide comprehensive explanations about the general mechanisms of the disease, the rationale behind the current treatment and care plan, and the clinical criteria which should prompt the family to seek medical advice, and whether as an emergency or not. Pertinent clinical and biological data must be given to the patient or the parents as a personal medical file.

There must be regular medical supervision, which should be monthly during the first year, then every 2 months until the age of 3, and thereafter adapted to clinical needs. Even if the disease remains apparently asymptomatic, a yearly consultation would seem to be the minimum frequency.

Investigations for early detection of complications should be carried out at regular intervals (38). Table 7 gives an example of a schedule for investigations that should be performed during the lifetime of an individual with SCD (39).

Table 7: Periodic health investigations

Tests	Before 3 years	3 to 15 years	>15 years
Hematology	Every 6 months	Once a year	Once a year
HbF %	"	Only for supervision of HU therapy	Only for supervision of HU therapy
Renal, hepatic functions	Once a year	Once a year	Once a year
Blood pressure	Any time	Any time	Once a year
Pulmonary function	ATCM	ATCM	ATCM
Bone aseptic necrosis			
Auditory exam			
Retinal examination	No	SS: Not required SC: after 12 yrs	Once a year ++ for SC
Transcranial Doppler velocity	Every 6 to 12 months	Every 2 yrs up to 8 yrs (?)	ATCM
Brain MRI	At 2 or 3 yrs	One before 15 yrs	Every 5 yrs (?)
Tricuspid regurgitation jet velocity	ATCM	ATCM	Every 3 yrs (?) or ATCM
Gall bladder ultrasonography	ATCM	At 5 and 10 yrs if there is severe icterus	Every 3 yrs or ATCM

ATCM = according to clinical manifestations; HU: hydroxyurea

Detection of abnormalities through such investigations will generally lead to collaborative therapeutic approaches, which tend to be more beneficial when the complication is detected early (40, 41).

3.2 Prevention of infection

A major goal in SCD clinical management is the prevention of severe, bacterial infection, which, otherwise, may often be lethal (Table 8) (42-44). This can be achieved by a relatively simple combination of twice daily administration of oral penicillin and an adapted immunisation programme (45). This therapeutic approach has been very effective in reducing infant mortality so long as there is compliance on the part of the parents. With a few exceptions, penicillin prophylaxis is no longer useful after the age of 5 (46). In areas where malaria is endemic, malaria prophylaxis or very early treatment is mandatory until the age of 5. Early diagnosis or treatment of probable infection remains extremely important even in adults.

Bone infections are possible at all ages; sites of chronic focal infection must be regularly detected and treated to avoid bacteraemia, that could colonise necrotic areas of bone. This is particularly true for sub-acute cholecystitis.

Recurrent tonsillitis, sinusitis and dental infection are often associated with more

frequent VOC, perhaps by promoting systemic inflammation and enhancing neutrophil (or leukocyte) activation.

Table 8: Infectious risk management

<p>1. Penicillin V orally from 2 months to at least 5 years of age</p> <ul style="list-style-type: none"> • 100,000 UI/kg/d up to 10 kg BW • 50,000 UI/kg/d from 10 to 40 kg BW 	<p>4. Immunisation</p> <ul style="list-style-type: none"> • Streptococcus pneumoniae • Haemophilus influenzae • Meningococcus • Influenzae • Salmonella typhi (for at risk individuals)
<p>2. Prompt administration of active or pneumococcus antibiotics in case of possible bacterial infection</p>	<p>5. Malarial prophylaxis when appropriate</p>
<p>3. Elimination of recurrent focal infection (dental infection, sinusitis, acute recurrent tonsillitis, cholecystitis, urinary infections)</p>	

4. Anaemia and principles of transfusion

4.1 Anaemia

The most prominent determinant of anaemia in SCD is the rate of haemolysis. For instance anaemia is moderate or absent in the SC genotype. However, the Hb level is an individual characteristic which remains stable in a given individual in the steady state and such a clinically well compensated chronic anaemia does not require transfusion. Conversely, any change in steady state Hb level is clinically meaningful and must be investigated.

In SCD, the effect of anaemia is partially compensated for by an elevated P50 and increased cardiac output at rest. Acute worsening of anaemia (Table 9) is common and may have an immediate prognostic impact (47, 48). This is why blood group and extended phenotype must be determined at the earliest opportunity when a new SCD patient comes to any hospital facility.

Acute anaemia is the result either of over-destruction of RBC by hyperhaemolysis, sequestration, or blood loss, or is the consequence of failure of red cell production, most often secondary to parvovirus B19 infection or extensive bone marrow necrosis (49).

Some patients, most often adults, may develop a persistent fall in Hb concentration. Besides simple explanations such as insufficient folate administration, chronic worsening of anaemia always has a serious clinical implication (Table 9).

Table 9: Causes of worsening anaemia in SCD

1. Sudden symptomatic anaemia	2. Chronically more severe anaemia
<ul style="list-style-type: none"> • Splenic and/or hepatic sequestration • Transient aplastic crisis secondary to Parvovirus B19 infection • Auto-immune haemolysis • Delayed haemolytic transfusion reaction (DHTR) • Acute malarial episode • Acute intestinal or urinary blood loss 	<ul style="list-style-type: none"> • Severe chronic inflammation • Cobalamin deficiency and/or hypothyroidism • Renal insufficiency (early sign) • Chronic hypersplenism

4.2 Transfusion

Transfusion remains a powerful tool for treating acute, potentially lethal, anaemia and severe vaso-occlusive complications (48). Simple transfusion must be limited in volume (<7 ml packed RBC/kg) to avoid hyperviscosity (which can promote vaso-occlusion) and haemodynamic overload. Most often simple transfusion is used for the emergency therapy of acute anaemia, or when transfusion is done some time after an episode of VOC.

Exchange blood transfusion is used in a growing number of paediatric and adult patients, for prevention or treatment of VOC. It is used to prevent recurrence of debilitating thrombotic accidents (strokes mainly) or to reduce the rheological and anaemic consequences of sickle RBC on a chronic organ failure (50). It can also be done during the last trimester of pregnancy to prevent maternal complications and in particular to reduce fetal mortality (51).

4.2.1 Adverse effects of transfusion

Adverse effects of blood transfusion are serious and for this reason transfusion should be restricted to recognised, although largely empirical, indications (Table 10) (52-54). Transfusions may be complicated by immunologic reactions: allo-immunisation and haemolytic reactions which often occur as a delayed haemolytic transfusion reaction (DHTR).

Allo-immunisation is very common but its frequency can be reduced by using blood products fully compatible with the recipient ABO, Rh and Kell phenotypes (Table 11). In countries where donors and recipients are ethnically different, there is an elevated risk of allo-immunisation. Some countries try to encourage blood donation from relevant ethnic groups. For a small sub- group of patients allo-immunisation is so complex that no compatible donors can be found, even within the family (55, 56).

DHTR may occur in 4 to 11% of transfused sickle cell patients. It can be due to a new or reactivated, previously undetected, allo-immunisation (57).

Table 10: Clinical indications for transfusion

<p>1. Simple or small volume exchange transfusion</p> <ul style="list-style-type: none">• ACS and any organ failure• Splenic or hepatic sequestration• Sepsis or malaria• Refractory painful VOC• Acute symptomatic anaemia• Pre-operative preparation	<p>3. Chronic transfusion programme</p> <ul style="list-style-type: none">• Brain vasculopathy• Recurrent severe VOC and/or ACS• Chronic organ failure: kidneys, heart, lungs, liver• Pulmonary hypertension• Severe growth retardation• Last trimester pregnancy• Psychosis• Severe chronic anemia unresponsive to HU or erythropoietin
<p>2. Large volume exchange transfusion</p> <ul style="list-style-type: none">• Stroke• Recent complete auditory loss• Central retinal artery thrombosis• Preparation for major surgery (thoracic, cardiac, ocular, using tourniquet etc.)• Acute refractory priapism	

Table 11: Blood product selection

<ul style="list-style-type: none">• Leukodepleted packed RBC• Phenotyped for ABO-Rh-Dce Kell antigens• Extended patient phenotyping before transfusion to permit extended matching after alloimmunisation	<ul style="list-style-type: none">• Negative for HbS to keep the ability of monitoring transfusion efficacy• Irradiated blood when indicated
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DHTR manifestations occur a few days after the last transfusion, are often severe and include profound anaemia, haemolysis, ACS and renal insufficiency. Typically, LDH levels rise rapidly, the transfused HbA disappears within a few days and reticulocytopenia is present. Besides intensive care, the therapeutic approach to these episodes should avoid further transfusion or, in case of absolute necessity, transfusion should be performed with simultaneous administration of corticosteroids and intravenous gammaglobulins. Erythropoietin may also be useful. Health education must comprise information on DHTR for discharged patients who have been recently transfused.

4.2.2 Iron overload

Iron overload is a common and potentially severe complication of chronic transfusion programmes. Significant iron toxicity may appear after the administration of 10 to

30 units of red cells, depending on the recipient's weight. The magnitude of iron accumulation can be best monitored by T2* MRI scan of the liver and the heart. The use of isovolaemic automated exchange transfusion, although needing a greater number of units of blood, results in no increase or even in a decrease in iron overload (58). Iron chelation therapy is an efficient means of reducing direct and indirect iron induced mortality. Sub-cutaneous Deferoxamine infusion is the standard therapy; however it is a cumbersome complicated and painful procedure and long-term compliance to treatment remains often very poor. Deferiprone is an interesting alternative since it is taken orally and has been shown to reduce cardiac iron overload. However, it has numerous serious side-effects which limit its use. A new, orally effective agent with limited side-effects should soon be available (Exjade®), which seems to be effective at a single daily dose of 20 to 30 mg/kg.

5. Acute painful episodes

Painful episodes are the hallmark of SCD (59, 60).

5.1 General VOC

Most sudden pain attacks (painful VOC) are treated at home and, when the problem persists and the patient seeks hospital treatment, may remain unrecognized by hospital physicians. Such patients require emergency treatment, rapidly and safely initiated. Mild pain can be treated with acetaminophen alone. If it does not control the pain effectively, a combination of oxycodone or codeine/acetaminophen can be used in combination with orally administered NSAID. Severe painful crises require parenteral analgesia. The initial pain assessment must be done without delay and then as often as necessary. The patient's own assessment must be taken into account regularly using adapted pain scales (visual analog scale; "faces" pain intensity scale for younger patients etc.).

An initial opioid administration scheme is designed using a titration curve and readapted every 4 h or less if necessary. Adverse effects of therapy and emergence of other clinical events like ACS, infection, or neurological involvement, must be monitored every 6 hours. In very rare cases, when pain remains intractable after 48 h of well conducted analgesia, an exchange transfusion may be indicated. General medical evaluation of the sickle cell patient is very important. Relevant clinical and biological parameters are given in [Table 12](#). A dedicated day hospital where critically ill patients can be frequently and fully evaluated by experts seems to be much appreciated by patients who, with early diagnosis and treatment, may be more rapidly cured of their VOC, and finally this could be a valuable alternative to classical hospitalisation (61). Each painful episode should be analysed

retrospectively with the patient in an attempt to determine the circumstances which may have caused the VOC (Table 13) and which could be avoided or modified to reduce the risk of recurrence. Keeping a diary is a very helpful means of globally evaluating the incidence and timing of painful crises.

It must be kept in mind that the frequency of severe painful crises in an independent predictor of increased mortality, indicating more aggressive therapies.

The prevention of painful VOC is one of the objectives of HU therapy (see below). A phlebotomy program may be effective for patients with an Hb level higher than 10-11 g/dl. A transfusion programme may be useful in the very rare cases with debilitating painful VOC recurrence.

Table 12: Useful clinical and biological parameters for monitoring painful VOC

Physical examination for	Biological evaluation
<ul style="list-style-type: none"> • Pain assessment • Early signs of ACS • Cardiovascular manifestations (systolic pressure, etc.) • Body weight loss • Neurological manifestations • Abdominal evaluation • Absence of urinary problem 	<ul style="list-style-type: none"> • Pulse oximetry and arterial blood gas • Complete blood count with reticulocytes • Inflammation markers • Hemolysis markers: LDH+++ • Chest X ray • Abdominal ultrasound • Bacteriological sampling when necessary

Table 13: Circumstances that may provoke VOC

<p>1. Exposure to:</p> <ul style="list-style-type: none"> • Cold • Altitude (mountains or unpressurized planes) • Alcohol, tobacco smoking and other drug uses • Excessive physical exercise 	<p>3. Vascular</p> <ul style="list-style-type: none"> • Prolonged involuntary arterial compression • Systemic hypertension • Exposure to adrenergic agents • Dehydration
<p>2. Respiratory diseases</p> <ul style="list-style-type: none"> • Asthma • Obstructive tonsillitis • Obstructive allergic rhinitis • Sleep apnea syndrome • Thoracic trauma 	<p>4. Miscellaneous</p> <ul style="list-style-type: none"> • Glucocorticoid administration • Emotional event • Stressful period of life • Excessive work load • Acute infection • Abdominal surgery

5.2 Acute chest syndrome

Acute chest syndrome (ACS) (62, 63) is defined as an acute event with pneumonia-like symptoms associated with a new infiltration on the chest X-ray, which may only appear after a delay of 24 to 48 h. ACS is a very common cause of hospitalisation, with a wide range of severity. It remains a leading cause of death in the adult, even in the less severe SC or Sβ⁺ thal genotype. The death rate remains high (4 to 9%) despite better comprehensive care including pain relief, infection control, oxygenation and ventilation management, and prompt decision to perform exchange transfusion. ACS is associated with lung infection in 50% of episodes, particularly during childhood. In adults, the most common causes of infection are *mycoplasma pneumoniae* and *Chlamydia pneumoniae* (25% of episodes). Pulmonary fat embolisation (PFE) is probably a very common event during VOC and massive PFE is a frequent finding during ACS. It can be detected by broncho-alveolar lavage or induced expectoration (64).

Systemic passage of fat emboli is a further cause of deterioration in patients with ACS (65). The most common consequences are mental confusion or coma. Renal failure may also occur, as well as thrombocytopenic purpura with intravascular coagulation. Such complications are more frequent in SC patients and in those with a right to left cardiac shunt such as a permanent foramen ovale. It reinforces the need for exchange transfusion. In situ thrombosis and fibrino-crucic pulmonary embolism also contribute to the heterogeneous pathophysiology of ACS.

Treatment of ACS comprises:

- Intravenous broad spectrum antibiotic administration including a quinolone or a macrolide.
- Efficient pain relief with parenteral opioids, with special attention to side effects like respiratory depression and restricted ventilation due to abdominal ileus.
- Oxygen administered nasally at 2 to 3 l/min.

When arterial O₂ saturation (blood gases) is between 91 and 96%, incentive spirometry may help to prevent further ventilation defects (66). In severely hypoxemic patients, management must take place in an intensive care unit where all types of respiratory support are available. There is almost always associated use of bronchodilators. The use of corticosteroids is very controversial (67).

- Exchange transfusions are mandatory in approximately 50% of the most severe ACS (those requiring intensive care). An early decision to use exchange transfusions may prevent severe organ failure (liver, kidneys) or death (68). Exchange transfusions should lead to at least 50% HbA (% of normal RBC) after completion. [Table 14](#) gives criteria for exchange transfusions during ACS.

Table 14: Indication for exchange transfusions in ACS

- | | |
|--|---|
| <ul style="list-style-type: none">• Any early biological sign of organ failure• Any neurological defect (confusion – motor defects – epilepsy)• Worsening respiratory failure• Intractable pain or opioid intolerance | <ul style="list-style-type: none">• Haemodynamic instability• Nosocomial infection• Acute worsening of anaemia or cardiovascular insufficiency• Acute enlargement of the spleen or liver |
|--|---|

Respiratory physiotherapy must be continued outside the hospital as long as respiratory discomfort persists. Pulmonary function testing with special attention to broncho-reactivity and sleep hypoventilation or apnoea should be performed 2 to 3 months after any ACS episode (69-71). A few limited, open trials have suggested a possible therapeutic benefit for inhaled NO (72, 73).

5.3 Priapism

Priapism is a very common acute event in SCD (74).

Priapism lasting more than 3 h is called prolonged (PP), while the shorter episodes, which have a mean duration of less than one hour, are called stuttering. Nocturnal occurrence predominates and may seriously impair rest and quality of life. Severity or recurrence of either SP or PP can produce penile fibrosis and impotence. Priapism may be favored by alcohol or illegal drug use.

Prevention of impotence is the ultimate goal of treatment and is the reason why patients and emergency room medical workers should receive regular specific information. An untreated or refractory PP lasting more than 4 to 6 hours carries a great risk of irreversible impotence.

Beside hydration and analgesia, penile blood from corpus cavernosum is aspirated gently without irrigation, until it appears arterial-like. Etilefrine is a α -agonist adrenergic agent which can be injected intra cavernously (ICI) to prevent recurrence following blood drainage. Patients could be trained to do intra cavernous injection themselves, so that PP can be effectively controlled at home. The patient should also know when to take oral Etilefrine and thus participate in the prevention and treatment of SP (75). Anti-androgens or stilbestrol have been used in small series and found to be effective in prevention (76). Transfusion programmes may be used for patients in whom previous therapeutic approaches were unsuccessful (77).

Penile prosthesis implantation for impotence is a difficult task and is not always effective.

5.4 Acute abdominal pain

Acute abdominal pain occurs most frequently in young patients under the age of 10. The two main causes are splenic (or hepatic) sequestration and gall bladder or biliary tract problems.

- Acute splenic sequestration (ASS) of sickle RBC provokes a very rapid fall (-2g/dl or more) in Hb level with sudden enlargement of the spleen. Parents must be trained to palpate the spleen and to recognise signs of anaemia. Although it can occur at all ages, most cases are seen between 3 months and 5 years of age (SS patients). Anaemic shock may be fatal in less than 3 hours, and emergency measures must be taken to correct hypovolemia and anaemia by parenteral fluid perfusion and small volume simple transfusion (47, 48). ASS has been estimated to occur in 10 to 30% children before the age of 6 and, as it has a high recurrence rate, splenectomy is recommended after the second episode.
- Biliary tract dysfunction is very common and by the age of 30 more than 60% of sickle cell patients are affected. Ultrasonic imaging shows cholelithiasis (78) and biliary sludge (79) as the two main underlying abnormalities. Small pigment gallstones may be detected by systematic survey and may remain asymptomatic for decades. They may also suddenly provoke cholecystitis, migration accidents, common duct obstruction, angiocholitis, acute pancreatitis and sepsis. Cholecystitis induced bacteremia may be a source of clinically delayed metastatic musculo-skeletal infection. Biliary tract MRI may be necessary to reveal the presence of small gallstones in the common duct. Elective laparoscopic surgery in suitably prepared patients (this may include exchange transfusion) is a safe procedure if incentive spirometry is used to prevent ACS and satisfactory pain relief are established during the 24 to 48 hours following surgery (80, 81).
- Sudden painful enlargement of the liver is far less common. It can occur as an autonomous liver sequestration episode similar in consequences and treatment to ASS. It can occur as a manifestation of right ventricular insufficiency.

6. Chronic painful complications

The two chronic and recurrent complications predominantly causing non-VOC severe pain in the adult patient are arthritis, resulting from osteonecrosis, and cutaneous leg ulcers.

6.1 Bone and joint complications

Bone involvement in SCD may result from three mechanisms: osteopenia due to bone marrow expansion, bone infarction, and osteomyelitis (82).

- The main consequence of osteopenia is vertebral instability with mechanically provoked pain and a greater risk of compression fractures.

Osteonecrosis of epiphyseal segments of bones (EAN – Epiphyseal Aseptic Necrosis) is a leading cause of chronic pain in the adults, and has a devastating effect on quality of life. Osteonecrosis prevalence can be defined clinically or radiologically, or by MRI. It may occur in all SCD genotypes and at least 40% of patients older than 30 years have one or more symptomatic EAN. In order of frequency, EAN affects the hips, the humeral heads and the knees. However bone infarction can be observed in any bone, or part of bones. Acute large bone infarction has the same clinical presentation as osteomyelitis, although MRI permits distinction. Symptomatic stages are often preceded by a pre-collapse period of undefined length but detectable by MRI (83). When collapse begins, local pain occurs. Contrary to what happens in adults, EAN before puberty, when conservatively treated, has a strong tendency to heal with well-functioning and painless epiphyseal remodelling (84). In adults, EAN will progress irreversibly and sometimes very rapidly to complete collapse and degenerative arthritis. Hence it is proposed that early detection of symptomatic EAN should lead to conservative surgery which takes into account the stage at which diagnosis is made. This approach, although still awaiting a clear demonstration of its beneficial effect, is reinforced by the very poor overall results of hip arthroplasties (85, 86).

- Humeral head osteonecrosis occurs frequently in all genotypes and particularly in individuals who already have femoral head involvement. Abnormal radiographic aspect may predict collapse which is clinically expressed by pain and reduction of abductor mobility (87). Compared to conservative surgery attempts, humeral head arthroplasty gives uncertain functional results.
- Osteomyelitis frequency is linked to the environmental setting. It is a severe complication which most often originates from bacteremia. For this reason, blood cultures must be done systematically when elevated temperature accompanies acute painful bone crisis. The two main bacterial species involved are *Salmonella* and *Staphylococcus* (88). Diagnosis may be difficult and local bone aspiration may be required, under surgical asepsis. Ultrasound imaging is often very useful in detecting soft tissue oedema or abscess. MRI has the best capacity for early identification or differentiation of acute bone remodeling in SCD.

6.2 Leg ulcers (LU)

These occur mainly in the more severely anaemic patients and are rare during childhood (89, 90). They have little or no spontaneous tendency to heal and even when well managed they may remain unhealed for years. Recurrence is the rule, although there may be long intervals between episodes. They are often very painful due to persistent inflammation, infection, or scarring.

Treatment remains empirical and comprises:

- Achievement of local asepsis
- Surgical debridement to remove the fibrous surface
- Dressing with hydrocolloids. RDG peptide matrix has been shown to have a clear advantage over classical dressings, but is no longer available
- As much bed rest as possible
- Zinc sulphate 600 mg/d
- Regular blood transfusions to maintain Hb in the 8-10 g/dl range and % HbS less than 50%
- Support bandage, particularly if venous incompetence is suspected
- Pain relief may be a serious problem inducing chronic use of orally active opioids. Local pain control before dressing is mandatory.

The number of other experimental procedures, or procedures used in isolated cases, is an indication of our therapeutic shortcomings.

7. Sickle cell vascular diseases

Some very common complications in SCD, although primarily arising from microvascular vaso-occlusion, become manifest as a vasculopathy. This is the case with retinal involvement, acute auditory loss, cerebral infarction and arteriopathy, and pulmonary arterial hypertension.

7.1 Retinal involvement

SCD patients must have regular ophthalmologic examinations starting at the age of 12 to 15 (91). Even in the less severe SCD genotypes, there is a high risk of vascular retinopathy. Bad management of SCD eye complications may lead to loss of vision. Any acute change in visual perception must be immediately referred to an ophthalmologist. Central retinal artery occlusion is rare and must be treated like a stroke. The most prevalent vascular retinopathy is neovascularisation, which takes place predominantly in the peripheral retina at the limit of permanent vascular occlusion, leaving large ischaemic retinal surfaces (92). Goldberg and Coworkers (93) have defined a widely used stage classification for retinal proliferative vasculopathy.

- *Stage I*: is simple peripheral ischaemia with arteriolar occlusion.
- *Stage II*: is defined by remodelling of vessels at the border of the vascularised retinal area. Anastomoses without neocapillaries are the distinctive sign of this stage.
- *Stage III*: neovascularisation (“Sea fan” like neovessels) is detected. These neovessels grow towards the vitreoretinal interface. They are best detected by intravenous fluorescein angiography, after wide-field indirect ophthalmoscopy.

- *Stage IV*: vitreous haemorrhage has occurred. Although this stage may remain quiescent, in most cases the visual consequences are manifest. Vitreous haemorrhages may heal without sequelae but may produce retractile membranes possibly inducing retinal detachment, which is *Stage V*.

Prevalence and severity are predominant in the less anaemic patients, particularly those with SC and S β + thalassaemia. Although auto-infarction occurs during sea fan development, efficient prevention of vitreous haemorrhage and vision loss is highly recommended. Elimination of neovascular zones is best obtained by laser photocoagulation (94). When eye surgery is necessary (vitrectomy or retinal detachment surgery), preoperative exchange transfusion should be considered.

7.2 Acute auditory loss

Acute auditory loss as a result of vaso-occlusion occurs predominantly in the less anaemic adult SC patients. Treatment is entirely empirical, but some positive results have been obtained using phlebotomy to reduce Hb concentration to the 9-11 g/dl range (SC patients mainly) or exchange transfusion.

7.3 Cerebral vasculopathy

This is a major issue in the aims of management, for sickle cell practitioners. Brain lesions are much more prevalent in the young and most anaemic homozygous SCD patients although stroke may occur in some adults and in the less anaemic genotypes. Systematic screening for brain involvement is the only way to reduce deterioration of neurological and cognitive functions.

The clinical history and brain MRI yield a clear picture of the risk of this complication. Overt clinical strokes happen in 10 to 15% of homozygous patients under the age of 10. Around 35% of the same population has overt or silent brain infarcts (95).

Although in places where systematic cerebral vasculopathy screening is carried out the clinical aspects of the problem have changed considerably, careful attention to neurological manifestations is still required. The vascular manifestations in the brain are: cerebral infarction and transient ischaemic attacks (TIA); intracranial haemorrhage (IH) and cognitive function deterioration (96).

- Cerebral infarction is almost always clinically evident. TIA may be underdiagnosed because sensori-motor impairment may happen during painful VOC or ACS. Precipitating factors may be an episode of acute anaemia or sepsis, due for example to splenic sequestration, erythroblastopenia, DHTR or a malarial episode. In all cases non-contrast computed tomography (CT) must be done immediately to exclude intra-cranial haemorrhage. However, the CT may remain negative during the first 3 hours; MRI and new MR imaging procedures (DWI and FLAIR) are effective for early detection of brain infarction (97).

Imaging of ischaemic tissue must be completed by MR angiography (MRA) which will also identify carotid and large intracerebral artery stenosis. It allows detection of Moya-Moya, which is a late vascular manifestation of cerebral artery stenosis. MR imaging is the most effective means of following the short-term course of brain involvement and therapeutic efficacy. The basic treatment of brain infarction or ischaemia is hydration and preferably exchange transfusion aiming at less than 30% residual HbS-containing RBC. Depending on clinical presentation, intensive care may be appropriate. All factors that could contribute to brain ischaemia must be corrected (fever, hypoxia, metabolic disorders, etc.). Following the treatment of the acute phase, a transfusion program designed to maintain Hb between 8 and 10 g/dl and % HbS below 35% is followed for at least 4 months, which allows sufficient time for a complete evaluation and long-term therapeutic decisions. HU has been proposed as a possible alternative to blood transfusion (98). The main argument favouring introduction of a long term transfusion program is the presence of large vessel disease as shown by MRA, or abnormal large vessel blood velocity as shown by transcranial doppler ultrasonography (TCD).

Other therapeutic modalities such as glucocorticoids or antithrombotic agents should not be used in sickle cell cerebral vasculopathy.

- A major predictor of brain infarction risk is accelerated large cerebral vessel blood flow (99). Trans cranial Doppler (TCD) should be performed in all sickle cell patients at the age of 2 and 3 years. It enables identification of those children with a consistent TCD velocity (in at least one major arterial trunk) over 2 m/sec. The multicenter STOP I trial (100) showed that this group of children is at high risk of brain infarction and that chronic well scheduled blood transfusion can prevent cerebral infarction as long as it is continued (STOP II) (101). When TCD velocity is between 1.7 and 2.0, a reassessment must be done within 3 to 4 months and if stable, TCD should be performed every 6 months until the age of 8 or 10.
- Intracerebral haemorrhage may be rapidly lethal and is one important cause of sudden death in the adult (102). The predominant mechanism is rupture of a small aneurysm. Emergency CT will identify the haemorrhage and in all cases MR imaging to localize the origin of the bleeding is useful since bleeding may recur and endovascular remodeling can prevent or even cure the vasculopathy. However aneurysms are often multiple and not always accessible to endovascular cure. Most often, ruptured aneurysms result in subarachnoidal and, less often, in parenchymal or intraventricular haemorrhage (which is more frequently a complication of Moya-Moya).
- Silent brain infarcts are also commonly detected by MR imaging (103, 104). This seems to be a clinically important observation, since a clear correlation has been shown between brain infarcts and low cognitive functioning and bad school results

(104-106) and may be considered as a risk factor for open stroke in children (107). These findings justify systematic screening where possible.

7.4 Pulmonary vascular disease

Pulmonary vascular disease is an age-related complication which is frequent and has great prognostic significance.

- Chronic lung disease in adult SCD patients may be detected in at least one-third of them.
- Doppler ultrasonography of the tricuspid valve backward blood flow velocity is considered to reflect pulmonary hypertension (PHT). PHT has been identified as a late, often rapidly fatal complication of sickle cell disease. Its pathophysiology comprises a complex network of causative mechanisms and is reflected in different underlying haemodynamic defects. Approximately one third of homozygous sickle cell patients over 18 years, have a measurable tricuspid regurgitation velocity (TRV) over 2.5 m/sec, which defines PHT (in this population). Patients with an elevated TRV have a very increased risk of mortality in the subsequent three years (108, 109). Although primary PHT is not the only cause of elevated TRV in SCD patients, it is important to identify it specifically for appropriate treatment (110, 111).

8. Organ insufficiencies

Amongst the various organ dysfunctions that may be observed in SCD, renal, hepatic, and cardiac involvement predominate and require specific therapies.

8.1 Renal manifestations of SCD

Renal manifestations have long been documented (112) Patients with SCD and even AS carriers may have renal manifestations (113). The earliest and most common renal abnormality is the concentrating defect. This leads to irreversible hyposthenuria and consequent polyuria, which must be regularly compensated for by abundant water intake. Restriction of fluid intake induces dehydration, with rapid weight loss and a high risk of new VOC. Enuresis, although not due to polyuria itself, is magnified by this renal defect.

- SCD patients have varying degrees of abnormal tubular function involving acid excretion, uric acid elimination, and efficient potassium regulation. The most common type of SCD tubular disease is distal type IV tubulopathy. The monitoring of tubulopathy is important since acidosis may precipitate VOC, or hyperuricemia with gout, and hyperkalemia may complicate ACE inhibitors, β blockers or diuretic administration.

- Haematuria in SCD is not rare and mainly occurs in SC patients. It may also occur in heterozygotes and, in these cases, should be carefully investigated. Haematuria may be a symptom of renal lithiasis, tumour (114, 115) or infection but is more often due to papillary necrosis. Renal ultrasound and urographic contrast imaging are useful diagnostic tools. Depending on the severity and duration of haemorrhage, treatment consists of bed rest, hydration (in part alkaline), blood transfusion, and vasopressin or α -aminocaproic acid.
- Glomerular dysfunction can be the result of other coincidental acquired diseases. However, in most cases it is the direct consequence of SCD-related kidney vascular disease (116). Manifestations include:
 - proteinuria and microalbuminuria
 - a gradual fall in steady state Hb level, which seems to be linked to a relative erythropoietin hypoproduction (117) and which may respond to parenteral administration of rhEpo (118)
 - systemic hypertension, which must be fully controlled
 - hyperuricemia and attacks of gout.

Renal biopsy should be considered but the higher risk of adverse events in SCD patients must be kept in mind. ACE are almost always used to reduce proteinuria (119, 120). End stage renal insufficiency is associated with an increased mortality. Haemodialysis or other dialysis procedures can be safely used for years in SCD.

Renal transplantation is indicated when the general health state of the patient makes it feasible. However, the long-term results of kidney transplantation seem to be worse in SCD than in matched controls (121).

8.2 Chronic liver disease

The aetiology of liver disease in SCD patients is usually mixed. Hepatitis C (122) and transfusion-induced iron overload are common findings in SCD adults. Many African patients have chronic hepatitis B infection. Autoimmune hepatitis has been rarely described. Treatment of iron overload in multitransfused patients is difficult to manage but it is the only way to improve the prognosis of such patients (123).

- Parenchymal hepatic ischaemia and vaso-occlusion may take place as a silent process with chronic cholestasis, leading ultimately to cirrhosis.
- Repeated episodes of painful acute liver enlargement with very high bilirubin levels and severe cholestasis and hepatic dysfunction are seen in a minority of adult patients. Exchange transfusion effectively controls such acute episodes and may be used repeatedly to prevent recurrence. In such cases, prevention or treatment of secondary iron overload is essential. When hepatic failure occurs, liver transplantation may be warranted (124).

8.3 Chronic myocardial insufficiency

Cardiovascular adaptation to anaemia is a constant feature in SCD.

Chronic heart failure is almost absent in children and its incidence in adults is age-linked (125). The risk of acute heart failure due to fluid overload (comprising transfusion) must be stressed. At rest, the cardiac index remains elevated and may be extremely high during exercise which is often badly tolerated, and may precipitate VOC. Mild mitral valve insufficiency and limited pericardial effusion are common in SC adults. Patients must be screened for conduction blocks since they may be a cause of sudden death (126). Left ventricular failure must be regularly screened for by echocardiography. Even a mild elevation of arterial blood pressure, identified by comparison with steady state previous data, must be treated. Although proximal coronary artery disease is rare, it is thought that parenchymal ischaemia is the principal mechanism inducing chronic congestion failure.

Treatment of chronic heart failure comprises reduction of anaemia and amelioration of blood rheology. These goals can be achieved by HU therapy but when the result is unsatisfactory, a chronic scheduled blood transfusion program to keep Hb between 9 and 11 g/dl and % HbS under 40% may have long term efficacy.

In terminal cardiac failure, heart transplantation has been successfully performed.

9. Other common problems

Many current or pathologically associated conditions may interfere with SCD.

9.1 Reproductive aspects of sickle cell disease

This represents a special area which requires careful management.

- Genital development is almost normal in good environmental conditions. However, delayed puberty and staturο-ponderal insufficiency is common when anaemia is severe and if the patient has had inadequate nutrition.
- Transient oligospermia after severe hyperthermia or VOC is commonly observed and transient secondary amenorrhoea may occur for similar reasons. Males who become impotent after PP may have reproductive difficulties, and patients with severe iron overload may develop hypogonadism. HU therapy is often associated with defective spermatogenesis.
- Contraception is an important issue in health education since pregnancy and/or abortion may worsen the clinical course of the disease. At the same time, genetic counselling is also necessary. Oral contraceptives are widely used and do not appear to produce more side effects than in the general population (127). Conversely, the use of intrauterine devices may be complicated by excessive bleeding and genital tract.

- Voluntary interruption of pregnancy before 12 weeks is very frequent in young adults. The method of choice is intrauterine aspiration under analgesia or sometimes anaesthesia. Other newer methods (RU, etc.) must be used with caution because they seem to increase VOC risk.
- Pregnancy, more than many other specific complications, needs management by a multidisciplinary team. There must be permanent and close collaboration between the maternity and sickle cell units. Incidence of maternal mortality remains around 10% despite adequate follow-up. A large population of pregnancies results in preterm birth and small for gestational age babies. Infant mortality remains high, in the 5 to 10% range (128). The major complication is gravid hypertension. Systemic hypertension is a well known aggravating factor in SCD. It happens in 10 to 20% of pregnancies and is the main source of foetal morbidity. Pregnant women will be screened every 2 weeks during the last 5 months for pre-eclampsia, gestational diabetes, proteinuria, pathologic oedema with rapid weight gain, early signs of urinary tract infection and worsening anaemia or poor tolerance of anaemia. Elevation of LDH is a clear and simple prognostic indicator. Transfusion is very often required during pregnancy but it is unclear whether a preventive scheduled transfusion program would be beneficial. However, pregnancies may be classified as higher risk if VOC frequency is high and if a previous pregnancy loss or pre-eclampsia has been observed. The objectives of prophylactic transfusion are to avoid VOC and severe anaemia and to optimise placenta blood perfusion. At the time of labour and delivery, Hb level should be in the 9 to 11 g/dl range with less than 40% HbS. Anecdotal reports on HU and erythropoietin use during pregnancy have been published, showing no major side effects (129). Breast feeding is not contra-indicated.

10. Major preventive and curative treatments

10.1 Hydroxyurea (HU)

HU is the only drug which has demonstrated efficacy in terms of reduced incidence of VOC and ACS, reduced need for hospitalisation and reduced number of blood transfusions in adults (130, 131) and children (132, 133).

HU has been shown to reduce mortality in a group of otherwise severely affected patients after 5 to 10 years follow-up (134). However HU has not demonstrated any clear beneficial effect on the risk of stroke (99), priapism, and progression of liver, renal, pulmonary or cardiac insufficiencies.

Side effects of HU (135, 136) include myelotoxicity, cutaneo-phanerian dystrophy and possibly development or recurrence of leg ulcers (137), and oligospermia. Long-

term cytotoxicity is theoretically a matter of concern considering the large number of SCD patients receiving HU for years. There are some anecdotal reports on possible secondary malignancies (138), although no foetal toxicity has been reported in women taking HU during pregnancy (129). Contraception in male and female patients receiving HU is required.

Monitoring of HU treatment needs the establishment of pre-treatment basal clinical and biological evaluations, particularly Hb, MCV, leucocytes, platelets, % HbF, bilirubin, LDH, and creatinine. Compliance can be assessed by MCV provided there is no iron deficiency. Doses of 15 to 35 mg/kg/d (single oral dose) are commonly used.

HU has a wide range of biological effects (113, 139, 140) on red cells and particularly on reticulocytes, haemoglobin, endothelium, leucocytes and platelets. However, the long-term clinical effects on sickling are related to the rise in % HbF.

10.2 Bone marrow transplantation

Bone marrow transplantation (BMT) (141-144). BMT has been performed in a limited number of severely affected young sickle cell patients or those with early predictive signs of severity (Table 15). BMT candidates must have an HLA-identical sibling donor. Conditioning regimens have evolved since the first treated case. Myeloablative procedures with antithymocyte globulin are now generally used. Post transplantation immunosuppression is most often obtained by long-term cyclosporine and methotrexate administration.

Disease-free survival is obtained in 80-90% of cases. Mortality, mainly from complications associated with GVHD, occurs in 5 to 10%. BMT has been performed in very few SC adults.

Table 15: Eligibility criteria for BMT in paediatric sickle cell patients

1. Age: below 16 years of age	3. Available HLA identical sibling donor
2. At least one of the following complications: <ul style="list-style-type: none"> • Brain infarction or ischemia evidenced by MR imaging • Secondary cognitive impairment with cerebral vasculopathy • Severe and recurrent ACS. Chronic low score lung disease • ≥ 3 VOC requiring hospitalisation and analgesia • Moderate glomerular dysfunction • Multiple epiphyseal aseptic osteonecroses 	4. To have received extensive explanations on the benefit/risk aspects of BMT

Other approaches such as non-myeloablative BMT (145) and cord blood stem cell transplantation (146, 147), which may reduce the incidence of GVHD, have opened interesting new avenues of curative therapy. The long-term toxicity of BMT should be carefully explained to the patient before transplantation and monitored regularly throughout the patient's lifetime (148).

11. Conclusions

The clinical profile of sickle cell disease has considerably changed in the last 25 years. Reduction in mortality during childhood allows more than 90% of SC patients to reach adult life in variable, but often good, clinical condition. Numerous new insights into the pathophysiology of SCD at the clinical, cellular and molecular levels have led to more rational therapeutic approaches. However, there are many questions, both old and new, which still need to be answered, and much clinical research is needed to obtain a satisfactory quality of life for SC patients.

From a practical point of view, a comprehensive system of care, in which the patient has full access to psychosocial facilities and multidisciplinary clinical advice, remains the most efficient therapeutic setting.

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