CHAPTER 13

Sickle cell disease

13.2

A short guide to management

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1. Introduction

Due to migrations of populations from countries with a high frequency of the mutated gene, a patient with sickle cell disease (SCD) may present to almost any doctor. All physicians must have a basic knowledge about the disease, and know how to get expert advice. Most importantly, all patients must be enrolled in comprehensive care programs acting as "expert resources".

Disease management must take into account the familial and genetic dimensions of the disease (Table 1) (1-3).

Table 1: **General health maintenance plan**

1. Environmental
- Altitude: less than 1500 m
- Avoid body cold exposure
- Avoid hot weather exposure

2. Way of life
- Regular hydration
- Avoidance of alcoholic beverages
- Avoidance of active (or passive) tobacco use
- No cannabis or other illegal drugs
- Avoidance of strenuous exercise
- Adoption of a quiet way of life

3. Nutrition
- Folic acid supplementation 5 mg/d, 10 d/month
- Zinc 10 mg/d (1 to 2 month/y) until puberty

4. Education
- Health education for the patient and relatives
- Information on symptoms requiring medical advice
- Genetic counselling
- Appropriate use of analgesia at home

5. Psycho-social management
- Implementation of care pathways
- Easy access to social workers
- Open access to psychologist
- Avoidance of stress

6. Occupational orientation
- Avoid physically tiring jobs
- Avoid occupations with cold exposure

2. General management

2.1 Health education

It must begin as soon as diagnosis is made, preferably in babies screened in the neonatal period. It 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 (4, 5).

Investigations for early detection of complications should be carried out at regular intervals (4). Table 2 gives an example of a schedule for investigations that should be performed during the lifetime of an individual with SCD (6). 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.

Table 2: **Periodic health investigations**

Tests	Before 3 years	3 to 15 years	>15 years
Haematology	Every 6 months	Once a year	Once a year
HbF %	"	Only for supervision of HbF stimulating agent therapy	Only for supervision of HbF stimulating agent therapy
Renal, hepatic functions	Once a year	Once a year	Once a year
Blood pressure	ATCM	ATCM	At least once a year
Pulmonary function Bone aseptic necrosis Auditory exam	ATCM	ATCM	ATCM
Retinal examination	ATCM	Once a year SS : after10yrs SC : after 6 yrs	Once a year ++ for SC
Transcranial Doppler velocity	12-18 months Once a year	Once a year	ATCM
Brain MRI	ATCM	One before 15 yrs	ATCM
Tricuspid regurgitation jet velocity	ATCM	ATCM	Once a year
Gall bladder ultrasonography	ATCM	Once a year	Every yr or ATCM

ATCM = according to clinical manifestations

2.2 Prevention of infection

A major goal in SCD clinical management is the prevention of severe bacterial infection, which, otherwise, may often be lethal (Table 3) (7-10). This can be achieved by a relatively simple combination of twice daily administration of oral penicillin and an adapted immunisation programme (11-17). Neonatal screening allows early implementation of penicillin therapy. With a few exceptions, penicillin prophylaxis is not proven useful after the age of 5 (4). The recommended immunisation schedule for previously unvaccinated children with SCD consists of 3 doses of conjugated vaccine 6 to 8 weeks apart followed by a booster dose 1 year later then by a polysaccharide vaccine after 2 years of age, with additional doses every 3 to

Table 3: **Infectious risk management**

1. Penicillin V orally from 2 months to at least 5 years of age • 100,000 UI/kg/d up to 10 kg BW • 50,000 UI/kg/d from 10 to 40 kg BW	**4. Immunisation** • Streptococcus pneumoniae • Haemophilus influenzae • Meningococcus • Influenzae • Salmonella typhi (for at risk individuals)
2. Prompt administration of antibiotics in case of possible pneumococcal infection	**5. Malarial prophylaxis when appropriate**
3. Elimination of recurrent focal infection (dental infection, sinusitis, acute recurrent tonsillitis, cholecystitis, urinary infections)	

5 years. Experts agree that regular immunisation with the 23-valent vaccine is appropriate in adults, but large well-conducted studies are needed to determine the optimal schedule for polysaccharide and conjugate vaccine administration.

This therapeutic approach has been very effective in reducing infant mortality so long as there is compliance on the part of the parents. In areas where malaria is endemic, malaria prophylaxis or very early treatment is mandatory until at least 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.

2.3 Prevention of cerebro-vascular accidents

Children at high risk for stroke can be identified using transcranial Doppler ultrasonography (TCD). Children with a cerebral blood flow rate of 200 cm per second or more have a 40% risk of stroke within 3 years (18). A randomised trial (STOP 1) compared regular blood transfusions to standard care in 130 children with abnormal TCD results. Stroke incidence was reduced by 92% in the transfused group (19). A subsequent randomised trial (STOP 2) was conducted in children transfused for a high stroke risk for 30 months or longer and having normalised under transfusion their TCD examination. The transfusions were continued in one arm and stopped in the other. Stopping the transfusions was followed by a high rate of stroke or reversion to abnormal cerebral blood-flow velocities (20). These well-designed

studies led to the recommendation that TCD be performed annually from 2 to 16 years of age in children with SCD and that regular blood transfusions be given to those with abnormal TCD findings (4).

3. Anaemia and principles of transfusion

3.1 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 4) is common and may have an immediate prognostic impact (21, 22). 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.

Table 4: **Causes of worsening anaemia in SCD**

1. Sudden symptomatic anaemia	2. Chronically more severe anaemia
• 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	• Severe chronic inflammation • Cobalamin deficiency and/or hypothyroidism • Renal insufficiency (early sign) • Chronic hypersplenism

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 (23).

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 4).

3.2 Transfusion

Transfusion remains a powerful tool for treating acute, potentially lethal, anaemia and severe vaso-occlusive complications (VOC) (24-26). 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), to reduce the rheological and anaemic consequences of sickle RBCs on a chronic or acute organ failure, or to prepare a patient to anaesthesia and surgery (27, 28). It can also be done during the last trimester of pregnancy to prevent maternal complications and in particular to reduce foetal mortality (29).

3.2.1 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 5) (24-26).

Immunologic reactions

Transfusions may be complicated by immunologic reactions: allo-immunisation

Table 5: **Clinical indications for transfusion**

1. **Simple or small volume exchange transfusion**
   - ACS and any organ failure
   - Splenic or hepatic sequestration
   - Sepsis or malaria
   - Refractory painful VOC
   - Acute symptomatic anaemia
   - Pre-operative preparation
2. **Large volume exchange transfusion**
   - Stroke
   - Recent complete auditory loss
   - Central retinal artery thrombosis
   - Preparation for major surgery (thoracic, cardiac, ocular, using tourniquet, etc.)
   - Acute refractory priapism
3. **Chronic transfusion programme**
   - 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 anaemia unresponsive to HU or erythropoietin

and haemolytic reactions which often occur as a delayed haemolytic transfusion reaction (DHTR).
In countries where donors and recipients are ethnically different, there is an elevated risk of allo-immunisation (30-33). Its frequency can be reduced by using blood products fully compatible with the recipient ABO, Rh and Kell phenotypes (Table 6). Some countries try to encourage blood donation from relevant ethnic groups. For a small subgroup of patients allo-immunisation is so complex that no compatible donors can be found, even within the family (30, 31).

Table 6: **Blood product selection**

- Leukocytes and plasma depleted packed RBC
- Routine use of blood units phenotyped for ABO, Rh-Dce and Kell antigens
- Extended patient blood group phenotyping after alloimmunisation
- Systematic compatibility testing between sera and transfused RBC
- Negative for HbS to keep the ability of monitoring transfusion efficacy
- Irradiated blood when indicated
- Banking of cryopreserved RBC for patients with very rare phenotypes

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 (34, 35).
DHTR manifestations occur a few days after the last transfusion, are often severe and include profound anaemia, haemolysis, acute chest syndrome (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.

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 (36).

Iron chelation therapy is an efficient means of reducing direct and indirect iron induced mortality. Subcutaneous 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. Two oral chelators, the deferiprone and the deferasirox, are now available. Deferiprone is for the moment not licensed in patients with sickle cell anaemia. However it 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, deferasirox (Exjade®), is now available. It is effective at a single daily dose of 20 to 30 mg/kg. Elevation in liver function tests and a mild non-progressive increase in serum creatinine have been observed in some patients (37). Mechanisms responsible for the elevation of creatinine are, so far, not known, and treatment by deferasirox prompts a monthly checking of renal and hepatic functions.

4. Acute painful episodes

Painful episodes are the hallmark of SCD (38-41).

4.1 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 unrecognised 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 non steroidal anti-inflammatory drugs (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 analogue 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 acute chest syndrome (ACS), infection, or neurological involvement, must be monitored every 4 hours. Pain and sedation scores should be recorded systematically and treatment adjusted accordingly (42). 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 7.

Table 7: **Useful clinical and biological parameters for monitoring painful VOC**

Physical examination for:	Biological evaluation
• Pain assessment • Early signs of ACS • Cardiovascular manifestations (systolic pressure, etc.) • Body weight loss • Neurological manifestations • Abdominal evaluation • Urinary problems: proteinuria, infection, or haematuria	• Pulse oximetry and/or arterial blood gas • Complete blood count with reticulocytes • Inflammation markers • Haemolysis markers: LDH^{+++} • Chest X ray • Abdominal ultrasonography • Bacteriological sampling when necessary

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 (43). Each painful episode should be analysed retrospectively with the patient in an attempt to determine the circumstances which may have caused the VOC (Table 8) 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 hydroxyurea (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.

4.2 Acute chest syndrome

ACS (44, 45) is defined as an acute event with pneumonia-like symptoms associated with a new infiltrate 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 in adults (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

Table 8: **Circumstances that may provoke VOC**

1. Exposure to:	**3. Vascular**
• Cold • Altitude (mountains or unpressurised planes) • Alcohol, tobacco smoking and other drug uses • Excessive physical exercise	• Prolonged involuntary arterial compression • Systemic hypertension • Exposure to adrenergic agents • Dehydration
2. Respiratory diseases	**4. Miscellaneous**
• Asthma • Obstructive tonsillitis • Obstructive allergic rhinitis • Sleep apnea syndrome • Thoracic trauma	• Glucocorticoid administration • Emotional event • Stressful period of life • Excessive work load • Acute infection • Abdominal surgery

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 (46).

Systemic passage of fat emboli is a further cause of deterioration in patients with ACS (47). 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-cruoric pulmonary embolism also contribute to the heterogeneous pathophysiology of ACS.

4.2.1 Treatment of ACS

Treatment of ACS comprises:

- Intravenous broad spectrum antibiotic administration including a macrolide, in combination with a quinolone in adults, and a third generation cephalosporin in children.
- 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 O_2 saturation (blood gases) is between 91 and 96%, incentive spirometry may help to prevent further ventilation defects (48). In severely hypoxaemic 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 (49).

- 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 (50). Exchange transfusions should lead to at least 50% HbA (% of normal RBC) after completion. Table 9 gives criteria for exchange transfusions during ACS.

Respiratory physiotherapy must be continued outside the hospital for 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 (51-53). A few limited, open trials have suggested a possible therapeutic benefit for inhaled NO (54-56).

Table 9: **Indication for exchange transfusions in ACS**

- Any early biological sign of organ failure
- Any neurological defect (confusion – motor defects – epilepsy)
- Worsening respiratory failure
- Intractable pain or opioid intolerance
- Haemodynamic instability
- Nosocomial infection
- Acute worsening of anaemia or cardiovascular insufficiency
- Acute enlargement of the spleen or liver

4.3 Priapism

Priapism is a very common acute event in SCD (57).

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 (SP). 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 favoured 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 can 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 (58). Anti-androgens or stilbestrol have been used in small series

and found to be effective in prevention (59). Transfusion programmes may be used for patients in whom previous therapeutic approaches were unsuccessful (60). Penile prosthesis implantation for impotence is a difficult task and is not always effective.

4.4 Acute abdominal pain

Acute abdominal pain occurs most frequently in young patients under the age of 10. Constipation is the most frequent cause of abdominal pain in children and may be responsible for acute painful episodes. Two severe causes of abdominal pain are splenic (or hepatic) sequestration and gall bladder or biliary tract problems. Saturnism related abdominal pain (due to lead-poisoning) is very rare, as is mesenteric ischaemia.

- 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 hypovolaemia and anaemia by parenteral fluid perfusion and small volume simple transfusion (61, 62). ASS has been estimated to occur in 10 to 30% children before the age of 6 and, as it has a high recurrence rate. Management of recurrent ASS is debated. According to authors, splenectomy is recommended either after the second episode whatever the age, or after the age of 5 years, children being in the meanwhile submitted to monthly transfusion.
- 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 (63) and biliary sludge (64) 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 bacteraemia 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 (65, 66).
- 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.

5. 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.

5.1 Bone and joint complications

Bone involvement in SCD may result from three mechanisms: osteopenia due to bone marrow expansion, bone infarction, and osteomyelitis (67).

- 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 magnetic resonance imaging (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 may sometimes permit distinction. Symptomatic stages are often preceded by a pre-collapse period of undefined length but detectable by MRI (68). 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 (69). 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 (70, 71).
- 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 (72). 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 bacteraemia. 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* (73). 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 remodelling in SCD.

5.2 Leg ulcers (LU)

Ulcers are more likely associated with a haemolytic phenotype (low Hb and elevated LDH levels) and with high rates of pulmonary hypertension, priapism, and renal dysfunction. They are rare during childhood (74-76). 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.

6. 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.

6.1 Retinal involvement

SCD patients must have regular ophthalmologic examinations starting at the age of 10 years (6, 77). 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 (78). Goldberg and co-workers (79) 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 (80). When eye surgery is necessary (vitrectomy or retinal detachment surgery), preoperative exchange transfusion should be considered.

6.2 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.

6.3 Cerebral vasculopathy

This is a major issue in 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 (see 2.3 Prevention of cerebro-vascular accidents).

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 (81). 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 (82).

- 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 MRI procedures (DWI and FLAIR) are effective for early detection of brain infarction (83).

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.). More than half the patients with a first stroke experience a recurrence. Long-term observational studies showed that monthly blood transfusions decreased the risk of recurrent stroke, although transient neurological events were not completely abolished (84). The target HbS percentage in patients on regular blood-transfusion regimens varied across studies from 30% to 50%, and the optimal target remains to be determined. Stroke is considered an indication for bone marrow transplantation in children and adolescents who have HLA-identical siblings (4). The optimal duration of chronic transfusion in adults having experienced a stroke is still debated.

HU has been proposed as a possible alternative to blood transfusion (85). 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.

- Intracerebral haemorrhage may be rapidly lethal and is one important cause of sudden death in the adult (86). The predominant mechanism is rupture of a small aneurysm. Emergency CT will identify the haemorrhage and in all cases MR imaging to localise the origin of the bleeding is useful since bleeding may recur and endovascular remodelling 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 subarachnoid 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 (87, 88). 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 (88-90) and may be considered as a risk factor for open stroke in children (91). These findings justify systematic screening where possible.

6.4 Pulmonary vascular disease

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

- Chronic lung disease may be detected in at least one-third of adult SCD patients.
- 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 (92-94). Although primary PHT is not the only cause of elevated TRV in SCD patients, it is important to identify it specifically for appropriate treatment (95, 96).

7. Organ insufficiencies

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

7.1 Renal manifestations

Renal manifestations have long been documented (97) Patients with SCD and even AS carriers may have renal manifestations (98). 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 hyperuricaemia with gout, and hyperkalaemia 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 (99, 100) 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 ε-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 (101, 102). Manifestations include:
  - proteinuria and microalbuminuria
  - a gradual fall in steady state Hb level, which seems to be linked to a relative underproduction of erythropoietin (103) and which may respond to parenteral administration of rhEpo (104, 105)
  - systemic hypertension, which must be fully controlled
  - hyperuricaemia 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 (106, 107). 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 (108).

7.2 Chronic liver disease

The aetiology of liver disease in SCD patients is usually mixed. Hepatitis C (109) 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 (110).

- 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 (111).

7.3 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 (112). 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 (113). 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.

8. Other common problems

Many current or pathologically associated conditions may interfere with SCD.

8.1 Reproductive aspects of SCD

This represents a special area which requires careful management.

- Genital development is almost normal in good environmental conditions. However, delayed puberty and staturo-ponderal (height and weight) insufficiency is common

when anaemia is severe and if the patient has had inadequate nutrition (114).

- 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 (115).
- 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 (116). 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 486 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 pre-term birth and small for gestational age babies. Infant mortality remains high, in the 5 to 10% range (117). 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 should be screened every 2 weeks during the last 5 months of pregnancy 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 is 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 rang with less than 40% HbS. Anecdotal reports on HU and erythropoietin use during pregnancy have been published, showing no major side effects (118), but HU treatment is contra-indicated during pregnancy. Breast feeding is not contra-indicated.

9. Major preventive and curative treatments

9.1 Hydroxyurea

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 (119, 120) and children (121, 122).

HU has been shown to reduce mortality in a group of otherwise severely affected patients after 5 to 10 years follow-up (123). However, HU has not demonstrated any clear beneficial effect on the risk of stroke (119), priapism, and progression of liver, renal, pulmonary or cardiac insufficiencies.

Side effects of HU include myelotoxicity, cutaneo-phanerian (nails, hair, etc.) dystrophy and possibly development or recurrence of leg ulcers and oligospermia (115, 124-128). 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 (129), although no foetal toxicity has been reported in women taking HU during pregnancy (118). Contraception in 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 (130-134) on red cells and particularly on reticulocytes, Hb, endothelium, leucocytes and platelets. However, the long-term clinical effects on sickling are related to the rise in %HbF.

9.2 Haematopoietic stem cell transplantation (HSCT)

HSCT (135-137) has been performed in a limited number of severely affected young sickle cell patients or those with early predictive signs of severity (Table 10). Candidates for HSCT 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%. HSCT has been performed in very few SC adults.

Other approaches such as non-myeloablative HSCT (138) and cord blood stem cell transplantation (139, 140), which may reduce the incidence of GvHD, have opened

Table 10: **Eligibility criteria for haematopoietic stem cell transplantation**

1. Age limit: below the age of 20 (?) Debatable	**3. Available HLA identical sibling donor**
2. At least one of the following complications: • Brain infarction or ischaemia 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. Fully informed about the benefit/risk aspects of BMT**

interesting new avenues of curative therapy. The long-term toxicity of HSCT should be carefully explained to the patient before transplantation and monitored regularly throughout the patient's lifetime (141, 142).

10. 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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Multiple Choice Questionnaire

To find the correct answer, go to http://www.esh.org/iron-handbook2009answers.htm

1. The first transcranial Doppler velocity measurement should be done at the age of:

a) Before 6 months ☐
b) After 5 years ☐
c) Between 18 and 24 months ☐
d) Depending on clinical examination ☐

2. The main indication for hydroxyurea therapy in an adult male is:

a) Priapism ☐
b) Leg ulcer ☐
c) More than 3 severe painful vaso occlusive crisis/year or more than one acute chest syndrome/year ☐
d) Proteinuria from sickle related glomerulopathy ☐

3. Pulmonary hypertension (systolic) should be accessed regularly in patients of 6 years old or more:

a) Using standard thoracic X-ray imaging ☐

b) Measuring right heart blood pressure by catheterisation ☐
c) Measuring tricuspid regurgitation jet velocity every year ☐
d) Using pulmonary perfusion radionuclide imaging ☐

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4. Specific infection risk management requires:

a) Life long daily penicillin V administration ☐
b) No need for malarial prophylaxis ☐
c) Regular immunisation against *Streptococcus pneumoniae* ☐
d) Systematic administration of antibiotics when a vaso-occlusive crisis occurs in the adult ☐

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5. Which adverse affect of hydroxyurea therapy is uncommon?

a) Cutaneo-phanerian dystrophies ☐
b) Disturbed spermatogenesis ☐
c) Increase recurrence of leg ulcers ☐
d) Hepatic cytoxicity ☐

NOTES