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European Network for Rare and Congenital Anaemias

ENERCA

WP4

SICKLE CELL DISORDERS

HAEMOGLOBINOPATHIES

RECOMMENDATIONS

2009 - 2012

CONTENT

D21 - GENERAL RECOMMENDATIONS ABOUT ANTENATAL SCREENING, PRENATAL DIAGNOSIS AND GENETIC COUNSELLING OF HAEMOGLOBINOPATHIES - 2012

Objective: recommendations for preconceptional or antenatal screening, prenatal diagnosis and genetic counselling of haemoglobinopathies.

Target population to be aware of: medical staff expert and non-experts in the field

On behalf of Enerca **http://www.enerca.org**

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I. Introduction

The inherited disorders of globin chain synthesis comprise a large group of monogenic disorders that include thalassaemia (reduction of α or β globin chain synthesis), sickle cell disease (resulting from a structural modification of β globin) and other haemoglobinopathies (can involve complex interactions between several different mutant genes). Management of thalassaemic patients is lifelong, complex and expensive, while poorly managed cases have a limited survival.

Haemoglobinopathies, a significant worldwide public health problem, are the most frequent group of monogenic disorders in Southern Europe and especially in the Mediterranean area. Nevertheless, the increasing immigration to Northern and Central Europe has resulted in a significant rise in the prevalence of haemoglobinopathies also in the rest of Europe with sickle cell disease being more frequent in the North while β-thalassaemia is more frequent in the South (Modell B, et al. 2007, 2007; Roberts I, de Montalembert M. 2007).

The laboratory antenatal screening and prenatal diagnosis of haemoglobinopathies is of growing importance and has to include different procedures:

- For definitive diagnosis i.e. to confirm a presumptive diagnosis of a minor or a major haemoglobinopathy, to predict serious disorders of globin chain synthesis, and o identify foetuses at risk of a significant haemoglobinopathy;
- To offer genetic counselling and reproductive choice if both parents are at risk of conceiving a child with a major haemoglobinopathy.

These guidelines review the most important aspects of carrier detection procedures, population screening, genetic counselling and prenatal diagnosis of haemoglobinopathies.

The **responsible** health professionals who should adopt the proposed guidelines and direct people from at-risk groups for screening to specified units or Centres are mainly family doctors and obstetricians, especially obstetricians, who are responsible for guiding couples at-risk to a team experienced in genetic counselling and prenatal diagnosis.

Role of the family doctor or obstetricians:

- To request identification of a pregnant woman (or ideally a woman who is not yet pregnant) as a carrier of a haemoglobinopathy;
- To request testing of her partner;
- If there is a risk of a major haemoglobinopathy in a foetus, either offering genetic counselling (if trained adequately) or send to a genetic counsellor.

Screening programmes have already been applied for β thalassaemia and sickle cell disease carrier identification, in a number of at-risk populations (e.g. Greek and Turkish Cypriots, Greeks, Continental Italians and Sardinians), (Angastiniotis M, Hadjiminas M, 1981; Cao A, et al. 2001; Loukopoulos D. 1996, 1998); they should be regarded as models for determining recommendations for prenatal diagnosis.

In these programmes the main strategies used were:

- Public awareness
- Carrier screening
- Prenatal diagnosis programme
    - Genetic counselling
    - Prenatal diagnosis
- Evaluation of the prevention programme

A prerequisite for such a programme to be effective is a national plan with central coordination, budgetary allocation, control of quality and ethical issues and also monitoring and evaluation. This requires recognition of the programme by health authorities through epidemiological information.

II. Public awareness

Selection of the appropriate population awareness approach must take into account local socio-economic parameters and additional factors which may influence the acceptance of the prospective parents towards carrier identification. These include the influence of various religious and political views and the national legal framework as well as the availability of prenatal diagnosis.

Such an approach should include information, sensitization and education of the involved population group who must understand what the consequences of the haemoglobin disorders are.

III. Carrier screening

1. The target population

The **target group** for screening may include: newborns, adolescents, premarital couples, preconception or antenatal. Preconception and especially premarital screening is most widely applied in those populations at highest risk. In other countries of northern Europe, an important target group is comprised of pregnant women whose ancestry is from high risk areas, during their first visit to the ante-natal clinic. Identification of the couple should ideally be premarital in order to offer the greatest number of choices or at least it must be completed before 11-12 weeks of pregnancy to be able to offer prenatal diagnosis. However, even women presenting for the first time late in pregnancy should be offered testing because the results will be relevant both to this and future pregnancies and they will benefit from a genetic counselling.

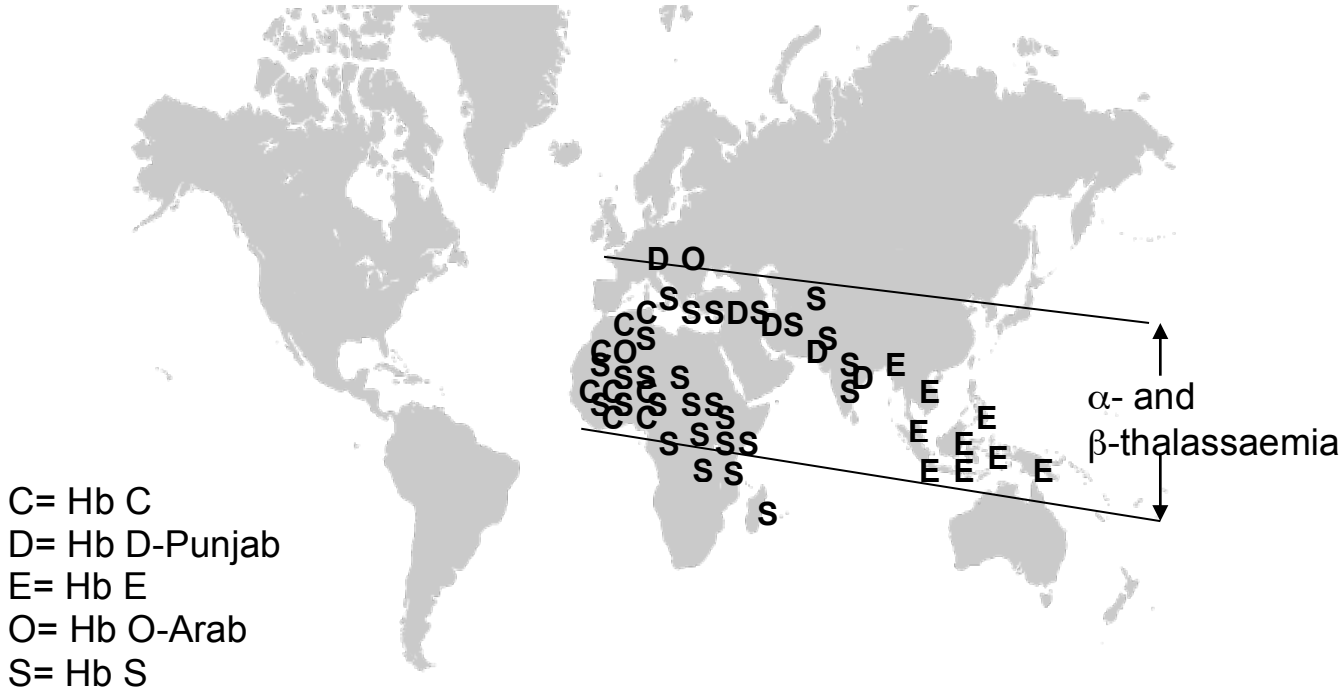


Figure 1. Schematic representation of the geographic origin of several haemaglobinopathies.

Carrier screening is most often offered as universal in southern European countries where the prevalence of the haemoglobinopathies is high i.e. Greece (9%), Cyprus (15%), and South of Italy (5%) (Angastiniotis et al., 1995). This is not the case in western and northern European countries with a low prevalence of these disorders. In these countries, the carrier screening should be selective as the design of a prevention program should take into account the mixture with the indigenous population not affected or uncommonly affected and immigrants from different regions at high risk of a haemoglobinopathy. Moreover, the variety of disorders to screen is high and complex due to the wide range of mutations, depending on the country of origin. In some locations where the density of immigrant groups is high a policy of universal screening is adopted (Streetly A. 2000 and NHS Sickle Cell and Thalassaemia screening Handbook for Laboratories 2009). For all the above mentioned reasons extensive education of scientific personnel involved, is required.

2. Laboratory techniques

A full blood count, a separation of the haemoglobin fractions and quantification of Hb A_2 and

Hb F are the key parameters in screening for haemoglobinopathies. The possibility of iron deficiency should be taken into account (Ryan K. et al.2010).

More precisely, carrier detection is carried out by:

a) <u>Phenotypic Tests</u>

- **Routine haematological tests**

  Measurement of total Hb, RBC count, mean cell volume (MCV), mean corpuscular haemoglobin (MCH) and red cell distribution width (RDW). Generally accepted cut-off values for adult patients indicating possible heterozygosity for thalassaemia include MCV < 80 fL and MCH < 27 pg (values depend on the analysis method). Sensitivity of the analyser to samples older than 24 hours should be evaluated. (Please specify time and preservation limit for the sample for reliable measurement).

- **Separation and quantification of the haemoglobin fractions:**

  can be performed using different techniques.

  Commercially available techniques for haemoglobin pattern analysis

  - High Performance Liquid Chromatography;
  - Haemoglobin electrophoresis at pH 8.6 using cellulose acetate membrane or by capillary electrophoresis;
  - Haemoglobin electrophoresis at pH 6.0 using citrate agar gel, acid agarose or by capillary electrophoresis;
  - Isoelectric focusing;
  - In case of suspicion of haemoglobin S, the solubility test could be used as a second line method in order to obtain a reliable diagnosis of the presence of Hb S.

<u>Recommendations</u>

- The technique or the combination of techniques used should allow the detection of the more common clinically significant haemoglobin variant;
- When a haemoglobin variant is detected (abnormal fraction), at least a second technique based on a different principle of separation and dedicated to haemoglobinopathies should be used to give a presumptive diagnosis;
- In case of high levels of foetal haemoglobin detection, evaluation of the sensitivity as well as the separation capability of the technique used to detect an abnormal haemoglobin fraction is required;
- The use of a fresh blood sample is required for the detection of a haemoglobin H;
- An external quality control must be performed.

Commercially available and recommended techniques for quantification of the haemoglobin fractions

- High Performance Liquid Chromatography (HPLC)
- Capillary electrophoresis
- Microcolumn chromatography for quantisation of Hb A_2 (BJH 1998 101 783-792)
- Alkali denaturation for quantification of Hb F

Recommendations

- Hb A_2 and Hb F analysis by electrophoresis using cellulose acetate membranes or agarose gels is appropriate only for qualitative results. Quantitative evaluation by automatic densitometry of these results is inappropriate. Currently most laboratories use HPLC or automated Capillary Electrophoresis and these are the recommended methods for identifying carriers;

- An external quality control must be performed.

➢ **Interpretation of results**

There is no international standardisation for quantification of Hb A_2. The cut-off value indicating suspicion of a β thalassaemia trait is method dependent. Borderline values (close to the upper limit of the reference values) should be interpreted together with the red blood cell indices results and may require further investigation with other techniques such as family studies or molecular studies.

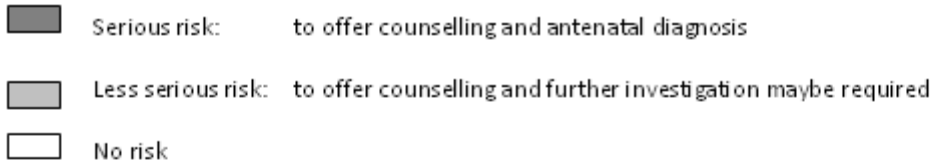
- In the presence of HbS, derivative products of HbS co-elute with Hb A2. In this case, the screening for β thalassaemia is based on the % ratio between HbA and HbS. A compound heterozygosity for haemoglobin S and beta thalassaemia may be suspected if the ratio HbS %/HbA% > 1.0.
- Cut-off value indicating heterozygosity for δβ-thalassaemia is Hb F >5 %.
- Pitfalls in diagnosis include the co-inheritance of alpha thalasaemia with beta thalassaemia and the co-inheritance of delta thalassaemia with beta thalassaemia trait. Most common is the presence of iron deficiency which may modify the picture of thalassaemia traits and must be excluded especially if screening in pregnancy. The presence of iron deficiency does not rule out the possibility of an underlying thalassaemia trait.

Table 1. Recommendations for preconception or antenatal screening for haemoglobinopathies

SCREENING (At distance of a blood transfusion)	
All women	- Full blood count - Ferritin
Women with one of these risk factors - MCH < 27 pg without iron deficiency - Clinical signs of a haemoglobinopathy - High risk ancestry (Mediterranean Basin, Middle-East, Asia, Africa) - Partner of high risk ancestry	- Complete blood count - Ferritin - Separation of the haemoglobin fractions, HbA_2 and HbF
PARTNER TESTING	
If maternal screening is positive, **test the partner**	- Full blood count - Ferritin - Separation of the haemoglobin fractions, HbA_2 and HbF
COUPLE AT RISK	
If both partners are at-risk and if not already performed (figure 2)	– Genetic counselling – Molecular diagnosis: identification of the mutation involved *

* Not always mandatory for a haemoglobin variant

Figure 2. Antenatal screening: combinations that give rise to the risk of a foetus affected by a severe haemoglobinopathy *(adapted from the work of Prof. B. Modell and published by the UK National Screening Committee)*



		Mother										
	Carrier of:	Hb S	β-thalassaemia	δβ-thalassaemia	Hb Lepore	Hb E	Hb O_{Arab}	Hb C	Hb D_{Punjab}	HPFH*	α^{o}-thalassaemia	α^{+}-thalassaemia
Father	Hb S											
	β- thalassaemia											
	δβ- thalassaemia											
	Hb Lepore											
	Hb E											
	Hb O_{Arab}											
	Hb C											
	Hb D_{Punjab}											
	HPFH*											
	α^{o}- thalassaemia											
	α^{+}- thalassaemia											

**HPFH: hereditary persistence of foetal haemoglobin*

Many other haemoglobinopathies combinations exist and can't be represented.

In case of an unexplained microcytosis or in any doubt, the advice of an expert in the field should be asked.

b) Genotypic tests

Molecular diagnosis is necessary to obtain a definitive diagnosis for α and β thalassaemia when one member of the couple is a carrier and the other has abnormal RBC indices and / or HbA_2 levels.

Examples are:

- Individuals suspected of being carriers of Beta-thalassaemia
- Individuals suspected of being carriers of alpha°-thalassaemia or in particular situations like the presence of an unstable alpha-globin chain variant which in combination with a^0 thalassaemia result in life threatening phenotypes. The choice should be done according to special ethnic mutation frequencies.
- When there is a borderline HbA_2 level with microcytosis and when family studies are not available.
- If there is a couple at risk for having a child with severe HbH disease or alpha thalassaemia hydrops foetalis.
- When there is suspicion of HbH interacting with beta thalassaemia heterozygosity or homozygosity.

Confirmation by a molecular method is not mandatory for a haemoglobin variant which has been demonstrated in a consistent way by at least two methods with two different principles of separation and one of these is quantitative.

IV. Prenatal diagnosis

Prenatal diagnosis along with genetic counselling, are significant aspects of prevention.

- Scientific personnel involved: haematologists, molecular geneticists, biologists in Prevention/Prenatal Units, genetic counsellors, obstetricians in public and private sectors, paediatricians in treatment Units.
- Target population: couples at risk of having an affected foetus (both parents are carriers).

1. General principles

- All couples considering prenatal diagnosis should have access to professionals who are knowledgeable in the field and skilled in the procedures.
- Each region should be organised so that an entire range of services is available.
- Each partner of the couple should have an appropriate assessment of family history and genetic counselling before invasive prenatal diagnosis is carried out.
- Counselling should be given in a non-directive manner in order to allow an informed choice by the couple.
- The distinction between screening and diagnostic investigations should be clarified, including the frequency of abnormal results, false-positive, and false-negative tests. Accuracy of results, frequency of need for repeat testing, and risk of pregnancy loss are of particular relevance with invasive prenatal diagnosis procedures. The couple should

be reminded that normal test results do not rule out every genetic or structural abnormality in their foetus.

- In the absence of a medical indication, genetic testing to determine paternity is not an indication for prenatal diagnosis with specific exceptions according to each country's laws.
- Introduction of any new prenatal diagnostic investigation, or alteration of previously established approaches, requires careful follow-up and audit to assess risk, accuracy, and impact.

Given the risk of foetal loss and morbidity related to the sampling procedure, prenatal screening should be offered for serious clinical conditions. It is offered to couples at risk of an affected pregnancy and specifically (see *figure 2*):

- Serious sickle cell disorders (Hb SS; Hb SC; Hb SO Arab; Hb SDPunjab, Hb S/β thalassaemia (β^+, β°, δβ thalassaemia, haemoglobin Lepore, Hb E);
- Homozygous β thalassaemia ;
- Hb Bart's hydrops foetalis.

Given the advances in treatment, these indications must be reviewed regularly. For example in the case of patients with a HbSC disease living in an industrialized country, their life expectancy is now more than 60 years, the indication is thus subject of debate.

2. Genetic counseling

Genetic counselling – Objectives

- To provide the information required in a simple, clear and non-directive manner following well-established recommendations
- To offer the screening and diagnostic procedures in a timely manner to ensure that the overall process is given at least by the end of 11 weeks of pregnancy
- To offer at couple at high risk of an affected pregnancy the possibility of informed decision-making
- To offer support to women or couples whether prenatal diagnosis is accepted or refused

Following counselling, most parents accept prenatal diagnosis, although not in all cultural or ethnic groups (Modell B. et al. 1997; Modell B. et al. 2000).

Under ideal conditions, the counselling session must be personal, confidential, adequate and friendly, thus enabling both partners to understand in a satisfactory manner the probabilities of having an affected child, the limitations and the potential consequences of the procedure. Counselling should be non-directive and should leave the final decision entirely within the responsibility of the involved individuals.

There are both theoretical and practical reasons to evaluate genetic counselling. Theoretical reasons include analysing factors affecting comprehension of genetic information, determining how genetic risks influence decision making and characterizing patterns of adjustments to genetic burdens. Practical reasons include improving the quality of services to patients and both improving the training and evaluating the performance of genetic counsellors.

Genetic counsellors should be trained, qualified and ideally experienced in counselling for haemoglobinopathies. The cultural background of the person provided genetic counselling should always taken into consideration.

- Prior to embarking on prenatal diagnosis testing, couples should be made aware of the full range of options when confronted with an abnormal test result. Prior commitment to termination of pregnancy following the diagnosis of fetal abnormality is not a prerequisite for prenatal diagnosis. Each centre must be aware of the local, regional, national, and international policies and protocols related to termination of pregnancy, and should advise the couple of such before undertaking prenatal diagnosis. This is particularly important for gestations beyond 20 weeks.

3. Prenatal diagnosis application

Prenatal / foetal diagnosis is carried out for couples at risk of an affected foetus (both parents are carriers). Most of the mutations involved in inherited haemoglobinopathies can be detected by DNA analysis of the foetus at risk. It is therefore vital to determine accurately the parental genotypes, preferably before foetal diagnosis in order to avoid mistakes if mutations are missed because of an incorrect diagnosis of the carrier state. Due to the large number of mutations and the complexity of evaluation of results, it is recommended that foetal diagnosis by DNA analysis is only undertaken in reference centres.

Recommendations

- Step by step:
    - Genetic counselling;
    - Parental mutation identification and ideally before foetal sampling;
    - Foetal sampling (chorionic villous sampling, amniotic fluid or foetal blood);
    - Foetal DNA analysis and test for maternal contamination;
    - Foetal DNA analysis results should be verified by newborn umbilical cord blood haemoglobin analysis or on a newborn blood sample obtained during the first days of life.

a) Parental mutation identification

Samples: EDTA – 5 to 7 ml

With the parent's samples, information should be provided according to the laboratory protocol or a form such as the one shown below should be completed for both parents:

Mother identification **Family name** **First name** **Birth date** **Ethnic origin**		**Father identification** **Family name** **First name** **Birth date** **Ethnic origin**	
First pregnancy	Yes / No		
Hb g/dl		Hb g/dl	
RBC 10^6/mm³		RBC 10^6/mm³	
MCV fl		MCV fl	
MCHC g/dl		MCHC g/dl	
MCH pg		MCH pg	
RDW/HDW		RDW/HDW	
Ferritin ng/ml		Ferritin ng/ml	
CRP mg/dl		CRP mg/dl	
HbA_2 %*		HbA_2 %*	
Hb F %		Hb F %	
Hb(s) variant? Identification? E.g. HbAS, Hb SS, Hb SC, …	Yes / No ……	Hb(s) variant? Identification? E.g. HbAS, Hb SS, Hb SC, …	Yes / No ……

*please notify your reference values

b) Foetal sampling

Invasive prenatal diagnosis techniques include chorionic villus sampling (CVS), amniocentesis and under certain circumstances cordocentesis or percutaneous umbilical blood sampling.

Table 2. Summary of amniocentesis and chorionic villus sampling information (see Canadian Guideline for Prenatal Diagnosis (2005) Change to 2005-Techniques for Prenatal Diagnosis).

	Amniocentesis	CVS
Procedure	Amniotic fluid removed by needle and syringe	Chorionic villi removed by transcervical or transabdominal pathway
Timing	15 to 17 weeks	10 to 11-6/7 weeks (greater than 12 weeks TA CVS only)
Added risk of miscarriage due to procedure	+/- 0.5%	+/- 1%
Fetal malformation risks	-	1 in 3.000 vascular limb malformation (suggested but not proven)
Chance of successful sampling	Approximately 99%	Approximately 99%. If unsuccessful, amniocentesis can be performed
Time required for prenatal diagnosis	to 7 working days (if cultured amniotic fluid cells: 2 to 3 weeks)	3 to 7 working days

Special attention: contamination by maternal residual tissue has to be checked, although this potential problem should be minimized with very careful attention to cleaning or stripping of the chorionic villi of maternal residual cells under the dissecting microscope prior to DNA isolation. This has not been a significant problem in most laboratories with long term experience in CVS (Rudd N. 1989; Ledbetter DH, Martin A. et al. 1990).

c) Foetal DNA analysis

Foetal DNA can be isolated from CVS or amniotic fluid foetal cells (cultured or not) or cord blood.

Genetic analysis approaches are direct (PCR, DNA Sequencing, HRMA analysis of QPCR products, RE digestion, ARMS, Reverse dot blot mutation analysis or indirect (PCR followed by DGGE analysis, MLPA, GAP PCR) mutation analysis.

Results should be verified by newborn umbilical cord blood haemoglobin analysis or on a newborn blood sample obtained during the first days of life.

In a normal sample HbA_2 should be absent and HbA should be approximately between 6-25% of the total haemoglobin.

V. Laboratory centre of expertise for haemoglobinopathies

Special analyses for haemoglobinopathies' diagnosis are performed in expert laboratories.

It concerns special phenotypic and molecular analysis; it should offer a combination of techniques in view to allow the detection and diagnosis of common and uncommon clinically significant haemoglobin variants, and of common and uncommon thalassaemia.

Recommendations

- If exist, the laboratory must be appropriately accredited with a nationally approved accreditation scheme.
- The laboratory must use a testing algorithm to determine those pregnancies at risk of severe haemoglobinopathy. This testing algorithm sets out the conditions to be tested for and the analytical methods that can be used.
- The laboratory must provide guidelines for the standardised reporting of antenatal screening results.
- The laboratory must have a standard operating procedure for the haemoglobinopathies screening service, describing the process of laboratory testing from initial receipt of the specimen until despatching of the report.
- There must be a documented risk management policy for the laboratory aspects of the haemoglobinopathy screening service. This should describe the steps in the testing protocol where mistakes could occur and the procedures that have been implemented to minimise the risk of the mistake occurring.
- The laboratory must participate in an accredited External Quality Assessment Scheme (EQAS) and must be able to able to demonstrate satisfactory performance as defined by the criteria specified by the EQA scheme organisers. If doesn't exist and feasible, inter laboratory evaluations on patients' samples or internal controls should be implemented.
- High level of expertise and experience must be documented through publications, grants or honorary positions, teaching and training activities
- There must be a strong contribution to research
- The laboratory must be Involved in epidemiological surveillance, such as registries
- The laboratory must have close links and collaboration with other expert laboratories at the national and international levels and a capacity to network
- The laboratory must have close links and collaboration with clinical centres of expertise.

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D22 - RECOMMENDATIONS FOR THE FOLLOW-UP OF SICKLE CELL DISEASE - CHILDREN AND ADULT PATIENTS - 2010

Objective: Recommendations for standard follow-up of children affected with sickle cell disease

Target population: medical staff expert and non-expert in the field

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Sickle cell disease (SCD) is related to a mutation in the b globin gene and is an autosomal recessive disorder. It is characterized by the presence of abnormal haemoglobin, haemoglobin S, either in a homozygous status (SS disease) or in association with other abnormal haemoglobin such as HbC (SC disease) or b-thalassaemia ($S\beta^{\circ}$ and $S\beta^{+}$ diseases). It is estimated that most probably several fold ten thousands of patients are living in Europe. Clinical expression of the disease is highly variable. Globally, SS disease and $S\beta^{\circ}$ disease are more severe than SC disease and $S\beta^{+}$ disease.

Management of SCD in children aims both in preventing acute complications (mostly infections, pain, and strokes), treating severe events, and trying to prevent the onset of chronic organ damages in adolescents and adults. Most likely, cares are to be given by a network of physicians involving both physicians from community settings and specialised secondary care centres.

INDEX

I. PREVENTION AND ANNUAL FOLLOW-UP

1. Neonatal screening and enrolment in comprehensive care programmes

Neonatal screening of SCD reduces mortality in infants, through education of parents and early implementation of daily prophylactic penicillin [Vichinsky, 1988)]. It is currently carried out using HPLC or isoelectric focusing. It is systematically performed in the USA, in England and in the Netherlands, systematic but targeted on "high-risk" population in France, and systematically performed in several cities of Belgium. Newborns diagnosed with a major SCD syndrome have to be addressed to an expertise centre [Consensus Conference. Newborn screening for sickle cell disease and other haemoglobinopathies. *JAMA*,258 (9),1205-1209 (1987)], where the parents will be informed that their child has SCD by an expert physician who will organize the care of the baby.

2. Prevention of infections

Fulminant infections related to encapsulated bacteria and explained by the functional asplenia were until these very recent years the first cause of death in SCD children aged less than 5 years [Leikin, 1989]. A randomised study published in 1986 showed that prophylaxis with penicillin twice a day in SCD children younger than 3 years at study inclusion was associated with an 84% reduction in the incidence of infection, compared to placebo therapy [Gaston, 1986]. Penicillin is therefore recommended twice daily starting at 2 months of age, but further research is needed to determine the age at which penicillin prophylaxis can be stopped safely [Hirst, 2002].

Given the risk of poor adherence to daily prophylaxis and the development of penicillin resistant *Streptococcus pneumoniae* strains, pneumococcal immunisation as well as prophylactic penicillin is recommended [Davies, 2004]. The recommended immunisation schedule for previously unvaccinated children with SCD consists of three doses of conjugated vaccine six to eight weeks apart, followed by a booster dose one year later, then by a polysaccharide vaccine after age 2 years, with additional doses every three to five years.

Transition from pediatric to adult clinics must be carefully presented and prepared.

3. Prevention of strokes

Up to these very last years, it was observed that 11% of patients with SCD will have an apparent clinical stroke by age twenty [Ohene-Frempong, 1998]. Silent infarcts are also evidenced in up to 35% of children, with possible impairment of cognitive functions. Adams demonstrated in 1992 that it was possible to screen early the children the more at risk to develop an overt stroke using a transcranial Doppler, showing that 40% of the children with an increased blood flow velocity in the internal carotid or middle cerebral artery will have an overt stroke in the next 3 years. [Adams, 1992]. Six years later, Adams demonstrated that a first stroke could be prevented by monthly transfusions in children with abnormal TCD findings, evidencing in a randomized study a 92% difference in the risk

of stroke between the transfused and non -transfused arms [Adams, 1998]. Lastly, he randomized discontinuation of transfusion in children undergoing chronic transfusion for an abnormal transcranial Doppler, during which time the transcranial Doppler ultrasonography became normal. Stopping the transfusions was followed by a high rate of stroke or reversion to abnormal velocities of cerebral blood flow [Adams, 2005]. These well designed studies led to the recommendation that transcranial Doppler ultrasonography be performed annually in children aged 2-16 years with SCD and that regular blood transfusions should be strongly considered in those with abnormal findings on transcranial Doppler ultrasonography [National Institutes of Health. *The management of sickle cell disease*. 4th ed. 2002. (NIH publication No 02-2117) www.nhlbi.nih.gov/health/prof/blood/sickle/index.htm].

4. Education and psychological support

Patients and families should be educated about the factors that increase the risk of vaso-occlusive episodes, such as exposure to cold, fever, dehydration, stress and tobacco. They are taught to manage mild pain with rest, hydration, and weak opioids (such as codeine or propoxyphene) and to recognize the signs that require an immediate visit to the emergency room, such as pallor, asthenia, fever, respiratory distress.

SCD is a chronic, painful and distressing disease. Most parents are despaired when diagnosis is given, and some of them experience thereafter repetition of life-threatening complications in their children. Children feel their parents' continuous fear, and some of them are victims of repeated painful events and hospitalizations, sometimes in Intensive Care Units. They may be unable to attend school regularly and fail to perform. Furthermore, silent microinfarcts may be responsible to learning difficulties. Proposing specific individual and family psychological interventions could very likely help to disrupt the vicious circle of pain and fear of pain in SCD children. Early detection of school difficulties may help to organize school support. Adolescents and their families should be informed and reassured about frequently delayed sexual development and growth but with normal final height in most of them. Lastly,

5. Annual follow-up investigations

Adult patients with SCD may suffer from several organ damages which can be, for some of them, detected in older children and adolescents and treated early. This justifies the organization of yearly check-ups assessing any chronic organ deficiency [Haute Autorité de Santé. *Prise en charge de la drépanocytose chez l'enfant et l'adolescent* [Clinical practice guidelines in French]. 2005. www.has-sante.fr/portail/display.jsp?id=c_272479].

Table 1. RECOMMENDED EXAMS TO BE PERFORMED ANNUALLY

	0 – 1 Year	2 years	3 - 5 years	6 - 9 years	10 – 15 years	16 -18 years
Physical examination	■	■	■	■	■	■
Transcutaneous O_2 saturation	■	■	■	■	■	■
Biological tests*	■	■	■	■	■	■
Pulmonary function tests	■	■	■	■	■	■
School success	■	■	■	■	■	■
Adherence (treatments, appointments)	■	■	■	■	■	■
TCD		■	■	■	■	
Hepatic US			■	■	■	■
Hip X-Ray				■	■	■
Electrocardiography				■	■	■
Ophtalmologic evaluation				**	■	■

* Complete blood count, liver profile, electrolytes, BUN, creatinine, γalbuminuria, ferritin if transfused, calcium metabolism including vitamin D and PTH, Parvovirus B19 serology until positive.

** Since the age of 6 y.o. if Hb SC disease

6. Preoperative preparation

The complications of sickle cell disease often require surgical procedures such as cholecystectomy, hip replacement, and splenectomy. However, patients with the disease are at high risk of perioperative complications, chiefly acute chest syndrome and pain. Transfusion or exchange transfusion are therefore recommended for surgeries requiring a prolonged time of anesthesia [Wayne, 1993].

II. TREATMENT INTENSIFICATION

Approximately 10% of SCD children have a severe form either because they have repeated painful episodes or acute chest syndromes, or because they have a risk of cerebral vasculopathy or severe baseline anaemia.

Three types of intensification of treatment can be proposed to these children, **hydroxyurea**, **chronic transfusion**, or **bone marrow transplant** when they have a HLA identical sibling.

1. HYDROXYUREA

Hydroxyurea has been used in SCD children affected with severe forms of the disease since more than 15 years. The rationale of its using was the findings that hydroxyurea increases fetal hemoglobin, which interrupts the elongation of the polymer of deoxyHbS. Secondarily, it was observed that the clinical benefit felt by the patients precedes the reactivation of HbF synthesis, suggesting that other mechanisms of action are involved, out of these a decrease of leucocytes number and activation, a decrease of adhesiveness of blood cells to endothelial cells, and an increase in NO production [Odièvre, 2008]. The clinical efficacy of hydroxyurea in children has been demonstrated by a Belgian trial in which children with severe SCD, median age 9 years, were randomized to receive either hydroxyurea or placebo for 6 months, and then switched to the other arm for the next 6 months. Hydroxyurea-treated children had significantly less hospitalizations (P = 0.0016), and fewer hospitalized days (P = 0.0027) [Ferster, 1996]. There are now many reports about the use of hydroxurea in SCD children affected with severe forms of the disease [Scott, 1996; Kinney, 1999; de Montalembert, 1999], and there is an ongoing trial in SCD infants (the HUSOFT extension study), the drug being used in this last setting in the hope of preventing the onset of the complications [Hankins, 2005]

Long-term studies on hydroxyurea use in children confirm a sustained efficacy in young patients [Ferster, 2001; Gulbis, 2005; Zimmerman, 2004; de Montalembert, 2006].

> *In the Belgian trial, there was a significant difference in the number of hospitalizations (P=0.0002) and hospitalized days (P < 0.01) during a 5-years treatment, compared to prior hydroxyurea therapy [33]. In the HUSOFT study, patients experienced 7.5 acute chest syndrome events/100 person-years, compared with 24.5 events/100 person-years among historical controls (P=0.001) [Hankins, 2005]. Hydroxyurea-treated infants had a relatively preserved splenic function compared to historical controls, the proportion of asplenic patients assessed by Tc-99m sulphur colloid uptake evidenced an absent uptake (= functional asplenia) in 43% patients after study completion, versus the 94% percent standard for that age.*

Indications

Globally, hydroxyurea is now recommended in children with SCD to prevent recurrences of painful crises and to prevent recurrences of acute chest syndromes. Many authors treat also children with chronic severe anemia (baseline hemoglobin level < 6 or 7 g/dl according to authors). There are more controversies about the use of hydroxyurea as an alternative to chronic transfusion to prevent cerebrovascular events, eventually after an overlap period where both transfusion and hydroxyurea are associated [Ware, 2004]. Important answers will probably be provided by the results of the ongoing study randomizing transfusion and hydroxyurea in children having already had a stroke [the SWiTCH trial].

In the United States, the Food and Drug Administration has approved hydroxyurea use only in adult SCA patients, and the children have to be enrolled in protocols, while European regulatory authorities have approved a coated breakable 1,000 mg tablet for adults and

children and 100 mg pills for children. Starting doses are generally around 15gm/kg/day and may be escalated by 5mg/kg/day until the maximum tolerated dose is reached, alternatively the dose may be increased until clinical benefit is obtained.

Table 2. INDICATIONS FOR HYDROXYUREA IN CHILDREN
❑ **Established**
Recurrent severe painful crisis
Acute chest syndrome
❑ **Postulated**
Stroke prevention
Prevention of organ dysfunction

Side effects and follow-up

❑ Tolerance

The short- and mid-term tolerances of hydroxyurea in children are good [de Montalembert, 2006]. The real questions concern the long-term tolerance of the drug. Knowing that hydroxyurea has been shown to exacerbate the alterations of semen parameters observed in SCD adults [Berthaut, 2008], there are uncertainties as to the long-term consequences on fertility of boys treated with hydroxyurea early and for several years. Storage of frozen sperm must systematically be proposed to mature boys and adults, though it is rarely accepted.

❑ Myelosuppression

Transient myelosuppression may occur and usually resolve after decreasing the dosage, or temporarily interruption of the drug.

Biologically, all of the studies reported a long-term increase in Hb, MCV, and HbF levels, and significant decrease in reticulocytes, PMN, and platelet counts. The minimal HbF level increase to observe a clinical benefit is yet undetermined, therefore no recommendation can be made for an optimal dosage.

Complete blood count must be performed before starting the treatment, 2 weeks after its beginning, at 2-4 week intervals during the initial phase, and then every 8 weeks. These

results should be monitored by a medical professional. Nail hyperpigmentation is common. The possibility that hydroxyurea, which had been shown to delay splenic infarct [Hankins, 2005], lengthens the period at risk for acute splenic sequestration is debated [de Montalembert, 2006]. A cautious strategy is to carefully monitor spleen size and blood tests at each evaluation particularly for children with prior splenomegaly or past history of splenic sequestration before starting hydroxyurea treatment.

- Risk of malignancies

The other issue related to the use of this cytostatic drug concerns the risk of malignancies. Hemoglobinopathies are not considered as having an increased risk of development of secondary malignancies. So far, several malignancies have been reported in patients with SCD receiving hydroxyurea [Ferster, 2003; Schultz, 2003; Couronné, 2008] but the implication of hydroxyurea in the pathogenesis of these malignancies is not possible. These observations lead us to recommend great caution. In vitro, quantitative analyses of acquired DNA mutations suggest that the mutagenic potential of hydroxyurea is low [Hanft, 2000].

Table 3. HYDROXYUREA MONITORING

- Full blood count and Hb F level each 2 weeks after initiation and after each dose increase; when stable every 8 weeks
- Monitor spleen size, particularly if splenomegaly is present or there is an history of splenic sequestration
- Propose storage of frozen sperm

2. RED BLOOD CELLS TRANSFUSION

See chapter " Recommendations of Red blood cells transfusion in children affected of SCD"

3. HEMATOPOIETIC STEM CELL TRANSPLANTATION

Transplantation of hematopoietic stem cells from HLA-identical siblings is the only curative therapy of SCD. Stem-cell source may be either bone marrow or cord blood. In a series of 87 patients transplanted between 1988 and 2004, the overall and event-free survival rates were respectively 93.1% and 86.1% [Bernaudin, 2007]. Ovarian tissue is systematically cryopreserved, but the risks of bone marrow transplant on the ulterior reproductive function are not clearly known [Brachet, 2007]. Both the immediate vital risk and the long-term uncertainties about fertility must lead the health care providers to discuss very carefully with parents the indications of transplant, whose decision to accept the risks is most often not correlated to the medical assessment of the severity of the disease [Van Besien, 2001].

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RECOMMENDATIONS FOR THE FOLLOW-UP OF SICKLE CELL DISEASE - ADULT PATIENTS– 2012

Objective: ENERCA recommendations for standard follow-up of young adult and adult patients with sickle cell disease (SCD)

Target population: medical staff expert and non-expert in the field

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Based on available published guidelines and national recommendations

INDEX

I. INTRODUCTION

Hereditary disorders of production and assembly of haemoglobin chains represent the most common cause of monogenic inherited anaemia; in fact, around 5 % of the world population has a globin chain variants: around 1.5 % are heterozygous for α or β thalassaemia and 2.% for sickle haemoglobin. A mutation in the β globin gene resulting in the substitution of the native glutamic acid at the 6th amino acid position with valine is the proximate cause of sickle cell disease (SCD). Patients with SCD can be homozygous for the pathological haemoglobin S (SS) or heterozygous with a co inherited haemoglobin disorder such as HbC (HbS/HbC) or β thalassaemia (HbS/Hbβ-thal). Other more rare conditions exist such as HbS- Punjab. The clinical manifestations of SCD are related to the peculiar biochemical properties of sickle haemoglobin, which polymerizes when deoxygenated. Studies of the kinetics of HbS polymerization following deoxygenation have shown that the kinetics of polymer formation is a high order exponential function of haemoglobin concentration, thus demonstrating the crucial role of cellular HbS concentration in sickling. HbS polymerization is associated with a reduction in cell ion and water content (cell dehydration), increased red cell density and further acceleration of HbS polymerization. Dense, dehydrated erythrocytes are likely to undergo instant polymerization in conditions of mild hypoxia due to their high HbS concentration, and HbS polymers may be formed under normal oxygen pressure. Pathophysiological studies have shown that the dense, dehydrated red cells play a central role in acute and chronic clinical manifestations of sickle cell disease, in which intravascular sickling in capillaries and small vessels leads to vaso-occlusion and impaired blood flow. However, the persistent membrane damage associated with HbS polymerization also favours the generation of distorted rigid cells and further contributes to vaso-occlusive events and cell destruction in the peripheral circulation. Thus, the two main clinical manifestations of sickle cell disease are the chronic haemolytic anaemia and, acute and chronic vaso-occlusive events (1-9)

II. PREVENTION AND FOLLOW UP

1. **Education and Psychology services** (10-18)

One of the major issues in clinical management of adult patients with SCD is prevention of vaso-occlusive crisis (VOCs) obtained mainly through education. The passage between childhood and adolescence to the adult life is critical on both personal (i.e. the modification of life style) and psychological point of view. Information of both clinical and biological data must be given to patients and their parents. Advice and training should be offered and monitored. They have to know what is important such as regular hydration, the adoption of a quiet style of life, or what should be avoided such as alcoholic beverages, active tobacco use and drugs, strenuous exercises, exposure to cold or emotional stresses. They have to know that high temperature promotes sickling and advice for often use febrifuges; they should also avoid staying over 1500 m of altitude. They should know all about symptoms requiring medical advice and the appropriate use of analgesia at home. The psychological management is very important either at home or in place of care. Trained nurses in reference centres have important role in the clinical management of adult SCD patients. A transition team (i.e. paediatricians together with medical doctors for adults as internal medical doctors or haematologists) should work together during clinical consultation of adolescents with SCD at least one year before their transition from the Paediatric to the Department of Adult Medicine or Haematology. The best policy is to connect from early life, with specialized sickle cell units in University Hospitals.

2. **Infection Risk Management** (19-23)

The prevention of severe bacterial infection is very important in adult patients with SCD. Table 1 summarized the recommended immunization in adult SCD patients. Although the vaccination strategy in SCD children (see SCD children ENERCA recommendations) is well defined, the SCD adults would receive antipneumococcal vaccine every five years as well as annual influenza vaccination. In addition, vaccination against hepatitis B and A is recommended. If required in case of travel in at risk countries yellow fever, typhoid, meningococcal vaccines should be considered. Recurrent focal infections like dental infections, sinusitis, acute recurrent tonsillitis, cholecistytis, urinary infections and osteomyelitis, should be promptly treated. Special consideration should be given to the recurrent urinary tract infection (rUTI) particularly frequent in women. In rUTI, urine culture is essential before therapy and should be repeated 1-2 weeks after the therapy withdrawn. Urological evaluation may be appropriated for SCD patients with repetitive infections.

TABLE 1. RECOMMENDED IMMUNIZATION IN ADULT SCD PATIENTS	
▪ *Streptococcus pneumoniae* ▪ *Haemophilus influenzae* ▪ Meningococcus ▪ Pneumococcal	Once in life in unvaccinated SCD adolescent and adult patients from low developed countries. Every 4 years
▪ Influenza	Annually

Special focus concerns the risk of nosocomial infections due to central devices in case of poor venous access. Blood stream infection (BSI) is hospital acquired in half of the cases, and mainly associated with venous catheters and *Staphylococcus aureus*. Bone joint infection occurs either during the initial BSI or 1 to 6 months after BSI resolution. The diagnosis of osteomyelitis or septic arthritis (affecting in most cases the hip) is suspected in case of pain, swelling, fever, leukocyte count exceeding 15,000/µl, C-reactive protein above 20mg/L. Staphylococcus and Gram-negative infection predominate. Pre-

existing factors for bacterial arthritis include osteonecrosis, osteomyelitis in childhood. Associated comorbidities are severe underlying disease and a venous catheter, diabetes, rheumatoid arthritis, glucocorticoids. CT and MRI confirm the diagnosis and allow joint aspiration and detection of soft tissue abscess. We summarized in Table 2 the management of adult SCD patients with acute clinical manifestations. We consider two different possibilities: the hospitalization or the strict follow-up in either dedicated day-hospital or ambulatory services based on symptoms and the clinical characteristics of the patient.

TABLE 2. MANAGEMENT OF ADULT SCD PATIENTS	
ADMISSION TO THE HOSPITAL	**TREATING AS OUT-PATIENT**
• Temperature > 39°(C) • Seriously ill appearance: respiratory symptoms, chest pain, any relevant neurological symptom • Patient with VOC alone at home • Abdominal pain • Any events occurring in the 3 weeks after blood transfusion • VOC occurring during pregnancy • Hypotension • Poor perfusion, dehydration, poor fluid intake • Long lasting priapism • Corrected WBC count > 30,000/µl or< 5,000/ µl • PLT count < 100,000/ µl • Hb < 5 g/dL • History of *S. pneumoniae* sepsis	• Patients with clinically low risk of sepsis • The patient, family and clinic are capable of impeccable follow up • A successful follow up program has been established

Hb: haemoglobin; VOC: vaso-occlusive crisis; WBC: white blood count; PLT: platelet

3. **Annual Follow-up** (18, 22, 24)

Adult patients with SCD should be seen at the reference centre every 4 to 6 months, in coordination with proximal physician and promptly in case of particular symptoms (i.e. stuttering priapism),or situation (i.e.pregnancy) or after hospitalization for acute vaso-occlusive complication (long term treatment such hydroxycarbamide may be considered) (Table 3). SCD patients should be evaluated in ambulatory regimen or in Day-hospital regimen based on the organ damage or chronic SCD related clinical manifestation. Special attention is required concerning evolution of body weight, blood pressure, proteinuria, evolution of haematological and biochemical parameters.

TABLE 3. ANNUAL FOLLW-UP OF ADULT SCD PATIENTS	
Annual Evaluation	**Note**
Regular clinical evaluation (and pregnancy, fertility options; education and training; social and psychology services)	
Blood pressure	More frequently if hypertension (consider also ABPM)
Laboratory tests: Hb, retics,CBC, HbF*,renal function, (creatinine, BUN, proteinurea/24h, creatinine clearance) hepatic function (AST, ALT, LDH, bilirubin), urine analysis, **ferritin, search for irregular antibodies and viral serology (HIV, HCV)	* In patients who take HbF inducer (HU) ** If chronic transfusion
Screening Procedures: ▪ Hearing ▪ Vision (complete retinal examination) ▪ Echography: tricuspidal regurgitation, EF ▪ Spirometry, 6 min walking test ▪ Gall bladder ultrasonography ▪ Search of osteonecrosis	 Suggestive bone and joints pain
Other Screening Procedures: ▪ Brain MRI ▪ PAP smear ▪ Mammogram and prostate examination	Neurological manifestations or familial history Only sexually active girls Adults following standard practice

**Iron studies must be done more frequently in adults are on chronic transfusions to monitor iron overload; CBC: complete blood count; HbF: haemoglobin F; BUN: blood urea nitrogen; Alanine aminotranferase *(*ALT*)* and aspartate aminotransferase *(*AST*);* LDH: Lactate dehydrogenase*;* ABPM: Ambulatory Blood Pressure Monitoring; HU: hydroxyurea; MRI: magnetic resonance imaging, PAP: Papanicolaou test; HbF: haemoglobin F

III. TREATMENT OF CHRONIC COMPLICATIONS

1. **Pulmonary hypertension (PH)** (24-35)

In SCD patients pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure (PAP) above 25 mmHg measured by right catheterism and suspected if tricuspid regurgitation velocity (TRV) is over 2.5 m/sec. PH could be secondary to SCD and progressive PH can lead to right heart failure. Recent hemodynamic studies performed in large cohorts of adult patients with SCD (SS or Sβ°thal) have established the prevalence of pulmonary hypertension in this disease about 6 to 10%. Over half of these correspond to postcapillary hypertension indicating diastolic dysfunction. Precapillary arterial hypertension seems to be rare and characterized by a different haemodynamic profile of idiopathic PH with lower levels of pulmonary pressures and pulmonary vascular resistances. However, PH has a significant impact on functional status and confers an increase risk of death even when mild or moderate. The predictive value of transthoracic echocardiography to detect PH is low

(about 30%) when the threshold of tricuspid regurgitation velocity (TRV) of 2.5m/s is used. Worsening of dyspnea is the main symptom that indicates the need of exploration. Previous history of systemic hypertension and/or leg ulcer; SS genotype; age over 40; existence of glomerular involvement (proteinuria and/or renal insufficiency) represent risk factors for PH. Reduced 6 min walk distance with desaturation, and increase of NT pro BNP combined with TRV ≥2.9m/s indicate the need of right heart catheterization which allows confirming PH and determining his mechanism. Two possible pathogenic mechanisms of PH have been identified: the recurrence of vaso-occlusive episodes, with progressive loss of the vascular bed, and chronic haemolysis, with chronic release of free haemoglobin scavenging nitric oxide and catalyzing the formation of oxygen-free radicals. Up to date there are no clear guidelines of PH treatment. General recommendations include the intensification of specific haematological therapy for SCD; identification and treatment of causal factors or associated diseases (like rest, exercise and nocturnal hypoxemia, sleep apnea, pulmonary thromboembolic disease); general supportive measures, prompt treatment of VOC and ACS. PH specific pharmacological agents may be useful but are still to be properly evaluated. Table 4 summarizes diagnosis, follow-up and clinical management of pulmonary hypertension in adult SCD patients.

TABLE 4. DIAGNOSIS, FOLLOW-UP AND CLINICAL MANAGMENT OF PULMONARY HYPERTENSION IN ADULT SCD PATIENT	
Diagnosis and follow-up of PH in SCD	**Note**
▪ Echocardiography for TRV measurement ▪ Right Catheterization if tricuspid regurgitation velocity (TRV) is over 2.5 m/sec. ▪ 6- minute walking test (6MW) ▪ Spirometry and pulmonary function tests; FVC, FEV1, TLC, DLCO ▪ Pulmonary angiogram ▪ Hb oxygen saturation, LDH ▪ NT-proBNP • Consider polysomnography if sleep-disorders are suspected	
Therapy of PH in SCD	**Note**
• Continuous or nocturnal oxygen therapy, treatment of spleep apnea • Red cell transfusion program • Consider used of hydroxyurea ± EPO • Consider systemic anticoagulation • Consider endothelin receptors antagonists (bosentan, ambrisentan) • Consider infusion of prostacyclin (vasodilator and inhibitor of platelets aggregation)	 <u>Adverse side effects:</u> hepatotoxicity, decrease Hb level <u>Adverse side effects:</u> flushing headache, jaw pain, rash, site pain, line sepsis/thrombosis

Hb: haemoglobin, LDH: lactate dehydrogensae, FVC: forced vital capacity, FEV1: forced expiration volume in 1, TLC: total lung capacity, DLCO: diffusion capacity for carbon monoxide; TEV: tricuspid regurgitation velocity; NT-proBNP: N-terminal pro-brain natriuretic peptide; EPO: erythropoietin

2. Renal disease in SCD (36-49)

Clinical manifestations of renal disease in adult SCD patients indicate the involvement of multiple targets in kidney functional units. Pathological findings in SCD are: (i) glomerula enlargement in particular in juxtaglomerular glomeruli; (ii) interstitial fibrosis, tubular atrophy and lymphoid cells in renal medulla; (iii) iron depositions in the proximal tubule; (iii) cortical infarction; (iv) focal segmental glomerulosclerosis without immune complex deposit. In SCD the involvement of the renal medulla is generally slowly and progressive due to the recurrent sickling in this kidney area. Microalbumiburia preceding proteinuria (20-30% of adult SCD patients) and microscopic haematuria are the most common pathological findings in SCD with kidney disease. Worsening of anemia precedes likely the renal failure (defined by creatinine clearance below 80 ml/min); systemic hypertension, proteinuria, nephrotic syndrome and microscopic haematuria are predictors of chronic renal failure. Management of sickle cell nephropathy is mainly directed to avoid possible toxic effects by NSAID used in pain treatment and to reduce proteinuria by either ACE inhibitors or angiotensin II receptor blockers; it is based on the evidence that proteinuria is associated with faster decline of renal function. Haemodialysis can be safely used in SCD, but these patients are very fragile. Realization of arterio-venous fistula must be anticipated. Renal transplantation for SCD patients with end-stage renal disease is an alternative to chronic dialysis and needs multidisciplinary approach (chronic transfusion first 6 months post-transplantation switched progressively if possible with hydroxyurea ± erythropoietin) for better long term outcome. Table 5 summarizes clinical manifestations of chronic renal disease in adult SCD patients and the relative clinical management.

TABLE 5. CLINICAL MANIFESTATIONS OF CHRONIC RENAL DISEASE IN ADULT SCD PATIENTS AND CLINCIAL MANAGEMENT

	NOTE
HYPOSTENURIA: inability to concentrate urine maximally, begins early in childhood for SS patients **TUBULE DYSFUNCTION:** defective urinary acidification (with normal aldosteron and renin excretion), defective potassium excretion resulting in hyperkalemia: hyperuricemia **MICROALBUMINURIA, PROTEINURIA:** it can progress to the nephrotic syndrome **HEMATURIA:** common renal abnormality in SCD. It appears to result from the HbS polymerization and red cell sickling in the renal medulla. It may be a manifestation of papillary necrosis. More frequently involved bleeding of left side kidney. **ACUTE RENAL FAILURE:** can be precipitated at any age by dehydration, sepsis, drugs or may occur in the context of multiorgan failure **CHRONIC RENAL FAILURE:** The severity of chronic renal failure appeares to be age related	Patients are more susceptible for dehydration Diagnosis: Complete blood count, creatinine, creatinine clearance, BUN, Ca, K, Na, Cl, urine examination, proteinuria (albuminuria), cystatin C, uremic acid; EPO level if Hb drop at steady state; regular vitamin D and parathormone dosage in case of renal failure. Abdomen ultrasonography and urographic contrast imaging Treatments: Acute events: bed rest, maintenance of high urinary flow, monitoring intake and output and, if blood loss is significant, iron replacement and blood transfusion. Avoid drugs with renal toxicity (i.e.: NSAID)

	Chronic therapy: ACE inhibitors or angiotensin II receptor blockers; control systemic blood pressure; consider EPO in case of severe anemia unless indication of chronic trasfusion regime.

BUN: blood urea nitrogen; LDH: Lactate dehydrogenase; ACE: angiotensin converting enzyme; EPO: erythropoietin; NSAID: non steroid anti-inflammatory drug; EPO: erythropoietin; Hb: haemoglobin.

3. Ocular SCD related complications (50-61)

SCD vaso-occlusive events can occur everywhere in the micro-vascular bed of the eye, often with severe visual complications. Acute macular ischemia is a rare but severe complication, mainly in SS patients, leading to visual loss and requiring prompt ophthalmological evaluation, and in most cases exchange transfusion. Patients with SC disease have been shown to be more susceptible to retinal complication than either SS or Sβ°thal. patients. Conjunctival vessel alterations (CVA) have been related to mechanical obstruction by sickle red cells and seem to be more frequent in older SCD patients with SS genotype. Retinal vessel alterations (RVA) may induce temporary or permanent visual loss and seems to be more frequent in SC genotype. SCD proliferative retinopathy is present in 20% of SCD patients by the fourth and fifth decades of life. Prospective annual search for vascular retinal proliferation is mandatory since the age of 15 years in genotypes with highest Hb level. Table 6 summarizes the type of chronic retinopathy that can be recognized in adult SCD patients and its clinical management.

TABLE 6. CHRONIC RETINOPATHY IN ADULT SCD PATIENTS AND CLINICAL MANAGEMENT	
NON-PROLIFERATIVE DISEASE	**PROLIFERATIVE DISEASE**
• Iris atrophy • Retinal haemorrhages • Retinal pigmentary changes: black sunburst, iridescent spots, white without pressure • Spontaneous hephema • Glaucoma	• Peripheral proliferative disease due to peripheral arteriolar occlusions. Local occlusions can lead to neoangiogenesis through the VEGF pathway. - stage I: peripheral arteriolar occlusion is present - stage II: vascular remodelling with arteriovenous anastomoses - stage III: preretinal neovascularization occur - stage IV: vitreous haemorrhages - stage V: retinal detachment
TREATMENT OF CHRONIC RETINOPATHY IN ADULT SCD PATIENTS	
• Cryotherapy and laser photocoagulation • Modern vitreoretinal microsurgery if persitent intravitreal haemorrhage and significant retinal detachment • Partial exchange transfusion are mandatory prior to surgery (HbS < 40 -50%) to avoid if possible of corticosteroids and/or diuretics	
RECOMMENDED ANNUAL CONTROL EVEN FOR YOUNG ADULTS	
• Accurate measurement of visual acuity**,** pupillary reactivity • Careful evaluation of the anterior structure of the eyes using a slit-lamp biomicroscope • Examination of the posterior structures of the eyes and peripheral retina through a dilated pupil • Fluorescin angiography	

VEGF: vascular endothelial growth factor; HbS: haemoglobin S;

4. **Bones and Joints** (19, 62-69)

In SCD bone and joint complications might result from different mechanisms: osteopenia due to bone marrow hyperplasia, bone infarction and osteomyelitis. As a consequence of osteopenia vertebral instability is described. SCD patients might describe mechanically induced pain. This condition exposes SCD patient to risk of compression fractures. Osteonecrosis related to vaso-occlusive events can be defined clinically or radiologically and followed by magnetic resonance imaging (MRI). Table 7 summarizes bone and joint involvements in adult SCD patient and clinical management. Osteomyelitis might be present as complication of bone involvement of SCD. The frequency of osteomyelitis is linked to the environmental setting. It is generally a complication of bacteraemia. Thus, blood cultures should be carried out when elevated temperature is present during acute painful crisis. MRI is required for diagnosis and detecting soft tissue oedema or abscess.

TABLE 7. BONE AND JOINT INVOLVEMENTS IN ADULT SCD PATIENTS AND CLINICAL MANAGEMENT	
Bone marrow hyperplasia	**Vaso-occlusive events**
Cellular proliferation in the marrow spaces results in bone deformity, which causes distortion and growth disturbance, particularly in the skull, vertebrae and long bones.	**METAPHYSEAL AND DIAPHYSEAL INFARCTS:** due to relative hypoxia in the sinusoids of the marrow spaces. The most common sites of involvement in the long bones are the humerus, tibia and femur in their distal segment. **AVASCULAR OSTEONECROSIS (AVN): all joints may be affected:** hip AVN due to endoarterial vessels ad often leads rapidly to painful collapse **Therapy:** Joint-preserving surgical procedures such as core decompression ± bone marrow injection and osteotomy. Hip arthroplasty is reserved for patients with advanced disease who are severely symptomatic. Prophylaxis of infection is essential.

IV. TREATMENT INTENSIFICATION

1. Hydroxyurea (HU) (70-79)

Hydroxyurea (HU) increases foetal haemoglobin, which interrupts the elongation of the polymer of deoxyHbS and limits sickling. It also decreases the leukocytes number and activation, the adhesiveness of blood cells to vascular endothelial cells and increases NO production. HU is the only molecule available that effectively reduces the number of VOCs, ACS, the patient hospitalization and the number of blood transfusion in adult SCD patient. HU has been shown to reduce mortality of SCD severely affected SCD patients (5-10 years follow-up). It increases the survival of patients with HU. The probability of 10-year survival was 86% and 65% for patients under HU and those without HU treatment, respectively (122). However, this treatment must be closely monitored to avoid side effects. Starting doses are around 15 mg/Kg/day once a day and may be escalated by 5mg/Kg/day until the maximum tolerated dose is reached, alternatively the dose may be increased until clinical benefit is obtained, generally from 15 to 35 mg/Kg/day. The starting dose should be 10 mg-Kg-day if creatinine clearance is below 100 ml-min and/or reticulocytes <150,000/µl or low erythropoietin levels. Increase MCV is a good marker of patient's compliance. Table 8 summarizes the indication for HU treatment, laboratory markers for follow-up and monitoring of HU treatment and side effects in adult SCD patients.

TABLE 8. INDICATIONS FOR HYDROXYUREA TREATMENT, LABORATORY MARKERS FOR FOLLOW-UP AND MONITORING OF HYDROXYUREA TREATMENT AND SIDE EFFECTS IN ADULT SCD PATIENTS		
Acute vaso-occlusive complications	**Laboratory markers of severity**	**Organ dysfunction**
▪ Recurrent severe painful crises ▪ Acute chest syndrome ▪ Frequent hospitalization	▪ Low Hb ▪ Low HbF ▪ Elevated WBC ▪ Elevated LDH	▪ Renal disease (eg, proteinuria) ▪ Pulmonary disease (eg, hypoxemia) ▪ Neurological disease (eg, stroke)
HU monitoring	**Side effects**	
II. Complete blood count before starting the treatment III. Complete blood count and HbF level each 2 weeks after initiation and after each dose increase IV. When stable every 4-6-8 weeks	V. Myelosuppression (resolve by decreasing dosage or temporally interruption of administration). Decreased reticulocytes and Hb, PMN and platelets count. VI. Incidence on men fertility (inform the patient and propose sperm storage); VII. In case of pregnancy occurrence stop HU treatment as soon as possible VIII. Decreased of reticulocytes, Hb, neutrophil and PLT count IX. Occurrence or recurrence of leg ulcer (skin protection, avoid trauma or cold creams) X. Melanonychia, dry skin (inform the patient)	

HU: hydroxyurea; Hb: haemoglobin, HbF: fetal haemoglobin; PLT: platelet

2. **Transfusion** (80-89)

See chapter “Recommendations of red blood cells transfusion in young adults and adults patients with SCD”

V. SPECIAL TOPICS

1. Leg ulcers (LU) (90-95)

Leg ulcers are generally associated with more markedly haemolytic SCD phenotype (low Hb and increase LDH levels) and with high rate of pulmonary hypertension, renal disease and priapism. The pathogenesis is complex and related to micro vascular obstruction by dense, rigid red cells, venous incompetence, local bacterial infections, abnormal autonomic control (increase vasoconstriction), in situ thrombosis and local hypoxia. The common sites for leg ulcer in SCD are the medial and lateral malleolus. Leg ulcers can be divided into acute leg ulcers if they persist less than 6 months and chronic leg ulcers when persist beyond 6 months. They have big impact on social status and lead to depression, as well as opioid abuse. Table 18 summarizes the clinical management of leg ulcers in SCD patients.

TABLE 9. CLINICAL MANAGMENT OF LEG ULCERS IN SCD PATIENTS	
Leg ulcers can be classified based on size and depth:	**Treatment of leg ulcers in SCD**
Stage 1: nonblanchable erythema of intact skin. In patients with darker skin: discoloration of the skin, edema and induration Stage 2: skin loss involving epidermidis, dermis, or both. Superficial ulcer as abrasion or shallow crater Stage 3: skin loss with damage or necrosis of subcutaneous tissue (deep crater) Stage 4: skin loss with extensive destruction, tissue necrosis or damage to muscle, bone or supporting structures.	Education, protection, infection control, support bandage if venous incompetence is suspected Surgical debridement to remove the fibrous surface Zinc sulphate 220 mg three times a day Regular blood transfusion to maintain Hb 8-10 g/dL range and HbS < 50% Pain relief: topical applications of analgesics Dressing with hydrocolloids. RDG peptide matrix has been shown some advantages

Hb: haemoglobin; HbS: haemoglobin S; RDG: Arginine- Glycine-Aspartic acid -peptide.

2. **Anaesthesia and surgery** (85-89, 96)

In SCD patients, surgery is related to an increased risk of peri-operative and post-operative complications. Although, ambulatory surgery is usually not at serious risk. Table 19 summarizes the clinical management of surgery and anaesthesia in adult SCD patients. Transfusion therapy in SCD is an important component in the management of SCD patients, who need major surgery. In fact, studies have shown that administration of transfusions before surgery reduces the post-operative complications such as painful crisis or ACS. At present there are no data available to define the respective advantages or disadvantages of the two main transfusion approaches, which are either an intensive transfusion regimen or a more limited transfusion in view to maintain Hb levels of 10 g/dL.

TABLE 190CLINICAL MANAGMENT OF SURGERY AND ANESTHESIA IN ADULT SCD PATIENTS	
Pre-operative evaluation Complete blood count, reticulocytes, urine analysis, coagulation, renal and liver function • Arterial oxygen pressure, echocardiogram • Multidisciplinary evaluation (haematologist-internist, anaesthesiologist, surgeon) • Look for signs of vaso-occlusion, fever, infection, dehydration, every abnormality of heart, liver, kidneys, brain and lungs.	**Note** • Lower surgery complication in laparoscopic surgery (risk of ACS) • Transfusion if Hb levels ≤ 10-11 g/dL • Reducing HbS is not necessary • History of ACS, asthma or other pulmonary complications: pulmonary function tests with bronchodilator response analysis

Pre-operative therapy	**Note**
• Fluids therapy at least 12 hours before surgery • Transfusion therapy (see below)	• Be careful of ischemia or hypoxia (more frequent in cardiothoracic and vascular surgery)
Intra-operative therapy • Avoid stenotic postures, lowering of body temperature, low arterial pressure	
Post-operative therapy • Fluids therapy at least 12-24 hours after surgery • Pain therapy as usual	
Attention: History of pulmonary or cerebral disease, recurrent hospitalization increases the peri-operative risk, especially for acute chest syndrome and vaso-occlusive events.	

Hb: haemoglobin; HbS: haemoglobin S; ACS: acute chest syndrome.

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D23 - RECOMMENDATIONS FOR THE MANAGEMENT OF RED BLOOD CELLS TRANSFUSION – CHILDREN 2010

Objective: Recommendations of red blood cells transfusion in children affected with sickle cell disease

Target population: medical staff expert and non-expert in the field

On behalf of ENERCA http://www.enrca.org:

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I. RED BLOOD CELLS TRANSFUSION

Chronic transfusion has been for many years the only therapy for patients with a severe form of SCD. More recently, hydroxyurea has been proposed in several conditions as an alternative to chronic transfusion, but there is, so far, no results of study randomizing these treatments, the SWiTCH trial in patients with a past history of stroke being, as exposed previously, still undergoing.

1. Indications

The most frequent indication for chronic transfusion in children is the prevention of cerebrovascular events, either of a first stroke (efficacy proven in the controlled STOP trial [Adams, 1992]), or of a recurrence [Wayne, 1993]. Chronic transfusion may be also proposed to children with recurrent splenic sequestrations aged less than 5 years, in order to delay the time of splenectomy after this age. It is also proposed to the minority of children having been treated with hydroxyurea because of recurrent pain or acute chest syndromes and who fail to respond to this drug [Miller, 2001].

INDICATIONS FOR CHRONIC TRANSFUSION
❑ Prevention of cerebrovascular events ❑ Recurrent splenic sequestration (children < 5 y.o.) ❑ Response failure to hydroxyurea for acute chest syndrome or recurrent painful crisis

2. Top-up versus exchange transfusion

Chronic transfusion may be performed through simple transfusion or exchange transfusion. The advantages of this last technique are to avoid an excessive increase of haematocrit, which would raise the already elevated viscosity characteristic of SCD, and to reduce the amount of transfused iron. Exchange transfusion can be performed manually or using a cell separator (this procedure is called erythrocytapheresis).

3. Target Hb S values

The target percentage of haemoglobin S in patients receiving regular blood transfusions varies across studies from 30% to 50%, and the optimal target remains to be determined.

4. Side effects

Complications of long-term transfusion programs are no more transfusion-transmitted infections in developed countries, but paucity of venous access, leading in many cases to use subcutaneous central venous access devices, and iron overload.

❑ Alloimmunisation

Red cells alloimmunisation is especially frequent in transfused SCD patients because of the discrepancies between the blood donor and recipient population [Vichinsky, 1990]. Extensive blood phenotyping must therefore be done before any transfusion and be available in the medical chart of

the patient. Blood products have to be phenotyped at least in the Rh and Kell systems and more extensively if alloimmunisation is known or suspected. An aspect of alloimmunisation almost specific to SCD is the delayed hemolytic transfusion reaction syndrome, associating typically 4 to 10 days after a transfusion a dramatic fall in hemoglobin count caused by the destruction of both donor and recipient red cells. A negative direct antiglobulin test and reticulocytopenia are often present. It is recommended to avoid additional transfusion which could worsen anemia. Steroids and intravenous immunoglobulin have been successfully used [Talano, 2003].

- Iron overload

Up to now, iron-related organ damages seem less severe in SCD than in thalassaemia [Wood, 2008; Fung, 2006], but this may be related to the fact that less sickle children have undergone long-duration transfusional programmes. For many years, deferoxamine has been the only available chelator, but this drug must be injected sub-cutaneously over 8-10 hours, almost every day. Recently, a once-daily oral chelator, deferasirox, has been demonstrated to have a similar efficacy than deferoxamine in reducing iron burden in children with SCD, with an acceptable tolerability [Vichinsky, 2007].

MINIMISING ALLOIMMUNISATION AND IRON OVERLOAD
❑ Phenotypic matching for Rh, Kell, C and E antigens and more extensively if alloimmunisation is known or suspected ❑ Iron chelation should be considered for patients who have received at least 20 top-up transfusion episodes or with a serum ferritin level of > 1000 ng/ml

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RECOMMENDATIONS FOR THE MANAGEMENT OF RED BLOOD CELLS TRANSFUSION – ADULTS - 2012

Objective: ENERCA recommendations of red blood cells transfusion in young adult and adult patients with sickle cell disease (SCD)

Target population: medical staff expert and non-expert in the field

On behalf of ENERCA **http://www.enerca.org**

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Based on available published guidelines and national recommendations

I. **TRANSFUSION – SCD YOUNG ADULTS AND ADULTS** (1-9)

Blood transfusion has two major goals in sickle cell disease: (i) to restore the Hb levels in patients with acute exacerbation of the anaemia such as aplastic anaemia or acute splenic sequestration in children with SCD; (ii) to reduce the HbS in order to prevent further sickling in case of VOC complications such as ACS or stroke. The management of transfusion therapy in SCD patients during acute events requires monitoring both total haemoglobin levels and HbS percentage. One goal is to correct anaemia but to avoid hyperviscosity (not exceed a post transfusion Hb of 10-11 g/dL. Another goal is to treat or prevent adverse SCD events by lowering the % of HbS (below 40%). There is still a large debate in the haematological community on clinical indication for transfusion therapy in SCD. Table 15 summarizes the three different transfusions strategies available and the related clinical indications.

1. **Transfusion complications: iron overload** (10-24)

A long-term complication of simple transfusion is the chronic iron-overload when the amount of iron introduced by transfusion exceeds the capacity to transport and storage iron in the body. Recently, Vichinsky et al. have reported a high proportion of SCD patients with haemosiderosis in a chronically transfused population of SCD patients, suggesting the need for a better monitoring and treatment of iron over-load in SCD patients (Table 16). Iron-chelation therapy should be considered in chronically SCD transfused patients. The large available experience in iron chelation is in β thalassaemic patients. Three iron chelators are clinically available for use in chronically transfused patients: deferoxamine mesylate (desferoxamine, DFO, Desferal), deferipone (Ferriprox ®) and deferasirox (Exjade ®) (see European recommendations: country/country). The current reference iron chelation therapy is the one based on deferoxamine, which has been extensively used in patients with iron overload showing significant morbidity and mortality benefits. However the frequent and prolonged subcutaneous infusion impacts on patient quality of life and compliance. Thus, the development of two new oral iron chelators has increased the possibility to effectively treat iron-overload in these patients. *Deferoxamine* is characterized by a very short plasma half-life (5-10 min) and needs a prolonged sub-cutaneous administration over a period of 8-12 hours to obtain an effective iron chelation. The routes of excretion are via urine and stools; major side effects are related to potential ear, eye, neurological toxicity, and arthropathy. The cardiac disease frequently observed in β thalassemic patients can be reversed by intensive infusion program. *Deferirpone* is characterized by a plasma life of 47-134 min., thus it needs 3 times daily administration and the excretion is primarily by urine (148, 152, 153). The major side effects are agranulocytosis, muscle, skeletal and joint pain, and zinc deficiency. A major concern in the chronic use of this compound is the lack of controlled long-term observations on the safety of this molecule. Studies have shown that deferiprone is effective in removing heart iron. Combined chelation with desferrioxamine and deferiprone has been evaluated in β thalassaemic major patients with severe cardiac or endocrine complications, indicating amelioration of left ventricular diastolic function and some beneficial effects on glucose intolerance. *Deferasirox* is the more recently approved oral iron chelator with plasma half-life of 8-16 h, allowing the mono-dose administration acting on 24 hours as iron chelator. The primary route of excretion is the stool and the most common side effects are gastrointestinal symptoms and rash, increased creatinine and transaminase(s) . The efficacy of deferasirox in iron-chelation is similar to that deferoxamine in chronically transfused patients. It chelates iron effectively but more slowly than deferiprone. Renal and liver functions should be monthly monitored.

TABLE 15. TRANSFUSIONAL STRATEGIES IN ADULT SICKLE CELL PATIENT AND RELATED CLINICAL INDICATIONS		
Acute simple transfusion	**Chronic simple transfusion or exchange transfusion**	**Acute exchange transfusion**
▪ Symptomatic anaemia ▪ Severe ACS with Hb < 7 g/dL ▪ Acute splenic or hepatic sequestration ▪ Preparation for major surgery ▪ Pregnancy ▪ Acute malarial episode	▪ Prevention of recurrent stroke ▪ Prevention of ACS recurrence (consider to switch to HU) ▪ Symptomatic anaemia with renal failure unresponsive to erythropoietin or with pulmonary hypertension	▪ Acute neurological events, ▪ Severe ACS ▪ Preparation for major surgery ▪ Chronically to avoid iron overload in place of simple transfusion treatment ▪ Pregnancy (3rd trimester if complications) ▪ Acute multi-organ failure ▪ Severe priapism
Controversial Indications		
Ocular complication, recurrent VOCs not responsive to HU treatment, and recurrent or acute priapism, chronic leg ulcer		

HU: hydroxyurea; ACS: acute chest syndrome; Hb: haemoglobin; VOC: vaso-occlusive crisis.

TABLE 16. EVALUATION OF TRANSFUSION THERAPY IN SCD PATIENTS	
	Note
▪ Mean pre- and post-transfusion Hb ▪ Levels of HbS ▪ Mean transfusion interval ▪ Red cell requirement (mL/Kg/year) ▪ Transfusion iron load ▪ LDH ▪ Serum ferritin (every 3 months)	> 20 RBC Units > 3,000 ng/mL; 1,500-3,000 ng/mL: equivocal Liver MRI is absolutely necessary to evaluate and monitor iron overload and therapy Heart and Liver iron assessment (MRI) is indicated

LDH: Lactate dehydrogenase; HbS: haemoglobin S; Hb: haemoglobin; MRI: magnetic resonance imaging; RBC: red blood cell.

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D24 - RECOMMENDATIONS FOR THE MANAGEMENT OF ACUTE SCD EVENTS – CHILDREN -2010

Objective: Recommendations for first line management of children affected with sickle cell disease

Target population: medical staff expert and non-expert in the field

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INDEX

I. THE MAIN FREQUENT COMPLICATIONS

Pain, infections, worsening of anaemia, and severe vasoocclusive events (such as acute chest syndromes, stroke, and may complicate the course of SCD. They may be difficult to disentangle, a painful crisis causing frequently fever for instance, and favour each other.

Vaso-occlusive episodes defined as new onset of pain that lasts at least 4 hr for which there is no explanation other than vaso-occlusion, and which requires therapy with parenteral opioids or ketorolac in a medical setting.

II. Pain

Pain is the hallmark of SCD. The frequency and severity of painful episodes vary widely both across patients and over time in each patient. Effective treatment of acute pain is one of the most common and challenging problems in the management of SCD.

Dactylitis is a common early manifestation of SCD that may occur before 6 months of age. Humerus, femur, and vertebra are often involved in older children, presenting with acute tenderness, swelling, often fever, and mimicking sometimes so closely osteomyelitis that the diagnosis is extremely difficult.

Repeated clinical examinations, blood counts, and C-reactive protein measurements, coupled with ultrasonography, and for some authors MRI, are used to help the diagnosis. Acute abdominal pain is frequent in young children, most often related to constipation, but specific complications of SCD such as acute splenic sequestration must be ruled out by palpation of the spleen and blood count, and cholelithiasis by abdominal ultrasound.

MANAGEMENT OF ACUTE PAIN [Rees, 2003]

- Hospitalize the child when pain is not relieved by codeine, or in case of fever, pallor, chest pain, respiratory signs
- Assess pain intensity.
- Always look for a cause (e.g., infection).
- Treatment: choose the analgesic, dosage, and route of administration.
- Reassess pain intensity and adjust the treatment.
- Be empathetic, reassuring, and supportive.
- Examine the patient often to ensure that pain relief is adequate and to check for evidence of complications such as acute chest syndrome or anaemia.

Treatment

There is general agreement among experts that paracetamol and hyperhydration are appropriate. Non-steroidal anti-inflammatory drugs are debated. Morphinics are often needed. Most authors

recommend intravenous administration for severe pain, using either a continuous infusion or patient-controlled analgesia. Regardless of the route of administration, the dosage should be titrated to achieve pain relief, particularly as the analgesic effect varies widely across patients.

III. Acute chest syndrome

A specific complication of SCD is the **acute chest syndrome**, defined as an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on a chest X-ray [Vichinsky, 2000].

1. Aetiology

Several causes may be associated, bacterial and/or viral infection, fat embolism, intravascular sickling of red cells in the lung, and hypoventilation related to pain and/or to opioids. More recently, an association between asthma and ACS was found [Boyd, 2006], which suggests that asthma should be systematically looked for and treated in SCD children.

2. Treatment

Antibiotics are given routinely, and the high rate of atypical micro-organisms requires combination of a macrolide with intravenous cephalosporin. Incentive spirometry can prevent atelectasis and infiltrates associated with acute chest syndrome in children and young adults admitted with chest or back pain above the diaphragm [Bellet, 1995]. Transfusion or exchange transfusion (procedure associating a phlebotomy and a transfusion) produced improvements in several uncontrolled studies. Hydroxyurea treatment is recommended in subjects having had at least 2 episodes of ACS [Rees, 2003].

IV. Infections

1. Aetiology

Due to routine immunization against Pneumococcus and *Haemophilus influenzae type b*, septicaemia and bacterial meningitis are becoming rare in developed countries.

Pneumonias remain extremely frequent.

Osteomyelitis is mostly related to salmonella species in patients with SCD [Chambers, 2000]. Except in the minority of cases where the diagnosis is confirmed by the positive culture of a joint or sub-periostal abscess aspirate, in most cases the diagnosis is made presumptively in a child with bone pain, swelling, fever, and hyperleucocytosis, all signs which may be also present in bone infarction. Radios and bone scans are unhelpful. MRI interest is debated. Ultrasonography of the painful zone may evidence a sub-periostal abscess or a contiguous effusion which may be aspirated.

2. Treatment

Given that bone infarcts are highly more frequent than infections, it can be recommended in children without obvious signs of sepsis to wait for some hours the effects of the treatment of vasoocclusion

before introducing intravenous antibiotics, but not to wait more than one day to begin antibiotics to avoid osteoarticular sequel. Antibiotic treatment must cover salmonella and staphyloccus.

V. Acute anaemia

Acute exacerbation of anaemia is defined as an acute lowering of the haemoglobin level from baseline by at least 2 g/dL.

SCD is characterized by a chronic haemolytic anaemia with a baseline haemogobin level in homozygous SS subjects at 8.0 ±1.5 g/dl [Neonata, 2000]. The most common causes of acute anaemia are acute splenic sequestration, transient red cell aplasia, and hyperhyperhaemolysis in patients with severe infection and/or pain.

1. Aetiology

Acute splenic sequestration defined as rapid intrasplenic trapping of cellular elements of the blood, which causes a precipitous fall in haemoglobin level and is often associated with a relative or absolute thrombocytopenia (<150,000/lL) and hypovolemia. It occurs mostly before age 6 years in homozygous SS patients, but may occur later in SC patients. The diagnosis is made on a fall in haemoglobin level of at least 2 g/dl in presence of an acutely enlarged spleen, typically associated with reticulocytosis and thrombocytopenia [Edmond, 1985]. Life is threatened both by acute anemia and hypovolemia. Transfusion is urgent, but must be cautious because the red cells sequestered in the spleen are remobilized after transfusion and hemoglobin levels increases more than expected given the amount of blood transfused [Ohene-Frempong, 2001]. About one half of children who have had a first splenic sequestration have a recurrence, and there is no consensus about the management, either splenectomy or conservative management, for those patients [Owusu-Ofori, 2002]

Transient red cell aplasia defined as a transient total or partial suppression of erythropoiesis characterized by a decrease in the haemoglobin level and reticulocytopenia (absolute reticulocyte count <50,000/lL)**.** The most common cause is parvovirus B19 infection [Smith-Whitley, 2004].

2. Treatment

Episodic transfusion is required in those settings. Its goal is to restore haemoglobin up to its baseline level and not above, in order to avoid increasing excessively blood viscosity. See section " Treatment intensification".

Red cells alloimmunization is especially frequent in transfused SCD patients because of the discrepancies between the blood donor and recipient population [Vichinsky, 1990]. Extensive blood phenotyping must therefore be done before any transfusion and be available in the medical chart of the patient. Blood products have to be phenotyped at least in the RH and Kell systems and more extensively if alloimmunisation is known or suspected. An aspect of alloimmunization almost specific to SCD is the delayed hemolytic transfusion reaction syndrome, associating typically 4 to 10 days after a transfusion a dramatic fall in haemoglobin count caused by the destruction of both donor and recipient red cells. A negative direct antiglobulin test and reticulocytopenia are often present. It is recommended to avoid

additional transfusion which could worsen anemia. Steroids and intravenous immunoglobulin have been successfully used [Talano, 2003].

VI. Stroke

Cerebrovascular accident is defined as an acute neurological syndrome secondary to occlusion of an artery or haemorrhage, with resultant ischemia and neurological signs and symptoms.

1. Treatment

Experts agree that exchange transfusion should be performed when a stroke occurs. More than half of patients with a first stroke have another. Long term observational studies showed that monthly blood transfusions decreased the risk of recurrent stroke, although transient neurological events were not completely stopped [Pegelow, 1995]. Stroke is considered an indication for bone marrow transplantation in children and adolescents who have siblings with identical HLA [National Institutes of Health. *The management of sickle cell disease*. 4th ed. 2002. (NIH publication No 02-2117) www.nhlbi.nih.gov/health/prof/blood/sickle/index.htm].

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RECOMMENDATIONS FOR THE MANAGEMENT OF ACUTE SCD EVENTS – ADULTS - 2012

Objective: ENERCA recommendations for first line management of young adult and adult patients with sickle cell disease (SCD)

Target population: medical staff expert and non-expert in the field

On behalf of ENERCA **http://www.enerca.org**

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Based on available published guidelines and national recommendations

INDEX

I. **ACUTE PAIN CRISIS** (1-13)

Pain is the most frequent and important clinical manifestations of SCD and requires a multidisciplinary approach with the major endpoint of successful pain control and pain relief. Sickle cell pain results from the combination of pain generated by somatic, neuropathic and vascular mechanisms. Studies on sickle cell patients have shown that an inadequate pain management influences how patients perceived their pain coping and their analgesic dependence during day-life. **Pain treatment: First class pharmacological treatment** is based on paracetamol or non-steroidal anti-inflammatory molecules (NSAID, such as ibuprofen) that should be given with attention if dehydration or previous history of renal dysfunction and/or suspicion of sepsis and/or **second class pharmacological treatment** on opioids as codeine, morphine or tramadol, an atypical-opioid (attention: for respiratory failure, paralytic ileus, or other side effects of opioids). To reduce the opioid related gastrointestinal side effects metoclopramide should be always associated with opioids. SCD patients should be educated in quantification of pain based on Visual Analogue Scale (VAS from 0: no pain to 10: the worsen pain) and in self-management of the low and moderate pain at home with auto-medication under physician's supervision. General indications such as resting, warm environment, avoid cold and reinforce hydration should be considered as part of the treatment of pain events. Now for acute recurrent and chronic complications of SCD are also indicated hydroxyurea 20 mg/Kg/day.

II. **VASO-OCCLUSIVE CRISIS (VOCS)**(1-13)

Vaso-occlusive crises (VOCs) (involving musculoskeletal system) are one of the main acute clinical manifestations of SCD (Table 1). They might be associated with bone infarction, detectable by magnetic resonance (MRN) few weeks after VOCs. In the large part of the bone VOCs, patients could be treated at home by increase hydration (two litters daily) and pain treatment with **first class pharmacological** treatment is based on paracetamol alone or non-steroidal anti-inflammatory molecules (NSAID, such as ibuprofen) and/or **second class pharmacological** treatment on opioids as codeine, morphine or tramadol, an atypical-opioid. SCD patients should be educated in quantification of pain based on Visual Analogue Scale (VAS from 0: no pain to 10: the worsen pain) and in self-management of the low and moderate pain at home with auto-medication under physician's supervision. It is also crucial to adopt an adequate life-style to prevent the worsening of sickle cell related symptoms such rest, hydration and avoid extreme temperature. In case of persistence of VOCs (pain-VAS>7 for more than 48 hours) patients should be admitted to Emergency Department (ED) for clinical evaluation, blood exams and more intense pain treatment.

When pain remains inacceptable after 48 hours of well-conducted therapy, an exchange transfusion could be indicated.

TABLE 1. EVALUATION OF SCD PATIENTS DURING VOCS INVOLVING MUSCOLOSKELETAL SYSTEM IN EMERGENCY DEPARTMENT	
	Note
Complete blood count and reticulocytes	
Creatinine, BUN, hepatic function (AST, ALT, LDH, bilirubin), urine analysis	
Pulse oxymetry (or arterial blood gas) and respiratory rate Systolic pressure	
Clinical evaluation: ▪ to detect early signs of ACS ▪ neurological or cardiovascular manifestations ▪ abdominal complication	**Based on the clinical evaluation** **consider:** Chest X-ray ECG Abdominal ultrasonography
Treatment of uncomplicated acute VOCs	**Note**
Saline infusion	Avoid over-hydration
Pain management: ▪ **First class pharmacological treatment**: o paracetamol: 15 mg/kg every 6 hs or o non-steroidal anti-inflammatory molecules as ketorolac: 0.9 mg/Kg/day (0.0375 mg/kg/h, see text for the correct use) ▪ **Second class pharmacological treatment:** o Morphine: 0.72 mg/kg/day (0.03 mg/kg/h) or o Tramadol (atypical-opioid): 7.2 mg/Kg/day (0.3 mg/kg/h) o Metoclopramide: 0.57 mg/Kg/day (0.02375 mg/kg/ora)	**Pain-VAS:** at the admittance and after 2-4hs and then every 4hs **Titration curve for opioid treatment**: every 30 min then every 4 hs or less **Monitor:** sedation. If severe respiratory depression or sedation stop opioid and give Naloxone 0.4 mg iv.

ACS: acute chest syndrome; ECG: electrocardiography; BUN: blood urea nitrogen; Alanine aminotranferase *(*ALT*)* and aspartate aminotransferase *(*AST*);* LDH: Lactate dehydrogenase; VAS: visual analogue scale; h: hour; iv: intravenous.

III. **ACUTE CHEST SYNDROME (ACS**) (14-23)

Acute chest syndrome (ACS) is definite as an *"acute event with pneumonia-like symptoms associated with a new infiltrate on the chest X-ray".* The new infiltrate might appear with 24 to 48 hours delayed after the patient complaint the respiratory symptoms (cough, chest pain or respiratory difficulty). ACS is a frequent cause of hospitalization and it remains an important cause of death in adult patients. ACS is rarely associated with a pulmonary infection in adults (viruses, atypical bacteria: *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* or *S. pneumoniae*) in all the other cases the following causes can be recognized: bone infarction of the thoracic cage, fat embolism from infracted bone marrow or acute pulmonary disease related to hypoventilation in particular in patients after abdominal surgery or with intestinal sub occlusion. Differential diagnosis is thromboembolism. Possible complications are: Mental confusion and coma: systemic passage of fat emboli, renal failure, acute pulmonary hypertension, multiorgan failure, erythroblastosis, thrombocytopenia with intravascular coagulation (especially if right to left cardiac shunt or permanent foramen ovale).

Table 2 summarizes the management of adult SCD patient with acute chest syndrome. In patients with recurrent episodes of ACS consider: hydroxyurea (HU) treatment or chronic transfusion programs as either exchange or simple transfusion. At 2-3 months after ACS patients should be re-evaluated with pulmonary function tests, in particular broncho-reactivity and sleep hypoventilation or apnea.

TABLE 2. MANAGMENT OF ADULT SCD PATIENTS WITH ACUTE CHEST SYNDROME	
Evaluation of SCD patients during ACS	**Note**
Complete blood count , creatinine, BUN, hepatic function (AST, ALT, LDH, bilirubin), NT-proBNP, urine analysis, blood culture if fever > 38°C	
Pulse oxymetry (or arterial blood gas) and respiratory rate Temperature Systolic pressure	
Clinical evaluation: ▪ Palpation of the chest: to identify rib and/or vertebral infarction ▪ Auscultation of the chest: o may be normal or minimal variations in ventilation (early stage) o rales and signs of consolidation (48-72 h after the respiratory symptoms) ▪ Abdominal evaluation: consider possible abdominal ileus	Chest X-ray ECG BAL or induced expectoration (indicated if infection is highly suspected)
Treatment of ACS	**Note**
Saline infusion (< 2L/ 24hs) **Antibiotics:** intravenous broad spectrum antibiotics such as a amoxicillin 3 gr/d iv (in case of severe clinical presentation	Avoid over hydration If tolerated consider to substitute the

consider the association with a macrolide or in case of allergy: erythromycin) or macrolide in combination with third generation cephalosporin. **Oxygen administration nasally** (2-3 L/min) to obtain peripheral oxygen saturation above 95%	cephalosporin with a quinolone When arterial blood saturation is between 91-96% incentive spirometry to prevent further ventilation defects Consider to use bronchodilators Consider early respiratory physiotherapy
Pain management: ▪ **First class pharmacological treatment**: o paracetamol: 15 mg/kg every 6 h or o non-steroidal anti-inflammatory molecules as ketorolac: 0.9 mg/Kg/day (0.0375 mg/kg/h) ▪ **Second class pharmacological treatment:** o Morphine: 0,72 mg/kg/day (0.03 mg/kg/h) avoiid the use of benzodiazepine or o Tramadol (atypical-opioid): 7.2 mg/Kg/day (0.3 mg/kg/h) o Metoclopramide: 0.57 mg/Kg/day (0.02375 mg/kg/h)	**Pain-VAS:** at the admittance, after 2-4 hs and then every 4 hs **Titration curve for opioid treatment**: every 30 min then every 4 hs or less **Monitor:** sedation. If severe respiratory depression or sedation stop opioid and give Naloxone 0.4 mg iv.
Exchange transfusion therapy or simple transfusion (if Hb is < 7 g/dL) • Worsening respiratory distress • Early signs of organ failure (kidney, liver, heart) • Neurological signs: confusion, motor defects • Intractable pain or opioid intolerance • Hemodynamic instability (cadiovascular insufficiency) • Severe anaemia • Nosocomial infection • Sepsis	Therapeutic target is to rapidly reduce HbS < 30 o 40% o 50 according to clinical course

ACS: acute chest syndrome; ECG: electrocardiography; BUN: blood urea nitrogen; Alanine aminotranferase *(*ALT*)* and aspartate aminotransferase *(*AST*);* LDH: Lactate dehydrogenase; VAS: visual analoguer scale; h: hour; HbS: haemoglobin S; iv: intravenous.

IV. **ACUTE ABDOMINAL PAIN RELATED TO BILIARY TRACT DYSFUNCTION** (23-27)

In adult SCD patients the acute abdominal pain is mainly related to biliary tract dysfunction. Adult SCD patients, 60% at the age of 30 and more than 40% at the age of 20, are affected by biliary tract dysfunction mainly represented by cholelitiasis or biliary sludge. The differential diagnosis should be done with common duct obstruction, angiocholitis, acute pancreatitis and sepsis.

Table 3 summarizes the clinical management of SCD patient with acute abdominal pain and biliary tract dysfunction

TABLE 3. CLINCAL MANAGMENT OF ADULT SCD PATIENT WITH ACUTE ABDOMINAL PAIN AND BILIAR TRACT DYSFUNCTION

Evaluation of SCD patient	**Note**
Complete blood count, creatinine, BUN, hepatic function (AST, ALT, LDH), amylase/lipase, total and conjugate bilirubin, urine analysis, blood culture if fever > 38°C	
Abdominal clinical evaluation Abdominal ultrasonography	Consider: splenomegaly, hepatomegaly, ileus constipation Consider biliary tract MRI to exclude the presence of gallstone in the common duct Consider other causes of abdominal pain: pneumopathy, pyelitis, gastric ulcer, mesenteric infarct (very rare)
Treatment of Acute Abdominal Pain with Biliar Tract Dysfunction in adult SCD patient	**Note**
Saline infusion **Antibiotics:** intravenous broad spectrum antibiotics such third generation cephalosporin	Avoid overhydration
Pain management: ▪ **First class pharmacological treatment**: o paracetamol: 15 mg/kg every 6 h or o non-steroidal anti-inflammatory molecules as ketorolac: 0.9 mg/Kg/die (0.0375 mg/kg/h) ▪ **Second class pharmacological treatment:** o Morphine: 0.72 mg/kg/day (0.03 mg/kg/h)	**Pain-VAS:** at the admittance, after 2-4hs and then every 4hs **Titration curve for opioid treatment**: every 10 min then every 2-4 hs or less **Monitor:** sedation. If severe

Or o Tramadol (atypical-opioid): 7.2 mg/Kg/day (0.3 mg/kg/h) o Metoclopramide: 0.57 mg/Kg/day (0.02375 mg/kg/h)	respiratory depression or sedation stop opioid and give Naloxone 0.4 mg iv.

BUN: blood urea nitrogen; Alanine aminotranferase *(*ALT*)* and aspartate; aminotransferase *(*AST*);* LDH: Lactate dehydrogenase; VAS: visual analogue scale; h: hour; HbS: haemoglobin S; iv: intravenous; MRI: magnetic resonance

V. **STROKE AND CEREBROVASCULAR ACUTE EVENTS** (27-45)

Strokes are more frequent in SCD patients in the first two decades of life, especially in children. Cerebral infarction is the most important manifestation and devastating complication of SCD. Silent cerebral infarcts have been detected in 17%-30% of paediatric patients (see also ENERCA recommendations for children with SCD). Studies have recently shown an impairment of dynamic cerebral auto regulation in SCD patients associated with reduced cerebrovascular reserve capacity most likely participating in the pathogenesis of stroke in SCD. The cerebrovascular clinical presentations are: (i) cerebral infarction and transient ischemic attacks (TIA); (ii) intracranial haemorrhage (IH) and (iii) cognitive function deterioration. Several precipitating factors such as episodes of acute anaemia or sepsis could be involved in cerebral infarction and transient ischemic attacks.

Intracerebral haemorrhage may be rapidly lethal and is one of most important cause of sudden death in adult SCD patients. Intracerebral haemorrhage is frequently due to the rupture of a cerebral aneurysm resulting in subarachnoid and less frequent parenchymal or ventricular haemorrhage as complication of Moya-Moya disease.

Table 4 summarizes the evaluation and clinical management of adult SCD patients with acute neurological manifestations.

TABLE 4. SCD PATIENTS WITH ACUTE NEUROLOGICAL CLINICAL MANIFESTATIONS AND MANAGEMENT	
Evaluation of SCD patient	**Note**
Complete blood count, creatinine, BUN, Ca, K, Na, Cl, total and conjugate bilirubin, albumin, coagulation, blood culture if fever > 38°C Pulse oxymetry (or arterial blood gas) and respiratory rate Temperature Systolic pressure Non contrast computed tomography (CT) head or MRI	 contact neurosurgery if positive for - intracranial haemorrhages - high intracranial pressure If negative: consider - to repeat it after 3 hrs - to carry out MRI
Treatment of stroke in adult SCD patients	**Note**
Saline infusion Exchange therapy to rapidly reduce HbS (<30%)	avoid over-hydration
Pain management according to clinical status (see above VOC): ▪ **First class pharmacological treatment**: o paracetamol: 15 mg/kg every 6 h ▪ **Second class pharmacological treatment:** o Morphine: 0.72 mg/kg/day (0.03 mg/kg/h) or o Tramadol (atypical-opioid): 7.2 mg/Kg/day (0.3 mg/kg/h) o Metoclopramide: 0.57 mg/Kg/day (0.02375 mg/kg/h)	**Pain-VAS:** at the admittance, after 2-4 hs and then every 4hs **Titration curve for opioid treatment**: every 30 min then every 4 hs or less **Monitor:** sedation. If severe respiratory depression or sedation stop opioid and give Naloxone 0.4 mg iv.

VAS: visual analogue scale; h: hour; HbS: haemoglobin S; iv: intravenous; MRI: magnetic resonance.

Stroke is an indication for chronic transfusion regimen in children with SCD, but the optimal duration is still debated in adult sickle cell patient. In case of diffuse vasculopathy, there is a consensus to continue transfusion program in adulthood. Stroke is considered an indication for bone marrow transplant in adolescents with HLA-identical siblings.

VI. PRIAPISM (41-46)

Priapism is a severe complication in young adult patients with SCD. Priapism is a persistent erection, occurring more frequently during the night. There are two types of priapisms: type 1: lasting more than 3 hours (prolonged, PP) and type 2: lasting < 1 hour (stuttering, SP). Priapism is a urologic emergency and it can be complicated by penile fibrosis and impotence; it seriously impairs the patient quality of life. Priapism's therapy is based on hydration and analgesia associated with decompression of the penis by needle aspiration, followed by intracavernous injection of alpha antagonist (etlefrine is preferred as no dilution is required). The recurrence of priapism is prevented by oral and/or self injections of etilefrine (in case of SP lasting more than 30 mm). Transfusions or exchange transfusions within the first 24 hours (HbS<30 %)may be indicated in the case of late care in order to preserve erectile function. Table 5 summarizes the clincical management of priapism in adult SCD patient.

TABLE 5. CLINICAL MANAGMENT OF PRIAPISM IN ADULT SCD PATIENT	
Evaluation of SCD patients with priapism	**Note**
Complete blood count, creatinine, BUN, Ca, K, Na, Cl, total and conjugate bilirubin, coagulation Pulse oxymetry (or arterial blood gas) and respiratory rate Temperature Systolic pressure	Contact urologist
Treatment of priapism in SCD patient	**Note**
Saline infusion Penile aspiration if duration > 3hs and etilefrine 10 mg) intra corpus cavernosum Consider hydroxyurea in case of recurrent priapism Search for sleep desaturations	Avoid over hydration Monitor blood pressure

Pain management: ▪ **First class pharmacological treatment**: o paracetamol: 15 mg/kg every 6 h ▪ **Second class pharmacological treatment:** o Morphine: 0.72 mg/kg/day (0.03 mg/kg/h) or o Tramadol (atypical-opioid): 7.2 mg/Kg/day (0.3 mg/kg/h) o Metoclopramide: 0.57 mg/Kg/day (0.02375 mg/kg/h)	**Pain-VAS:** at the admittance, after 2-4h and then every 4h **Titration curve for opioid treatment**: every 30 min then every 4 h or less **Monitor:** sedation. If severe respiratory depression or sedation stop opioid and give Naloxone 0.4 mg iv.

BUN: blood urea nitrogen; Alanine aminotranferase *(*ALT*)* and aspartate; aminotransferase *(*AST*);* LDH: Lactate dehydrogenase; VAS: visual analogue scale; h: hour; HbS: haemoglobin S; iv: intravenous.

VII. **ACUTE EXACERBATION OF BASELINE ANAEMIA** (47-49)

SCD is characterized by a chronic haemolytic anaemia with a baseline haemoglobin level at 8.0 ± 1.5 g/dL in SS subjects. In adult SCD patients, the aplastic crisis represents one of the major causes of acute exacerbation of baseline anaemia. Acute exacerbation of anaemia is defined as an acute lowering of the haemoglobin level from baseline by at least 2 g/dL. Since in SCD the sickle red blood cell lifespan is shortened, every transient suppression of erythropoiesis can result in severe anaemia. Infection by Parvovirus B-19 is the most frequent cause of reticulocytopenia in SCD patients. The symptoms are fatigue, dyspnea, more severe anaemia than usual and few or no reticulocytes; fever and signs of upper respiratory infection are also common. An acute Parvovirus B-19 infection is confirmed by serological and microbiological tests. Erythroid aplasia terminates spontaneously after 5-10 days. Treatment of aplastic crisis is supportive. Because of severe tachycardia and tachypnea, packed red blood cell transfusions are often necessary. In rare cases evolution may be complicated with bone marrow necrosis. Beside the Parvovirus B19 infection**, other possible causes** of worsening anaemia in SCD can be divided into: **(i) acute**: auto-immune haemolysis, delayed haemolytic transfusion reaction (DHTR), acute malarial episode, acute intestinal or urinary loss, acute splenic sequestration (rare in adults), and sepsis; **(ii) chronic**: chronic inflammation, rarely cobalamin deficiency, hypothyroidism, renal insufficiency (see also section 3.3), and chronic hypersplenism.

TABLE 6. CLINCAL MANAGMENT OF ADULY SCD PATIENTS WITH APLASTIC CRISIS	
Evaluation of SCD patients with aplastic crisis	**Note**
Complete blood count, reticulocytes, creatinine, BUN, Ca, K, Na, Cl, total and conjugate bilirubin, coagulation, blood culture if fever > 38°C Pulse oxymetry (or arterial blood gas) and respiratory rate Temperature Systolic pressure	Reticulocytes count is importan every febrile patient, because could be an early sign of Parvovi infection Search for Parvovirus B19 infectic
Treatment of aplastic anemia	**Note**
Saline infusion **Antibiotic therapy** **Transfusion** if needed (Hb ≤ 11 g/dL) **Ig treatment** (20-30 g/Kg/d i.v. for 5-7 ds)	Avoid over-hydration Prolonged anaemia

BUN: blood urea nitrogen; Alanine aminotranferease *(*ALT*)* and aspartate; aminotransferase *(*AST*);* LDH: Lactate dehydrogenase; VAS: visual analog scale; h: hour; Hb: hemoglobin; iv: intravenous; Ig: immunoglobulin; d: day.

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D25 - RECOMMENDATIONS FOR THE MANAGEMENT OF PREGNANCY – 2012

Objective: ENERCA recommendations for management of pregnancy

Target population: medical staff expert and non-expert in the field

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Based on available published guidelines and national recommendations

I. CONTRACEPTION AND PREGNANCY

1. **Contraception** (1-5)

Oral contraception (OC) is an established risk factor for venous thromboembolism among women. In adult SCD patients the coagulation system is more activated than in normal people. Although women with SCD are fertile as healthy ones and contraception is frequently requested. Low-dose combined oral contraceptive, depo-medroxyprogesterone (DMPA) acetate and cooper intrauterine devices (IUDs) can be used as contraceptive. If interruption of pregnancy is required before 12 weeks of gestational age, the method of choice is intrauterine aspiration, other newer methods as RU 486 (mifepristone) should be avoided because they seem to increase VOC risk.

2. Genetic counselling

It must be done prospectively in women and men as well . Many patients have wrong or negative ideas about pregnancy, fertility, sexual capacities or genetic transmission. When a genetic risk for a given pregnancy is established, genetic counselling must remain non directive during a specific appointment, as early as possible during the pregnancy and setting the conditions of a participative discussion about all aspects of the problem including but not limited to prenatal diagnosis and optional selective abortion.

3. **Pregnancy** (6-11)

The management of pregnancy is still subject of intense discussions in the scientific community, mainly due to the limited number of well-designed clinical trials. SCD women show increased tendency to pre-term labor and pre-eclampsia and low-birth-weight babies with neonatal mortality rate < 5%. Prophylactic transfusion therapy in SCD patients during pregnancy still depends on physician judgment. In addition to prophylactic transfusion therapy, there are other indications for transfusion in pregnant SCD women: (i) the presence of anaemia with cardiac or respiratory compromise; (ii) the severity of sickle cell related clinical manifestations (ACS); (iii) refractory eclampsia and (iv) preparation for Caesarean section. Table 1 summarizes the clinical management of pregnancy in SCD patients.

TABLE 1. CLINCAL MANAGEMENT OF PREGNANCY IN SCD PATIENTS	
Initial assessment • Medical history (medical complication: renal, neurological, pulmonary difficulties) • Chemical dependency (drugs, tobacco, alcohol) • All routine prenatal screening examinations • Genetic counselling and in case of foetal risk for SCD propose the prenatal diagnosis	**Note** 1 mg folic acid daily Also other vitamins, minerals and iron if necessary
Evaluation during pregnancy ▪ Close monitoring every 2 weeks until the 28th week, then weekly ▪ Value intrauterine growth by ultrasound (intrauterine growth retardation is more frequent in SS patient than SC) ▪ Systemic hypertension (10-20% pregnant SCD women)	**Note** HU is contraindicated during pregnancy (advise to stop treatment as soon as pregnancy is recognized) Toxemia of pregnancy, thrombophlebitis, pyelonephritis and spontaneous abortion have increased frequency If intrauterine growth retardation: bed rest is recommended and value early delivery
Delivery During periods of uterine contractions, hemodynamic of anaemia and cardiac output are accentuated Avoid steroid use	**Note** Hb should be 9-11 g/dL with HbS < 40% at delivery Oxygen and hydration should be administered during labour and delivery Blood loss should be replaced according to the usual obstetrical practice
Evaluation after delivery ▪ Maintain hydration ▪ Prevention of thromboembolism	**Note** Preventing atelectasis in postpartum with incentive spirometry and treat fever aggressively

Hb: haemoglobin; HbS: haemoglobin S

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