



HEREDITARY DISEASES PROGRAMME  
 DIVISION OF NONCOMMUNICABLE DISEASES AND HEALTH TECHNOLOGY

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REPORT OF THE VITH ANNUAL MEETING OF THE WHO WORKING GROUP  
 ON THE FEASIBILITY STUDY ON  
 HEREDITARY DISEASE COMMUNITY CONTROL PROGRAMMES (HEREDITARY ANAEMIAS)

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ANNEX: Guidelines for the management of sickle cell disease

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## 1. INTRODUCTION

About 12% of the human population are symptomless carriers of one or more of the hereditary anaemias - sickle cell disease (SCD), the thalassaemias, and glucose-6-phosphate-dehydrogenase (G6PD) deficiency. It is estimated that together they account for a high infant mortality, and also cause significant chronic morbidity (Tables 1 and 2)<sup>1-10</sup>.

The hereditary anaemias were originally confined to the sub-tropics and tropics, their high incidence being due to the fact that healthy carriers are protected against lethal effects of infection with *Falciparum malaria*. However, global migration is mixing human populations, and the hereditary anaemias are now found in most countries of the world. Their medical implications must be taken into account in most health care systems.

G6PD deficiency has been discussed separately<sup>9,10</sup> and will not be mentioned further here, except to raise the possibility of screening for G6PD deficiency when screening for carriers of haemoglobin disorders.

The haemoglobin disorders, the thalassaemias and SCD, are inherited in a Mendelian recessive manner. That is, when one partner is a carrier and one is not, on average half their offspring will be carriers but none has the major disease. However, when both partners are carriers there is a one in four chance in each pregnancy of an affected (homozygous) child.

The issues surrounding thalassaemia are relatively clear. The WHO Working Group on Hereditary Anaemias concluded at its first meeting in 1982 that "a major effort should be expended on a programme of prevention for thalassaemia. However, since the clinical expression of SCD is not fully understood, it is not yet appropriate to develop a widespread preventive programme for this disorder; rather a major effort should be put in to learning more about its natural history, which varies with both genetic and environmental factors". WHO activities therefore initially focussed mainly on thalassaemia. A global network of WHO centres has been created, and the Working Group has held annual or biennial meetings<sup>1-5,8,9</sup>, with biennial training courses in laboratory methods for community control. There have also been numerous formal and informal WHO consultations in different countries, namely Bahrain, Burma, China, Cuba, Cyprus, India, Indonesia, Lebanon, The Maldives, Pakistan, Portugal, and Trinidad. The WHO Regional Office for Europe sponsors a European/Mediterranean Working Group on Haemoglobin Disorders<sup>11</sup>.

A "control programme" describes an integrated approach for a genetic disease, that combines the best possible patient care with community information and availability of carrier screening, genetic counselling and prenatal diagnosis<sup>12</sup>. Existing thalassaemia control programmes now provide a model for this concept. Because of the level of public interest in prevention, the number of new births of affected patients has fallen to a very low level in the Mediterranean area, and at the same time the standard of patient care has improved<sup>11</sup>.

We now have rather more understanding of the natural history of SCD, and simplified methods are available for early prenatal diagnosis in the first trimester of pregnancy. In many developing countries, infant mortality continues to fall, and hereditary disease is increasingly recognized as a health problem. It is now necessary to develop appropriate approaches for control of SCD in developing countries.

The frequency of an inherited disease may be expressed either in terms of the percent of the population that are symptomless carriers, or in terms of the birth rate of affected infants. The relationship between the two is not linear. Globally

there are more carriers of thalassaemia than of SCD, but the high frequency of the sickle cell gene in certain areas leads to a high birth rate of homozygotes, and as a result, SCD accounts for about 70% of haemoglobin disorders worldwide. Nearly 70% of affected births occur in sub-Saharan Africa where up to 2% of all infants are born with SCD (Table 1). This high frequency makes the African Region a global focus of haemoglobin disorders, and indeed of inherited disease.

The term "SCD" includes a spectrum of conditions in which the constant feature is HbS. In decreasing order of severity, there are: homozygous SS disease (sickle cell anaemia), Hb S/D disease, HbS/ $\beta$  thalassaemia, and Hb S/C disease. However, the clinical picture in all is variable, and any complication of SCD can occur in any one of them.

The clinical implications of SCD differ from those of thalassaemia. In general, the thalassaemias are predictable diseases with a slow evolution and increasingly successful but burdensome treatment, that place a severe strain on the patient, the family and the medical service<sup>1,13</sup>. By contrast, SCD is unpredictable. Complications arise suddenly, and vary in severity between populations, between individuals within populations, and in the same individual from time to time, the reasons for these variations being mostly unknown. Early diagnosis, and simple supportive management can significantly reduce morbidity and mortality. The clinical picture has been fully described by Serjeant<sup>14</sup>. The anaemia of 7-9 g/dl in sickle cell anaemia is usually well tolerated, but problems arise from acute unpredictable complications. In infancy and early childhood, the main risks are of sudden death due to trapping of sickled red cells in the spleen. This can lead either to sudden profound anaemia and death from an acute "splenic sequestration crisis", or to functional asplenia and sudden death from overwhelming infection. These complications often occur before a diagnosis has been made: even in developed countries there is no guarantee that all infants dying of SCD will be diagnosed. Neonatal screening is therefore recommended, both to obtain accurate epidemiological information, and to protect affected infants<sup>15</sup>. Many complications may arise in later life, when the picture is of a chronic debilitating condition, often punctuated by acute, unpredictable and life-threatening exacerbations which occur as acute emergencies. The natural history of SCD therefore varies markedly with the amount of health care and social support available. Guidelines for the management of sickle cell disease developed at the request of WHO, are appended (Annex).

The unique feature of the haemoglobin disorders is that symptomless carriers can be identified by simple, cheap and accurate blood tests, and therefore couples of carriers can be detected and informed of their genetic risk prior to reproduction. Prenatal diagnosis is also available, using increasingly simple obstetric and laboratory technology. The majority of couples at risk for thalassaemia request prenatal diagnosis, and continue only unaffected pregnancies<sup>16</sup>. A smaller proportion of couples at risk for SCD request prenatal diagnosis, and not all terminate affected pregnancies<sup>17</sup>.

In many developing countries, the haemoglobin disorders are the first genetic problem to emerge as primary health care reduces the infant mortality and more vulnerable infant survive. It is naturally difficult to establish these services in developing countries, even when haemoglobin disorders present a serious public health problem. Attempts are now being made to introduce thalassaemia control into India (Bombay area) and Thailand. An SCD programme has been established in Cuba, Guadeloupe and Martinique. However, the widespread preconception that developing countries have many higher priorities than medical genetics impedes the evolution of an appropriate approach. This is unfortunate for several reasons:

- (a) Inherited disease has an even more severe impact on families in developing than in developed countries, because of the heavy economic burden it places on the family, the fear of recurrence and the absence of prenatal diagnosis, and prevailing social prejudices<sup>18</sup>.
- (b) Urbanization brings an increasing proportion of the population within reach of basic health care: this leads to increased survival of children with SCD.
- (c) The existence of children with chronic disease inevitably makes demands on existing health services. It has been shown that if the problem is faced and planned for, resources can be used more cost effectively than if the issue is evaded<sup>18</sup>.

Since they are so common, the haemoglobin disorders provide a convenient model for working out an approach to chronic childhood disease in developing countries. Most experience with thalassaemia control has been gained in countries with a developed health service, and a primary care infrastructure that permits population screening. To what extent can it be extended to developing countries, and applied to sickle disease? As the problem, the population and the health services available differ in each country, information must be presented so that health planners in each country can work out their own situation for themselves.

The objectives of this meeting were:

- (a) To review experience in thalassaemia.
- (b) To review experience in SCD.
- (c) To make recommendations for guidelines that could be generally useful.

## 2. UPDATED INFORMATION ON DISTRIBUTION

The world distribution of the main types of haemoglobin disorders has previously been tabulated on a country basis<sup>5</sup>. These tables now require updating. New evidence shows more  $\alpha$  and  $\beta$  thalassaemia in southern China than had been realized, and that thalassaemia is a priority health problem in the Maldiva islands, Albania and the Azerbaijan SSR. Information on the distribution of SCD in South America needs to be improved.

Though the point mutation in the  $\beta$  gene that causes HbS is the same in all cases, it may exist on different genetic backgrounds, and the clinical severity of SCD differs considerably between areas. The mild SCD found in eastern Saudi Arabia and tribal populations in southern India has been shown to be due to an associated polymorphism in the  $\gamma$  gene promoter, that allows depression of the  $\gamma$  gene in homozygotes. This leads to a relatively high HbF production and a mild disease<sup>19</sup>. In sub-Saharan Africa, SCD is usually severe, but there is some variation according to the genetic background. Recent studies have shown that the clinical picture may differ considerably even with the same sickle cell mutation: e.g., homozygotes with the same mutation typically have a more severe disease in Jamaica than in Greece<sup>20</sup>.

Both  $\beta$  and  $\alpha$  thalassaemia may be caused by a wide range of different mutations<sup>21,22</sup>. It is important to understand which mutations are present in a population at the DNA level for (a) phenotype/genotype prediction - certain mutations lead to a milder phenotype, (b) DNA-based prenatal diagnosis, and planning the strategy for prevention, and (c) fundamental information on human evolution and gene migrations.

A recent distribution of DNA mutations is given in Tables 3 and 4.

### 3. UPDATE OF ONGOING HEREDITARY ANAEMIA CONTROL PROGRAMMES

Awareness of progress depends on the ability to monitor these programmes. Criteria for monitoring were defined in the 1983 report of the Working Group<sup>4</sup> as follows:

#### Treatment and prevention

- (a) Number and age distribution of patients.
- (b) Annual number of new births, and their causes.
- (c) Annual number of deaths, age at death, and causes.

The basic instrument for collecting the above information is a patient register. Suitable methodology has been developed in Italy<sup>23</sup>. The general principle is:

- (a) To create a patient register and plot the age distribution of the patients.
- (b) To update the register annually or biennially.
- (c) A confidential enquiry is then carried out into deaths and their causes, and new births and their causes. For example, were the at risk couple identified prior to or during pregnancy?, were they counselled, and if so, by whom?, was the birth the result of their informed choice, or of an error?

The records from prenatal diagnosis laboratories should be included, and children born after prenatal diagnosis followed up to confirm the accuracy of the diagnosis.

This approach, which allows simultaneous monitoring of treatment and prevention, is promoted by the WHO and is now being developed on a European basis in a Concerted Action supported by the European community.

In the case of thalassaemia, the uptake of prenatal diagnosis by informed couples is so high that simply monitoring the annual births of homozygotes gives a good indication of the level of development of a national programme. The most up-to-date results (1989) are shown in Figure 1. Very few new births of thalassaemic children now occur in Cyprus or Sardinia, and the birth rate is down to about 25% of that expected and still falling in Greece and mainland Italy.

It is now recognized that it is particularly difficult to deliver a prevention service for thalassaemia in countries such as England, France and Belgium where the haemoglobin disorders affect different ethnic minorities scattered in a larger population not at risk. In such areas, these services need to be integrated into a larger package of genetic and reproductive screening, delivered as an integral part of health care. Special ethnic counsellors may be required to provide genetic counselling to some of the ethnic minorities involved<sup>7</sup>.

#### Patient management

- (b) Recording the degree of correspondence between the treatment provided, and that recommended by WHO.
- (c) Growth in height and weight.
- (d) Age at puberty and stage of puberty.
- (e) Marriage, reproduction and employment.

The studies that exist show that a major cause of death in thalassaemia is inability of adolescents and young adults to comply with treatment. This clearly shows the need for adequate psychological support for the affected patient and

family. Where treatment facilities are not yet optimal, improving the physical care of the patients also provides the best psychological support. Once management has reached the best standard, intensive support is needed to help the families to live with the burdensome treatment and the uncertainties about the future. Psychological support must be included from the beginning and medical and nursing staff should know the disease intimately and have some training in giving psychological support. A WHO sponsored collaborative European research project is now under way on this subject. Recommendations from this collaborative group included into Annex 1 on management of sickle cell disease, also apply for thalassaemia.

#### 4. ORGANIZATION OF A CONTROL PROGRAMME: GLOBAL APPROACH

Ideally, the organization of a control programme requires the support of the Ministry of Health and medical research organizations. However, the first steps towards a programme are often taken by motivated individuals with support from the community.

The key requirement is for a highly motivated "programme manager" trained in genetics and public health. A second vital step is the organization of professional working groups bringing together those interested in the field, in order to share information and develop and test policies for treatment and prevention. Figure 2 shows how a thalassaemia control programme may be rationally developed, as in Cyprus, where its development was strongly influenced by the activities of the Cyprus Anti-Anaemia Association.

It is unlikely that a developing country will organize a nation-wide programme from the outset, because of other priorities and insufficient infrastructure to deliver the service. The initial aim should be to establish one or a few reference centres, able to develop approaches for treatment and prevention that are appropriate for that community. As demand increases, these approaches can be transferred to other centres within the country and in neighbouring countries.

The objectives of a centre should be:

- (a) To improve curative services. At the beginning it may be very difficult to obtain resources to set up the service, because of general ambivalence and a pessimistic outlook on the disease. However, as patient care improves, families become more optimistic. Increased optimism leads to the formation of Support Associations, which play a crucial role in mobilizing community support for improved treatment, and public awareness. They often contribute to organizing a blood donation campaign to permit adequate patient care. They may approach governments directly with a request for better services, increase the awareness of politicians, the public and health professionals, and often mobilize independent resources for key areas of treatment, prevention and public education.
- (b) To establish prenatal diagnosis. The first step is to establish a reference laboratory for both carrier diagnosis and prenatal diagnosis. The reference laboratory must work to the highest possible standards and use a quality control system. An obstetrician capable of obtaining fetal samples must also be trained.
- (c) To establish prospective carrier detection and counselling. In the first instance, prenatal diagnosis will usually be offered to parents who already have an affected child. However, this makes little impact on the frequency of the disease. Once prenatal diagnosis is running reliably, the next step is to move on to population screening, in order to detect couples of

carriers before they have any affected children. The uptake of prenatal diagnosis by such prospectively-diagnosed couples can bring about a major reduction in affected births.

In India, the Thalassaemia Association of Bombay has done a great deal to increase public awareness. Prenatal diagnosis by fetal blood sampling is now available, and DNA methods will be introduced. The Indian population consists of very diverse groups, the group at highest risk being Sindhis, between 6-10% of whom carry  $\beta$  thalassaemia trait. Health workers and the public in a specific Sindhi settlement are now targets of an educational campaign to promote screening. Births of affected children in the area are being recorded and will be monitored.

In Thailand, there has been active research for many years on clinical and genetic aspects of the thalassaemias. Though prenatal diagnosis is now possible, it has proved difficult to establish a service. The Thalassaemia Association of Thailand includes doctors working in the field throughout the country, and research projects on screening, counselling and prenatal diagnosis are planned for the next few years.

The results of the Cuban programme for community control of SCD have recently been reported<sup>24</sup>. The programme includes patient management, neonatal screening, and screening of pregnant women, with the offer of prenatal diagnosis. It is estimated that as a result the birth-rate of children with SCD has fallen by about 30%. An important reason for the successful establishment of a nation-wide programme in Cuba is the prior existence of a primary health care infrastructure, including an organized genetics programme. A trained paediatrician and obstetrician and ultrasound screening are available at every provincial hospital<sup>25</sup>.

Information and education is obviously essential for getting a programme started. In Lagos the Sickle Society of Nigeria is organizing a treatment centre, and supports training courses for sickle cell counsellors. In this way it is establishing the core of a community organization. The training programme includes short (3 days) certified training courses for doctors and nurses, and a two-week training course for counsellors<sup>26</sup>. Counsellors may be doctors, nurses, educated relatives of patients, or other suitable interested individuals. Certificates are provided, and counsellors may join the counsellors' section of the Sickle Cell Association of Nigeria and attend the annual meeting. It is now planned to extend training, for instance, on how to diagnose hand/foot syndrome, often the first indication of SCD, into the Community Health Workers' training schools.

In short, in both developed and developing countries an organization is needed, preferably on a national basis, that involves all those interested, both health professionals and the public. Two important and relatively inexpensive instruments for an effective organization are educational materials, and a monitoring system (see above).

Production and distribution of educational materials for health workers and the public is a high priority. Existing educational materials produced by the WHO Working Group should be translated into as many languages as possible and made widely available.

## 5. OUTLINE OF A MANUAL

The situation and requirements differ so much from one country to another, depending on the level of economic and medical development, the distribution of genes in the population, control of reproduction, etc., that it is necessary for local professionals to plan and develop the appropriate approach according to the local

situation. To assist in this, it is proposed to produce a practical manual covering the many facets of a haemoglobinopathy control programme. This manual will be further developed at the next meeting of the WHO Working Group.

## 6. CONCLUSIONS AND RECOMMENDATIONS

Specific control programmes combining treatment and prevention for both SCD and thalassaemia should now be promoted in developing as well as developed countries.

A manual summarizing available information on how to plan, organize and monitor such services should be produced to assist doctors and policy makers.

The next training course organized by the WHO Working Group should aim to help health decision makers develop appropriate strategies for the control of haemoglobin disorders and other genetic diseases.

In countries where optimal management is available, increased emphasis should be placed on psychological support for families.

Specific resources should be set aside for training and public and professional education in order to improve service delivery.

Further research is needed on the simplest possible methods for screening and prenatal diagnosis, for use in developing countries.

The desirability of screening for carriers of G6PD deficiency at the same time as for the haemoglobinopathies should be further investigated.

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TABLE 1  
Estimated global annual births of infants with a major haemoglobinopathy

REGION	AFFECTED BIRTHS /1000	THOUSANDS OF CHILDREN BORN WITH:				TOTAL	% OF TOTAL
		SS	SC	S/ $\beta$ THALASSAEMIA	HbE/ $\beta$ THALASSAEMIA		
Africa	9.2	127	32	>1.2	>3.1	163	63
Americas	0.5	4.3	2.0	1.0	0.5	8	3
Asia	1.15	19	-	1.4	25.0	86	33
Europe	0.16	0.3	+	+	1.9	2.2	0.8
Oceania	0.21	-	-	-	0.1	0.1	0.04
TOTAL	2.1	150	34	3.6	31	259	100
% OF TOTAL		58	13	1.4	>17	12	9.0
		SCD = 72%		Thalassaemia = 28%			

\* Homozygous  $\alpha^0$  thalassaemia (hydrops fetalis) or HbH disease.

(Based on Modell and Bulyzhenkov 1988)

TABLE 2  
Global Frequency of G6PD Deficiency

(Assuming that birth incidence is approximately equal to adult prevalence)

Region	% of all births (male + female)			total with 1 or 2 genes for G6PD deficiency	G6PD deficient* estimated total
	male hemizygote	female homozygote	female heterozygote		
Africa	5.6	0.9	9.4	15.9	7.4
Americas	1.4	0.09	2.4	3.9	1.7
Asia	2.3	0.2	4.2	6.7	2.9
Europe	0.34	0.02	0.67	1.0	0.4
Oceania	0.9	.06	1.8	2.8	1.1
Total	2.6	0.3	4.6	7.5	3.4

Calculated independently

\* Figure obtained by adding % of male hemizygotes, % of female homozygotes, and 10% of female heterozygotes

TABLE I  
Frequencies of Different Beta-Thalassaemia Mutations in Mediterranean Populations

	PORTUGAL	GERMANY	LYBIAN	FRANCE	TUNISIA	LEBANON	EGYPT	SPAIN	ITALY	SARBINIA	YUGOSLAVIA	BULGARIA	GREECE	TURKEY
-101												0.78		0.96
-87									1.1	0.20	0.92	3.91	1.72	0.38
-30													0.29	3.08
-28														0.38
CODON 1 (-1bp)										0.10				
CODON 5 (-2bp)					16.0						0.92	4.69	1.15	1.15
CODON 6 (-1bp)							6.2	5.0	1.9	2.10	1.39	4.69	2.87	0.19
CODON 8 (-2bp)						6		1.7			0.86	5.46	0.57	6.75
CODON 8/9 (+1bp)												5.46	0.29	0.96
CODON 29						8					0.92			
CODON 39	53.57	50.0	1.5	41.9	19.0	4	2.1	64.0	41.2	95.70	3.70	21.88	16.95	4.63
CODON 76 (-1bp)										0.70				
IVS1-1	12.90	2.5	11.7	10.5	1.5		10.6	3.5	10.7		10.65	3.14	13.22	2.50
IVS1-5						4							0.86	2.30
IVS1-6													7.18	18.16
IVS1-110	10.71	7.5	69.9	25.7	7.5	8	18.8	15.5	10.3	0.10	23.15	10.15	42.55	39.96
IVS11-1		5.0		1.0		62	27.1	8.5	23.2	0.50	43.05	26.21		
IVS11-705						4	4.2		3.6	0.03	0.92	1.56	2.01	11.77
IVS11-745								1.7						
OTHERS	2.82	35.0	2.6	9.5	38.0	4	8.3		5.8	0.40	1.39	10.15	6.90	2.89
							25.0	0.1	2.2	0.00	12.53	3.92	3.44	3.96

Information on the frequencies was taken from the following publications:

PORTUGAL: Coutinho-Gomes et al. Human Genetics, vol. 78:13, 1988.  
GERMANY: Laif et al. Human Genetics, vol. 85:135, 1990.  
CYPRUS: Sazouk et al. Human Genetics, vol. 25:266, 1988.  
FRANCE: Mollaud et al. Hemoglobin, vol. 11:317, 1987.  
TUNISIA: Chihani et al. Human Genetics, vol. 73:190, 1988.  
LEBANON: Chehab et al. Blood, vol. 69:1141, 1987.  
EGYPT: Navejedo et al. Human Genetics, vol. 85:272, 1990.  
SPAIN: Anselm et al. Am. J. Hum. Genet., vol. 43:94, 1988.  
ITALY: Rosatelli et al. Unpublished results.  
SARBINIA: Rosatelli et al. Unpublished results.  
YUGOSLAVIA: Dimovski et al. Hemoglobin, vol. 14:15, 1990.  
BULGARIA: Petkov et al. Hemoglobin, vol. 14:25, 1990.  
GREECE: Kallialis et al. Br. J. Haematol., vol. 74:342, 1990.  
TURKEY: Oner et al. Hemoglobin, vol. 15:1, 1990.

TABLE 4

Frequencies of Different  $\beta$ -Thalassaemia Mutations in Asians

	THAILAND	CHINA	INDIA	MALAYSIA	INDONESIA
-88			2.0		
-29					
-28	10.3	6.5			
CODON 8/9 (+1bp)			19.6		
CODON 14/15 (+1bp)		0.6			
CODON 15			4.9		5.55
CODON 16 (-1bp)			1.0		
CODON 17	10.3	11.8		2.4	1.39
CODON 19	1.7			14.6	
CODON 26					18.05
CODON 35 (-1bp)				4.8	1.39
CODON 35	2.6				
CODON 41/42 /-4bp)	50.9	31.8	11.8	12.2	1.39
CODON 43					
CODON 71/72 (+1bp)	0.8	14.1			
IVSI-1	1.7	0.6	13.7	7.3	9.72
IVSI-5	5.2	5.3	22.5	48.8	44.44
IVSII-654	11.2	17.0		7.3	9.72
619 bp DELETION			20.5		
OTHERS	4.2	12.3	4.0	2.4	8.35

Information on the frequencies for each country was taken from the following publications:

- THAILAND: Thein et al. Am. J. Hum. Gen., vol. 47:369. 1990.  
 CHINA: Huang et al. Human Genetics, vol. 84:129. 1990.  
 INDIA: Thein et al. Am. J. Hum. Gen., vol. 47:369. 1990.  
 MALAYSIA: Thein et al. Am. J. Hum. Gen., vol. 47:369. 1990.  
 INDONESIA: Lie-Injio et al. Am. J. Hum. Gen., vol. 45:971. 1989.

FIG. 1

Development of Policy for Control of a Disease

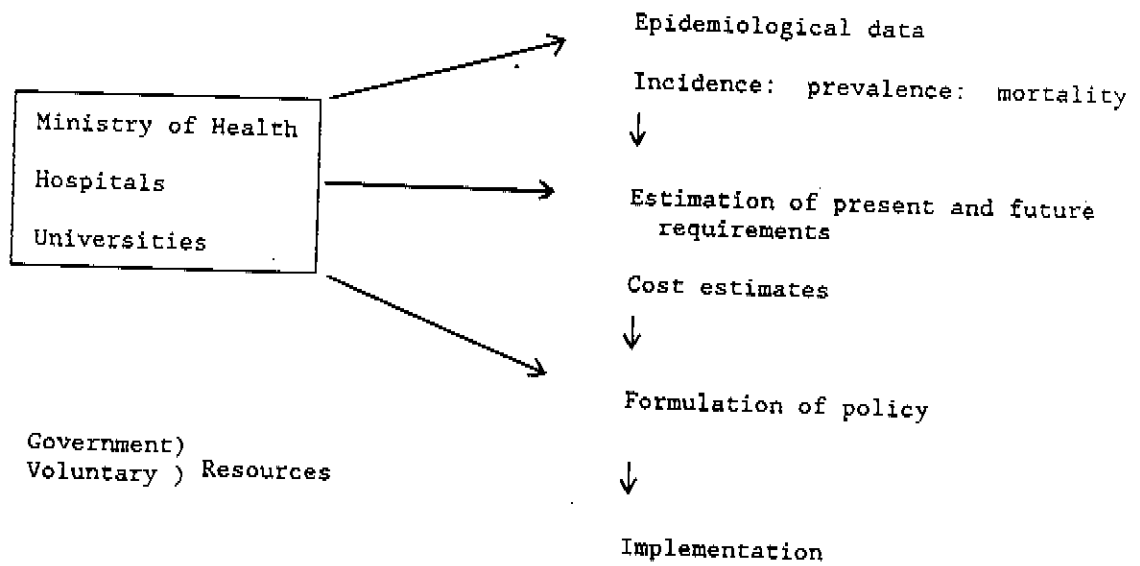
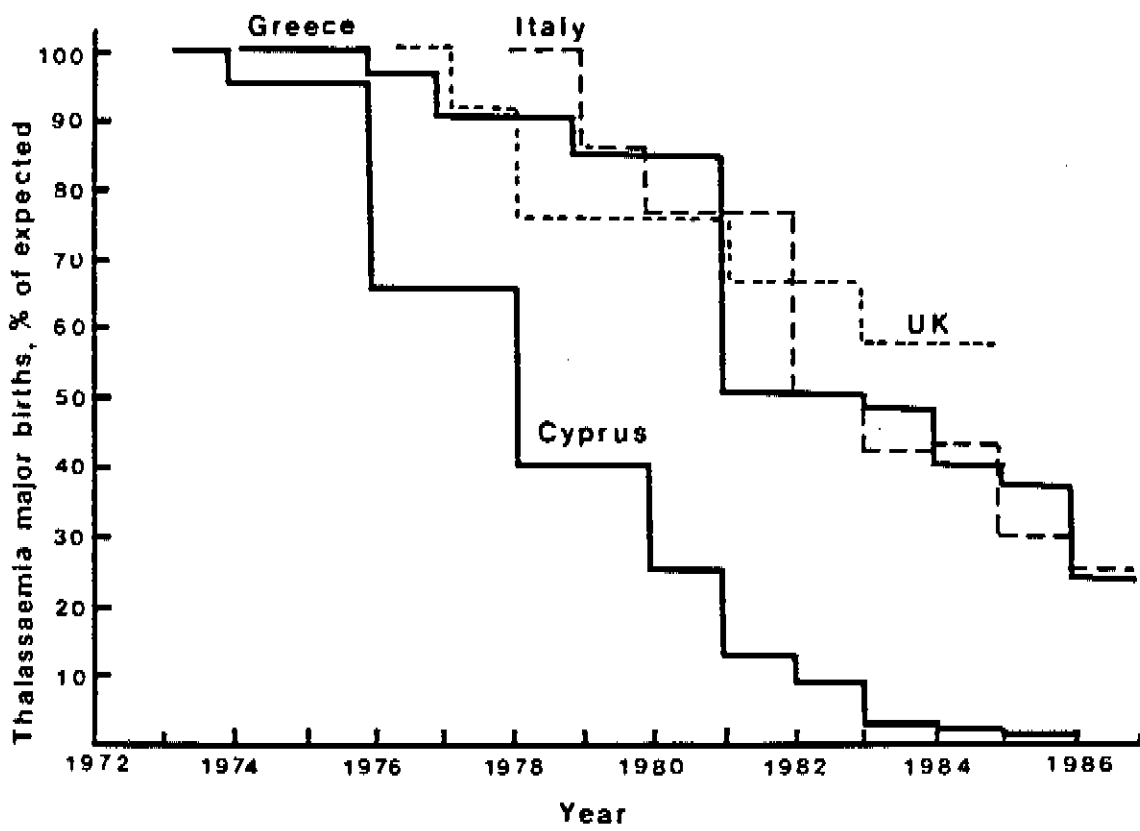


FIG. 2



GUIDELINES FOR THE  
MANAGEMENT OF  
SICKLE CELL DISEASE

Prepared by

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on behalf of the VIth Annual Meeting of the  
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## 1. INTRODUCTION

Sickle cell disease (SCD) is a common inherited disorder of haemoglobin. The disease cannot be cured but its various and variable manifestations can be effectively treated and often prevented, to allow the patient to lead a long and useful life. This brief manual is an attempt to summarize the current state of knowledge of the management of SCD. Each country has its own specific problems and differs in its pharmaceutical policies. Some sections of the manual should be altered to suit local needs and capacities of the health care system.

It is important to emphasize that patients with SCD, like those with beta thalassaemia major, require a global approach, which is best achieved if a group of specialists (including paediatricians, haematologists, one or more specialists in bone, eye and CNS diseases, specialist nurses, psychologists and patient representatives) work together with the primary care team to provide a balanced and comprehensive approach.

The following aspects are considered in this manual: diagnosis, management of acute problems (including vaso-occlusive problems, painful crisis, sequestration and chest syndromes, infections, aplastic crisis, stroke and other acute CNS manifestations, and priapism), the special problems of children, transfusion, chronic complications (including bone, eye, lung and renal problems, gall stones, peptic ulceration, and leg ulcers), puberty, contraception and pregnancy, as well as the management of the steady state and general health care in both children and adults.

## 2. DIAGNOSIS

### Obligatory tests

- Full blood count, reticulocyte count and blood film.
- Haemoglobin electrophoresis on cellulose acetate and citrate agar with quantitation of all bands.
- Measurement of Hb A<sub>2</sub> using microcolumn chromatography or electrophoresis and elution.
- Measurement of Hb F with the Betke method.
- Sickle solubility test or a confirmatory test using an anti-Hb S monoclonal antibody.

All tests and investigations must be subject to the appropriate national and local quality control regulations.

### Optional tests

- Family studies.
- Further studies of the characteristics of any haemoglobin abnormality: globin chain synthesis, DNA studies to establish the presence of alpha and beta thalassaemia interaction.

### Other useful investigations but not required for diagnosis

- ABO, Rh, K, and other red cell phenotypes.
- Steady state bilirubin, liver function tests, ferritin and lactic dehydrogenase (LDH) or hydroxy butyric dehydrogenase (HBD) and ferritin.
- Urea, electrolytes and creatinine.

### 3. MANAGEMENT OF ACUTE PROBLEMS

#### 3.1 ACUTE VASO-OCCLUSIVE PROBLEMS

There is no specific or curative treatment. The mainstay of management is:

- (a) Fluid replacement.
- (b) Pain relief.
- (c) Prophylactic antibiotics.
- (d) Transfusion of blood (rarely).
- (e) Oxygen therapy may be used in some cases.

It is often helpful to have a flow sheet summarizing the diagnostic and management options for situations which may require emergency admission in SCD, as shown in the appendix.

#### (a) Fluid replacement

##### Rationale:

Patients with SCD have hyposthenuria. They cannot concentrate their urine, and so lose large amounts of fluid. This may cause reduction in plasma volume with an increase in blood viscosity and aggravation of sickling (page 20).

##### Dose:

70-100 ml/kg body weight per 24 hours (approximately 4 litres in 24 hours for most adults).

##### Route:

Oral, if bowel sounds are present (a fine bore nasogastric tube can be used) or intravenous.

##### Fluids given:

NaCl 0.9%, dextrose 5% with 20 mmol KCl.

##### Problems:

Fluid overload is rare. Maintain fluid balance chart; if the urinary output falls, check that the patient is not in urinary retention. Hypokalaemia is rare and should be corrected with 20 mmol KCl in iv fluids (or effervescent KCl orally).

##### Venous access:

May be very difficult. Use oral fluids in the absence of abdominal problems. Avoid central vascular lines unless there is a life threatening situation. Use of leg veins should be avoided as extravasation of iv fluids or blood may lead to skin necrosis and persistent ulceration.

Duration of fluid replacement:

Stop iv fluids when the patient can drink freely and ensure adequate oral intake thereafter.

(b) **Pain relief**Rationale:

Pain in SCD is due to vaso-occlusion and may be severe. Medical and nursing staff often underestimate the severity of pain and deal with it inadequately. The failure to appreciate and relieve pain quickly, remains the main complaint of patients, pressure groups, independent surveys, and charitable organizations.

Comments on analgesia:

Prompt pain relief is essential. Adequate doses at the correct time intervals are required. For example, the half life of pethidine is only 1 to 1.5 hours. Thus an injection every 4 hours cannot control pain.

TABLE 1 - ANALGESIA FOR ACUTE PAINFUL CRISES

INDICATION	DRUG	DOSE			
		<u>Adult</u>	<u>Child</u>		
			<1y	1-5y	6-12y
Mild pain	Paracetamol	1g/4h	60mg/4h	120mg/4h	250mg/4h
	Aspirin	600mg/4h			
	Co-Proxamol	1-2t/4h			
	Naproxen	1-2t/4h			
	Ibuprofen	1200-2400mg/d		20mg/kg/d	
Moderate pain	Dihydrocodeine	60mg/24h		1mg/kg/6h	
	Oxycodone	40mg/4h			
Severe pain	Pethidine	1.5mg/kg/h		0.5-1.5mg/kg/h iv or im	
	Morphine	0.15mg/kg/4h		0.1mg/kg/4h	

Side effects:

Do not use aspirin, co-proxamol, naproxen, or oxycodone in children. Opiate analgesics may induce nausea, constipation, urinary retention and respiratory depression. Close observation of the patient is necessary. Pethidine should be avoided in large doses, since it may induce fitting and cause dysphoria through the action of its toxic metabolite, nor-pethidinic acid, which has a long half life. Morphine can cause broncho-constriction and pruritus.

Chronic pain:

A small number of patients are frequently admitted in severe pain, but with minimal constitutional upset, and require very high doses of opiate analgesia to control the pain.

Suggested plan of action:

Make a detailed plan for pain control, discuss it with the patient, parents (if appropriate) and the nursing staff. Do not exceed the planned dose or shorten the interval unless there are convincing physical signs such as fever, tachypnea, tachycardia, swollen joint etc. Exclude serious pathology (aseptic necrosis of hip or shoulder, gall bladder disease, osteomyelitis etc). Enlist the help of specialist agencies to solve the patient's social and psychological problems. If all fails and a period of reasonable health is essential (schooling, examinations, travel), consider regular transfusion for 3 - 6 months (see page 9).

Drug addiction:

A small number of patients become addicted to analgesics. Such patients may have to be registered as drug addicts and referred to a specialist service. Some may benefit from referral to a formal pain clinic.

Alternative pain management techniques:

Relaxation therapy, self hypnosis, behaviour modification and distraction techniques are useful adjunctive approaches and the patients should be encouraged to participate in efforts of this kind.

Pain relief in children:

Pain relief in children can be achieved by continuous iv infusion of pethidine, started at 2 mg per kg body weight per hour and adjusted to a lower dose as required.

**(c) Antibiotics**

These should be given to patients who are pyrexial and to those with the sequestration syndromes. Always collect blood samples, urine and swabs (if indicated) for bacteriological investigation before starting the antibiotic treatment.

Muscle, bone or chest pain:

Amoxycillin 500 mg 3 x daily for adults, 125 - 500 mg 3 x daily for children; or Pivampicillin 500 mg 2 x daily for adults, 40 - 60 mg/kg daily in children; or Ampicillin 250mg 4 x daily for adults, 62.5 - 250 mg 4 x daily for children.

Abdominal pain:

Amoxycillin + Metronidazole 400 mg 3 x daily for adults.

Causative organism identified or strongly suspected:

Always give the most specific antibiotic available, e.g., Benzyl penicillin for pneumococcal infection, Flucloxacillin for staphylococcal infections, etc.

(d) **Transfusion**Rationale:

Transfusion is used in SCD to replace red cells containing Hb S with those containing Hb A, and with the intention of arresting or preventing vaso-occlusive events and improving oxygen delivery to the tissues. Transfusion is only rarely indicated to raise haematocrit. Anaemia is not usually an indication for transfusion unless Hb falls to 5 g/dl or lower and the patient is clinically compromised, both because Hb S is a low affinity Hb, efficient in delivering oxygen, and because transfusion will increase the whole blood viscosity and may aggravate sickling. A list of potential indications for transfusion is shown in the Table 2.

Simple or 'top-up' transfusion:

This is indicated only in the conditions shown in Table 2, or if there is a sudden drop of Hb concentration to 5 g/dl or less.

Exchange transfusion:

This is indicated to reduce sickling either in an acute condition, or to prepare the patient for a surgical or radiological procedure (see Table 2), or to start a period of regular transfusion as in stroke.

TABLE 2 - SOME INDICATIONS FOR TRANSFUSION

TYPE OF TRANSFUSION	INDICATIONS	
	Transfusion commonly needed	Transfusion sometimes needed
Top-up	Aplastic crisis Acute splenic sequestrian	Hepatic sequestrian Bleeding (gynaecological, GI tract, haematuria, etc.) Severe cardiac failure
Exchange	Hepatic sequestrian Chest syndrome Girdle syndrome Stroke and other CVS complications Priapism Acute problems in pregnancy	Infection (severe) Preoperative, for major and intermediate surgery Preparation for some radiological investigations requiring contrast media
Regular	After a stroke Chronic renal, lung or cardiac complications	Prophylactic in pregnancy Unsatisfactory quality of life Recurrent severe painful crisis Leg ulcers

To exchange:

Good vascular access must be available. Use plasma reduced blood, except in babies who should be given fresh blood (less than 48 hours old). Use leukocyte depleted blood to remove white cells and platelets in patients with a history of febrile or allergic reactions. The total volume of blood exchanged depends on the patient's body weight and on the haematocrit. If the haematocrit is below 20%, start by transfusing the equivalent of 8 ml of blood per kg body weight and then exchange the equivalent of 1.5 to 2 x patients blood volume, (blood volume in ml = 70 x weight in kg) as 3 - 5 units of blood per day. If the haematocrit is over 20%, start with venesection and exchange 2 blood volumes; up to 6 or even 8 units can be exchanged per day in an adult, proportionately less in a child.

How to venesect:

Have a saline drip running freely. Peripheral venous lines are preferable, but a central venous line may be used. In very sick patients, arterial cannulation allows both arterial oxygen monitoring and a speedy, efficient exchange transfusion. When only a single line is available, it is possible, using a three way tap, to perform an exchange by serial withdrawal and replacement of small aliquots of blood (not over 100 ml at a time for an adult; not more than 20 to 30 ml for a child depending on size). When two lines are available, venesection is usually started with the largest syringe which can be comfortably handled (usually 20 to 50 ml). Adjust the speed of the saline drip to match the speed of venesection so that the patient remains isovolaemic. When blood equivalent to 8 ml per kg of body weight (i.e., 8 ml per kg for a 50 kg person is 400 ml) is removed, donor red cells are transfused. It is usually possible to use a blood bag to collect the blood removed after 1 or 2 units have been exchanged.

How to transfuse:

If haematocrit is below 20% start by transfusing at a rate of 2-3 ml/kg/h. If haematocrit is above 20%, start transfusing when the first unit of blood is venesected, at a rate of 2-3 ml/kg/h. When an arterial line is used one unit may be transfused over 10 to 30 minutes; it is then advisable to pause for up to 30 minutes between units.

What to monitor:

Always monitor blood pressure, pulse, respiratory rate and weigh the blood removed and transfused. In very sick patients with one of the sequestration syndromes, the exchange transfusion should be carried out while monitoring the central venous pressure. This is not necessary in patients undergoing elective or less urgent exchange. When large volumes of blood are exchanged, metabolic and haematological disturbances can occur: electrolytes and calcium should be measured, and platelets and coagulation tests regularly performed. Fresh frozen plasma and platelet support may occasionally be required. Cell separators can be used for elective exchange transfusion in patients with high haematocrit, undergoing the second part of the exchange by which time in vitro sickling does not occur in the tubing.

Investigations at the end of exchange:

- Full blood count - aim for Hb of 12 - 14.5 g/dl with a haematocrit of not more than 45%.
- % Hb S - aim for an Hb S < 25%.

*Untoward effects*

- Hypertension/convulsion syndrome if the Hb too high, especially in the presence of high Hb S.

*Management*

- Venesect immediately.
- Anticonvulsants.
- Antihypertensive treatment (beta-blocker and or nifedipine, never diuretic).

For non haemolytic transfusion reactions:

*Management*

- Stop transfusion.
- Give antihistamines and antipyretics.
- Use leucocyte depleted blood for further transfusions.

Regular transfusion

*Definition*

- Repeated transfusions over a period of at least 6 months to keep Hb S < 25%.

*Method*

Start with exchange transfusion, then transfuse at 2 to 5 week interval to suppress erythropoiesis and keep Hb S < 25% and total Hb between 11 and 14.5 g/dl. Patients vary in the frequency and amount of blood required to suppress Hb S production. Repeated partial exchanges may be necessary.

*Untoward effects*

- Iron overload.
- Alloimmunization to red cell, white cell and platelet antigens.
- Transmission of infection.
- Regrowth of the spleen with consequent hypersplenism.

Which blood to give to SCD patients?:

ABO compatible, Rh compatible; (C and E negative blood should be provided whenever possible for R<sup>0</sup>(cDe) patients). K negative blood for K negative patients. Use whole blood, OAS (optimum additive solution) blood or plasma reduced blood. Packed cells should be avoided for patients with haematocrit over 20%. Use filtered blood to minimize the risks of alloimmunization to white cell and platelet antigens.

Other measures:

- Consider immunisation against hepatitis B.
- Monitor ferritin and liver function tests, HIV, HTLV I, HVB, HVC status.
- Monitor platelet count (as an indicator of splenic regrowth).
- Keep a careful note of the blood administered and removed by venesection, and of the patient's body weight.
- Consider chelation if regular transfusion continues for over 6 months or if the ferritin is in excess of 2000  $\mu\text{g}/\text{l}$  while in the steady state.

(e) **Oxygen Therapy**

Oxygen therapy is of unproven value until  $\text{PaO}_2$  drops significantly: if arterial  $\text{PaO}_2$  is  $< 11$  kPa on air, 28% oxygen is administered via a mask. If it is between 8 - 9kPa 35% oxygen. Other measures to be used in respiratory insufficiency are mentioned on page 20.

3.2 **PAINFUL CRISES**

*Depends on*

Location of pain; severity of pain; presence of pyrexia.

Hand-foot syndrome:

- In children, usually under the age of 3 years.
- Diffuse soft tissue swelling of the dorsum of hands and feet.
- Increase fluid intake.
- Analgesia.
- Rest.
- If fever and swelling persist beyond 2-3 weeks investigate for osteomyelitis.

Pain in the limbs, excluding shoulders and hips:

- Analgesia.
- Increase fluid intake (see page 4).
- If pyrexial prophylactic antibiotic (see page 6) until the bacteriological results are available.

Pain in the shoulders or hips:

If repeated or prolonged, x-ray 8-12 weeks after the episode to exclude aseptic necrosis.

*Investigations*

- Full blood count, reticulocyte count.
- Blood cultures if pyrexial.

*Differential diagnosis*

- Osteomyelitis.
- Septic arthritis.
- Distinguished by swinging pyrexia, severe systemic disorder, positive blood cultures.

**NOTE:**

- Swellings over long bones and joint effusions are common in vaso-occlusion.
- Do not aspirate joints as a first line investigation (see page 20).

Abdominal pain:

- Analgesia.
- iv fluids.
- If there is vomiting, or the abdomen is distended, or bowel sounds are absent, give nothing by mouth and consider nasogastric suction.
- Measure abdominal girth at the umbilicus at regular intervals to monitor distension.
- Measure liver size.
- If bowel sounds are absent, examine chest, consider monitor oxygen saturation or arterial blood gases.
- Give antibiotics (see page 6).

*Investigations*

- Chest and plain abdominal x-ray, supine and erect to exclude the girdle syndrome (see page 13).
- Full blood count.
- Urea and electrolytes, liver function tests, HBD or LDH.
- Blood group, antibody screen and save serum for crossmatching.

(IF CHEST OR GIRDLE SYNDROMES DEVELOP SEE PAGE 13)

Chest pain, and pain in the spine, sternum, ribs, scapula, and waist:

- Analgesia.
- iv fluids.
- Antibiotics.

*Investigations*

Arterial blood gases:

- Chest x-ray.
- Full blood count.
- Urea and electrolytes, liver function tests, HBD or LDH.
- Blood group, antibody screen and save serum for crossmatching.
- IF PO<sub>2</sub> = 11 kPa or less on air see chest syndrome (page 13).

### 3.3 SEQUESTRATION SYNDROMES

#### Splenic sequestration:

- Generally in infants and young children.
- Often leading to a sudden collapse.
- Rapidly enlarging painful spleen.
- Abdominal pain, child may pull knees to the abdomen.
- Hb drops by at least 2 g/dl from the stable state value.
- Often associated with septicaemia particularly pneumococcal.
- High mortality, the child may die before arrival at hospital.

#### *Management* (also see Appendix)

- Supportive (treatment of shock).
- Emergency transfusion, use uncrossmatched O Rh negative blood if necessary.
- Benzyl penicillin iv.

#### *Investigations*

- Blood group and crossmatch if possible.
- Full blood count.
- Blood cultures.

#### Indications for splenectomy:

The child is likely to experience recurrent episodes of sequestration and splenectomy should be considered. Exchange transfusion may be required preoperatively. Pneumococcal vaccine should be administered and penicillin prophylaxis continued.

#### Hepatic sequestration:

- All age groups, after infancy.
- Abdominal distension with hypochondrial pain.
- Enlarging tense liver.
- Sometimes increasing jaundice.
- Collapse, less frequent and sudden than with splenic sequestration.
- Most reported cases are associated with infection.

#### *Management*

- Transfusion.
- Analgesia.
- iv fluids.
- Antibiotics.
- O<sub>2</sub> by mask if PaO<sub>2</sub> low.

#### *Investigations*

- Full blood count.
- Blood group and crossmatch.
- Blood cultures.
- Liver function tests.
- Urea and electrolytes.
- Arterial blood gases, if the patient becomes tachypnoeic, develops chest signs or cyanosis.

Chest syndrome:

- Rare before the age of 8 years.
- Pain in chest wall, upper abdomen and/or thoracic spine.
- Signs of lung consolidation usually bilateral and starting at the bases.
- High fever.
- Tachypnoea.
- Tachycardia.
- Cough is a late symptom.
- Physical signs always precede x-ray changes.

**NOTE:**

- Consolidation in the upper lobes or in the middle lobe without basal changes is characteristic of chest infection rather than of chest syndrome.

*Management (also see Appendix)*

**If  $PO_2 > 11$  kPa on air:**

- O<sub>2</sub> 28% by mask.
- iv fluids.
- Analgesia
- Antibiotics.
- Monitor  $PO_2$  on air, pulse, respiratory rate, arterial gases, abdominal girth, Hb.

**If  $PO_2 < 11$  kPa on air, or there is a rapid clinical deterioration:**

- Exchange transfuse (see page 7)
- Analgesia.
- iv antibiotics.
- Oxygen by mask (intubation and ventilation may be necessary).
- Consider VENTILATION if  $pO_2 < 11$  kPa on O<sub>2</sub> by mask or  $pCO_2 > 6$  kPa or patient becomes markedly acidotic.

*Investigations*

Arterial blood gases:

- Full blood count.
- Blood group, antibody screen and crossmatch.
- Chest x-ray.
- Blood cultures, sputum cultures.

Girdle syndrome:

- Silent, distended abdomen without localising signs or rebound.
- Some hepatic enlargement is common.
- Often associated with bilateral basal lung consolidation.
- Characteristic distended bowel loops or fluid levels on x-ray.

*Management*

- As for chest syndrome, but with nasogastric suction. Give nothing by mouth.
- Measure abdominal girth at hourly intervals.

### *Investigations*

- As for chest syndrome.
- Supine and erect/lateral decubitus abdominal x-rays.
- Serum amylase.
- CONSIDER the possibility of surgical pathology such as acute appendicitis or acute pancreatitis, cholecystitis, splenic abscess, ischaemic colitis, peptic ulcer etc.

### 3.4 INFECTIONS

#### Pneumococcal infections:

- May occur from infancy.
- Mortality is highest in the first three years of life.
- Case fatality over 30% despite appropriate antibiotic therapy.

#### *Presentation*

- Septicaemia.
- Meningitis.
- Peritonitis.
- Pneumonia.
- Osteomyelitis.

ACUTE SPLENIC SEQUESTRATION IS OFTEN ASSOCIATED WITH PNEUMOCOCCAL INFECTIONS

#### *Diagnosis*

- Isolation from blood or cerebrospinal fluid.

#### *Treatment*

- Benzyl penicillin.
- Transfusion, if associated with sequestration.
- Treatment of shock, convulsions etc.

#### *Prophylaxis*

- Diagnose SCD at birth.
- Start prophylactic oral penicillin by the age of 2 months.
- Doses: 62.5 mg orally daily in the 1st year, 125 mg daily until 3 years of age, 250 mg daily thereafter (500 mg daily for adults).
- Vaccinate with Pneumovax or a similar preparation at 7 months of age and boost 3 yearly. Note that vaccination does not provide full protection. Penicillin prophylaxis is still necessary in children and adolescents.

#### Haemophilus influenzae infection:

Common in children, even on penicillin prophylaxis.

*Presentation*

- Meningitis.
- Pneumonia.
- Osteomyelitis.
- Cellulitis.

*Diagnosis*

- Isolation from blood, sputum, cerebrospinal fluid, tissue biopsy.

*Treatment*

- If meningitis consider using chloramphenicol.
- For other presentations use ampicillin.

Salmonella infections:

All age groups.  
Common cause of osteomyelitis in SCD.

*Presentation*

- Osteomyelitis.
- Septicaemia.
- Food poisoning.

MAY PRECIPITATE SEQUESTRATION CRISIS

*Diagnosis*

- Isolation from the blood, faeces, or infected tissue.

*Treatment (also see Appendix)*

- Discuss with the microbiologist as sensitivities are unpredictable. The drugs commonly used are: ciproflaxin; ampicillin; septrin; only use chloramphenicol in resistant cases.
- In osteomyelitis intravenous antibiotic treatment may be required up to 12 weeks.
- Long term oral antibiotic treatment is needed to abolish bone infections.

Other infections:

- coli infections of the urinary tract are common.
- Septicaemia and osteomyelitis are occasionally encountered.
- Staphylococcal osteomyelitis is not infrequent and should be treated with penicillinase resistant penicillins in high doses.
- Mycoplasma pneumoniae can cause a severe pneumonia in SCD occasionally with hypoplastic bone marrow. This is treated with erythromycin.

Viral infections:

- Parvovirus B-19 infection: CAUSE OF APLASTIC CRISIS
- Children and adolescents.
- Small epidemics.
- School and family contacts affected.

*Presentation*

- 10 - 14 day incubation.
- Nonspecific febrile illness.
- Sometimes rash, abdominal pain, swollen joints.
- In the 3rd week: erythropoietic arrest with fall of Hb by 3 g/dl or more from the steady state value.
- Pallor, fatigue, headaches. Congestive cardiac failure in severe cases.

*Diagnosis*

- Reticulocyte count < 1%.
- Viral particles in serum on electron microscopy during the first few days of illness.
- Presence of specific IgM anti-viral antibodies from the 10th day of the illness.

*Treatment*

- Transfusion if patient is clinically compromised.
- Warn parents of patients at the time of epidemic.
- Check Hb in contacts regularly.

Other viral infections:

- Chickenpox and mumps may present in a severe form requiring hospital admission.
- HIV and HVB infections are usually transfusion transmitted.

3.5 **STROKE AND OTHER CNS MANIFESTATIONS**

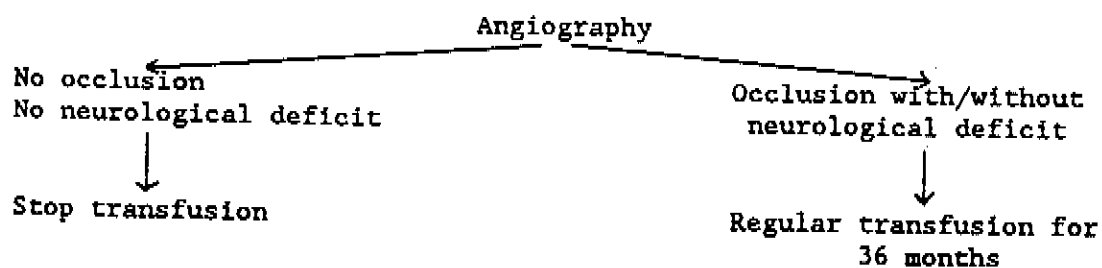
Stroke:

- May occur at all ages, but most common in children.
- Median age 7 years.
- Recurs in two-thirds of patients within the first 36 months.
- Precipitating factors: dehydration, fever.
- Sometimes in otherwise well children.

*Management*

- Stroke or TIA or a fall in level of consciousness:
- Admit, rehydrate, arrange immediate neurological assessment.
  - Start exchange transfusion over 2-3 days, to achieve Hb S < 20%.

Then:



#### *Investigations*

- Full blood count, blood group and crossmatch.
- Blood biochemistry.
- CT scan of brain may be useful if positive, but a negative scan at an early stage does not exclude brain infarction.
- Before starting regular transfusion obtain: ferritin concentration, liver function tests, HIV and hepatitis status, red cell genotype. For details see also page 7.

#### *When to stop transfusion*

- It is usual to continue transfusion for at least 24 months.
- Some children experience a recurrence within months of stopping transfusion. Therefore many centres now continue for 36 months, and on occasion it is difficult to stop transfusing.

#### Subarachnoid haemorrhage:

- Occurs at all ages, but median age of onset 22 years.
- Often multiple aneurysms.

#### *Management and Investigation*

- Exchange transfuse as for stroke, refer to neurosurgeons.

#### Fits:

- Common after stroke or SAH.
- May be caused by large dose of pethidine.

#### *Investigations*

- EEG.
- CT or MRI.

#### *Management*

- Immediate: anticonvulsants, usually diazepam (slow iv injection 200 to 300  $\mu\text{g}/\text{kg}$  body weight or rectally in small children, 5-10 mg iv in older children).
- Definitive: if no abnormality on EEG or no recurrence, no long term medication is needed.
- If EEG abnormal but CT or MRI normal: long term anticonvulsants.
- If infarction on scanning, exchange transfuse and arrange angiography.
- Consider regular transfusion.

### 3.6 PRIAPISM

Usually not before the age of five years.  
Common in sexually active men.

#### *Presentation*

- (a) Acute, fulminant.
- (b) Stuttering (repeated painful erections lasting more than 30 minutes).

*Management* (also see Appendix)

(a) **Acute**

- iv fluids.
- Analgesia.
- Catheterization.
- Exchange transfusion.
- If no detumescence, corporo spongiosum drainage, stab or shunt.
- Saphenous shunt has been shown to be of little or no use.

(b) **Stuttering**

- iv fluids
- Analgesia.
- Anti-androgens (cyproterone 50 mg 3 times daily, stilboesterol 5 mg daily for 3 weeks to 6 months to prevent spontaneous erections).
- If no improvement, consider a period of hypertransfusion.

#### 4. SOME CHRONIC COMPLICATIONS OF SCD

##### **Aseptic necrosis of hip and shoulders**

In approximately 15% of all patients. Onset in adolescence and after, but uncommon after the age of 30 years.

##### *Presentation*

- Pain in the hip, leg, groin, or knee on movement, later at rest.
- Limitation of movement particularly abduction of the hip; external rotation of the shoulder.
- May be aggravated or start in pregnancy (even when transfused).

##### *Diagnosis*

- Radiological.
- Isotope bone scan using a colimator head may be helpful in the early stages (hot spots in the femoral or humeral head).

##### MRI

##### *Management*

##### Early:

- Avoidance of weight bearing and rest is sometimes recommended, but their role remains uncertain.
- Consider exchange transfusion.
- Analgesia with non steroidal anti-inflammatory agents or codeine derivatives.

##### Late:

- Joint replacement may become necessary if pain is continuous or very severe, and if the patient's mobility is seriously affected.
- Exchange transfuse pre-operatively and for 3 months post-operatively to maximise bone healing.
- Different types of prosthesis, hip fusion or bone grafting are used depending on individual case. Cemented prostheses are best avoided.
- Infection and loosening of the prosthesis are common.
- The possibility of failure, the likelihood of some residual pain, the potential life of the prosthesis and the limitations imposed must always be discussed with the patient pre-operatively.

##### **Other bone and joint problems**

Joint effusions are common and usually due to periarticular infarction. Secondary gout is relatively common and is diagnosed by the presence of uric acid crystals in the joint fluid (see below) and hyperuricaemia.

##### *Management*

- Hydration.
- Analgesia.
- Rest.

- If the effusion persists over 5 days, consider aspiration of the joint for culture, protein and microscopic analysis.
- If patient febrile and there is marked local inflammation, perform a joint aspiration early - BUT ALWAYS IN HOSPITAL AND UNDER STRICT ASEPTIC CONDITIONS.

### Upper airways obstruction

Upper airways obstruction is present in up to 35% of children with sickle cell anaemia (SS) and sickle beta zero thalassaemia (HbS $\beta$ b<sup>0</sup>) and in occasional children with HbSC disease (HbS + HbC). It occurs much less frequently in adults.

Suspect in the presence of regular snoring and poor concentration and/or daytime sleepiness.

Confirm by abnormal inspiratory pattern and hypoxaemia while asleep.

#### *Management*

- Operative removal of tonsils and adenoids.
- Preoperative transfusion is rarely required.

### Hypersplenism

Hypersplenism is common in some countries where sickle-thalassaemia interactions occur frequently. An enlarged spleen, when associated with pancytopenia should be removed. If the patient is very anaemic, he or she should be transfused preoperatively or intra-operatively, as soon as the splenic blood vessels are clamped (to prevent pooling in the spleen). Haemostatic abnormalities, if present, need correction, and the operation should not be undertaken unless platelet and fresh frozen plasma cover is available. For details see also page 26.

### Renal problems

#### Hyposthenuria:

This is present by or before the age of 3 years, resulting in an obligatory high urinary output.

#### Enuresis:

Common in both sexes, due to hyposthenuria and the consequent large urinary output.

#### *Management*

- Explain the nature of the problem to both the parents and the child and inform them that it frequently resolves by the late teens.
- Do not restrict fluids.
- Arrange to wake and lift the child regularly late evening.
- Reassure: few adults with SCD remain enuretic.

Renal tubular dysfunction:

The inability to acidify urine in the presence of ammonium chloride load, may cause metabolic acidosis and aggravate sickling.

Hyperuricaemia:

Some 40% of adults and 15% of children have hyperuricaemia due to a combination of decreased urinary clearance and of increased production. Uric acid stones are common, as is clinical gout.

Haematuria:

Rare in sickle cell disease except in pregnancy when it may be massive (due to papillary necrosis).

Management

- Hospitalization and bed rest.
- Hydration to ensure urinary output of 2 to 3 ml/kg body weight/hour.
- Transfusion may be necessary if Hb drops and haematuria continues.
- Intravenous urography may be necessary to establish the diagnosis of papillary necrosis. The newer, non-ionic contrast media are considered safe for administration even without exchange transfusion.

Proteinuria and nephrotic syndrome:

Found in a small number of patients and may herald true nephrotic syndrome with membrano-proliferative changes in the glomeruli. Investigate every patient with persistent proteinuria in the absence of infection.

Investigations

- 24 hour urinary protein (quantity and electrophoretic pattern).
- Creatinine clearance.
- Blood biochemistry.
- Consider renal biopsy if the urine protein > 2g/24h.

Management

- Arrange regular follow-up.
- Regular transfusion may be necessary for progressive disease or when the urine protein loss is sufficient to cause a reduced plasma volume with a resultant increase in severe sickling episodes.
- Specific treatment according to the biopsy findings.

Urinary tract infections:

Common, particularly in women with SCD. Should be vigorously treated to prevent serious renal pathology. Haematuria can predispose, but other factors must be excluded. If a person has had recurrent urinary tract infections the urine should be regularly checked for sterility since long term antibiotic prophylaxis may be required.

Chronic renal failure:

Chronic renal failure is uncommon in patients living in temperate climate. It usually occurs in the older patients (over 40 years of age) and should be suspected if the steady state Hb falls to below 6 g/dl, particularly in patients with previous renal pathology. The onset is often insidious.

*Treatment*

- Top-up transfusion for the anaemia if clinically compromised, or regular transfusion to arrest the pathological process.
- Dialysis and transplant may be considered in patients with the end stage failure.

**Eye problems**

Patients with SCD should have annual ophthalmological examinations including visual acuity screening.

Non proliferative retinopathy:

This arises as a result of previous neovascular changes and includes retinal haemorrhages, angioid streaks, vascular occlusions, black sunbursts and macular changes. They may sometimes affect visual acuity.

Proliferative sickle retinopathy:

Peripheral retinal occlusions may start in early childhood but retinal neovascularization generally starts between the age of 15 and 35 and is most commonly found in HbSC Disease (HbS + HbcC). Untreated proliferative retinopathy may cause blindness through vitreous haemorrhage and retinal detachments.

*Management*

- Early laser or photocoagulation of the neovascularized areas.

Vitreous haemorrhage and retinal detachment:

Surgical treatment should not be undertaken without prior exchange transfusion.

HypHEMA:

Usually due to blunt trauma. It may lead to raised intraocular pressure and thus to retinal vessel occlusion with blindness. Refer to a specialist IMMEDIATELY. If surgery is required, exchange transfuse.

**Chronic lung problems**

A small number of patients develop chronic hypoxia progressing to pulmonary hypertension, and cor pulmonale. Regular transfusion may arrest the progression of this condition. Associated segmental myocardial ischaemia may cause sudden death.

Asthma, bronchitis, sarcoidosis and tuberculosis may be severe in SCD and in turn exacerbate the sickle pathologies; specialist opinion must be sought.

### **Gall stones, biliary tract and liver disease**

#### Gall stones:

Occur in at least 30% of children and over 70% of adults. Often asymptomatic but can cause:

- Acute cholecystitis.
- Chronic cholecystitis.
- Biliary colic.
- Obstruction of the common bile duct.
- Related acute pancreatitis.

#### *Diagnosis*

- Plain abdominal x-ray (as many as 50% of stones may be radio-opaque).
- Ultrasound or if unavailable, oral cholecystogram.

#### *Differential diagnosis*

- Hepatitis (viral).
- Peptic ulcer.
- Vasocclusive episodes.
- Hepatic sequestration.
- Chest syndrome.

#### *Management*

##### Acute episode:

- Antispasmodics.
- Hydration.
- Antibiotics.

#### Common bile duct obstruction:

Endoscopic retrograde cholangiopancreatography (ERCP) or emergency surgery.

#### *Recurrent problems*

- Elective surgery.
- Exchange transfusion is needed for many patients, although some patients may be operated on successfully without exchange transfusion. The protocol described later should be followed.

#### Intrahepatic cholestasis:

Some patients experience episodes of severe hyperbilirubinaemia, associated with fever and hepatic pain in the absence of demonstrable stones. These episodes are thought to be due to severe intrahepatic sickling.

#### *Management*

- Analgesia (care as most opiates are metabolised in the liver).
- Hydration.
- Antibiotics.
- Monitoring of liver function tests.
- In very severe cases exchange transfusion may be needed.

#### **Peptic ulcer**

Common in men.  
Epigastric pain, dyspepsia, nocturnal pain.

#### *Investigation*

- Endoscopy or barium meal.

#### *Management*

- Medical (H<sub>2</sub> receptor blockers, antacids etc).
- Failure of medical treatment is common. Early surgical treatment is indicated.
- Exchange transfusion should be considered pre-operatively.

#### **Leg ulcers**

Uncommon in temperate climates.  
Troublesome when they occur.  
Almost invariably infected.

#### *Management*

- Identify organism (usually *Staphylococcus aureus* in Britain), treat both topically and systemically (care: antibiotic resistance).
- Patients need stringent hygiene with frequent dressings.
- Prevent trauma.
- In resistant cases consider bed rest, pig skin, amnion or skin grafting (when ulcer sterile) or regular transfusion for 3 - 6 months.
- Zinc sulphate orally may aid healing.

#### **NOTE:**

Healed ulcers often break down on return to tropical climate.

5. PUBERTY, FERTILITY, CONTRACEPTION AND PREGNANCY

Delayed puberty

Common, particularly in boys.

Related to lower body mass for age in children with SCD.

Reassure, as most will progress smoothly through puberty despite the delay.

Management

- In the very thin patient attempt to improve the appetite and quality of nutrition in order to increase the body weight.
- Regular transfusion for 6 - 12 months almost always initiates puberty.
- Where a hormonal deficiency can be demonstrated, treat appropriately.
- Exceptionally, infarcts in the hypophysis and hypothalamus are responsible. Refer to a specialist for appropriate replacement therapy.

Fertility

Women are normally fertile whereas many men with sickle cell anaemia (HbSS) and sickle beta/zero thalassaemia ( $S\beta^0$ ) have reduced sperm counts and reduced sperm motility. Some may be impotent because of past priapism. They should be referred to a urologist for consideration of a penile prosthesis.

Contraception

Barrier methods, the progesteron only pill, and Depo-Provera intramuscularly are the preferred methods, because of the theoretically increased risk of stroke and venous thromboembolism with the oestrogen containing pill. However, none of these methods offers complete contraception.

If the first three methods are unacceptable or unsuitable, a low dose oestrogen contraceptive pill can be used, but only after a full discussion of the potential risks with the patient.

Intrauterine device (coil) may cause severe menorrhagia in some women with SCD, as well as recurrent infections, and has proved to be rarely acceptable in the long term.

Termination of pregnancy

This should be avoided if possible by contraception as it carries a high risk of post operative complications. Cover termination as described in the section on anaesthesia and surgery (page 26).

Pregnancy

*Women with SS or  $S\beta^0$*

The optimum management is not established. Some women may go through pregnancy without transfusion and suffer no ill-effects giving birth to healthy (small for dates but usually healthy) babies. Others may experience severe SCD related complications (crises, sequestration syndromes, aseptic necrosis of the hip, worsening retinopathy etc.) or have miscarriage, intrauterine death, or stillbirth.

### *Options*

- Transfuse all patients from the first trimester in order to achieve normal foetal growth.
- Transfuse only if and when a woman develops a SCD related complication.
- Transfuse the women with a history of severe sickle cell disease or obstetric problems from presentation and transfuse the previously mildly affected women only if severe complications ensue.

### **NOTE:**

- Careful and regular obstetric and haematological follow up is essential whichever option is taken.
- The Hb may fall to 6 g/dl or less at the end of second trimester. If the mother is feeling well, there is no need to transfuse to correct Hb.
- If transfusion is used, crossmatching and genotyping as described on page 7 should be used.

### Delivery

There is no contraindication to normal obstetric practice nor to epidural anaesthesia. The delivery should be vaginal whenever possible. General anaesthesia for caesarian section may need pre-operative exchange transfusion and patients should be closely monitored post-operatively. Subcutaneous heparin (5000 iu bd) may be helpful in preventing post partum vasoocclusive events. It may be given from 36 weeks gestation to 6 weeks post partum in those who are not transfused.

### *Women with Hb SC Disease or Hb S/b+thalassaemia*

The majority go through pregnancy without transfusion, provided meticulous obstetric care is provided. Transfusion is only needed if there are severe sickle related problems or poor obstetric history (stillbirth, intrauterine death). Subcutaneous heparin (see above) may minimize the risk of pulmonary complications post partum.

6. GENERAL NOTES ON CHILDREN WITH SCD

Infancy

A programme of neonatal screening for haemoglobinopathies should be instituted in all regions where the frequency of Hb S gene is high in the population as a whole or in a section of it. Babies found to have no Hb A at birth should be recalled for testing at 6 weeks and if found to have SCD, should be entered into a programme of comprehensive care which includes: counselling of parents; paediatric follow up; prophylactic penicillin; folic acid. The role of regular folic acid is disputed in SCD in the temperate climates. Although the risk of megaloblastic crisis in SCD precipitated by acute folic acid deficiency appears remote, folic acid is generally prescribed for children, adolescents and pregnant women, as well as patients recovering from an acute infection or crisis. It should be prescribed for patients whose MCV rises.

Early childhood

Specific SCD related manifestations are uncommon in the first three months of life, but jaundice, anaemia, hepatosplenomegaly and failure to thrive have been reported. From two months of life the child is at risk of pneumococcal infection and acute splenic sequestration. The highest risk is during the second six months of life; it diminishes after the second year but it never disappears.

From 4 months to 2 years of life, the hand foot syndrome (dactylitis, see page 10) due to bony infarcts in the small bones of the hand and foot, is common.

Classical painful crises generally start later. The modal age for stroke is 7 years, but it can occur as early as 18 months.

Normal routine vaccinations against childhood illnesses are essential in all children with SCD, and should be given despite the children taking prophylactic penicillin.

The age for giving antipneumococcal vaccination is debatable; it can be given from 6 months of age and "boosted" every 3 years. Penicillin prophylaxis (which offers a more complete cover) is best continued indefinitely although the risk does fall with advancing age.

7. GENERAL NOTES ON ADULTS WITH SICKLE CELL DISEASE

General advice

- Good fluid intake at all times.
- Avoid dehydration.
- Avoidance of and prompt attention to all infections.
- Suitable career and leisure activities.
- No smoking.
- No alcohol.
- Regular once yearly OPD visits even when well to check:
- Full blood count.
- Blood biochemistry.
- Urine test.
- Ophthalmological examination.

Surgery and anaesthesia/minor or intermediate surgery

- Exchange transfusion is not usually required unless the patient already has a serious chronic complication of SCD or frequent vasoocclusive crises.
- Start iv fluids when oral fluids are stopped and continue until patient is able to take fluids freely.
- Give subcutaneous heparin 5000 iu bd starting 2h preoperatively and until the patient fully mobile.
- Administer prophylactic antibiotics (antibiotic choice depends on local policy and type of surgery).
- Ensure careful oxygenation from the premedication throughout the operation and until fully awake.
- Hyperoxygenation at induction of anaesthesia.
- Chest physiotherapy is invariably needed.

Major surgery

- Exchange transfuse to achieve Hb S < 25% preoperatively.
- Other measures as for minor surgery.

## 8. PSYCHOSOCIAL SUPPORT

Experience collected in Europe over the last few years has allowed the formulation of the following guidelines with respect to psychosocial issues.

Patients should be helped to:

- Cope with the psychosocial consequences of their disease.
- Achieve full integration into society.

Psychosocial support is and must remain an integral part of the total management of patients with haemoglobin disorders. It should be included in the service provided by the multidisciplinary team. It is essential for the overall responsibility for clinical care and co-ordination to rest with the treating physician, who should remain the same for as long as possible, given the close relationship which develops between the treating physician and patient. The team led by this physician should include: a psychiatrist and/or psychologist and a social worker. Other team members, especially nursing staff, should remain the same as long as possible, and should have a thalassaemia/sickle oriented training. In particular, the mental health professionals should have some experience in management of patients with chronic and inherited disease. The obligation of the team to reserve time and space for meetings with both patients and parents following each major visit to the treatment centre is of prime importance.

The families of children with inherited disorders such as the haemoglobin disorders face an initial emotional crisis at the time of diagnosis. This can challenge the parental partnership and shift the whole balance of their family life. The family should be helped to accept the illness of the affected child and to understand its implications. They should be encouraged to understand and accept the need for orderly and continued surveillance and therapy. The parent should be helped to avoid overprotection of the affected child/children in order to maintain the characteristics of a normally functioning family. They should therefore behave towards the affected child in a manner as similar as is feasible to that used toward healthy siblings. In order to help the family in this, active participation in specific social programmes and interaction with other parents, self-help groups and patient associations are generally very helpful.

The child with moderate or severe sickle cell disease has to grow up in continuous contact with health care professionals, and on medical treatment. The child may therefore appear (or feel) different from other children and have difficulty as a result in establishing his or her body image. Later on, particularly if puberty is delayed, the adolescent may feel dependent and experience problems in belonging to his peer group. The adolescent emotional crisis can be aggravated and the patient's development into adult life may become particularly complicated. If the adolescent is not helped to come to terms with the implications of their disease they may fail to cope, and this may result in hospital admissions which are inappropriately frequent.

All patients should be helped to understand and accept their illness so that they will be able to accept the necessary treatment. They should be reassured that any complications which occur over the years do not necessarily mean a deterioration, and they should be encouraged to look to the future with optimism. It is therefore essential to develop active participation of the patients in their own treatment programmes and to help them to develop other interacting processes aimed at promoting patients' control of their own disease.

Medical and psychosocial intervention should take account of the educational level and psychological strengths and weaknesses of individual patients and help each according to his or her individual needs. The integration of the child with a haemoglobin disorder into his or her class and school constitutes a critical step in psychological development. It has as its ultimate goal the development of that child into an adult who can actively participate in society. In order to achieve this, the treatment team should contact the patients' schools and discuss the problems associated with their treatment, growth and development with both the governing bodies and the patients' individual teachers. Schools should be encouraged to promote sensitization of the teachers with respect to inherited diseases. The school staff should avoid allowing special privileges to children with haemoglobinopathies, except those which are medically indicated, in order to further reduce the patients' dependency.

The aim of everyone involved in the patients' care (family, physicians, psychiatrists and educationalists) must be to optimise the integration of the patient into society. Their efforts should concentrate on preparing the patient for the highest achievable level of work rather than giving him or her privileges which could lead to continued dependency.

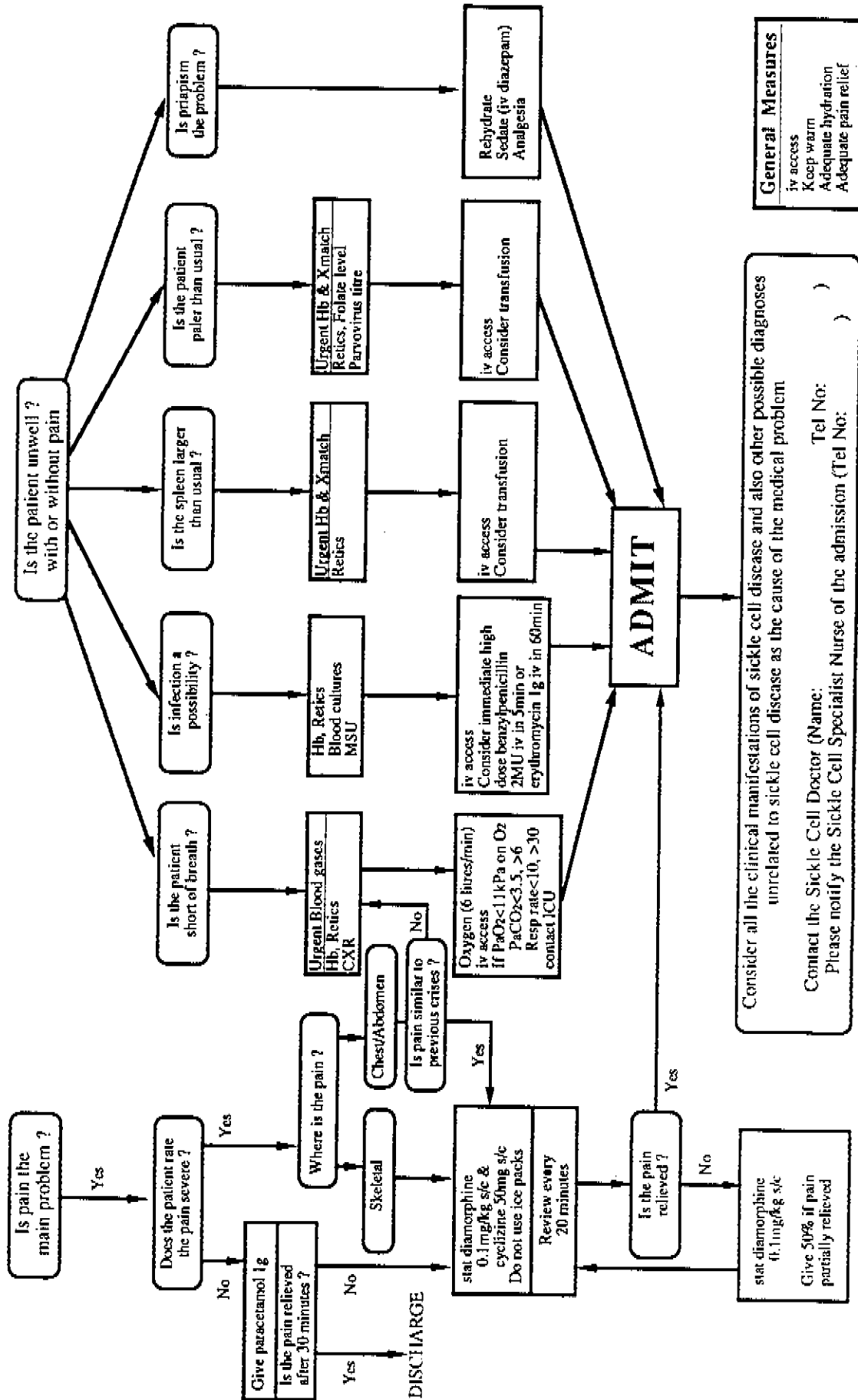
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A P P E N D I X

# EMERGENCY MANAGEMENT OF SICKLE CELL DISEASE



Further details are available in the full protocols