Current Trends in the Management of Sickle Cell Disease: REVIEW ARTICLE

Abdelaziz Elamin*

Abstract

Sickle cell disease (SCD) is common in Sudan and in sub-Saharan Africa. It is also prevalent in the Arabian Gulf countries and in India. Despite the tremendous advances in diagnostic and therapeutic modalities, Children with sickle cell anemia continue to suffer from repetitive crisis and have frequent severe complications. These morbid events as well as mortality can be greatly reduced by specialized medical care that focuses on prevention and active intervention. This article reviews the most recent and evidence-based guidelines for preventive care and medical management of SCD and its most commonly encountered complications.

Keywords: hemolytic crisis, children, pain management, bone marrow transplant

Background

Sickle cell disease (SCD) denotes all genotypes that contain at least one sickle gene in which hemoglobin-S (HbS) makes up at least half of the hemoglobin present. In addition to the homozygotic HbSS (sickle cell anemia), in which only HbS is produced, at least 5 other major genotypes are linked to the disease. These include the following:

- HbS–beta-thalassemia: Severe form of disease; almost indistinguishable from sickle cell anemia phenotypically.
- HbSC disease: Condition with intermediate clinical severity
- HbS/hereditary persistence of fetal hemoglobin: Mild form of SCD.
- HbS/HbE syndrome: Rare condition with generally mild clinical course
- Rare combinations of HbS with HbD and HbO Arab, among others.

Sickle cell anemia (SCA) is common in tropical Africa and the clinical manifestations of the disease were recognized by the native Africans centuries [1] before the first case report appeared in the medical literature in 1910 [2]. Since then, several studies have documented the presence of the disease in other parts of the world particularly in the Arabian Peninsula, the Mediterranean, India and the United States [3-5]. SCA is the most severe and most common form. It is characterized by persistent hemolysis due to the short life span of the sickled red cells and repetitive painful crisis that result from vascular obstruction, ischemia, and incremental infarction.. Although a diagnosis of the disease can be made at birth, clinical abnormalities usually do not occur before the age of 6 months, when fetal hemoglobin, which has protective effect, fades away and gets replaced by HbS. functional asplenia develops by the end of first year of life and results in increased susceptibility to overwhelming infection with encapsulated respiratory bacteria.

* Professor of Child Health, Omdurman Islamic University

Preventive measures

It is estimated that there were about 80 million carriers of sickle cell trait in the world in 1992 and each year 156 000 infants are born with SCD[6]. Prenatal diagnosis of SCD is now technically possible from the 9th weeks of gestation [7]. In some countries the prenatal diagnosis is followed by abortion of homozygous fetuses if parents requested. This practice, however, is illegal in many countries. Screening to recognize couples at risk and diagnosis of SCD in the neonatal period are universally accepted and recommended. It is very useful for education of the parents and genetic counseling and allows the prevention of some of the expected complications. Preventive care should begin at three months of age. Complete blood count including reticulocyte count is essential to determine baseline values. A leucocyte differential count is important since many children have high levels of nucleated red cells which will result in spuriously elevated leucocyte count. The problems encountered by children with SCD should be discussed with the parents at each visit. They should be taught how to recognize the sickling crisis and what steps to take when complications arise; the most important issue is when to bring the child to medical attention. By six months of age, penicillin prophylaxis should be started for all children who are homozygous for Hb-S and continued till the age of 16 years. This practice has proved to be valuable in reducing the frequency of Streptococcus pneumoniae bacteraemia and its associated high mortality rate [8]. Oral penicillin should be given at a dose of 125 mg twice daily until age three after which the dose is increased to 250 mg twice daily. Some authorities prefer amoxycillin 250 mg for children, who are younger than 10 years of age in

order to cover the risk of Haemophilus influenzae infection. Children allergic to penicillin should take erythromycin: 250 mg 12-hourly for children aged 2 years or more; 125 mg 12-hourly for children under the age of 2 years. The other macrolides Azithromycin once daily and Clarithromycin twice daily can also be used. The use of Benzathine penicillin for prophylaxis in patients with SCD was evaluated in Jamaica. The study was terminated when significant compliance problems were encountered due to the discomfort caused by the intramuscular injections given at three weeks interval[9]. Although fewer infections were detected in those children receiving this form of penicillin, the difference was not statistically significant. Penicillin prophylaxis has not been evaluated for children with Hb-SC disease, but the finding that their incidence of bacteraemia during the first two years of life is similar to that of children with sickle cell anemia [10] caused some physicians to recommend it for these children as well. In fact, some hematologists recommend penicillin prophylaxis for all variants of SCD [11].

At 18 months, conjugated Heamophilus influenzae vaccine should be given as recommended by the American Academy of Pediatrics [12]. Although no conclusive studies have yet been reported in children with SCD, immunization with heamophilus influenzae vaccine has been shown to be effective in normal children [13] and in splenectomized children and adolescents [14]. This is followed at 24 months of age by polyvalent pneumococcal vaccine [15]. The current pneumococcal vaccine is unconjugated and is less effective in children under 2 years of age compared to its effect in older children. This is because unconjugated polysaccharides do not produce adequate antibody response in young children. Booster doses of the latter vaccine at 5-10 years intervals have been suggested by some investigators and have been administered with no reported complications [16]. Other workers do not recommend re-immunization because a severe arthus type-III immune reaction might occur. In the absence of consensus, the decision to re-immunize must be individualized and if believed appropriate, undertaken with caution. Unfortunately, the use of these measures does not ensure freedom from infection. Pneumococcal bacteraemia has been documented shortly after a dose of prophylactic penicillin was missed [17]. In addition bacteraemia has been detected in children immunized with the pneumococcal vaccine [18]. Since the current vaccine contains only those serotypes most frequently causing infection in patients with SCD, the observed bacteraemia could be due to one of the less common serotypes [19]. However, it has also been described with serotypes included in the vaccine but which provoke an inadequate antibody response [20].

Medical management

Pain: Although pain is the hallmark of SCD, many affected children never have pain sufficiently severe to require treatment. The cause for this differential severity is one of the many mysteries of this disease. When pain is encountered it is almost always due to erythrocyte sickling, thrombosis, vaso-occlusion and infarction. Precipitating factors include upper respiratory tract infection, fever, dehydration, hypoxemia; exposure to cold temperatures, weather changes, and emotional stress. Mechanical or traumatic events that result in an interruption of blood flow to tissue can also result in ischemia and subsequently severe pain. For mild pain, the parents should be advised to encourage oral fluids intake to ensure good hydration and to give acetaminophen or paracetamol for analgesia. The application of warm compresses may also be helpful. However, the greatest benefit will be derived from the parents' calm approach and reassurance that the pain will disappear. If the pain is too severe to respond to these simple measures, the child should be seen at hospital. If the pain is believed to be due to a vaso-occlusive crisis, subcutaneous morphine at a dose of 0.1 mg/kg may provide sufficient relief to allow the child to return home [21]. There, acetaminophen with codeine or meperidine suspension may provide adequate relief for the duration of the painful episode. Children two years old or younger are more prone to develop dactylitis and the hand-foot syndrome. These result in tender swelling of fingers and toes and considerable pain, which is usually so severe that parenteral narcotic analgesics are required [22]. Pain that does not respond to this regimen or that persists for more than two days deserves hospitalization. In hospital intravenous hydration with a crystalloid solution should be started and a narcotic, morphine sulphate or pethidine, should be given intravenously at a dose of 0.2 mg per kg every two hours till the episode is over [23]. Injectable meperidine at a dose of 1 mg/kg every 3 hours is an alternative. Repeated doses of this drug should be given with caution since seizures can result from the accumulation of one of its metabolites [24]. The intravenous route is preferred

because it provides a more predictable analgesic response. In addition it avoids the fibrosis that accompanies prolonged intramuscular administration of certain analgesics especially meperidine. Parenteral narcotic analgesics should be administered on a regular basis and not on as needed basis since the pain can be expected to continue at same degree of severity for several days. Additionally it has been established that narcotic analgesics given only on request result in poorer pain control and the need for larger doses. The hand-foot syndrome may persist for 2-3 weeks and when the pain begins to diminish the dose of the parenteral narcotics should be decreased gradually until analgesia can be accomplished by oral medications. Oral morphine sulphate or codeine can be used till the episode is over and the child is pain-free.

Bacterial infections: Bacteraemia and meningitis caused by Streptococcus pneumoniae and Haemophilus influenzae occur with an extremely high incidence in children with sickle cell anemia during the first five years of life [25]. Children with Hb-SC disease have been shown to have a comparable rate during the first two years of age, but the risk decreases as they grow older. Fever is the initial presentation of sepsis in children with SCD. The frequency with which pneumococcal bacteraemia occurs in children with SCD and the reported 24% mortality for such episodes requires a different approach from what would be considered appropriate for fever in normal children [26]. Parents must be instructed to watch carefully for fever and when a fever is found, they should avoid the common practice of treating the fever rather than its cause. Since a minor temperature elevation might indicate a serious infection, any febrile child with SCD should be evaluated by a doctor without waiting to see if the child is going to get better or worse. It cannot be over emphasized that sepsis can occur even when the child is immunized and using prophylactic penicillin. Parents should be informed that an extra dose of penicillin prophylaxis is not a substitute for bringing their febrile child for medical checkup. However, physicians know that the evaluation of these children is not easy. Leucocyte counts cannot be relied upon to distinguish between viral and bacterial infections in normal children and seem to be even less reliable in children with SCD where baseline values are elevated [27]. Similarly, the erythrocyte sedimentation rate and the C-reactive protein levels have both been shown not to be helpful in identifying the presence or severity of infection in children with SCD [28, 29]. Finally, even the spinal fluid leucocyte count cannot be relied upon as an indicator of meningitis as shown in a report of six febrile patients with SCD who had normal spinal fluid cell count with culture documented Streptococcus pneumoniae meningitis [30]. Since there is no reliable laboratory test to distinguish viral from bacterial infections in the initial evaluation of febrile children, the imprecision of clinical judgment requires that in most instances the child should be hospitalized, appropriate cultures obtained and suitable parenteral antibiotics given as empirical measure. Following admission, if the child became afebrile and the blood cultures show no growth at 72 hours, treatment can be completed with oral antibiotics at home. When the child is found to have meningitis or septicemia the course of treatment is completed with parenteral antibiotics according to the sensitivity of the isolated organism.

Malaria: Individuals with sickle cell trait are known to be resistant to malaria infection [31]. Parasite growth is reduced in red cells containing Hb-S. Because of increased oxygen consumption in the parasitized erythrocytes, these cells sickle more rapidly than unparasitized cells and are easily removed from the circulation by phagocytosis. Unfortunately, protection against plasmodium falciparum is not complete for patients with sickle cell anaemia [32, 33]. In countries where falciparum malaria is prevalent children with SCD are at increased risk of developing severe complicated malaria or cerebral malaria. In such places regular drug prophylaxis is recommended. Proguanil is still the prophylactic of choice, being safe and effective [34]. However, long-term prophylaxis is difficult to maintain in developing countries and with the recent reports of multiple drug resistance the desired protection may not be achieved. On the other hand, because malaria may present with a wide spectrum of symptoms and signs any ill child with SCD, whether febrile or not, should has several blood smears examined for malaria parasites and anti malarial therapy started until the cause of the illness is identified.

Splenic Sequestration: This severe life threatening complication may be encountered in any of the variants of SCD. usually occurring when the child is very young [35]. It is commonly associated with febrile illnesses and enlarged spleen but splenomegaly is not a necessary prerequisite. The problem results from the sudden shunting of a volume of blood to the spleen

sufficiently large to result in hypovolaemic shock. Parents of children with splenomegaly should be taught how to monitor its size by abdominal palpation. They should be informed of the implications of sudden onset of pallor and weakness and advised to determine if the spleen size has increased. If their child becomes symptomatic they should proceed immediately to the nearest medical facility. There they should provide this information to the medical personnel at once since considerable time might be lost if the child is assigned to the routine evaluation process common in busy emergency departments. For the child who presents with sudden onset of pallor, tachypnoea, hypotension and increasing splenomegaly, laboratory data will show low haemoglobin with reticulocytosis and thrombocytopenia. Treatment is directed toward correction of shock and includes crystalloid or colloid restoration of the circulatory volume. Blood transfusion is usually required as 10 ml/kg infusion of packed red cells. Such treatment may cause the spleen to disgorge a large proportion of the trapped blood which can result in an unexpectedly high haematocrit and significantly increased viscosity which may then cause vaso-occlusive complications. If splenic sequestration recurs, splenectomy should be considered. For the young child chronic transfusion therapy has been recommended to prevent further sequestration episodes while preserving splenic function [36].

Stroke: Cerebral vascular accidents occur in patients with SCD with an incidence much higher than that found in normal subjects. In children, the strokes are usually caused by thrombosis of the cerebral vessels. Large blood vessels are usually involved which results in extensive neurologic damage [37]. Adolescents and adults are more likely to have subarachnoid hemorrhages [38]. Patients may present with seizures, hemiplegia, speech disorder, difficulty with swallowing, impaired vision or disturbed sensorium. When a stroke occurs, CT examination is very useful but should be done without contrast media since its use might increase blood viscosity sufficiently to cause further interruption of the already compromised circulation [39]. Certain types of contrast are said to cause few problems [40] but their use in vessels which are only minimally patent must be undertaken with caution. Once the diagnosis is made, Hb S or SC concentration should be reduced to below 30% as promptly as possible using exchange transfusion or erythrocytopheresis [41, 42]. Care must be taken to ensure that the haematocrit remains low until HbS is reduced to the desired level since viscosity increases exponentially with increasing haematocrit when Hb S level is high. To avoid the 66% stroke recurrence rate [38], transfusion therapy must be given at a frequency sufficient to maintain Hb S below 30% [41]. This usually requires blood transfusion at four week intervals. Unfortunately, the duration of this treatment has not yet been established. In one report, when transfusions were stopped in ten patients after one to two years, strokes recurred in seven [43]. This finding and the progressive neurologic damage caused by recurrent strokes has led many pediatricians to continue blood transfusions indefinitely.

Acute Chest Syndrome: Chest pain, cough, haemoptysis, low grade fever and pulmonary infiltrates occur frequently in patients with SCD. Since it is usually impossible to determine whether pneumonia, pulmonary infarction or some combination of the two is causing such symptoms, the clinical presentation is referred to as the acute chest syndrome [44]. In children the predominant cause is infection. Many of the infections are due to Streptococcus pneumoniae but viruses are responsible for a considerable proportion. Other bacterial infections were reported including mycoplasma pneumoniae, which causes unusually severe pulmonary infections in these children [45]. Pulmonary infarction is thought to be the most common cause of the syndrome in adolescents and adults. However, since infection cannot be easily excluded and pulmonary infarction has no specific therapy, antibiotics are usually prescribed for these patients too. With any pulmonary complication in SCD oxygenation is a major concern. To compensate for chronic anaemia the oxygen dissociation curve is shifted to the left in affected patients. This allows more efficient oxygen delivery to the tissues. As a result, if the haemoglobin is not fully oxygenated in the lungs, deoxygenating at the tissue level may be sufficient to cause sickling. Consequently patients with the acute chest syndrome should have their oxygen saturation maintained at normal levels by increasing the concentration of inspired oxygen. Blood transfusion is indicated for those patients who showed evidence of respiratory failure. The use of partial or complete exchange transfusion has been reported to be beneficial in such instances [46]. The simple transfusion of blood without exchange must be approached cautiously to avoid the problems associated with increased blood viscosity.

Priapism: The incidence of priapism among children with SCD is grossly underestimated because many parents do not regard it as a complication of the disease while other families are too embarrassed to report its occurrence unless specifically asked [47]. This complication should be discussed with the child and his parents who can be informed that its usual manifestation is a brief painful erection which generally responds to various interventions at home. Possible approaches include micturition, relaxation in a warm bath and distraction with any type of physical activity. Masturbation should not be tried as it is unlikely to result in either ejaculation or detumescence. In a study conducted in adult with SCD, Serjeant has described the occurrence of frequent brief episodes of painful erections which he called "stuttering priapism". He showed that the problem could be treated and prevented by daily administration of stilbesterol [48]. Certain side effects such as gynaecomastia and failure of normal erection were reported which could be avoided by manipulation of the dose. No experience has been published regarding this form of therapy in children. If an erection persists for more than three hours it is unlikely to resolve spontaneously and hospital treatment is needed. Parenteral hydration and effective narcotic analgesics should be initiated and Hb S reduced as quickly as possible to about 20% using exchange transfusion or erythrocytopheresis. If detumescence does not occur within 24 hours surgical intervention is necessary. It has been reported that the use of winter procedure has resulted in a decreased rate of impotence, which frequently follows severe episodes of priapism [49].

Aplastic Crisis: The sudden cessation of erythropoiesis has been shown to result from a parovirus infection but may have additional etiologies [50]. Due to extremely short red cell survival in SCD, the haemoglobin will fall rapidly when red cell production is interrupted. Pallor, weakness and signs of severe anaemia develop gradually. Pancytopenia with low reticulocyte count is demonstrated. Patients can be observed at two to three days intervals until reticulocytosis occurs and the haemoglobin increases to its baseline value. However, if the hemoglobin level drops to 3-4 g/dl or signs of heart failure develop, a packed red cells transfusion of 10 ml/ kg should be given. The need for subsequent transfusion is very unusual.

Osteomyelitis: Osteomyelitis is a common complication of SCD. Salmonella or staphylococci are the responsible bacteria in the majority of patients but others organisms such as streptococcus pneumoniae are occasionally isolated [51]. The differentiation between an acute bone infarction and acute osteomyelitis is difficult to make [52]. Both conditions present with fever, pain and leucocytosis. Conventional radiology is not helpful in the early stages. A variety of radio-isotope techniques have been proposed but to date none have proved reliable [53]. Ultrasound examination is useful in detecting pus collection and periosteal reactions, but the magnetic resonance imaging is the most helpful investigation. Blood culture is mandatory to confirm the diagnosis and to determine the offending organism. Salmonella osteomyelitis is so often thought of in association with SCD that other possible etiologies are ignored [54]. While waiting for culture results or if no organism is isolated, antibiotics effective against both salmonella and staphylococci should be used.

Aseptic Necrosis of Bone: Aseptic necrosis of the femoral or humeral head is seen with high frequency in adolescents with SCD [55]. Usually it follows an episode of a vaso-occlusive crisis. Parents and children should be instructed to report pain that persists in their shoulders or hips during periods between painful crisis episodes. When the diagnosis is made, symptomatic treatment should be provided to minimize pain and discomfort. Necrosis of the humeral head seldom causes significant problems while necrosis of the head of the femur causes hip joint dysfunction. Minimization of weight bearing may allow some degree of healing to occur, but the usual treatment is surgery. Several approaches are adopted including head resection, bone grafting and implantation of a prosthetic device. Hip protheses are frequently implanted in adults but surgeons are reluctant to provide this type of surgery to children and adolescents since the protheses may need to be replaced as frequently as every 10 years [56].

Leg Ulcers: Chronic leg ulcers are most often encountered between the age of 10 and 30 years [57]. Their underlying cause is unknown but since they are thought to be related to vascular stasis and trauma, subjects with SCD should be advised to avoid standing for long periods and to protect their feet and ankles by wearing shoes and stockings. Patients should be instructed to seek medical attention for any slowly healing lesion that occurs below the knee. When an ulcer develops, it must be debrided at frequent intervals to promote healing. If it persists, the skin of the

36. Topley J, Rogers D, Stevens M, et al. Acute splenic sequestration and hypersplenism in the first five years in homozygous sickle cell disease. Arch Dis Child 1981; 56: 765-769.
37. Rao S, Gooden S. Splenic sequestration in sickle cell disease: role of transfusion therapy. Am J Pediatr Hematol Oncol 1985; 7: 298-301.
38. Stockman JA, Nigro MA, Mishkin MM, et al. Fusion of large cerebral vessels in sickle cell anaemia. N Engl J Med 1972; 287: 846-850.
39. Powars D, Wilson B, Imbus C, et al. Natural history of stroke in sickle cell disease. Am J Med 1978; 65: 461-471.
40. Imbus C, Powars D, Pegelow C, et al. Complications of CT in sickle cell disease. Arch Neurol 1978; 11: 213-215.
41. Rao VM, Rao AK, Steiner RM, et al. Effect of ionic and non-ionic contrast media on sickling phenomenon. Radiology 1982; 144: 291-293.
42. Russell M, Goldberg J, Hodson A, et al. Effect of transfusion therapy on arteriographic abnormalities and on recurrence of stroke in sickle cell disease. Blood 1984; 63: 162-169.
43. Sarniak S, Lusher J. Neurologic complications of sickle cell anaemia. Am J Pediatr Hematol Oncol 1982; 4: 386-394.
44. Williams J, Goff J, Anderson H, et al. Efficacy of transfusion therapy for one to two years in patients with sickle cell disease and cerebrovascular accidents. J Pediatr 1980; 96: 205 -208.
45. Poncz M, Kane E, Gill F. Acute chest syndrome in sickle cell disease: etiology and clinical correlates. J Pediatr 1985; 107: 861-866.
46. Shulman ST, Bartlett J, Clyde WA, et al. Unusual severity of mycoplasma pneumonia in children with sickle cell disease. N Engl J Med 1972; 287: 164-167.
47. Davies SC, Luce PJ, Win AA, Riordan JF, Brozovic M. Acute chest syndrome in sickle cell disease. Lancet 1984; I: 36-38.
48. Emond A, Holman R, Hayes R, et al. Priapism and impotence 111 homozygous sickle cell disease. Arch Intern Med 1980; 140: 1434-1437.
49. Serjeant G, De Ceulaer K, Maude GH. Stilboestrol and stuttering priapism in homozygous sickle cell disease. Lancet 1985; 2: 1274-1276.
50. Noe H, Williams J, Jerkins G. Surgical management of priapism in children with sickle cell anaemia. J Urol 1981; 126: 770-771.
51. Kelleher J, Luban N, Cohen B, et al. Human serum parovirus as a cause of aplastic crisis in sickle cell disease. Am J Dis Child 1984; 138: 401-403.
52. Givner L, Luddy R, Schwarz A. Etiology of osteomyelitis in patients with sickle hemoglobinopathies. J Pediatr 1981; 99: 411-413.
53. Keeley K, Buchanan GR. Acute infarction of long bones in children with sickle cell anaemia. J Pediatr 1982; 101: 170-175.
54. Rao S, Solomon N, Miller S, et al. Scintigraphic differentiation of bone infarction from osteomyelitis in children with sickle cell disease. J Pediatr 1985; 107: 685-688.
55. Mallauoh A, Talab Y. Bone and joint infection in patients with sickle cell disease. J Paediatr Orthop 1985; 5: 158-162.
56. Hawker J, Nielson H, Hayes R, et al. Haematologic factors associated with avascular necrosis of femoral head in homozygous sickle cell disease. Br J haematol 1982; 50: 29-34.
57. Gunderson C, De Ambrosia R, Shoji H. Total hip replacement in patients with sickle cell disease. J Bone Joint Surg 1977; 59: 760-762.
58. Wilfort FG, Krizet TJ. Skin ulceration in sickle cell anaemia. Plast Reconstr Surg 1969; 43: 71-77.
59. Rennels M, Dunne M, Crossman N, et al. Cholelithiasis in patients with major sickle hemoglobinopathies. Am J Dis Child 1984; 138: 66-67.
60. Fullerton MW, Philippart AI, Sarnaik S, et al. Pre-operative exchange transfusion in sickle cell anaemia. J Pediatr Surg 1981; 16: 297-300.
61. Schmalzer E, Chein S, Brown AK. Transfusion therapy in sickle cell disease. Am J Pediatr Hematol Oncol1982; 4: 395-406.
62. Davies SC, Roberts JA. Bone marrow transplant for sickle cell disease: an update. Arch Dis Child 1996; 75: 3-6.
63. Davies Se. Bone marrow transplantation for sickle cell disease-the dilemma. Blood Rev 1993; 49: 4-9.
64. Mentzer WC; Heller S, Pearle PR, et al. Availability of related donors for bone marrow transplantation in sickle cell anaemia. Am J Pediatr Hematol Oncol1994; 16: 27-29.
65. Vermylen C, Cornu G. Bone marrow transplantation for sickle cell disease: the European experience. Am J Pediatr Hematol Oncol1994; 16: 18-21.
66. Ferster A, Bujan W, Corazza F, et al. Bone marrow transplantation corrects the splenic reticuloendothelial dysfunction in sickle cell anaemia. Blood 1993; 81: 11021105.
67. Johnson FL, Mentzer WC, Kalinyak KA, et al. Marrow transplantation for sickle cell disease: the US experience. Am J Pediatr Hematol Oncol 1994; 16: 22-26.
68. Ferster A, Corazza F, Vertongen F, et al. Transplanted sickle cell disease patients with autologous bone marrow recovery after graft failure develop increased levels of fetal haemoglobin which corrects disease severity. Br J Haematol 1995; 90: 804-808.
69. Bernaudin F, Vilmer E, Souillet G, et al. Stroke and sickle cell disease: BMT can prevent recurrence (French experience). Bone Marrow Transplant 1995; IS (supp12): 161.
70. Thilaganthan B, Nicolaides KH, Morgan G. Intra-uterine bone marrow transplantation at 12 weeks gestation. Lancet 1993; 342: 234.
71. Gluckman E, Wagner J, Hows J, et al. Cord blood banking for hematopoietic stem cell transplantation: an international cord blood transplant registry. Bone Marrow Transplant 1993; 11: 199-200.
72. Touraine JL, Rudrant D, Rebaud A, et al. In utero transplantation of stem cells in humans: immunological aspects and follow up. Bone Marrow Transplant 1992; 10 (suppl 1): 121-126.
73. Kohn BD, Weiberg KJ, Nolta JA, et al. Engraftment of gene-modified umbilical cord blood cells in neonates with adenosine deaminase deficiency. Nature Medicine 1995; I: 1017 – 1023.
74. Kaufman RE. Hydroxyurea: specific therapy for sickle cell anaemia. Blood 1992; 79: 2503-2506.
75. Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anaemia. N Engl J Med 1995; 332: 1317-1322.
76. Rodgers GP, Dover GJ, Uyesaka N, et al. Augmentation by erythropoietin of the fetal hemoglobin response to hydroxyurea in sickle cell disease. N Engl J Med 1993; 328: 73-80.
77. Sher GD, Ginder GD, Little J, et al. Extended therapy

with intravenous arginine butyrate in patients with p hemoglobinopathies. N Engl J Med 1995; 332: 1606-1610.
78. Perrine SP, Olivieri NF, Faller DV, et al. Butyrate derivatives: new agents for stimulating fetal globin production in the beta-globin disorders. Am J Pediatr Hematol Oncol 1994; 16: 67-71.
79. Hankins JS, Ware RE, Rogers ZR, et al: Long-term hydroxyurea therapy for infants with sickle cell anemia: the HUSOFT extension study. Blood 2005 Oct 1; 106(7): 2269-75.80.
80. Wang WC, Helms RW, Lynn HS, et al: Effect of hydroxyurea on growth in children with sickle cell anemia: results of the HUG-KIDS Study. J Pediatr 2002; 140(2): 225-229.
81. Walters MC, Patience M, Leisenring W, et al: Bone marrow transplantation for sickle cell disease. N Engl J Med 1996 Aug 8; 335(6): 369-376.