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REVIEW

Novel insights in the management of sickle cell disease in childhood

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Abstract

Sickle cell disease (SCD) is a life-threatening genetic disorder characterized by chronic hemolytic anemia, vascular injury and multiorgan dysfunctions. Over the last few decades, there have been significant improvements in SCD management in Western countries, especially in pediatric population. An early onset of prophylaxis with Penicillin and a proper treatment of the infections have increased the overall survival in childhood. Nevertheless, management of painful episodes and prevention of organ damage are still challenging and more efforts are needed to better understand the mechanisms behind the development of chronic organ damages. Hydroxyurea (Hydroxycarbamide, HU), the only medication approved as a disease-modifying agent by the United States Food and Drug Administration and the European Medicines Agency, is usually under-used, especially in developing countries. Currently, hematopoietic stem-cell transplantation is considered the only curative option, although its use is limited by lack of donors and transplant-related toxicity. SCD symptoms are similar in children and adults, but complications and systemic organ damages increase with age, leading to early mortality worldwide. Experts in comprehensive care of young patients with SCD, especially those approaching the transition age to adulthood, are missing, leading people to rely on urgent care, increasing health care utilization costs and inappropriate treatments. It would be important to establish programs of comprehensive healthcare for patients with SCD from birth to adulthood, to improve their quality and expectancy of life.

Key words: Clinical management; Hydroxyurea; Sickle cell disease; Children; Hematopoietic stem-cell transplantation

Core tip: The correct management of sickle cell disease (SCD) requires a comprehensive medical care. Both a wider use of hydroxyurea and an early treatment of pain in children are needed to improve long-term outcomes. Moreover, we report in details the possibility offered by hematopoietic stem cell transplantation as a future curative option for SCD patients.

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INTRODUCTION

Sickle cell disease (SCD) is an inherited red blood cell disorder, characterized by chronic haemolysis, vaso-occlusive complications and progressive multi-organ damage, with a major impact on patients' life expectancy and quality of life[1,2]. The incidence is estimated as more than 300000 new cases worldwide per year, mostly from sub-Saharan Africa, Arabian Peninsula and India[3]. Migration of affected populations from their native countries makes SCD a global disease.

SCD results from a single-point mutation (replacement of glutamic acid with valine in position 6) on the β-globin subunit of hemoglobin, creating the sickle hemoglobin (HbS)[4]. Homozygous (HbSS) patients inherit two copies of the HbS mutation and present clinical symptoms and complications of the disease while heterozygous carries (HbAS) do not exhibit clinical manifestations except in extremely rare cases.

Other sickle-related hemoglobinopathies occur when HbS is inherited in heterozygosis with other β globin chain mutation (HbSC) or quantitative defects in β-globin production (HbSβ^0 and HbSβ^+ thalassemia). HbSS and HbSβ^0 patients have the most severe clinical course, while patients with HbSC and HbSβ^+ have milder phenotypes[5]. Hypoxia, acidity and cellular dehydration influence the polymerization of HbS within erythrocytes and their deformation into the characteristic sickle shape.

Interaction between vascular endothelium and sickle red blood cells leads to episodic microvascular occlusion, with consequent tissue ischemia and further reperfusion; these processes are characterized by severe vascular and inflammatory stress due to increased expression of vascular oxidase, inflammatory cytokines and adhesion molecules[6].

Severe SCD-related complications may begin during early infancy, but thanks to the current multidisciplinary care, almost all SCD children have a chance to achieve adulthood. The improvement in survival rate results from important interventions including newborn screening, prophylaxis with penicillin, immunization against Heamophilus influenzae type B and Streptococcus pneumoniae, advances in supportive care and increased use of disease modifying treatments.

The aim of the review is to provide an overview of SCD management in childhood, focusing on common complications, current standard treatments, implementation of neonatal screening and comprehensive care programs.

NEWBORN SCREENING AND INFECTIONS PROPHYLAXIS

Bacterial infection is the primary cause of death in childhood; infants and children younger than 3 years of age are at risk of mortality and morbidity from sepsis.

In the 1970s, SCD had a very poor prognosis with high mortality in the first 5 years of life[7]. More recently, the mortality rate has been significantly reduced, and the number of children with SCD able to achieve adulthood is continuously growing[8-11]. The main cornerstones that have influenced SCD prognosis improvement are the introduction of neonatal screening and the antibacterial prophylaxis. In fact, neonatal screening leads to precocious identification of SCD subjects and provides the opportunity for early initiation of antibiotic prophylaxis, coupled with early immunization against *Streptococcus pneumoniae* and *Haemophilus influenzae*. Thirty years ago the PROPS Study showed the effectiveness of daily penicillin prophylaxis (starting before two months of age at 125 mg twice/day *per os*) in reducing incidence of pneumococcal infections in children with SCD[12]. A recent review confirmed that prophylactic penicillin significantly reduces the risk of pneumococcal infections in children with homozygous SCD, and is associated with minimal adverse reactions. However, further clinical trials are needed to determine the ideal age to safely discontinue penicillin[13].

Unfortunately, neonatal screening programs are still insufficient: Each newborn affected by SCD should rapidly achieve a definitive diagnosis and appropriate intervention[14] to avoid complications and reach the optimal development.

The implementation of newborn screening programs in Western countries (especially in Europe) is recommended by WHO and European Community, seen the large diffusion of a wide spectrum of hemoglobinopathies, caused by high migration rate from Middle East, South East Asia and malaria-endemic countries.

VASO-OCCLUSIVE CRISIS AND PAIN MANAGEMENT

Painful vaso-occlusive crisis (VOC) is the most common debilitating manifestation of SCD and the first cause of hospitalization for both children and adults[15]. Patients with SCD averagely refer pain more than the half of the days of the year[16] and approximately 60% of them have at least one episode of severe pain per year. Subjects with highest pain rates have an increased risk of early death compared to those with the lowest rates[17]. The sites more affected are extremities, chest and back although first episodes, that may occur as early as 6 mo of age, often present as dactylitis. For healthcare professionals, pain management in SCD is challenging and often complicated by the subjective nature of pain and the lack of standard care[18]. The treatment of painful VOC consists of non-opioid and opioid analgesics and intravenous hydration[19,20]. Early opioids administration, within 30-60 min from pain onset, improves VOC outcomes together with the use of an adequate starting dose, and frequent repeat doses until pain is reduced[21]. Parenteral administrations should be scheduled according

to an individualized protocol agreed by patients and clinicians or, when not available, guided by an institutional SCD-specific protocol[22].

The management of VOC has not significantly changed during the last decades. Recent studies about novel agents including inhaled nitric oxide and purified poloxamer-188, have demonstrated little benefits[23,24]. Among other emerging treatments for the management of vaso-occlusive events, pan-selectin inhibitor (GMI-1070)[25], anti-platelet therapies (*e.g.,* prasugrel), antioxidants (*e.g.,* N-acetyl cysteine), and anti-inflammatory medications (*e.g.,* regadenoson) have been tested in early-phase clinical trials and may represent future therapeutic opportunities[26].

Patients with SCD and acute pain crises may be wrongly identified as those with drug seeking or addiction. SCD patients are not drug- but care-seekers, seen the lack of psychosocial support, poor coping skills and inappropriate therapeutic expectations[27].

ABDOMINAL AND GENITO-URINARY COMPLICATIONS

Children with SCD often present vaso-occlusive pain as abdominal pain. The differential diagnosis of abdominal pain is broad in any child, and more complicated in patients with SCD. The most urgent cause of abdominal pain is splenic sequestration. It is defined as an acute enlargement of the spleen with a drop in hemoglobin of at least 2 g/dL from baseline associated with normal or increased reticulocyte count. In severe cases it may result in hypovolemic shock and death[28]. Early transfusion can be life saving, the starting volume is usually 5 mL/kg. Splenic sequestration can occur as early as 3 mo of age but is rarely seen beyond the age of 6 years. Hepatic sequestration is rare, caused by the obstruction of hepatic sinusoidal blood flow and characterized by painful hepatomegaly, anemia and reticulocytosis. Severe abdominal pain in patients with sickle cell disease often unresponsive to analgesia and associated with intestinal ileus and acute ischemic colitis is "Girdle syndrome" owing the circumferential distribution of pain.

Even if early implementation of supportive therapy may prevent irreversible ischemic damage to the gut, some authors have reported abdominal perforation requiring emergency surgery. Although most of these cases have been reported in adult patients, this syndrome should be considered in pediatric patients with abdominal pain.

Other more common causes of abdominal pain to be considered in children with SCD are: Cholelithiasis due to gallstones derived by unconjugated bilirubin and constipation. In children with SCD urinary tract impairment is frequent and include: Renal infarction, urinary tract infections/pyelonephritis[29].

A typical complication that occurs in male with SCD is priapism defined as unwanted painful erection of the penis. It can occur as young as 3 years of age and 90% of males with HbSS will have at least one episode by 20 years. Usually at the onset of priapism urinate, drink water, take a warm shower promote detumescence. Oral analgesic for pain and pseudoephedrine can be given at home and usually terminates priapism. Prolonged episode (> 4 h) represent a urological emergency[28,30].

ACUTE CHEST SYNDROME

Acute chest syndrome (ACS), an acute illness characterized by fever and/or respiratory symptoms associated to pulmonary infiltrate on chest X-ray[31], is a life-threatening complication of SCD with at least one episode during life in 30% of patients[32,33].

ACS usually originates from a lung injury due to pulmonary infection, fat embolism and/or pulmonary infarction. Consequently, alveolar oxygenation tension falls causing the HbS polymerization[34] and the ischemia-reperfusion process in lung vessels leads to the respiratory impairment[35].

Infective triggers are more common in children than adults and are frequently associated with viral infections especially in patients under 10 years of age. Multicenter studies, in particular in United States, demonstrate that the most common virus isolated is the respiratory syncytial virus while the most common bacteria are the Chlamydia pneumoniae in adults and the Mycoplasma pneumoniae in children[34].

Symptoms vary depending on age. Young patients often present with fever, cough and wheezing while adults show more painful episodes and impaired clinical conditions due to severe hypoxia, higher requirement for transfusion and higher mortality.

The optimal management of ACS requires an aggressive and comprehensive approach. Vital signs (pulse rate, systemic blood pressure, respiratory rate), oxygen saturation, frequent assessment of symptoms, should be monitored at least every four hours. Chest X-ray, full blood count, basic biochemistry tests, blood cultures, infectious respiratory disease testing, and blood group and screen are also needed. Oxygen administration or more aggressive respiratory supports, as Bi-level positive airway pressure or mechanical ventilation, should be used to maintain $SpO_2 \geqslant 95\%$, while intravenous fluids and opioids should be carefully managed to avoid risks of acute pulmonary edema and alveolar hypoventilation.

Other therapeutic tools include: Incentive spirometry, chest physiotherapy, antibiotic, and for those patients with progressive hypoxia or clinical deterioration, simple or exchanged red blood cell transfusion[36,37].

Although it is not confirmed by randomized controlled trials, it has been reported that blood transfusion can produce rapid improvements in clinical and radiological parameters in ACS[34,38]. Both "top up" and exchange transfusions increase oxygenation but exchange blood transfusion may have additional benefits in terms of reduction of circulating sickle cells and it is more indicated in patients with severe disease or with higher hemoglobin

concentration (> 90 g/L)[36].

It is important to bear in mind that approximately 50% of ACS occurs in patients hospitalized for other causes such as VOC or surgical intervention. This percentage could be reduced by incentive spirometry during hospitalization or by preoperative transfusion[22]. ACS consequences are scarring, pulmonary fibrosis and chronic sickle lung disease: Prevention of infections with antibiotic prophylaxis, administration of annual influenza vaccination, and avoidance of smoking may decrease the risk of ACS. Furthermore, children recovered from an episode of ACS should be offered therapy with hydroxyurea[39], at least to those with homozygous sickle cell anemia.

NEUROLOGICAL IMPAIRMENT

Neurological complications in SCD include silent cerebral infarct, stroke, and intracranial bleeding. Sickle cell anemia (SCA; HbSS and HbSβ^0) is associated with a high prevalence (4.01%) and incidence (0.61/100 patient years) of cerebrovascular accidents[40] and is higher still in the absence of primary prevention. Overt stroke has been reported in about 10% of children with HbSS with a peak incidence between 2 and 5 years of age[41]. Prior transient ischemic attack, low steady-state hemoglobin concentration, recent episode of ACS, and elevated systolic blood pressure are considered risk factors for ischemic stroke. Despite limited available evidences to guide best practice in the acute management of ischemic stroke in SCD, initial supportive strategies including co-operation of a multidisciplinary team of specialists (hematologist, neurologist, neuroradiologist, and transfusion medicine specialist) and exchange transfusions are recommended[42]. The risk of stroke recurrence, in the absence of secondary preventative measures, has been reported to be as high as 60%-90%. Chronic transfusions are currently considered the standard for care of secondary stroke prevention. Moreover, the use of Hydroxyurea, although not as effective as regular blood transfusions, represents a reasonable therapeutic alternative and recently it has also been showed that hematopoietic stem-cell transplantation (HSCT) reduces rate of stroke recurrency when compared with regular blood transfusions in the following five years[43-46].

Children with HbSS and HbSβ^0 should be routinely monitored by Transcranial Doppler (TCD) from the age of 2 until 16[47,48]. The STOP trial (Stroke Prevention Trial in Sickle Cell Anemia) showed that an abnormal TCD flow velocity exceeding 200 cm/s is associated with a 40% increased risk of stroke within 3 years. In patients with abnormal velocity, the introduction of regular transfusions resulted in a reduction in stroke incidence by almost 95%[49]. Although long-term transfusions have major long-term side effects, the STOP 2 trial showed that cessation of transfusions after the normalization of TCD resulted in a recurrence of abnormal blood flow velocity on TCD and increased risk of stroke[50]. The role of hydroxyurea for prevention of primary and secondary stroke has also been investigated. An ongoing phase III trial, TWiTCH (Transcranial Doppler with Transfusions Changing to Hydroxyurea) (ClinicalTrials.gov identifier number NCT01425307) intends to compare hydroxyurea *vs* transfusions for pediatric patients with SCA and abnormally high TCD velocities, who currently receive chronic transfusions to reduce the risk of primary stroke. The SWiTCH study (Stroke with Transfusions Changing to Hydroxyurea) was designed to compare alternative therapy of hydroxyurea and phlebotomy with standard therapy (transfusions and iron chelation) for the prevention of secondary stroke. However, this study was stopped, as alternative therapy was associated with a higher stroke rate[51]. Lifelong transfusion remains the standard of care for secondary stroke prevention, and in those with high flow velocity on TCD (primary prevention)[37]. However, hydroxyurea is a reasonable alternative in patients with complications of transfusions, with poor compliance, or in countries with limited blood supplies.

Silent cerebral infarcts

Silent cerebral infarcts (SCI) are characterized by an abnormal brain MRI in the absence of history or physical findings of an overt stroke. SCI occur in approximately one-quarter of the children with SCA before six years of age and in one-third of those younger than fourteen. Risk factors include male sex, lower baseline hemoglobin concentration, higher baseline systolic blood pressure and previous seizures[52]. While overt strokes are typically located in both cortex and white matter, SCI usually occur in deep white matter of the frontal, parietal lobes or, less frequently, in basal ganglia, thalamus and temporal lobes[53]. Children with SCI have lower cognitive test scores compared with the general population, and have additional specific functional impairment, impacting such executive functions as selective attention, card sorting, working memory and processing speed, visual motor speed and coordination, vocabulary, visual memory and abstract reasoning and verbal comprehension[54-59]. Children with SCD and SCI have twice the chance of academic difficulties than those without SCI[60]. The presence of SCI is a risk factor for additional neurologic injury, with a higher risk of both clinical stroke (14-fold), and progressive silent infarction. It has been showed that approximately 25% of children with SCI, have new and/or enlarging lesions on follow-up MRI scan[53,61]. Despite the high prevalence of SCI in patients with SCD, no established therapy is available for primary or secondary prevention. The STOP Trial showed that the presence of SCI in the setting of an abnormal TCD measurement is associated with increased risk of stroke compared to those with no SCI (52% *vs* 21%). In the same group of patients the stroke risk decreased with blood transfusion therapy compared to those with only elevated TCD measurement (0% *vs* 5%, respectively)[49]. These results provided the preliminary evidence suggesting that regular blood transfusion therapy may be effective in

preventing neurologic injury. At the end of STOP2 study, when children with elevated TCD measurements were randomized to continue or stop transfusions, 8% of those who continued transfusions developed new brain MRI lesions compared with the 28% of those who stopped[50]. Similarly, the SIT trial showed that children with SCA had a relative risk reduction of infarcts recurrence of 58%, if they were receiving regular blood transfusions. The optimal timing to detect SCI is still unclear but most data support commencing MRI from around 5 years or school entry[62]. Developmental delay or declining school performance may be the only clinical signs of SCI and therefore in this instance an early neurocognitive evaluation should be offered in patients with SCD.

DISEASE-MODIFYING AGENTS

Hydroxyurea (HU) is an inhibitor of ribonucleotide reductase that increases fetal hemoglobin (HbF) in red blood cells, rising cellular size and deformability. HU also impairs leukocytes and reticulocytes production and the expression of adhesion molecules, reducing vascular occlusion. In addition, when metabolized, HU releases nitric oxide, contributing to local vasodilation[63,64]. HU is the only medication approved for treatment of SCD by the United States Food and Drug administration (1998) and by the European Medicines Agency (2007)[65]. A multicenter, randomized, double-blind, placebo-controlled clinical trial in infants from 9-18 mo of age with SCA (BABY-HUG) demonstrated that treatment with HU was associated with statistically significant lower rates of initial and recurrent episode of pain, dactylitis, ACS, and hospitalization compared to placebo group[66]. Similar results have been also showed by the Multicenter Study of Hydroxyurea, with positive effects of HU on painful vaso-occlusive events at all ages[67]. HU treatment seems to be associated with decreased mortality[68,69] and it is generally well tolerated in both children and infants, with no influence on growth and development[70]. Leukopenia, neutropenia and thrombocytopenia are the most frequently reported side effects, but they are generally mild and reversible with discontinuation or with dose decreasing[66,71]. However, several concerns about the HU long-term side effects have been expressed especially in pediatric population. Even though HU does not appear to increase the risk of malignancy in SCD patients[63], potential effects on fertility and teratogenicity have been described[72-75]. Considering the benefit of HU in preventing end organ damage and improving survival, it seems reasonable to recommend hydroxyurea to SCD patients with HbSS or HbSβ^0 genotypes, regardless of their disease severity. Recently, it was suggested to offer HU therapy in children starting at 9 mo of age, including those who are asymptomatic[22]. When considering the use of hydroxyurea for patients with SCD, it is important to balance its well-established benefits with its hypothetical long-term side effects, in particular in asymptomatic children[37].

HEMATOPOIETIC STEM CELL TRANSPLANTATION AND GENE-THERAPY

Despite the development of supportive care including HU and transfusion programs, hematopoietic stem cell transplantation (HSCT) remains the only curative treatment for patients affected by severe SCD. The first successful pediatric HSCT was performed in 1984[76], and since there, several hundreds of patients with SCD have been transplanted, mainly from an HLA-identical sibling donor. Results of major clinical studies on allogeneic HSCT from an HLA-identical sibling donor in children with SCD, in the past decade, reported an overall survival rate (OS) greater than 90% and an event-free survival rate (EFS) greater than 80%[44,46,77-81]. Recent studies on HLA-identical sibling HSCT are summarized in Table 1[82-87]. Of interest, 37/38 subjects, treated with HU before HSCT survived free of SCD, with an estimate EFS of 8-year, significantly higher compared to those who did not receive hydroxyurea before HSCT ($P < 0.001$)[85]. HSCT from matched-sibling related donor offer the best outcomes of transplantation and it seems to be curative in 90%-95% of pediatric recipients with severe SCD following a conventional conditioning regimen[88]. Transplants outcomes are best in young people (< 16 years) before long-term transfusions become necessary, in absence of comorbidities and organ damages[46]. With the achievement of such survival rates, the risk of transplant related morbidity has become a major concern and clinical focus has recently shifted to the minimization of the regimen-related toxicity. A recent Italian study[89] showed that a conditioning regimen with treosulfan/thiotepa/fludarabine for HLA-matched sibling and unrelated donor HSCT was well tolerated with no case of grade Ⅲ and Ⅳ regimen-related toxicity. The 7-year OS and DFS for the whole cohort were 100% and 93%, respectively.

Umbilical cord blood (UCB)-derived hematopoietic stem cells in pediatric patients with hematological disorders are increasing as alternative source of hematopoietic stem cells, seen the safe technique of hematopoietic collection, the low risk of viral contamination of the graft and the reduced incidence and severity of acute and chronic graft *vs* host disease (GVHD)[90,91]. A recent update of HLA-identical sibling UCB transplantation compared marrow and UCB transplants outcomes of 485 recipient cases with thalassemia major and SCD. The overall 6-year DFS in 160 patients with SCD was 92% ± 2%: 90% ± 5% in 30 patients after UCB transplantation and 92% ± 2% in 130 patients after bone marrow transplantation. None of the patients developed chronic extensive GVHD and none died of GVHD after UCB transplantation[92]. UCB and marrow from HLA-identical donors might be used interchangeably, and UCB from a sibling donor appears to be useful in terms of lower risk of acute and chronic GVHD. For patients with no HLA-identical sibling donor hematopoietic

Table 1 Recent series of human leukocyte antigen-identical transplant for sickle cell disease in children

Ref.	Conditioning regimen	*n*	Age range in years	Deaths	Follow-up (yr)	Outcome
Krishnamurti *et al*[82]	BU, Flu, eATG, total lymphoid irradiation	7	6-18	None	2-8.5	All patients alive EFS 86%
McPherson *et al*[83]	BU, CY, ATG	25	3.3-17.4	1	0.1-10	OS and DFS 96% (median survivor follow-4.9 yr)
Lucarelli *et al*[84]	BU, CY, rATG ± Flu	40	2-17	3	1-10	5-yr OS and DFS 91%
Dedeken *et al*[85]	BU, CY, ± rATG, ± HU	50	1.7-15.3	2	0.4-21.3	8-yr EFS 85.6% and OS 94.1%
Bhatia *et al*[86]	BU, Flu, Alem	18	2.3-20.2	None	0.4-7.5	2-yr EFS and OS both 100%
Soni *et al*[87]	BU, CY, rATG	15	1.5-18	None	0.9-7.5	3-yr EFS and OS both 100%

ATG: Antithymocyte globulin; BU: Busulfan; CY: Cyclophosphamide; DFS: Disease free survival; eATG: Equine antithymocyte globulin; EFS: Event free survival; Flu: Fludarabine; HU: Hydroxyurea; OS: Overall survival; rATG: Rabbit antithymocyte globulin; Alem: Alemtuzumab.

cells from an HLA-mismatched related donor could help. The Johns Hopkins group in 2012 reported the largest study of HLA haploidentical bone marrow transplantation in severe SCD. In this pilot investigation, 14 recipients of haploidentical HSCT were treated and all had prompt recovery after HSCT, although 6 of these patients developed graft rejection, all were alive with a median follow-up of 711 d[93]. Despite promising data, allo-HSCT is underutilized[94]. The main barrier is the limited availability of suitable donor. It has been estimated that only 14% of those patients with SCD have a suitable HLA-identical sibling donor and that only 19% have a very well matched unrelated marrow donor in the volunteer registry[95,96]. Nevertheless, conventional treatment itself is a high-risk of mortality procedure and of treatment-related morbidity, due to GVHD, infertility and gonadal failure[88]. Considering all the allogenic HSCT limitations, the gene therapy using autologous stem cells can potentially cure SCD, and could overcome the problems of lack of available donors and immunologic side effects. Inherited hematopoietic disorders are potentially targetable, because hematopoietic stem cells can be readily isolated from bone marrow or mobilized from peripheral blood, manipulated *ex vivo*, and transplanted back using current tools and knowledge of bone marrow transplant technology. Gene therapy has exploited the ability of retrovirus vectors, which are equipped with the machinery to reverse, to transcribe their RNA into complementary DNA and integrate this latter into the host cell genome to deliver therapeutic genes into cells. Seen the success in β-thalassemia gene therapy, similar studies on SCD are started. Both γ-globinbased and modified β-globin-based vectors have been developed for SCD gene therapy[97]. There are still no data available, but clinical trials using lentiviral vectors have begun in France (NCT02151526) and in United States (NCT02140554, NCT02186418, NCT02247843)[98]. The development of gene therapy technologies holds the promise of genetic correction of future hemoglobinopathies.

TRANSITION FROM PEDIATRIC TO ADULT HEALTHCARE

Management programs for pediatric patients with SCD in Western world areas include acute care, routine prevention, monitoring and treatment of complications[99]. The management of SCD in adult patients is more complex, because of the additional co-morbidities, increased multi-organ involvement, chronic pain and psychosocial and socioeconomic factors. Although an increasing number of children with SCD are achieving adulthood, there has not been a corresponding increase in medical experts trained to treat older patients, delaying transition from adolescent to adult care[100]. Epidemiological studies indicate that SCD-related mortality and morbidity are increased in young adults and most patients feel that they are not ready for transition to adult healthcare[101]. These data supported by findings of a recent study of the Dallas Newborn Cohort show that SCD patients are at greatest risk of mortality when they are transition-aged. In this cohort, seven of the most recent patients died were aged 18 years or older, and six of these patients had recently transitioned out of the pediatric care[8]. With no adult SCD care providers, patients become dependent of acute care services and do not receive the necessary coordinated multi-disciplinary care[102]. Identification of a designated adult SCD provider and enhanced early education of all pediatric SCD patients regarding the need to continue comprehensive care in the adult setting is imperative for a successful transition from pediatric to adult care.

CONCLUSION

Sickle cell disease is a global health problem that affects more than 300000 newborns per year, predominantly in sub Saharan Africa. In this area, mortality is estimated to be more than 50% by the age of 5 years for those with homozygous hemoglobin S. With the implementation of neonatal screening programs and new therapeutic approaches, SCD related morbidity in childhood is decreasing, raising the number of patients achieving adulthood. Currently, there are few pharmacological treatments available for SCD, while promising disease-modifying agents, as HU, are still significantly under-utilized. Moreover, the use of curative options as HSCT, is limited because of the lack of matching donors and some concerns regarding long-term toxicity. Although

comprehensive management programs for SCD pediatric patients have started in the last years in United States and Europe, an improvement in transition age care, to reduce early mortality in young adults and hospital costs, is needed.

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