Treatment Options for Complications of Sickle-cell Disease in Children

Cylia Evda Deckous Dassy*, Manou Irmina Saramba* and Dongchi Zhao*,1
*Department of Pediatrics, Children's Digital and Health Data Research Center, Zhongnan Hospital of Wuhan University, Wuhan, China

ABSTRACT Prospecting clinical, comprehensive and approach paradigms of therapeutic management in pediatric age groups with the sickle-cell disease is the mainstay indigence. Data over the last two decades was gathered to perform this review through multiple databases such Pubmed, Medline (OvidSP), Embase, Cochrane library, CINAHL (EBSCOHost), Web of Science CPCI-S and from manual search in google scholar. The search terms included anaemia, sickle cell, sickle cell disease, acute pain, complication, treatment, and management with a highlight on pediatric age. Those who have full text recoverable with the English language were involved in this review. Sickle-cell disease is an umbrella term of hereditary illness, the most common of hemoglobinopathy worldwide with epidemiological importance and challenges in public health. The disease is encompassing the mutations in the gene of haemoglobin subunit β and manifesting via the acute vaso-occlusive crisis. It is highlighted with a troika of pain syndromes, anaemia and its corollaries, and end-organ dysfunction, involving infection states whence its classification into a multisystem illness. Acute pain crisis, therefore, is the hallmark of the condition and tyrannizes its clinical presentation during the whole life of the patients. In some children, the remedy has been accomplished by practising cord blood transplantation or allogeneic bone marrow transplantation. Careful management of the disease on approach supportive, symptomatic, preventive, acute, and curative based, enhances in timely the quality of life of patients, except the cost burden of the healthcare system which is higher.

KEYWORDS Sickle cell disease, complications, management, costs, treatment, paediatrics

Introduction

Sickle-cell disease (SCD) is an autosomal recessive inherited red cell disorder depicted by the synthesis of pathological structure and capacity of haemoglobin (Hb). The modification, consecutively, derives in substitute of a normal hydrophilic glutamic acid residue (Glu) with a hydrophobic valine residue (Val) at position 6 of the β-globin chain, followed in a sickled Hb tetramer formation Hb-S ($\alpha 2\beta S2$) [1-2]. The disease is prevalent among the black population and an archetype of relocation haematology for western countries [3, 4].

Furthermore, 3.2 million people are living with SCD, 43 million people having the sickle mutation carriers (sickle-cell trait), and per year 176,000 people perish with complications related to SCD, as stated in the systematic analysis of the Global Burden of Disease Study [5]. According to the World Health Organization (WHO), SCD deserves being a public health dilemma. Meantime of the years 2010 and 2050, the overall SCD number cases would expand from 305,800 to 404,200 cases per year, emerging 14,242,000 the estimated number of people living with the disease by 2050 [6, 7]. The condition management metes huge strain and financial burden, which can conduct substantial health care cost on the patients, both in developing and developed countries setting [8]. This review discusses on the troika of SCD clinical comprehensive with regards to this actual breakthrough of management and cost-effect-burden in pediatric.

DOI:10.5455/IJMRCR.Sickle-cell-Disease-Children
First Received: January 19, 2020
Accepted: February 04, 2020
Manuscript Associate Editor: Ivan Inkov (BG)

[1]Dongchi Zhao; Donghu Road, Pin 430072, Wuhan City, Wuchang District, Hubei Province, PR China Email: zhao_wh2004@hotmail.com

Table 1 Time stage of clinical complication over the lifespan from birth to adolescence with SCD.

	Infancy (0-23 mo)	Toddler (2-4y)	Childhood (5-12y)	Adolescence (13-18 y)
Clinical complication sequences	Hb-F high-level No clinical manifestation (0- < 6 mo) Clinical picture manifestation from 6 mo	Hb-F lowest-level with incremented Hb-S	Hb-S reaches peak	Hb-S highest-level
	Painful Crises			
	Lowest pain	Acute, intermittent pain crises	Intermittent pain crises along with continued acute pain	Acute pain crises increment with frequency
	Hand-foot syndrome or dactylitis			Chronic pain event onsets
			Priapism	
		ACS		
		Cerebrovascular accident Fever		Damaged cognition
	Infection			
	Pneumonia Meningitis			Osteomyelitis
	Splenic sequestration			Absenteeism (Pain disturbs school attendance)
Treatments	Transfusion			
	Curative			Palliative

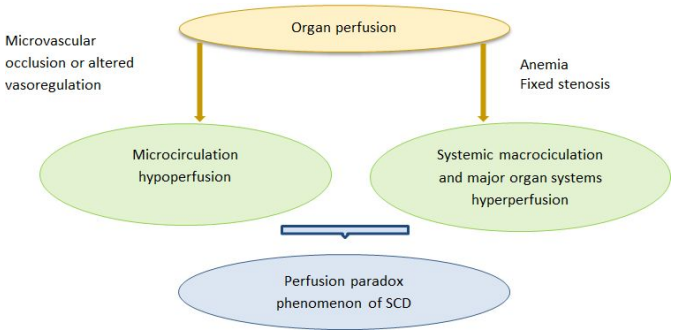

Figure 1: Sequence of organ perfusion paradox in SCD.

Clinical comprehensive

Sickle-cell anaemia (SCA) defines the homozygous state. Sickle-cell syndromes are the coinheritance of the sickle gene with other mutations particularly to HbC gene (Hb-SC), β-thalassemia genes (Hb-Sβ0-thalassemia, Hb-Sβ+-thalassemia), HBO/Arab gene (Hb-SO/Arab), Hb-E gene (Hb-SE) and Hb-D gene (Hb-SD). The major prevalent denominations of SCD involve homozygous HbSS and the combination heterozygous states Hb-Sβ0-thalassemia, Hb-Sβ+-thalassemia, and Hb-SC disease. Moreover, clinical pictures of Hb-SS and Hb-Sβ0-thalassemia are very akin, also related with the most significant clinical severe events involving acute painful crisis, severe anaemia and acute chest syndrome (ACS) – wherefore are given them the eponym as SCA [2, 4]. It has been founded that the SCA is less significant when the Hb F rate is substantial [9].

The SCD has been known as three major clinical scenes: pain conditions, hemolytic anaemia, and its corollaries, and organ damage. The age plays a crucial role in the incidence of complication stages which differ from early infancy across adolescence. The palliative treatments are for the whole life of patients with the condition, but curative treatments are only practising from birth to the first period of childhood (Table 1).

Pain conditions

Pain syndrome is the mainstay of the clinical picture of the SCD and occurs throughout the life expectancy of affected patients. Patients report SCD pain via both nociceptive and neuropathic index terms. It may appear somatically or viscerally, in one-sided or two-sided, restricted or disseminated and light, moderate or severe. It is also subordinate of tissue damage describing pathophysiologically as nociceptive. Shooting, throbbing, dull and stabbing are the words many times utilize to indicate sickle-cell pain [10].

The three or more times of acute sickle-cell painful episode crises in the affected individual suggested the severe SCD. The VOC necessitates a hospitalization since it develops along four well-defined junctures involving prodromal, initial, installed, and resolving.

Furthermore, to discontinuous acute pain events, patients with SCD may transpire chronic sickle-cell pain which manifests along with incrementing age. In children and adolescents aged between eight to 18 years, 40% affected by chronic sickle-cell pain with the daily pain recorded at 35% [10].

Table 2 Main complications of SCD

System	Complications	Pathology
Immune	Infection	1. Malaria (Plasmodium falciparum, except sickle-cell trait) 2. Streptococcus pneumonia infection 3. Haemophilus influenza infection 4. Urinary tract infection (Escherichia coli) 5. Osteomyelitis (Streptococcus Typhimurium and aureus) 6. Necrotic bone (Salmonella)
Central nervous system	Cerebrovascular accidents (strokes)	1. Large and medium artery intimal hyperplasia of the middle carotid artery and/or internal carotid artery 2. Large-vessel thrombosis 3. Saccular aneurysms 4. Infarctive stroke (Children) 5. Moyamoya syndrome
	Neurocognitive impairment	1. Silent cerebral infarct 2. Small-vessel rarefaction 3. Transient ischemic attacks
Ophthalmologic	Proliferative sickle retinopathy (age, 10-20 years)	1. Retinal detachment 2. Vitreous hemorrhage 3. Decreased visual acuity 4. Visual impairment

Cardiopulmonary system	Acute chest syndrome	1. Pneumonia 2. Bone morrow fat embolism 3. Wedge pulmonary infarction 4. In situ pulmonary thrombosis 5. Rib/Sternal infarction 6. Infection 7. Pleural effusions 8. Multilobar consolidations 9. Pulmonary embolism 10. Foamy alveolar macrophages 11. Arteriolar thrombosis
	Pulmonary hypertension	1. Plexiform lesions 2. Vascular obstruction 3. Intimal hyperplasia 4. Intraluminal thrombosis
	Restrictive lung disease	1. A decreased diffusive capacity of the lungs for carbon monoxide and total lung capacity 2. Lung fibrosis at the bases
Genitourinary system	Urinary tract infection	1. Escherichia coli infection
	Enuresis	
	Hyposthenuria, renal medulla infarction and hematuria (gross or microscopic)	1. Renal medulla hypoxic, acidotic and hypertonic microenvironment
	Renal papillary necrosis Nephropathy (very scarce) Acute renal failure Chronic renal failure (end-stage renal disease (very scarce)	1. Hematuria 2. Clubbed calyces 3. Renal Parenchymal enhancement 4. Triangular hypoattenuated areas
	Priapism	1. deteriorated venous outflow from the penis

Hepatobiliary system	Hepatic sequestration (30% children < 6 years of age)	1. Liver enlargement (acute hepatomegaly) 2. Decreased Hb concentration 3. Dilated sinusoids (sequestration of red blood sickle-cell)
	Intrahepatic cholestasis (hepatic crisis)	1. Sinusoidal obstruction by sickle red cells 2. Dilated biliary canalicules with bile plugs 3. Kupffer cell hyperplasia 4. Centrilobular necrosis
Other	Acute multi-organ dysfunction	1. Rapid decrease in Hb level and platelet count 2. Nonfocol encephalopathy 3. Rhabdomyolysis
	Dermatologic Growth retardation Delayed sexual function Underweight	1. Dactylitis (hand-foot syndrome) 2. Avascular necrosis (very scarce) 3. Leg ulcers (very scarce)

Hemolytic anaemia with its corollaries

The normochromic and normocytic anaemia is typical of SCA haematological manifestations along with 7.8 ± 1.13 mean Hb (milder anaemia) and 90 fl mean corpuscular volume (low). In SCA, there is also incremented marrow activity successive to chronic hemolysis and autosplenectomy (no stocked platelets in the spleen). All these components engender the increased white blood cell and platelet counts. Microcytosis and hypochromia along higher of Hb A2 rates and inconstant Hb-F accounts are typified of a haematological picture of the affected patients with Hb-Sβ0-thalassemia. In patients with Hb-Sβ+-thalassemia, anaemia is light (Hb rate > 10g/dL). Patients with Hb-SC disease, therefore, have a haematological picture of RBC indices as microcyte and hyperthermia [2].

In general, SCD is typically characterized by chronic hemolytic anaemia. Thus, in the case of the lack of known reason in particular splenic and hepatic sequestration, hyperhemolysis may affect the patients with SCA via an indicated lowering in Hb, which defined by the increment RBC impairment. Compared along with initial values without restoration by bone morrow repression, hemolysis evidence may be marked by an increment of lactate dehydrogenase (LDH), unconjugated bilirubin, or aspartate aminotransferase [11]. Moreover, an infection such as mycoplasma pneumonia, a glucose-6-phosphate-dehydrogenase deficiency concomitant with risk to oxidant stress and, a retarded hemolytic transfusion response may be reasons for hyperhemolysis.

End-organ dysfunction

In general, SCD affects several organs due to the widespread of perfusion abnormalities, and SCA is the most incriminated compared to other sickle-cell types (Figure 1) [12,13]. The central nervous system and cardiopulmonary system are the most affected areas radically by perfusion abnormalities which are liable for characteristic, destructive complications in children and adolescents. The primary complications of SCD by significant systems will be summarized in Table 2.

Paradigms of the breakthrough of the SCD management

The initial approaches are supportive management which includes providing the primary need for well-being having good health and a good quality-of-life. These encompass well-balanced diet, no overweight, no smoking, moderate or no alcohol and soft drinks, no illicit drugs, well-sleeping, oral hydration always with water, folic acid and adherence to medical health programs.

The symptomatic treatment intended to mitigate the symptoms of the condition as they present. Usually, blood transfusions targeted to alleviate symptomatic anaemia such in case of severe anaemia, ACS, aplastic crisis, acute stroke, multi-organ damage and finally to impede the primary and secondary

strokes. Analgesics (non-pharmacologic and pharmacologic approaches) are for the pain frames. Pharmacologic approaches include opioids, non-opioids, and adjuvants. Usually, short-acting of opioids are used for an acute sickle-cell pain crisis. Sustained-release, sometimes short-acting opioids are for chronic sickle-cell pain. Antibiotics are (prophylaxis or treatment) for some infections. Psycho-social maintains as required [2].

The significant target of the main preventive treatment for SCD was to recognize an anti-sickling agent that would abort the polymerization process in sickle Hb of RBCs. Sodium cyanate in particular, in vitro state, is polymerization inhibitor of Hb-S but in vivo state, it is unbeneficial at stages that yield tolerable side effect. In an accurate situation, several searches for compounds of advantageous anti-sickling proceed [2]. Aside the major up-and-coming pathways to abort the incidence and intensity of VOCs consists the prevention of infection such as antibiotic prophylaxis since in infancy to childhood, vaccination, reverse of stressful states, blood transfusion, induction of Hb-F production, anti-adhesion treatment, etc.

Fetal haemoglobin (Hb-F) induction

In patients with SCA, the higher Hb-F levels have utmost beneficial aftermath in their health condition. Also, that level of Hb-F expression is a particular situation of the most significant modifiers of disease manifestation for the patients with the condition. The frequency of painful vaso-occlusive events decreases significantly once the Hb-F parameter is increased, and thus leading the condition in the mild state. Aside, the intracellular Hb-S concentration is low when of the higher of Hb-F levels. Haemoglobin F impedes along with Hb-S polymerization. Some states of patients are not following this rule with the higher Hb-F levels and the severe disease and inversely [14]. To date, Hydroxyurea or hydroxycarbamide is among the agents and the prototype as a monotherapy that increments the Hb-F level expression in the human body. It is a ribonucleotide reductase inhibitor [15]. In addition to that, Hydroxyurea is the agent has the approval by the Food and Drug Administration (FDA) to treat SCD in 1998 only for adults and following by the European Medicines Agency. These other drugs such as decitabine, arginine butyrate, valproic acid have been described shortly to increment Hb-F level but never in use in a controlled phase III clinical study to date [16].

Hydroxyurea

The molecular actions via which Hydroxyurea is playing a crucial role to increase the Hb-F expression are poorly known.

Nevertheless, Hydroxyurea was described presenting the main mechanism to remove the mature erythrocytes while increasing the younger erythrocytes number, which engenders a higher Hb-F expression [17]. The favourable beneficial of Multicenter Study of Hydroxyurea (MSH) motivated several paediatricians to demonstrate the safety and efficiency of Hydroxyurea in paediatrics. Hydroxyurea treatment which is managed by a pediatric haematologist department under-investigated of a multicenter phase I/II study of Hydroxyurea in pediatric with SCA (HUG-KIDS) and a Hydroxyurea Safety and Organ Toxicity, another two-year, prospective, multicenter, open-label, single-arm, pilot study of Hydroxyurea, proved that the agent is very well tolerated and safe in children with SCA. The tolerated doses in pediatric age groups of Hydroxyurea were up to 30 mg/kg per day [18]. The agent affects hematology and may retard the function of asplenia. These studies reported that Hydroxyurea engendered the prolonged salutary effects hematologic, minimal ACS events, and maintained the function of the organ. All of these prompted the Pediatric Hydroxyurea Clinical Trial (BABY HUG) to Phase III of study.

The paramount target of phase III BABY HUG study is to establish in infants and young children with SCA if in use of Hydroxyurea can preclude the early stages of chronic end-organ failure [19]. The trial demonstrated that hydroxyurea therapy for infants with SCA has no differences for a splenic function parameter or glomerular filtration expression which were the primary endpoints, but the study approved its safety, tolerated and efficiency. The study showed that hydroxyurea therapy is related to a reduction pain in the hydroxyurea arm (177 events in 62 participants) versus placebo arm (375 events in 75 participants), P=0.002, significant difference for dactylitis cases in the active arm (24 events in 14 participants) versus placebo arm (123 cases in 42 participants), P<0.0001, and decreased the frequency of ACS cases, need for blood transfusions and admission to the hospital [19]. Therapy of Hydroxyurea escalated Hb and expression of Hb-F and ameliorated hematologic laboratory values, reduced white blood cell count, and possibly raised the preservation and maintenance of organ function [19, 20]. One trial demonstrated (Transcranial Doppler with Transfusion Changing to Hydroxyurea [TWiTCH]), in selected pediatric patients if they encountered the study measure, the transition of children patients from transfusion to Hydroxyurea was safe [21]. In malaria-endemic areas, the agent occurs to be safe in use in children with SCA [22]. The risk of developing a stroke is common in children with SCD; Hydroxyurea may, therefore, impede the conversion of conditional Transcranial doppler velocities into aberrant Transcranial doppler velocities [23]. Most recently, the TWiTCH investigation exemplified that Hydroxyurea may be a benefit to prevent the primary stroke in pediatric patients with SCD having abnormal transcranial doppler velocities and at significant risk of stroke, transiting from chronic transfusion treatment at least one year to Hydroxyurea [21]. Given this later is the only agent accepted disease-modifying medication for individual with SCA, the 2014 SCD Expert Guidelines from the National Heart, Lung and Blood Institute suggest that all patients under hydroxyurea prescription should undergo frequent monitoring in order to minimize the risks of toxicity such as potential myelotoxicity (neutropenia, reticulocytopenia, and thrombocytopenia) and increase the salutary. Recently an updated of Cochrane review summarized that there is, actually, deficient evidence of long-term benefits of hydroxyurea regimen respecting to delay the chronic complications of the condition [24]. Nevertheless, Hydroxyurea could be used most early in life (nine to 18 months of age) [19]. The Hb-F reaction to Hydroxyurea and the myelosuppression are dose-dependent, such as the increasing Hydroxyurea to the maximally tolerated dose may be significant for optimizing the effects of hydroxyurea treatment.

A Cochrane review recently has provided and sustained the benefits of maximally tolerated dose and the fixed low dose of Hydroxyurea in clinical trials. The BABY HUG study had investigated on the fixed low dose of hydroxyurea regimen (20 mg/kg fixed-dose) in children with SCA [25]. The benefits of patients with a low dose of Hydroxyurea are that they may undergo less toxicity, for instance, a reduction of myelotoxicity risk and other toxicity which was related to dose. Hence, the fixed low dose regimen may not need recurrent monitoring and

adherence regarding that needed for the maximally tolerated dose treatment. It has large benefits for patients with SCD in low and middle-income settings.

Most lately, a trial of L-glutamine powder (phase III randomized clinical study) showed that the agent is safe and efficient in minimizing the incidence of VOCs in getting participants aged five years and older with SCA. This justified case gives rise of the L-glutamine to agreement and approval by the FDA. The molecular mechanism by which L-glutamine is reduced RBC adhesion decreased vaso-occlusion, and mitigated the sickle pain vaso-occlusives consists of decreasing the oxidative stress in sickle RBC [26]. Endari (sample of L-glutamine) was the first FDA approved drug for children with HbSS disease. Thus, diminution of sickling events is promising a high good life quality and translating into colossal mortality reduction in patients with SCD.

Other new strategies of treatment

Generally speaking, an expanded number of unconventional preventive treatment patterns may have undertaking functions in the management of SCD and particularly sickle-cell pain. These involve, included in other things, pharmacologic therapy such as surfactants [27], zileuton (a 5-lipoxygenase inhibitor) [28], anti-adhesion molecules [29] and levocarnitine [30], and non-pharmacologic therapy such as green tea [31], herbal extracts [32], botanical drug (SCD-101) [33] and aged garlic [31]. Certain of these active agents was presenting in use on an experimental study basis and reported a short episode of success in a few numbers of patients. Zileuton, for example, may decrease the immune response of individuals with SCD while may also be salutary by decreasing without any connection with the Hb-F generation the process of inflammation. The efficiency of the agent remains to undergo the evidence in the randomized, double-blind, placebo-controlled trials, in phase III [34]. Several clinical trials met diver barriers during the implementation of their study. For instance, phase III trial of senicapoc and/or sildenafil which was ended owing the patients who treated by these two agents had more sickle-cell pain crisis compared to control participants. Several works of literature highlighted that various trials were terminated early due to the paucity of the number of participants or clinical trial targets also was not achieved. The majority of the studies were not conducted in multicenter and led in the low burden of sickle-cell disease areas.

Acute management of the condition

The recurrent VOCs define the decreased quality-of-life for individuals with SCD. The more critical target of this acute management is to abort sickle-cell pain crises while impeding them from turning into severe or accelerating other complications. As mentioned beforehand, Hydroxyurea, as known plays a crucial role in the abortive treatment of occurrence sickle-cell crisis [35]. Nitric oxide aborted the sickle-cell crisis in the emergency department, however not in hospitalization. Aside, some investigations showed none of these agents such as intranasal fentanyl, intravenous magnesium, arginine, and inhaled nitric oxide had given an accurate conclusion of their managing these acute painful VOCs.

Allogeneic hematopoietic stem cell transplant (HSCT)

Stem cell transplant is remaining the only curative treatment convenient for SCD in general but particularly more for SCA. The paucity of availability of appropriate donors and the barriers to its implementation in large-scale, this method abides, therefore, a significant challenge [36]. Furthermore, allogeneic bone marrow transplant, in a temporary report on the effect of bone marrow transplant for patients symptomatic with SCD, showed that it sets up erythropoiesis stability and is related with increased growth and constant of imaging outcomes of the central nervous system and stable pulmonary function [37]. In 2000, the barriers of transplant modality have been got over including, the occurrence of high-resolution human leukocyte antigen categorizing, the option of stem cell origin such as from bone marrow, and umbilical cord blood or peripheral blood, less toxic treatment approaches, eased immune regeneration or reconstitution, novel immunosuppressive drugs and enhanced supportive management [38,39]. In 2010, several individuals with SCD who treated with the transplant (about 500 patients) had been declared in the Center for International Blood and Marrow Transplant Research database [38]. Nevertheless, these standard regimens to transplant are unfortunately related to comorbidities involving, among other things, gonadal dysfunction, infertility, and chronic Graft Versus Host Disease.

Gene-based treatment

Gene therapy is another utterly promising pathway to succeed for SCD curative therapy which is yet under study. The straightforward definition, gene therapy is to insert a functioning gene of βA-globin into the hematopoietic stem cells of the individual with SCD to substitute the affected βS-globin gene [40]. Among other methods of gene-based therapies, transplantation of autologous of the normal βA-globin gene into hematopoietic stem cells to individual unrelated to a compatible sibling bone marrow donor have blossomed significant advancement in recent years. The Hb-F generation could be elevated via this manipulation of autologous hematopoietic stem cell [41]. This is a harvest of the patient's self-stem cells from bone marrow or peripheral blood, genetically corrected, and transferred back into the same individual. The modification of gene includes in use of vector transporting genes of γ-globin for SCD or genes of β-globin for β-thalassemia. The method has already been set up a successful of evidence in phase I and II trial in mice which expected advantage for Hb diseases [42]. The addition of a gene of antisickling β-globin into the transplantation of autologous hematopoietic stem cell by the retroviral vectors that have been modified to treat the patients with SCD has been successfully achieved [40]. However, these approach therapies will require proceeding via a colossal of an investigation, cogent evidence, effectiveness, and safety states prior it can turn into a reality for SCD treatment.

Cost effect burden of SCD

The economic burden of SCD is dependent on the area settings, screening approaches, age of the first onset of the symptom and management of the disease, number of hospitalization, monitoring and healthcare policies. Overall, the financial cost of patients with SCD is high and huge. In most developing countries, health care is mainly funded by out-of-pocket spending. The modality of this health care does not present any financial coverage, neither protection risk, and may tend to financial catastrophe for the family. A study from southwest Nigeria has reported, where SCD has a high prevalence, only 7.2% of households were registered into the health insurance scheme. Most of the family incomes were average and low [8]. In contrast, these scenarios

are sharply in most high-income countries paradoxically where SCD has a low prevalence, health care expenditures are primarily supplying via prepayment modalities by health insurance policies. A study performed in the United States, for instance, have shown, 60% of hospitalizations were from the awaited primary source of payment of government program, 20% from private insurance, 7% self-payment, 4% another source, and only 3% were not declared [43]. But the cost of medical care is still considerable. The estimated average direct cost per hospitalization, which was a data investigated by a National Hospital Discharge Survey (1989-1993) and the Nationwide Inpatient Sample (1992) was the US $ 6300. The cost is also elevated with age. The individual with SCD may spend the estimated total direct cost of US $ 475.2 million for hospitalizations per year [43]. Both in children and adults with SCD, more recently, data of the estimated total health care cost per year was evaluated up to the US $ 1.1 billion [44]. Adam et al. reported a higher in use and cost of health care in SCD-individual with depression compared to SCD-individual without depression [43]. Another study led in sub-Saharan African, a cradle of SCD, the yearly cost of the part exchange transfusions, per individual under regular treatment requirement, was estimated the US $ 3,345 without chelation and higher at the US $ 5000 with chelation [45]. According to Ngolet et al. in Congo, the overall average cost effect for hospitalization of SCD-related acute complication was XAF 65,460 (US $ 115.21) [46]. A study from England showed that with 6077 admissions related to SCD-crisis, which was the majority of diagnostic in 2010-2011, the total cost for commissioners was estimated £ 18,798,255 for these admissions [47]. Almost all the studies described the cost-effectiveness of SCD differently, among of them, it depends on clinical pictures and approach management. The health care cost is increased with age. The literature confirmed that SCD is one of expensive disease and engender a huge expenditure of healthcare system in the part world. It is, therefore, a considerable economic burden for the affected individual and its family. The low-, middle-income countries need of involvement of policies for the implementation of well-codified approaches and supplement to managing the condition.

Conclusion

Albeit treatment of SCD, in manner, persists in being mainly palliative, a promising preventive and curative remains the huge approaches to treat. In the use of pain management is requiring a good practice of opioid and non-opioid analgesics knowing it should be differentiated and unified with its own use. The comorbidities and morbidities are possibly avoiding and mitigating through the early identification and management of organ dysfunction. The utilization of Hydroxyurea leads to the improvement of the quality-of-life to SCD-patients while decreasing the morbidity and mortality. Bone marrow, stem cell, and cord blood transplantation depict the curative picture of SCD in selected children. The molecular and cellular pathways account for future research to treat involving gene therapy and procedures of prevention of sickle-RBC adhesion to endothelium. Health care cost overall increase with age and depending on the clinical manifestation of the disease. In low-, middle-, and high-income countries, SCD abides an economic burden healthcare system.

Acknowledgement

We thank Dr Gérald Michel Raeliarijaona for his valuable suggestions and linguistic support.

Funding

No funding sources.

Consent for publication

All authors approve the manuscript for publication.

Ethics approval and consent to participate

All authors are compliant with ethical standards.

Conflict of interest

No conflict of interests.

References

1. De Franceschi L, Mura P, Schweiger V, Vencto E, Quaglia FM, Delmonte L, et al. Fentanyl buccal tablet: a new breakthrough pain medication in early management of severe vaso-occlusive crisis in sickle cell disease. Pain Pract. 2016;16:680-7.
2. Ballas SK. Sickle cell disease: classification of clinical complications and approaches to preventive and therapeutic management. Clin hemorheol Microcirc. 2018;68:105-128.
3. Uwaezauoke SN, Ayuk AC, Ndu IK, Eneh CI, Mbanefo NR, Ezenwosu OU. Vaso-occlusive crisis in sickle cell disease: current paradigm on pain management. J Pain Res. 2018;11:3141-50.
4. Sundd P, Gladwin MT, Novelli EM. Pathophysiology of sickle cell disease. Annu Rev Pathol. 2018;14:263-92.
5. GBD Mortal Causes Death Collaborators Collaborator. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385:117.
6. World Health Organization. The fify-ninth world health assembly. 2006;A59/9 2006.
7. Piel FB, Hay SI, Gupta S, Weatherall DJ, Williams TN. Global burden of sickle cell Anaemia in children under five, 2010-2050: modelling based on demographics, excess mortality, and interventions. PLoS Med. 2013;10:e1001484.
8. Olatunya OS, Ogundare EO, Fadare JO, Oluwayemi IO, Agaja OT, Adeyefa BS, et al. The financial burden of sickle cell disease on households in Ekiti, Southwest Nigeria. Clinicoecon Outcomes Res. 2015;7:545-53
9. Piel FB, Williams TN. Sickle Cell Anemia: History and Epidemiology. In: Costa FF, Conran N, editors. Sickle cell anemia: From basic science to clinical practice. Cham: Springer International Publishing AG; 2016. p. 23-47.
10. Brandow AM, Zappia KJ, Stucky CL. Sickle cell disease: a natural model of acute and chronic pain. PAIN. 2017;158: S79-S84.

11. Ballas SK, Marcolina MJ. Hyperhemolysis during the evolution of uncomplicated acute painful episodes in patients with sickle cell anemia. Transfusion. 2006;46:105-10.

12. Expert Panel Report. Evidence-Based Management of Sickle Cell Disease Bethesda MD: National Heart, Lung, and Blood Institute. US Department of Health and Human Services. 2014. Available from: http://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines/ Accessed March 20, 2018.

13. Piel FB, Steinberg MH, Rees DC. Sickle cell disease. N Engl J Med. 2017;377:305.

14. Ware RE, Eggleston B, Redding-Lallinger R, Wang WC, Smith-Whitley K, Daeschner C, et al. Predictors of fetal hemoglobin response in children with sickle cell anemia receiving hydroxyurea therapy. Blood. 2002;99:10-4.

15. Zimmerman SA, Schultz WH, Davis JS, Pickens CV, Mortier NA, Howard TA, et al. Sustained long-term hematologic efficacy of Hydroxyurea at maximum tolerated dose in children with sickle cell disease. Blood. 2004;103:2039-45.

16. Cokic VP, Andric SA, Stojilkovic SS, Noguchi CT, Schechter AN. Hydroxyurea nitrosylates and activates soluble guanylyl cyclase in human erythroid cells. Blood. 2008;111:1117-23.

17. Torres L, Conran N. Emerging pharmacotherapeutic approaches for the management of sickle cell disease. Expert Opin Pharmacother. 2019;20:173-86.

18. Kinney TR, Helms RW, O'Branski EE, Ohene-Frempong K, Wang W, Daeschner C, et al. Safety of Hydroxyurea in children with sickle cell anemia: results of the HUG-KIDS study, a phase I/II trial. Pediatric Hydroxyurea Group. Blood. 1999;94:1550-4.

19. Wang WC, Ware RE, Miller ST, Iyer RV, Casella JF, Minniti CP, et al. Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomized, controlled trial (BABY HUG). Lancet. 2011;377:1663-72.

20. Lebensburger JD, Miller ST, Howard TH, Casella JF, Brown RC, Lu M, et al. Influence of severity of anemia on clinical findings in infants with sickle cell anemia: analyses from the BABY HUG study. Pediatr Blood Cancer. 2012;59:675-8.

21. Ware RE, Davis BR, Schultz WH, Brown RC, Aygun B, Sarnaik S, et al. Hydroxycarbamide versus chronic transfusion for maintenance of transcranial doppler flow velocities in children with sickle cell anaemia-TCD With Transfusions Changing to Hydroxyurea (TWiTCH): a multicentre, open-label, phase 3, non-inferiority trial. Lancet. 2016;387:661-70.

22. Opoka RO, Ndugwa CM, Latham TS, Lane A, Hume HA, Kasirye P, et al. Novel use Of Hydroxyurea in an African Region with Malaria (NOHARM): a trial for children with sickle cell anemia. Blood. 2017;130:2585-93.

23. Hankins JS, McCarville MB, Rankine-Mullings A, Reid ME, Lobo CL, Moura PG, et al. Prevention of conversion to abnormal transcranial Doppler with Hydroxyurea in sickle cell anemia: A Phase III international randomized clinical trial. Am J Hematol. 2015;90:1099-105.

24. Nevitt SJ, Jones AP, Howard J. Hydroxyurea (hydroxycarbamide) for sickle cell disease. Cochrane Database Syst Rev. 2017;4:CD002202.

25. Strunk RC, Cohen RT, Cooper BP, Rodeghier M, Kirkham FJ, Warner JO, et al. Wheezing symptoms and parental asthma are associated with a physician diagnosis of asthma in children with sickle cell anemia. J Pediatr. 2014;164:821–6.e1.

26. Gardner RV. Sickle Cell Disease: Advances in Treatment. Ochsner J. 2018;18:377-89.

27. Adams-Graves P, Kedar A, Koshy M, Steinberg M, Veith R, Ward D, et al. RheothRx (poloxamer 188) injection for the acute painful episode of sickle cell disease: a pilot study. Blood. 1997;90:2041-6.

28. Kuvibidila S, Warrier RP, Haynes J, Baliga SB. Hydroxyurea and Zileuton Differentially Modulate Cell Proliferation and Interleukin-2 Secretion by Murine Spleen Cells: Possible Implication on the Immune Function and Risk of Pain Crisis in Patients with Sickle Cell Disease. Ochsner J. 2015;15:241-7.

29. Kaul DK, Tsai HM, Liu XD, Nakada MT, Nagel RL, Coller BS. Monoclonal antibodies to $\alpha V\beta 3$ (7E3 and LM609) inhibit sickle red blood cell–endothelium interactions induced by platelet-activating factor. Blood. 2000;95:368-74.

30. Lal A, Suh J, Atamna W, Canty B, Hagar W, Vichinsky E, et al. Anti-Oxidant Treatment with α-Lipoic Acid and Acetyl L-Carnitine in Hemoglobinopathies. Blood. 2007;110:3799.

31. Ohnishi ST, Ohnishi T, Ogunmola GB. Green tea extract and aged garlic extract inhibit anion transport and sickle cell dehydration in vitro. Blood Cells Mol Dis. 2001;27:148-57.

32. Ballas SK. Hydration of sickle erythrocytes using a herbal extracts (Pfaffia paniculata) in vitro. Br J Haematol. 2000;111:359-62.

33. Wambebe C, Khamofu H, Momoh JA, Ekpeyong M, Audu BS, Njoku OS, et al. Double-blind, placebo-controlled, randomized cross-over clinical trial of NIPRISAN in patients with Sickle Cell Disorder. Phytomedicine. 2001;8:252-61.

34. Singh PC, Ballas SK. Emerging drugs for sickle cell anemia. Expert Opin Investig Drugs. 2015;20:47-61.

35. Ballas SK, Bauserman RL, McCarthy WF, Castro OL, Smith WR, Waclawiw MA. Hydroxyurea and acute painful crises in sickle cell anemia: Effects on hospital length of stay and opioid utilization during hospitalization, outpatient acute care contacts, and at home. J Pain Symptom Manage. 2010;40:870-82.

36. Walters MC. Bone marrow transplantation for sickle cell disease: Where do we go from here? J Pediatr Hematol Oncol. 1999; 21:467-74.

37. Leonard A, Tisdale JF. Stem cell transplantation in sickle cell disease: therapeutic potential and challenges faced. Expert Rev Hematol. 2018;11:547-65.

38. Buchanan G, Vichinsky E, Krishnamurti L, Shenoy S. Severe sickle cell disease-pathophysiology and therapy. Biol Blood Marrow Transplant. 2010;16:S64-7.

39. Mahadeo KM, Weinberg KI, Abdel-Azim H, Miklos DB, Killen R, Kohn D, et al. A reduced-toxicity regimen is associated with durable engraftment and clinical cure of nonmalignant genetic diseases among children undergoing blood and marrow transplantation with an hla-matched related donor. Biol Blood Marrow Transplant. 2015;21:440-4.

40. Demirci S, Uchida N, F. TJ. Gene therapy for sickle cell disease: an update. Cytotherapy. 2018;20:899-910.

41. Antoniani C, Meneghini V, Lattanzi A, Felix T, Romano O, Magrin E, et al. Induction of fetal hemoglobin synthesis by CRISPR/Cas9-mediated editing of the human beta-globin locus. Blood. 2018;131:1960-73.

42. Dong A, Rivella S, Breda L. Gene therapy for hemoglobinopathies: Progress and challenges. Transl Res. 2013;161:293-306.

43. Adam SS, Flahiff CM, Kamble S, Telen MJ, Reed SD, De Castro LM. Depression, quality of life, and medical resource utilization in sickle cell disease. Blood Adv. 2017;1(23):1983-92.

44. Kauf TL, Coates TD, Huazhi L, Mody-Patel N, Hartzema AG. The cost of health care for children and adults with sickle cell disease. Am J Hematol. 2009;84:323-7.

45. Boma Muteb P, Kaluila Mamba JFJ, Muhau Pfutila P, Bilo V, Panda Mulefu JD, Diallo DA. Effectiveness, safety, and cost of partial exchange transfusions in patients with sickle-cell anemia at a sickle cell disease center in sub-Saharan Africa. Med Sante Trop. 2017;27(4):387-91.

46. Ngolet LO, Moyen Engoba M, Kocko I, Elira Dokekias A, Mombouli JV, Moyen GM. Sickle-Cell Disease Healthcare Cost in Africa: Experience of the Congo. Anemia. 2016;2016:2046535.

47. Pizzo E, Laverty AA, Phekoo KJ, AlJuburi G, Green SA, Bell D, et al. A retrospective analysis of the cost of hospitalizations for sickle cell disease with crisis in England, 2010/11. J Public Health (Oxf). 2015;37(3):529-39.