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Sickle Cell Disease: Classification of Clinical Complications and Approaches to Preventive and Therapeutic Management

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Abstract

Sickle cell disease (SCD) is an inherited disorder of hemoglobin structure that has no established cure in adult patients. Cure has been achieved in selected children with sickle cell anemia (SCA) using allogeneic bone marrow transplantation or cord blood transplantation. SCD is essentially a triumvirate of (1) pain syndromes, (2) anemia and its sequelae and (3) organ failure, including **infection**. Pain, however, is the hallmark of SCD and dominates its clinical picture throughout the life of the patients. The prevalence of these complications varies with age from infancy through adult life. However, pain, infections and anemia requiring blood transfusion occur throughout the life span of affected patients. The overall medical care of patients with SCD in developed countries has improved such that their life expectancy has almost doubled since 1951. Currently, there are at least five major approaches for the general management of SCD and its complications. These include (i) symptomatic management, (ii) supportive management, (iii) preventive management, (iv) abortive management, and (v) curative therapy.

Introduction

Hemoglobinopathies are inherited disorders of the structure and/or function of hemoglobin (Hb). They are broadly divided into two major groups: structural variants and thalassemias. Structural variants are, most commonly, the result of single base mutations in the globin genes. Thalassemias are characterized by decreased synthesis of any one or more of the globin chains.

The sickle mutation is the result of a single base change (GAG→ GTG) in the sixth codon of exon 1 of the β-globin gene responsible for the synthesis of the β-globin polypeptide of the Hb molecule (α2β2). This change, in turn, results in replacement of the normal glutamic acid (E/Glu) with valine (V/Val) at position 6 of the β-globin chain and the formation of sickle Hb [1-3].

Over two million U.S. residents are estimated to be either heterozygous or homozygous for the genetic substitution. Most of those affected are of African ancestry or self-identify as Black; a minority are of Hispanic or southern European, Middle Eastern, or Asian Indian descent [4]. It is estimated that between 70,000 and 100,000 African Americans have SCD. Although SCD is associated with major morbidity, currently more than 90 percent of children with SCD in the United States and the United Kingdom survive into adulthood [5-7]. However, their lifespan remains shortened by two or three decades compared to the general population [8, 9].

Classification of Sickle Cell Disorders

Sickle cell disease comprises a group of clinically significant hemoglobinopathies in which the sickle gene is inherited from at least one parent. Sickle cell anemia (SCA) is the homozygous state where the sickle gene is inherited from both parents. Sickle cell syndromes also result from the co-inheritance of the sickle gene with Hb C gene giving rise to Hb SC diseases, with β-thalassemia genes (β^0 or β^+) giving rise to sickle - β^0-thalassaemia or sickle - β^+-thalassemia respectively or with other β-globin structural variants giving rise to other combinations such as HbSO Arab, HbSD disease, and so. The most prevalent SCD types include homozygous Hb SS and the compound heterozygous conditions HbSβ^0-thalassemia, HbSβ^+-thalassemia, and Hb SC disease. Hb SS and HbSβ^0-thalassemia are clinically very similar and therefore are commonly referred to as SS or SCA; these genotypes are associated with the most severe clinical manifestations. Certain complications of SCD may be more common in one category than another. Thus, frequent painful crises, severe anemia that requires blood transfusion and acute chest syndrome (ACS) are more common in SCA than other types of SCD. Sickle retinopathy **and otologic disorders**, on the other hand, are more common in Hb SC disease than in SCA. It must be emphasized that the order of severity in SCD is based on population statistics. Thus, if one compares the overall clinical picture of 100 patients with SCA, for example, with that of 100 patients with Hb SC disease then the latter will be milder as far as frequency of painful episodes, morbidity and mortality are concerned. On the individual basis, however, there are exceptions. Thus, an individual patient with SCA may have a mild disease whereas an occasional patient with S-β^+-thalassemia may have a severe disease.

Genetics and Epigenetics

Sickle cell syndromes can also be divided into subcategories depending on the α genotypes and β haplotypes [10-12]. About 65% of patients with SCA have normal α genotypes

($\beta^S\beta^{S;}$ αα/αα), 30% have one α gene deleted ($\beta^S\beta^S$; -α/αα), and the remaining 5% have two α genes deleted ($\beta^S\beta^S$; -α/-α). The effect of α gene deletion on the clinical picture of sickle cell syndromes is controversial. Generally speaking, α gene deletion is associated with milder anemia [13] and less blood transfusion. The increased Hb level associated with α gene deletion, however, **presumably** increases the blood viscosity, which is often accompanied by increased frequency of painful crises [14, 15] and vaso-occlusive episodes such as avascular necrosis (AVN) [16, 17]. **Recently, Renoux et al [18] observed increased frequency of crises in children with alpha-thalassemia but it was not explained by increased blood viscosity. Instead, children with alpha-thalassemia had greater RBC deformability and RBC aggregation. The number of patients studied, however, was relatively small and the diagnosis of avascular necrosis was not ruled out [18].** The effect of α gene deletion on the clinical picture is best illustrated in SCA with two α gene deletions. Table 1 lists the unique features of this type of SCD [19, 20]. Noteworthy is that HbA2 is elevated in SCA with two α gene deletions, a finding that confuses this diagnosis with $S\beta^0$ thalassemia that is, typically, also associated with elevated HbA2 levels. The clinical picture, family history, hematological data and molecular diagnostics can differentiate the two diagnoses [20].

β-Haplotypes refer to the nucleotide sequence 5' and 3' to the sickle gene. Three major types have been described in Africans and African Americans [11]. These are the Senegalese (Sen), Benin (Ben) and Central African Republic (CAR) haplotypes. The significance of these haplotypes pertains to their effect on Hb F production. It has been established that the higher the Hb F level, the milder is the SCA [15, 21]. Again, these conclusions are based on population data and may not apply to an individual patient.

Epigenetic factors that could affect phenotypic expression include the environment, aging, drugs/pharmaceuticals and diet. The exact mechanism of action of epigenetic factors at the molecular level is not well known. It seems that some drugs may cause methylation or demethylation of DNA or modification of histones resulting in activation or deactivation of certain genes that could affect the phenotypic expression of the gene in question [22].

Genetic Markers

Sickle cell disease is a complex genetic disorder characterized by intricate genotypic/phenotypic interactions that include correlations among multiple genetic and environmental markers and modifiers. Genetic markers may predict the severity of the disease and the possible or probable incidence of certain complications. This, in turn, allows for the implementation of certain therapeutic measures that may prevent or ameliorate the severity of some of these complications. Traditional approaches to identify genetic markers have included studies of the transgenic sickle cell mouse and natural history studies and family pedigrees [23, 24]. With the advent of the Human Genome Project, novel genetic polymorphisms associated with disease have been identified, thus allowing for the performance of genetic association studies [24-31].

Although these findings are novel and interesting, their validity and utility in predicting and treating the clinical complications of SCD should be confirmed by large controlled multi-institution studies. The studies performed to date are too small to make definite conclusions.

Other Factors

In addition to the factors mentioned above, there is growing evidence that psychosocial and environmental factors precipitate vaso-occlusion and affect the frequency and severity of painful episodes. Physical stress, trauma, dehydration and infections are such known factors.

Clinical Complications of Sickle Cell Disease

Major complications of SCD include three sets of clinical adverse effects: (1) pain syndromes, (2) hemolytic anemia and its sequelae and (3) organ damage/failure. The prevalence of these complications varies with age from infancy through adult life as shown in Figure 1. However, pain, infections and anemia requiring blood transfusion occur throughout the life span of affected patients.

Pain Syndromes

The Acute Painful Vaso-occlusive Crisis (VOC)

Sickle cell pain has unique features. Pathophysiologically, it is nociceptive (ie, secondary to tissue damage). It may be acute or chronic, somatic or visceral, unilateral or bilateral, localized or diffuse and mild, moderate or severe [32]. Typically, VOCs affect long bones and joints, with the low back frequently reported site of pain [33]. Other regions of the body, including the scalp, face, jaw, abdomen, and pelvis, may be involved. A severe acute sickle cell painful episode has been defined as one that requires treatment in a medical facility with parenteral opioids for 4 or more hours [34, 35]. The occurrence of three or more such crises indicates that the affected patient has severe SCD. The words most often used to describe sickle

pain include “throbbing,” “sharp,” “dull,” “stabbing,” and “shooting,” in decreasing order of frequency [33].

Objective signs of a VOC, such as fever, leukocytosis, joint effusions, and tenderness, occur in about 50% of patients at initial presentation [13]. During the evolution of the VOC, however, objective laboratory signs become evident in most patients, provided that these parameters are determined serially [36]. The VOC that requires hospitalization appears to evolve along four distinct phases: prodromal, initial, established, and resolving [37]. Each phase may be associated with certain clinical and laboratory findings. As the pain of a VOC intensifies, the percentage of dense RBC increases with a concomitant decease in RBC deformability. Some patients develop hyperhemolysis during the evolution of the VOC, with decrease in Hb level and increase in the reticulocyte count [37]. As pain resolves, the pattern is reversed, with a decrease in the number of dense red cells and an increase in RBC deformability [36].

Chronic sickle cell pain

Avascular Necrosis

Avascular necrosis (also called ischemic necrosis or osteonecrosis) is the most commonly observed complication of SCD after the number of VOCs in adults. Although it tends to be most severe and disabling in the hip area, it is a generalized bone disorder in that the femoral and humeral heads as well as the vertebral bodies may be equally affected. The limited terminal arterial blood supply and the paucity of collateral circulation make these three areas especially vulnerable to sickling and subsequent bone damage. **In the Cooperative Study of Sickle Cell Disease (17) that included 2804 p**atients, with SCA and α-gene deletion **had** a higher incidence of AVN because the relatively high hematocrit increases blood viscosity and thus, enhances

microvasculopathy in the aforementioned anatomic sites [16, 17]. The mean corpuscular volume (MCV) and AST levels were reported to be negatively correlated with avascular necrosis **especially in patients with homozygous alpha gene deletion [17]. In a study involving about 100 patients with SCA, Lemonne et al. [38] found no difference in blood viscosity between patients with and those without osteonecrosis, despite difference in hematocrit/Hb. Together, all these findings suggest that Hb seems to have a negative effect on the frequency of AVN irrespective of its effect on viscosity. The roles of Hb/Hct, viscosity, deformability and aggregation in the pathophysiology of certain complications of SCD need further studies.**

Medical treatment of AVN is symptomatic and includes providing non-opioid and/or opioid analgesics for pain relief as well as physical therapy. Advanced forms of the disease require total bone replacement. Core decompression in the management of AVN appears to be effective if done in the early stages of AVN [39]. This, however, was not supported by a prospective randomized multi-center comparing physical therapy alone with core decompression and physical therapy for femoral head AVN in 46 patients with SCD [40]. Physical therapy alone appeared to be as effective as hip core decompression followed by physical therapy in improving hip function and postponing the need for additional surgical intervention at a mean of three years treatment. Results of hip arthroplasty in patients with SCA are not as encouraging as results of arthroplasty performed for arthritic hip [41]. Placement of an internal prosthesis may be difficult owing to the presence of hard sclerotic bone in patients with SCD. Other problems associated with hip arthroplasty in these patients include an increased incidence of infection [42, 43], a failure rate of about 50% and a high morbidity due to loosening of both cemented and

uncemented prosthesis. Recent techniques of arthroplasty may improve the life expectancy of hip prostheses [44].

Leg ulcers

Leg ulceration is a painful and sometimes disabling complication of SCA that occurs in 5 to 10% of adult patients. The most common site for the appearance of leg ulcers is the distal third of the leg, especially on the inner area, just above the ankle and over the medial melleoli. Ulceration involves the skin and underlying tissues of the involved areas. The deeper the ulcer the more severe. Leg ulcers are classified into stages depending on their depth and not surface area. Severe pain may necessitate the use of opioid analgesics. The use of topical analgesics seems to be effective in relieving pain and decreasing the use of oral analgesics, especially opioids [45].

Leg ulcers are more common in males and older patients, and less common in patients with α-gene deletion, high total Hb level or high levels of Hb F [19]. Leg ulcers seem to be more common in patients who are also carriers of the CAR β-gene cluster haplotype [46]. As was mentioned above leg ulceration seems to be associated with priapism, pulmonary hypertension and death in a subtype of SCD characterized by high levels of lactate dehydrogenase (LDH) as a marker of hyperhemolysis.

Treatment of leg ulcers includes wound care using wet to dry dressings soaked in saline or Burrow's solution. With good localized treatment, many ulcers heal within a few months. Oral zinc sulfate therapy (660 mg per day) may be beneficial for some patients [47]. However, a Cochrane review [48], showed that oral zinc for arterial or venous leg ulcers due to causes other than SCD had no significant difference compared to placebo. Leg ulcers that persist more than 6

months present a challenge to the treating physician and the patient. In addition, survival of patients with chronic leg ulcers seems to be decreased compared to patients without leg ulcers [49].

Certain modalities for the management of leg ulcers that are not commonly used in SCD include topical application of platelet-derived growth factor prepared either autologously (Procuren) [50] or by recombinant technology (Regranex) **[51], topical sodium nitrite for chronic leg ulcers [52],** and the use of cultured skin grafts [53]. In addition, mānuka honey from New Zealand has been reported to heal diabetic foot ulcers [54, 55]. Amputation, a last resort for recalcitrant and severely painful ulcers, is rarely used [56, 57].

The induction of Hb F production by hydroxyurea (HU) [34] would imply that it may prevent or heal leg ulcers in patients with SCD. However, HU has been reported to be associated with leg ulcers in patients with myeloproliferative disorders [58, 59]. Whether the same association exists in patients with SCD is controversial. Leg ulcers were a common complication among 123 adult patients treated with HU in a retrospective French study [60]. Although controlled studies have not been reported to support the role of Hb F induction in the management of leg ulcers, future randomized, multicenter trials of HU may provide further information on this subject.

Pain between Crises

Some patients with SCD complain of pain between VOCs and take opioids with or without nonopioid analgesics on a chronic basis. They have no evidence of precipitating cause such as infection, dehydration, or ischemia. Many of these patients are often referred to as having

chronic pain despite the fact their pain is not similar to other chronic pain syndromes such as low back pain in the general population, fibromyalgia, osteoarthritis, migraine, etc.

Neuropathy and neuropathic pain

Neuropathy and neuropathic pain are not the same and not all patients with neuropathy have pain. Neuropathic pain is not well documented as a complication of SCD. The scales to assess neuropathic pain are different than those used in assessing sickle cell pain and their use has not been validated in SCD. Neuropathy, especially peripheral neuropathy, has been reported in patients with SCD, albeit uncommonly. Mental nerve neuropathy (AKA numb chin syndrome) is the most commonly reported neuropathy in SCD usually associated with VOC. More studies are needed to determine the prevalence of neuropathy and neuropathic pain in patients with SCD and to find whether these are complications of the disease itself or due to co-morbidities [61].

Hematological Manifestations

Hemolytic anemia and its sequelae

Sickle cell anemia is characterized by normochromic, normocytic anemia with a mean Hb of 7.8 ± 1.13 and a mean corpuscular volume (MCV) of 90 fl. The presence or absence of α-gene deletion has an effect on the anemia, the indices and the hemoglobin electrophoresis pattern. Thus, patients with SCA and homozygous α-thal 2 ($\beta^S\beta^S$; -α/-α) have milder anemia, a lower reticulocyte count, a low MCV and a high Hb A2 level. Both the white blood cell and platelet counts are increased in SCA due to increased marrow activity secondary to chronic hemolysis and, in the case of SCA, to "autosplenectomy", where platelets are not stored in the spleen. Normally, about one-third of circulating platelets are stored in the spleen and patients with splenectomy typically have high platelet counts. Patients with splenomegaly (S-β-

thalassemia, Hb SC disease and SCA with α-thalassemia) typically have low or low-normal platelet counts, depending on the degree of splenomegaly.

Patients with S-β^0-thalassemia have a hematological picture that is characterized by microcytosis, hypochromia, high Hb A2 levels and variable Hb F values. The anemia in Hb S-β^+-thalassemia is mild and usually with Hb level greater than 10 g/dL. Hb SC disease is typically characterized by microcytic and hyperchromic RBC indices.

In addition to the chronic hemolytic anemia typical of SCD, patients with SCA may develop other types of anemia. Hyperhemolysis (or hyperhemolytic crisis) is characterized by a marked drop in Hb with evidence of increased red blood cell destruction in the absence of other identifiable causes such as splenic or hepatic sequestration. The decrease in Hb should be ≥20% from baseline and the increase in reticulocyte by 25% or presence of nucleated RBC in the peripheral smear. Moreover, there should be evidence of hemolysis [increased LDH, unconjugated bilirubin, or aspartate aminotransferase (AST)], compared with baseline without recovery from bone marrow suppression [62]. Hyperhemolysis may be caused by infection (example, mycoplasma pneumonia), a co-existent G6PD deficiency with exposure to oxidant stress or by a delayed hemolytic transfusion reaction. Aplastic crisis characterized by a decrease both in Hb and reticulocyte values, is most commonly caused by infection, both bacterial and viral. Megaloblastic crisis is occasionally seen in those patients who become folate-deficient because of poor dietary habits and no folic acid supplementation. Iron deficiency anemia may complicate SCA, especially in young menstruating women who refuse blood transfusion if needed. Whether iron deficiency anemia has a salutary effect on the phenotypic expression of SCA because of impaired Hb S polymerization secondary to decreased mean corpuscular hemoglobin concentration, or not, is an issue that is not settled in the literature.

Hyperviscosity

Whole blood viscosity is a function of the number, deformability, **and aggregability** of erythrocytes, as well as of the quantity and nature of plasma proteins **(see the review by Connes et al in this special issue of Clinical Hemorheology and Microcirculation)**. In SCD, viscosity is dominated by Hb S gelation and the presence of dense sickle cells. The hyperviscosity syndrome in SCD (and other hemoglobinopathies) occurs most frequently post-transfusion [63].

Transfusional Hemosiderosis

Transfusional hemosiderosis or iron overload refers to an increase in total body iron due to multiple blood transfusions of ≥20 units or ≥200mL/kg of red blood cells and serum ferritin level of >1000 ng/mL and transferrin saturation >50% on ≥3 serial determinations in the steady state or measurement of abnormally increased iron by liver biopsy, magnetic resonance imaging (MRI) $T2^*$ or Ferriscan [64-66].

Organ Damage/Failure

Almost all organs are affected in SCD in general and SCA in particular. These were recently reviewed in a few publications [67-69]. The major systems affected and their management will be summarized below.

Infection

Sickle cell anemia has an unusual relationship to certain infectious agents. Individuals with sickle trait are resistant to infection by Plasmodium falciparum but patients with SCA are susceptible. Individuals with Fy (a-b-) RBC are resistant to infection by other types of malarial parasites. Several acquired abnormalities render patients with SCD immune compromised and,

hence, susceptible to a number of infections that are a major cause of mortality and morbidity in these patients. The increased susceptibility of patients to infection with the polysaccharide-encepsulated bacteria (S. pneumoniae and H. influenzae) is secondary to the absence of splenic function. Cellular immunity may be compromised by transfusion-related iron overload and abnormalities in B-cell immunity may explain antigen processing defects. Infections due to E. coli are usually associated with urinary tract infection in adult patients. Patients with SCA are susceptible to osteomyelitis secondary to S. typhimurium in addition to the usual causes of bacterial osteomyelitis such as S. aureus. The susceptibility to infection by Salmonella may reflect the ability of this organism to flourish in partially necrotic bone [70].

Neurological complications

These include cerebrovascular accidents (strokes), transient ischemic attacks, silent infarcts and neurocognitive impairment. Cerebrovascular accidents include infarctive stroke mostly in children, hemorrhagic stroke mostly in adults and moyamoya. Infarctive stroke is an acute neurological syndrome resulting from impaired cerebral blood flow without evidence of hemorrhage lasting more than 24 hours. Hemorrhagic stroke is intracranial hemorrhage causing neurologic symptoms and signs. Moyamoya is abnormal vascular network (“puff of smoke” appearance) indicative of collateral circulation secondary to stenosis or occlusion of large cerebral arteries [71, 72].

Transient ischemic attack is a brief episode of neurologic dysfunction caused by focal brain ischemia, with clinical symptoms typically lasting less than 1 hour, and without subsequent evidence of cerebral infarction [71, 73]. Silent cerebral infarcts (SCI) are changes on MRI of brain consistent with infarction without associated history of neurologic symptoms or abnormal

neurological exam [71, 74]. Most SCI are localized in the deep white matter and less commonly in the subcortical grey matter structures. In the Comprehensive Study of SCD (CSSCD), about 25% of the children with SCI had new and/or enlarging lesions on follow-up MRI scan [75]. In comparison only 2.5% of the children without SCI, had new and/or enlarging lesions on follow-up MRI scan. The SIT trial showed that regular blood transfusion to children aged 5–14 years with SCI reduced the risk of reinfarction, both overt stroke and silent infarcts [76].

Neurocognitive impairment is defined by the presence of abnormal nonverbal function assessed by the Wechsler Adult Intelligence Scale III Performance IQ Index in adult patients with SCA who are neurologically asymptomatic. This impairment is most likely secondary to cerebral hypoxemia undetectable by standard neuroimaging studies [77, 78].

Ophthalmological Complications

The most important and serious ophthalmological complications of SCD include the following:

Proliferative sickle retinopathy which is neovascular fronds that emerge from the retinal vasculature at the interface of perfused and non perfused retina in response to vascular growth factors produced by ischemic retina. The neovascular tissue is predisposed to hemorrhage and vitreoretinal traction forces. Although these pre-retinal neovascular formations, which may resemble and are called sea fans, are bright red when viable, they appear white when autoinfarcted or caused to involute by laser photocoagulation [79].

Retinal detachment is separation of the retina from the choroid and eye wall due to holes in the retina and traction on the retina by vitreous bands and condensed pre-retinal membranes

(usually as sequelae of proliferative sickle retinopathy). Retinal detachment is the most severe complication (Stage V) of proliferative sickle retinopathy [80].

Vitreous hemorrhage is bleeding into the vitreous cavity caused by mechanical stress (from trauma or normal vitreous movement) on the delicate neovascular fronds growing from the retina into the vitreous chamber. Vitreous hemorrhage is a severe complication of proliferative sickle retinopathy [81].

Cardiac Complications

High output failure, right heart and/or congestive heart failure, cardiac hemosiderosis and cardiomegaly are known manifestations of SCD. Recent evidence suggests that myocardial ischemia may occur as well and myocardial infarction has been reported [82]. Mitral valve prolapse was reported to have high prevalence (23%) in SCD [83]. This finding, however, was not confirmed by another group [84]. The signs and symptoms of mitral valve prolapse (chest pain, fatigue, syncope, palpitations, etc.) overlap with those of SCD and may elucidate the protean manifestations of SCD in case there is an association between these two disorders.

Pulmonary Complications

Acute Chest syndrome

The incidence of ACS is age and genotype dependent, with no difference between sexes. It is approximately three times more common in young children than in adults but more severe in adults [85, 86]. Acute chest syndrome is most common in SCA, sickle β^0-thalassemia, Hb SC disease, and sickle β^+thalassemia in decreasing order of frequency. Coexistent α-gene deletion, PLT count, and mean corpuscular volume of RBCs do not appear to affect the incidence of ACS

[86]. The incidence of ACS decreases in the presence of high Hb F level and severe anemia but is directly proportional to the steady state white blood cell count [86]. Acute chest syndrome is closely associated with VOCs, especially in adults [87, 88]. It occurs in approximately 50% of hospitalized patients with SCA for VOC [87, 89-91]. These episodes account for 15% of acute admissions and are potentially fatal [92-94]. Moreover, ACS appears to be the most common cause of death among patients and second to VOC as the most common cause of hospitalization of patients with SCD [95-98]. Although ACS is usually self-limited and resolves with treatment, it can be associated with respiratory failure, with a mortality rate of 1.8% in children and 4.8% in adults [87, 99].

Causes of ACS include pneumonia, bone marrow fat embolism, pulmonary infarct due to in situ sickling, rib/sternal infarction, infection, and pulmonary embolism (PE) (149-151). Approximately 50% of patients with ACS have no identifiable etiology [87]. Pulmonary bone marrow fat embolism in patients with SCA appears to be more common than previously thought [87, 99]. The characteristic clinical picture is that of severe bone pain, usually in long bones, followed by dyspnea, hypoxia and fever. Tissue infarction of the bone marrow within long bones appears to generate a source of fat and necrotic tissue that has been demonstrated in the lung on autopsy.

Diagnostic work-up should include serial chest radiographs, cultures of sputum and blood, monitoring of arterial blood gases and Hb level, ventilation and perfusion (V/Q) scans, analysis of induced sputum, bronchial washings, and analysis of urine for fat globules, and ruling out thrombophlebitis in the pelvis or lower extremities. The diagnosis of fat embolism entails the identification of fat-laden macrophages in induced deep sputum, or better by bronchoalveolar lavage fluid obtained by bronchoscopy [87, 100].

The management of ACS involves multiple modalities to prevent possible catastrophic outcomes. The most important aspect of management is to maintain adequate ventilation. In mild cases, incentive spirometry may be sufficient to achieve this. However, in severe cases, mechanical ventilation in the intensive care unit is essential.

Once adequate ventilation is maintained, specific treatment includes oxygen, antibiotics, simple blood transfusion or exchange transfusion, judicious use of analgesics, bronchodilators, careful hydration, and possible vasodilators. Incentive spirometry prevents splinting and atelectasis and may actually prevent ACS in patients with rib infarction [101]. Intravenous antibiotics are indicated because it is difficult to rule out pneumonia or infected lung infarcts.

A combination of a third-generation cephalosporin and a macrolide or a quinolone antibiotic should be used to cover typical and atypical pathogens. Simple transfusion or exchange transfusion is indicated in patients with worsening respiratory function. The beneficial effects of blood transfusion may not be due simply to decreasing the proportion of sickled RBCs; other mechanisms may be involved. These include (1) an immunomodulatory mechanism by which inflammatory cytokines (interleukin [IL]-8 in particular) bind to the Duffy antigen present on transfused RBCs but often absent on RBCs of Africans and African Americans [102]; and (2) the albumin that is present in transfused units or used in blood exchange may bind free fatty acids, thus neutralizing their damaging effect on the pulmonary endothelium.

Pulmonary Hypertension

Pulmonary hypertension is increased blood pressure in the pulmonary vasculature (both micro & macro vasculature). Clinical picture includes dyspnea, palpitations, pain (chest and abdomen), syncope, cyanosis, edema, fatigue and heart failure. The World Health Organization (WHO) classifies pulmonary hypertension into five groups. Among these the pulmonary arterial hypertension (PAH) and the pulmonary venous hypertension (PVH) are the most common and most important in SCD.

The pathophysiology of PAH includes two mechanisms: vascular obstruction and intimal hyperplasia. The vasoconstriction is due to decreased nitric oxide **bioavailability** and increased production of vaso-constrictors such as endothelin [103]. Intimal hyperplasia is the result of the hypoxia response pathway [104]. Specifically, hypoxia induced factors α and β (HIF-α and HIF-β) translocate to the nucleus across the cell membrane. The α/β complex activates the transcription of genes that increase cell proliferation and inflammation thus causing intimal hyperplasia and vaso-occlusion. The PVH, on the other hand, is due to left ventricular failure.

Pulmonary hypertension is technically defined by a mean pulmonary artery pressure (MPAP) ≥ 25 mmHg which can be determined by echocardiography. In order to determine whether it is PAH or PVH, however, depends on the mean pulmonary capillary wedge pressure which cannot be determined by echocardiography but requires right heart catheterization (RHC). PAH is characterized by MPAP ≥ 25 mmHg and capillary wedge pressure ≤ 15 mmHg whereas in PVH the capillary wedge pressure is > 15 mmHg.

Treatment of pulmonary hypertension depends on its etiology. Thus the treatment of PVH targets the management of left ventricular failure. Treatment of PAH includes the use of vasodilators. This worked in PAH in the general population but not in PAH in patients with

SCD. For now management of PAH in SCD includes blood transfusion and HU. More studies and controlled trials are needed to determine the appropriate treatment of the PAH of SCD.

Genitourinary Complications

Table 2 lists the major genitourinary manifestations of SCD. Urinary tract infection is usually caused by E. coli and is more common in females than in males. Its increased frequency in SCD may relate to renal infarction or immunodeficiency. The hypoxic, acidotic and hypertonic microenvironment of renal medulla causes sickling of red cells in the vasa recta leading to infarction of the renal medulla, hyposthenuria and hematuria (gross or microscopic). Inability to acidify the urine after an acid load can also occur. These tubular defects of the kidney (hematuria, hyposthenuria) occur not only in patients homozygous for the sickle gene, but in heterozygotes as well (AS, SC, SD, SO, etc.). Hematuria may be due to acute renal papillary necrosis, urinary tract infection, and less commonly to glomerulonephritis, obstruction, analgesic toxicity, mycobacterial infection, nephrolithiasis, tumor (renal cell carcinoma or medullary cell carcinoma), arterio-venous malformations, and vasculitis [105]. Hematuria, especially gross hematuria, may be the first sign of renal medullary carcinoma. Enuresis occurs in children. Potassium excretion is also impaired and episodes of hyperchloremia acidosis have been reported. Papillary necrosis seems to be more common in Hb SC disease. Hyperuricemia in SCA is due to increased marrow activity with consequent enhanced purine metabolism and to an acquired defect in the renal tubules. Gout has been described in a few patients.

Nephrotic syndrome occurs infrequently with or without hypertension. Microscopic hematuria, proteinuria, hypertension and the nephrotic syndrome are markers of incipient end-stage renal failure. The pathologic lesion is usually glomerulosclerosis. Once chronic renal

failure sets in, patients require chronic hemodialysis and are candidates for kidney transplantation.

Acute renal failure is characterized by an abrupt decline in renal function resulting in an inability to excrete metabolic wastes and maintain proper fluid and electrolyte balance [106, 107]. Chronic renal failure is an irreversible and usually progressive reduction in renal function in which both kidneys have been damaged to the extent that they are unable to adequately remove the metabolic products from the blood and regulate the body's electrolyte composition and acid-base balance. End stage renal disease (ESRD) is the final stage in chronic renal insufficiency and, by definition, requires dialysis or renal transplantation to prevent death [108].

Priapism

Priapism occurs when sickle cells congest the corpora and prevent emptying of blood from the penis. It is a common complication of SCD, affecting 35% of boys and men [109]. It is most common in patients with SCA, who account for approximately 80% to 90% of reported cases [110-113]. However, it does occur in males with all forms of SCD including Hb SC disease, all types of sickle thalassemia, and in those with sickle trait [110, 114]. In one survey, a single episode of priapism was reported by 31% to 64% of patients, mostly children; approximately 50% of all patients had recurrent episodes, from 2 to 50 times or more, and the estimated mean duration of an episode was 125 minutes (range 50–480 minutes) [112, 113, 115, 116]. Priapism is not unique to SCD; it could be secondary to trauma, infection, neoplasm, hemoglobinopathies other than SCD, polycythemia, other hemolytic disorders, or hematologic malignancies [117-121].

Clinically, priapism may be stuttering, minor, or major. Stuttering priapism is the occurrence of short, repetitive, and reversible painful episodes with detumescence occurring within a few hours after the onset of erection. This pattern has a good prognosis and is associated with normal sexual function and rarely **requires medical intervention**. The prevalence of stuttering priapism varies from approximately 2% of men with SCD according to some investigators [113] to 40% to 60% of men and boys with SCD according to others [115, 122].

Management of priapism is highly controversial. Controlled studies are lacking, therapeutic approaches are controversial and often conflicting, and medical and surgical therapies fail in most patients. Minor episodes of priapism and stuttering priapism usually last less than 4 hours and are often treated at home with analgesics, benzodiazepines, or pseudoephedrine and do not require treatment at the ED or hospital. Patients are advised to report to the ED if an episode lasts longer than 4 hours. Initial treatment in the ED should include hydration and opioid analgesics. Catheterization of the urinary bladder may be indicated to promote emptying. If these measures fail to cause detumescense, penile aspiration and epinephrine irrigation should be performed. Mantadakis et al. [123] recommend that aspiration of blood from the corpora cavernosa, followed by irrigation with dilute epinephrine, should be the initial therapy used for patients with SCA and prolonged priapism.

Simple transfusion or exchange transfusion may be performed for patients whose priapism does not respond to aspiration and irrigation procedures and persists for 24 hours or longer [124-126]. An association between blood exchange transfusion for priapism due to SCD and severe neurologic events including severe headache, seizures, focal neurological deficits, and obtundation has been made [127, 128]. This association has been named the ASPEN syndrome (Association of Sickle cell disease, Priapism, Exchange transfusion, and Neurologic events).

However, analysis of their data shows that the Hb level after blood exchange was much greater than the patient's baseline level. Thus, the neurologic complications were most likely due to transfusion- induced hyperviscosity. A larger study of blood exchange transfusion in patients with priapism, which maintained the post-exchange Hb level similar to baseline values, showed no neurologic complication in any of the patients [129]. Patients responding to transfusion therapy usually experience detumescence within 24 to 48 hours after the procedure. If detumescense does not occur within 24 hours after the completion of blood exchange transfusion, surgical intervention should be considered. Surgical intervention includes various shunt procedures between the cavernosa and the spongiosum [130, 131]. Without intervention, severe priapism results in impotence in >80% of patients. The combination of transfusions and surgery can decrease this to 25% to 50%. Patients who become impotent may benefit from psychologic counseling and the insertion of a prosthetic penile implant.

Hepatobiliary Complications

Hepatic sequestration is sequestration of red blood cells in hepatic sinusoids, leading to liver enlargement and decreased Hb concentration by ≥2 g/dL from baseline with reticulocytosis, without other explanation and liver enlargement of ≥3 cm for children and ≥5 cm for adults (from previous physical examination) without other explanation [132, 133]. Intrahepatic cholestasis is intrahepatic obstruction of bile formation or flow leading to hyperbilirubinemia. In SCD, this syndrome may occur in the context of hepatic sequestration with the addition of striking hepatic dysfunction with marked increase in direct bilirubin (>50% of total) compared to baseline and absence of extrahepatic biliary system obstruction and absence of evidence of marked accelerated hemolysis [134].

Viral hepatitis (Hepatitis B or C) is usually a consequence of chronic blood transfusion therapy. The right upper quadrant (RUQ) syndrome refers to patients with SCD who present with pain in the RUQ. Differential diagnosis of this entity includes VOC, cholecystitis, acute hepatic sequestration and intrahepatic cholestasis (hepatic crisis).

Musculoskeletal/Dermatologic Complications

Dactylitis (hand-foot syndrome) is inflammation caused by ischemia/ infarction of bone and/or bone marrow of the hands and/or feet, resulting in swelling, redness, and pain in affected areas. One of the earliest manifestations of SCD, dactylitis is seen primarily in children from 6 months to 3 years of age, and generally does not occur beyond 5 years of age, due to the lack of hematopoietic marrow activity in the hands and feet [135].

Avascular necrosis (AVN) and leg ulcers were described above in the pain syndromes section.

Acute Multiorgan Failure (MOF)

This is a catastrophic life threatening complication of SCD in the context of VOC that may even occur in patients with otherwise mild SCD [136]. Fever, rapid decrease in Hb level and PLT count, nonfocol encephalopathy and rhabdomyolysis are associated with MOF. Prompt and aggressive simple blood transfusion or blood exchange transfusion could be lifesaving with rapid recovery of organ failure in most cases MOF may occur in patients with history of relatively mild disease with little or no evidence of chronic organ damage and may be recurrent. High Hb levels in the steady state may be a predisposing factor.

Differential diagnosis of MOF includes ACS and drug overdose. MOF is initially heralded by a rapid fall in Hb and PLT counts from baseline. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), total and direct bilirubin, serum creatinine, and CPK are elevated by the third or fourth day of a VOC.

Management of Sickle Cell Disease

Management of SCD in general and its complications in particular follow five major approaches (Table 3). These include supportive management, symptomatic treatment, preventative management, abortive, and curative approaches to management. Although these approaches apply to the disease as a whole, at least one of them applies to each complication as well.

Supportive Management

The approach to supportive management is to maintain the essential requirements for good health and good quality of life including balanced diet, no obesity, no smoking, minimum or no alcohol, no illicit drugs, sleep, hydration, adherence to medical plans and folic acid. Oral hydration should be with water not soft drinks.

Symptomatic Management

The goal of symptomatic management is to alleviate the symptoms of the disease as they occur. These include: 1) management of pain with nonpharmacologic and/or pharmacologic approaches. The latter include opioids, non-opioids and adjuvants. Opioids used are usually short-acting for acute pain and long-acting or with extended or sustained release ± short-acting for chronic pain; it is important to note that the current national opioid phobia in the USA may,

unwittingly, deny opioids to patients who really need them, especially those patients who experience recurrent episodes of acute pain such as patients with SCD who are innocent bystanders guilty by association within the frame of the current opioid epidemic; 2) RBC transfusion for severe anemia, aplastic crisis, acute chest syndrome, acute stroke, multi-organ failure, and for the prevention of primary and secondary strokes. Blood transfusion could be simple or exchange depending on the nature of the clinical complication; 3) antibiotics for prophylaxis or for the treatment of infections; 4) Psycho-social supports as needed.

Preventative Management

The goal of preventive therapy is to ameliorate the clinical picture of SCD in general and to decrease the frequency and severity of VOCs in particular. For many years, the major goal of primary therapy for SCD was to identify an anti-sickling agent that would prevent or reverse the polymerization of sickle Hb in RBCs. Sodium cyanate inhibits polymerization of Hb S in vitro but is not beneficial in vivo at levels that provide acceptable toxicity [137]. The use of sodium cyanate was associated with peripheral neuropathy and subcapsular cataracts, which prevented its use as an antisickling agent. Although the search for beneficial antisickling compounds continues, the most promising approaches to prevent the frequency and severity of VOCs include the prevention of infection (including antibiotic prophylaxis in infancy and childhood), vaccination, avoidance of stressful situations, induction of Hb F production, blood transfusion, anti-adhesion therapy and many agents that await confirmation of benefit in clinical trials.

Fetal Hemoglobin (Hb F) Induction

High levels of Hb F have a beneficial effect in patients with SCA. Platt et al. [15] demonstrated a significant inverse correlation between the frequency of VOCs and Hb F levels

greater than 4%; the higher Hb F level, the milder the disease. Hemoglobin F interferes with the polymerization of Hb S; the higher (and the more pancellular) the Hb F level, the lower the intracellular concentration of Hb S. Exceptions to this rule include some patients with high Hb F level and severe disease and vice versa.

Among the agents that increase the level of Hb F in humans these, **hydroxyurea (HU)** as monotherapy seems to be the least toxic and most effective [34, 35, 138]. Moreover, HU is the only drug studied for efficacy in a relatively large scale, placebo-controlled, randomized clinical trial. All the other agents such as decitabine, arginine butyrate, valproic acid, etc. have been reported anecdotally to increase Hb F levels. None of the others was used in a controlled phase III clinical trial to date.

Hydroxyurea

The molecular mechanism(s) by which HU increases the production of Hb F is (are) unknown. Possible mechanisms include perturbations in cellular kinetics and/or recovery from cytotoxicity, recruitment of early erythroid progenitors and recruitment of primitive erythroid progenitors (BFU-E) that lead to production of Hb F-containing reticulocytes (F-reticulocytes). Long-term HU therapy with the maximum tolerated dose (mean dose 21.3 mg/kg) with respect to myelosuppression raises Hb F by as much as 15% to 20% (mean 14.9%, range 1.9% to 26.3%).

In the randomized, placebo-controlled, double blind Multi-center Study of Hydroxyurea (MSH) in SCA, among 299 adult patients with SCA with three or more VOCs per year, HU resulted in a significant ($p < 0.001$) reduction in the incidence of VOCs, ACS, and transfusion requirement [34, 35]. Hydroxyurea improved the quality of life of the patients taking it [139]. There was no difference between the placebo and HU arms in the incidence of death, stroke, or

hepatic sequestration. Maximum tolerated doses of HU were not required to reduce the incidence of VOCs. Although an increase in Hb F seems to be the obvious and logical explanation for the salutary effects of HU, other reasons for its beneficial effects include changes in RBC volume, cellular hydration, the cell membrane, and a direct effect on endothelial cells.

Hydroxyurea and the HUG Trials

The success of MSH prompted pediatricians to follow suit and determine the efficacy of HU in children. A multicenter Phase I/II trial of HU in children with SCA (HUG-KIDS) showed that HU therapy is safe for children with SCA when treatment is directed by a pediatric hematologist. Treatment of children with HU induced similar laboratory changes as in adults, and children could tolerate doses of HU as high as 30 mg/kg/day [140].

Another 2-year, prospective, multicenter, open-label, single-arm, pilot study (Hydroxyurea Safety and Organ Toxicity [HUSOFT]) of HU in very young children with SCA showed that HU treatment for infants with SCA is feasible and well tolerated, has hematologic efficacy, and may delay functional asplenia [141]. An extension study of the HUSOFT trial, in which the dose of HU was increased to up to 30 mg/kg/day, showed that infants with SCA tolerated prolonged HU therapy, with sustained hematologic benefits, fewer ACS events, and possibly preserved organ function [142]. These early studies in infants and children led to the Pediatric Hydroxyurea Phase III Clinical Trial (BABY HUG).

The main objective of BABY HUG was to determine if HU can prevent the onset of chronic end-organ damage in young children with SCA [143]. The primary endpoints of the study were splenic function (determined by qualitative uptake on 99Tc spleen scan) and renal function (determined by glomerular filtration rate by 99mTc-diethylene triamine pentaacetic acid

[DTPA] clearance). Other endpoints included blood counts, Hb F, chemistry profiles, spleen function biomarkers, urine osmolality, neurodevelopment, transcranial Doppler ultrasonography, growth, and mutagenicity [143]. A total of 96 patients received HU, and 97 patients received placebo. The study confirmed the safety and efficacy of HU therapy for infants with SCA. However, treatment with HU showed no significant differences for the primary endpoints: splenic function, or glomerular filtration rate [144].

A different prospective HU study of long-term effects (HUSTLE) showed that HU at maximum tolerated dose is associated with a decrease in hyperfiltration in young children with SCA [145]. In the BABY HUG trial, treatment with HU was associated with decreased pain (177 events in 62 patients on HU vs 375 events in 75 patients in the placebo group, $P = 0.002$), decreased dactylitis (24 events in 14 patients on HU vs 123 events in 42 patients in the placebo group, $P < 0.0001$), and decreased incidence of ACS, hospitalizations, and blood transfusions [143]. Treatment with HU increased Hb and Hb F and improved hematologic values, decreased white blood cell count, and perhaps increased preservation of organ function [143, 146].

Toxicity was limited to mild to moderate neutropenia. The TCD with Transfusions Changing to Hydroxyurea (TWiTCH) trial showed that the transition of pediatric patients from transfusion to HU was safe if they met the criteria of the study [147]. Whether this would be the same in adults remains to be seen.

Most recently, a phase 3 randomized clinical trial of L-glutamine powder in getting patients with SCA age 5 years and older demonstrated its safety and efficacy in reducing the frequency of VOCs that lead to approval by the FDA [148]. The mechanism of action of L-glutamine is the reduction of oxidative stress in sickle RBC resulting in decreased RBC

adhesion, decreased vasoocclusion, and thus, fewer VOCs. Fewer VOCs, in turn, translate into decreased mortality in SCD.

Other Novel Approaches to Therapy

A large number of novel preventive therapeutic modalities may have promising roles in the management of SCD in general and sickle cell pain in particular. These include, among other things, anti-adhesion molecules [149], surfactants [150], levocarnitine, zileuton (a 5-lipoxygenase inhibitor), green tea [151], aged garlic [151], and herbal extracts [152]. Some of these agents are being used on an investigational basis. There are anecdotal reports of success in a few patients using some of these agents. However, the efficacy of any of these agents awaits proof in Phase III, randomized, double-blind, placebo-controlled trials. Such trials will determine if a certain drug is safe, efficacious, and capable of improving the quality of life of treated patients. Recently, Singh and Ballas reviewed about 38 drugs that were tried or about to be tried in several clinical trials for the prevention of VOCs and related complications [153]. As mentioned above, the Phase III trial of senicapoc was terminated because patients who took senicapoc had more VOCs than control subjects. A Phase III trial of sildenafil to treat patients with elevated tricuspid regurgitant velocity and low exercise capacity was terminated for the same reason [154].

Abortive management

The major purpose of this approach is to abort painful VOCs thus preventing them from getting worse or precipitating other complications. In a sense, HU achieved this partially by reducing the length of hospital stay by 2 days compared to the placebo group [155]. Nitric oxide aborted VOCs in the ED but not in hospitalization [156, 157].

Curative Therapies

Allogeneic Hematopoietic Stem Cell Transplant

The only curative therapy available at present for SCD in general, and SCA in particular, is stem cell transplant. In 1998, 70 patients with SCA had undergone bone marrow transplant worldwide. By the end of the 20th century, at least 100 patients with SCA had undergone transplant worldwide [158-161]. At that time, most patients were children who received bone marrow allografts from siblings with identical human leukocyte antigen (HLA) match and who underwent myeloablative conditioning. Although the estimated risk of mortality from HLA-identical bone marrow transplant was relatively low (~5%), there was some concern regarding short-term and long-term toxicity, lack of availability of suitable donors, and barriers to wider application [162]. Nevertheless, an interim report on the impact of bone marrow transplant for symptomatic SCD found that allogeneic bone marrow transplant establishes normal erythropoiesis and is associated with increased growth and stable central nervous system imaging results and pulmonary function in most patients [158]. Things have changed for the better since 2000; some of the barriers have been overcome, and more patients are awaiting appropriate donors for transplant. The advent of high-resolution HLA typing, the choice of stem cell sources (bone marrow, peripheral blood or cord blood), less toxic conditioning regimens, new immunosuppressive agents, facilitated immune reconstitution, and improved supportive care have made transplant a more viable option for patients with SCD [163-167]. By 2010, less than 500 patients with SCD who have undergone transplant have been reported in the Center for International Blood and Marrow Transplant Research database [163].

Allogeneic hematopoietic stem cell transplant is the only curative treatment for SCD at present. It is successful in approximately 90% of patients. Unfortunately, conventional approaches to transplant are associated with comorbidities including, among other complications, infertility, gonadal failure, and chronic **Graft Versus Host Disease (GVHD)**. The use of umbilical cord blood has been shown to be as effective as, and possibly safer than, traditional bone marrow transplant in children with SCD. The use of nonmyeloablative conditioning regimens induce mixed chimerism in transplant recipients, resulting in decreased complications of allogeneic hematopoietic stem cell transplant in adults [168-170].

Gene Therapy

Although allogeneic bone marrow transplant can cure SCD, its widespread use is limited by the availability of suitable donors and by the complication of GVHD. Gene therapy is an alternative approach to achieve a cure of SCD. In simple terms, gene therapy is the introduction of normal genes into abnormal cells, either in vitro or in vivo. One potential approach to cure SCA is to introduce a functional β^A-globin gene into hematopoietic stem cells of the affected individual to replace the abnormal β^S-globin gene [171]. Methods to achieve this goal include the following:

• Targeted insertion of the transferred gene into the endogenous globin locus by homologous recombination, such that the transferred β^A-globin gene is located in the proper chromosomal environment and expressed at the same level as endogenous β-globin. This would be the ideal approach, but it is not yet feasible in hematopoietic stem cells.

• Chimeroplasty or gene repair, which introduces chimeric oligonucleotides composed of DNA and modified RNA residues into stem cells to direct correction of the mutation in the β^S gene [172].

• Transfer of normal β^A-globin gene into hematopoietic cells via retroviral vectors that have been modified such that they do not become infective.

Recent years have witnessed significant progress in the third method mentioned above. Basically, this is stem cell gene transfer or autologous transplant, in which the patient's own stem cells are harvested from the bone marrow or peripheral blood, genetically modified, and transplanted back into the patient. Genetic modification involves the use of vectors carrying γ-globin genes for SCD or β-globin genes for β-thalassemia. This approach has already been established in mice and was successful in a Phase I/II study, with anticipated benefit for Hb disorders. Successful conversion of a patient with β-thalassemia major to transfusion independence has been reported [169, 173-176].

Conclusion

Although management of SCA continues to be primarily palliative in nature, there have been promising preventative and curative approaches to therapy. Pain management should be individualized and coupled with the proper utilization of opioid and nonopioid analgesics in order to achieve adequate pain relief. Early recognition and treatment of organ failure minimizes morbidity and improves outcome. The use of HU decreases the morbidity and mortality of SCD. Cure is possible in selected children and young adults with bone marrow, stem cell or cord blood transplantation. Future research seems to focus on refining the molecular and cellular approaches

to therapy including gene therapy and mechanisms that prevent the adhesion of sickle RBC to vascular endothelium.

Legend to Figure 1

Sequence of complications of SCA from birth through adult life. Cure is possible in selected patients. The mainstay of management in most patients is palliative, with pain management being most important. ACS, acute chest syndrome; AVN, avascular necrosis; CVA, cerebrovascular accident. (Modified from Ballas SK. Sickle cell disease: current clinical management. Semin Hematol 2001;38(4):308; with permission).

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