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IM - REVIEW

Sickle cell disease: a review for the internist

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Abstract
Sickle cell disease (SCD) is the most important hemoglobinopathy worldwide in terms of frequency and social impact, recently recognized as a global public health problem by the World Health Organization. It is a monogenic but multisystem disorder with high morbidity and mortality. Vaso-occlusion, hemolytic anemia and vasculopathy are the hallmarks of SCD pathophysiology. This review focuses both on "time-dependent" acute clinical manifestations of SCD and chronic complications commonly described in adults with SCD. The review covers a broad spectrum of topics concerning current management of SCD targeted at the internists and emergency specialists who are increasingly involved in the care of acute and chronic complications of SCD patients.

Keywords Hemoglobinopathy · Sickle cell disease · SCD management · Sickle cell crises · Time-dependent · SCD chronic complications

Sickle cell disease: a review for the internist

Sickle cell disease (SCD) is an inherited hemoglobinopathy caused by a single amino acid substitution at the sixth residue of the beta (β)-globin subunit (p.Glu6Val), which results in the production of the characteristic Hemoglobin S (HbS) [1].

Hemoglobin S displays particular biochemical characteristics [2]: when HbS is deoxygenated, it undergoes crystallization with associated polymers that deform the structure of red blood cells (RBC) (the characteristic sickle shape). Cyclic deoxygenation is associated with a reduction in cell ion and water content (cell dehydration), increased RBC density, and further acceleration of HbS polymerization that makes RBCs irreversibly sickled [3, 4]. These sickle-shaped RBCs are rigid and dysfunctional, and they play a central role in acute and chronic clinical manifestations of SCD.

First of all, the increased adhesiveness of the sickle cells causes microvascular obstructions in capillaries and small vessels, blocking blood flow with ischemic/reperfusion injury [4–6]. In microcirculation, vaso-occlusive events (VOC) result from a complex scenario, that is still only partially understood, involving the interactions between different cell types, including dense RBCs, reticulocytes, abnormally activated endothelial cells, leukocytes, platelets and plasma factors [4, 6–8] (Fig. 1). In addition, the presence of free hemoglobin (Hb) and free heme contribute to the local reduction in nitric oxide (NO) bioavailability, and high levels of pro-oxidant and pro-inflammatory agents [4, 6–8]. The increased RBC rigidity and the resultant reduced deformability causes either removal by macrophages (liver or spleen) or destruction within the circulation, leading to extra- and intra-vascular hemolytic anemia, respectively.

The HbS mutation can be inherited in homozygosis (i.e., the most frequent genotype, homozygous hemoglobin SS disease (HbSS)), or in heterozygous with other mutations, known as double heterozygous forms [2, 9]. These forms have the same characteristic clinical features as SS disease, but severity can vary. The most common double heterozygous mutation is an S mutation coupled with a thalassemia mutation (Sβ-thalassemia). This has a clinical picture similar to HbSS disease [9]. The hemoglobin C (HbC), characterized by an amino acid substitution of lysine for glutamic acid at position six of the β-hemoglobin chain (HbSC disease), causes crystallization of Hb, and in homozygous or in compound heterozygous with HbS or Hbthal mutation, is associated with forms of mild severity [1]. Other less common genetic variants associated with the clinical phenotype

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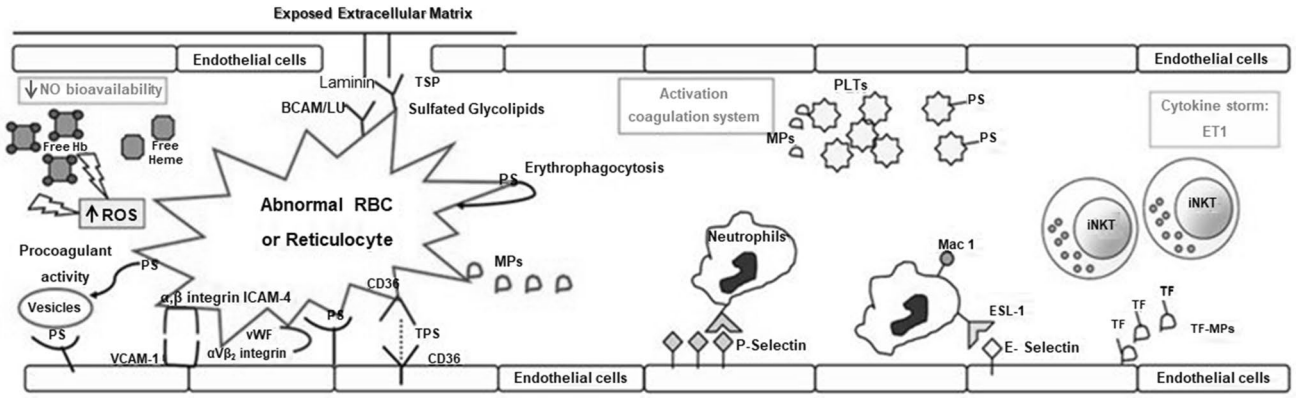

Fig. 1 Schematic diagram of the mechanisms involved in the pathogenesis of acute sickle cell-related vaso-occlusive events. These involve the adherence of sickle red blood cells (RBC) or reticulocytes and neutrophils to the abnormally activated endothelial cells, with the participation of activated and phosphatidylserine (PS)-rich platelets (PLTs), activation of the coagulation system, and the activation of a cytokine storm. *PS* phosphatidylserine, *TSP* thrombospondine, *vWF* von Willebrand factor, *BCAM/LU* Lutheran blood group protein, *ICAM-4* Landstein-Weiner blood group glycoprotein, *VCAM-1* vascular cell adhesion molecule-1, *MPs* microparticles, *TF* tissue factor, *Mac1* β2 integrins (αMβ2 or CD11b/CD18), *ESL-1* neutrophil E-selectin ligand-1, *Hb* hemoglobin, *ROS* reactive oxygen species, *iNKT* invariant natural killer T cells, *ET-1* endothelin-1, *NO* nitric oxide. (Modified from De Franceschi et al. [4])

of SCD are: HbS/D Punjab, HbS/O Arab, HbS/C Harlem [1]. The phenotypic variability could also be due to the presence of a percentage of HbF and co-inheritance of alpha (α)-thalassemia [10, 11]. The heterozygous state (sickle cell trait, HbAS) is not asymptomatic [12].

Sickle cell disease is the most important hemoglobinopathy worldwide in terms of frequency and social impact, and it has recently been recognized as a global public health problem by the World Health Organization (WHO) and the United Nations (UN) [13]. It is estimated that approximately 300,000 newborns are affected each year, and that 75% of them are born in Sub-Sahara African regions where SCD is endemic [13–15]. It is also highly prevalent in India. Approximately 100,000 individuals are affected in the United States. The number of subjects affected in Europe is estimated to be between 20,000 and 25,000, but numbers are rising steadily in many countries, e.g., in northern Europe, because of recent migration [13–16]. In Europe, SCD is found in Southern Italy, the Balkans and Greece [16]. In Italy, SCD, and in particular S/ß thalassemia, is endemic in the native population. A national hemoglobinopathy prevention campaign has kept the number of affected subjects stable [17–19]. However, over recent years, the number of affected subjects has increased to approximately 1900 [20] due to immigration from northern and central Africa, the Balkans, central and south America, and the Far East [21]. The life expectancy of patients with SCD differs around the world and varies from the fifth to the seventh decade of life in well-resourced countries to the first 5 years of life for the vast majority of patients born in Africa [22–24]. Causes of death include infection, acute chest syndrome, stroke, renal failure, and pulmonary hypertension [25]. However, the frequent lack of autopsy data [26] and the fact that SCD is a multiorgan disease mean that the final cause of death is often unknown.

Physiopathological causes of complications

Vaso-occlusion, hemolytic anemia and vasculopathy are the hallmarks of SCD. Other factors such as hypercoagulability and inflammation are also involved in organ damage caused by SCD. Despite being a monogenic disorder, SCD is a multisystem disease associated with organ damage due to either acute events [pain crisis, acute chest syndrome (ACS), stroke] or from subacute events in chronic SCD in progression (pulmonary hypertension, complications affecting multiple organs, including the eyes and the kidney) and shows phenotypic variability with a wide range of severe, and even life-threatening, consequences. Thus, SCD patient care is complex and this is emerging as an important issue throughout Italy.

Acute complications commonly described in adults with sickle cell disease (Table 1)

Acute clinical manifestations of SCD are time-dependent, so patients should have clinical priority for evaluation and treatment.

The prompt identification of a sickle cell crisis, and well-timed therapeutic intervention are the most important prognostic factors, as a delay in diagnosis and/or treatment could be life threatening, especially if organs such as lung (ACS) or brain (stroke) are involved. The “Interactive

Table 1 Acute complications commonly described in adults with sickle cell disease

Complications	Risk factors	Treatment and notes
ACS (any age)	Asthma/prior ACS events/ After surgical procedure (especially abdominal)	Antibiotics: intravenous broad spectrum (es. amoxicillin/clavulanic) or intravenous cephalosporin and oral macrolide Note: if tolerate replace cephalosporin with quinolone Oxygen supplemental to maintain > 95% oxygen saturation Hydration 2 l/24 h (avoid over-hydration) Low molecular weight heparin (prophylaxis dosage) Bronchodilatators Simple blood transfusion if Hb is < 7 g/dL Eritroexchange with HbS target 30% if Hb > 8 g/dL Note: consider intensive unit transfer in case of increasing respiratory distress, signs of multisystem organ failure, decline in Hb concentration (despite simple transfusion), onset of confuse state, sepsis Pain management
Hepatobiliary complications Cholecystitis Acute choledocholithiasis (< 20 years - 40% pts, < 30 years -60%pts)	Gallstones/Gilbert syndrome	Antibiotics and surgical consultation Cholecystectomy is symptomatic gallstones, prefer laparoscopic approach
Acute hepatic sequestration (any age)	Some cases reported in literature are associated with splenic sequestration, viral infections (parvovirus B19) and bacterial infections	Simple transfusion starting with low quantity and monitoring Hb post transfusional Note: risk of hyperviscosity syndrome due to "restitution" of blood transfused; monitor Hb closely
Acute intrahepatic cholestatis (any age)	Gallstones	Urgent eritroexchange Note Attention to extrahepatic manifestations as renal failure, bleeding, diathesis, encephalopathy Risk of rapid progression in massive hepatic necrosis and fatal acute liver failure
Stroke Ischemic (children/adolescents) Hemorrhagic (young adults)	Anemia/sepsis	Hydration i.v. 1500 cc/24hours (avoid over-hydration) Neurologic consultant Eritroexchange Note Hemorrhagic: prefer manual eritroexchange to avoid bleeding risk due to anticoagulants used in an automatic separator In case of diffuse cerebral vasculopathy start transfusion regimen
Splenic sequestration (children/young adults)	Splenectomy/genotype βS/ Previous splenic sequestration events/Viral or bacterial infections/ACS	Urgent simply transfusion Antibiotics if fever Urgent treatment if shock is present Note: monitor very closely and carefully Hb value and spleen size

Table 1 (continued)

Complications	Risk factors	Treatment and notes
Priapism (young adults)	Previous priapism events	Hydration i.v. 1500 cc/24 h (avoid over-hydration) Urologist consultant Surgical decompression followed by injection into the penis of sympathomimetic medication (ethyleprine) Pain management Simple transfusion or eritroexchange if surgical intervention is required (pre-operative procedure) or if penis decompression is delayed (HbS target 30%) Note: delayed diagnosis and therapy can result in erective disfunction
Acute anemia (any age)	Depends on cause	If associated with hepatic sequestration, splenic sequestration, viral infections (parvovirus B19, CMV, EBV) like aplastic crises, simply transfusion Do not transfuse in case of hyperemoltic syndrome Note: exclude anemia due to hemolysis from blood transfusion (suspect of hyperemoltic syndrome)
Fever (any age)	Splenectomy Functional asplenia	Prompt antibiotics oral or i.v If patient can't come to hospital in 2 h start amoxicillina 2 g or levofloxacina 500 mg and come to hospital asap If patient can come to hospital: ceftriaxone i.v. or i.m Note Hospitalization if fever is > 39 °C or if is necessary close observation and parental antibiotics therapy Parental antibiotics with coverage against streptococcus pneumoniae and gram negative enteric organism for children If associated shortness of breath, tachypnea or cough investigate for ACS Transfusion depends on other indications

Table 1 (continued)

Complications	Risk factors	Treatment and notes
VOC (any age)	Trigger factors as: Hypoxia and dehydration Infections Fever Vomiting Diarrhea Profuse sweating High altitude Prolonged immobility Extreme temperatures Physical stress Emotional stress Trauma Diving under water Use of diuretics Steroids and anesthetics	First evaluation of pain measured by usual analogic scale (VAS) If VAS 3–7: Hydration 2 l/24 h Paracetamol 1000 mg every 8 h (or paracetamol + codeine) for 3 days maximum or FANS ibuprofene 600 mg every 12 h for 3 days maximum After 24–48 h in case of persistence of pain add opiod like drugs as codein or tramadol 100 mg every 8 h for 3 days maximum If VAS > 7 Administration of analgesic therapy within 30 min of triage: bolus of tramadol 50 mg i.v. followed by continued infusions of Ketoralolac 0.0375 mg/kg/h; Tramadol 0.3 mg/kg/h; Metaclopramide 0.57 mg/kg/h in saline solution 0.9% 500 cc Note: in case of renal failure use doses adjusted IF VAS is unchanged after 1 h add fentanyl oral formulation 100 mg IF VAS is unchanged after balanced analgesia plus fentanyl Stop infusion and start after 1 h with infusion of morphine bolus 5 mg i.v. followed by continuous infusion 0.03 mg/kg/hour plus metoclopramide 0.023/kg/h Hydration 2 l/24 h Proton pump inhibitor Low molecular weight heparin if not neurologic symptoms (prophylaxis possible) Note: transfusion is not indicated unless there are other indications for transfusion

algorithm for the clinical management of acute events related to Sickle Cell Disease in the emergency department" (available from https://www.site-italia.org/file/Triage_SCD.pdf), published by the Società Italiana Talassemie ed Emoglobinopatie (SITE) [27–29] indicates that it is essential to provide at least a yellow tag for all patients with SCD at triage in the Emergency Department, and recommends administration of a first dose of an appropriate analgesic drug within 30 min (min) of arrival, including waiting time for triage [27–31] (Fig. 2). Prompt treatment within a similar timeframe of coronary heart disease or stroke can halt the clinical course and abort the crisis. A minimum 30% target of pain reduction measured by the Visual Analog Scale (VAS) should be reached within 2 hours (h) after access to assistance. Acute pain is the major and the most frequent symptom of SCD. It develops when sickle RBCs block blood flow in capillaries and small vessels. It can affect all tissues (e.g., chest, abdomen, joints, bone) and is the most common reason for admission to hospital for both adults and children.

Vaso-occlusive crisis (VOC)

The most common complication of SCD is an acute episode of severe pain referred to an acute VOC involving target organs such as bone, spleen, liver, kidney, lung and brain.

A key role is played by prevention of VOCs through educating patients and their caregivers on how to identify trigger factors of crises and to manage their early stages. Trigger factors are caused by hypoxia or dehydration (e.g., infections, fever, pernicious vomiting, diarrhea, profuse sweating, high altitude, diving under water, prolonged immobility, extreme temperatures, physical and emotional stress, trauma, and use of diuretics, steroids or anesthetics).

Pain management

The mainstay of pain management during sickle cell crisis is use of paracetamol or non-steroidal anti-inflammatory drugs (FANS, e.g., ketoralac), also in combination with further second-level opioid analgesics (tramadol or morphine) in the

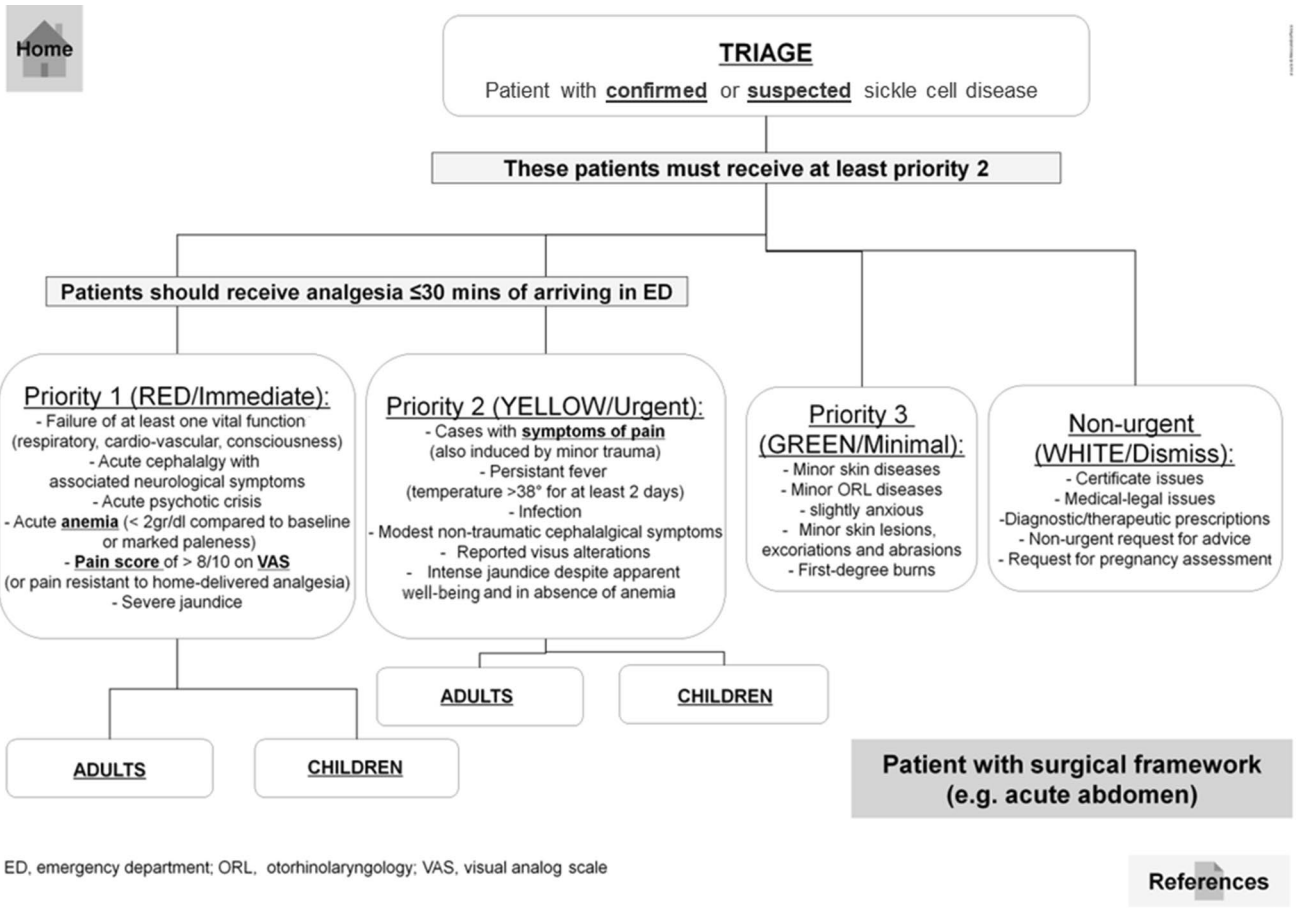

Fig. 2 Schematic representation of Triage for patient with confirmed or suspected sickle cell disease. *Mins* minutes. Each triage is code-linked to the main text where details of the related therapy or information about the differential diagnosis or the literature are provided adapted from the Società Italiana Talassemie ed Emoglobinopatie "Algoritmo per la gestione in pronto soccorso degli eventi acuti nei pazienti affetti da Anemia Falciforme" [27]

case of severe and persistent pain. In the "Interactive algorithm for the clinical management of acute events related to Sickle Cell Disease in the emergency department" [27], a 'multimodal analgesia' was introduced as an innovative approach to treat SCD-related pain. Combined use of these drugs (opioid or opioid-like plus FANS) promotes a synergistic effect by either reducing vascular and inflammatory pain (FANS) or by acting on the neuropathic (opioid) component, and, in the case of high doses, on the ischemic component. We suggest using multimodal analgesia with a bolus infusion of tramadol 50 mg followed by continuous infusion of ketorolac 0.9 mg/Kg/day (0.0375 mg/Kg/h), tramadol 7.2 mg/Kg/day (0.3 mg/Kg/h) and metoclopramide 0.57 mg/Kg/day (0.023 mg/Kg/h) in saline 0.9% 500 cc for patients with VAS > 7 [32, 33]. (For a detailed description of the management and treatment of acute pain crisis see the interactive algorithm [27, 28]). This approach reduces side effects since each molecule is used at a lower dosage to obtain the same degree of analgesia as a single molecule at a higher dosage. This is particularly important to prevent addiction to opioids, a risk of prescribing these drugs for the treatment of VOC-related pain in SCD. Opioids have a high potential for causing addiction. Individuals who become addicted may prioritize getting and using these drugs over other activities in their lives, often negatively impacting their professional and personal relationships. Opioid addiction can cause life-threatening health problems, including the risk of overdose. In acute pain setting we suggest using opioid-like drugs and/or opioids in case of persistence of pain after one hour from starting multimodal analgesia. In chronic pain (if it lasts more than 3 months) medications should be tailored to the individual and they should include not only pharmacological approaches (nonsteroidal anti-inflammatory drugs, opioids, antidepressants, and anticonvulsant) but also psychological intervention, occupational therapy, behavioral and cognitive interventions.

Transfusion is indicated when required to rapidly reduce HbS levels or to correct acute anemia (i.e., spleen sequestration, hemolytic or aplastic crisis). Viable transfusion procedures in sickle cell crises are either transfusion of packed

RBCs or RBC exchange transfusion, which can be performed manually (i.e., bloodletting followed by transfusion) or through an automatic separator. The procedures should be performed as soon as possible. Exchange transfusion is mandatory if patient Hb is > 10 g/dL in order to reduce the risk of increased blood viscosity. Manual RBC exchange transfusion is preferable in case of brain hemorrhage to avoid bleeding risk due to anticoagulants used in an automatic separator. RBC exchange transfusion is also mandatory in the case of acute intrahepatic cholestasis, which is manifested by frank jaundice associated with painful symptoms, and an increase in total bilirubin and transaminase in the absence of acute anemia [34–36]. Acute intrahepatic cholestasis is a very serious complication of SCD because it may evolve into fatal acute liver failure [35, 36].

Acute anemia, spleen and hepatic sequestration

Acute anemia can occur independently of, or concomitant with, splenomegaly (spleen sequestration), hepatomegaly (hepatic sequestration), or parvovirus B19 infections (also cytomegalovirus and Epstein-Barr virus) [2], manifesting as an aplastic crisis. It is one of the most frequent causes of chronic anemia in young adult SCD patients. A reduction in total Hb ≥ 2 g/dL from the patient's baseline value is suggestive of an erythroid-type aplastic crisis. If patients present with acute hemolytic anemia, it is important to verify if they have recently undergone blood transfusion (particularly if given at another site) in case of suspected delayed hemolytic transfusion reaction or hyperhemolytic syndrome [37]. It is important to verify this before choosing transfusion support therapy, which has a very high risk in hyperhemolytic syndrome and is, therefore, absolutely not to be recommended [37]. It is also essential to provide the blood bank with all the information available about the patient as soon as possible. An extended RBC phenotype match is recommended for all SCD patients. It is also important to carefully monitor laboratory tests before and after every transfusion, and keep an updated electronic database of patient transfusion history [37–39].

Another emergency situation characterized by acute anemia requiring transfusion is acute spleen sequestration, which can occur without previous splenomegaly in children and young adults affected by βS with splenomegaly [40]. Hepatic sequestration is also another emergency that needs transfusion therapy [41]. Acute spleen sequestration is very rare in young adults with SS or SC, which is characterized by functional asplenia following repeated splenic infarcts. All patients with SCD should be considered to be immunocompromised even if they have not undergone splenectomy.

Preventive anti-infective care among patients with SCD is crucial. The introduction of vaccinations together with the use of prophylactic penicillin in children with SCD has contributed to a reduction in childhood mortality and has improved life expectancy [42]. (For a detailed description, see the interactive algorithm "Management of infections in patients with anatomic (splenectomy) or functional asplenia" [43].).

Acute chest syndrome

Acute chest syndrome (ACS) and acute cerebral events are other emergency situations that require transfusion (simple transfusion or RBC exchange transfusion).

ACS is defined as combinations of respiratory symptoms (cough, chest pain, tachypnea, bronchospasm), and fever with evidence of new radio-density on chest X-ray [44]. Appearance on X-ray imaging could have a latency period of 24–48 h after the emergence of breathing problems/respiratory symptoms. These are a common reason for hospital admission and are a leading cause of death. Several factors have been identified as causing ACS [45]: pulmonary hypoventilation during pain crises with skeletal muscle involvement, infarction due to in situ thrombosis, and embolic phenomena due to fat and necrotic bone marrow embolism from infarcted bone marrow and venous thromboembolic disease, infectious diseases (virus, atypical bacteria *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* or *Streptococcus pneumoniae*), abdominal surgery, or mesenteric ischemia due to VOCs. Clinical presentation may include acute desaturation and/or a confused state or coma due to fat embolism. Acute renal failure and pulmonary hypertension may be present leading to multi-organ failure in severe cases. A differential diagnosis should be made with pulmonary embolism because ACS may be complicated by pulmonary embolism or may occur secondary to pulmonary embolism. A computerized tomography pulmonary angiogram is recommended if there is a high clinical suspicion of pulmonary embolism. Treatment will be required for both conditions simultaneously. Recommended treatment is intravenous cephalosporins and oral macrolide antibiotics, oxygen therapy, low molecular weight heparin, transfusion (simple transfusion or RBC exchange transfusion). ACS is more common in children with reactive airways disease, and asthma should be carefully controlled [46]. Even in the absence of wheezing, treatment with bronchodilators should be considered to prevent the development of ACS.

Cerebral acute events

The clinical presentation of cerebral acute events in SCD varies according to age. In childhood and adolescence, stroke occurs in 7.4% of subjects under 14 years of age and in 11% of those under 20 years of age [47]. In young adults, stroke may present as a bleeding event between 20 and 29 years of age and as an ischemic event in those aged over

30 years [48]. Patients with history of stroke may present throughout life permanent neurocognitive deficit associated with physical impairment such as hemiparesis, monoparesis and/or aphasia [49]. The ischemic event may expose patients to the risk of formation of brain aneurysms or constriction of the cerebral blood vessels leading to neoangiogenesis of fragile vessels, e.g., moya-moya disease, with an elevated risk of acute bleeding. Acute anemia and sepsis are trigger factors for stroke. Definitive guidelines for transfusion therapy following major cerebrovascular events in young adults are still to be defined. In cases of diffuse cerebral vasculopathy, there is a general consensus among experts to maintain a transfusion regimen also into adulthood. Stroke is an indication for hematopoietic stem cell transplantation from a sibling HLA-identical donor in childhood.

Priapism

Sickle cell disease is the most common cause of ischemic priapism, a severe complication in young males that represents a genitourinary emergency. It consists of a prolonged erection of the penis that occurs more frequently during the night hours. Prompt treatment for priapism is usually needed to prevent tissue damage (fibrosis) that could result in inability to obtain or maintain an erection (erectile dysfunction) and in poor patient quality of life. According to duration, priapism can be classified as type 1 (< 3 h, prolonged priapism) or type 2 (< 1 h, discontinued priapism). Therapy includes: hydration (saline 0.9% 1500 cc/24 h), balanced analgesia, surgical decompression where the excess blood is drained by aspiration followed by injection into the penis of sympathomimetic medication, such as ethylephrine [50]. If penis decompression is delayed, transfusion therapy (packed RBC or RBC exchange transfusion) should be given within 24 h to rapidly reduce HbS levels (HbS < 30%) and avoid erectile dysfunction [51].

Chronic complications commonly described in adults with sickle cell disease (Table 2)

Pulmonary hypertension

Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure (PAP) ≥ 25 mm Hg at rest, measured during right heart catheterization. PH is suspected if tricuspid regurgitant velocity (TRV) is > 2.5 m/s (s) measured by transthoracic echocardiography (ECHO). Predominant causes of PH in SCD are: recurrent VOCs resulting in a progressive reduction in pulmonary vascular flow and chronic hemolysis with release of free hemoglobin which neutralizes NO and catalyzes oxygen free radicals, leading to amplification of vaso-occlusive mechanisms [44]. Based on hemodynamic studies in young-adult SCD patients (SS or Sβ°), prevalence of PH has been estimated to be 6–10% [52, 53]. More than half of these diagnoses are made on the basis of evidence of postcapillary PH, suggestive of diastolic dysfunction. Precapillary PH, less common in SCD, shares the characteristics of idiopathic PH (reduced pulmonary pressure and vascular resistance). The predictive value of PH by ECHO is low (approx. 30%) when a TRV threshold of 2.5 m/s is used. Right heart catheterization is essential to define PH in the case of abnormal 6-minute walk distance (6MWD), with low pulse oxygen saturation and an increase in serum concentrations of the amino-terminal pro-B-type natriuretic peptide (NT-proBNP) associated with TRV ≥ 2.9 m/s. There are still no clear guidelines on PH treatment in SCD. General recommendations suggest: (1) intensification of medical SCD therapy (hydroxyurea, transfusion); (2) identification and treatment of triggers or disease-associated factors; (3) supportive therapies; (5) VOCs and/or ACS treatment. General therapies for PH (not targeted for physiopathology of SCD) may be useful but are still under evaluation and need to be validated for the management of PH in young adult SCD patients. Non-randomized trials have shown efficacy and safety of cGMP-specific phosphodiesterase type 5 inhibitors (PDE5 inhibitors) such as sildenafil [54, 55]which acts on smooth muscle thus promoting selective pulmonary vasodilatation; endothelin receptor antagonists (bosentan, ambrisentan) [56, 57]; prostacyclin analogs (iloprost) [58]; β- or calcium channel blockers. Prospective randomized clinical trials are needed.

Hepatopathy

Hepatic damage occurs in 10% of SCD and is heterogeneous, ranging across a wide variety of acute and chronic manifestations [34, 59]. Sickle hepatopathy may be primarily caused by the sickling process (ischemia, sequestration and intrahepatic cholestasis) or chronic hemolysis (gallstones, cholecystitis, choledocholithiasis) or may be related to the consequence of SCD treatment such as blood transfusions (liver iron overload or viral hepatitis) [34, 59]. Therefore, both SCD itself and correlated therapies may lead to hepatic damage, resulting in fibrosis/cirrhosis. In chronic liver diseases, stage of fibrosis is an important predictor of morbidity and mortality so early identification of liver fibrosis by transient elastography with specific serum markers (GGT, ALP, albumin, conjugated bilirubin) may improve outcome [60]. Hepatitis C virus (HCV) due to blood transfusions is another important factor involved in the etiology of liver fibrosis, cirrhosis, and hepatocellular carcinoma. Today, oral direct-acting antiviral drugs (DAAs) appear to be safe and effective in patients with hemoglobinopathies [61]. In a subset of patients with end stage liver disease and minimal SCD-related other organ damage, liver transplantation

Table 2 Chronic complications commonly described in adults with sickle cell disease

Complications	Risk factors	Treatment and notes
Pulmunary hypertension (PH) (young adults)	Recurrent VOCS resulting in a progressive reduction in pulmonary vascular flow Chronic hemolysis History of hypertension and leg ulcers Genotype SS Age > 40 years Proteinuria and/or kidney disease	Intensification of medical therapy of SCD Intensification and treatment of trigger factors and/or factors associated (rest, physical activity, nocturnal hypoxia, pulmonary thromboembolic disease) Treatment of VOC and ACS events Cardiologic consultant for general therapy of PH (sildenafil, bosentan, ambrisentan, iloprost, even if their efficacy and safety in SCD population were tested in not randomized trials)
Hepatic iron overload (any age)	Chronic transfusion regimen	Iron chelation therapy Deferoxamine (subcutaneous) 30–50 mg/kg over 8–12 h/day Note: attention to side effects on ear, eye, nervous system and joint Deferasirox (oral) 7–28 mg/kg Note: attention to side effects on kidney and liver
Kidney disease (young/adults)	Recurrent VOCS of medulla Sepsis Dehydratation Nephrotoxix drugs Multiorgane disfunction	ACE inhibitor therapy in case of microalbuminuria or proteinuria Prevent side effects of FANS Avoid prolonged use of FANS Recombinant erythropoietin Hemodialysis, peritoneal dialysis and renal transplantation in end stage renal disease Note: monitoring blood pressure strictly
Avascular necrosis (any age)		For early stage conservative treatment management of pain and orthopedic consultant For advanced stage orthopedic surgeon
Eye—retinopathy (youngs/adults)	Age, male-gender, high HbS levels, low HbF levels, genotype SC and Sβ	Preventive retinal photocoagulation in selected patients Preventive eritroexchange with HbS target < 40% in case of eye surgery Note: beginning at age 10 with screening for retinopaty
Legs ulcers (youngs/adults)	Hemolitic disease phenotype (low Hb, high LDH), trauma, infection, male-gender, age	Local therapy with gel hydrocolloid or low level laser therapy Zinc supplementation

may be useful [62]; around 25 cases have been reported so far. Gallstones, usually related to chronic hemolysis, are frequent in childhood, but less frequent in patients with Sβ-thalassemia or HbSC disease [1, 9]. As for other anemias with a hemolytic component, cholelithiasis/cholecystitis are frequent in SCD, and laparoscopic cholecystectomy is the treatment of choice in symptomatic patients. The presence of polymorphic (AT) repeats in the promoter of the *UGT1A1* gene in homozygous (Gilbert Syndrome) cases increases the risk of cholelithiasis.

Kidney disease

Kidney disease is a common and serious complication in young adult patients with SCD; it may occur in the sickle cell trait HbAS [12]. The ambient conditions of the renal medulla promote polymerization of HbS. Hyposthenuria, polyuria and enuresis are very early signs of kidney involvement, hyposthenuria being the most frequent. In SCD patients, renal involvement can occur throughout life. Microalbuminuria usually precedes proteinuria and may be associated with microscopic hematuria due to papillary necrosis [63]. Renal disease in SCD can also occur as tubulopathy with impaired urinary acidification in the presence of normal blood levels of aldosterone and renin. This leads to hyperkalemia due to reduced potassium tubular excretion, which is often associated with hyperuricemia. Monitoring of tubular function is important since metabolic acidosis could lead to VOC while hyperkalemia could aggravate ongoing medical therapy [diuretics and angiotensin-converting enzyme inhibitors (ACE)]. Recurrent VOCs can lead to the involvement of wide areas of medulla with massive necrosis and/or

clots that cause anemia and hydroureteronephrosis, with evolution into renal acute failure. Treatment includes hydration, analgesics, and transfusion. Management of kidney disease aims to prevent the side effects of FANS [64] and to reduce proteinuria using ACE inhibitors or angiotensin II inhibitors since proteinuria is associated with more rapid impairment of renal function [65]. Patients with proteinuria need to have their blood pressure strictly checked by ambulatory blood pressure monitoring (ABPM) with a target value of 130/70 mmHg/24 h. In SCD patients, acute kidney failure occurs at any age or stage of disease, concurrent to events such as dehydration, sepsis, administration of nephrotoxic drugs or multiple organ dysfunction [66]. Chronic kidney failure, defined as reduction of creatinine clearance < 80 ml/min, occurs in 5–30% of patients; it is usually preceded by worsening anemia [66]. In SCD, hypertension, worsening of proteinuria, or microscopic hematuria or appearance of nephrotic syndrome are all predictive factors for rapid progression to end-stage renal disease [66]. Treatment of anemia includes use of recombinant erythropoietin also in combination with hydroxycarbamide at a renal-adjusted dose. In chronic kidney failure, prolonged use of FANS should be avoided. In end-stage renal disease, hemo- and peritoneal dialysis and kidney transplant should be considered [67]. Recently, patient survival among SCD kidney recipients has greatly improved [67, 68].

Splenomegaly

Splenomegaly is more frequently found in patients with SCD βS than SS in which the spleen usually undergoes repeated infarcts due to recurrent VOCs leading to functional asplenia. It can also occur in children and young adults due to sequestration [40]. Splenectomy is indicated in cases of recurrent acute splenic sequestration crisis, hypersplenism, massive splenic infarctions and splenic abscess [69, 70].

Bone-joint diseases

Bone-joint diseases include avascular necrosis (AVN), osteomyelitis/abscess, osteopenia and osteoporosis, resulting in vertebral fragility with possible compression fracture [71]. AVN related to VOCs most commonly affects the femoral head or shoulder joint, and it should be verified and monitored by magnetic resonance imaging (MRI). Treatment consists of orthopedic surgery when there is pain or functional impairment. Conservative treatment is reserved for early stages; physiotherapy has been shown to be as effective as core decompression. Osteomyelitis/abscess are more frequent in long bones (humerus, tibia and femur) due to infections from: *Mycobacterium tuberculosis*, *Salmonella typhimurium*, enteritidis, *choleraesuis, paratyphi B*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Escherichia coli*, *Enterobacter* spp. It is often paucisintomatic and is accompanied by signs of inflammation/infection detected by traditional X-ray. Better definition is achieved by MRI that can reveal the presence of tissue edema or delimited abscess lesions. Vitamin D deficiency is highly prevalent at all ages in SCD. Investigation of prevalence and etiology of osteopenia and osteoporosis are not considered standard management procedures [72].

Eye disease

Eye involvement is very frequent in young adult patients also in the less aggressive SCD genotypes (e.g., SC or Sβthal). Annual eye tests are recommended from childhood and requested whenever patients report any change in their vision to identify and promptly treat SCD-related complications. Different clinical manifestations (proliferative or non-proliferative) are reported regarding both the anterior and the posterior segment. Clinical non-proliferative manifestations are usually non-progressive without the loss of vision rather than proliferative retinopathy that could impair vision and develop complications of vitreous hemorrhages and retinal detachment. Proliferative retinopathy occurs in 20% of adults between 40 and 60 years of age [73]. Risk factors are: age, male sex, high HbS levels, low HbF levels. Preventive retinal photocoagulation may have a role in selected patients; however, no studies report improved long-term results. During eye surgery, preventive RBC exchange is strongly recommended to maintain HbS levels under 40%.

Iron overload

Iron overload is a long-term complication of transfusion therapy and occurs when iron accumulated from transfusion exceeds the iron binding capacity, leading to iron overload in tissues. Available iron chelator drugs in SCD are deferoxamine, given parenterally, and oral deferasirox [74]. Deferoxamine is the first iron chelator used in SCD with proved efficacy, however the long parental administration (8–12 h) limits adherence to the therapy and quality of life; side effects concern ear, eye, neurological system and joint. Deferasirox is given once day, side effects concern gastrointestinal symptoms, rash, alteration in creatinine and transaminases value. Efficacy of deferasirox is similar to deferoxamine in patients regularly transfused [74]. The oral chelator deferiprone is currently not indicated and is used off-label.

Leg ulcers

Leg ulcers are usually associated with a hemolytic disease phenotype (low Hb, high LDH) at greater risk of developing PH, kidney disease and priapism. The pathogenesis is

complicated and is related to rigid and dense sickle cells in the microcirculation, venous insufficiency, local bacterial infections, dysautonomic local disorder, in situ thrombosis and hypoxia [75]. Leg ulcers are most common around the malleolar regions. They have a strong impact on patient quality of life and may cause abuse of opioid analgesics. Treatment includes: local therapy with compressive bandage [76], gel hydrocolloid or low-level laser therapy. Hydroxycarbamide, commonly used for the treatment of SCD, has been shown to be associated with leg ulceration in patients with SCD [77].

Pregnancy

Sickle cell disease-related mortality rates during pregnancy are sixfold higher than those of healthy age- and ethnic-matched populations, and are also significantly higher during delivery [78]. Women with SCD have an increased risk of preeclampsia and maternal death, preterm deliveries, and small-for-gestational-age newborns, urinary tract infections and pyelonephritis, thromboembolism, VOCs, ACS and hemolytic crisis. RBC exchange transfusion should be performed in all women with SCD to reduce the risk of complications [79]. Pregnancy in SCD requires a multidisciplinary management program including the early detection and treatment of complications during pregnancy and postpartum, follow-up by obstetric and sickle cell teams, and appropriate pain management protocols.

Sickle cell trait

The heterozygous state has also been linked to sudden death when subjects are exposed to extreme conditions (dehydration, high/low temperature) and it seems to be a risk factor for several other clinical complications, such as kidney disease and venous thromboembolism [12].

Treatment

Hydroxyurea or hydroxycarbamide (HU) is the only drug approved for SCD by the US Food and Drug Administration and the European Medicines Agency. HU is a ribonucleotide reductase inhibitor and acts in different ways by: (1) increasing fetal hemoglobin (HbF) production, reducing hemolysis and increasing NO availability by targeting cGMP production; (2) modulating endothelial activation; and (3) reducing neutrophil counts, thus helping to reduce chronic inflammation [80]. Preclinical and clinical studies have demonstrated that HU can reduce mortality and morbidity in both children and adult patients, and is safe and well tolerated in the short and long term in large cohorts of children and adults with SCD. US and European guidelines emphasize that HU should be made available to all SCD patients, both children and adults [81]. Clinical scenarios for which HU therapy is recommended are: two or more VOCs/year requiring treatment and hospitalizations, history of ACS, frequent hospitalizations. HU therapy is limited by the poor adherence of adult SCD patients due to chronic side effects of treatment, socio-economic reasons, and problems in the transition from pediatric to adult care systems.

Chronic transfusion

Red blood cell or RBC exchange transfusion is usually used to prevent acute or relapsed cerebrovascular disease, or when HU therapy is not well-tolerated or is not effective (HU non-responder), or during pregnancy. It can lead to iron overload [74] or alloimmunization [37–39]. Ensuring a good extended RBC phenotype match is recommended for all SCD patients, as well as careful monitoring of laboratory tests before and after every transfusion, and an updated electronic database of patient transfusion history [37–39]. Strategies to increase the pool of donors of African origin should also be recommended to have access to RBC phenotype typical of that population.

Bone marrow transplantation

Bone marrow transplantation from HLA-identical siblings or from umbilical CB is a curative option. It is recommended in patients under 16 years, before the onset of SCD-related organ damage. Indications to transplant are: stroke, history of frequent hospitalization for ACS or severe pain crises (> 3/year) requiring transfusion therapy [82].

Novel therapies

An improved understanding of both the pathogenesis and the pathophysiology of sickle cell-related organ damage based on mouse models for SCD has allowed new therapeutic options to be identified [83]: (1) agents that induce HbF [84]; (2) agents that reduce or prevent sickle cell dehydration and sickling (GBT440) [85]; (3) agents targeting SCD vasculopathy and sickle cell endothelial adhesive events (haptoglobin and hemopexin infusion, bosentan, selectins blockers, regadenoson, antibodies against iNKT cells, Omega-3 fatty acids supplementation, ticagrelor) [86]; and (4) anti-oxidant agents (*N*-acetyl-cysteine, L-glutamine).Various clinical trials on lentiviral gene therapy in SCD are currently ongoing worldwide and this has been shown to be safe with a good effect on phenotype [87, 88].

CRISPR/Cas9 gene-editing technology has recently emerged as a new treatment modality to correct the SCD

mutation of the β-globin gene in hematopoietic stem cells, although for the moment it is still limited to cell and/or animal-based studies [89].

Conclusion

Sickle cell disease is a multisystem disease with phenotypic variability associated with acute, chronic, and acute-on-chronic complications leading to end-organ damage and even life-threatening consequences. In the last 2 decades, knowledge of SCD pathogenesis and pathophysiology has grown with an improvement in health care and life expectancy, and new therapies. Care of SCD is highly complex and requires a multidisciplinary team approach in which the role of the internist is becoming increasingly important.

Compliance with Ethical Standards

Conflict of interest The authors declare they have no conflict of interest.

Human and animal rights statement This article does not contain any studies with human and animals performed by any of the authors.

Informed consent For this study, formal consent was not required.

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