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General review

The vaso-occlusive pain crisis in sickle cell patients: A focus on pathogenesis

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ABSTRACTS

Vaso-occlusive pain crisis (VOC) is recognized as a prominent complication of sickle cell disease, accompanied by debilitating pain and serious consequences for patients, making it the primary cause of visits to hospital emergency departments. In the etiology of VOC, the intricate interaction of endothelial cells, hypoxia, inflammation, and the coagulation system is pivotal. Hemoglobin S polymerization under hypoxic conditions leads to the formation of rigid and adhesive red blood cells that interact with vascular endothelial cells and other blood cells, causing occlusion and subsequent inflammation. Hemolysis of red blood cells results in anemia and heightened inflammation, whereas oxidative stress and involvement of the coagulation system further complicate matters. In this review, we strive to examine the pathophysiology of VOC from these mentioned aspects by consolidating findings from various studies, as a comprehensive understanding of the causes of VOC is essential for the development of targeted therapeutic interventions and the prevention and management of pain, ultimately improving the quality of life for patients.

Introduction

Sickle cell disease (SCD) stands as one of the most prevalent monogenic disorders, characterized by defective hemoglobin polymerization, leading to a disease with widespread ramifications. This condition arises from a transversion point mutation in the beta chain of hemoglobin, causing a substitution of the sixth amino acid from glutamic acid to valine. This mutation alters the solubility of hemoglobin, ultimately resulting in the formation of hemoglobin S (HbS), which transforms normally discoid red blood cells (RBCs) into a sickle-shaped form. These sickle-shaped RBCs have a shorter lifespan and higher fragility [1,2]. In SCD, the aggregation of sickle cells and their interaction with other blood cells, such as leukocytes, and subsequently with vascular endothelial cells (ECs) leads to Vaso-occlusive pain crisis (VOC). This occlusion, due to disrupted blood flow to tissues, results in serious complications, such as episodes of pain, hemolytic anemia, and organ damage throughout the body. The organs affected by this disease include the cardiothoracic system, nervous system, spleen, eyes, bones, kidneys, and reproductive urinary system. Notably, the most prominent clinical manifestation of SCD is the VOC, characterized by severe pain in various parts of the body, including the hands, feet, abdomen, and back, serving as the primary reason for patient clinic visits [3–5]. To manage pain resulting from VOC, a three-pronged approach involving pain assessment, pain measurement, and pain management is imperative,

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wherein the cause, history, intensity, and duration of pain are determined before instituting pharmacological or non-pharmacological interventions. The World Health Organization's three-step analgesic ladder guides pharmacological pain management based on the severity of pain, employing opioid and non-opioid analgesics, along with adjuvants. Non-pharmacological treatment methods, such as cold and heat compression and acupuncture, serve as complementary modalities alongside pharmacotherapy [6,7]. Given the recent focus on VOC management in various studies, this research aimed to delve into the disorder with a focus on its pathogenesis, drawing insights from studies related to SCD.

Overview of vaso-occlusive pain crisis

VOC stands as the most common complication associated with SCD, accounting for approximately 197,000 emergency department visits annually. This complication manifests in various parts of the body and in diverse forms, such as dactylitis (hand–foot syndrome), hepatic sequestration, or even chronic pain syndromes, such as chronic osteomyelitis and neuropathic pain [8]. In conditions of oxygen deficiency due to genetic defect, HbS is polymerized in the patient, leading to the formation of sickle cells and damage to RBC membranes. The compromised RBCs undergo lysis, releasing contents such as Free hemoglobin, labile iron, Oxidative stress, and more. The release of these substances triggers inflammation and activates white blood cells (WBCs), platelets (PLTs), and ECs, leading to their adhesion to each other and ultimately causing occlusion and damage to blood vessels, especially in microcirculation. Vascular occlusion, by interrupting blood supply, causes tissue damage, exacerbates ischemia-reperfusion injury, and ultimately leads to damage to limbs and organs. The culmination of these events typically results in severe pain at a specific site. Additionally, damaged vessels contribute to the occurrence of subsequent episodic pains. Damage to vital organs such as the kidneys and liver significantly impacts the quality of life for patients [9–12]. Past treatments for this complication focused on symptom relief, such as oral or parenteral hydration, analgesics, and nonsteroidal anti-inflammatory agents. However, nowadays, the use of hydroxyurea to increase Fetal hemoglobin (Hb F), Chronic transfusion therapy in high-risk patients, and hematopoietic stem cell transplantation are more prevalent. Moreover, there seems to be a future focus on targeted therapies to reduce cell adhesion and inflammation, such as the use of Oxygen affinity agents and anti-inflammatory agents, which are crucial for providing better and more definitive treatments by understanding the pathogenesis of VOC more thoroughly [13,14].

Hb S polymerization

The polymerization of Hb S is the initial pathogenic event in the development of SCD. The genetic substitution of glutamic acid with valine induces the establishment of hydrophobic interactions between valine of one hemoglobin S molecule and alanine, phenylalanine, and leucine of adjacent Hb S in the deoxy state, creating a hydrophobic patch. This patch, upon binding to the hydrophobic groove of a third Hb S molecule, forms an Hb S tetramer. Intermittent aggregation of Hb S tetramers results in the formation of double-stranded polymer chains, which subsequently combine seven units of these chains with each other to form long helical fourteen-stranded insoluble fibers or 14-member fibers [15].

The occurrence of HbS can be caused by genetic changes in patients. These changes are caused by mutations, deletions, or additions of codons, polymorphisms. These genetic changes cause the substitution of the amino acid valine for glutamine. The amino acid valine causes the polymerization of Hb S in conditions of hypoxia. Previous clinical trials showed that the reduction of expression of the BCL11A factor can play an important role in preventing the polymerization of Hb S. This reduction in expression causes the increase of expression of Hb F, which ultimately increases oxygen delivery to tissues and prevents hypoxia [16,17]. Increased Hb S production can predispose to metabolic diseases, including heart and kidney diseases. Hb S production increases intravascular hemolysis in patients. Increased hemolysis leads to a decrease in hemoglobin concentration in patients. In a meta-analysis study, patients with cerebrovascular disease had a concentration of 0.4 g/dL, and those with pulmonary artery systolic pressure and albuminuria had concentrations of 0.9 and 0.6 g/dL, respectively [18].

Kaminski et al. showed that increased Hb S levels in animal models (mice) can predispose to senescence of liver sinusoidal endothelial cells (LSEC). Therefore, disruption of LSEC can cause iron release from Hb S and lead to oxidative stress reactions. Their results also showed that lack of p-selectin expression in Hb S samples can cause a decrease in monocyte levels and lead to impaired clearance of Hb S [19]. In addition to the liver, the spleen is also damaged by Hb S. The spleen is the main site of filtration of old red blood cells. RBCs containing Hb S become trapped in the white and red pulp of the spleen. This accumulation increases iron overload and increases the incidence of inflammation. Also, stimulation of the immune system can cause autoimmune diseases. In addition, impaired spleen function can predispose patients to infection [20]. Also, exposure of Hb S patients to cold air can exacerbate the occurrence of VOC in them. Ivy et al. showed that mice with SCD, when exposed to cold, had increased activity of the Nf-kB pathway and expression of VCAM-1 and ICAM-1. Expression of these molecules caused chemotaxis of immune cells and exacerbated VOC pain [21,22].

The main factor in the occurrence of Hb S is the occurrence of mutations. To date, many new mutations have been identified in patients of different races, however, there is no specific panel that can be used to identify patients with SCD. Therefore, it is better to evaluate mutations that have a high frequency and are present in many races in future studies so that they can be used to prevent the development of Hb S and manage patients.

Endothelial dysfunction: A key driver of vascular complications in SCD

ECs line the inner surface of blood vessels, acting as a critical barrier between the vessel wall and circulating blood. They play essential roles in maintaining hemostasis, regulating vasomotor tone, and modulating immune and inflammatory responses. Dysfunction or damage to ECs is implicated in numerous vascular pathologies, including atherosclerosis and VOC in SCD [23,24]. Studies indicate that up to 50 % of SCD patients experience endothelial dysfunction, primarily due to diminished NO bioavailability [25]. This reduction results from NO scavenging by cell-free plasma hemoglobin and L-arginine depletion by cell-free arginase released from hemolyzed red blood cells. The subsequent endothelial activation triggers increased expression of adhesion molecules (VCAM-1, ICAM-1, P-selectin, and E-selectin) and platelet activation, promoting vascular occlusion and vasoconstriction, thereby exacerbating VOC [26,27].

ECs contribute to VOC through multiple mechanisms. Their structural properties provide an adhesive substrate for sickled RBCs and leukocytes, facilitating intravascular obstruction. Additionally, endothelial cells actively participate in coagulation by producing prothrombotic factors, further predisposing vessels to occlusion [28]. Moreover, ECs dynamically respond to inflammatory mediators circulating in SCD patients, amplifying the inflammatory cascade and worsening vascular dysfunction [29]. This interplay between endothelial activation, adhesion molecule expression, and inflammatory signaling is central to VOC pathogenesis, highlighting the pivotal role of endothelial dysfunction in SCD-related vascular complications.

The heterogeneity of RBCs in SCD includes a subset with compromised membrane integrity and reduced lifespan, making them highly prone to adhesion with ECs and other circulating cells. The initial attachment of sickled RBCs to ECs is mediated by P-selectin, facilitating cell-cell interactions [30]. This adhesion is further reinforced by VCAM-1, integrins, and adhesive glycoproteins such as CD36 and thrombospondin-1 (TSP-1) [31]. Recurrent endothelial damage, a

consequence of hypoxia, hemolysis, and VOC episodes, exacerbates this process by exposing subendothelial structures that deepen RBC attachment [32,33]. This cascade of events perpetuates vascular obstruction, impairing blood flow and exacerbating ischemic injury.

Endothelial dysfunction in SCD is further intensified by leukocyte recruitment and inflammation. Damage to the endothelium triggers an upregulation of adhesion molecules, promoting the binding of WBCs, particularly monocytes and neutrophils, via selectins and ICAMs [34]. Once adhered, these immune cells infiltrate the subendothelial space, initiating inflammatory pathways that further compromise vascular integrity. Oxidative stress generated by hemolysis and VOC episodes amplifies endothelial activation, creating a vicious cycle of adhesion, inflammation, and microvascular occlusion [35]. These interconnected events activate the NLRP3 pathway in endothelial cells, leading to inflammasome formation and the robust release of proinflammatory cytokines like IL-1. This inflammatory cascade ultimately drives endothelial pyroptosis, further amplifying vascular injury and systemic inflammation.

Emerging evidence suggests that CD16+ monocytes may play a protective role in mitigating endothelial dysfunction. These cells produce heme oxygenase-1 (HO-1), an enzyme that degrades heme and exerts potent anti-inflammatory effects. By breaking down free heme, HO-1 not only reduces oxidative stress but also downregulates adhesion molecule expression on ECs, thereby limiting further RBC and leukocyte attachment [36,37]. This protective mechanism highlights a potential therapeutic avenue in SCD, where enhancing HO-1 activity or increasing CD16+ monocyte populations could help alleviate endothelial damage and reduce VOC severity. Liu et al. demonstrated that increased levels of CD16+ monocytes may have a protective role against endothelial dysfunction [38]. Their results showed that these cells produce HO-1, which reduces inflammation through heme degradation while simultaneously decreasing the expression of adhesion molecules on ECs.

ECs also influence platelet behavior in VOC. The binding of platelet CD47 to endothelial TSP triggers the exhibition of α2β3 on platelet surfaces, facilitating attachment to ICAM-4 on ECs and worsening vascular occlusion [39]. Additionally, α2β3 binds to endothelial ICAM-1 via fibrinogen, reinforcing the adhesive interactions that drive vaso-occlusion. In healthy individuals, ECs maintain an anticoagulant and anti-inflammatory phenotype. However, in SCD, endothelial dysfunction shifts the hemostatic balance toward a prothrombotic state [40]. Inflammatory responses in ECs lead to heightened expression of adhesive molecules, trapping platelets and other cells while simultaneously releasing granules containing prothrombotic factors such as von Willebrand factor (VWF) and factor VIII, thereby exacerbating VOC severity [41]. Shi et al. demonstrated that in animal models, TNF-α production induced by VOC led to increased VWF expression in ECs, causing further endothelial dysfunction [42]. Conversely, administration of ADAMTS13 reduced the severity of VOC by degrading VWF, underscoring the pathological role of VWF accumulation.

Endothelial dysfunction also leads to increased expression of tissue factor, which promotes thrombin production [43]. Thrombin, upon activation and binding to protease-activating receptors (PARs) on ECs, exacerbates vascular and endothelial damage, further compounding VOC severity [44]. One of the most critical functions of ECs is the production of NO, which initiates a cGMP-dependent signaling cascade that inhibits vasoconstriction, platelet aggregation, leukocyte adhesion, and cell proliferation [45]. In SCD, maladaptive dysfunction in endothelial nitric oxide synthase (eNOS) further impairs NO availability. This dysfunction arises from decreased levels of arginine and tetrahydrobiopterin (BH4) and increased concentrations of steric inhibitors such as asymmetric dimethylarginine (ADMA), which shift eNOS activity toward superoxide production instead of NO, resulting in inflammation and vascular constriction [46]. Additionally, hemolysis-released factors and inflammatory cytokines, such as TNF-α, elevate arginase activity in ECs, leading to decreased arginine availability [47]. The accumulation of arginase in circulation further exacerbates ADMA-mediated inhibition of eNOS [46]. Moreover, NO interacts with superoxide to form peroxynitrite, which oxidizes BH4, thereby perpetuating eNOS dysfunction and exacerbating vascular injury [48].

Given the critical role of inflammation and oxidative stress-related pathways in endothelial dysfunction, precise identification of these signaling mechanisms is essential for developing targeted strategies to manage endothelial dysfunction and prevent VOC exacerbation in SCD. Notably, the impaired vasodilatory function of ECs, driven by NO depletion and eNOS dysfunction, exacerbates vascular constriction and reduces perfusion, further limiting oxygen delivery to tissues [49]. This restriction in blood flow, coupled with increased RBC adhesion and microvascular occlusion, fosters localized hypoxia, a key driver of HbS polymerization, erythrocyte sickling, and subsequent hemolysis. As hypoxia intensifies, it triggers maladaptive cellular responses, reinforcing the cycle of endothelial injury, oxidative stress, and VOC progression. Understanding the interplay between endothelial dysfunction and hypoxia is crucial for developing therapeutic strategies aimed at breaking this vicious cycle in SCD.

Hypoxia as a central driver of sickle cell pathophysiology

Oxygen desaturation is a hallmark of SCD, where arterial partial pressure of oxygen (PO_2) correlates positively with Hb and Hb F levels while inversely associating with WBC count [50]. This inverse correlation reflects the complex interplay of chronic inflammation, hemolysis, and endothelial dysfunction, which collectively impair oxygen transport and exacerbate tissue hypoxia. Notably, a strong relationship exists between oxygen desaturation and the prevalence of dense RBCs, erythrocytes with elevated intracellular Hb S concentrations [51]. These cells are highly prone to sickling, further amplifying hypoxia-induced vascular injury and setting the stage for a self-perpetuating cycle of erythrocyte sickling, hemolysis, VOC, and progressive tissue damage [52,53].

Oxyhemoglobin desaturation in SCD arises from multiple interrelated mechanisms, each of which contributes to systemic hypoxia. A key driver is the rightward shift of the (ODC), which reflects a decreased affinity of Hb for oxygen and a corresponding increase in P50 (the partial pressure of O_2 at which hemoglobin is 50 % saturated) [54]. This shift is primarily mediated by the intrinsically low O_2 affinity of Hb S and the compensatory upregulation of 2,3-diphosphoglycerate (2,3-DPG) in response to chronic anemia [55]. While this metabolic adaptation enhances peripheral oxygen unloading, it paradoxically promotes deoxygenated Hb S polymerization, increasing erythrocyte sickling and vascular obstruction [56].

Further compounding hypoxia is the accumulation of dysfunctional hemoglobin derivatives, such as carboxyhemoglobin (COHb) and methemoglobin (MetHb), which result from chronic oxidative stress and hemolysis. These dyshemoglobins have impaired O_2-binding capacity, further reducing arterial oxygen saturation and exacerbating systemic hypoxia [57]. The combined effects of anemia, dysregulated ODC, and dyshemoglobin accumulation create a state of profound oxygen deprivation, particularly in the microvasculature, where VOCs and ischemia-reperfusion injury drive progressive organ damage.

Microvascular occlusion, hemolysis, and hypoxia-driven vascular dysfunction

The altered morphology and adhesive properties of sickled RBCs further intensify hypoxia through two primary mechanisms: [1] a reduced oxygen-carrying capacity due to chronic hemolytic anemia and [2] impaired microvascular perfusion due to sickled RBC adhesion and aggregation [58]. The premature destruction of erythrocytes drastically diminishes systemic oxygen transport, while the obstruction of capillaries by sickled RBCs disrupts local blood flow, creating ischemic microenvironments that perpetuate tissue hypoxia [59,60].

A crucial amplification mechanism in this hypoxic cascade is the dysregulation of NO homeostasis. Hemolysis releases free Hb into circulation, where it scavenges NO with high affinity, effectively neutralizing its vasodilatory function. In parallel, oxidative stress and inflammatory cytokines such as TNF-α impair eNOS activity, further depleting NO bioavailability. This dysregulation initiates a vicious cycle of vasoconstriction, increased endothelial adhesion, and further microvascular occlusion, exacerbating oxygen deprivation and promoting VOC [61].

The activation of HO-1 in response to hemolysis represents a critical yet paradoxical adaptation to hypoxia in SCD . HO-1, a cytoprotective enzyme induced by oxidative stress and heme overload, degrades free heme into biliverdin, carbon monoxide (CO), and free iron [62]. While CO can exert vasoprotective effects by enhancing NO signaling and limiting oxidative injury, excess free iron contributes to Fenton reactions, generating ROS that further exacerbate endothelial dysfunction and inflammation [63]. Thus, although HO-1 induction offers temporary protection against hemolysis-induced oxidative damage, its long-term effects in SCD are double-edged, as chronic HO-1 overexpression may potentiate endothelial dysfunction and promote VOC severity [64].

Hypoxia, vaso-occlusion, and the amplification of disease severity

VOC represents the most overt clinical manifestation of this hypoxic cascade, where localized ischemia triggers severe pain, endothelial activation, and end-organ damage [63]. VOC itself exacerbates systemic hypoxia by further obstructing blood flow, inducing widespread ischemia, and compromising oxygen delivery [65]. The ensuing hypoxic stress triggers a suite of maladaptive cellular responses that reinforce erythrocyte sickling and hemolysis [66,67].

A key component of this hypoxia-driven pathology is the extracellular accumulation of ATP, released from lysed RBCs. ATP is rapidly metabolized to adenosine, which binds to adenosine receptor A2B (ADORA2B) and induces upregulation of 2,3-DPG synthesis, thereby further reducing Hb O_2 affinity and exacerbating erythrocyte sickling [64]. The role of hypoxia-inducible factors (HIFs), particularly HIF-1α, is also pivotal in regulating the cellular response to hypoxia. HIF-1α increases ADORA2B expression, reinforcing RBC sickling and vascular occlusion [68]. However, HIF-1α also upregulates HO-1, contributing to heme degradation and bilirubin production, which can have both protective and pathological effects in the SCD vasculature [69].

Animal models suggest that hypoxia triggers compensatory increases in plasma hemopexin (Hx) and haptoglobin (Hp), two scavenger proteins that reduce the oxidative burden of free hemoglobin and heme, mitigating hemolysis-related endothelial injury. However, whether these protective mechanisms sufficiently counteract VOC-induced hypoxia in human SCD remains uncertain [70].

The hypoxia paradox: A double-edged sword in SCD

The interplay between hypoxia, erythrocyte sickling, hemolysis, endothelial dysfunction, and vaso-occlusion establishes a self-perpetuating cycle that defines SCD pathophysiology. Hypoxia both initiates and sustains VOC, amplifying oxidative stress, systemic inflammation, and endothelial dysfunction. However, its effects are paradoxical, while oxygen therapy transiently reduces the proportion of reversibly sickled cells, it does not appear to significantly alter VOC duration or severity [71–73]. Clinical studies suggest that oxygen supplementation fails to provide significant analgesic benefit during VOC, raising questions about its therapeutic efficacy [74]. This paradox underscores the need to differentiate between adaptive and maladaptive hypoxic responses in SCD.

Given the dual role of hypoxia in SCD, further research is essential to clarify its precise contribution to disease pathophysiology and therapeutic outcomes. Understanding how hypoxia-driven signaling pathways, particularly those involving HIF-1α, HO-1, and ADORA2B, shape the course of VOC could lead to novel therapeutic interventions aimed at disrupting the vicious cycle of erythrocyte sickling, hemolysis, and vascular occlusion. By targeting the maladaptive responses to hypoxia while preserving protective mechanisms, new treatment strategies may emerge to mitigate SCD severity and improve patient outcomes.

Hemolysis-Driven inflammation and its role in vaso-occlusion

The chronic hemolysis of sickled RBCs in SCD serves as a potent trigger for systemic inflammation, exacerbating vascular dysfunction and VOC. Approximately one-third of hemolysis occurs intravascularly, leading to the uncontrolled release of cell-free Hb and heme into circulation [75]. Under normal conditions, free Hb is rapidly sequestered by haptoglobin, while free heme is neutralized by hemopexin. However, in SCD, persistent hemolysis overwhelms these scavenging systems, allowing excess Hb to scavenge NO, thereby depleting its bioavailability and promoting endothelial dysfunction and vasoconstriction [76]. Beyond this, the accumulation of cell-free heme and iron catalyzes the generation of ROS, driving oxidative stress beyond the body's antioxidant capacity [77].

The oxidative environment in SCD is fueled by multiple converging pathways, including HbS autoxidation [78], increased xanthine oxidase (XO) activity [79], heightened NADPH oxidase activation [80], and excessive ROS production by cytochrome P450 and cyclooxygenase enzymes [81]. The cumulative oxidative burden damages ECs, activates inflammatory pathways, and upregulates adhesion molecule expression, fostering leukocyte and platelet recruitment to the vascular endothelium, hallmark features of VOC.

Innate immune activation and the amplification of inflammation

The release of damage-associated molecular patterns (DAMPs), including heme, ATP, mitochondrial DNA, and heat shock proteins (HSPs), further amplifies inflammation by engaging pattern recognition receptors (PRRs) such as toll-like receptors (TLRs) expressed on macrophages, ECs, and platelets [82]. This activation triggers inflammasome formation, a cytoplasmic protein complex composed of apoptosis-associated speck-like protein containing a CARD (ASC) and procaspase-1 [83]. The inflammasome, once activated, converts pro-IL-1β and pro-IL-18 into their mature, bioactive forms, igniting acute inflammation and triggering pyroptosis, a highly inflammatory form of programmed cell death (Fig. 1) [84,85].

Additionally, inflammatory mediators such as interleukin (IL)-23, released by tissue-resident macrophages and dendritic cells, stimulate T cells to produce IL-17A, which in turn promotes granulocyte colony-stimulating factor (G-CSF)-driven neutrophil recruitment [86]. These neutrophils infiltrate the vascular endothelium through adhesion molecules and chemokines, further intensifying endothelial damage. Activated neutrophils also form neutrophil extracellular traps (NETs) web-like chromatin structures laced with antimicrobial proteins that ensnare RBCs and platelets, solidifying vascular occlusions and perpetuating VOC [87].

Meanwhile, activated platelets serve as key inflammatory mediators by secreting IL-8 via NF-κB-dependent pathways, further enhancing neutrophil activation and NETosis [88]. Platelets also release IL-1β, TNFSF14, and IL-6, reinforcing the inflammatory cascade [89]. This interdependent network of endothelial, neutrophil, and platelet activation establishes a self-sustaining loop that intensifies vaso-occlusion (Fig. 1).

Invariant natural killer T (iNKT) cells and complement pathway activation

Beyond neutrophils and platelets, invariant iNKT cells are increasingly recognized as crucial mediators of SCD inflammation. These glycolipid-reactive cells are activated by damage-associated lipids released from injured tissues. Upon activation, iNKT cells secrete

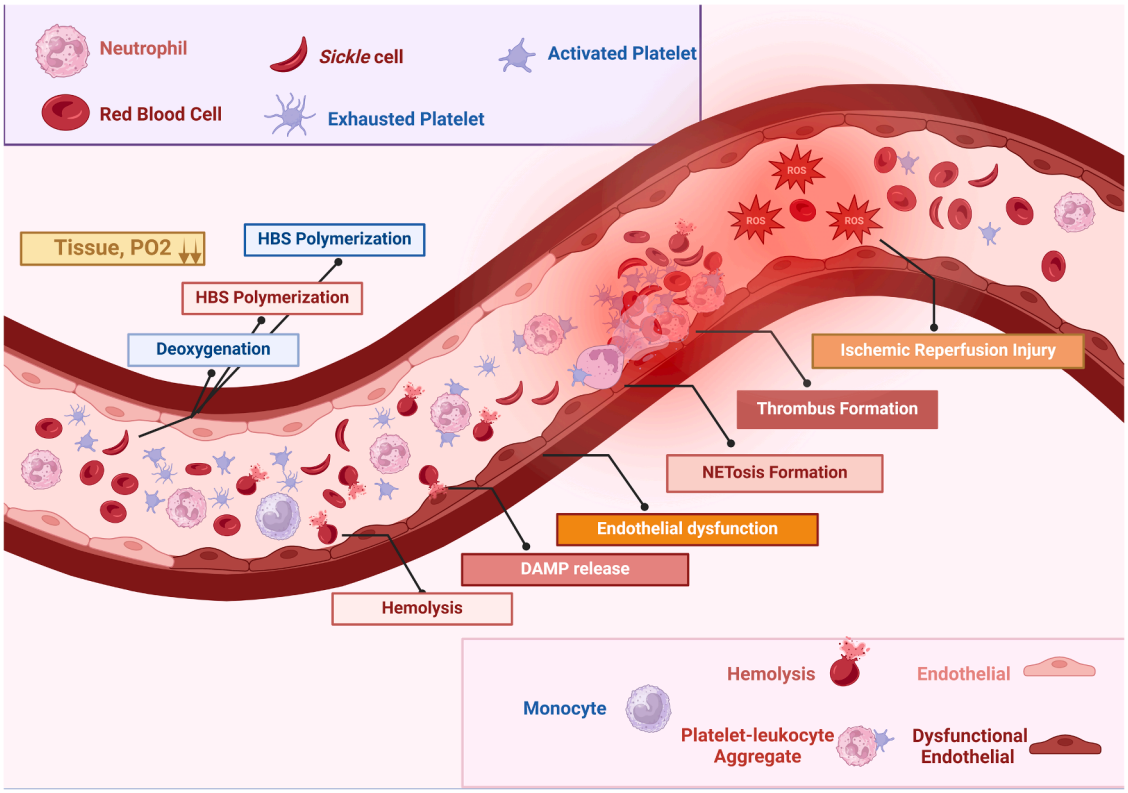

Fig. 1. Pathogenesis of Vaso-occlusive Crisis
Under conditions of low oxygen availability, hemoglobin S undergoes polymerization, driving the formation of sickled erythrocytes. This process precipitates extensive hemolysis, releasing large quantities of cell-free hemoglobin and DAMPs into circulation. Beyond exacerbating endothelial dysfunction, these factors trigger the activation of both platelets and leukocytes, fostering their aggregation and amplifying intercellular crosstalk. This hyperactivation culminates in NET formation, a key driver of thromboinflammation, ultimately fueling the pathogenesis of VOC. Compounding this pathology, ischemia-reperfusion injury ensues upon reoxygenation, intensifying cellular necrosis and generating a surge of reactive oxygen species (ROS). This oxidative burden, alongside persistent vascular injury, further deteriorates patient outcomes, perpetuating the cycle of inflammation and vascular occlusion in sickle cell disease.
DAMPs: damage-associated molecular patterns, **NETs**: neutrophil extracellular trap, **ROS**: reactive oxygen species, **VOC**: vaso-occlusive crises.

interferon-γ and CXCR3 ligands, further recruiting neutrophils and amplifying inflammatory damage [90]. Notably, iNKT cell activation is elevated during VOC, underscoring their role in exacerbating acute vaso-occlusive events

The complement system, another key player in inflammation, is also dysregulated in SCD [91]. Heme-mediated endothelial activation triggers exocytosis of Weibel-Palade bodies, leading to P-selectin expression. P-selectin binds to C3b, initiating complement activation and amplifying inflammation [92]. Additionally, heme directly stimulates the release of C5a and the membrane attack complex (C5b-9), further exacerbating endothelial injury through NF-κB-mediated inflammatory signaling [93].

Ischemia-Reperfusion injury: A catalyst for persistent inflammation

Ischemia-reperfusion (I/R) injury, a pathological consequence of transient blood flow restoration following vaso-occlusion, serves as a potent catalyst for sustained inflammation in SCD [94]. The abrupt reoxygenation of previously ischemic tissues triggers a cascade of oxidative and metabolic disturbances, prominently characterized by a surge in ROS production and intracellular calcium overload. This oxidative burst perturbs cellular homeostasis, exacerbating endothelial dysfunction, promoting leukocyte-endothelial interactions, and intensifying nociceptive signaling, which collectively contribute to heightened pain perception and a self-perpetuating inflammatory milieu [95].

A hallmark of I/R injury in SCD is excessive ROS generation, driven by mitochondrial dysfunction, NADPH oxidase activation, and xanthine oxidase activity [94]. This oxidative stress disrupts redox balance, leading to lipid peroxidation, protein oxidation, and endothelial barrier dysfunction, which further aggravate vascular injury [35]. Simultaneously, intracellular calcium overload contributes to endothelial activation, increased vascular permeability, and hypercoagulability, reinforcing the cycle of recurrent vaso-occlusive episodes. The oxidative stress and endothelial dysfunction promote the upregulation of adhesion molecules such as P-selectin and E-selectin, enhancing leukocyte-endothelial interactions and facilitating leukocyte and platelet adhesion, which further obstructs microvascular flow [96].

Beyond its vascular effects, I/R injury also exacerbates pain crises in SCD. ROS and inflammatory mediators sensitize nociceptors, amplifying pain perception and establishing a feedforward loop of neurogenic inflammation. Moreover, the release of DAMPs, including ATP and high-mobility group box 1 (HMGB1), engages pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), triggering inflammasome activation and excessive cytokine release. This inflammatory cascade not only worsens acute vaso-occlusive pain but also contributes to chronic pain and progressive organ damage in SCD [81].

Collectively, I/R injury serves as a critical driver of vascular dysfunction, systemic inflammation, and pain sensitization in SCD. By perpetuating oxidative stress, endothelial activation, and immune dysregulation, it plays a central role in disease severity and progression, increasing the risk of long-term complications [80,81].

The inflammatory-voc cycle: A therapeutic target

The bidirectional relationship between inflammation and VOC

creates a vicious cycle wherein recurrent vaso-occlusion triggers escalating inflammatory responses, which, in turn, predispose patients to further VOC episodes. Studies reveal that inflammatory cytokines, particularly IL-8 and IL-17, are significantly elevated in patients experiencing VOC compared to those in steady state [97,98]. Consequently, targeting inflammatory pathways has emerged as a promising strategy in SCD management. Recent efforts have focused on modulating inflammatory mediators and disrupting leukocyte-endothelial interactions to mitigate VOC severity and improve patient outcomes [99]. By addressing inflammation at its core, novel therapies have the potential to break this self-perpetuating cycle, reducing VOC frequency and minimizing long-term vascular complications in SCD.

Coagulation disorders and platelet activation in sickle cell disease

Coagulation abnormalities represent a critical factor in the pathogenesis and exacerbation of VOC in SCD patients [100]. The complex interplay between platelets, neutrophils, and ECs significantly contributes to the inflammatory milieu that underpins VOC [101]. Elevated serotonin levels, commonly observed in SCD patients, are a key factor in this process [102]. Increased serotonin secretion promotes the chemotaxis of CXCR4hi neutrophils towards ECs, a process that subsequently triggers platelet aggregation and activation [103]. This interaction leads to the formation of platelet-neutrophil aggregates, which intensify the inflammatory response [104]. Further activation of neutrophils through caspase-4/11 signaling leads to the formation of gasdermin D (GSDMD) [105]. This process is closely linked to NETosis, where neutrophils release nuclear content, forming extracellular traps. These structures not only contribute to local inflammation but also promote thrombotic events by inducing platelet aggregation. The migration of activated platelets from the liver to the lungs can result in thromboembolism, which complicates VOC and exacerbates pain crises [106].

In vitro studies, such as those conducted by Bennewitz et al. [107]., have highlighted the role of endotoxin-induced platelet-neutrophil interactions in VOC pathogenesis. Their research demonstrated that LPS-induced activation of ECs upregulated P-selectin on platelets and Mac-1 on neutrophils. The reciprocal interaction between these markers activated the coagulation cascade and caused vasoconstriction, both of which contributed to the exacerbation of VOC. Dietary interventions, such as alpha-linolenic acid (ALA) supplementation, have also been shown to influence platelet-neutrophil interactions by increasing P-selectin and PSGL-1 expression, though it did not affect platelet activation via GpIbα shedding or αIIbβ3 integrin inactivation [108].

In addition to P-selectin, TSP-1, another platelet-derived protein, plays a crucial role in the progression of VOC. Elevated TSP-1 levels in SCD patients are associated with increased disease severity, with TSP-1 emerging as a potential biomarker for crisis episodes [109]. Platelet activation also leads to the expression of tissue factor (TF) on various cells, including ECs. TF induces the expression of protease-activated receptor-1 (PAR-1) on ECs, promoting the chemotaxis of immune cells and the release of inflammatory mediators, which, in turn, perpetuate platelet activation and exacerbate the inflammatory state [110].

Moreover, studies have shown that during high-severity VOC episodes, VWF multimer levels are elevated. This increase in VWF contributes to platelet aggregation and a subsequent decrease in platelet count, providing a potential biomarker for thrombosis and exacerbation of VOC [111]. Similarly, elevated homocysteine levels in VOC patients have been linked to the induction of P-selectin expression, facilitating platelet adhesion to ECs and contributing to thrombosis [112].

Biomarkers for monitoring platelet activation and thrombosis in VOC

Given the role of platelets and neutrophils in promoting thrombotic events during VOC, numerous surface markers, such as P-selectin, TSP-1, and VWF, have emerged as potential biomarkers for monitoring platelet activation and thrombosis in SCD patients [113–115]. These biomarkers can assist in assessing disease severity, guiding treatment decisions, and evaluating the efficacy of therapeutic interventions. The complex mechanisms of platelet-neutrophil interactions and coagulation abnormalities present significant therapeutic challenges but also highlight key targets for intervention. Current management of VOC largely revolves around pain relief and prevention of thrombotic events [116]. Opioids and NSAIDs remain the cornerstone of pain management, though the use of NSAIDs must be cautious in patients with renal or cardiovascular comorbidities [117–119]. For more effective management of the underlying coagulopathy, strategies such as blood transfusions to reduce sickled red blood cells and reduce blood viscosity are commonly used [120].

Emerging therapies that target the coagulation cascade, platelet activation, and neutrophil interactions could offer novel approaches to VOC management. For example, inhibitors of P-selectin and TSP-1 may be explored as adjunctive therapies to prevent platelet aggregation and thrombosis in SCD patients [121–123]. Furthermore, the potential for gene editing techniques, such as CRISPR/Cas9, to modulate the expression of pro-inflammatory and pro-thrombotic genes could provide a more targeted approach to managing the exacerbated coagulation seen in VOC.

In summary, understanding the role of platelet-neutrophil interactions and coagulation abnormalities in VOC pathogenesis opens up new avenues for therapeutic intervention. By targeting specific molecules and pathways involved in thromboinflammation, these novel strategies could significantly enhance the management of VOC and improve clinical outcomes for SCD patients.

Strategy treatment

Management of VOC-Induced pain in sickle cell disease

The management of VOC-induced pain in SCD presents a multifaceted challenge due to the complex interplay of peripheral and central nervous system mechanisms. VOC episodes are characterized by acute, severe pain that can affect multiple organs and systems, leading to debilitating symptoms and potential life-threatening complications. As such, implementing effective pain management strategies is crucial for enhancing patient quality of life and improving clinical outcomes.

Primarily, opioid analgesics are the cornerstone of pain management during VOC episodes [124]. Medications such as morphine and hydromorphone are frequently utilized for their potent analgesic properties [125]. These opioids can be administered via various routes, including oral, intravenous, or patient-controlled analgesia (PCA), allowing for tailored therapy based on the patient's needs and pain severity. For those experiencing moderate pain, non-opioid analgesics like acetaminophen or NSAIDs such as ibuprofen may be used in conjunction with opioids to provide additional relief and minimize opioid consumption [126].

Adjunct therapies play a vital role in addressing VOC-induced pain. Non-pharmacological approaches, such as heat application [127], hydration [128], and relaxation techniques [129], can complement medication regimens. Fluid replacement is an essential strategy in VOC management. Dehydration exacerbates blood viscosity, which in turn accelerates HbS polymerization and vascular occlusion, leading to increased pain. By restoring fluid balance, the viscosity of the blood is reduced, improving overall circulation and mitigating VOC-associated pain.Additionally, the use of adjuvant medications, including gabapentin or pregabalin, may help manage neuropathic pain components associated with prolonged VOCs [130].

In conclusion, the management of VOC-induced pain in sickle cell disease requires a comprehensive and individualized approach that encompasses both pharmacologic and non-pharmacologic interventions. By effectively addressing pain, healthcare providers can significantly enhance patient outcomes, reduce complications, and foster a better quality of life for individuals living with SCD. The

collaborative effort of a multidisciplinary team is vital to ensure optimal pain control and ongoing support for patients navigating the complexities of this challenging condition (Table 1).

Blood transfusion therapy

Red blood cell transfusions, a key therapeutic option for VOC management, aim to alleviate the blockage caused by sickle-shaped red blood cells. By replacing these dysfunctional cells with normal red blood cells, transfusions improve oxygen delivery to tissues and reduce the likelihood of VOC. This approach has been shown to significantly reduce the frequency and severity of VOC episodes in SCD patients [139–141].

Fetal hemoglobin (HbF) inducers

One promising pharmacologic strategy to manage VOC is the induction of HbF, which inhibits HbS polymerization. Hydroxyurea, a well-established HbF inducer, has demonstrated efficacy in reducing VOC frequency and improving overall clinical outcomes in SCD patients [142]. Recent studies have also explored additional HbF-inducing agents, such as decitabine in combination with tetrahyrouridine, which have shown promising results in early-phase clinical trials, increasing HbF production without intolerable side effects (Fig. 2) [133].

Gene therapy and CRISPR/Cas9-Based approaches

Recent breakthroughs in gene therapy, particularly CRISPR/Cas9-based gene editing, are redefining the therapeutic landscape for VOC in SCD. This cutting-edge technology offers a potentially curative approach by reactivating HbF production and directly correcting the genetic mutation responsible for HbS polymerization [143]. By precisely targeting regulatory elements of the γ-globin gene, CRISPR/Cas9 overrides the fetal-to-adult hemoglobin switch, restoring HbF expression and preventing sickling-induced vascular occlusion [144].

CRISPR-mediated strategies disrupt key transcriptional repressors, such as BCL11A and LRF (ZBTB7A), effectively lifting the suppression of γ-globin and ensuring sustained HbF synthesis [145]. Additionally, direct correction of the pathogenic mutation in the β-globin gene (HBB) restores normal hemoglobin function, while modifications in erythroid-specific regulatory elements further enhance HbF persistence [146]. These mechanisms collectively diminish HbS polymerization, reduce hemolysis, and alleviate the chronic inflammation and endothelial dysfunction that fuel VOC episodes.

Despite its transformative potential, CRISPR-based therapy presents critical challenges, including optimizing editing efficiency, minimizing off-target effects, and ensuring the long-term safety of genetically modified hematopoietic stem cells. Moreover, ethical considerations surrounding gene editing, particularly in germline modifications, and the accessibility of these high-cost treatments in low-resource settings must be addressed.

Ongoing clinical trials and preclinical investigations are refining gene-editing techniques, enhancing delivery methods, and establishing robust safety profiles. If successfully translated into widespread clinical application, CRISPR/Cas9 could fundamentally alter the course of SCD, offering patients a durable, potentially curative alternative that

Table 1
Current Clinical study on VOC treatment.

Author	Study phase/trial type	Agent	outcome	Mechanisms	Ref
Howard J et al	Phase I and II, randomized, placebo-controlled trial	Voxelotor, formerly known as GBT440	Drug was well tolerated, and pharmacodynamic data established the proof-of-mechanism of voxelotor for increasing hemoglobin oxygen affinity in the RBC	Increases hemoglobin's affinity for oxygen, thus preventing the polymerization of HbS.	[131]
Reid ME et al	Phase II study randomized, placebo-controlled trial	HQK-1001	The study yielded disappointing results, revealing no significant increase in HbF levels and indicating a concerning trend of increased pain crises in the HQK-1001 group.	Elevate HbF levels, resulting in better outcomes and a reduced incidence of VOCs.	[132]
Molokie R et al	Phase I study, placebo-controlled trial	Decitabine and tetrahydrouridine	The study results demonstrated significant increases in HbF and total hemoglobin, along with improvements in hemolysis, coagulation, and inflammation biomarkers. The treatment was well tolerated and is advancing to further clinical development for individuals with SCD.	Elevate HbF levels, resulting in better outcomes and a reduced incidence of VOCs.	[133]
Field JJ et al	Phase II, randomized, placebo-controlled trial	Regadenoson	Regadenoson had no significant effect on the primary endpoint ($p = 0.07$) and did not influence hospital stay duration, parenteral opioid use, or pain levels as assessed by visual analog scale.	Regadenoson is an adenosine A2A receptor agonist that enhances the anti-inflammatory effects of invariant natural killer T (iNKT) cells, which are linked to the pathogenesis of SCD.	[134]
Joshua J Field et al	Phase I study, placebo-controlled trial	NKTT120	In adults with SCD, NKTT120 achieved rapid, specific, and sustained iNKT cell depletion without any infusion-related toxicity or serious adverse events.	NKTT120, a humanized monoclonal antibody demonstrated to induce rapid and sustained deletion of iNKT cells in SCD patients.	[135]
Daak AA et al	Phase I study, placebo-controlled trial	Omega-3 fatty acids eicosapentaenoic acid (EPA)	In the EPA treated group, the rate of clinical VOCs was significantly lower than in the placebo group (0 vs. 1 per year; $p < 0.0001$), with reduced hospitalization days due to VOCs ($p < 0.05$) and fewer annualized VOCs.	EPA exert anti-inflammatory effects as substrates for cyclooxygenases and lipoxygenases, generating anti-inflammatory leukotrienes, thromboxane, and lipoxins, while also offering antiplatelet and antioxidant benefits.	[136]
Hoppe CC et al	Phase III, placebo-controlled DOVE trial	Prasugrel	Prasugrel showed no significant effect on secondary endpoints. Although the reduction in VOCs was greater in participants aged 12–17 and those not on HU, the study was not designed to confirm age-specific improvements in VOCs.	Anti-platelet drug	[137]
Ataga KI et al.	phase II SUSTAIN trial	Crizanlizumab	Crizanlizumab significantly reduced the median crisis rate per year during the treatment period. Get smarter answer from GPT-4°	Crizanlizumab is a humanized monoclonal antibody that functions by binding to P-selectin, effectively inhibiting its interaction with PSGL-1. This mechanism reduces cell adhesion and inflammation, contributing to its therapeutic effects.	[138]

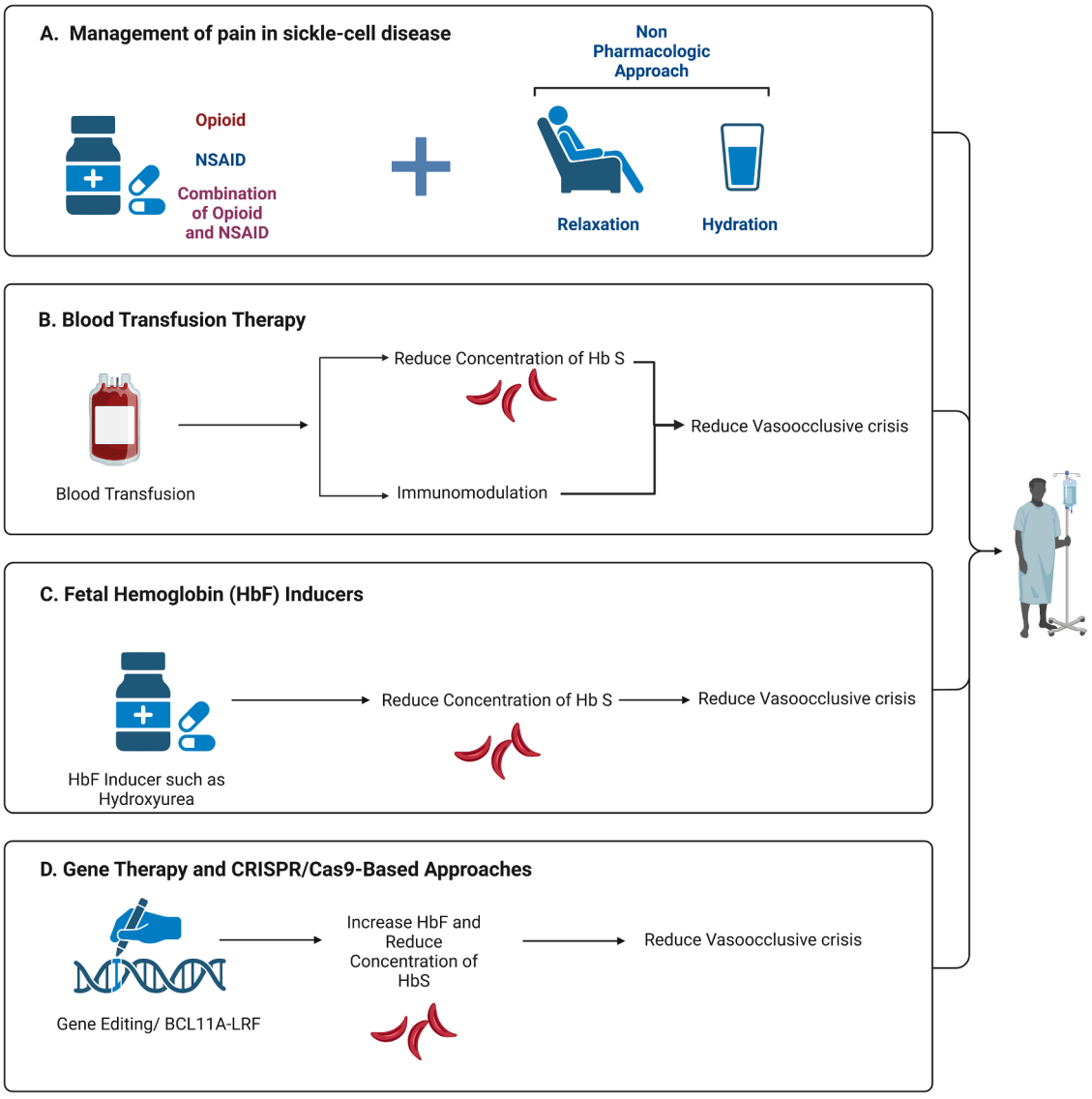

Fig. 2. Therapeutic Approaches for Sickle Cell Disease
Multiple strategies are employed to manage SCD and mitigate VOC:
(A) **Pain Management:** Pain control remains a cornerstone of SCD treatment, encompassing both pharmacologic interventions—such as opioid and non-opioid analgesics—and non-pharmacologic approaches, including relaxation techniques and adequate hydration.
(B) **Blood Transfusion Therapy:** Transfusions effectively lower HbS concentrations while simultaneously exerting immunomodulatory effects, collectively reducing the severity and frequency of VOC and associated complications.
(C) **Fetal Hemoglobin (HbF) Induction:** Pharmacologic agents that promote HbF synthesis serve as a promising therapeutic avenue by enhancing oxygenation and reducing HbS polymerization, thereby mitigating sickling and vascular dysfunction.
(D) **CRISPR-Cas9 Gene Editing:** Gene-editing technologies offer a cutting-edge approach by upregulating or suppressing key genes involved in HbF synthesis. This targeted intervention increases HbF levels while decreasing HbS, ultimately reducing VOC severity and disease complications.
VOC: vaso-occlusive crises, **SCD**: Sickle Cell Disease.

eliminates the burden of lifelong symptomatic management.

Non-Pharmacologic treatment

Transcutaneous electrical nerve stimulation (TENS) is a non-invasive and cost-effective modality that has gained attention for its ability to alleviate pain. By applying electrical currents through the skin, TENS promotes analgesia through both peripheral and central mechanisms, offering a valuable adjunct to pharmacologic therapies, especially for patients who experience inadequate pain relief from traditional medications (Fig. 2) [147].

Challenges and future directions

Despite significant progress in VOC management, challenges remain. Although some HbF-inducing agents, such as hydroxyurea, are FDA-approved, they are not without side effects, which may limit their use in certain populations [148]. Additionally, while CRISPR/Cas9 shows great promise in preclinical models, its clinical application is still in its infancy. Ethical concerns, potential long-term effects, and the need for further validation in human trials are critical issues that must be addressed before widespread adoption.

In conclusion, a multimodal approach, combining pharmacologic therapies, fluid management, blood transfusions, gene therapy, and non-invasive techniques like TENS, represents the most effective strategy for

managing VOC-induced pain in SCD patients. Continued research into novel therapies, particularly gene editing and advanced HbF inducers, holds the potential to revolutionize the treatment landscape for this challenging condition.

Conflict of interest

The authors declare that they have no conflict of interest.

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Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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