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Challenges in the Management of Sickle Cell Disease During SARS-CoV-2 Pandemic

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Abstract

The management of sickle cell disease (SCD) and its complications in the COVID-19 era is very challenging. The recurrent sickling process in SCD causes tissue hypoxemia and micro-infarcts, resulting in end organ damage. Since the outbreak of SARS-CoV-2 pandemic, little data has been published about SCD concerning clinical presentation with COVID-19 and management. Hydroxyurea has been the cornerstone of management in children and adults with SCD, with evidence of its effect on controlling end organ damage. There are several anti-sickling drugs that have been approved recently that might have an additive value toward the management of SCD and its complications. The role of simple and exchange transfusions is well established and should always be considered in the management of various complications. The value of convalescent plasma has been demonstrated in small case series, but large randomized controlled studies are still awaited. Immunomodulatory agents may play a role in reducing the damaging effects of cytokines storm that contributes to the morbidity and mortality in advanced cases. Prophylactic anticoagulation should be considered in every management protocol because SCD and COVID-19 are thrombogenic conditions. Management proposals of different presentations of patients with SCD and COVID-19 are outlined.

Keywords

sickle cell disease, SARS-CoV-2/COVID-19, hydroxyurea, L-glutamine, crizanlizumab, voxelotor, Heparin/LMWH

Introduction

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has swept the globe and has become a major public health crisis.[1] It causes coronavirus disease 2019 (COVID-19), which is a severe respiratory illness that puts patients with chronic medical illnesses at risk of increased morbidity and mortality.[2] Patients with chronic hereditary and acquired hematological diseases represent a special group of patients, many of whom have sustained end organ damage and / or immunocompromised state due to their underlying disease or treatment.[3] If infected, they will be at risk of severe respiratory complications including COVID-19 related pneumonia, acute respiratory distress syndrome (ARDS), and secondary bacterial infections.[2,4]

Sickle cell disease (SCD) is the most common hereditary hematological disorder that affects millions of people worldwide, with the highest prevalence in sub-Saharan Africa, Mediterranean basin, Middle East, and India.[5] The current experience with optimal management of SCD patients presenting with COVID-19 is still evolving given the scarcity of the published data. Our past experience with H1N1 outbreak showed high incidence of respiratory complications including acute chest syndrome (ACS).[6-8] It has also been demonstrated that children with SCD have a substantially higher rate of influenza-related hospitalizations in comparison to other children, with the rate of hospital admissions of children with SCD approximately double that of children with cystic fibrosis.[9] Thus, it is likely that such complications would be occurring at an increasing rate in patients with SCD presenting with COVID-19.

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End Organ Damage and Immune Dysfunction in SCD

SCD causes several well-known complications that can vary in intensity depending on the inherited genetic phenotypes and coexistence of other hemoglobinopathies.[10] These complications include: vasoocclusive crisis (VOC), chronic hemolytic anemia, osteopenia, ACS, pulmonary hypertension, asplenia, severe infections, stroke, kidney failure, priapism, and neurological alterations.[11] The hallmark of SCD is hemoglobin S polymerization upon deoxygenation, which causes red cells to adapt a sickle shape. This process results in impaired rheology of the blood and aggregation of sickled erythrocytes with neutrophils, platelets, and endothelial cells, thus promoting blood stasis. The result is vasoocclusion, tissue ischemia, and reperfusion injury. Hemolysis-mediated endothelial dysfunction through the release of free hemoglobin, which depletes endothelial nitric oxide (NO), results in more vasoconstriction and ischemia as well as the release of free radicles. This will result in sterile inflammation, which promotes adhesiveness of neutrophils, platelets, and endothelial cells, causing more vasoocclusion.[12,13]

The spleen, which is a lymphoid tissue with an important role in innate and adaptive immunity, is one of the first organs to be affected in SCD. There is evidence of hyposplenism present before 12 months of age in the majority of children.[14] Repeated splenic vasoocclusion leads to the formation of granuloma-like nodules, called "Gamna-Gandy bodies" (GGBs), resulting from periarteriolar hemorrhage followed by fibrosis and deposition of iron pigments, leading to progressive atrophy of the organ (auto-splenectomy), which is generally complete by 5 years in most children.[15] Hyposplenism predisposes SCD patients to infection with encapsulated bacterial organisms like Streptococcus pneumoniae and Hemophilus influenzae *type b*. This happens because of impaired opsonization and antibody production, especially IgM, which is produced by B-lymphocytes in the marginal zone.[16] In addition, the function of macrophages in the red pulp and marginal zone of the spleen will be affected. These macrophages play an important role by removing damaged, aged, and opsonized cells and bacteria from the blood. Further, these macrophages function with the dendritic cells as antigen presenting cells to T-lymphocytes in the white pulp.[13,17]

COVID-19 in SCD: Clinical Experience

The clinical experience in patients with SCD presenting with COVID-19 is inadequate at this time due to paucity of data. International registries have been initiated (International COVID-19 SCD registry and ASH Registry), in which health care providers managing SCD patients with COVID-19 are encouraged to report their cases.[18] However, there are a few small case series and case reports in the literature that can give us an insight into the clinical presentation and outcome in these patients.

In a case report, 2 patients with SCD and positive RT-PCR for SARS-CoV-2 presented with VOC. In addition, one of them had pneumonia. They responded well to conventional supportive management without the need for exchange transfusion or mechanical ventilation.[19] Another case report from New York was of a patient with Hb S/β^o-thalassemia presenting with hip pain that later evolved to hemolytic anemia, fever, and hypoxemia. After being diagnosed with COVID-19 and ACS, he required exchange transfusion, which resulted in improvement of his condition.[20]

A case series of 4 patients with SCD (2 with Hb SS, one with Hb Sβ^+, and one with Hb SC disease) and COVID-19 were managed successfully with oxygen, intravenous fluids, analgesics and antibiotics. Only one patient developed ACS and was successfully managed with exchange transfusion.[21]

A series of 10 patients from the UK with SCD and COVID-19 was recently published. Six patients were RT-PCR positive using nasopharyngeal swabs, and 4 patients tested negative but they had clinical and radiological features of COVID-19. The presenting symptoms were fever, cough, dyspnea, and hypoxia. There was great variability between patients regarding different hematological and biochemical parameters. None of the patients developed coagulopathy or thrombocytopenia. Nine patients made full recovery with supportive therapy that included prophylactic dose of Low Molecular Weight Heparin (LMWH) (enoxaparin 40 mg OD) that was later increased to the therapeutic dose after emerging evidence of the thrombotic nature of COVID-19. There was one fatality in a bedbound patient with past history of stroke.[22]

There are 2 case reports showing successful treatment of COVID-19 related pneumonia with tocilizumab, which is a humanized monoclonal antibody against the interleukin-6 (IL-6) receptor. The first case report was describing an adult male with past history of sickle cell nephropathy, tubular acidosis, retinopathy, cardiac disease and pulmonary embolism (on rivaroxaban), presenting with VOC, that progressed to COVID-19 induced pneumonia and ACS. The treatment with tocilizumab was initiated with rapid improvement of his overall condition and O2 saturation.[23] The second report was in a 16 year old girl with severe form of SCD complicated with bilateral ischemic retinopathy and recurrent VOC. Because of the aggressive nature of her disease, she had been managed with exchange transfusions until she became 11 years old and was later switched to hydroxyurea. She presented with fever and later developed severe chest pain and hypoxemia secondary to ACS. Acute pulmonary embolism was suspected because of elevated D_Dimer level and was confirmed radiologically. She was treated with anticoagulation, in addition to exchange transfusion and non-invasive ventilation. Tocilizumab was also added because of the severity of her condition and elevated IL-6 level. She made rapid recovery and was discharged from the intensive care unit without the need of O2 therapy.[24]

Approved Pharmacological Drugs for SCD in Current Clinical Practice

There is still no effective treatment for SCD that completely reverses the sickling process and eventually prevents end organ damage that starts from early childhood. Stem cell

transplantation is the only available cure for SCD. However, a limited number of patients benefit from this procedure.[25] Gene therapy is a new treatment modality that has come a long way in the last decade with promising results in recent trials.[26] Novel approaches to reduce SCD-related complications from early childhood started in the 1980s with the introduction of penicillin prophylaxis and using transcranial Doppler screening for detection of cerebral vasculopathy and stroke prevention in children.[25]

Since the late 1980s, hydroxyurea (HU) or hydroxycarbamide has emerged as an effective disease modifying agent for SCD in children and adults.[27] HU inhibits ribonucleotide reductase enzyme, which converts ribonucleotide diphosphates to deoxyribonucleotide triphosphates (dNTPs), leading to cell arrest in the S phase of the cell cycle. The mechanism of action of HU in SCD is discussed elsewhere.[25,27,28] HU lowers the rate of VOC events, the number of hospitalizations, and the need for blood transfusions. It also prevents or slows down end organ damage, which is reflected in improved survival of SCD patients.[29,30] During the H1N1 pandemic in 2009, HU was proven to be effective against the incidence of ACS in children.[7,31] Compliance is the main obstacle toward obtaining the desired effects with HU. Fear of side effects, especially infertility and possible teratogenicity, compromises compliance.[32]

Crizanlizumab has been recently approved for treatment and prevention of VOC in patients with SCD.[33] It is a monoclonal antibody that binds to P-selectin, thereby blocking its interaction with P-selectin glycoprotein ligand-1. P-selectin, an adhesion molecule expressed on activated vascular endothelial cells and platelets, facilitates cell-to-cell and cell-to-endothelium interactions that are involved in the pathogenesis of VOC in SCD.[33] The SUSTAIN trial, a multicenter randomized double blind study, showed that crizanlizumab decreased the incidence of VOC by 45% in patients with or without HU. Crizanlizumab also prolonged the median time to the first and second VOC. Adverse events were mild to moderate and no patients discontinued the treatment.[34] There are several ongoing clinical trials that are trying to explore crizanlizumab's safety and efficacy in pediatric patients with SCD.[33]

Voxelotor belongs to a new class of medications that inhibit HbS polymerization. It reversibly binds to hemoglobin, increasing its affinity for oxygen, and consequently inhibits its polymerization when subjected to hypoxic conditions.[35] In HOPE, a phase 3, double blind randomized controlled trial, 2 doses of voxelotor (1500 mg and 900 mg, administered orally once daily) were compared with placebo in persons with SCD. The primary endpoint was a hemoglobin response of 1 g/dL from baseline at week 24. Patients on 1500 mg had higher hemoglobin response in comparison to the placebo group (51% vs. 7%). In addition, patients in the voxelotor group had lower indirect bilirubin and reticulocytes count, indicating less hemolysis.[36] Based on the HOPE trial results, voxelotor was granted accelerated FDA approval for adults and pediatric patients 12 years of age and older with SCD.

L-glutamine is an amino acid that plays an important role in reducing the oxidative stress inside red cells. It is essential in the synthesis of nicotinamide adenine dinucleotide (NAD^+) and its reduced form (NADH), which play a major role in maintaining the redox balance in red cells. In sickle red cells, the redox ratio ([NADH]:[NAD+ NADH]) is lower than in normal red cells, thus contributing to the pathophysiology of SCD.[37] L-glutamine (ENDARI) was approved to manage SCD-related complications in patients 5 years of age and older. The safety and efficacy of L-glutamine was documented in a phase 3 multicenter, randomized placebo controlled study, where the pharmaceutical-grade L-glutamine (0.3 g per kg of body weight per dose) was administered twice daily by mouth, as compared with placebo. Fewer pain crises occurred in the L-glutamine group than in the placebo group ($P = 0.005$), in addition to fewer hospitalizations ($P = 0.005$). Side effects were constipation, nausea, headache, abdominal pain, cough, pain in the extremities, back pain, and chest pain.[38]

Supportive Therapeutic Modalities in SCD

Simple red cell and exchange transfusion play an important role in managing children and adults with SCD. Simple red cell transfusion is often required in treating anemia that accompanies acute hemolytic crises, splenic sequestration, anemia associated with parvovirus B19 infection, perioperative management, and anemia in pregnancy.[10,11] Regular red cell transfusion is also recommended for primary and secondary stroke prevention in children with SCD.[39] The most common transfusion-related complications are alloimmunization, infection, and iron overload. Red cell exchange transfusion is indicated in ACS, acute stroke, major organ failure, and priapism that doesn't respond to conservative measures.[40]

Venous thromboembolism (VTE) is a major risk in acutely ill medical patients. In patients with SCD with an acute medical illness, the risk of VTE is even higher. A study in the United States reported the overall prevalence of pulmonary embolism (PE) in patients with SCD to be 4 times higher in comparison to those without SCD.[41] In another study, using a large cohort of SCD patients ($n = 6,237$) in California, the incidence of VTE by age 40 was 17.1% for SCD patients with severe disease (hospitalized $\geq$ 3 times a year), and 6.8% for those with less severe disease.[42] In COVID-19, the risk of VTE is increased according to recent observational studies. In a study from the Netherlands, 184 patients with COVID-19 pneumonia were evaluated for incidence of thrombotic episodes while being on VTE prophylaxis. The cumulative incidence of thrombosis was 31%.[43] Another observational study from China found that 25% of 81 severely ill COVID-19 patients developed VTE.[44] Autopsy series have confirmed the presence of diffuse thrombi in small pulmonary arterioles in patients who died of COVID-19.[45,46] Given the fact that both SCD and COVID-19 are thrombogenic conditions, prophylactic anticoagulation is mandatory in SCD patients presenting with COVID-19.

Therapeutic Approach for COVID-19 in SCD

What will be presented in the following account concerning treatment of COVID-19 in SCD patients is based on experience of managing SCD-related complications, in addition to the accumulated data on the best available COVID-19 management protocols.[18,47,48] Optimizing the treatment in stable, non-infected SCD patients and compliance to the general preventive measures is the cornerstone of care. Patients should be encouraged to adhere to their prescribed anti-sickle cell medications, i.e. HU, L-glutamine, voxelotor, and crizanlizumab. An online platform or telephone counseling with the treating physician should be established for monitoring, education, and follow up. Minor sickle cell painful crises should be managed at home with simple analgesics and good hydration. Dietary supplements with vitamins D and C, which were reported to be effective in reducing the severity of COVID-19 illness, can be supplemented to SCD patients.[49,50] Management of SCD patients presenting with COVID-19 depends on the severity of the illness and the presence of sickle cell acute complications. It should include standard care given to this category of patients and the best available evidence toward the management of COVID-19.

As of writing this report, there is no effective antiviral therapy against SARS-CoV-2 and related COVID-19. However, clinical trials are still underway, testing several antiviral drugs with known activity against other viruses. One of those drugs is remdesivir, which was shown to be superior to placebo in shortening the time to recovery in adults hospitalized with mild to moderate COVID-19 related chest infection, but not in patients requiring high flow oxygen or mechanical ventiltion.[51] Lopinavir-ritonavir combination was also tested in severe COVID-19 patients with no observed benefit in comparison to standard care.[52] Hydroxychloroquine and chloroquine were showing promising results in earlier case reports and short case series and have been prescribed to COVID-19 patients with or without azithromycin as part of treatment protocols. However, a recent observational study involving a large cohort of patients with COVID-19 who had been treated with hydroxychloroquine revealed no additional advantages on disease progression, mainly the need for intubation and death.[53] Adding azithromycin did not improve the outcome.[53] Ivermectin is FDA-approved for parasitic infections and has been shown to be an effective inhibitor of SARS-CoV-2 in vitro. Clinical trials that assess the therapeutic effect of ivermectin in COVID-19 are underway and results are still pending.[54]

Convalescent plasma has been proposed as a possible therapeutic option in COVID-19 based on previous experiences with Ebola virus, SARS-Cov-1 and Middle East Respiratory Syndrome (MERS). In a recent study of 5,000 hospitalized patients with severe life-threatening COVID-19, the overall frequency of adverse events within 4 hours following the transfusion of COVID-19 convalescent plasma was less than 1%, confirming its safety.[55] Duan et al. published results of 10 patients with severe COVID-19 who received 200 ml of convalescent plasma with neutralizing antibody titer of 1:640. Viremia resolved in all 10 patients with recovery of laboratory parameters and improvements of O2 saturation within 3 days.[56] In another study from New York where 45 patients were identified as eligible for convalescent plasma transfusion (39 patients were included) and compared with 156 control cases, convalescent plasma recipients were more likely than control patients to remain stable or have improvements in their supplemental oxygen requirements by post-transfusion day 14. They also showed improved survival, especially for non-intubated patients.[57]

In COVID-19, cytokines storm is associated with the severity of the disease and affects morbidity and mortality.[58] Elevated levels of the inflammatory cytokine IL-6 in the blood have been reported to predict the outcome in patients with COVID-19.[59] Tocilizumab, a monoclonal antibody that blocks IL-6 receptor, has been used in critically ill COVID-19 patients with confirmed elevated level of IL-6. In a retrospective study from China, 21 severely ill patients with COVID-19 were treated with tocilizumab and standard care. Tocilizumab led to a reduction in fever and rapid improvements of lung lesions, with recovery and discharge of most patients in 2 weeks.[60] Two SCD patients with COVID-19 were treated successfully with tocilizumab and were discussed earlier in this article.[23,24] Sarilumab, a human IgG1 monoclonal antibody that binds to both soluble and membrane-bound IL-6Rs, and siltuximab, an anti-IL-6 chimeric monoclonal antibody, are currently being tested in COVID-19 patients.[61] Interferon beta-1b has been utilized in the past as a therapeutic option in SARS-CoV-1 and MERS because of its antiviral activity. Recently, it was found to improve symptoms and shorten the duration of viral shedding and hospital stay in patients with mild to moderate COVID-19 when combined with lopinavir and ritonavir.[62] Corticosteroids are among the most commonly used drugs because of their immunomodulatory effects in severe infection. In one study, the use of corticosteroids in patients with mild COVID-19 did not influence viral clearance time, length of hospital stay, or duration of symptoms.[63] In another study, which included 201 patients with COVID-19, treatment with methylprednisolone decreased the risk of death among patients with ARDS.[64] More recently, dexamethasone has been shown to reduce death in hospitalized patients with severe respiratory complications of COVID-19. This finding was one arm from the RECOVERY trial that included 2,104 patients randomized to dexamethasone 6 mg daily for 10 days against 4,321 patients randomized to standard care alone. Dexamethasone reduced deaths by one-third in ventilated patients and by one-fifth in other patients receiving oxygen. The benefit was not seen among patients who were not requiring respiratory support.[65]

Unfractionated heparin (UFH) or LMWH binds with high affinity to coronavirus, which might impact its functions.[66] Additionally, the high binding affinity of heparin to viruses including COVID-19 viruses might be potentially therapeutic for treating COVID-19 viruses. Because UFH has high plasma protein binding, which causes the UHF to be trapped and become unviable for a desired antithrombotic effect, LMWH

or preferably sulfated non-anticoagulant LMWH (S-NACH), which has low plasma protein binding and antithrombotic activities without bleeding side effects, should be considered.[67]

Coagulopathy and thrombosis documented in coronavirus infection have been shown to be associated with high mortality with high D-dimers being a particularly important marker for the coagulopathy.[68,69] Additionally, heparin, LMWH and other glycosaminoglycans demonstrated polypharmacological effects in the inhibition of complement activation and inflammation, which are key drivers in COVID-19 complications.[67-70]

Prophylaxis against VTE is of paramount importance in this setting. Using full anticoagulation has been shown to be effective in treating patients with VOC. Qari et al randomized 253 patient with VOC to receive either tinzaparin at therapeutic dose (175 IU/kg) or placebo. The tinzaparin group did better in terms of reduction in number of days with the severest pain score, overall duration of painful crisis, and duration of hospitalization.[71]

The following are possible presentations of COVID-19 in SCD with suggested management plans:

a. Asymptomatic SCD patient with positive SARS-CoV-2 RT-PCR:
   - Admit to hospital for observation or stay at home with close monitoring by telecommunication
   - Optimize current sickle cell therapy (e.g. Hydroxyurea) and reiterate the importance of adherence to treatment and other supportive therapies
   - Consumption of adequate amounts of fluids
   - Monitor vital signs and symptoms daily. Check the blood parameters initially for RBC hemolysis indicators (rise in reticulocytes count, LDH and indirect bilirubin from baseline) and order blood coagulation tests (PT, APTT, Fibrinogen and D-Dimer)
   - Advise prophylactic LMWH (e.g. enoxaparin 40 mg OD) in the event of hospital admission or prolonged immobilization at home
b. Symptomatic SCD patient with mild to moderately severe COVID-19 and O2 saturation > 94% (or PaO_2/FIO_2 > 300 mm Hg) in room air or with mask / nasal cannula and low flow oxygen:
   - Start hydration with I.V. fluid in addition to analgesics when needed. Optimize Hydroxyurea dosage. Add empiric prophylactic wide spectrum antibiotic
   - Simple RBC transfusion if Hb < 10 g/dL
   - Add remdesivir to the management
   - Add Intravenous Dexamethasone (6 mg daily for 10 days)
   - Consider convalescent plasma infusion if no signs of improvement or requiring more oxygen to sustain O2 saturation > 94% despite the previous measures
   - Start LMWH high prophylactic dose (e.g. enoxaparin 60 mg OD or 40 mg BID) if not contraindicated
c. Severe COVID-19 in SCD with O2 saturation < 94% (or PaO_2/FIO_2 < 300 mm Hg) on high flow oxygen mask or BiPAP but not requiring mechanical ventilation:
   - I.V. fluids, broad spectrum antibiotics, and optimize Hydroxyurea dosage
   - Start remdesivir and add Intravenous Dexamethasone (6 mg daily for 10 days)
   - Consider convalescent plasma if no improvement.
   - Use therapeutic LMWH (e.g. enoxaparin 1 mg/kg BID) if not contraindicated
   - Assess the need for IL-6 receptor blockers by measuring IL-6 level and assessment of the lung fields for signs of ARDS or disease progression
d. Severe COVID-19 in SCD requiring mechanical ventilation or extracorporeal membrane oxygenation (ECMO):
   - Apply all therapeutic measures described in the previous step. i.e. I.V. fluids, broad spectrum antibiotics, optimize Hydroxyurea dosage, remdesivir, Intravenous Dexamethasone and consider using convalescent plasma when appropriate
   - Use immunomodulatory agent, e.g. IL-6 receptor blocker
   - Consider adding a second anti-sickling drug if SCD-related complication is present
   - Use therapeutic LMWH if not contraindicated
   - Consider exchange RBC transfusion in case of worsening hemolytic markers or progressive lung infiltration
e. VOC and/or acute hemolytic crisis in association with COVID-19:
   - Apply all appropriate measures in the previous steps i.e O2 therapy, adequate hydration with I.V. fluids and broad spectrum antibiotics, optimize Hydroxyurea dosage, remdesivir, Intravenous Dexamethasone and consider using convalescent plasma when appropriate
   - Start analgesia as per local protocol with close monitoring of O2 when using narcotics
   - Add an additional anti-sickling drug (e.g. crizanlizumab) to the current management
   - Use therapeutic LMWH if not contraindicated
   - Give simple RBC transfusion to maintain Hb > 10 g/dL. Consider exchange RBC transfusion with the aim to reduce HbS to 30% or less in case of no response to above measures
f. ACS with COVID-19:
   - Apply all appropriate measures in the previous steps i. e. O2 therapy, adequate hydration with I.V. fluids and broad spectrum antibiotics, optimize Hydroxyurea dosage, remdesivir, Intravenous Dexamethasone and consider using convalescent plasma when appropriate
   - Add an additional anti-sickling drug (e.g.crizanlizumab) to the current management
   - Use therapeutic LMWH if not contraindicated

  - Use immunomodulatory agent, e.g. IL-6 receptor blocker
  - Exchange RBC transfusion with the aim to reduce HbS to 30% or less

g. Splenic sequestration crisis in association with COVID-19:

  - Apply all supportive measures and therapies in the previous steps including I.V. fluids, broad spectrum antibiotics, optimize Hydroxyurea dosage, remdesivir, Intravenous Dexamethasone and consider using convalescent plasma when appropriate
  - Simple or exchange RBC transfusions when indicated
  - Add an additional anti-sickling drug (e.g. crizanlizumab) to the current management
  - Use therapeutic LMWH if not contraindicated
  - Consider splenectomy in selected cases and when the clinical condition allows to do surgery

Conclusion

COVID-19 has recently emerged as a challenging health hazard to patients suffering from chronic disorders including those affected with SCD. The experience of managing SCD patients with COVID-19 is still in its infancy but plans for international registries have been put in action to assess the clinical course and outcomes in this patient population. The new therapeutic agents for SCD that have been recently approved should be used alongside the classical treatment to improve the outcome. In addition, available therapies with potential antiviral activity must be considered as part of the management. This is the first comprehensive review on managing SCD with COVID-19 that would be of benefit to busy health care providers until evidence-based management recommendations become available.

Authors' Note

The authors contributed equally to the concepts, rationales, and literature-supported evidence in the management of sickle cell patients with COVID-19.

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