Review Article

Aspects of care in patients with Sickle Cell Disease in the context of the COVID-19 pandemic

Aspectos da assistência em pacientes com Doença Falciforme no contexto da pandemia da COVID-19

Olivia Franco dos Santos[1], Thaís Sette Espósito[2], Rodrigo De Martin Almeida[3], Augusto Cézar Apolinário dos Santos[2], Jordana Alícia Silveira Lopes[1], Amanda do Carmo Gusmão[3], Nathalia Noyma Sampaio Magalhães[3], Daniela O.W. Rodrigues[4*]

ABSTRACT

Introduction: The pandemic caused by the new coronavirus (Sars-CoV-2), a disease called COVID-19, has reached more than 219 countries with great damage and impact on global health. The viral infection triggers an explosive, hyperactive and uncontrolled immune response, with severe clinical manifestations in people with underlying diseases. Sickle Cell Disease (SCD), a genetic condition that determines immunosuppression, causes patients a greater risk of respiratory infections and pulmonary complications within the context of the pandemic. Objective: To analyze the impact of COVID-19 in patients with SCD and propose a guideline to care for this population. Methods: This is a systematic literature review where studies were analyzed, originally published in English, between March and December 2020, using the MedLine, SciELO and LILACS databases as references. The search was carried out by consulting MeSH with the descriptors "sickle cell disease", "covid-19" and "guideline". 64 articles were identified from the search phrase. After applying the inclusion criteria, 7 articles were chosen for the study. Results and Conclusion: The infection with the new coronavirus could cause complications in patients with SCD, such as vaso-occlusive crises and acute chest syndrome. Considering these data, the authors formulated a guideline for guidance and care for individuals with SCD.

Keywords: Sickle cell disease; Hemoglobinopathies; COVID 19.

[1] Universidade Federal de Juiz de Fora (UFJF) Liga Acadêmica de Hematologia (HemoLiga). Juiz de Fora, Minas Gerais – Brazil.

[2] Centro Universitário Presidente Antônio Carlos Liga Acadêmica de Hematologia (HemoLiga). Juiz de Fora, Minas Gerais – Brazil.

[3] Faculdade de Ciências Médicas e da Saúde de Juiz de Fora (Suprema) Liga Acadêmica de Hematologia (HemoLiga). Juiz de Fora, Minas Gerais – Brazil.

[4] Fundação Hemominas and Universidade Federal de Juiz de Fora , Minas Gerais - Brazil

Institution:

Fundação Hemominas. Liga Acadêmica de Hematologia (HemoLiga). Juiz de Fora, Minas Gerais – Brazil.

Supporting Sources:

None.

Conflict of Interests:

The authors declare no conflict of interest

*** Corresponding Author:**

Daniela de Oliveira Werneck Rodrigues

E-mail: danielawerneckhemato@hotmail.com

Received on: 07 March 2021.

Approved on: 13 January 2022.

Publication Date: 31 March 2022.

DOI: 10.5935/2238-3182.2022e32204

RESUMO

Introdução: A pandemia determinada pelo novo coronavírus (SarsCoV-2), doença intitulada COVID-19, atingiu mais de 219 países com grande agravo e impacto à saúde mundial. A infecção pelo vírus desencadeia uma resposta imune explosiva, hiperativada e descontrolada, com manifestações clínicas graves em pessoas com doenças subjacentes. A Doença falciforme (DF), uma condição genética que determina imunosupressão, coloca os pacientes em maior risco de infecções respiratórias e complicações pulmonares dentro do contexto da pandemia. Objetivo: Analisar o impacto da COVID-19 em portadores de DF e propor uma diretriz de atendimento a esta população. Métodos: Trata- se de uma revisão sistemática de literatura onde foram analisados estudos, publicados originalmente em inglês, entre março a dezembro de 2020, tendo como referência as bases de dados MedLine, SciELO e LILACS. A busca foi efetuada mediante a consulta ao MeSH com os descritores "sickle cell disease", "covid-19"e "guideline". Foram identificados 64 artigos a partir da frase de pesquisa. Ao aplicar os critérios de inclusão, 7 artigos foram eleitos para o estudo. Resultados e Conclusão: A infecção pelo novo coronavírus pode precipitar intercorrências em pacientes com DF, como crises vaso-oclusivas e síndrome torácica aguda. Considerando esses dados, os autores formularam uma diretriz para orientação e cuidado aos indivíduos com DF.

Palavras- chave: Doença Falciforme; Hemoglobinopatia; COVID 19.

Introduction

The new coronavirus, which caused the COVID-19 pandemic, affected more than 219 countries with nearly 96 million cases since the first report in China in 2019 to January 2021[1-3]. The clinical characteristics of this disease are not yet fully understood, however it is believed that severe manifestations occur mainly in adults with advanced age, obesity and with underlying chronic diseases[4].

Amongst the most remarkable characteristics of COVID-19 are the vascular alterations associated with the disease. Considering the diffuse alveolar damage in the infection, it was observed the formation of fibrin thrombi in many patients. Clinically, there is an increase in D-dimer levels and cutaneous changes in the extremities, suggesting microangiopathy with immunothrombosis. The inflammatory storm occurs because of endothelial injury, diffuse intravascular coagulation, release of cytokines and of proinflammatory proteins, with thrombosis in large and small vessels associated to multiple organ failure[5].

Sickle Cell Disease (SCD) is a group of inherited alterations in hemoglobin (Hb), it is a multisystemic recessive genetic disease. Morphologically, the sixth codon suffers a mutation in the eleventh chromosome, with glutamic acid being replaced by valine. The homozygotes genotype causes severe manifestations, being known as Sickle Cell Anemia (SCA). Prevalence in Brazil is high, with almost 30,000 people affected across the country, consisting of the most common monogenic hereditary disease. The annual incidence is about 1 for every 1,000 new-born[6].

The disease's physiopathology is triggered by HbS intolerance to hypoxic scenarios, with polymerization and consequent sickling of erythrocytes. The red blood cells become inflexible, causing vaso-occlusive phenomena and tissue damage, with disordered interactions between erythrocytes, endothelial cells, leukocytes and platelets. Patients with SCD have impaired humoral response due to asplenia, altered opsonization and are predisposed to a higher risk of respiratory diseases and subsequent pulmonary complications, such as Acute Chest Syndrome (ACS)[6,7].

Although vaso-occlusive phenomena is complex, HbS polymerization is the essential physiopathological occurrence in SCD[6]. The endothelial cells are suspected to be activated by direct contact with sickle cells, heme group and free Hb, induced by hypoxia. Reducing nitric oxide (NO) bioavailability can stimulate vasoconstriction, expression of adhesion molecules and production of endothelin 1. Increased expression of endothelial adhesion

molecules (such as vascular cell adhesion protein 1 (VCAM1), molecule of intercellular adhesion 1 (ICAM1), P-selectin, E-selectin, CD47 leukocyte surface antigen and αVβ3 integrin), exposed heparin sulfate proteoglycans and phosphatidylserine are responsible for the adhesion of erythrocytes and leukocytes. Activated endothelial cells produce inflammatory mediators, such as interleukins (IL) -1β, IL-6 and tumor necrosis factor (TNF), which lead to a chronic inflammatory state[7,8].

Studies published in 2020 suggested that vaso-occlusive crisis (VOC) and/or ACS can be triggered by COVID-19, with the risk for severe evolution risk and high lethality rates[9,10]. Although literature is still scarce about the association between COVID-19 and SCD, a special care is needed regarding the related complications. Health-care workers should be aware of the precautions to be taken in order to reduce SCD's mortality in the face of the pandemic[11,12].

Fundação Hemominas (FH) is a public health institution linked to the State Secretariat of Health of Minas Gerais and the Ministry of Health, reference for the diagnosis, monitoring and treatment of patients with SCD. FH is part of a network formed by a Central Administration in Belo Horizonte and 22 decentralized units in the macro-regions of Minas Gerais. Considering the institutional mission of acting in hematology with excellence and responsibility with the production of knowledge and innovation. Thus, FH developed guidelines for patients with SCD and primary health care professionals assisting them in coping with COVID-19[13].

Objective

To analize the impact of COVID-19 in patients patients with Sickle Cell Disease and to propose a health care guideline.

Review of literature

This is a systematic review of the literature, with the evaluation of articles published in scientific journals, originally in English, between March and December 2020, using the MedLine, SciELO and LILACS databases as a reference. The search was carried out by consulting the Medical Subject Headings (MeSH) and Health Science Descriptors (DeCS) with the keywords "sickle cell disease", "covid-19" and "guideline". 126 results were found, among them 64 repeated. The abstracts were separated independently and analyzed by two researchers. The inclusion criteria were: studies relating to the themes SCD and COVID-19. Articles that did not include all descriptors were excluded. Final analysis was carried out with seven articles. The selection process is outlined below (Figure 1).

Results

Seven scientific productions that correlated coronavirus infection to patients with SCD were selected. The authors agreed with the increased need for care for people with hematological disorders in view of the risk of worsening the underlying clinical condition, the description is shown in Table 1.

The health care treatment and attention guidelines proposed by the authors in the selected articles are shown in Table 2.

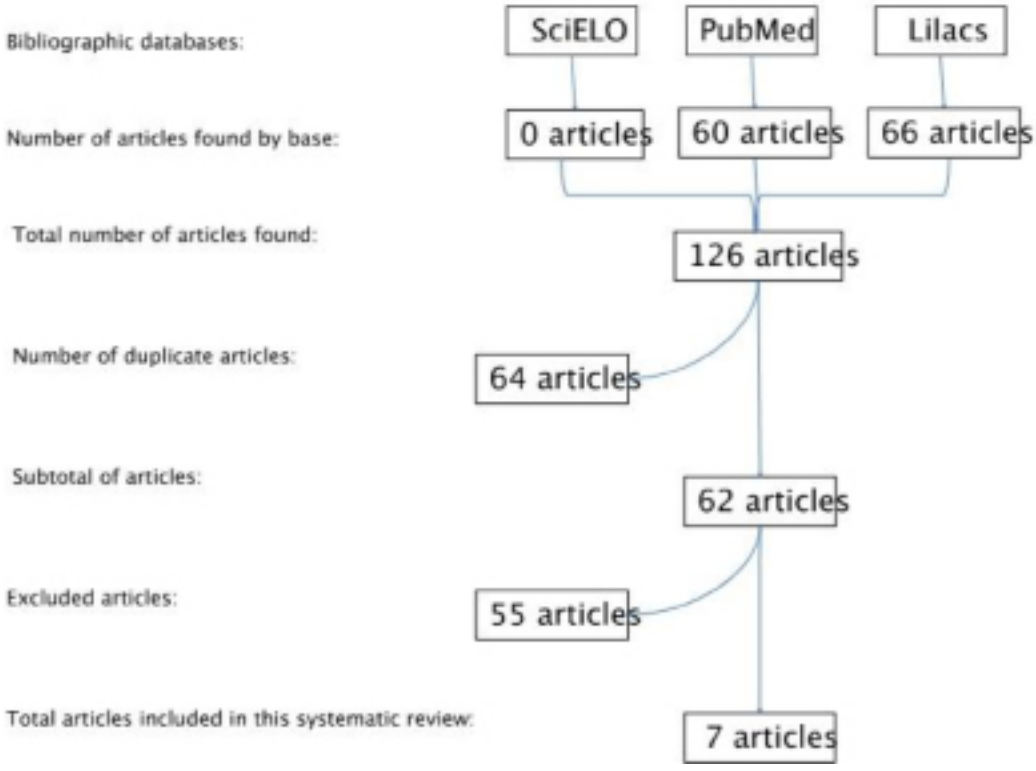

Figure 1: Flowchart with the article selection process.

Table 1 - Result of the Literature Review

Author and year	Objective	Results
Chowdhury SF et al. (2020)[14]	Point out important measures in the care of patients with hemoglobinopathies during the COVID-19 pandemic.	• People with SCD should avoid going out of the house and contact individuals with respiratory symptoms or fever as much as possible. • Patients with SCD and respiratory symptoms or VOC should have a chest X-ray. • Hospitalize cases of ACS for intensive care.
Taher AT et al. (2020)[15]	Recommendations for the care of patients with hemoglobinopathies and COVID-19.	• ACS can be triggered by COVID-19. • Coronavirus infection can cause: hypoxemia, dehydration, metabolic acidosis, VOC and ACS. • Physicians should recognize signs of rapidly progressive ACS, including multiple organ failure, liver dysfunction, thrombocytopenia and acute kidney injury.
Appiah-Kubi A et al. (2020)[16]	Describe the varied presentations and outcomes in children and young adults with SCD and Covid-19.	In patients with SCD and COVID-19, with fever, cough, worsening of anemia, evidence of hypoxia and / or changes in the pulmonary image, there is a recommendation for aggressive blood transfusions or early exchange.
Nickel RS et al. (2020)[17]	Evaluate the use of a dose of hydroxyurea and regular transfusion to prevent complications in SCD.	• In children with SCD who regularly receive blood transfusion therapy for primary or secondary stroke prevention, in areas that may have a blood supply deficiency due to a pandemic, a low dose of hydroxyurea is recommended.
Morrone KA et al. (2020)[18]	Show radiographic abnormalities, clinical course and treatment strategies in children with SCD infected with Sars-CoV-2.	• The therapeutic benefit of hydroxyurea may be related to a lower absolute monocyte count, a reduction in inflammatory cytokines and a decrease in endothelial adhesive markers, which may favor the treatment of people with SCD infected by Covid-19.
Arlet JB et al. (2020)[9]	Assess the risk of admission to the intensive care unit of patients with SCA infected with Sars-CoV-2.	• Older patients with SCD should be considered vulnerable to Sars-CoV-2 and should follow the guidelines of their respective countries to avoid exposure to the virus. • Monitoring should be done closely if hospitalization occurs due to COVID-19.
Balanchivadze Net al. (2020)[19]	Evaluate a series of cases showing the main complications of patients with SCD infected with Sars-CoV-2.	• Specialized clinic in SCD with well-established orientation for patients with COVID-19, including outpatient care for painful crises and mild viral diseases, intravenous hydration based on an infusion room and pain control.

Authors, 2021.

Discussion

The new coronavirus, an RNA virus, of the Coronaviridae family, triggered a global health crisis begning December 2019 with devastating outcomes and high mortality in populations with underlying diseases[20]. COVID-19 is associated with a wide spectrum of clinical respiratory syndromes, from mild upper airway symptoms to life-threatening progressive viral pneumonia. Studies confirmed higher lethality related to the age group above 60 years, obesity, male gender and the presence of comorbidities (cardiovascular, metabolic and immunosuppression)[9].

Clinically, the patients with severe COVID-19 show dyspnea, progressive hypoxemia and frequently need mechanical ventilation support. Radiologically, pulmonary ground-glass opacity lesions, as evidenced by chest computed tomography, are the most common and early finding, in addition to septal thickening, pleural effusion and consolidations. In severe forms, clinical deterioration is usually rapid and, in large part, the unfavorable evolution of the disease is due to systemic hyperinflammation and immunothrombosis[20].

SCD is a general term which describes a hereditary group of disease characterized by the presence of abnormal Hb, caused by a pontual genetic mutation with nucleotide replacement that results in HbS. Under deoxygenation conditions, the abnormal red blood cell can polymerize and cause the erythrocytes to assume the shape known as crescent or sickle cell[6,7].

The sickling of the red blood cells leads to hemolysis, occurring ischemia and infarct in target-organs, such as brain, eyes, heart, kidneys, liver and lungs. Pulmonary complications are an important cause of mortality, the main ones being ACS, Pulmonary Embolism, Pulmonary Hypertension and Asthma. ACS is the most common pulmonary manifestation, with high risk of respiratory insufficiency, what may require mechanical ventilation[7,8].

Table 2: SCD X COVID 19: Guidelines for Coping.

GUIDELINES FOR THE CARE OF PEOPLE WITH SICKLE CELL DISEASE DURING THE COVID-19 PANDEMIC
1. Social isolation: patients should avoid contact with people who are experiencing respiratory symptoms or fever;
2. Self-care: wash hands, use alcohol gel and masks, maintain adequate hydration;
3. Maintain control medications such as folic acid, penicillin V, hydroxyurea and analgesics;
4. Adult patients, adolescents and children aged 5 years and under must receive the recommended vaccines, as recommended by the National Immunization Program;
5. Look for an emergency in the presence of fever or respiratory symptoms (difficulty in breathing, persistent cough and bleeding from the nasal wing);
6. Inclusion of an outpatient emergency care unit prepared for cases of painful crises and mild viral diseases;
7. Patients with sickle cell disease (SCD) and respiratory symptoms or vaso-occlusive crises should undergo chest radiography;
8. Acute Chest Syndrome (ACS), a serious complication of SCD, can be triggered by respiratory infections, including COVID-19. Coronavirus infection can also lead to hypoxemia, dehydration and metabolic acidosis, causing vaso-occlusive crises. Therefore, physicians should recognize signs of rapidly progressive ACS, including multiple organ failure, liver dysfunction, thrombocytopenia and acute kidney injury. ACS patients should be hospitalized and monitored in intensive care;
9. In patients with SCD diagnosed with COVID-19, with persistent fever and cough, worsening of anemia, evidence of hypoxia and / or changes in the pulmonary image, there is a recommendation for aggressive blood transfusions or early exchange;
10. Considering pediatric SCD patients, for those receiving regular blood transfusion therapy for primary or secondary stroke prevention in areas that may have a blood supply deficiency due to pandemic, a reduced dose of hydroxyurea is recommended;
11. Among older patients, monitoring should be more intense, being considered vulnerable;
12. Encourage vaccination against Sars-CoV-2 to prevent complications in this group, as already provided for in Phase 3 of the National Immunization Program;
13. In case of doubts about the characteristics of patients with SCD, the Fundação Hemominas is available to discuss the cases through a call center and on call 24 hours a day, contacts made available through the website (http://www.hemominas.mg.gov.br/doacao-e-atendimento-ambulatorial/atendimento-ambulatorial/tipos-de-atendimento/601-pacientes-com-hemoglobinopatias).

Authors, 2021.

Patients with SCD present a higher risk of developing COVID-19 complications due to underlying diseases, which have huge repercussion in the immune system. Besides the specific morbimortality related to the virus, COVID-19, in this group of people, can trigger and lead to VOC and ACS, with increase morbimortality. The pro-thrombotic state is a clinical condition that deserves to be highlighted in this population, due to the reduction of nitric oxide, release of cytokines, platelet activation and endothelial dysfunction associated with hemolysis[8].

Chowdhury SF, *et al.* 2020 concluded that, in the existence of respiratory symptoms or VOC, SCD patients infected by Sars-CoV-2 should undergo chest radiography for the rapid adoption of the correct treatment and monitoring[14]. Taher AT, *et al.* 2020 also described the possibility of ACS being triggered by COVID-19, with chances of worsen hypoxia, dehydration, metabolic acidosis and VOC[15]. These authors emphasize the need of early recognition by the health team of rapid progressive ACS's signs, such as multiple organ failure, liver disfunction, thrombocytopenia and acute kidney injury.

Appiah-Kubi A, *et al.* 2020, showed that simple transfusion, followed by ex-blood transfusion in patients with SCD who required respiratory support in the ICU, had a positive impact on the clinical course of COVID-19. Drug therapy including Hydroxychloroquine, Anakinra and Remdesivir has been used and well tolerated, with success in individuals with high inflammatory markers[16]. Balanchivadze N, *et al.* 2020, reported that the low incidence of those infected with coronavirus and evolution with mild symptoms in sickle cell patients resulted from social detachment, implemented early in the state of Michigan, United States and the inclusion of outpatient care for painful crises and other mild viral diseases, with intravenous hydration in infusion rooms and effective analgesia[19].

Nickel RS, *et al.* 2020, performed a single-arm clinical trial using scaled-dose hydroxyurea and regular transfusions to prevent AF complications. The group studied and recommended the use of reduced dosage of hydroxyurea in children with SCD in a chronic transfusion program for primary or secondary prevention of stroke, considering the impact of the pandemic on shortages and reduction in the stocks of blood components in blood banks[17].

Morrone KA, *et al.* 2020, conducted a study comparing children with COVID-19 who developed ACS and children infected by the same virus, but without the occurrence of ACS. The authors observed that the use of hydroxyurea reduced the number and severity of ACS, as well as the need for transfusions[18].

The study conducted by Arlet JB, *et al.* 2020, noted that COVID-19 did not present an increased risk of morbidity or mortality in people with SCD, it should be noted that most patients were under the age of 45 years. The researchers suggested that patients over the age of 45 should be strictly monitored in case of hospitalization[9].

Regarding immunobiologicals, the recommendation is to promote anti-pneumococcal vaccination in children, according to the rules of the Immunization Programs recommended in each country[21]. With the implementation of vaccines against coronavirus, people with SCD should be encouraged and have priority access, aiming to minimize the impacts of COVID -19 in SCD[22,23].

A greater understanding about the impact of the pandemic in SCD is necessary, for this, the scientific community created a database to ad knowledge for better management of these patients through the analysis of the genotype, clinical complications, therapeutic management and care. (https: // covidsicklecell.org)[17].

Conclusion

The authors and researchers participating in the Academic League of Hematology of the FH sought, through these strategic actions, to minimize the impact of COVID-19 on the well-being of patients with SCD, with the dissemination of information and knowledge through social networks and in person at outpatient clinics of FH.

References

1. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult in patients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 March 28: Vol 395.
2. Johns Hopkins Coronavirus Resource Center. Johns Hopkins [Internet]. Cited 2021 Jan 22. Available from: https:// coronavirus.jhu.edu/.
3. Shibo J, Shuai X, Tianlei Y, Lu L. A novel coronavirus (2019-nCoV) causing pneumonia-associated respiratory syndrome. Cell Mol Immunol. 2020 May 17:554.
4. Preliminary Estimates of the Prevalence of Selected Underlying Health Conditions Among Patients with Coronavirus Disease 2019 — United States. MMWR Morb Mortal Wkly Rep. 2020 March 28: 69:382-386.
5. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, Vanstapel A, Werlein C, Stark H, Tzankov A, Li WW, Li VW, Mentzer SJ, Jonigk D. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. N Engl J Med. 2020 Jul 9: 383(2):120-128.
6. Steinberg MH. Management of Sickle Cell Disease. N Engl J Med. 1999 Apr 1: 340:1021-1030.
7. Hussain FA, Njoku FU, Saraf SL, Molokie RE, Gordeuk VR, Han J. COVID-19 Infection in Patients with Sickle Cell Disease. Br j Haematol. 2020 Jun:189:851-852.
8. Kato GJ, Piel FB, Reid CD, Gaston MH, Ohene-Frempong K, Krishnamurti L, Smith WR, Panepinto JA, Weatherall DJ, Costa FF, Vichinsky EP. Sickle cell disease. Nat Rev Dis Primers. 2018 Mar 15: 4:180104.
9. Arlet JB, Luna G, Khimoud D, Odièvre MH, Montalembert M, Joseph L, Chantalat-Auger C, Flamarion E, Bartolucci P, Lionnet F, Monnier S, Guillaumat C, Santin A. Prognosis of patients with sickle cell disease and COVID-19: a French experience. Lancet Haematol. 2020 Sep: 20:S2352-3026.
10. Panepinto JA, Brandow A, Mucalo L, Yusuf F, Singh A, Taylor B, Woods K, Payne AB, Peacock G, Schieve LA. Coronavirus Disease among Persons with Sickle Cell Disease. Emerging Infectious Diseases. 2020 Oct: 26,10.
11. Nur E, Gaartman AE, van Tuijn CFJ, Tang, MW, Biemond BJ. Vaso-occlusive Crisis and Acute Chest Syndrome in Sickle Cell Disease due to 2019 Novel Coronavirus Disease (COVID-19). Am J Hematol. 2020 Jun:95(6):725-7262020.
12. ABHH cumpre papel de informar a especialidade e informa sobre decisão do CGSH. [Internet]. Cited 2021 Jan 22. Available from: https://abhh.org.br/noticia/apos-decisao-do-stf-anvisa-revoga-restricao-a-doacao-de-sangue-por-hshs/
13. http://www.hemominas.mg.gov.br/doacao-e-atendimento-ambulatorial/atendimento-ambulatorial/tipos-de-atendimento/601-pacientes-com-hemoglobinopatias acessada em 17 de Janeiro de 2021.
14. Chowdhury SF, Anwar S. Management of Hemoglobin Disorders During the COVID-19 Pandemic. Front Med. 2000 Jun:7:306.
15. Taher AT, Bou-Fakhredin R, Kreidieh F, Motta I, De Franceschi L, Cappellini MD. Care of patients with hemoglobin disorders during the COVID-19 pandemic: An overview of recommendation. Am J Hematol. 2020 May 20: 95(8):E208-E210.
16. Appiah-Kubi A, Acharya S, Fein Levy C. Varying Presentations and Favourable Outcomes of COVID-19 Infection in Children and Young Adults with Sickle Cell Disease: An Additional Case Series with Comparisons to Published Cases. Br J Haematol. 2020 Aug:190(4):e221-e224.
17. Nickel RS, Margulies S, Frazer B, Luban N, Webb J. Combination dose-escalated hydroxyurea and transfusion: an approach to conserve blood during the COVID-19 pandemic. Blood. 2020 May 27:135:2320-2322.
18. Morrone KA, Strumph K, Liszewski MJ, Jackson J, Rinke ML, Silver EJ, Minniti C, Davila J, Mitchell WB, Manwani D. Acute chest syndrome in the setting of SARS-COV-2 infections-A case series at an urban medical center in the Bronx. Pediatr Blood Cancer. 2020. Nov:67(11):e28579.
19. Balanchivadze N, Kudirka AA, Askar S, Almadhoun K, Kuriakose P, Fadel R, Dabak V. Impact of COVID-19 Infection on 24 Patients with Sickle Cell Disease. One Center Urban Experience. 2020. Jul. 44(4): 284-289.
20. Kim JS, Lee JY, Yang JW, Lee KH, Effenberger M, Szpirt W, Kronbichler A, Shin JI. Immunopathogenesis and treatment of cytokine storm in COVID-19. Theranostics. 2021. Jan 1:11(1):316-329.
21. COVID-19: 8 recommendations for sickle cell patients. Sickle Cell Association of Quebec. Cited 2021 Jan 24. Available from: anemie-falciforme.org
22. Moradi L. Sickle Cell Disease and COVID-19. J Arch Mil Med. 2020. 8(2):e109727.
23. MARAC Advisory Statement: COVID-19 Vaccines. Cited 2021 Jan 22. Available from: https://www.sicklecelldisease.org/2020/12/15/marac-advisory-statement-covid-19-vaccines/