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Acute chest syndrome in sickle cell anemia: Diagnostic challenges and therapeutic strategies

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ABSTRACT

Sickle cell disease is a genetic blood disorder caused by a mutation in the amino acid glutamic, which is replaced by valine in the beta chain of the hemoglobin molecule. In this context, acute chest syndrome is a serious disease with a high rate of morbidity and mortality, accounting for approximately 25% of deaths in patients with sickle cell anemia. Thus, the objective of this study is to describe the main aspects of Acute Thoracic Syndrome (ASS) in patients with sickle cell anemia. This is a review study of a scoping review in which data collection was carried out in the research portal of the Virtual Health Library (VHL), the databases used were: Online *System* for Search and Analysis of Medical Literature (*MEDLINE)* and Latin American and Caribbean Literature in Health Sciences *(LILACS)* where the following were used as descriptors for the search: "Sickle Cell Anemia" *AND* "Acute Chest Syndrome". From the use of descriptors, 451 articles were found. The inclusion criteria were: articles published between 2019 and 2024, available in full and free of charge; and the exclusion criteria were repeated articles, paid articles, and methods with an emphasis on literature review. Through the established criteria, 20 studies were used for the final sample. Acute chest syndrome is characterized by fever and/or respiratory symptoms with pulmonary infiltrates, which can lead to sepsis and stroke in patients with sickle cell anemia. In addition, hemolysis increases during sickle cell crises, causing a faster depletion of nitric oxide, which is a potent vasodilator of metabolism and a factor for cardiopulmonary hemodynamics. In this context, ultrasonography is recognized as the gold standard in the diagnosis of the syndrome, due to the absence of radiation, with high precision, sensitivity and specificity. Changes in pulmonary function in acute chest syndrome cause variation in the rates of inflammatory markers that can help to recognize the condition and treat it more effectively, such as phosphatidylserine, a specific type of phospholipid that is essential in cell membranes, serum ferritin, the increase is due to the attempt to compensate for the increase in hemolysis and IL-6, which reflect the recruitment of monocytes and other innate immune cells in the lungs. In the face of intense hemolysis, red blood cell transfusions can be seen as a protective factor for acute chest syndrome and can even be considered the definitive therapy for the syndrome, as it improves the supply of oxygen to the tissues, increases the general hemoglobin level, and decreases the sickle-shaped fraction of red blood cells. This makes it possible for the patient to have relief from respiratory symptoms more quickly. Therefore, acute chest syndrome in patients with sickle cell anemia requires appropriate interventions and should be treated just like rare diseases in health units, whether in the primary health care unit or emergency room care, to ensure adequate treatment without delay. Thus, the

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management that should be performed is analgesia, hydration, antibiotic therapy, bronchodilators, ventilation, which may or may not be invasive, oxygen, and blood transfusion.

Keywords: Sickle cell anemia, Acute Thoracic Syndrome, Hemolysis, Blood disease.

INTRODUCTION

Sickle cell disease (SCD) is a genetic blood disorder that affects approximately 100,000 people in the United States and is one of the most common genetic disorders (Piel, Steinberg, and Rees, 2017). It is caused by a mutation in the amino acid glutamic, which is replaced by valine in the beta chain of the hemoglobin molecule (Ware *et al.*, 2017).

Although the pathophysiology of sickle cell anemia primarily involves hemoglobin polymerization, emerging evidence suggests that lipid metabolism alterations play a crucial role in disease progression (Kubong *et al.*, 2020). Reduced plasma cholesterol in sickle cell anemia is associated with an increase in cholesterol in the red blood cell membrane (Nieson *et al.*, 2022).

Abnormalities of lipid metabolism in sickle cell anemia are thought to result from a combination of factors, including genetics, chronic hemolysis, inflammation, oxidative stress, and altered cell membrane composition (Kubong *et al.*, 2020).

In addition, dyslipidemia in sickle cell anemia has been associated with reduced nitric oxide bioavailability, oxidative stress, inflammation, impaired vasodilation, which may contribute to the development of complications such as pneumonia, leg ulcers, and vasculopathy (Conceição *et al.*, 2020). High triglyceride (TG) levels are also correlated with pulmonary hypertension and endothelial dysfunction (Zorca *et al.*, 2010).

Erythrocytes during sickle cell anemia also exhibit higher levels of phosphatidylserine due to altered membrane stability and compromised integrity of these cells (Qu *et al.*, 2022). A possible complication is multiple organ failure, marked by acute dysfunction of at least two organ systems, mainly acute kidney injury and liver dysfunction (Chaturvedi *et al.*, 2016).

Hypoxia, acidosis, and dehydration induce polymerization of sickle hemoglobin (HbS), resulting in the deformity of red blood cells or erythrocytes. This causes vaso-occlusive crisis (CVO), ischemia-reperfusion injury, and endothelial dysfunction (Shah & Dwivedi, 2020).

Acute chest syndrome is a serious disease with a high rate of morbidity and mortality (Koehl *et al.*, 2022) and is a form of acute lung injury that encompasses vaso-occlusive events in the pulmonary vasculature (Spring & Munshi, 2022). Overall, acute chest syndrome accounts for approximately 25% of deaths in patients with sickle cell anemia (Novelli & Gladwin, 2016).

In addition, inflammation contributes to the development of acute chest syndrome. Interleukin-6 (IL-6) in blood and sputum is reported to be a marker of the development of acute chest syndrome (Domingos *et al.*, 2020).

OBJECTIVE

To describe the main aspects of Acute Chest Syndrome (ATS) in patients with sickle cell anemia.

METHODOLOGY

A scoping study or scoping review is defined as a type of study that seeks to explore the main concepts of the topic in question, ascertain the size, scope and nature of the study, condensing and publishing the data, thus pointing out the gaps in existing research (Arksey & O'Malley, 2005).

Data collection was carried out in the research portal of the Virtual Health Library (VHL), the databases used were: *Online* System for Search and Analysis of Medical Literature (*MEDLINE)* and Latin American and Caribbean Health Sciences Literature *(LILACS)* where the following were used as descriptors for the search: "Sickle Cell Anemia" *AND* "Acute Chest Syndrome". The survey was conducted in May and June 2024.

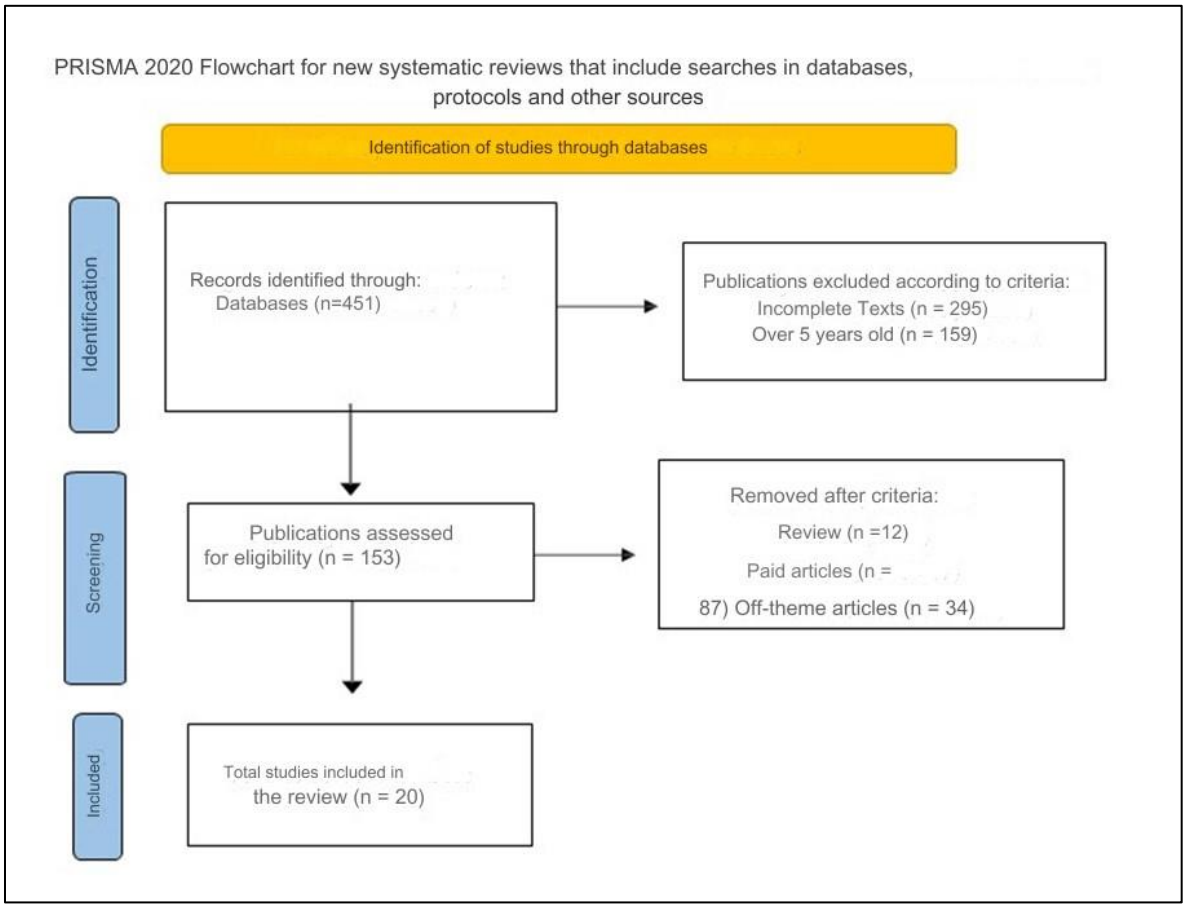
From the use of descriptors, 451 articles were found. The inclusion criteria were: articles published between 2019 and 2024, available in full and free of charge; and the exclusion criteria were repeated articles, paid articles, and methods with an emphasis on literature review. Through the established criteria, 20 studies were used for the final sample.

The selection of articles was made by reading the abstracts, in order to confirm the proposed theme and statements about the subject. It was based on the aspects contained in the abstracts and implemented in the reading of the full text of the chosen works, in order to find what was coherent with the theme.

The present study, as it is a scoping review, was not submitted to the evaluation of the Research Ethics Committee in accordance with Resolution 466/12 complemented by 510/16 of the National Health Council (CNS), but all established ethical precepts were respected, and the legitimacy of the information was ensured.

Regarding the types of study, it was observed that there are 10 cohort studies, 4 case reports, 3 case-control studies, 1 analysis study, 2 clinical trials, 2 retrospective studies and 1 exploratory study. In this context, in relation to the year of publication, 06 articles are from 2024, 06 are from 2023, 3 from 2022, 3 from 2021 and 2 from 2020.

Chart: Characterization and metadata information of the articles included in this research.



Title	Author/year	Type of Study	Objective	Results found
Lipid and hemolysis parameters predicting acute chest syndrome in adulthood with sickle cell disease.	Feugray, G. *et al*., 2024.	Cohort Study	To assess hemolysis and lipid parameters in a cohort of patients with confirmed SCD to predict the development of acute chest syndrome in the following year.	This study demonstrated that several readily available biomarkers can be used at steady state to predict acute chest syndrome in the following year.
Decreased risk of underdosing with continuous infusion versus intermittent administration of cefotaxime in patients with sickle cell disease and acute chest syndrome.	Razazi *et al*., 2024.	Cohort study	Antibiotic underdosage is common in patients with sickle cell disease (SCD). We hypothesize that in critically ill patients with sickle cell disease receiving cefotaxime during acute chest syndrome, continuous infusion may outperform intermittent administration in achieving harmacokinetic/pharmacodynamic goals.	Compared to intermittent administration, continuous infusion of cefotaxime maximizes pharmacokinetic/pharmacodynamic parameters in patients with SCD. The clinical outcome did not differ between the two methods of administration; However, the study was not powered enough to detect such a difference.

Multi-center study on mortality in children, and adults with sickle cell anemia-risk factors and causes of death.	Alkindi *et al.*, 2024.	Cohort study	OBJECTIVE: To evaluate the risk factors associated with mortality in SCD patients between 2006 and 2020 in three hospitals in Oman.	The ability to identify risk factors associated with increased mortality among SCD patients allows for an accurate prognosis and provides effective prophylactic management strategies. This study shows that male gender, low HbF, substantial drop in hemoglobin and platelets, as well as increased leukocyte count, serum LDH, ferritin, and CRP, were significantly correlated with the risk of mortality during the terminal event in patients with SCD.
Risk factors for acute chest syndrome among children with sickle cell anemia hospitalized for vaso-occlusive crises.	AlghamdI *et al.*, 2024	Case-control	To discern early indicators of impending acute chest syndrome in children with SCA who were initially hospitalized due to painful vaso-occlusive crises (VOCs).	The acute chest syndrome group had a longer mean length of hospital stay compared to those with VOCs alone (7.6 vs. 5.8 days). Among the patients initially admitted for VOC, 15.7% were diagnosed with acute chest syndrome. Most cases of acute chest syndrome were treated with transfusions and antibiotics, and nearly one-third of patients required admission to an ICU or high-dependency area.
Unmasking Acute Chest Syndrome: Understanding the Role of Nonpharmacologic Interventions on Children with Sickle Cell Disease During the COVID-19 Pandemic.	Willen & Cohen, 2024	Time Series Analysis	To compare the incidence of hospitalizations for acute chest syndrome during the pre-pandemic period (January 2015 to March 2020), implementation of NPI (April 2020 to March 2021), and NPI survey periods (April 2021 to May 2022). .	It suggests that S pneumoniae and influenza infections play a significant role in pediatric acute chest syndrome.
Managing pregnancy in patients with sickle cell disease from a transfusion perspective.	Habibi *et al.*, 2023.	Case Report	To describe transfusion treatment in pregnant women with sickle cell disease.	Prophylactic transfusion therapy should be initiated, both to prevent and treat complications of sickle cell disease, especially episodes of acute pain, and to reduce recurrent episodes of acute vaso-occlusive pain in pregnant patients with sickle cell disease.

Acute chest syndrome in children with sickle cell disease: Data from a national AIEOP cohort identify priority areas of intervention in a hub-and-spoke system.	Munaretto *et al.*, 2024.	Retrospective and observational cohort study	To evaluate the epidemiology and characteristics of acute chest syndrome in the setting of the Italian national public health system	Specific actions, which require coordinated national approaches and local educational initiatives, in line with the recent strategy of the European Reference Networks (ERNs) to improve collaboration between hub-and-spoke centres, can now be implemented and will focus on stimulating the application of early preventive measures for acute chest syndrome that are still underused, better pain management in vaso-occlusive crises, and the use of incentive spirometry.
Recurrence of acute chest syndrome post stopping Crizanlizumab, the dilemma of stopping vs continuation in patient with sickle cell disease: case report.	Afana *et al.*, 2023.	Case report	To evaluate the potential of Crizanlizumab in the prevention of new acute chest syndrome events.	Patients taking Crizanlizumab and with life-threatening complications (e.g., acute chest syndrome) may benefit from continuing Crizanlizumab beyond the standard 14-dose regimen.
Sputum IL-6 level as a potential predictor of acute chest syndrome during vaso-occlusive crisis in children with sickle cell disease: Exploratory prospective prognostic accuracy study.	Allali *et al.*, 2023.	Exploratory cohort study of prognostic accuracy	To investigate the prognostic accuracy of IL-6 level in sputum to predict acute chest syndrome in children with SCD hospitalized for VOC	The level of IL-6 in sputum appears as a potential predictor of acute chest syndrome during VOC and may help identify patients who could benefit from targeted preventive anti-inflammatory therapy, such as tocilizumab.
Acute chest syndrome in adult patients with sickle cell disease: The relationship with the time to onset after hospital admission.	Cheminet *et al.*, 2023.	Clinical Study	To describe 105 consecutive episodes of acute chest syndrome in 81 adult patients over a period of 32 months and compare the characteristics as a function of time of onset after hospital admission for a vaso-occlusive crisis (VOC), i.e., early onset.	Most cases of acute chest syndrome occurred within a few days of hospital admission because of a vaso-occlusive crisis, but which was sometimes already present on admission. The secondary and early forms of acute chest syndrome do not appear to differ significantly. Disease-modifying treatments should be re-evaluated after each episode of acute chest syndrome because the recurrence rate is high. In addition, to combat the rise of antibiotic resistance, evidence-based antimicrobial stewardship and optimized dosing regimens are needed; Although fever is frequent in acute chest syndrome, infectious triggers are rare and the prognosis is good.

Acute chest syndrome, airway inflammation and lung function in sickle cell disease.	De *et al.*, 2023.	Exploratory study	To evaluate whether children with acute chest syndrome have worse lung function than children without acute chest syndrome, and to investigate the association of pulmonary function deficits with inflammatory cytokines.	Changes in lung function were more common and inflammatory markers were elevated in patients with acute chest syndrome compared with those without acute chest syndrome. These findings suggest that airway inflammation is present in children with sickle cell anemia and acute chest syndrome, which may be contributing to impaired lung function.
Early recognition of pulmonary complications of sickle cell disease.	Breakfastly, 2023.	Retrospective study	To discuss the pathophysiology, clinical manifestations, diagnosis, and treatment options of pulmonary complications of SCD, such as acute chest syndrome, pneumonia, pulmonary thromboembolism, pulmonary fat embolism (FEP), chronic sickle cell disease (SCLD), and pulmonary hypertension (PH).	The acute and chronic pulmonary complications of SCD cause profound morbidity and mortality. Preventive measures should be taken into account and early recognition of such complications and identification of their etiologies are crucial for the management of the disease. Initiation of empiric therapy with a low threshold for blood transfusion could prevent catastrophic deterioration. Screening for pulmonary hypertension and chronic sickle cell disease should be established in patients with persistent respiratory symptoms and a history of recurrent acute chest syndrome.
Arginine Therapy and Cardiopulmonary Hemodynamics in Hospitalized Children with Sickle Cell Anemia: A Prospective, Double-blinded, Randomized Placebo-controlled Clinical Trial.	Onalo *et al.*, 2022.	Cohort, double-blind, randomized, placebo-controlled clinical study.	To evaluate the effects OF l-arginine supplementation on Doppler indices of cardiopulmonary hemodynamics in children with sickle cell anemia with pain.	Oral arginine supplementation improves cardiopulmonary hemodynamics during the occlusive vessel pain of sickle cell disease and acute chest syndrome.
The role of immature granulocyte percentage in predicting acute chest syndrome and the severity of the vaso-occlusive crisis in sickle cell disease.	Karahan *et al.*, 2022.	Cohort study	To investigate the role of GA percentage in the prediction of acute chest syndrome (STA) and vaso-occlusive crisis (VOC) severity in patients with SCD.	The significant increase in GI% in patients with VOCs compared to baseline values suggested a role for GI% in the prediction of VOCs. Although the GI% was higher in STA, its usefulness in predicting STA was low.

Hemoglobin Target and Transfusion Modality for Adult Patients With Sickle Cell Disease Acute Chest Syndrome.	Simonson *et al.*, 2022.	Retrospective cohort study	To compare the length of hospital stay (RT) in intensive care unit (ICU) patients with acute chest syndrome transfused with hemoglobin ≥ 8 g/dL versus patients transfused with hemoglobin < 8 g/dL; and to compare the length of hospital stay in patients with acute chest syndrome treated with and without exchange transfusion.	Transfusion to a target hemoglobin ≥ 8 g/dL is associated with decreased length of hospital stay in patients with acute chest syndrome. There was no difference in length of stay between patients who received exchange transfusion and those who did not.
Acute chest syndrome and COVID-19 in sickle cell disease pediatric patients	Elia *et al.*, 2021.	Case report	OBJECTIVE: To describe three cases of sickle cell anemia and acute chest syndrome that tested positive for SARS-CoV-2 and were admitted to a tertiary university hospital in São Paulo, Brazil.	Pulmonary viral infections, such as that caused by SARS-CoV-2, may predispose patients with sickle cell anemia to painful vaso-occlusive crisis and acute chest syndrome and generate a greater need for hospitalization.
Nocturnal hypoxemia measured by polysomnogram is associated with acute chest syndrome in pediatric sickle cell disease.	Nourani *et al.*, 2021.	Retrospective study	Associated with nocturnal hypoxemia and acute chest syndrome.	Nocturnal hypoxemia later in life is associated with previous hospitalizations for acute chest syndrome in children with sickle cell anemia.
Association of Antibiotic Choice With Hospital Length of Stay and Risk Factors for Readmission in Patients With Sickle Cell Disease and Acute Chest Syndrome: An Observational Cohort Study.	Badaki-Makun *et al.*, 2020.	Retrospective cohort study.	To determine the association between the use of cephalosporins and specific macrolides and the length of hospital stay in sickle cell disease (SCD) patients hospitalized with acute chest syndrome, and to determine the risk factors of treatment for 30-day readmission related to acute chest syndrome.	Guideline-consistent therapy for acute chest syndrome could preferably include ceftriaxone and azithromycin. All-cause readmission at 30 days for acute chest syndrome is lower than that reported for all-cause readmissions for sickle cell disease and more consistent with pneumonia readmission rates in the general population.
Utility of Point-of-Care Lung Ultrasonography for Evaluating Acute Chest Syndrome in Young Patients With Sickle Cell Disease.	Cohen *et al.*, 2020.	Cohort study	To determine the accuracy of point-of-care lung ultrasound to identify an infiltrate suggestive of acute chest syndrome in patients with sickle cell disease, compared to chest X-ray as the gold standard.	Point-of-care lung ultrasound is a viable alternative to chest x-ray for screening for acute chest syndrome in young patients with sickle cell disease.
Severe COVID-19 with acute respiratory distress syndrome (ARDS) in a sickle cell disease adult patient: case report.	Teulier *et al.*, 2021.	Case report	To report the case of a 33-year-old man with a history of homozygous SS homozygous sickle cell anemia who was consulted on March 24, 2020 for febrile dyspnea 11 days after symptom onset.	This case recalls the importance of a greater prevention policy against COVID-19 among the population with sickle cell anemia. In addition, it suggests a different pathophysiology of lung disorders in patients with sickle cell anemia in the case of SARS COv2. May be associated with marked hypoxemia secondary to pulmonary vascular vasodilation.

Source: Author (2024).

DEVELOPMENT

Sickle cell anemia is so named due to the sickle-shaped conformation of red blood cells that was described by Herrick in 1910. However, it was not until 1949 that sickle hemoglobin (HbS) was identified by Pauling electrophoresis (Almusally, 2023).

Sickle cell disease is a genetic disorder characterized by the production of abnormal hemoglobins, leading to the formation of sickle-shaped red blood cells (Feugray *et al.,* 2024). This change in the shape of the red blood cell is caused by the formation of the HbS tetramer during the deoxygenation phase, which produces abnormalities in the cell membrane that include rigid cells with distorted shapes and that can affect microvascular blood flow, causing vaso-occlusion at the capillary level and hemolysis (Almusally, 2023).

This vaso-occlusion caused by sickle cell disease is characterized by painful episodes, hemolytic anemia, and increased risk of infections that can lead to sepsis (Alkindi *et al*., 2024). One of the main vaso-occlusive complications of sickle cell disease is acute chest syndrome (Feugray *et al.,* 2024). Acute chest syndrome can be classified as a more severe type of vaso-occlusive crisis (Almusally, 2023).

Acute chest syndrome is characterized by fever and/or respiratory symptoms with pulmonary infiltrates (Razazi *et al.*, 2024). In fact, sepsis can precipitate this syndrome and stroke in patients with sickle cell anemia (Alkindi *et al*., 2024).

Decreased or absent splenic function in patients with sickle cell disease also occurs and represents a risk factor for severe bacterial infections (Razazi et al., 2024).

Older age, history of asthma or previous acute chest syndrome, back pain, blood transfusion within the first 24 hours, initial platelet count, and decreased hemoglobin are some signs that have been linked to increased risk of acute chest syndrome (Alghamdi *et al*., 2024). In addition, the results of Alghamdi *et al.* (2024) show that most cases of thoracic syndrome arose in children during the hospitalization period.

This syndrome is one of the leading causes of death in children and adults with sickle cell disease (Nourani, *et al*., 2021). However, in relation to the severity and mortality rate of acute chest syndrome, the numbers of adult patients exceed the number of children (Feugray *et al.,* 2024). Thus, it can be considered an acute, severe, and potentially fatal complication of sickle cell disease (Willen & Cohen, 2024).

Several risk factors have been associated with the development of this syndrome, such as young age, elevated baseline hemoglobin, steady-state leukocytosis, and airway hypersensitivity (Karahan *et al.,* 2022). However, even today, the factors that contribute to vaso-occlusive crises in patients with acute chest syndrome are not known (Alghamdi *et al*., 2024). Some patients are more susceptible to this syndrome than others, but it is still unclear whether it is related to genetic or environmental factors (Cheminet *et al.,* 2023).

Willen & Cohen (2024) report that episodes of acute chest syndrome in children are often related to an infectious agent, with 30% of acute chest syndrome cases being attributed to *S pneumoniae* and another large part to influenza in pediatric patients. In this context, due to the severity of the syndrome, a greater understanding of the pathophysiology is essential to advance the care of children with sickle cell anemia.

It occurs from increased polymerization of hemoglobin during deoxygenation. Thus, nitric oxide can be inactivated by free plasma hemoglobin and reactive oxygen due to increased hemolysis rate, causing a microvascular occlusion by sickle cells. In addition, secretory phospholipase A2 converts bone marrow fats into free fatty acids, which can accumulate in the pulmonary vasculature. If this accumulation is in the lungs, it can cause hypoventilation and atelectasis, generating pulmonary and systemic hypoxemia (Almusally, 2023).

In addition, increased hemolysis during sickle cell crises contributes to the release of free hemoglobin and erythrocyte-derived arginase into the circulation. This process leads to a faster depletion of NO, a potent vasodilator of metabolism and an important factor for cardiopulmonary hemodynamics, and arginine, one of the essential amino acids and an indispensable substrate for the manufacture of nitric oxide (Onalo *et al.*, 2022).

Changes in pulmonary function are common and inflammatory markers are elevated in patients with acute chest syndrome when compared with those without the syndrome. Thus, it suggests that the markers may be a finding that enables early care of these patients, avoiding airway inflammation and impaired lung function (De *et al.*, 2023).

It has been identified that there is an association between abnormalities in relation to free lipids in the blood and clinical manifestations of sickle cell disease. Changes in the phospholipid bilayer induce anemia and increase exposure to phosphatidylserine, a specific type of phospholipid that is essential in cell membranes, leading to vascular dysfunction, and which can be evaluated as a marker of acute chest syndrome (Feugray *et al.*, 2024).

CRP has also been recognized as a marker of acute and chronic inflammation that can be used in patients with sickle cell anemia. High CRP rates are related to acute chest syndrome and can be found both in stable patients or during vaso-occlusive crisis (Karahan *et al.*, 2022).

Elevated serum ferritin in sickle cell disease was thought to be associated with iron overload and inflammatory status of the patient. However, increased absorption has been reported as a form of compensation for hemolysis associated with anemia (Alkindi *et al*., 2024). In addition, it has been observed that early changes in hemoglobin can help anticipate the occurrence of acute chest syndrome and guide preventive practices (Alghamdi *et al*., 2024).

Increased levels of IL-6 in sputum may reflect the recruitment of monocytes and other innate immune cells in the lungs in cases of respiratory symptoms. The relationship between acute chest syndrome and pathologies that affect lung function indicates that inflammatory mediators may be responsible for this syndrome, such as interferon-induced cytokines and inflammation-causing monocytes from IL-6 (De *et al.*, 2023). Thus, the increase in IL-6 may be an early indicator of acute chest syndrome, since the levels of this sputum interleukin increased 2 days before the episodes of acute chest syndrome. Therefore, helping to identify these patients aids in the preventive anti-inflammatory therapy that can be done with tocilizumab (Allali *et al.*, 2023).

Patients with acute chest syndrome experience decreased oxygen delivery not only due to acute lung disease but also due to acute or chronic hemolytic anemia, so transfusion aimed at increasing hemoglobin can improve oxygen delivery more effectively than increasing oxygen saturation alone (Simonson *et al.*, 2022). Thus, red blood cell transfusions can be seen as a protective factor for acute chest syndrome (Alghamdi *et al*., 2024) and can even be considered the definitive therapy for acute chest syndrome (Almusally, 2023).

The physiological rationale for red blood cell transfusion in acute chest syndrome is to improve oxygen delivery to tissues, increase the overall hemoglobin level, and decrease the sickle-shaped fraction of red blood cells. This allows the patient to have relief from respiratory symptoms more quickly and allows for earlier hospital discharge (Simonson *et al.*, 2022).

Transfused patients also require additional transfusions after diagnosis of acute chest syndrome (Alghamdi *et al*., 2024). In this context, transfusion is necessary to reduce blood viscosity and consequently vaso-occlusive crises and hemolytic crises, increasing oxygen transport capacity (Almusally, 2023).

The hemoglobin level of at least 8 g/dl obtained in the transfusion is related to the decrease in the length of hospital stay and can be used in patients with acute chest syndrome. This is because supplemental oxygen has the ability to improve oxygen supply with limitations in the face of acute or chronic hemolytic anemia due to sickle cell disease (Simonson *et al.*, 2022).

According to Sharma *et al.* (2024), prophylactic transfusion therapy should be initiated to prevent and treat complications of sickle cell disease, especially acute pain crises. However, Alghamdi *et al.* (2024) reports that it remains uncertain whether acute early transfusion improves patients' prognosis. It was observed that patients transfused with packed red blood cells in the first 24 hours after admission for vaso-occlusive crises had a significantly higher risk of developing acute chest syndrome during hospitalization. Therefore, it states that further studies are needed to compare transfusions with supportive care approaches to better guide clinical management (Alghamdi *et al*., 2024).

The therapeutic concentration to achieve the effect of the antibiotic is 4 times higher than the minimum inhibitory concentration of the pathogen, ensuring bacterial death. However, patients who have already been diagnosed with sepsis have high renal clearance, which may decrease antibiotic therapy (Razazi *et al.*, 2024). In mild cases, if acute chest syndrome is suspected, it is necessary to start therapy as soon as possible as the general health condition can deteriorate rapidly (Almusally, 2023).

However, empiric antibiotic therapy is often used in these cases, due to the impossibility, in most cases, of establishing a definitive etiology. This is because untreated infections can be fatal within hours in patients with sickle cell disease (Razazi *et al*., 2024).

The administration of ceftriaxone or ceftriaxone + azithromycin was associated with shorter hospital stay than the administration of cefuroxime + azithromycin and cefotaxime + azithromycin. However, the administration of any antibiotic was associated with a lower risk of readmission and the need for red blood cell transfusion. Therefore, the administration of these drugs in conjunction with beta agonists, which act as bronchodilators, in the emergency department can help reduce the frequency of infections (Badaki-makun *et al*., 2020).

Although fever is frequent in acute chest syndrome, infectious triggers are rare and have a good prognosis. Thus, there should be a re-evaluation in relation to treatment due to the high rate of recurrence after each episode of the syndrome and in relation to antibiotic therapy with optimized dosing regimens, avoiding bacterial resistance (Cheminet *et al.*, 2023).

The differential diagnosis between pneumonia and acute chest syndrome is challenging. This is due to the tendency of infections after splenectomy, due to complications of the spleen or splenic dysfunction due to repeated vaso-occlusive crises. Therefore, it is recommended that there be preventive management for both possibilities with simultaneous administration of antibiotics and blood transfusion (Almusally, 2023).

Sickle cell anemia and sleep-disordered breathing share some common pathogenic pathways, especially when it comes to ischemia and reperfusion. Nocturnal hypoxemia is a risk factor in children with sickle cell disease and is associated with previous acute chest syndrome events, as hypoxemia induces sickling of red blood cells in patients with sickle cell disease, which leads to increased morbidity and mortality (Nourani, *et al*., 2021).

Another event that can happen is pulmonary fat embolism, which is found with some frequency in autopsies and manifests clinically with respiratory distress, fever, delirium, confusion and decreased consciousness. Embolization occurs from microvascular sickling in the intramedullary cavity of the bone, which leads to fat necrosis and spinal embolism and which can penetrate the lungs causing pulmonary fat embolism (Almusally, 2023).

Acute chest syndrome is a severe pulmonary complication of sickle cell disease that can lead to respiratory failure and is usually treated in an intensive care unit (ICU) (Simonson *et al.,* 2022). Lung infection, such as that caused by the SARS-CoV-2 virus, can predispose to more painful acute chest syndrome, leading to the need for hospitalization and even ICU admission. Even the symptoms can be very similar, such as fever, desaturation, and dyspnea, requiring a differential diagnosis that is still complex to establish due to the lack of studies on the subject (Elia *et al.,* 2021).

In this context, patients with acute chest syndrome are at higher risk of developing much more severe vascular lung damage during SARS-CoV-2 infection than the rest of the population (Teulier *et al.,* 2021).

Repeated episodes of acute chest syndrome in non-asthmatic patients with sickle cell anemia induce airway hyperresponsiveness. This condition produces wheezing heard on clinical examination and can be confused with asthma, which is an airway disease characterized by recurrent coughing attacks, shortness of breath, and wheezing (Almusally, 2023).

Treatment for acute chest syndrome requires analgesia, hydration, antibiotic therapy, bronchodilators, ventilation, which may or may not be invasive, oxygen, and blood transfusion (Almusally, 2023). Oral arginine supplementation can also be used to improve cardiopulmonary hemodynamics during the vaso-occlusive crisis of sickle cell disease and acute chest syndrome, due to its safety and low cost, and can be very useful in low-resource environments (Onalo *et al.,* 2022).

Another factor that should be kept in mind is the various barriers that hinder the advancement of research in pregnant women with sickle cell anemia. A reduction in episodes of acute vaso-occlusive crisis has been reported in pregnant patients with sickle cell anemia who received prophylactic transfusions. However, only a few approaches can be formulated based on strong evidence, due to the lack of studies related to the subject. In this situation, physicians make decisions based on their clinical judgment, which leads to discrepancies in the health services received by pregnant women with sickle cell anemia (Sharma *et al.,* 2024).

Crizanlizumab can also be used to treat the syndrome. It is a human monoclonal antibody that binds to P-selectin, an adhesion molecule found in platelets and endothelial cells that is activated in response to inflammation and trauma, and blocks the adhesion of blood cells to the endothelium. Thus, patients with life-threatening complications such as acute chest syndrome may benefit from treatment with Crizanlizumab by reducing inflammation (Afana *et al.,* 2023).

Chest X-ray is not a screening method that is considered ideal due to radiation exposure by the patient (Cohen *et al.,* 2020). However, in febrile patients with SCD and who do not have clinical signs and symptoms of respiratory distress, they should be referred for chest x-ray, given that one third of patients with acute chest syndrome have normal results (Almusally, 2023).

Point-of-care lung ultrasound is a non-invasive imaging modality that does not require radiation. In this context, it has been used to identify pulmonary pathologies and may play an important role in the early identification of acute chest syndrome with high accuracy, sensitivity, and specificity (Cohen *et al.,* 2020).

Thus, there is an urgent need to improve the care provided to patients with sickle cell anemia, similar to patients with other rare diseases, in general hospitals (Munaretto *et al.,* 2024). Diagnosis is often delayed, and patients end up receiving other diagnoses before acute chest syndrome (Cohen *et al.,* 2020).

However, there are significant discrepancies in the care of patients with sickle cell anemia in referral centers, with specialized professionals, and general hospitals. In the latter, patients receive care below what would be considered ideal, which includes the administration of analgesics, morphine, and antibiotic therapy. Therefore, the support of referral centers to general hospitals could develop strategies and protocols for better assertiveness in the care of these patients (Munaretto *et al.,* 2024).

FINAL THOUGHTS

Therefore, acute chest syndrome, despite being a frequent occurrence of patients with sickle cell anemia, requires appropriate interventions and should be treated just like rare diseases in health units, whether it is the primary health care unit or emergency room care.

Despite the heterogeneous opinions among the authors, the management performed by health professionals is based on analgesia, hydration, antibiotic therapy, bronchodilators, ventilation, which may or may not be invasive, oxygen and blood transfusion.

Finally, it is essential that more research be carried out to complement the material available in the literature, aiming to improve the care of patients with sickle cell anemia who develop acute chest syndrome and, consequently, the quality of life of these individuals.

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