Acute chest syndrome in sickle cell disease. A brief review

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Abstract

Acute chest syndrome (ACS) is a severe complication of sickle cell disease. It affects all disease genotypes, leads to prolonged hospitalisations, and is a common cause of disease-attributed mortality. Prompt diagnosis plays a crucial role in the treatment of ACS patients. Hydroxyurea and infection prevention contribute to lower rate of ACS. Moreover, transfusions and supportive care alleviate the symptoms in the acute phase of the disease. This brief review presents all aspects of ACS, from the pathophysiology and risk factors to the treatment and prevention options.

Key words: *Acute chest syndrome; sickle cell disease; complications of sickle cell disease*

INTRODUCTION

Sickle cell disease (SCD) is an autosomal recessive inherited disease with very high prevalence, especially in sub-Saharan Africa [1,2]. The disease is caused by a single nucleotide mutation of the β-globin gene (HBB) that replaces glutamate with valine. The altered haemoglobin causes shape changes to the red blood cells (RBCs) resembling sickles. The misshapen RBCs are trapped in the small blood vessels causing vessel obstruction, tissue hypoxia, and severe pain.

The severity of the symptoms varies between the affected individuals. The most common symptom is the vaso-occlusive crisis (VOC), a painful event resulting from capillary obstruction. Some patients experience life-threatening complications such as splenic sequestration crisis, neurologic complications like haemorrhagic or ischaemic stroke, and acute chest syndrome. Acute chest syndrome (ACS) is a severe complication of SCD, mainly affecting respiratory capability. Chest pain, pulmonary infiltrates, dyspnoea, and fever characterise it.

It is known that over 50% of children with homozygous SCD (HbSS) will suffer from ACS at least once in their decade of life [3]. Furthermore, ACS is a common cause of hospital admission, with a mean length of stay over seven days and in-hospital mortality of just below 2% [4]. However, some older studies have reported mortality rates up to 3% in all ACS patients, 2% in the pediatric population, and 9% in adults [5]. ACS affects all SCD genotypes but is more common in those with homozygous SS and S/beta-thalassemia-null genotypes [6]. More specifically, the incidence of ACS ranges from 3.9/100 patient-years in the HbSβ+ population to 12.8/100 patient-years in the HbSS population [7]. Recurrent episodes of ACS may lead to debilitating lung disease [8].

ACS diagnosis & clinical manifestations

According to the British Society of Haematology (BSH), ACS is defined as an acute illness with a newly developed pulmonary infiltration accompanied by fever and/ or respiratory symptoms. The symptoms include cough, chest pain, wheezing, tachypnoea, and increased work of breathing, among others [9]. Older publications described ACS as a new pulmonary infiltrate on a chest radiograph [7] or as a condition that includes chest pain, increased leukocytosis, fever, and pulmonary infiltrate [10]. Hypoxia is a worrying clinical sign, and though

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it was not initially included in the definition of ACS, others consider it part of it [8]. Hypoxia which can be defined as PaO_2 less than 60 mmHg or relative hypoxia to baseline, which is defined as more than a 2% decrease in SpO_2 from a steady state on room air, is a worrying sign. Hypoxia may precede other clinical symptoms or X-ray findings. Moreover, the clinical manifestations of ACS depend on the patient's age; for example, younger patients usually do not experience chest pain. In addition, wheezing, cough, and fever were most common among children, whereas pain in the arms and legs and dyspnoea were more common among adults [5].

An ASC severity index was proposed by Ballas et al. in 2010 (Table 1) [11]. This index was mainly used in clinical research and is not widely validated in real-world settings [12].

ACS can occur during a VOC. A predictive score, including reticulocyte and leukocyte counts and spine and pelvic pain, can be used to identify the patients that will not develop ACS. Despite its high negative predictive value (98.8%), it has a low positive predictive value (39.5%). Nevertheless, it can be a helpful tool for the early discharging of low-risk patients [13]. Secretory phospholipase A2 was evaluated as a predictive marker for developing ACS during VOC in the PROACTIVE study but showed a 24% positive predictive value [14].

As may be noted, the preceding definition lacks specificity. The clinical signs of ACS resemble those of pneumonia. These two entities usually cannot be distinguished. As a result, all patients should be treated with antibiotics for severe community-acquired pneumonia. Furthermore, other urgent medical entities should be excluded. The differential diagnosis algorithm should include acute coronary syndrome, acute myocardial infarction, pneumothorax, pleural effusions, empyema, aortic dissection, and ARDS [8].

The initial workup of a patient with suspected ACS should at least include a chest X-ray, complete blood count, basic biochemistry, blood group, and screen or crossmatch, blood cultures, ABG measurement in cases with hypoxia, serology for atypical respiratory organisms and urine for Pneumococcal and Legionella antigen, sputum for bacterial culture and nasopharyngeal swab for virus testing [9]. Moreover, a lung CT scan will be needed in only a few cases as part of the initial workup because a chest X-ray can easily identify lung infiltrates [15].

Risk factors for developing ACS

High white blood cell (WBC) counts, low haemoglo-

Table 1. *The ACS severity index, as it is first described in Ballas et al [11].*

Mild ACS	Moderate ACS	Severe ACS	Very Severe ACS
Meets the diagnostic criteria above AND all of the following:	***Meets the diagnostic criteria above AND all of the following:***	***Meets the diagnostic criteria above AND 1 or more of the following:***	***Acute Respiratory Distress Syndrome (ARDS), as defined by the 3 criteria of the American-European Consensus Conference, includes:***
Transcutaneous oxygen saturation >90% in room air (FiO2 = 0.21)	Transcutaneous oxygen saturation ≥85% in room air (FiO2 = 0.21)	Respiratory failure (PaO2 <60 mmHg or PCO2 >50 mmHg) Mechanical ventilatory support required Transcutaneous oxygen saturation <85% in room air or ≤90% despite maximal supplemental oxygen	Acute onset of bilateral infiltrates on chest radiograph
Segmental or lobar infiltrates that involve no more than 1 lobe by chest radiography	Segmental or lobar infiltrates that involve no more than 2 lobes by chest radiography	Segmental or lobar infiltrates that involve 3 or more lobes by chest radiography	Pulmonary artery wedge pressure of <19 mmHg or the absence of clinical evidence of left atrial hypertension
Responsive to simple transfusion of no more than 2 units of red blood cells (or 15 cc/kg packed red blood cells)	Responsive to transfusion of ≥3 units of red blood cells (or more than 20 cc/kg packed red blood cells)	Requiring transfusion or exchange transfusion of red blood cells to achieve haemoglobin A ≥70%	PaO2/FiO2 ≤200 regardless of positive end-expiratory pressure (PEEP) level

bin F (HbF), young age, and more than 3 VOC episodes in the past years are well-established risk factors. Asthma and tobacco use are also related to ACS occurrence. Another risk factor is the genotype; individuals with more severe SCD (HbSS and HbSβ0) tend to develop more frequently ACS than those with mild SCD (HbSC and HbSβ+ genotypes) [16].

Acute chest syndrome pathophysiology

ACS is a type of acute lung injury. The exact events that lead to the syndrome manifestation are not fully known. The triggering causes contributing to the presentation of ACS are infections, pulmonary fat embolism, and pulmonary artery infarctions [17]. These events eventually lead to ventilation-perfusion mismatch, hypoxemia, and acute pulmonary artery and right ventricular pressure increases. At the microscopic level, there is vaso-occlusion, sickling of the abnormal red blood cells, adhesion of leukocytes, and inflammation of the pulmonary vascular endothelium. The inflammation is promoted to the nearby alveolar and small airway tissues [18].

Pulmonary infection is detected in up to 38% of patients with ACS. In children with ACS, the most typical cause is viral infections. The respiratory syncytial virus (RSV) is the main culprit. Moreover, atypical bacteria such as *Mycoplasma pneumoniae* can also be detected in children with ACS. Other bacteria, such as *Staphylococcus aureus* and *Streptococcus pneumoniae*, can be detected, especially in adult patients. Infections can induce excessive acute lung injury in a SCD patient. This is proven in SCD mouse models, which developed acute lung injury with a low dose of endotoxin, while the wild-type mice remained unaffected [19]. SARS-CoV-2 infection was identified as a triggering event of ACS. These two entities have overlapping symptoms and radiological signs. The patients that develop ACS usually have more localised infiltrates consistent with consolidation rather than a more diffuse pattern [20–23].

Pulmonary fat embolism is associated with ACS [24]. The emboli are derived from the infarcted and necrosed bone marrow. The fat is turned into free fatty acids in the lung's blood vessels, promoting inflammation and endothelial damage. Fat embolism is shown in autopsy studies. In the living, the diagnosis of pulmonary fat embolism is based on the presence of fat-laden macrophages in the bronchoalveolar lavage (BAL). However, BAL cannot be performed in every ACS case.

Pulmonary vessel infarction is another cause of ACS. The misshapen red cells obstruct the pulmonary vessel leading to exacerbations of hypoxemia. CT pulmonary angiogram (CTPA) is not routinely done in patients with ACS. However, Dessap et al., in a prospective study, have shown a 17% prevalence of pulmonary artery embolism detected by CTPA [25].

Management of ACS

There are no randomised clinical trials for the ACS. ACS is potentially fatal; therefore, early diagnosis and treatment are essential. The treatment aims to minimise irreversible lung damage that leads to long-term sequelae.

Oxygen supply should be given to maintain SpO_2 levels beyond 95%. SpO2 levels should be regularly monitored. ICU specialists should be informed in case of an increased need for oxygen support. Noninvasive ventilation (NIV) has been used in ACS cases with severe hypoxia. The NIV could reduce the need for intubation and mechanical intubation. Bilevel positive pressure (BiPAP), continuous positive pressure support (CPAP), and high-flow oxygen can be used in trained centers and wards [26,27]. NIV lowers the respiratory rate, raises PaO2, and reduces heart rate. Mechanical ventilation may be required in patients with worsening acute respiratory despite NIV or with a failing level of consciousness [9,28]. Furthermore, few reported cases of successful use of veno-venous extracorporeal membrane oxygenation (VV-ECMO) despite the increased risk of haemolysis and thrombosis from SCD [29,30].

Intravenous (IV) hydration should be provided to all patients with ACS. The amount of IV crystalloids needed depends on the patient's cardiopulmonary status. Fluid intake and outtake should be closely monitored to avoid fluid overload and acute pulmonary oedema.

In many cases, ACS is accompanied by VOC affecting the thoracic bones (sternum, ribs, and thoracic spines). The chest pain affects normal breathing and leads to lung atelectasis. Therefore, sufficient pain relief treatment can ameliorate breathing function. Acetaminophen, non-steroid anti-inflammatory drugs and opioids can be used. Other drugs, such as inhaled nitric oxide, have not been proven effective [31]. However, opioid overdose can lead to alveolar hypoventilation and ACS [32]. A strategy that can lead to lower doses of morphine is patient-controlled analgesia. It is a strategy in which the patients can titrate the analgesia by themselves, leading to lower cumulative doses of morphine [33].

Incentive spirometry can be combined with the

appropriate pain relief to reduce the incidence of ACS in case of thoracic bone infarction. It is studied in the pediatric population and post-operative setting [34–36]. Usually, ten inspirations every two hours when the patient is awake are sufficient. Despite the encouraging results in the pediatric population, incentive spirometry was not proven effective in adult patients. In a recently published small randomised trial, incentive spirometry did not significantly reduce the incidence of ACS [37].

As mentioned above, ACS cannot be distinguished from lower respiratory tract infections. Therefore, antibiotics are recommended in all cases [9]. Despite the lack of randomised controlled trials on this topic [38], all patients should receive community-acquired pneumonia treatment. It should be noted that the antibiotic regimen covers causes of atypical pneumonia, such as *Mycobacterium pneumoniae* and *Chlamydia pneumoniae*. Ceftriaxone plus a macrolide (azithromycin or clarithromycin) or a fourth-generation fluoroquinolone such as moxifloxacin or levofloxacin can be used [39].

The use of blood transfusions is a generally accepted clinical practice in the context of critically ill ACS patients [40]. However, no randomised clinical trials support this practice, except for one inconclusive trial due to a small group of participants [41]. Not all patients with ACS require a blood transfusion. The clinician should choose between a simple or top-up transfusion and an exchange transfusion. A simple transfusion can be used when the patient is anaemic. An exchange transfusion can be used when the patient is severely ill or continues to deteriorate despite the simple transfusion. A haemoglobin higher than 9 gr/dl before the exchange transfusion is preferred [9]. Most clinicians aim at haemoglobin S (HbS) levels lower than 30-40% when performing exchange transfusions.

Corticosteroids have been used in the treatment of ACS. The patients recovered faster but had higher readmission rates due to recurrent VOCs [42,43]. Moreover, a small retrospective study showed that inhaled corticosteroids do not decrease the morbidity of ACS [44]. Therefore, the use of corticosteroids is generally not suggested. Patients with ACS in combination with acute asthma or COVID-19 may be the exception [9,45,46].

ACS prevention

Hydroxyurea (HU) has been used for VOC prevention. The drug elevates the HbF levels, interrupting the elongation of deoxy-HbS polymers, decreases the adhesion of blood cells to the vascular endothelium, and finally improves vascular tone. It is shown that HU reduces the ACS in the first year of the treatment. The beginning dose is 15 mg/kg/day and gradually increases to the maximum tolerated dose (usually 30-35 mg/kg/day) [47,48]. If the HU is ineffective or cannot be tolerated by the patient, long-term transfusion may be a solution. It is shown that sickle cell patients that receive long-term transfusions for stroke prevention or silent cerebral infarct prevention have lower rates of ACS [49,50]. The major side effect of chronic transfusion is iron overload. Individuals receiving frequent transfusions should receive chelation therapy and monitor with MRI for liver haemochromatosis [40].

Another option, in case HU is not tolerated or is ineffective, is disease-modifying drugs such as crizanlizumab and L-glutamine. It is not proven that these drugs are effective in preventing ACS. However, they reduce the preceding VOCs. It is to be noted that the L-glutamine is not approved by the European Medicines Agency (EMA). Voxelotor is a recently approved drug that acts as an HbS polymerisation inhibitor. Voxelotor increases haemoglobin and reduces haemolysis. It is yet unclear whether the voxelotor improves the clinical symptoms of SCD [51].

Hopefully, new drugs are on the way, such as the first-in-class, oral, small-molecule allosteric activator of pyruvate kinase, mitapivat. This drug is being evaluated in clinical trials and is expected to increase haemoglobin levels and reduce VOCs and other complications like ACS, osteonecrosis, and nephropathy [52].

Another strategy for reducing the risk of ACS is infection prevention. The prophylactic use of penicillin V until at least the age of five years, pneumococcal vaccination, and annual influenza vaccination are highly recommended. Apart from the routine vaccination series with the pneumococcal conjugate vaccine PCV13, children with SCD should receive the pneumococcal polysaccharide vaccine PPSV23 at age of two years for additional protection against *S. pneumoniae* with a booster given at five years of age. The influenza vaccine should be started at the age of six months. There is no evidence for prophylactic antibiotics to prevent ACS in patients with VOC [9,36,53].

Long term complications

Interstitial lung disease and pulmonary hypertension were considered long-term complications of recurrent ACS, although no causation is documented [8]. Radiologic studies have shown increased scarring

and fibrotic lesions in patients with repeated ACS [54]. Furthermore, a case series study showed diffuse cystic lung disease in SCD patients, which has never been reported again, although a correlation with ACS was not established [55]. A relatively recent study from Nigeria in paediatric patients showed that abnormal lung function assessed by spirometry was correlated with repetitive ACS [56]. An older study in the adult population showed only a trend toward lower total lung capacity and haemoglobin-adjusted diffusing capacity in those with repeated ACS [57].

CONCLUSION

ACS is a complication and a common cause of death in patients with SCD [58]. However, mortality has decreased over the years with the introduction of antibiotics, vaccinations, hydroxyurea use, and therapeutic education for families. VOC prevention can lead to less ACS incidence and a better quality of life [59]. Hydroxyurea has shown effectiveness against the complications of SCD and ACS. New studies should address ACS's incidence, morbidity, and mortality in the post-hydroxyurea era. Furthermore, new drugs recently approved for SCD need to prove effective in preventing ACS. Apart from these classical treatment approaches, ongoing and planned gene therapy trials aim to cure SCD.

In addition, patients with suspected ACS should be aggressively treated. Oxygen supply, hydration, pain relief, and blood transfusions are the cornerstones in the management of ACS (Figure 1). The role of novel drugs in shortening hospital staying or ACS outcomes is unknown. Clinical trials regarding the optimal management of ACS are needed.

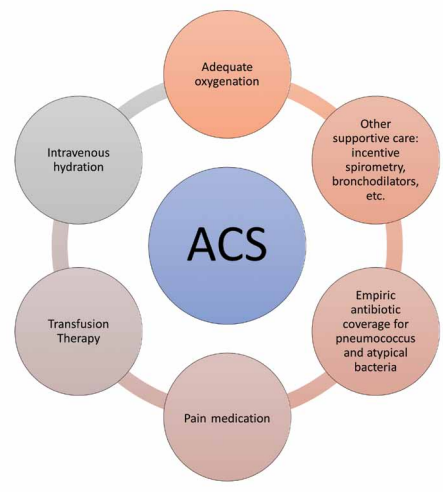

Figure 1. The main cornerstones in treating ACS.

Overall medical advances have changed the quality of life of SCD patients in the last decades, yet many aspects need improvement. Lastly, action should be taken to ameliorate the disparities between SCD patients with different socio-economic or racial statuses to have access to medical care and optimal management of their disease complications [60].

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REFERENCES

1. Wastnedge E, Waters D, Patel S, Morrison K, Goh MY, Adeloye D, et al. The global burden of sickle cell disease in children under five years of age: a systematic review and meta-analysis. J Glob Health. 2018;8(2):021103.
2. Colombatti R, Birkegård C, Medici M. PB2215: Global epidemiology of sickle cell disease: A systematic literature review. HemaSphere. 2022;6:2085.
3. Gill FM, Sleeper LA, Weiner SJ, Brown AK, Bellevue R, Grover R, et al. Clinical events in the first decade in a cohort of infants with sickle cell disease. Cooperative Study of Sickle Cell Disease. Blood. 1995;86(2):776–83.
4. Allareddy V, Roy A, Lee MK, Nalliah RP, Rampa S, Allareddy V, et al. Outcomes of Acute Chest Syndrome in Adult Patients with Sickle Cell Disease: Predictors of Mortality. PLoS One. 2014;9(4):e94387.
5. Vichinsky EP, Neumayr LD, Earles AN, Williams R, Lennette ET, Dean D, et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. N Engl J Med. 2000;342(25):1855–65.
6. Pahl K, Mullen CA. Original Research: Acute chest syndrome in sickle cell disease: Effect of genotype and asthma. Exp Biol Med (Maywood). 2016;241(7):745-8.
7. Castro O, Brambilla DJ, Thorington B, Reindorf CA, Scott RB, Gillette P, et al. The acute chest syndrome in sickle cell disease: incidence and risk factors. The Cooperative Study of Sickle Cell Disease. Blood. 1994;84(2):643-9.
8. Friend A, Girzadas D. Acute Chest Syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 [cited 2023 Feb 18]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK441872/
9. Howard J, Hart N, Roberts-Harewood M, Cummins M, Awogbade M, Davis B. Guideline on the management of acute chest syndrome in sickle cell disease. Br J Haematol. 2015;169(4):492–505.
10. Charache S, Scott JC, Charache P. "Acute chest syndrome" in adults with sickle cell anemia. Microbiology, treatment, and prevention. Arch Intern Med. 1979;139(1):67–9.
11. Ballas SK, Lieff S, Benjamin LJ, Dampier CD, Heeney MM,

Hoppe C, et al. Definitions of the Phenotypic Manifestations of Sickle Cell Disease. Am J Hematol. 2010;85(1):6–13.
12. Mittal N, Hsu LL. A Survey of Resident Physicians' and Nurses' Knowledge of Severity Assessment of Acute Chest Syndrome and Role of Incentive Spirometry in Management. Blood. 2015;126(23):2064.
13. Bartolucci P, Habibi A, Khellaf M, Roudot-Thoraval F, Melica G, Lascaux AS, et al. Score Predicting Acute Chest Syndrome During Vaso-occlusive Crises in Adult Sickle-cell Disease Patients. EBioMedicine. 2016;10:305–11.
14. Styles L, Wager CG, Labotka RJ, Smith-Whitley K, Thompson AA, Lane PA, et al. Refining the value of secretory phospholipase A2 as a predictor of acute chest syndrome in sickle cell disease: results of a feasibility study (PROACTIVE). Br J Haematol. 2012;157(5):627–36.
15. Vichinsky EP, Styles LA, Colangelo LH, Wright EC, Castro O, Nickerson B, et al. Acute Chest Syndrome in Sickle Cell Disease: Clinical Presentation and Course. Blood. 1997;89(5):1787–92.
16. Risk Factors for Development of Acute Chest Syndrome. AAP Grand Rounds. 2018;39(5):59.
17. Jain S, Bakshi N, Krishnamurti L. Acute Chest Syndrome in Children with Sickle Cell Disease. Pediatr Allergy Immunol Pulmonol. 2017;30(4):191–201.
18. Platt OS. Sickle cell anemia as an inflammatory disease. J Clin Invest. 2000;106(3):337–8.
19. Holtzclaw JD, Jack D, Aguayo SM, Eckman JR, Roman J, Hsu LL. Enhanced pulmonary and systemic response to endotoxin in transgenic sickle mice. Am J Respir Crit Care Med. 2004;169(6):687–95.
20. Beerkens F, John M, Puliafito B, Corbett V, Edwards C, Tremblay D. COVID-19 pneumonia as a cause of acute chest syndrome in an adult sickle cell patient. Am J Hematol. 2020;95(7):E154–6.
21. Justino CC, Campanharo FF, Augusto MN, Morais SC de, Figueiredo MS. COVID-19 as a trigger of acute chest syndrome in a pregnant woman with sickle cell anemia. Rev Bras Hematol Hemoter. 2020;42(3):212–4.
22. Morrone KA, Strumph K, Liszewski MC, Jackson J, Rinke ML, Silver EJ, et al. 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;67(11):e28579.
23. Calderwood S, Sabir A, Rao L, Baker B, Balasa V, Sathi BK. SARS-CoV-2 Infection Presenting as Acute Chest Syndrome in a Child With Hemoglobin SD-Los Angeles Disease: A Case Report and Review of Literature. J Pediatr Hematol/Oncol. 2023;45(2):82.
24. Vichinsky E, Williams R, Das M, Earles AN, Lewis N, Adler A, et al. Pulmonary fat embolism: a distinct cause of severe acute chest syndrome in sickle cell anemia. Blood. 1994;83(11):3107–12.
25. Dessap AM, Deux JF, Abidi N, Lavenu-Bombled C, Melica G, Renaud B, et al. Pulmonary Artery Thrombosis during Acute Chest Syndrome in Sickle Cell Disease. Am J Respir Crit Care Med. 2011;184(9):1022–9.
26. Heilbronner C, Grimaud M, Oualha M, Sommet J, Rambaud J, Brousse V, et al. Therapeutic approach to pediatric patients with acute chest syndrome: national multicenter survey of non invasive ventilation (NIV) and transfusion. Arch Pediatr. 2021;28(7):559–66.
27. Guenther CS, Pae VJ, Neri CM, Barry K, Duggan MA, Cohen RT. SNAP: Supportive noninvasive ventilation for acute chest syndrome prevention in children with sickle cell disease. Pediatr Blood Cancer. 2021;68(8):e29136.
28. Fartoukh M, Lefort Y, Habibi A, Bachir D, Galacteros F, Godeau B, et al. Early intermittent noninvasive ventilation for acute chest syndrome in adults with sickle cell disease: a pilot study. Intensive Care Med. 2010;8(36):1355–62.
29. Koh W, Malik P, Whitehead J, Morales DLS, Hayes Jr. D. Successful use of veno-venous extracorporeal membrane oxygenation for acute chest syndrome in a child with sickle cell disease and SARS-CoV-2. Pediatr Pulmonol. 2022;57(4):1096–9.
30. Alashkar F, Herbstreit F, Carpinteiro A, Baum J, Tzalavras A, Aramayo-Singelmann C, et al. Veno-Venous Extracorporeal Membrane Oxygenation in Adult Patients with Sickle Cell Disease and Acute Chest Syndrome: a Single-Center Experience. Hemoglobin. 2020;44(2):71–7.
31. Gladwin MT, Kato GJ, Weiner D, Onyekwere OC, Dampier C, Hsu L, et al. Nitric oxide for inhalation in the acute treatment of sickle cell pain crisis: a randomized controlled trial. JAMA. 2011;305(9):893–902.
32. Kopecky EA, Jacobson S, Joshi P, Koren G. Systemic exposure to morphine and the risk of acute chest syndrome in sickle cell disease. Clin Pharmacol Ther. 2004;75(3):140–6.
33. van Beers EJ, van Tuijn CFJ, Nieuwkerk PT, Friederich PW, Vranken JH, Biemond BJ. Patient-controlled analgesia versus continuous infusion of morphine during vaso-occlusive crisis in sickle cell disease, a randomized controlled trial. Am J Hematol. 2007;82(11):955–60.
34. Reagan MM, DeBaun MR, Frei-Jones MJ. Multi-modal intervention for the inpatient management of sickle cell pain significantly decreases the rate of acute chest syndrome. Pediatr Blood Cancer. 2011;56(2):262–6.
35. Bellet PS, Kalinyak KA, Shukla R, Gelfand MJ, Rucknagel DL. Incentive spirometry to prevent acute pulmonary complications in sickle cell diseases. N Engl J Med. 1995;333(11):699–703.
36. Yawn BP, Buchanan GR, Afenyi-Annan AN, Ballas SK, Hassell KL, James AH, et al. Management of Sickle Cell Disease: Summary of the 2014 Evidence-Based Report by Expert Panel Members. JAMA. 2014;312(10):1033–48.
37. van Tuijn CFJ, Gaartman AE, Nur E, Rijneveld AW, Biemond BJ. Incentive spirometry to prevent acute chest syndrome in adults with sickle cell disease; a randomized controlled trial. Am J Hematol. 2020;95(7):E160–3.
38. Martí-Carvajal AJ, Conterno LO, Knight-Madden JM. Antibiotics for treating acute chest syndrome in people with sickle cell disease. Cochrane Database of Systematic Reviews [Internet]. 2019 [cited 2023 Mar 15];(9). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006110.pub5/full

39. Wang K, Das-Ireland M. Acute Chest Syndrome: A narrative review to guide inpatient management. AJHM [Internet]. 2022 Jun 30 [cited 2023 Mar 18]; Available from: https://medicine.missouri.edu/sites/default/files/ajhm/2022_AJHM_April-June_REVIEW_ARTICLE.pdf
40. Chou ST, Alsawas M, Fasano RM, Field JJ, Hendrickson JE, Howard J, et al. American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support. Blood Adv. 2020;4(2):327–55.
41. Dolatkhah R, Dastgiri S. Blood transfusions for treating acute chest syndrome in people with sickle cell disease. Cochrane Database Syst Rev. 2020;2020(1):CD007843.
42. Bernini JC, Rogers ZR, Sandler ES, Reisch JS, Quinn CT, Buchanan GR. Beneficial effect of intravenous dexamethasone in children with mild to moderately severe acute chest syndrome complicating sickle cell disease. Blood. 1998;92(9):3082–9.
43. Strouse JJ, Takemoto CM, Keefer JR, Kato GJ, Casella JF. Corticosteroids and increased risk of readmission after acute chest syndrome in children with sickle cell disease. Pediatr Blood Cancer. 2008;50(5):1006–12.
44. Leonard A, Godiwala N, Herrera N, McCarter R, Sharron M, Meier ER. Early initiation of inhaled corticosteroids does not decrease acute chest syndrome morbidity in pediatric patients with sickle cell disease. Blood Cells Mol Dis. 2018;71:55–62.
45. Christian J, Lanzkron S, Naik RP. COVID-19 outcomes in sickle cell disease and sickle cell trait. Best Pract Res Clin Haematol. 2022;35(3):101382.
46. Glassberg JA, Strunk R, DeBaun MR. Wheezing in children with sickle cell disease. Curr Opin Pediatr. 2014;26(1):9–18.
47. de Montalembert M, Voskaridou E, Oevermann L, Cannas G, Habibi A, Loko G, et al. Real-Life experience with hydroxyurea in patients with sickle cell disease: Results from the prospective ESCORT-HU cohort study. Am J Hematol. 2021;96(10):1223–31.
48. Tonin FS, Ginete C, Ferreira J, Delgadinho M, Santos B, Fernandez-Llimos F, et al. Efficacy and safety of pharmacological interventions for managing sickle cell disease complications in children and adolescents: Systematic review with network meta-analysis. Pediatr Blood Cancer. 2023;70(6):e30294.
49. Miller ST, Wright E, Abboud M, Berman B, Files B, Scher CD, et al. Impact of chronic transfusion on incidence of pain and acute chest syndrome during the Stroke Prevention Trial (STOP) in sickle-cell anemia. J Pediatr. 2001;139(6):785–9.
50. DeBaun MR, Gordon M, McKinstry RC, Noetzel MJ, White DA, Sarnaik SA, et al. Controlled Trial of Transfusions for Silent Cerebral Infarcts in Sickle Cell Anemia. N Engl J Med. 2014;371(8):699–710.
51. Howard J, Ataga KI, Brown RC, Achebe M, Nduba V, El-Beshlawy A, et al. Voxelotor in adolescents and adults with sickle cell disease (HOPE): long-term follow-up results of an international, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Haematol. 2021;8(5):e323–33.
52. van Dijk MJ, Rab MAE, van Oirschot BA, Bos J, Derichs C, Rijneveld AW, et al. Safety and efficacy of mitapivat, an oral pyruvate kinase activator, in sickle cell disease: A phase 2, open-label study. Am J Hematol. 2022;97(7):E226–9.
53. Sobota A, Sabharwal V, Fonebi G, Steinberg M. How we prevent and manage infection in sickle cell disease. Br J Haematolol. 2015;170(6):757–67.
54. Klings ES, Steinberg MH. Acute chest syndrome of sickle cell disease: genetics, risk factors, prognosis, and management. Expert Rev Hematol. 2022;15(2):117–25.
55. Kort F, Habibi A, Lionnet F, Carette MF, Parrot A, Savale L, et al. Diffuse cystic lung disease in sickle cell anaemia: a series of 22 cases and a case–control study. Thorax. 2022;77(1):91–3.
56. Adegoke SA, Kuti BP, Omole KO, Smith OS, Oyelami OA, Adeodu OO. Acute chest syndrome in sickle cell anaemia: higher serum levels of interleukin-8 and highly sensitive C-reactive proteins are associated with impaired lung function. Paediatr Int Child Health. 2018;38(4):244–50.
57. Klings ES, Wyszynski DF, Nolan VG, Steinberg MH. Abnormal Pulmonary Function in Adults with Sickle Cell Anemia. Am J Respir Crit Care Med. 2006;173(11):1264–9.
58. Ngo S, Bartolucci P, Lobo D, Mekontso-Dessap A, Gellen-Dautremer J, Noizat-Pirenne F, et al. Causes of Death in Sickle Cell Disease Adult Patients: Old and New Trends. Blood. 2014;124(21):2715.
59. Osunkwo I, Andemariam B, Minniti CP, Inusa BPD, El Rassi F, Francis-Gibson B, et al. Impact of sickle cell disease on patients' daily lives, symptoms reported, and disease management strategies: Results from the international Sickle Cell World Assessment Survey (SWAY). Am J Hematol. 2021;96(4):404–17.
60. Power-Hays A, McGann PT. When Actions Speak Louder Than Words — Racism and Sickle Cell Disease. N Engl J Med. 2020;383(20):1902–3.

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