REVIEW

Acute Chest Syndrome: A Narrative Review to Guide Inpatient Management

Kevin Wang, DO,[1] Monisha Das-Ireland[2]

[1]Department of Internal Medicine, University of Missouri – Kansas City School of Medicine, Kansas City, MO, USA
[2]Department of Pulmonary-Critical Care, University of Missouri – Kansas City School of Medicine, Kansas City, MO, USA

Corresponding author: Kevin Wang (kkwcvb@umkc.edu)

Received: 3/29/2022 Revised: 5/10/2022 Accepted: 5/17/2022 Published: 12/31/2022

Am j Hosp Med 2022 Oct;6(4): 2022. DOI: https://doi.org/10.24150/ajhm/2022.013

Keywords: Acute Chest Syndrome, Sickle Cell Disease, Vaso-Occlusive Crisis, Opioid, Antibiotics, Transfusion, Consolidation

ABSTRACT

Introduction: Acute Chest Syndrome (ACS) is a leading complication of sickle cell disease (SCD) with significant morbidity and mortality. The current practice guidelines lack sufficient detail on the evidence behind our standard of practice.

Materials and Methods: A comprehensive literature search was accomplished with PubMed with a particular focus on literatures published between 2015-2021 with the keywords ACS management, vaso-occlusive crisis, sickle cell, antibiotics, opioids, transfusion, fluid, steroids, bronchodilators, incentive spirometry, anticoagulation, oxygen, prevention, and SARS-CoV2. We included literatures both in the adult and pediatric population.

Results/Discussion: ACS is defined as a new infiltrate in a chest radiograph involving at least one broncho-pulmonary segment in an individual with one additional clinical finding. There are multiple causes of ACS which include infections, pulmonary edema, hypoxemia, and hypoventilation. The goal is to quickly diagnose and treat this condition to prevent irreversible lung damage and mortality. In this narrative review, we discuss why a balanced approach to fluid and pain management will provide better outcomes for patients, and the evidence behind using antibiotics, steroids, bronchodilators, nitric oxide, incentive spirometry, as well as the current management of patients with concomitant ACS and SARS-CoV2.

Conclusions: All patients admitted with ACS should be started on a third-generation cephalosporin and macrolide or a fourth-generation fluoroquinolone, incentive spirometry, thromboprophylaxis, oxygen, and simple or exchange transfusion if needed, with a balanced approach to fluid resuscitation and pain control.

INTRODUCTION

Acute Chest Syndrome (ACS) is the leading cause of death and second most common cause of hospitalization in patients with sickle cell disease (SCD).[1] It is diagnosed with the presentation of new radiographic findings and often accompanied by fever or respiratory symptoms. Prompt diagnosis and management are crucial to prevent irreversible lung damage

and death. This review article will provide a framework to guide hospitalists to manage patients admitted with ACS. We will also present the available literature to date to support these guidelines. A comprehensive literature search was accomplished with PubMed with a particular focus on literature published between 2015-2021 with the keywords ACS management, vaso-occlusive crisis, sickle cell, antibiotics, opioids, transfusion, fluid, steroids, bronchodilators, incentive spirometry, anticoagulation, oxygen, prevention, and SARS-CoV2. We included literatures both in the adult and pediatric population.

ETIOLOGY

Any pathologies that cause hypoxia may be an inciting event for ACS, including but not limited to infection, asthma, oversedation, fluid overload, obstructive sleep apnea, or hypoventilation. This is because hypoxemia promotes sickling in the pulmonary vasculature.[2]

The most common causes of infection in the pediatric population are viral or *Chlamydia pneumoniae*, and in the adult population is *Mycoplasma pneumoniae*. Infectious causes of ACS are more common in the pediatric population and have three times prevalence during winter.[3] Infections trigger ACS by promoting excessive lung inflammation due to the damaged lung microvasculature in a person with an already high inflammatory state, on top of having the Virchow's Triad.[4]

In the adult population, fat embolism is suspected to be the most common cause, as postmortem bronchoalveolar lavage in many patients who have died from SCD demonstrates fat-containing alveolar macrophage.[5]

Opioid-induced hypoventilation is another etiology common in the adult population. It has been observed that adult patients often are not admitted due to ACS but rather with vaso-occlusive crisis (VOC), then later during the hospital course develop ACS. Opioids, commonly used to treat VOC**,** may cause hypoventilation and atelectasis in these adult patients, resulting in ACS.[5]

PATHOPHYSIOLOGY

ACS is an acute lung injury that is a product of the prothrombotic nature of SCD: the Virchow's triad, elevated levels of inflammatory cytokines, abnormal rheology of sickled red blood cells (RBCs) adhering to leukocytes, resulting in vaso-occlusion and tissue hypoxia. This promotes inflammation and infarction in the pulmonary vasculature, which leads to atelectasis, hypoventilation, and ventilation-perfusion mismatch and can become a vicious cycle that further worsens infarction and inflammation. If patients are not treated promptly or face repeated insults, they can be left with elevated pulmonary artery and right ventricular pressure, and heart failure.[3]

CLINICAL PRESENTATION

Diagnosis of ACS must have both a radiographic finding and at least one clinical finding. The radiographic finding must include a new pulmonary infiltrate involving at least one lung segment that is not due to atelectasis (Figures 1 and 2). Clinical findings include tachypnea, temperature greater than 38.5 degrees Celsius, hypoxemia, rales, and respiratory symptoms **s**uch as chest pain, shortness of breath, wheezing, and cough. It is important to note, however, that radiologic signs often lag behind clinical symptoms. Therefore, if a patient has hypoxia with a normal chest x-ray, ACS should still be on the differential and a CT chest should be obtained**.**[2,6]

Some patients may present with symptoms consistent with severe ACS including multi-lobar disease, inability to maintain oxygen saturation >95% on supplemental oxygen, increased difficulty breathing, or pleural effusions.[7]

MANAGEMENT

Fluids

We recommend conservative and individualized fluid resuscitation with IV crystalloids to patients who are hypovolemic, while being cognizant of the patients' fluid balance and cardiopulmonary status. Maintenance fluid should only be provided to patients who cannot take in oral hydration. Any fluid administration must be closely monitored to prevent fluid overload, pulmonary edema, and worsening of ACS.

The theory behind providing fluid is to stop or slow the rate of sickling by increasing plasma volume to decrease blood viscosity. There is, however, significant heterogeneity in the amount of fluid provided across different institutions. This comes with significant risk of fluid overload in patients with ACS.[8]

The reason to be conservative and selective with fluid management is that fluid overload has been implicated in triggering ACS by inducing atelectasis or pulmonary edema. This is especially problematic as SCD patients have a higher incidence of concomitant renal or cardiovascular comorbidities compared to the general population. The data on efficacy and safety of IV fluids are also scant. One retrospective study in 2020 demonstrated a higher association of adverse events when an increased amount of IV fluids was given in the first 24 hours and over an entire hospitalization. Adverse events were defined by new oxygen requirement, ACS, aspiration event, hospital-acquired infection, acute kidney injury, or ICU transfers. However, the incidence of ACS itself was not increased in the group that received more IV fluids.[8] To date, we could not find any data supporting the use of IV fluids to prevent or improve ACS. Current evidence demonstrates that fluid administration to SCD patients experiencing VOC is purely theoretical and that higher fluid administration, especially in the first 24 hours, is concerning for increased adverse events. There is a need for double-blind randomized controlled trials (RCTs) before making conclusions about the efficacy and risk of IV fluids in regard to treating VOC and ACS.

Oxygen

Supplemental oxygen therapy is recommended for any patients with low SpO2 or PaO2. The optimal SpO2 is not known**.** The general guideline is to use supplemental oxygen therapy for signs of tachypnea, or to keep SpO2 above 92% or within 3% of their baseline while ensuring PaO2 is above 70mmHg. If needed, we also recommend escalating to noninvasive ventilation (NIV), mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

This recommendation is founded on the mechanism of hypoxia causing ACS. In alveolar hypoxia, sickle cells are trapped within small alveolar vasculature, thereby inducing sickling even more. There is minimal evidence on whether oxygen therapy prevents ACS or the best oxygen delivery method. We found only one prospective randomized controlled study comparing NIV to supplemental oxygen delivered via face mask. NIV did not improve the patient's hypoxemia but did improve the patient's respiratory rate and A-a gradient. The length of hospitalization, however, did not differ.[9]

Antibiotics

A third-generation cephalosporin and a macrolide, or a fourth-generation fluoroquinolone is recommended for all patients diagnosed with ACS to cover for Chlamydia, Mycoplasma, *Streptococcus pneumoniae*, and *Haemophilus influenzae*.[2] These are the most common organisms associated with ACS, and antibiotics should be given regardless of blood or sputum cultures.

To date, there are no RCTs to fully determine the efficacy or safety of antibiotics in the treatment of ACS. The only study we could find to date on this topic is a retrospective study in the pediatric population demonstrating a decrease in all-cause readmission at 7 and 30 days and 30 days ACS-related readmission after receiving guideline adherent antibiotics.

However, these patients also had a longer length of hospital stay, ICU stay, and higher mortality.[10-12]

Pain Control/Opioids

We recommend treating pain aggressively with non-opioids or non-pharmacological therapies such as acetaminophen, NSAIDs, and heat, massage, while being judicious with parenteral opioids. The goal is to prevent atelectasis while also being cautious of oversedation and hypoventilation, all of which can exacerbate ACS.

Some studies have suggested that narcotics may be beneficial if given judiciously. Patient-controlled analgesia, for example, has been associated with shorter hospital stay, decreased total opioid consumption, and higher patient satisfaction.[13] Another small pediatric retrospective study showed patients treated with nalbuphine had a fivefold decrease in the rate of ACS development, theorized to be due to the different receptors nalbuphine targets by effectively controlling pain while not causing as much hypoventilation compared to morphine.[14]

High doses of opioids, however, have been associated with worse outcomes in some studies. A small (15 pediatric patients) RCT of oral versus continuous IV morphine to treat VOC demonstrated that patients receiving oral morphine have a higher plasma morphine concentration and morphine metabolite (morphine-6-glucuronide) concentration compared to patients receiving IV. The result showed patients receiving oral morphine had an increased risk of developing ACS.[15] Another study similarly demonstrated that children who received higher cumulative doses of morphine due to acute pain crisis had a higher risk of developing ACS during hospitalization.[16]

It is difficult to draw conclusions about the degree to which pain medications, including opioids, prevent or cause ACS due to a lack of quality clinical studies. Given our understanding of the pathophysiology of ACS that narcotics may be beneficial in small quantities and harmful in large quantities, it may be prudent to maximize other pain treatment modalities (Tylenol, NSAIDs, massage therapies, heat, etc.) prior to starting someone on opioids.[17]

RBC Simple or Exchange Transfusions

For simple red blood cell transfusion, we recommend 10ml/kg of RBC to children, or 1 or 2 units of RBC to adults, who meet all of the following criteria:

1. Symptomatic ACS
2. Hemoglobin <9 g/dL
3. Decrease in hemoglobin >1 g/dL from baseline

For exchange transfusion, we recommend this to patients who meet one of the following criteria:

1. Severe ACS, as defined previously
2. Progressive ACS with one of the following criteria:
    a. Continued hypoxia despite supplemental oxygen
    b. Worsening pulmonary infiltrates
    c. Decreasing hemoglobin despite simple transfusions

The target hemoglobin is up to 10g/dL for both simple and exchange transfusion.

The above recommendations are founded on expert consensus from the National Heart, Lung, and Blood Institute (NHLBI), British and American Society of Hematology, and from our experience.[18-20] The theory behind simple transfusion is to help compensate for the symptomatic acute on chronic anemia in the setting of hypoxia, and to reduce the further sickling and worsening of ACS.

Patients with more severe ACS symptoms or those who failed simple transfusion therapy may benefit from exchange transfusions. The theory behind exchange transfusion is to allow for a large volume of blood transfusion without the risk for hyperviscosity syndrome. This allows for improved oxygenation by removing patients' HbS and replacing them with HbA, resulting in reduced blood sickling and hemolysis. The end goal is to reduce vaso-occlusive events while increasing RBC oxygen-carrying capacity. This

theory has been demonstrated in a study where patients who received double exchange transfusions had a short-lived (less than 24-hour) decrease in white blood count, absolute neutrophil count, and soluble adhesion molecule. Soluble adhesion molecule causes adhesion of sickled erythrocytes or neutrophils to the vascular endothelium. It is, however, unclear whether there is any clinical significance associated with this short-lived effect.[21] There is so far only one small RCT involving 10 patients that showed decreased ACS in patients who received exchange transfusions.[22] In addition, transfusions in general carry significant risk of alloimmunization.

Due to the limited evidence and the potential for serious adverse effects, the above recommendations are conditional and the decision to transfuse should involve consultations with hematologists and intensivists.

Bronchodilators

Bronchodilators should be considered in patients with history of asthma or patients exhibiting signs and symptoms of bronchospasms.

There are, however, no clinical trials to date demonstrating the effectiveness of bronchodilators in patients with ACS. Wheezing is also a less common presentation in adults compared to the pediatric population, so bronchodilators may be less beneficial in adults for that reason.[10, 23]

Nitric Oxide

There is not enough evidence for us to recommend routine use of nitric oxide.

Nitric oxide has been proposed to improve oxygenation in patients with ACS by selectively vasodilating areas of the lung with good oxygenation, in an attempt to improve ventilation-perfusion ratio. This may, in theory, decrease pulmonary hypertension and sickling.[24] One clinical trial demonstrated no difference in mortality, rate of mechanical ventilation, Alveolar-arterial gradient, or rate of transfusion. However, a posthoc analysis with larger sample size does show a significant benefit in hypoxemic ACS patients compared to placebo. Hypoxemic patients in this study had a worse ventilation-perfusion mismatch, likely due to a significant right-to-left shunt, a pathology nitric oxide is theorized to mitigate.[25] There is a need for a repeated study with a larger sample size focusing on hypoxemic patients to definitively demonstrate the benefit of nitric oxide in hypoxemic ACS patients.

Steroids

Routine use of corticosteroids is not recommended unless there are concerns about concomitant pathologies that have been proven to improve with corticosteroids such as reversible airway disease or acute respiratory distress syndrome (ARDS).

There are no data on the use of steroids in the adult population in the setting of ACS whereas the results in pediatrics are mixed at best. Studies have shown mixed results of increased rates of readmission and hospital stay,[26] no difference in hospital stay or readmission rates,[27] and decreased length of hospitalization, transfusion rates, opioid doses, and rates of clinical deterioration with no statistically significant increases in readmission rates.[28] Therefore, routine use of corticosteroids is not recommended in the treatment of ACS.

Incentive Spirometry (IS)

We recommend that all patients admitted to the hospital with SCD or ACS be encouraged to perform 10 maximal breaths every 2 hours.

A pediatric RCT study demonstrated decreased length of hospital stay in patients admitted for VOC who were placed on mandatory IS, and two pediatric RCT studies have demonstrated decreased chance of developing ACS when admitted for VOC.[29,30] An adult study attempted to replicate the pediatric study without any differences.[31] The difference in outcome between the adult and pediatric study could be due to the different etiology of ACS in these two populations. Pediatric ACS is most commonly associated

with infections, which IS has been demonstrated to prevent. In contrast, adult ACS is most commonly due to fat emboli, which IS is not able to prevent.[31] Despite the study in adults not demonstrating any significant differences, there is little harm in starting patients on IS, with some theoretical benefit.

There have been no studies to date to determine the efficacy of incentive spirometry to prevent worsening of ACS.

Anticoagulation

We recommend all patients over age 18 be placed on thromboprophylaxis. Thromboprophylaxis may be any of the following:

1. Low-molecular-weight heparin
2. Unfractionated heparin
3. Fondaparinux

This is in alignment with the guidelines provided by the American College of Chest Physicians (ACCP), as both SCD and ACS place patients in a hypercoagulable state. Pulmonary vasculature occlusion due to thrombosis has been theorized to cause ACS due to the Virchow's triad. There is, however, a lack of clinical trials demonstrating efficacy of venous thromboembolism (VTE) prophylaxis.[32] One randomized clinical trial attempted to demonstrate the efficacy of unfractionated heparin in patients with ACS. However, no conclusions were drawn from the study due to insufficient enrollment resulting in early termination of the study.[33]

Hydroxyurea

Hydroxyurea should be used as a preventative therapy to all patients with a history of ACS as it has been shown to decrease the incidence (50%) of ACS.[34]

Hydroxyurea works by increasing HbF production and inhibiting production of HbS, thereby reducing hemolysis and vaso-occlusion. It should be titrated up to a maximum of 35mg/kg while aiming for ANC > 2×10^9/L and platelet count $\geq 80 \times 10^9$/L. Contraindication to hydroxyurea includes GFR <30mL/Minute/1.73m^2, pregnancy, or breast-feeding female. Therefore, it is important to also offer contraception to both males and females who are taking hydroxyurea.[35]

L-Glutamine

We suggest the use of L-glutamine as a preventative therapy to patients diagnosed with ACS despite being placed on maximal therapy of hydroxyurea, or those who cannot take hydroxyurea due to the above contraindication. This recommendation is founded on the results of a phase 3 clinical trial demonstrating decreased incidence of ACS, (8.6% vs 23.1%) independent of hydroxyurea use.[36]

The mechanism of L-glutamine is uncertain, but it is hypothesized to increase reduced glutathione to counteract the oxidative damage in RBCs of patients with SCD.[37]

Special Consideration: SARS-CoV2

Like many pulmonary viral infections, SARS-CoV2 can also cause ACS. This has been demonstrated in several adult and pediatric case studies. Since the common upper respiratory virus and SARS-COV2 can present with almost identical symptoms, it is crucial to consider both in patients with a history of SCD. Two of the most common complications of SARS-CoV2 associated with patients with SCD or ACS are cytokine release syndrome and pulmonary embolism. This is due to SARS-CoV2, SCD, and VOC all inducing a hypercoagulable state, and elevated IL-6. Therefore, in addition to the standard therapy, many experts recommend a lower threshold to perform exchange transfusion to prevent or decrease sickling. Additionally, there are two case reports to date documenting successful treatment with tocilizumab, an IL-6 inhibitor.[38-41]

Exchange transfusions, however, have not been demonstrated to prevent ICU admission in a recent French study. Therefore, the use of tocilizumab should also be experimental due to a current lack of evidence.[42]

CONCLUSION

ACS is a common and serious cause of morbidity and mortality in patients with SCD. We recommend all patients with ACS be treated with a combination of antibiotics, pain control, incentive spirometry, thromboprophylaxis, and providing supplemental oxygen or transfusions/exchange transfusions if clinically indicated. Unfortunately, there is a considerable gap in research supporting these treatments. As physicians and researchers, we should strive to conduct larger clinical trials in the management of ACS, especially considering the prevalence and affliction this disease has on many of our patients.

Notes
Conflicts of Interests: None declared
Funding: None declared
Acknowledgements: None

Figure 1. PA chest radiograph showing consolidation in lingula and left lower lobe

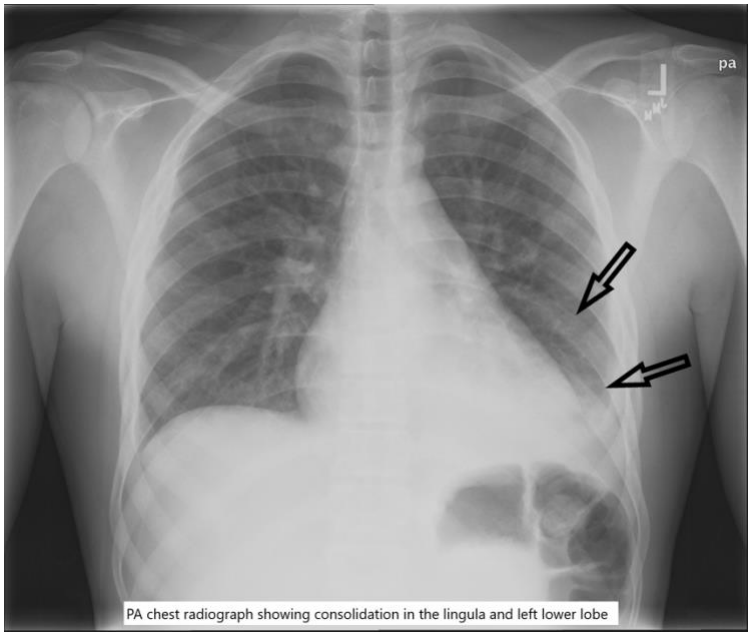
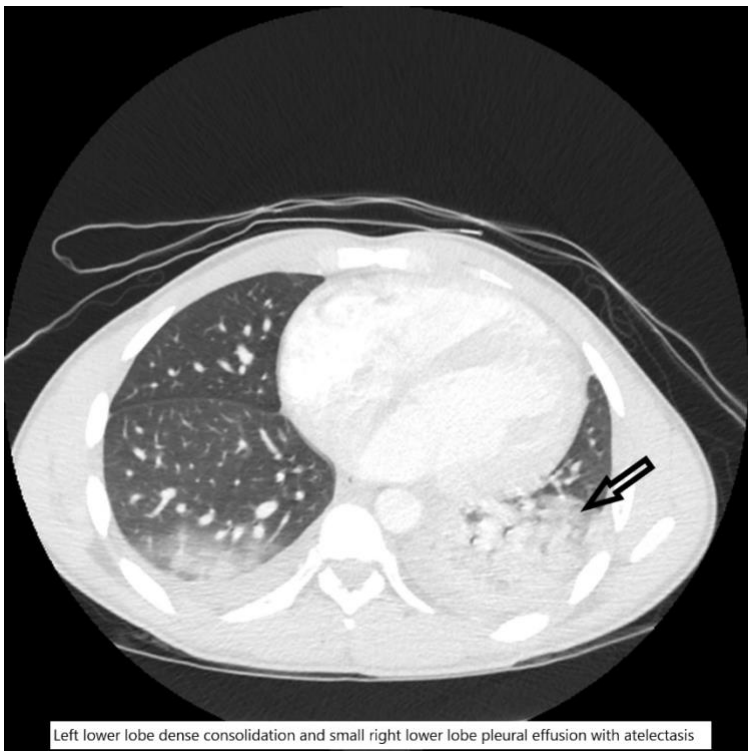
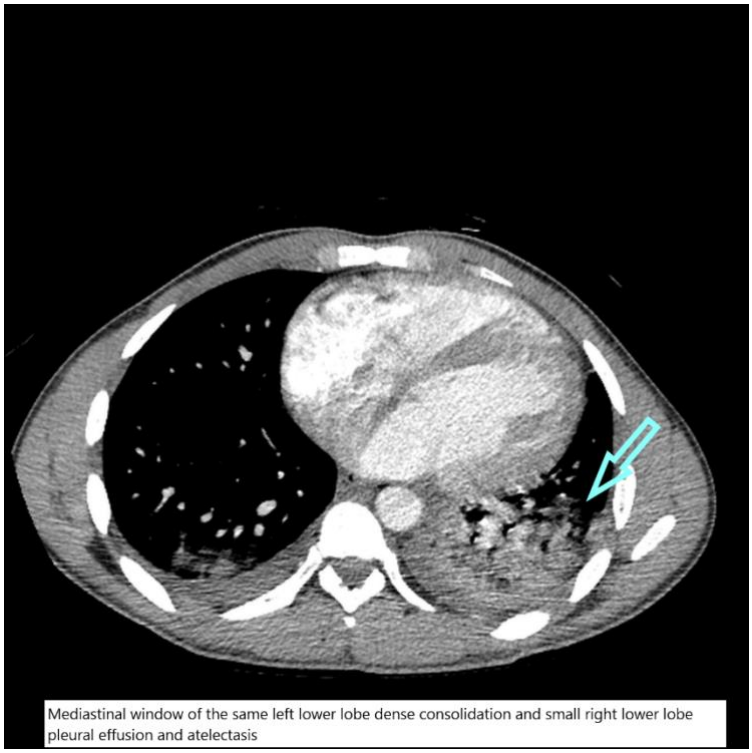


Figure 2. Left lower lobe consolidation and small right lower lobe pleural effusion with atelectasis





REFERENCES

1. Barrett-Connor E. Acute pulmonary disease and sickle cell anemia. *Am Rev Respir Dis*. 1971;104(2):159-165. doi:10.1164/arrd.1971.104.2.159
2. Friend A. Acute chest syndrome. StatPearls [Internet]. https://www.ncbi.nlm.nih.gov/books/NBK441872/. Published June 24, 2021. Accessed October 7, 2021.
3. Jain S, Bakshi N, Krishnamurti L. Acute Chest Syndrome in Children with Sickle Cell Disease. *Pediatr Allergy Immunol Pulmonol*. 2017;30(4):191-201. doi:10.1089/ped.2017.0814
4. Williams TN, Thein SL. Sickle Cell Anemia and Its Phenotypes. *Annu Rev Genomics Hum Genet*. 2018;19:113-147. doi:10.1146/annurev-genom-083117-021320
5. Vichinsky EP, Styles LA, Colangelo LH, Wright EC, Castro O, Nickerson B. Acute chest syndrome in sickle cell disease: clinical presentation and course. Cooperative Study of Sickle Cell Disease. *Blood*. 1997;89(5):1787-1792.
6. Howard J, Hart N, Roberts-Harewood M, et al. Guideline on the management of acute chest syndrome in sickle cell disease. *Br J Haematol*. 2015;169(4):492-505. doi:10.1111/bjh.13348
7. Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members [published correction appears in JAMA. 2014 Nov 12;312(18):1932] [published correction appears in JAMA. 2015 Feb 17;313(7):729]. *JAMA*. 2014;312(10):1033-1048. doi:10.1001/jama.2014.10517
8. Gaut D, Jones J, Chen C, Ghafouri S, Leng M, Quinn R. Outcomes related to intravenous fluid administration in sickle cell patients during vaso-occlusive crisis. *Ann Hematol*. 2020;99(6):1217-1223. doi:10.1007/s00277-020-04050-1
9. Fartoukh M, Lefort Y, Habibi A, et al. Early intermittent noninvasive ventilation for acute chest syndrome in adults with sickle cell disease: a pilot study. *Intensive Care Med*. 2010;36(8):1355-1362. doi:10.1007/s00134-010-1907-4
10. Vichinsky EP, Neumayr LD, Earles AN, et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group [published correction appears in N Engl J Med 2000 Sep 14;343(11):824]. *N Engl J Med*. 2000;342(25):1855-1865. doi:10.1056/NEJM200006223422502
11. Martí-Carvajal AJ, Conterno LO, Knight-Madden JM. Antibiotics for treating acute chest syndrome in people with sickle cell disease. *Cochrane Database Syst Rev*. 2019;9(9):CD006110. Published 2019 Sep 18. doi:10.1002/14651858.CD006110.pub5
12. Bundy DG, Richardson TE, Hall M, et al. Association of Guideline-Adherent Antibiotic Treatment With Readmission of Children With Sickle Cell Disease Hospitalized With Acute Chest Syndrome. *JAMA Pediatr*. 2017;171(11):1090-1099. doi:10.1001/jamapediatrics.2017.2526
13. Brandow AM, Carroll CP, Creary S, et al. American Society of Hematology 2020 guidelines for sickle cell disease: management of acute and chronic pain. *Blood Adv*. 2020;4(12):2656-2701. doi:10.1182/bloodadvances.2020001851
14. Lewing K, Britton K, DeBaun M, Woods G. The impact of parenteral narcotic choice in the development of acute chest syndrome in sickle cell disease. *J Pediatr Hematol Oncol*.

2011;33(4):255-260. doi:10.1097/MPH.0b013e31820994d0

15. 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):140-146. doi:10.1016/j.clpt.2003.10.007
16. Birken CS, Khambalia A, Dupuis A, et al. Morphine is associated with acute chest syndrome in children hospitalized with sickle cell disease. *Hosp Pediatr*. 2013;3(2):149-155. doi:10.1542/hpeds.2012-0067
17. Brandow AM, DeBaun MR. Key Components of Pain Management for Children and Adults with Sickle Cell Disease. *Hematol Oncol Clin North Am*. 2018;32(3):535-550. doi:10.1016/j.hoc.2018.01.014
18. National Heart, Lung, and Blood Institute. (2016). *Evidence-Based Management of Sickle Cell Disease: Expert Panel 2014*. U.S. Department of Health & Human Services, National Institutes of Health. Evidence-Based Management of Sickle Cell Disease: Expert Panel, 2014 (nih.gov)
19. Davis BA, Allard S, Qureshi A, et al. Guidelines on red cell transfusion in sickle cell disease Part II: indications for transfusion. *Br J Haematol*. 2017;176(2):192-209. doi:10.1111/bjh.14383
20. Chou ST, Alsawas M, Fasano RM, et al. American Society of Hematology 2020 Guidelines for Sickle Cell Disease: Transfusion Support. American Society of Hematology. https://ashpublications.org/bloodadvances/article/4/2/327/440607/American-Society-of-Hematology-2020-guidelines-for. Published January 27, 2020. Accessed October 6, 2021.
21. Liem RI, O'Gorman MR, Brown DL. Effect of red cell exchange transfusion on plasma levels of inflammatory mediators in sickle cell patients with acute chest syndrome. *Am J Hematol*. 2004;76(1):19-25. doi:10.1002/ajh.20054
22. Dastgiri S, Dolatkhah R. Blood transfusions for treating acute chest syndrome in people with sickle cell disease. *Cochrane Database Syst Rev*. 2016;(8):CD007843. Published 2016 Aug 30. doi:10.1002/14651858.CD007843.pub3
23. Knight-Madden JM, Hambleton IR. Inhaled bronchodilators for acute chest syndrome in people with sickle cell disease. *Cochrane Database Syst Rev*. 2016;9(9):CD003733. Published 2016 Sep 27. doi:10.1002/14651858.CD003733.pub4
24. Wrigge H, Costa EL, Busch T. Adjunctive therapy with inhaled nitric oxide for severe acute chest syndrome in patients with sickle cell disease. *Intensive Care Med*. 2015;41(12):2213-2215. doi:10.1007/s00134-015-4084-7
25. Maitre B, Djibre M, Katsahian S, et al. Inhaled nitric oxide for acute chest syndrome in adult sickle cell patients: a randomized controlled study. *Intensive Care Med*. 2015;41(12):2121-2129. doi:10.1007/s00134-015-4060-2
26. 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):1006-1012. doi:10.1002/pbc.21336
27. Kumar R, Qureshi S, Mohanty P, Rao SP, Miller ST. A short course of prednisone in the management of acute chest syndrome of sickle cell disease. *J Pediatr Hematol Oncol*. 2010;32(3):e91-e94. doi:10.1097/MPH.0b013e3181c29c52
28. 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):3082-3089.
29. 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. doi:10.1056/NEJM199509143331104
30. Ahmad FA, Macias CG, Allen JY. The use of incentive spirometry in pediatric patients with sickle cell disease to reduce the incidence of acute chest syndrome. *J Pediatr Hematol Oncol*. 2011;33(6):415-420. doi:10.1097/MPH.0b013e31821ed4ce
31. 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-E163. doi:10.1002/ajh.25805
32. Naik RP, Streiff MB, Lanzkron S. Sickle cell disease and venous thromboembolism: what the anticoagulation expert needs to know. *J Thromb Thrombolysis*. 2013;35(3):352-358. doi:10.1007/s11239-013-0895-y
33. Seaman CD, Novelli E, De Castro L, Ragni MV. Unfractionated heparin in acute chest syndrome: a pilot feasibility randomized controlled trial of unfractionated heparin vs. standard of care in acute chest syndrome. *Pilot Feasibility Stud*. 2020;6(1):174. Published 2020 Nov 10. doi:10.1186/s40814-020-00715-w
34. Steinberg MH, Barton F, Castro O, et al. Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment [published correction appears in JAMA. 2003 Aug 13;290(6):756]. *JAMA*. 2003;289(13):1645-1651. doi:10.1001/jama.289.13.1645
35. Qureshi A, Kaya B, Pancham S, et al. Guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease: A British Society for Haematology Guideline. *Br J Haematol*. 2018;181(4):460-475. doi:10.1111/bjh.15235
36. Niihara Y, Miller ST, Kanter J, et al. A Phase 3 Trial of l-Glutamine in Sickle Cell Disease. *N Engl J Med*. 2018;379(3):226-235. doi:10.1056/NEJMoa1715971
37. "DailyMed - Endari- Glutamine Powder, for Solution." *U.S. National Library of Medicine*, National Institutes of Health, 27 Oct. 2020, https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d5a783f4-12ef-4326-8faa-40018e45ba3b.
38. 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;95(6):725-726. doi:10.1002/ajh.25821
39. Sivalingam T, Inusa B, Doyle P, Oteng-Ntim E. COVID-19 and the pulmonary complications of sickle cell disease. *EJHaem*. 2020;1(2):545-547. doi:10.1002/jha2.105
40. Odièvre MH, de Marcellus C, Ducou Le Pointe H, et al. Dramatic improvement after tocilizumab of severe COVID-19 in a child with sickle cell disease and acute chest syndrome. *Am J Hematol*. 2020;95(8):E192-E194. doi:10.1002/ajh.25855
41. De Luna G, Habibi A, Deux JF, et al. Rapid and severe Covid-19 pneumonia with severe acute chest syndrome in a sickle cell patient successfully treated with tocilizumab. *Am J Hematol*. 2020;95(7):876-878. doi:10.1002/ajh.25833
42. Arlet JB, de Luna G, Khimoud D, et al. Prognosis of patients with sickle cell disease and COVID-19: a French

experience [published correction appears in Lancet Haematol. 2020 Sep;7(9):e635]. *Lancet Haematol*. 2020;7(9):e632-e634. doi:10.1016/S2352-3026(20)30204-0