ELSEVIER

Blood 142 (2023) 5337–5338

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

114.SICKLE CELL DISEASE, SICKLE CELL TRAIT AND OTHER HEMOGLOBINOPATHIES, EXCLUDING THALASSEMIAS: CLINICAL AND EPIDEMIOLOGICAL

A Working Definition of Acute Chest Syndrome without the Requirement of Chest X-Rays

Alejandro R. Gonzalez-Barreto[1], *Jose A. Mejias*[2], *Michael R. DeBaun, MD MPH*[3], *Eugenia Vicky Asare, MD*[4], *Samuel A. Oppong, MD*[5]

[1] University of Puerto Rico, School of Medicine, San Juan, PR
[2] University of Puerto Rico, School of Medicine, Guaynabo, PR
[3] Vanderbilt-Meharry Center of Excellence in Sickle Cell Disease, Vanderbilt University Medical Center, Nashville, TN
[4] Department of Obstetrics and Gynecology, Korle-Bu Teaching Hospital, Accra, GHA
[5] Department of Obstetrics and Gynecology, University of Ghana Medical School, Accra, GHA

Introduction: Sickle Cell Disease (SCD) is a rare genetic disease in high-income countries where most of the cited literature used to guide clinical management emanate from. One of the most serious and potentially fatal complications of SCD is acute chest syndrome (ACS) which requires immediate medical attention. Approximately 50% of individuals with SCD will eventually develop ACS (*Blood* 84, 643-649 (1994)). Despite the high frequency of ACS and its associated risk of death, no consensus diagnosis has been established that applies to children and adults living in low-middle income countries, where 95% of the children born with SCD are found.

To create a uniform definition of ACS in both low, middle, and high-income countries, we propose using a new ACS definition that does not require a chest X-ray. Additionally, the new ACS definition should have a quantifiable and reproducible physical examination and clinical findings to allow for the reproducibility of the definition in all settings. This definition was developed over several years at Korle Bu Teaching Hospital, Accra Ghana, in pregnant women with SCD. Before we started the multidisciplinary team care in pregnant women with SCD, ACS was the most common cause of maternal death. Subsequently, based on the new ACS definition that did not require a chest X-ray, we developed strategies to prevent, aid early diagnosis, and treat ACS resulting in an 89% relative risk reduction of death. We refer to this new definition as the Korle Bu Teaching Hospital (KBTH)-ACS definition.

In this study, we compare the ACS definition in the top 20 cited ACS articles as of July 2023 with our proposed KBTH-ACS definition.

Methods: Using Google Scholar, we identified the top 20 cited articles with ACS in children or adults with SCD as primary or secondary outcomes. Each article was reviewed for the presence of the following criteria: chest x-ray, vitals, hemoglobin oxygen saturation, and lung physical exam findings. We compared the definition of ACS in the top 20 cited ACS articles to the KBTH-ACS definition that included the following features: "abnormal findings on lung auscultation and the presence of at least 2 of the following criteria: 1) temperature $\geq$ 38.0°C, 2) increased respiratory rate greater than the 90th percentile for age, positive chest pain or pulmonary auscultatory findings, 3) hemoglobin oxygen saturation decrease by $\geq$3% from a documented steady-state value on room air, and 4) a new radiodensity on chest roentgenogram. A diagnosis of pneumonia was considered an ACS episode.".

Results: The 20 most cited ACS articles required radiographical criteria to diagnose ACS. Fourteen of twenty articles included fever in their ACS definition. However, only 4 articles specified any temperature and all specified $\geq$ 38.5 ºC.

A total of 17 articles mentioned the presence of lung or respiratory findings, but only 12 articles specifically identified the pulmonary findings. Among the 12 articles that specified lung findings, 5 included increased respiratory rate (tachypnea) without a specific definition, 2 included abnormal auscultatory findings, and 3 included hypoxemia/hypoxia in their definition. However. One study defined hypoxemia/hypoxia as "transcutaneous oxygen saturation <85% despite supplemental oxygen.". Another article included "SpO2 of $\geq$ 3% compared to baseline steady-state values.". In addition, among the twelve studies that specified respiratory findings, the following were present or absent features: chest pain (n=12), wheezing (n=3), coughing(n=3), and respiratory distress without a formal definition (n=3). No article included pneumonia in the ACS definition nor defined a threshold for tachypnea that was age-adjusted. None of the articles would allow for a direct comparison with the KBTH-ACS definition.

Conclusion: All the 20 most cited ACS articles required a chest X-ray with various clinical and physical examination findings. Many of the ACS definitions in these studies were based on clinical impressions that were not quantifiable or reproducible. We propose using the KBTH-ACS definition in future ACS studies to improve generalizability, reproducibility, and genotype and phenotype studies designed to elucidate the genetic variation of lung disease in children and adults with SCD.

Disclosures DeBaun: *Novartis, Forma, Vertex:* Consultancy, Other: Consulting.

	Article Amount	Reference #
Is chest X-ray required for diagnosis?	20	1-20
Explicit lung findings (tachypnea, dyspnea, wheezing, cough, respiratory distress, nasal flaring, abnormal lung auscultation)	7	1,7,9,15,18,19,20
Implicit lung findings (no lung findings specification)	7	4,10,11,12,14,16,17
Hypoxia/hypoxemia	3	9,15,20
Chest pain	12	1,5,7,8,9,10,12,13,15,18,19,20

Table 1. ACS definition criteria

Article	References	Cited #
1) Causes and Outcomes of the Acute Chest Syndrome in Sickle Cell Disease	*N Engl J Med* **342**, 1855-1865 (2000)	1318
2) The Acute Chest Syndrome in Sickle Cell Disease: Incidence and Risk Factors	*Blood* **84**, 643-649 (1994)	884
3) Acute Chest Syndrome in Sickle Cell Disease: Clinical Presentation and Course	*Blood* **89**, 1787-1792 (1997)	683
4) Pulmonary fat embolism: a distinct cause of severe acute chest syndrome in sickle cell anemia	*Blood* **83**, 3107-3112 (1994)	286
5) Asthma is associated with acute chest syndrome and pain in children with sickle cell anemia	*Blood* **108**, 2923-2927 (2006)	252
6) Impact of chronic transfusion on incidence of pain and acute chest syndrome during the Stroke Prevention Trial (STOP) in sickle-cell anemia	*J Pediatr* **139**, 785-789 (2001)	246
7) Extracellular hemin crisis triggers acute chest syndrome in sickle mice	*J Clin Invest* **123**, 4809-4820 (2013)	239
8) "Acute chest syndrome" in adults with sickle cell anemia. Microbiology, treatment, and prevention.	*Arch Intern Med* **139**, 67-69 (1979)	238
9) Beneficial effect of intravenous dexamethasone in children with mild to moderately severe acute chest syndrome complicating sickle cell disease.	*Blood* **92**, 3082-3089 (1998)	232
10) Phospholipase A2 levels in acute chest syndrome of sickle cell disease.	*Blood* **87**, 2573-2578 (1996)	205
11) Asthma in children with sickle cell disease and its association with acute chest syndrome	*Thorax* **60**, 206-210 (2005)	203
12) Sickle cell acute chest syndrome: pathogenesis and rationale for treatment.	*Blood* **94**, 1555-1560 (1999)	202
13) Pulmonary hypertension and cor pulmonale during severe acute chest syndrome in sickle cell disease	*Am J Respir Crit Care Med* **177**, 646-653 (2008).	190
14) Effect of transfusion in acute chest syndrome of sickle cell disease.	*Pediatr* **127**, 901-904 (1995)	179
15) Guideline on the management of acute chest syndrome in sickle cell disease	*Br J Haematol* **169**, 492-505 (2015)	157
16) Acute chest syndrome in sickle cell disease: etiology and clinical correlates	*J Pediatr* **107**, 861-866 (1985)	152
17) Acute chest syndrome in adults with sickle cell disease	*Chest* **117**, 1386-1392 (2000)	146
18) Pulmonary function in sickle cell disease with or without acute chest syndrome	*Chest* **117**, 1386-1392 (2000)	143
19) Pulmonary artery thrombosis during acute chest syndrome in sickle cell diseas	*Eur Respir J* **12**, 1124-1129 (1998)	124
20) Acute Chest Syndrome in Children with Sickle Cell Disease	*Pediatr Allergy Immunol Pulmonol* **30**, 191-201 (2017)	122

Table 2. ACS definition reference and cited number

Figure 1

https://doi.org/10.1182/blood-2023-191001