

The Clinical Practice of Diagnosing Asthma in Children with Sickle Cell Disease

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Abstract

Children who suffer from sickle cell disease (SCD) are commonly admitted to the hospital for pulmonary related problems, such as acute chest syndrome. The link between sickle cell disease and asthma as co-morbidities has been discussed, yet many health care centers do not screen or diagnose children with sickle cell disease for asthma. This paper explores the way four academic health care centers screen and diagnose asthma in children with sickle cell disease and aims at uncovering the most effective methods amongst these institutions. Using I2B2, a de-identified data repository, information about patients who had sickle cell disease, asthma diagnoses, and the development of acute chest syndrome was gathered for the institutions used in this study. One institution had significantly better results in comparison with the other three care centers, and this project aimed to uncover the methods that this specific institution used to screen and diagnose their SCD children with asthma. Questions were formulated in collaboration with UF Health Shands' pediatric hematologist and were posed to these institutions regarding the practices used in each center. Responses from the sites are currently pending.

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In patients with Sickle Cell Disease (SCD), a major cause of morbidity and mortality includes pulmonary complications. Acute Chest Syndrome (ACS) is the leading cause of premature death and is also the second most common reason for hospitalization in patients with SCD (Miller, 2011). Although asthma is common in children with SCD, it remains underdiagnosed and poorly managed in this population. This problem is likely due to the difficulty in discerning asthma exacerbations from airway changes that are commonly seen in patients with SCD, such as shortness of breath, wheezing, and chest pain (DeBaun & Strunk, 2016). In a study that examined common reasons SCD children were referred to a pediatric respiratory clinic, although only a small number of patients were referred to the clinic due to suspected asthma and wheezing (~13%), 48% of all patients who were referred to the clinic for any reason was discovered to have asthma (Akthar et al., 2016). This study emphasized the idea that asthma is often unrecognized and subsequently underdiagnosed in patients with SCD. An asthma diagnosis in a patient with a co-morbidity of SCD could ultimately lead to decreased hospital admissions for ACS and sickle cell crises. During an asthma attack, bronchoconstriction and altered ventilation-perfusion can result in hypoxic areas, leading to decreased oxygen saturation and sickling in SCD children. These conditions are what ultimately predispose these SCD patients to developing ACS (Knight-Madden et al., 2005).

The main objective for this project is to find out what four academic medical centers are doing to diagnose their children who have SCD with asthma. Because there is a proven correlation of sickle cell disease and asthma, it is important to determine what can be done for children with SCD who need an asthma diagnosis. This diagnosis can ultimately help children be prescribed the proper medication they need in order to prevent asthma attacks and possibly sickle

cell crises and incidences of acute chest syndrome. The results of this project will not only benefit the families and children with SCD who remain undiagnosed with asthma, but it may also help reduce the number of admissions in the hospital for respiratory related illnesses in sickle cell disease children. The findings may be able to help institutions across the United States implement new and efficient ways at diagnosing asthma in SCD children.

This project is needed at this time because despite the literature about SCD, asthma, and ACS as co-morbidities, asthma diagnoses in SCD patients remain low. The purpose of conducting this project is to compare the clinical practices of each of the four academic medical centers to find out what practices are effective and which are ineffective. Many hospitals do not have a single protocol for diagnosing SCD patients with asthma, and therefore, many children and even adults, go undiagnosed for the remainder of their life. Currently at the University of Florida, the pediatric hematology clinic for children with SCD makes a referral for them to see a pulmonologist if asthma is suspected. However, these referrals seem to have an insignificant impact at improving asthma diagnoses rates at this institution, as well as other institutions across the United States. In fact, one study at Johns Hopkins Hospital showed that out of seventy-four pediatric patients who were referred to their pediatric pulmonary clinic after abnormal spirometry and/or positive asthma screening questionnaire, only 22% of those referred were actually seen in a pulmonary clinic (Sadreameli, Alade, Mogayzel, McGrath-Morrow, & Strouse, 2017).

Because asthma is a major risk factor for ACS, a diagnosis in children with SCD could possibly prevent a pain crisis or asthma exacerbation in these patients if they are properly medicated for the condition. A study by Boyd et al. (2006) reported that children with SCD and a clinical diagnosis of asthma had increased sickle cell-related morbidity and had nearly twice as

many ACS episodes than patients without this diagnosis, confirming the association between asthma and ACS. The findings of the study also suggest that identifying and treating asthma in children with SCD may have an impact on decreasing SCD-related morbidity (Boyd et al., 2006). Comparing the current practices of multiple academic health care centers and subsequently identifying their merits and faults can help determine if feasible and appropriate ways to screen and diagnose asthma in children with SCD exists.

Asthma and SCD both occur more commonly in African-Americans over any other race. In 2016, the Centers for Disease Control and Prevention (CDC) estimated that SCD affects 1 out of every 365 African-American births and that African-American children are 2 times more likely to have asthma than White children. Despite these numbers, the likely potential for these two diagnoses as co-morbidities remains understated. It is also important to note the differences between races when discussing asthma-like symptoms. One study found that the differences in the words used by patients to describe their asthma-like symptoms varied based on the race of the patient. African-Americans suffering from airflow obstruction primarily used word descriptors pertaining to the upper airway, whereas Whites typically used lower airway and chest wall descriptors (Hardie, Janson, Gold, Carrieri-Kohlman, & Boushey 2000).

Many physicians may be quick to dismiss a child that does not use the correct asthma “language” and choose to forgo a diagnosis of asthma in a child who needs it. Many healthcare professionals screen patients for asthma by looking for key word descriptors meant to describe breathlessness; these descriptors include words describing shortness of breath, chest tightness, and wheezing (Hardie et al., 2000). However, these terms are culturally limiting. These word descriptors are how most White patients describe their asthma, rather than African-Americans, despite the latter race being much more susceptible to asthma. This fact is significant, as many

children may go undiagnosed with asthma simply because of the word descriptors they use in describing their breathlessness. Physicians and other members of the healthcare team need to be able to provide culturally competent care to their patients and can help do so by understanding these differences between African-American and White patients with regards to asthma management.

Other challenges with diagnosing SCD children with asthma involves the high prevalence of wheezing and airway hyperresponsiveness that already occurs amongst patients with SCD. The significance of this lower airway obstruction that occurs in patients with SCD is not really understood, and because of these pulmonary complications, many disagree about whether SCD is associated with a diagnosis of asthma (Cohen, Klings, & Strunk, 2015). Additionally, risk factors for ACS in children with SCD is similar to that of an asthma exacerbation, and both conditions can present with pulmonary complications, including shortness of breath, coughing, wheezing, and pain upon breathing. However, it is important to note that both asthma and ACS are two separate conditions, needing two specific care strategies to properly manage a child with SCD who presents with pulmonary symptoms that mimic either condition (DeBaun & Strunk, 2016).

This project began with existing data conducted by Dr. Laurie Duckworth, PhD, ARNP about the relationship between sickle cell disease, asthma, and acute chest syndrome at 4 academic medical centers (AMCs). These centers included: Harvard University, the University of Texas at Houston, Indiana University, and the University of Florida, labeled A, B, C, and D, respectively. The Electronic Medical Record (EMR) using i2b2, (a de-identified data repository) for 4 AMCs was queried for the number of patients 5-34 years of age who were seen between 12/01/2010 and 12/01/2015 having co-morbidities of Asthma, Sickle Cell Disease and Acute Chest Syndrome. The i2b2 query included: (1) Number of patients with SCD (2) Number of

patients with SCD + Asthma, (3) Number of patients with SCD + ACS, and (4) Number of patients with SCD + ACS + Asthma. The combined total number of patients for each category were as follows, respectively; (1) 2749, (2) 577, (3) 409, and (4) 249.

The project to uncover each academic medical center's clinical practices began with the results of the data from i2b2. Results from academic medical center C, Indiana University, was significant in proving the correlation between sickle cell disease, asthma, and acute chest syndrome. Indiana was found to have a significantly higher percentage of asthma diagnoses amongst their SCD population over every other institution tested (See Appendix A). It was also found that nearly all SCD patients at Indiana who developed ACS during the specified period of the data query had a diagnosis of asthma, emphasizing the increased risk of developing ACS with an asthma co-morbidity (see Appendix B). This data also suggests that asthma may be more common amongst patients with SCD than with those without it. If Indiana University has a unique way at diagnosing their SCD children with asthma and it is deemed effective and practical, then the University of Florida, University of Texas, and Harvard University can all implement this new practice in their pediatric hematology/pulmonology clinics. Other institutions across the U.S. can also use the findings of this study to improve the rate at which they diagnose SCD children with asthma.

Throughout this project, communication went back and forth between the pediatric hematologists of each medical institution. After gathering the results of the data collection of the sites from i2b2, six questions regarding each medical center's clinical practices was formulated. Questions were sent to each site's pediatric SCD hematologist to be answered via email. Although no responses have been received yet, part of this project focused on developing and curating the questions that needed to be asked to each institution to gather the necessary

information. Questions were created and then redrafted before being sent to each site. The original six questions are as follows:

1. How do you define asthma? Is it usually physician-diagnosed or per parent report?
2. How do you define acute chest syndrome?
3. How is asthma managed in your clinic?
4. How would you describe your populations' adherence rates?
5. Do your patients receive a pulmonary referral?
6. Do you screen for asthma in your clinic?

These questions were then given to UF Health's pediatric hematologist for review, who then helped alter the questions to make them more focused. The finalized questions that were sent to the sites are as follows:

1. Does your sickle cell team use a standardized definition for asthma diagnosis?
2. Does your sickle cell team use a standardized definition for the diagnosis of acute chest syndrome?
3. How would you describe your patient populations' adherence to prescribed asthma therapy?
4. Do you perform screening pulmonary function tests in your pediatric patients with asthma? If so, how often or at what age?
5. Do you perform pulmonary function testing on all children with sickle cell disease who have a suspected asthma diagnosis?
6. Do you routinely screen for asthma in your sickle cell clinic? If yes, how do you screen patients (e.g. history, screening questionnaires, PFTs)?

The definition of asthma may vary amongst institutions and may affect asthma diagnosis rates in children with SCD. For this reason, the questions that were drafted for each academic medical center hoped to address each center's definitions of asthma and acute chest syndrome, while also questioning asthma screening practices and management in their SCD patients. Some clinicians define asthma as a personal or parenteral report of a physician-diagnosis of the condition (Subramanian & Kennedy, 2009). Others define asthma simply as the report of a medical history that includes wheezing and other asthma-like symptoms (Arteta et al., 2014). The definition of acute chest syndrome may vary as well, with some definitions requiring different symptoms to be present than others. Vichinsky et al. (2000) defines acute chest syndrome as having a new pulmonary infiltrate on a chest x-ray with chest pain, tachypnea, or wheezing. Another definition of acute chest syndrome requires having chest pain with a fever, pulmonary infiltrates, and an increased number of leukocytes (Charache, Scott, & Charache, 1979).

Patient adherence rates to asthma therapy is also essential information to find out from each site. Ultimately, if a child is diagnosed with asthma but does not adhere to their medication regimen, then their risk for developing acute chest syndrome due to pulmonary complications markedly increases. In one study that followed 93 children with SCD and their adherence to daily medications, which included asthma medications, it was found that the adherence rate for all asthma medications prescribed to children with SCD who had asthma was only 59.3% (Patel, Lindsey, Strunk, & DeBaun, 2010). These results show that even if an asthma diagnosis exists in a SCD patient, they may not adhere to the medication and may cause complications leading to ACS.

The next two questions seek to find out if the pediatric SCD patients from each medical center have a pulmonary function test (PFT) done once they are suspected of having asthma or if there is another way that each site goes about diagnosing their patients. As previously mentioned, some clinicians use a “physician-based” diagnosis as their primary method of giving a child an asthma diagnosis. Because of this, many children may go their whole life without ever having pulmonary function tests done, which are universally viewed as the most accurate indicator of asthma. If all children with SCD who are seen at their hematology clinic are ultimately given PFTs during their visit to screen for asthma, then the rate of asthma diagnoses in this population would, predictably, increase.

The last question that was asked to each site focuses on the different methods that healthcare centers may possibly use to screen their patients for asthma. As previously mentioned, some healthcare professionals consider a diagnosis of asthma to be based on physician discretion, whereas others emphasize the need for a pulmonary function test (PFT) to be done before a diagnosis of asthma should be made. Screening questionnaires are another useful tool that clinicians can use to screen SCD children for asthma to determine if a diagnosis should or should not be made. If it is found that multiple sites do use screening questionnaires as part of their clinical practice, then asthma screenings and diagnoses that were able to be obtained due to these questionnaires should be explored. It is also important to determine and compare the questions and word descriptors used by each site who does use a screening questionnaire. By doing so, one may be able to determine if different words or questions can help assess a child with SCD for asthma better than others.

Some clinics and hospitals choose to use screening questionnaires to help screen a child for asthma. Many studies have shown how these asthma screening questionnaires can ultimately

help lead to a diagnosis of asthma in children with sickle cell disease. One study, where 41 out of 51 eligible participants completed an asthma screening questionnaire as well as spirometry, had over half of the participants (51.2%) demonstrate evidence of airway obstruction. It was also found that baseline demographics, previous respiratory complications, and complete blood counts did not have a significant difference in the findings between the obstructive and nonobstructive groups (Yadav, et al., 2015). In this study, 13 children received a physician diagnosis of asthma, and out of these 13, 11 were placed on asthma controlling medications after being evaluated by pulmonologists. This study was one of many that emphasized the importance of screening tools for SCD children, and how it could possibly lead to an asthma diagnosis and a subsequent medication regimen for the disease.

At the present time, there has been no response back to these questions. The main barrier to this project has been waiting for the responses from each academic medical center. Without these responses, the study cannot move forward because the clinical practices of the sites are unknown. Although questions were sent out in January of 2018, no replies have been received yet. Follow-up emails were sent out, but at the time of this being written, there are still no answers. The project was originally set to be a conference call between the centers, but because of the difficulty in scheduling a time that would work for all the institutions, it was decided that email would be the best way to communicate with the centers. Even so, communications between the pediatric hematologists have proven to be more difficult than originally anticipated.

In the meantime, state demographics of each academic medical center were explored. The purpose of exploring this data was to determine if there were any significant trends in these states that each academic medical center resides in based on the African-American population and number of asthma diagnoses. Because African-Americans have a much greater chance at having

asthma than any other race, it was assumed that the states with a higher percentage of African-Americans would also have higher percentages of asthma diagnoses. Exploring state demographics was also helpful in determining if environmental or racial influences played a significant role in the results of the data set.

According to State Data Profiles published by the CDC, the prevalence of asthma in children 0-17 years of age living in Florida in 2007 was 8.3% compared to the U.S. rate of 9.0%. In 2008, the prevalence of asthma in Texas, Indiana, and Massachusetts of children 0-17 years of age were as follows, respectively: 9.2%, 8.6%, and 9.8% (Centers for Disease Control and Prevention, 2011). Additionally, the 2010 Census reported the African-American population for Florida, Texas, Indiana, and Massachusetts in respect to their overall populations were as follows, respectively: 21.3%, 16.8%, 10.8%, and 8.2% (U.S. Census Bureau, 2010).

These percentages show all the states that each academic medical center resides in have similar asthma prevalence rates for their children. However, Florida and Texas have a significantly higher percentage of African-Americans in their population in comparison to both Indiana and Massachusetts. While one would assume that this might signify a greater number of asthma diagnoses for these states, there was not a significant difference in the percentages of children with asthma between the four states. It is also important to note that the University of Texas and the University of Florida, Academic Medical Centers B and D, respectively, had the two lowest rates of asthma diagnoses in their children with SCD compared to the other two medical centers (See Appendix A). Having the two lowest rates of asthma diagnoses implies that individual clinical practices by each site play a crucial role in how these children are being screened and diagnosed for asthma.

Additionally, it was surprising to note that Indiana University had the highest rates of asthma diagnoses in their children with SCD when the state of Indiana had the lowest percentage of asthma diagnoses and second lowest percentage of African-Americans residing in that state compared to the other three states. These results imply that the data results of the academic medical centers are probably not influenced by environmental or racial factors. Rather, it highlights the idea that Indiana University is doing something unique with their clinical practice of diagnosing children with SCD with asthma.

Conclusions

The goal of this project was to uncover the most effective clinical practice at diagnosing asthma in children with SCD by examining the current practices of four academic medical centers. Although there have been no official results from the project, the link between SCD, asthma, and ACS in pediatric patients has been established. The correlation between these comorbidities highlights the need and importance for new and inventive ways to address undiagnosed asthma in children with SCD. While the University of Florida currently refers their pediatric SCD patients to a pulmonary clinic, the number of asthma diagnoses in this population is unpromising and suggests that many patients never receive any sort of pulmonary screening or pulmonary function test. Although pediatric SCD patients are being referred to be seen by a pulmonologist, it is highly unlikely that they are ever seen in a clinic. Thus, these children remain undiagnosed with asthma. Because the data from Indiana University was so promising, their clinical practices of diagnosing their SCD children with asthma, once uncovered, may ultimately be able to help shape the way for other healthcare institutions to improve their own asthma diagnosis rates in this population.

While Indiana's practices are unknown at this time, there remains speculation about what Indiana's clinical practices could be. Possibly, but unlikely, Indiana University could have a pulmonologist directly in the pediatric hematology clinic that tests sickle cell disease children for asthma while they are already at the hospital. This would erase the referral aspect of the practice that many other institutions use for their patients with suspected asthma. While this practice would explain Indiana's high rates of asthma diagnoses in their SCD population, it seems unlikely that a hospital would have a pulmonologist working on call for hematology. Perhaps the pulmonology and hematology clinics are near each other and patients could simply see both doctors the same day, rather than having to make an appointment and a subsequent trip to the hospital to get tested for asthma.

Throughout this project, I have learned the difficulty in collaborating with stakeholders and the great amount of time it takes to gather the necessary data and research. Any further research endeavors I partake in, I would probably start communications between stakeholders at an earlier time to anticipate any potential barriers that may come about. Once the results of this project have been determined, the next steps involve incorporating key aspects of the other institutions' clinical practices into the practices here at the University of Florida. Hopefully, any successful methods that are found to be used by the other medical centers are attainable, efficient, and cost-effective so that they can be easily incorporated into practice at other medical centers. The results, although not confirmed, look to be hopeful for SCD children who remain undiagnosed with asthma to receive the diagnosis and care they need to be able manage their disease effectively.

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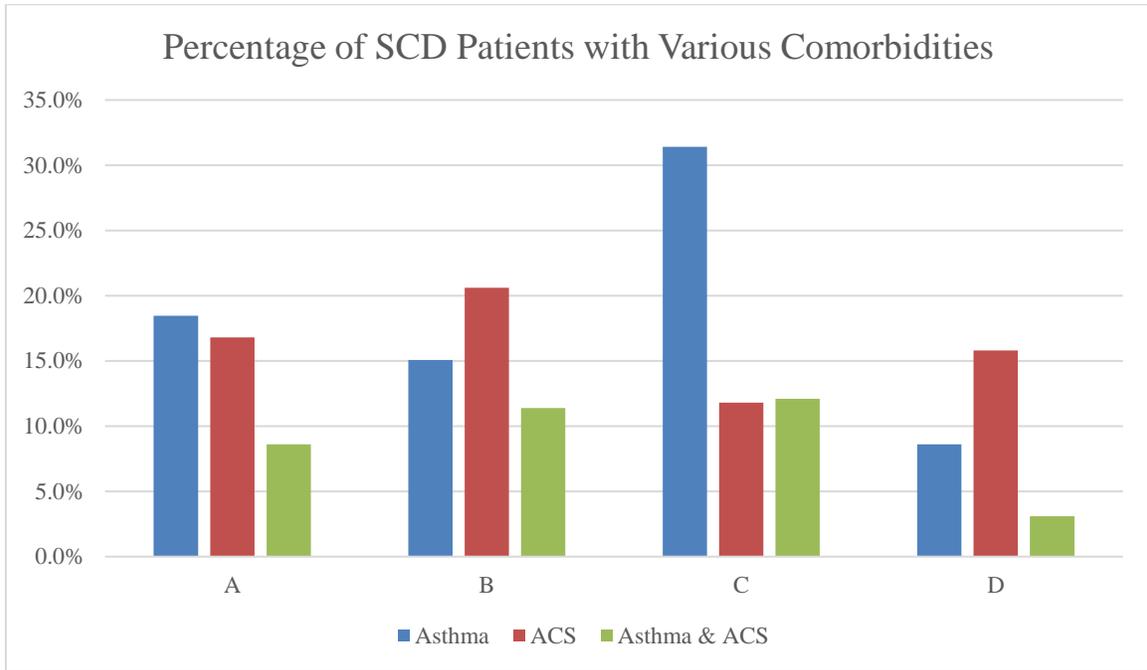
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Appendix A



Appendix B

Facility		Asthma diagnosis	No Asthma diagnosis	OR	p
A	ACS	37 (47%)	35 (10%)	7.9	<.001
	no ACS	42 (53%)	314 (90%)		
B	ACS	43 (75%)	35 (11%)	24.7	<.001
	no ACS	14 (25%)	286 (89%)		
C	ACS	144* (38%)	0* (0%)	Inf	<.001
	no ACS	233 (62%)	825 (100%)		
D	ACS	23 (36%)	94 (14%)	3.5	<.001
	no ACS	41 (64%)	583 (86%)		