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Acute chest syndrome in sickle cell disease patients: Experience from a resource constrained setting

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Abstract:

BACKGROUND: Sickle cell anemia is the most common inheritable hemoglobin disorder in the world with very high prevalence, morbidity, and mortality in Sub-Saharan Africa. Acute chest syndrome (ACS) is one of the most common causes of mortality among individuals with the condition. The management of this condition involves watchful waiting which may be deleterious in resource-constrained settings. The use of exchange blood transfusion (EBT) has been reported to be beneficial. The use of this great intervention is even further hampered in most of the developing world. The aim of this study was to review the outcome data of children managed with an algorithm adopted in 2015 at a University Teaching Hospital in a resource-constrained setting.

MATERIALS AND METHODS: This was a retrospective study from January 2015 to December 2017 at a University Teaching Hospital. Ethical approval was obtained from the Hospital's Health, Research, and Ethics committee.

RESULTS: A total of 324 children with sickle cell disease were admitted in the period under review with a male-to-female ratio of 1.5:1. Thirty-three patients were suspected of having ACS, but only 12 were confirmed using the algorithm. The mean age at presentation was 8 years with over 85% of the patients having a triad of fever, cough, and chest pain. All the patients had EBT within 48 h of admission and mortality rate recorded was 16.7%.

CONCLUSION: The use of the algorithm as well as the preemptive EBT improved the outcome of the children accessing care at our facility.

Keywords:

Acute chest syndrome, exchange blood transfusion, sickle cell disease

Introduction

Sickle cell disease (SCD) is an important contributor to childhood morbidity and mortality, especially in the tropics.[1] Acute and chronic pulmonary complications of SCD are not uncommon, with the most common acute complication been acute chest syndrome (ACS).[2] ACS is defined as the presence of fever and/or new respiratory symptoms in the presence of a new pulmonary infiltrate on chest radiographs.[3] It is quite common in the first 5 years of life and is associated with significant morbidity and mortality. In the report from the Cooperative Study of SCD, most patients with ACS were aged between 2 and 4 years with 25% of recorded mortality due to ACS.[2]

ACS was reputed to be the most common cause of death among children with SCD;[4] however, more recent reports have confirmed infections as the most common cause of death among these children.[5,6] Most children who developed ACS have

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been found to have had prior exposure to tobacco smoke as well as a previous history of asthma.[7] It has been observed to be inversely related to fetal hemoglobin levels and directly related to total white blood cell count.[8] The etiology of ACS is complex and multifactorial, and recurrent ACS may lead to lung infarction and fibrosis. Infection was the most common cause of ACS ahead of pulmonary infarction and fat embolism, while etiology was undetermined in approximately 30%–46% of cases.[9] Asthma has been known to increase the risk of ACS among children with SCD as well as worsening the course of the condition.[10] Other precipitants of ACS include chronic hypoxemia and more frequent vaso-occlusive crises.[8,11] The general rule is to monitor closely children with pulmonary symptoms and observe progression of disease. However, in resource-constrained settings, this approach may lead to worsening disease and mortality. Furthermore, intensive respiratory support is not available for such children in most resource-constrained settings. The use of blood transfusion in the management of ACS is contentious with a review reporting limited benefit.[12] This same review encouraged personal and local preferences in the management of children with ACS.[12] Thus, the management of ACS largely depends on local preferences. The use of preemptive blood transfusion was associated with reduction in the incidence of ACS among a population in the United States.[13] We developed a protocol of aggressive exchange blood transfusion (EBT) for children with ACS at our hospital in light of the above considerations.

Thus, this review is on children with ACS and the aggressive use of EBT in the setting of poor respiratory support for children with SCD managed at the pediatric hematology unit of a tertiary comprehensive sickle cell center.

Materials and Methods

This was a retrospective study of children with ACS from January 2015 to December 2017 at the PediatricWards of the Lagos University Teaching Hospital, Idi-Araba, Lagos. The charts of children with SCD were separated from all admitted children. The charts of those with ACS were then reviewed for bio data, admitting complaints, clinical course, investigations, treatment offered, and outcome. The pro forma developed was populated and data inputted and analyzed using the Statistical Package for the Social Sciences version 22 (IBM Corp, Armonk, NY, United States of America). Proportions and percentages were calculated for the variables of interest.

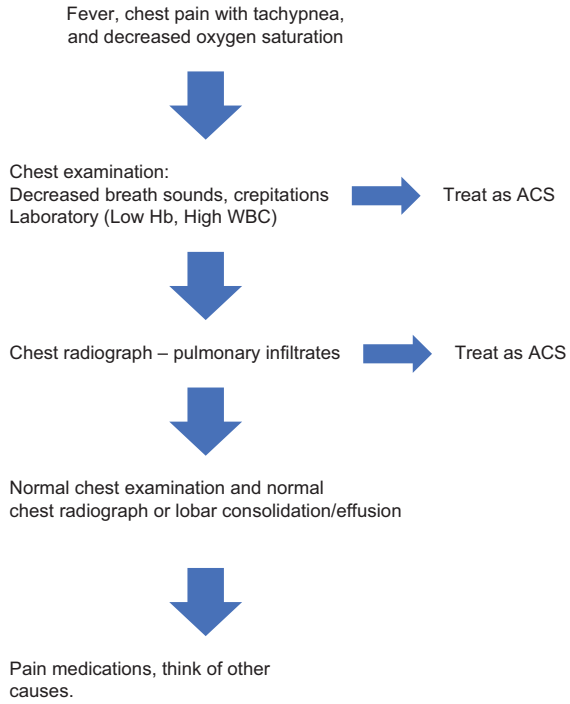
Diagnosis of acute chest syndrome

1. Diagnosis is suspected with a history of body pains and/or chest pain, fever, and cough in a known SCD patient. All patients with complaints of chest pain and cough get a chest radiograph
2. If symptoms persist or worsen after 48 h, repeat radiographs are requested, and if new infiltrates are seen, ACS is diagnosed. On the contrary, if symptoms worsen with progressive hypoxemia and repeat radiographs are not available, ACS is diagnosed
3. If chest pain, cough, and fever are present at diagnosis with segmental infiltrates on radiograph and associated hypoxemia, ACS is diagnosed in our setting.

Treatment offered

1. Intravenous infusion
2. EBT for all confirmed patients immediately following diagnosis by our algorithm. The EBT was manually done
3. Oxygen therapy
4. Broad-spectrum antibiotics with concomitant macrolide administration.

Algorithm for acute chest syndrome



Inclusion criteria

All children with SCD who satisfied the diagnostic criteria for ACS were enrolled for EBT.

Ethical consideration

Ethical approval was obtained from the Health, Research, and Ethics Committee of the Lagos University Teaching Hospital.

Results

The pediatric hematology unit of the Lagos University Teaching Hospital admitted 324 children with SCD between January 2015 and December 2017 with a male-to-female ratio of 1.5:1. The most common reason for

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presentation to the emergency room was vaso-occlusive crises. The mean age at presentation was 7 years [Table 1].

Of the 324 children seen in 3 years, 33 patients were suspected to have ACS on admission, however, following review documented in the charts by the team, ACS was diagnosed in 12 patients using the algorithm. Of the remaining number, ten had lobar pneumonia, two had pleural effusion, and five had vaso-occlusive crises with the remaining four managed as sepsis without a focus. There were more male than female patients.

The mean age at presentation for patients confirmed to have ACS was 8 years. Majority of these patients had <3 crises yearly [Table 2].

Half of the patients seen with ACS had at least two previous blood transfusions, while only one of the patients was on chronic blood transfusion [Table 2].

At presentation, almost all of the patients had a triad of cough, fever, and chest pain. All of the patients presented with dyspnea. Hepatomegaly was present in almost all patients [Figure 1]. On examination, over half of the patients had oxygen saturation lower than 90% [Table 3].

Discussion

SCD is an important cause of childhood morbidity and mortality in the tropics. It accounted for 23% of the pediatric admissions at this tertiary institution over a 3-year period. Expectedly, recurrent painful episodes were the most common reason for admission into the wards. Recurrent painful episodes have been described globally as the most common manifestation of SCD, and this is the most common phenotypic expression of the condition among individuals in different settings.[14-16] ACS which was earlier reported as the second most common cause of admission among individuals with SCD was not as common in this review.

ACS has been described as a common cause of morbidity and mortality among individuals with SCD. In an

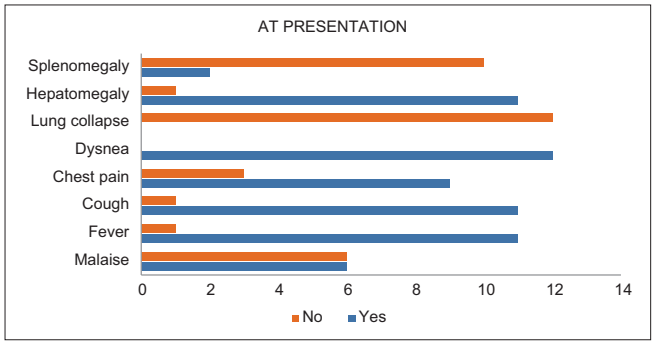

Figure 1: Clinical presentation of patients

Table 1: Sociodemographic characteristics of sickle cell disease patients in Lagos (*n*=324)

Variable	*n* (%)
Mean age at presentation (years)	7.35±4.25
Minimum age	6 months
Sex	
Female	128 (39.5)
Male	196 (60.5)
Reason for presentation	
Vaso-occlusive crises	179 (55.2)
Cerebrovascular accident	40 (12.3)
Priapism	17 (5.2)
Acute chest syndrome	12 (3.7)
Dactylitis	12 (3.7)
Abdominal VOC	11 (3.4)
Lobar pneumonia	10 (3.1)
Hyperhemolysis	8 (2.5)
Sepsis with unknown focus	7 (2.2)
Osteomyelitis	6 (1.8)
Septic arthritis	4 (1.2)
Gastroenteritis	3 (0.9)
Sequestration crises	3 (0.9)
Cellulitis	2 (0.6)
Renal papillary necrosis	2 (0.6)
Pleural effusion	2 (0.6)
Abscess	1 (0.3)
Acute viral hepatitis	1 (0.3)
Avascular necrosis	1 (0.3)
Empyema thoracis	1 (0.3)
Malaria	1 (0.3)
Meningitis	1 (0.3)
Nephrotic syndrome	1 (0.3)

VOC=Vaso-occlusive crisis

Table 2: Clinical history of acute chest syndrome patients (*n*=12)

Variable	*n* (%)
Age at presentation of ACS (years)	8.17±3.88
Minimum age at presentation (years)	2
Maximum age at presentation (years)	16
Age at diagnosis of SCD (years)	3.18±3.96
Minimum age at diagnosis (months)	6
Maximum age at diagnosis (years)	15
Mean duration between crises (years)	1.83±1.40
Frequency of sickle cell crises	
<3	6 (50.0)
>3<5	1 (8.3)
>5	5 (41.7)
Previous blood transfusion	
0	4 (33.3)
1	2 (16.7)
>2<5	3 (25.0)
>5	3 (25.0)
In need of chronic transfusion	1 (8.3)
Outcome	
Discharged	10 (83.3)
Died	2 (16.7)

ACS=Acute chest syndrome, SCD=Sickle cell disease

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Table 3: Examination and investigation findings (*n*=12)

Variable	*n* (%)
Blood culture	
Not done	4 (33.3)
No growth	8 (66.7)
Initial chest X-ray	
Clear	2 (16.7)
Infiltrates	9 (75.0)
Not done	1 (8.3)
Oxygen saturation	
<80	3 (25.0)
80-84	2 (16.7)
85-89	2 (16.7)
90	5 (41.7)

Table 4: Mean blood levels at admission (*n*=12)

Variable	Male (g/dl)	Female (g/dl)
Hemoglobin levels, mean (years)		
1-5	7.5	5.5
6-11	8.0	6.7
12-18	5.6	-
WBC count (cells/mm^3)		
Mean	31,688±14,763	
Range	20,000-65,750	
Lymphocyte count (cells/mm^3)		
Mean	29,142±19,457	
Range	14,000-87,000	
Neutrophil count (cells/mm^3)		
Mean	62,116±18,467	
Range	10,000-80,000	
Platelet count (cells/mm^3)		
Mean	542,670±139,915	
Range	285,000-808,000	

WBC=White blood cells

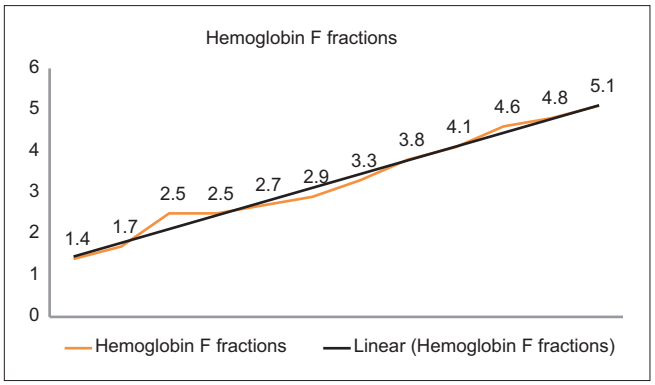

Figure 2: Hemoglobin F fraction values

earlier report, the most common age at presentation was 2–4 years;[3] however, in this study, the mean age at presentation for ACS was 8 years which was similar to the mean age of the study from French Guiana.[17] This similarity in the age at presentation may be as a result of the similarity in the socioeconomic status of both populations which differs markedly from the affluent nations that report earlier ages of presentation. It may also be due to early exposures to pathogens in the less affluent societies which are not as clean or the increased mortality that may have occurred among the younger age groups. Only three of the patients with ACS were <5 years representing 25% of the study cohort. Phenotypes of the disorder differ in their severity and clinical presentation with ACS expectedly common among individuals with more severe phenotypes of the disease.[2] This is consistent with more episodes of recurrent painful episodes as well as more hospitalizations.[2,18] In this report, approximately 50% of the population had more than three episodes of vaso-occlusive crises in the 6 months preceding admission. The most prevalent phenotype in Nigeria is vaso-occlusive crises which has also been described as an independent risk factor for ACS.[18]

The diagnosis of ACS is dependent on demonstration of oxygen desaturation and new infiltrates on chest radiograph. In our report, 75% of the population had infiltrates on their chest radiographs, and all the cohort had oxygen saturation 90% or less, with a quarter of them saturating at <80%. In a resource-constrained setting with prevailing poverty and inadequate critical care facilities, it is somewhat difficult to utilize the diagnostic criteria of the more affluent societies, thus we had to fashion out a process which will assist with prompt diagnosis and treatment as well as reducing the associated morbidity and mortality. An earlier report had suggested the use of clinical criteria for the diagnosis of ACS with less emphasis on radiologic and laboratory data.[19] This is particularly important because it is difficult to predict the patients that may develop progressive disease. Thus, we developed an algorithm which enabled aggressive therapy translating to reduced morbidity and improved outcome. This algorithm encourages aggressive EBT to improve oxygen carrying capacity early in the course of the condition.

The use of a more clinical algorithm is in line with the realities of our practice. This algorithm relied more on the use of detailed physical examination with oxygen saturation values using a pulse oximeter and chest radiographs to predict and diagnose ACS. It was discovered that all the patients were dyspneic with most having cough, chest pain, and fever. These clinical findings have been better defined and validated by a larger clinical study group and are thus an important guide.[2] The average hemoglobin documented was <8 g/dl for the patients managed for ACS in this report [Table 4] which was similar to what was reported by Elenga *et al*., and this has been found to be inversely proportional to the risk of ACS.[2,8,17] Furthermore, all the patients with ACS had elevated leukocyte counts which have also been reported as a risk factor for ACS [Table 4].[2,8] However, due to the small sample size of

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this cohort, it will be difficult to ascribe cause and effect or determine risk factors for ACS.

The utilization of laboratory values, especially hemoglobin concentration and total white cell count further aided the diagnosis of ACS [Figure 2].

Although contentious, the use of blood transfusion has been recommended in the management of people with ACS.[13,20,21] This improves the oxygen-carrying capacity of the blood and the clinical course of the condition. However, whether a simple transfusion which is thought to expose the patient to the risk of increased blood viscosity and volume overload or EBT should be the gold standard is still a matter to be decided. We preferred EBT which we figured will reduce the burden of sickled hemoglobin and enhance oxygen-carrying capacity without the added problem of volume overload. All the children received EBT within 48 h of diagnosis. This was to forestall worsening symptoms and improve clinical outcome. This aggressive EBT protocol has reduced the need for unavailable invasive respiratory support for children with ACS in our setting. Furthermore, it has been suggested that where facilities permit, a more aggressive approach to ACS may be advocated, especially in a resource-constrained setting.[22] Following the commencement of the algorithm, the mortality rate of the unit after 3 years dropped to 16.7% from almost 90% in the 3 years preceding the use of the algorithm. Although this mortality rate is far higher than the 3% described by the larger clinical study on ACS and a single hospital report from the Middle East,[3,14] for our settings, it is an improvement considering the previously poor outcome.

Conclusion

The use of a more clinical algorithm has assisted with the reduction in morbidity and mortality due to ACS. A clinical trial to compare simple transfusion versus EBT will be desirable. Furthermore, risk factors and determinants of severity of disease in resource-constrained settings should be studied.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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