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SHORT REPORT

Acute chest syndrome in children with sickle cell disease: Data from a national AIEOP cohort identify priority areas of intervention in a hub-and-spoke system

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Summary

Acute chest syndrome (ACS) is a frequent cause of hospitalization in sickle cell disease (SCD). Despite advances in acute care, many settings still lack knowledge about ACS best practices. After the AIEOP Guidelines were published in 2012, suggesting standardized management in Italy, a retrospective study was performed to assess the diagnostic and therapeutic pathways of ACS in children. From 2013 to 2018, 208 ACS episodes were presented by 122/583 kids in 11 centres. 73 were male, mean age 10.9 years, 85% African, 92% HbSS or Sβ°. In our hub-and-spoke system, a good adherence to Guidelines was documented, but discrepancies between reference centres and general hospitals were noted. Improvement is needed for timely transfer to reference centres, use of incentive spirometry, oxygen therapy and pain management.

KEYWORDS
acute chest syndrome, children, guideline adherence, Italy, sickle cell disease

INTRODUCTION

Acute chest syndrome (ACS) is a major cause of death as well as a leading cause of admission for children and adults with sickle cell disease (SCD).[1] Figures regarding morbidity and mortality due to ACS have remained similar throughout the years in spite of wide implementation of health maintenance preventive measures and general standardized comprehensive follow-up, suggesting that strategies to improve prevention and management are needed.[2–4]

An ACS episode is usually defined as an acute illness characterized by the finding of a new pulmonary infiltrate along with one or more new respiratory symptoms or signs.[5,6] SCD patients may develop ACS independently from an acute painful episode or as a complication of a vaso-occlusive event (VOE).[7,8]

Several guidelines identify the following as cornerstones of ACS treatment[5,8–11]: antibiotics for infection management, oxygen supplementation and red blood cell (RBC) transfusion to increase oxygen delivery, bronchodilators, incentive spirometry and supportive care. While these treatments are well established, other treatment options, like inhaled nitric oxide and corticosteroids, have limited evidence supporting their effectiveness in ACS management.[5] Real-world scenarios can present challenges in adhering to guidelines, as different settings like community care, general hospitals or reference centres may implement prevention and treatment strategies differently. Additionally, networking and coordination among various levels of care can be difficult, potentially impacting the consistency of ACS management.[12,13]

Italy has registered an increasing number of individuals with SCD in the past 15 years due to population movements in traditionally low-incidence regions.[14,15] However, the absence of a national newborn screening programme and a national registry in the country has made it difficult to gather comprehensive data on SCD and to diagnose the disease in infancy. Despite the rising frequency of ACS,[16] there is a lack of data regarding the national epidemiology, outcomes and general management of the condition. This information gap may hinder the ability to deliver guidelines-based care and implement targeted interventions to improve ACS management.

The primary aim of this study was to assess ACS epidemiology and characteristics in the setting of the Italian public national health system in which paediatric care for rare diseases is organized in a hub-and-spoke model; the secondary aim was to evaluate the diagnostic and therapeutic pathway of ACS in the 5-year period (2013–2018) after the dissemination of the Italian Association of Pediatric Hematology Oncology (AIEOP) Guidelines for the Management of SCD in Childhood, which included specific recommendations for the diagnosis and management of ACS, published in Italian in 2012 (www.aieop.org) and in English in 2013.[17]

METHODS

Study design and definitions

We conducted a retrospective, observational cohort study on ACS among paediatric patients with SCD followed in AIEOP Centres, which are paediatric haematology–oncology reference centres and constitute the hubs of hub-and-spoke networks with general hospitals as spokes. Children with SCD can be admitted for acute events in the paediatric wards of the spoke centres.

ACS was defined according to the AIEOP Guidelines[17] as an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on chest X-ray (CXR), which mirrors the ones of international guidelines.[5,8] The management of ACS required a CXR for diagnosis, inpatient admission, blood culture in case of fever, broad-spectrum antibiotic therapy with a cephalosporine and macrolide, red blood cell transfusion (RBC) to maintain Hb above 8 g/dL, oxygen supplementation if $SatO_2 < 96\%$, incentive spirometry, bronchodilator in case of wheezing and adequate pain control.

A VOC was defined as a hospitalization for SCD-associated pain requiring treatment with non-steroidal anti-inflammatory drugs (NSAIDS) and/or opioids. Children with SCD, aged 0–18 years, with at least one episode of ACS between January 2013 and January 2018 were included. ACS episodes that occurred before 2013 and the total number of ACS experienced by each patient were recorded. ACS and pain episodes were reviewed by a single investigator at each participating site, with over-reading by the two investigators at the coordinating site, to ensure uniform definitions of ACS and pain episodes.

The standard of care during the study (2013–2018) was provided according to AIEOP guidelines.[17] Briefly, hydroxycarbamide (HU) was prescribed in case of recurrent VOCs, ACS or anaemia with Hb <8 g/dL. Pulmonary function tests were part of standard protocol of care and performed starting at age 6 years. Investigations for allergy were made based on clinical need as well as sleep apnoea studies. Recurrent wheezing was defined as at least two documented acute bronchospasm episodes with clinical evaluation by a physician and the diagnosis of asthma had to be performed by a paediatric pulmonologist. Vaccinations were provided according to the SCD guidelines and the National Immunization Plan.[17,18] Annual influenza was considered performed before the ACS if administered in the autumn season before the ACS episode occurred.

Demographic, clinical and laboratory characteristics, treatment and follow-up were extracted from the patients' medical records, de-identified and collected in a dedicated standardized excel database in each centre by the local investigator. Comorbidity, history of allergy, asthma and recurrent wheezing were recorded. Laboratory values were recorded at steady state, 4 weeks after acute clinical events and blood transfusions. Data were centralized at the Azienda

Ospedale-Università di Padova for revision and statistical analysis.

The study was carried out in compliance with the ethical principles of the Declaration of Helsinki and Good Clinical Practices. The study was approved by the local ethics committee, and all subjects provided informed consent.

Statistical analyses

Continuous variables were summarized as means and standard deviations and compared using the two-sided Student's *t*-test and the Mann–Whitney non-parametric test (whichever was appropriate). Categorical variables were described with frequencies and percentages and compared using Pearson's chi-square test and Fisher's exact test (when appropriate). The Pearson test and the Spearman test (when appropriate) were used to test for any linear correlation. Values of $p < 0.05$ were considered statistically significant. Statistical calculations were made by IBM SPSS Statistics version 26.

RESULTS

Patient population

Eleven centres (nine in northern-central Italy and two in southern Italy) took part in the study. Five hundred and eighty-three patients with SCD were followed in those centres in 2018. Over the 5-year study period, 122/583 (21%) children presented one or more ACS for a total of 208 episodes. Seventy-three were males (60%) and 49 (40%) were females. At the time of data collection, the median age was 11 years (range: 18 months–23 years, SD 4.67).

One hundred and twelve were SS or Sß° (102 SS, 10 Sß°), and 10 were SC or Sß + (nine SC, one Sß+). Mean age at diagnosis of SCD was 25.33 months (range 0–16.8). The majority of patients originated from Sub-Saharan Africa (101/122, 83%; 35 Nigeria, 22 Ghana, 9 Senegal, 8 Ivory Coast as the most frequent countries of origin), Europe (17/122, 14%; Italy and Albania), three patients were of mixed ethnicity (Italy and Nigeria) and one from the Dominican Republic.

At the beginning of the retrospective study, 121 patients were alive, one patient had died from pneumococcal sepsis and 6 were lost to follow-up.

Medical history, clinical characteristics of ACS episodes and haematological variables did not differ from the literature and are reported in Data S1. The ACS diagnostic pathway is also reported in the Data S1.

ACS treatments

Antibiotics

The use of empirical antibiotics was reported in 205/206 episodes (99.5%). In 168/205 (82%) episodes, a combination of third-generation cephalosporin and macrolide was administered. Vancomycin or teicoplanin was added for coverage of *Staphylococcus aureus* infection in severely ill patients in 43/205 (21%) episodes.

Respiratory therapy

Supplemental oxygen was given in 91/208 (44%) events, including 70 with $SatO_2$ <96% at admission. Use of humidified high-flow nasal cannula oxygen (HHFNC) was needed in 7/91 (8%) of the admissions requiring oxygen therapy; non-invasive and mechanical ventilation were needed in 2/91 (2%) and 3/91 (3%) episodes respectively. No supplemental oxygen therapy was administered to 54/119 (45%) episodes with oxygen saturation ≤96%. Oxygen was needed for a median of 5.5 days (range 1–16 days).

Incentive spirometry was utilized only in 33/208 (16%) episodes (22/33 at ACS admission; 11/33 as preventive therapy, during other causes of admissions); in 24 ACS episodes, data were not available. Bronchodilators for the presence of wheezing or a history of reactive airway disease were given in 80/208 (38%) ACS events. The use of antivirals (oseltamivir) was documented in two admissions when influenza virus was isolated from a nasopharyngeal sample. Corticosteroid therapy was reported in 19 of ACS events: in three cases to treat a post-transfusion haemolytic reaction, and in the remaining cases to manage wheezing or respiratory distress.

Analgesia

Of the 208 ACS episodes, 158 presented pain, but the use of pain medication was requested only in 135/158 (85%); in about half of these cases (68/135) morphine was needed to achieve adequate analgesia.

RBC transfusion

Simple packed RBC (pRBC) transfusion was administered in 151/208 (72%) episodes, with an average of 1.5 per episode. Red cell exchange (RCE) transfusion was used in patients with severe or rapidly progressive illness and was registered in 31/208 (15%) events. Multiple RCEs were performed during 4/208 (1.9%) episodes. Simple pRBC was performed on the median day 1 of admission, while RCE was performed on the median day 4 of admission. In 11 admissions with Hb ≤ 8 g/dL, no transfusion was performed.

Outcomes of the ACS episodes

Of the 208 ACS episodes, 207 were managed in hospital, and 1 case in the emergency department and then discharged. Most patients were admitted directly to AIEOP Haemoglobinopathy Reference Centres during the ACS episode

(148/207 admissions, 72%), while hospitalization occurred in general hospitals without a dedicated hemoglobinopathy team in 59/207 admissions (28%). Of the latter, 35% requested a transfer to a reference centre due to worsening clinical conditions and the need for multidisciplinary team care, exchange transfusion or ventilatory support.

In 7/208 episodes (3.4%), respiratory failure was documented, and patients were transferred to the Intensive Care Unit. In three cases, invasive ventilation was required. RBC alloimmunization with haemolytic transfusion reaction was detected in three patients. Neurological complications were not observed. One patient had to be readmitted due to a VOC within 7 days after discharge, and three patients had to be readmitted for another ACS episode within 30 days after discharge.

TABLE 1 Implementation of the Italian Association of Pediatric Hematology Oncology (AIEOP) acute chest syndrome recommendations in this study.

Recommendations from the AIEOP guidelines	Rate of implementation of the recommendation (%)
Inpatient admission	99.9
Chest X-ray at admission	100
Blood culture if fever	57.8
Other micro/nasopharyngeal aspirate	36
Broad-spectrum antibiotics	100
O_2 therapy if $SatO_2$ <96%	100
Blood transfusion if Hb <8 g/dL	78
Incentive spirometry	16

The mean length of hospitalization was 9.3 days (range 1–43 days). One death associated with pneumococcal septicaemia during an ACS episode occurred.

Adherence to the AIEOP guidelines

Overall, adherence to the guidelines was good for certain recommendations but suboptimal for others (Table 1). Most patients with ACS episodes developing independently from an acute painful episode were admitted to the hospital (99.5% adherence). The therapeutic diagnostic pathway showed that all patients received a CXR at the diagnosis of ACS, and antibiotic therapy was administered to all patients (100% adherence). However, there were areas that needed improvement. RBC transfusion to maintain haemoglobin levels above 8 g/dL was utilized in 75% of episodes. Blood culture during ACS episodes with fever was only performed in 57.8% of cases, with significant variation among different healthcare centres (ranging from 95% to 10%). Nasopharyngeal aspirate was used in only 36% of cases, and incentive spirometry was employed in just 16% of episodes. Furthermore, differences in the management of ACS were observed between general hospitals and reference centres, suggesting potential variations in practice patterns and access to resources (Table 2).

DISCUSSION

In this retrospective, multicentre study conducted in Italy, the hospitalization burden of ACS in children with SCD was found to be high. Overall, there was good adherence to national guidelines for crucial aspects of the diagnostic and

TABLE 2 Differences between management for specific treatments between sickle cell disease reference centres and paediatric general hospitals.

	A. Care in general hospital with paediatric ward % (*N*)	B. Care in paediatric haematology oncology reference centre % (*N*)	C. Transferred from general hospital to reference centre % (*N*)	Comparison between A–B–C	Comparison between A–B
No. of ACS episodes[a]	100 (57)	100 (142)	100 (21)		
ACS on admission	44 (24)	54 (77)	52 (11)	0.2996	0.1219
Antibiotic therapy at ACS onset yes	88 (50)	99 (141)	95 (20)	0.0009	0.0002
Morphine therapy yes	23 (13)	32 (46)	57 (12)	0.0159	0.1263
Pain medication no	16 (9)	29 (42)	19 (4)	0.1021	0.00412
Oxygen supplementation yes	28 (16)	44 (63)	71 (15)	0.0022	0.0231
Incentive spirometry yes	10 (6)	16 (23)	43 (9)	0.0031	0.1647
Incentive spirometry data not known	33 (19)	6 (8)	5 (1)	0.000	0.000
Patients with at least 1 top up transfusion	74 (42)	16 (23)	81 (17)	0.000	0.000
Patients exchange transfusion	2 (1)	15 (21)	57 (12)	0.000	0.0041
Transferred to PICU	0	5 (7)	5 (1)	0.2340	0.0926
Blood culture yes	42 (24)	56 (80)	71 (15)	0.0467	0.0583
Blood culture in case of fever No	28 (16)	24 (34)	14 (3)	0.5550	0.6904

[a]Acute chest syndrome episodes with all the information available were included; therefore, 57/59 of the episodes were for Group A, 142/148 for Group B and 21/21 for Group C.

therapeutic pathway of ACS, with high rates of hospitalization (99.5%), radiography (98%), and antibiotic therapy (99%).

However, the study also revealed areas that need improvement in the implementation of guideline recommendations. These include the use of incentive spirometry (which encourages deep breathing and prevents lung complication), oxygen therapy (given in 75% of patients even when their oxygen saturation levels were below 95%), blood culture during febrile ACS episodes (performed in only 58% of cases) and microbiological diagnosis through nasopharyngeal aspirate (performed in only 29% of cases).

Additionally, the study highlighted significant discrepancies in management between reference centres with specialized haemoglobinopathy teams and general hospitals. Patients managed in general hospitals received suboptimal care in various measures, including the use of analgesics, morphine and the timing of antibiotic therapy.

The findings emphasize the urgency of enhancing the care provided to patients with SCD, similarly to patients with other rare diseases, in general hospitals.[19] This could involve the identification of specific guideline-based indicators that are not being met and implementing ongoing monitoring with dedicated resources.[13] Collaboration and support from reference centres in the network could aid general hospitals in developing strategies to improve patient outcomes.

Furthermore, the limited use of analgesics and opioids, especially in spoke centres, indicates the necessity to train healthcare staff in optimal pain management and gain a better understanding of different types of pain, including acute, chronic and acute–chronic pain.[20]

35% of the children who were first admitted to regional hospitals required transfer to haemoglobinopathy centres for various reasons (for PICU support, highly specialized transfusion, haematological multidisciplinary team for exchange transfusion and management of severe cases), highlighting the importance of close collaboration between hub-and-spoke centres.[5,8–9] We could not evaluate if standardized referral pathways were present or the timing and appropriateness of the transfer.[9,10] These aspects will be considered in future prospective studies in order to determine the quality measures for regional treatment centres and referral procedures.[7]

In conclusion, the analysis of ACS guideline-defined outcomes in a hub-and-spoke model of care for children with SCD is feasible. Dedicated actions, requiring coordinated national approaches and local educational initiatives in line with the recent European Reference Networks (ERNs) strategy to enhance collaboration between hub-and-spoke centres, can now be implemented and will focus on stimulating the application of early preventive measures for ACS that are still underutilized, better management of pain in VOCs and the use of incentive spirometry. Following the results of our study, it will be possible to develop regionally standardized clinical pathways for timely transfer to reference hospitals and tailor training events for the local and regional spoke hospitals. Similar approaches could be useful in other settings in which hub-and-spoke models are being developed and strategies to monitor the implementation of guideline-based outcomes are being looked for.[13]

AUTHOR CONTRIBUTIONS

V. Munaretto, R. Colombatti and L. Sainati designed the study and analysed the results. V. Munaretto and R. Colombatti wrote the manuscript. All authors collected the data and reviewed the manuscript.

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CONFLICT OF INTEREST STATEMENT

No conflict of interests for this study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was approved by the local ethics committee, and all subjects provided informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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