Clinical Factors and Incidence of Acute Chest Syndrome or Pneumonia Among Children With Sickle Cell Disease Presenting With a Fever

A 17-Year Review

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Objectives: The objectives of this study were to determine the incidence of acute chest syndrome (ACS) in children with sickle cell disease (SCD) presenting with fever before and after the introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) and to determine clinical factors associated with ACS for a febrile child with SCD.

Methods: A retrospective chart review was undertaken for children with SCD from 1993 to 2009 in a single, urban, tertiary-care pediatric center. Clinical and laboratory data for each febrile event for each child with SCD were recorded. We compared incidence of ACS for the 3 PCV7 eras: pre-PCV7, inter-PCV7, and post-PCV7. Univariate analysis and stepwise logistic regression were used to identify clinical factors most associated with ACS in the post-PCV7 era.

Results: Of 2504 febrile events in 466 children with SCD, we found 492 diagnoses of ACS. The incidence of ACS cumulatively decreased over time from 27.0% to 17.4% among febrile children with SCD ($P < 0.001$), although no change was seen in children younger than 2 years ($P = 0.89$). Independent predictors of ACS in the post-PCV7 era include history of previous ACS, upper respiratory tract infection symptoms, noncompliance to penicillin, male sex, hypoxemia, an absolute neutrophil count greater than 9×10^9/L, and hemoglobin less than 8.6 g/dL.

Conclusions: The incidence of ACS has decreased over time in febrile children with SCD. No effect was seen in those 2 years or younger. Children with SCD presenting with a fever had higher odds of developing ACS when accompanied by certain clinical, demographic, and laboratory features.

Key Words: acute chest, invasive pneumococcal disease, *Streptococcus pneumoniae*, sickle cell, pneumonia, bacterial pneumonia

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Acute chest syndrome (ACS) is a common life-threatening condition in children with sickle cell disease (SCD), with significant morbidity and mortality.[1–5] Almost one-third of patients with SCD will have ACS once in their life.[4] Known causes include asthma,[6] fat emboli,[1,5] and infectious etiologies such as *Mycoplasma pneumoniae* and *Streptococcus pneumoniae*.[1–3] In children with SCD, the diagnosis of ACS is difficult to distinguish from pneumonia (PNA) because ACS presents often with fever and cough[1,4,5,7]—but not chest pain, which is more common in adults. For clinical purposes and for the purposes of this study, ACS and PNA are treated similarly. Although not every fever is ACS, a clinician must be vigilant for these diagnoses in a child with SCD.

When a child with SCD presents with fever, patient management focuses on the risk of bacteremia from *S. pneumoniae*; the National Institutes of Health has very concrete guidelines for febrile children, but recommends only routine chest x-rays (CXRs) for fever without a source.[8] In some children, ACS is associated with culture-proven *S. pneumoniae* bacteremia.[5] For this reason, febrile SCD children with respiratory findings and radiographic infiltrates are usually treated for *S. pneumoniae*.[5,7,9]

The conjugated 7-valent pneumococcal vaccine Prevnar (PCV7) (Wyeth Pharmaceuticals, Philadelphia, PA) was introduced in 2000, and it has been shown to decrease invasive pneumococcal disease (IPD) in children with SCD and healthy children, as well as pneumococcal PNAs in healthy children.[10–14] Although ACS has many causes, one cause is *S. pneumoniae*. If the rate of *S. pneumoniae* pulmonary infections is reduced from PCV7, this may result in a reduction in ACS rates.[1–3,5,6]

The purpose of our study was to report the incidence of ACS for patients with SCD who develop a fever, before and after widespread PCV7 vaccination. For our secondary analysis, we searched for clinical factors that predict ACS in a febrile child with SCD in the post-PCV7 era.

METHODS

Study Design

We conducted a retrospective review of all pediatric patients with SCD who received care from a single, urban, tertiary-care children's hospital from January 1, 1993, to December 31, 2009. The Pre-PCV7 era was defined as 1993 to 1999, and the post-PCV7 era as 2003 to 2009.[3] The inter-PCV7 era composed the 2000 to 2002 time span. The study received approval from the institutional review board.

Study Setting and Population

Any child with SCD who presented to our institution during the study period was included. Our institution is the largest provider of pediatric hematology care in a metropolitan county, including SCD care. Eligible patients were identified using *International Classification of Diseases, Ninth Revision* codes for SCD and the SCD variants and diagnoses unique to SCD such as vaso-occlusive crisis and ACS. Sickle cell disease

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was defined as homozygous SS disease, SC disease (hemoglobin C), or any SCD and thalassemia variant (sickle-α, β^+, or β^0). Clinical notes or hemoglobin electrophoresis results were used to confirm the SCD diagnosis.

Study Protocol

We then set out to find all febrile events for these children with SCD occurring from 1993 to 2009, using electronic and paper records, irrespective of chief complaint of the visit. These included routine clinic visits, emergency department visits, and a fever that developed as an inpatient. For this study, we defined a febrile event as a temperature greater than 38.0°C (100.4°F) documented in the history, the physical examination, or the nursing records; this included measured home temperatures. Patient encounters while older than 21 years were excluded. Three authors (T.P.C., W.K., V.J.W.) abstracted data in duplicate sampling for the first 10 patients—45 febrile events—to establish consensus. Thereafter, data were abstracted by 1 of 3 authors who were not blinded to the study hypothesis. The 3 abstractors met biweekly to address chart review progress.

Measurements

The primary outcome was diagnosis of ACS. This was defined as both a documented diagnosis of ACS and a positive CXR within 24 hours of the child's febrile event.[7,8] Chest x-rays were considered positive if an attending radiologist noted a perihilar, lobar, or interstitial infiltrate. The study included patients who had ACS immediately upon presentation, as well as patients who developed a fever and ACS as an inpatient for a different medical issue. The incidence was calculated by dividing the number of ACS by the total number of febrile events in all patients with SCD within the given time frame. Chest x-rays were ordered at the discretion of the treating physician or consultant.

For our secondary analysis, we looked at potential clinical factors that correlate with ACS per febrile event. We recorded these variables that predict morbidity in SCD[4–7]: SCD type; age; sex; comorbid diagnoses including neurological, rheumatologic, renal, hepatic, or cardiopulmonary disorders; documented noncompliance to penicillin prophylaxis; documented missing vaccination; and any history of ACS, dactylitis, priapism, cerebrovascular accident, splenic sequestration, and frequent vaso-occlusive crises requiring more than 2 admissions per year. Patient charts were reviewed until documentation of these factors appeared; for example, a child may have had a first splenic sequestration in 1999. Febrile episodes before that documentation were considered to not have any history of sequestration, whereas febrile episodes after 1999 were considered to have a positive history of sequestration. For certain patients, the hematologists continued penicillin prophylaxis beyond 5 years,[8] and noncompliance documented past 5 years of age was also noted as noncompliance for our analysis.

Variables per febrile event included maximum temperature on presentation, number of days of previous fever, documented toxic appearance, upper respiratory tract infection (URTI) symptoms, hypoxemia, an obvious focal infection, or the presence of a central venous line. Laboratory data included white blood cell (WBC) and the differential count, absolute neutrophil count (ANC), absolute band count (ABC), hemoglobin levels, and final blood culture results.

Data Analysis

Trend analyses were performed on all febrile events with ACS as the primary event. Febrile events were classified into 1 of the 3 PCV7 eras based on the date. We compared incidences of ACS per febrile event between the 3 PCV7 eras using the Mantel-Haenszel χ^2 test for trend. Statistical significance was defined with a $P < 0.05$. A separate trend analysis was also performed just on the cohort of patients with SCD who were born on or before the pre-PCV7 era and therefore were adolescents or adults by the post-PCV7 era. A post hoc subanalysis was also performed on SCD patients younger than 2 years, those most affected by PCV7. The incidence of ACS is reported as ACS per febrile event.

The secondary analysis was on clinical factors associated with ACS in febrile children with SCD, which was performed on post-PCV7 data. The febrile event was the unit of measurement. Univariate analysis assessed the association between each risk factor and the outcome of ACS. Continuous variables found to be significantly associated with ACS were converted to dichotomized variables for multivariate regression. We determined cutoffs only once, after visual inspection of the histograms for each variable, and rounded to the nearest usable clinically relevant value. All factors that had $P < 0.2$ were included in the stepwise logistic regression model.

Variables with $P < 0.05$ in the stepwise multivariate logistic regression were considered statistically significant predictors for ACS for each PCV7 era, and 95% confidence intervals for odds ratio were calculated. For all analyses, ACS were treated the same, independent outcome.[7] All statistical analyses were performed using SAS 9.1 software (SAS Institute, Cary, NC).

RESULTS

From 1993 to 2009, 466 pediatric patients with SCD were found within our institution. Chart reviews of their medical care yielded 2504 febrile events with 1876 CXRs performed because of fever (75.0%). Six hundred forty-five (34.4%) of the 1876 CXRs were positive. Of all febrile events, 492 were associated with a final discharge diagnosis of ACS; the incidence of ACS from a febrile event was 492 (19.6%) per 2504 over the entire study period.

The mean number of febrile events per patient was 5.37 ± 6.60, and the mean number of CXRs per patient for febrile events was 4.02 ± 5.28. Sixty-seven of 466 patients with SCD had no documented febrile event at the hospital.

The mean ages of patients with SCD during their febrile events did not change between the PCV7 eras ($P = 0.445$), and the proportion of children younger than 2 years did not change ($P = 0.436$).

Primary Analysis

A total of 3220 person-years were available for analysis from 1993 to 2009. Comparison between the PCV7 eras found a statistically significant decline in incidence of ACS from 27.0% to 17.4% ($P < 0.001$) (Table 1). When isolating the data just to patients who were born in or before the pre-PCV7 era, the incidence of ACS had also decreased over time as they aged ($P = 0.047$) (Table 2). A subanalysis on patients younger than 2 years at the time of the febrile event did not show any change in the incidence of ACS over the PCV7 eras ($P = 0.89$) (Table 3).

Secondary Analysis

Tables 4 and 5 illustrate the univariate and multivariate regression analyses. Factors found positively associated with ACS by univariate analyses include (*a*) demographic factors including male sex, older age, and comorbid conditions; (*b*) SCD characteristics portending severity of disease, such as frequent vaso-occlusive crises, and previous ACS; (*c*) clinical factors including toxic appearance, URTI signs, hypoxemia, and higher temperature; and (*d*) laboratory data including higher WBC,

TABLE 1. Incidence of ACS Among All Febrile Children With SCD ($P < 0.001$)

	Rate, %	95% Confidence Intervals for Rate, %	Cases per Febrile Visits
Pre-PCV7 (1993–1999)	27.0	23.3–31.0	144/533
Inter-PCV7 (2000–2002)	18.8	15.0–23.0	72/384
Post-PCV7 (2003–2009)	17.4	15.6–19.4	276/1587

ANC, ABC, and lower hemoglobin levels. All factors except toxic appearance (9 ACS vs 8 without) had at least 10 events.[15] These are summarized in Table 4.

Table 5 shows the results of stepwise logistic regression for the post-PCV7 era. The clinical factor most associated with increased odds of ACS in the post-PCV7 era was a history of previous ACS. Others associated with ACS include hypoxemia, an elevated ANC, low hemoglobin, male sex, and noncompliance to penicillin.

DISCUSSION

Incidence of ACS

We demonstrated a significant decrease in the incidence of ACS per febrile event in this longitudinal study of children with SCD from 1993 to 2009. There was no statistical difference in the incidence of ACS among SCD children younger than 2 years between the 3 PCV7 eras; however, the children with SCD in the pre-PCV7 cohort, when followed over time, continued to have decreased incidence of ACS per febrile event. This suggests that although there is documented decrease in IPD in patients with SCD,[10,16] there is no parallel decrease in ACS for SCD children younger than 2 years. One explanation is that ACS, unlike IPD, has many causes besides *S. pneumoniae*.[1,5,6] It is difficult to attribute PCV7 to the general decrease in ACS per febrile event noted in our study for all patients, given its lack of effect on SCD patients younger than 2 years. We cannot conclude that PCV7 decreased the incidence of ACS per febrile event based on our data; however, further decreases in incidence following the 13-valent pneumococcal vaccine would support a delayed or herd immunity effect for older children with SCD and ACS. Alternatively, older children with SCD may have afebrile ACS[5]; these were not captured in our data.

In our study, we grouped ACS and PNA together, reflecting clinical practice in the acute care setting. A febrile child with SCD with a radiographic pulmonary infiltrate and respiratory complaints should not require differentiation between the 2 entities.[7] Even with no initial sickling, pulmonary infiltrates lead to focal or lobar hypoxemia, which could incite a secondary ACS.[8]

In the general population, rates of IPD were highest among young infants, approximately 228 per 100,000 children aged 6 to 12 months in the pre-PCV7 era.[17] In 2007, the rate dropped to 22 to 23.6 per 100,000 children younger than 5 years.[12,18] In addition, PCV7 has made substantial impact against PNAs in the non-SCD population. Pleural fluid cultures with *S. pneumoniae* decreased from 16.3 to 8.3 per 100,000 children younger than 5 years with PNA.[12] Epidemiologic reports using insurance data found similar decreases in PNA, particularly in infants younger than 2 months, suggesting a herd immunity effect.[11,14] It should be noted that the latter epidemiologic reports had either too few pneumococcal PNAs[11] or defined pneumococcal PNAs by *International Classification of Diseases, Ninth Revision* codes,[13] similar to our low numbers of ACS in SCD children younger than 2 years.

In children with SCD, PCV7 has profoundly decreased the incidence of IPD. The Centers for Disease Control data demonstrated a decrease to 0.5 per 100 person-years rate of IPD in 2002, representing an 88.5% decrease in the inter-PCV7 era.[16] In 2007, children with SCD living in Tennessee were found to have a 90.8% decrease in IPD incidence for those younger than 2 years and a 93.4% decrease for those younger than 5 years.[14] This represented an IPD rate of 134 per 100,000 person-years for children with SCD younger than 5 years. There are no large-scale epidemiologic data on PNA—pneumococcal or otherwise—in children with SCD.

The simultaneous incidence of *S. pneumoniae* bacteremia during ACS is rare in children with SCD. Pre-PCV7 reports showed a *S. pneumoniae* incidence of 1% to 3% in those with ACS.[19,20] Vichinsky et al[5] found an incidence of 0.4% to 10.9% *S. pneumoniae* bacteremia, with the higher percentage in children younger than 2 years with ACS. In our study, only 3 children (0.6%) had both an infiltrate on CXR and *S. pneumoniae* bacteremia. Among our 492 cases with ACS, only 5 had positive sputum cultures that grew *Pseudomonas aeruginosa, Haemophilus influenzae*, *Moraxella catarrhalis*, and 2 normal flora.

Clinical Factors With Acute Chest Syndrome in Febrile SCD Children

Fever is the most common presentation of ACS in a child,[20] followed closely by cough[21]; in children younger than 2 years, up to 97% of those with ACS are febrile.[5] Vichinsky et al[5] reported cough in only 69% of children with ACS between 10 to 19 years of age but in 86% in the 2- to 4-year range. There was less uniformity in physical examination findings: 35% of children with ACS had an initial normal lung examination.[5] We looked at whether clinical factors associated ACS could be gleaned in the initial visit of a febrile child with SCD in the post-PCV7 era.

TABLE 2. Incidence of ACS Among Febrile SCD Children Enrolled Before 1999 and Followed Longitudinally Over Time (Pre-PCV7 Cohort) ($P = 0.047$)

	Rate, %	95% Confidence Intervals for Rate, %	Cases per Febrile Visits
Pre-PCV7 (1993–1999)	27.0	23.3–31.0	144/533
Inter-PCV7 (2000–2002)	22.5	17.7–28.0	61/271
Post-PCV7 (2003–2009)	21.9	18.6–25.5	125/571

TABLE 3. Incidence of ACS Among Febrile SCD Children Younger Than 2 Years ($P = 0.89$)

	Rate, %	95% Confidence Intervals for Rate, %	Cases per Febrile Visits
Pre-PCV7 (1993–1999)	7.6	2.9–13.1	7/92
Inter-PCV7 (2000–2002)	6.6	0.9–12.3	5/76
Post-PCV7 (2003–2009)	6.4	3.6–9.1	19/299

Hypoxemia and a history of previous ACS were both associated with increased odds of ACS in the post-PCV7 era. These have been shown in adult studies, and our data support these associations.[2,7] A history of noncompliance to penicillin was associated with increased odds of ACS in our multivariate regression analysis. Because judicious penicillin prophylaxis is associated with a lower incidence of IPD, this may suggest *S. pneumoniae* as a causative agent for ACS.[22] Alternatively, noncompliance to penicillin is a proxy for poor self-care or another risk factor not measured in our data analysis for ACS. We should note that, in univariate analysis, noncompliance was actually associated with decreased odds of ACS. Upon further analysis, it was found that patients labeled as noncompliant to penicillin had a significantly higher median number of febrile events (8 vs 2, $P < 0.01$), which would have increased the denominator of febrile events in this population.

Male sex appeared to increase the odds for ACS in febrile children with SCD in our data. There is no correlation between sex and ACS in the literature, and we are uncertain of the significance of this finding. We have identified no significant difference in sex among post-PCV7 febrile events. Two laboratory values were found to be risk factors for ACS in febrile children with SCD in the post-PCV7 era. Lower hemoglobin levels have been shown to be a risk factor for ACS and increased mortality rates in other studies.[5,23] This is consistent with findings in our study, in which hemoglobin levels less than 8.6 g/dL were associated with increased odds of ACS. The association of leukocytosis and elevations in the subtypes of leukocytes in ACS has been shown in previous studies.[2,4,5,23] Leukocytosis may simply be a reflection of the inflammatory process inherent in pulmonary vaso-occlusion or fat emboli, or it may signal an infectious process such as bacteremia.[24] Our data showed an association with an elevated ANC greater than 9×10^9/L and ACS. Although the PCV7 vaccine did decrease IPD rates, leukocytosis in ACS is a likely marker of inflammation rather than definitive IPD.[2]

LIMITATIONS

Patients with ACS were identified by diagnoses provided by written documentation, which can underestimate or overestimate the incidence of ACS. Some medical records may reflect a cautionary diagnosis; that is, a febrile child with SCD was admitted to "rule out" ACS. However, we corroborated all documented diagnoses of ACS with pulmonary infiltrates on a CXR. Given that a febrile child with SCD with pulmonary infiltrates is usually treated as ACS,[7] we felt this method of chart identification still had validity.

There was a significant discrepancy in the number of febrile events between the pre-PCV7 and post-PCV7 eras (533 to 1587); this partially reflects the growth of the institution and increased monitoring, although there is a possibility of missing charts, particularly older charts in the 1990s. To address this, we conducted 3 separate chart requests for the same 466 patients to capture archived patient information. It is still possible that this

TABLE 4. Univariate Analysis of Potential Risk Factors Associated With ACS in Febrile Children With SCD in the Post-PCV7 era

Risk Factor	Odds Ratio (95% Confidence Interval)
Toxic appearance	4.81 (1.19–19.33)
URTI symptoms	1.73 (1.31–2.29)
Hypoxemia (oxygen saturation <93% on room air)	4.74 (2.70–8.30)
Focal infection (cellulitis, etc)	0.73 (0.33–1.64)
Central line present	0.83 (0.49–1.42)
Male sex	1.23 (0.94–1.59)
SCD SS vs non-SS types	1.24 (0.91–1.68)
Other comorbid diagnoses (asthma, autoimmune disorder, etc)	1.32 (1.01–1.71)
Noncompliance to penicillin	0.26 (0.20–0.35)
History of ACS	5.19 (3.77–7.14)
Pain crises >every 6 mo	1.37 (1.06–1.78)
History of dactylitis	0.94 (0.68–1.30)
History of cerebrovascular accident	0.83 (0.56–1.24)
History of sequestration	1.12 (0.85–1.47)
Age ≥6 y	1.64 (1.26–2.14)
Temperature ≥38.8°C	1.17 (0.89–1.55)
ANC $\geq 9 \times 10^9$/L	2.57 (1.93–3.42)
ABC $\geq 0.15 \times 10^9$/L	1.21 (0.92–1.58)
More than 1 d of fever on presentation	1.09 (0.74–1.60)
WBC count $\geq 16 \times 10^9$/L	2.01 (1.53–2.63)
Hemoglobin level ≥8.6 g/dL	0.56 (0.43–0.73)

TABLE 5. Stepwise Logistic Regression Analyses for Clinical Factors Associated With ACS in Febrile Children With SCD in the Post-PCV7 era

Factor	Adjusted Odds Ratio (95% CI)
History of ACS	15.9 (7.4–33.8)
ANC $\geq 9 \times 10^9$/L	2.4 (1.8–3.3)
URTI symptoms	2.1 (1.5–2.9)
Noncompliance to penicillin	3.2 (1.5–6.4)
Hemoglobin level <8.6 g/dL	1.6 (1.2–2.3)
Male sex	1.5 (1.1–2.0)
Hypoxemia (oxygen saturation <93% on room air)	1.9 (1.0–3.5)

discrepancy may reflect lost pre-PCV7 charts, which would affect the conclusions of ACS incidence but not the post-PCV7 regression analysis.

It is also possible that not all febrile episodes or all cases of ACS were captured. Not all febrile episodes had a CXR as it was based on clinical suspicion; it is possible that those who did not have a CXR had ACS, particularly among those younger than 2 years, for whom ACS is a difficult clinical diagnosis.[5,7] Also, some febrile events had missing data. For this reason, we excluded events with incomplete data for stepwise logistic regression.

Our study was a single-institution review in an urban area in which distance to the hospital may have been a factor in patient visits. Every effort was made to track transfer records and original reports from outside facilities; however, patients may have been treated elsewhere, and these records, radiographs, and treatments were not always available for review.

Finally, we decided not to perform a general estimating equation analysis, as we approached our analysis from an emergency department frame: SCD in a child presenting with a febrile episode is most often treated independently from any other febrile episode and is not treated as repeating events. General estimating equation is used for repeating measures in the same patient. Although it is possible that regression may overestimate certain odds ratios, we feel that it is still a valid statistical analysis.

CONCLUSIONS

The overall incidence of ACS in febrile SCD has significantly decreased from the pre-PCV7 to post-PCV7 era, but current incidence remains clinically significant at 17.4% of febrile children with SCD. It is unclear whether PCV7 contributed to this decrease. A history of ACS purports the greatest odds for ACS in a febrile child with SCD among all clinical factors. Other risk factors specific to the post-PCV7 era with increased risk for ACS include hypoxemia, elevated neutrophils, low hemoglobin levels, male sex, URTI symptoms, and poor penicillin compliance. These findings in a febrile child with SCD should alert the clinician to an increased risk of ACS, and our data support the use of empiric CXRs in any febrile child with SCD with a history of ACS.

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