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Incidence of Invasive *Haemophilus influenzae* Infections in Children with Sickle Cell Disease

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Abstract

Background: Children with sickle cell disease (SCD) are at increased risk for invasive infection with encapsulated bacteria. Antibiotic prophylaxis and immunizations against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) have decreased the overall incidence of invasive infections and have shifted distribution of serotypes causing disease towards those not covered by immunizations. We sought to determine the current incidence of invasive *H. influenzae* infections in children with SCD and to describe the clinical features and management of these infections.

Methods: Microbiology reports of a large pediatric tertiary care center were reviewed to identify all isolates of *H. influenzae* detected in sterile body fluid cultures from 01/01/2010 – 12/31/2017. Results were compared to the center's comprehensive clinical database of all children with SCD to identify all cases of children ages 0 – 18 years with SCD with invasive *H. influenzae* disease for the same time period.

Results: We captured 2,444 patients with SCD, with 14,336 person-years. There were 8 episodes of *H. influenzae* bacteremia in 7 children with SCD (5 type f, 2 non-typeable, 1 type a). Most episodes (7 of 8) were in children <5 years. The incidence rate of invasive *H. influenzae* in SCD was 0.58/1,000 person-years for ages 0–18 years and 1.60/1,000 person-years for children age <5 years. There were no deaths from *H. influenzae* infection.

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Conclusions: In the era of universal antibiotic prophylaxis and immunization against Hib, invasive *H. influenzae* disease due to nonvaccine serotypes remains a risk for children with SCD, particularly those under 5 years.

Keywords

sickle cell disease; *Haemophilus influenzae*; bacteremia

INTRODUCTION

Children with sickle cell disease (SCD) are at increased risk for invasive encapsulated bacterial infections such as *Haemophilus influenzae* due to impaired splenic function.^{1, 2} The advent of prophylactic penicillin and widespread immunization against *Streptococcus pneumoniae*, *H. influenzae* type b (Hib), and *Neisseria meningitidis* have decreased but not eliminated the incidence of invasive bacterial infections. Children with SCD remain at risk for infection with bacterial serotypes not covered by immunizations, including non-b and non-typeable *H. influenzae*.³

H. influenzae is a potentially devastating and fatal invasive bacterial infection, particularly among children under age 5 years.⁴ The appropriate acute management of such infections as well as long-term infection prophylaxis strategies for children with SCD after *H. influenzae* infection are not well defined.⁵ Prior to the introduction of penicillin prophylaxis and vaccination against Hib, the incidence of systemic *H. influenzae* disease in young children with SCD was estimated at 4.8 per 1,000 person-years (5.6/1,000 person-years for hemoglobin SS (HbSS), 4.2/1,000 person-years in HbSC) by the Cooperative Study of Sickle Cell Disease (CSSCD) which enrolled 694 infants with 2,908 person-years of observation from 1978 – 1988.⁶ An earlier study by Powars et al. found a higher incidence of 12.4 cases/1,000 person-years in children with SCD less than 5 years age.⁷ Although Powars described a non-fulminant presentation with an upper respiratory infection prodrome in most children with *H. influenzae* bacteremia, mortality rate for invasive infection was high at 20–30%.^{6, 7}

The first vaccine against *H. influenzae* type b (Hib) was licensed in the U.S. in 1985, and a conjugate vaccine with improved immunity for infants became available in 1990, leading to a nationwide decrease in invasive Hib disease in children from 20,000 cases/year to <40 cases/year in children under 5 years old.⁸ However, from 1998–2008, the incidence of non-type b *H. influenzae*, particularly type f and non-typable *H. influenzae* increased.^{9, 10} During 2009 – 2015, the estimated incidence of invasive *H. influenzae* continued to increase, primarily due to non-typeable and non-type b disease. From 2009 – 2015, in children under age 5 years, the incidence of invasive *H. influenzae* was 2.84/100,000 (0.13/100,000 for Hib, 1.65/100,000 for non-typeable *H. influenzae*, and 1.06/100,000 for non-b serotypes). For all age ranges, case fatality and population incidence were greatest for non-typeable *H. influenzae* (1.22/100,000; 16% fatality) and non-b encapsulated *H. influenzae* (0.45/100,000, 11% fatality), as compared to Hib (0.03/100,000, 4% fatality).⁴

The objectives of this study were (1) to determine the incidence of invasive *H. influenzae* disease in a large population of children with SCD from 2010 – 2017, and (2) to summarize

the clinical presentation, *H. influenzae* serotypes, and subsequent medical management of children with SCD and invasive *H. influenzae* infections.

METHODS

To identify all cases of invasive *H. influenzae* infections that were identified in the population of children (ages 0 – 18 years) with SCD, the microbiology laboratory reports for cultures of all sterile body fluids for the laboratories serving all Children's Healthcare of Atlanta (Children's) hospital locations were reviewed to identify all isolates of *H. influenzae* from January 1, 2010 – December 31, 2017. Culture results reviewed included all specimen drawn at Children's 3 Atlanta-area hospitals and 7 urgent care centers, but excluded cultures drawn at hospital systems outside of Children's. Blood cultures were tested at the laboratories of Children's (for 2 hospitals and all urgent care) or the laboratory of Grady Health System (for 1 hospital affiliated with Grady Health). The list of patients who had a positive culture for *H. influenzae* was then referenced to the Sickle Cell Clinical Database of Children's, a comprehensive, prospective database containing all patients with SCD with 1 encounter at Children's to identify *H. influenzae* infections in children with SCD.

For patients who were determined to have a diagnosis of SCD and had a positive blood or cerebrospinal fluid (CSF) culture for *H. influenzae*, the electronic medical record was reviewed to determine immunization history, use of antibiotic prophylaxis, surgical splenectomy, clinical presentation of infection (including symptoms, vital signs, laboratory values), culture results, duration of treatment and hospitalization, use of subsequent antibiotic prophylaxis, future invasive bacterial infections, and long-term sequelae of the infection. Adherence with antibiotic prophylaxis was assessed by review of clinical documentation prior to and during the hospital encounter for invasive *H. influenzae*.

Blood for culture was processed in automated, continuous monitor systems. Isolates were identified by phenotypic tests or matrix assisted laser desorption ionization mass spectrometry time of flight (MALDI-TOF). Typing was performed by standardized agglutination methods for each isolate. All cultures were sent to the Georgia Emerging Infections Program and Georgia Public Health Laboratory to determine *H. influenzae* serotype. Beta lactamase activity was determined in the individual hospital laboratories for all but 1 isolate which was determined by the Georgia Emerging Infections Program at a later date.

Statistical Analysis

The incidence rate of *H. influenzae* infection in children with SCD was estimated as the number of cases of *H. influenzae* infection divided by person-years of exposure for each calendar year and for the 8-year observation period.

RESULTS

From 2010–2017, there were 2,444 children and adolescents ages 0 – 18 years with SCD who were treated at Children's, with 13,816 person-years of follow-up. We identified 8 bloodstream *H. influenzae* infections in 7 children with SCD (5 type f, 2 non-typeable, 1

type a) (Table 1). The incidence rate of invasive *H. influenzae* was 58/100,000 person-years for all children with SCD (ages 0 – 18 years) and 160/100,000 person-years for children with SCD age <5 years. The majority of episodes (5 of 8) occurred during the year 2017, corresponding with the increase in the incidence of invasive *H. influenzae* nationwide from 2010 to 2016.¹¹

The median age at infection was 2.1 years (range 0.9 – 7.9 years) with only 1 case in a child over age 5 years who also had previous surgical splenectomy (Table 2). All children had received all recommended immunizations for children with SCD for age, including the Hib immunization. In 7 of the 8 cases, the child was receiving penicillin prophylaxis prior to the infection, while in 1 case (Case 5) the child was receiving amoxicillin prophylaxis instead of penicillin (at parental preference) but had missed 1 week of treatment prior to presentation.

In all cases, the primary reason for presentation was fever. Seven patients presented without signs of hemodynamic instability or organ dysfunction, while 1 patient presented with hypotension and meningitis. Of the 7 patients without hemodynamic compromise, all presented with a prodrome of upper respiratory tract symptoms. Five of these 7 patients were initially discharged from emergency department care prior to positive blood culture reports. The median duration of hospitalization was 3 days, and none of these 7 children had long-term sequelae of the *H. influenzae* infection.

In contrast, one child (Case 2) with meningitis presented at 2-years of age with fever, lethargy, nuchal rigidity, and no respiratory symptoms. There was initial hypotension, evidence of organ dysfunction (serum creatinine 0.9 mg/dL, AST 219 U/ml, ALT 167 U/ml, total bilirubin 11.9 mg/dL, direct bilirubin 6.7 mg/dL), leukocytosis with bandemia (WBC 25,500/ μ L, 43% segmented neutrophils, 47% band neutrophils), and CSF with 241 WBC/ μ L. Blood culture grew *H. influenzae* type f, and CSF culture which was obtained after administration of parental antibiotic showed no growth. The patient was hospitalized 8 days, with 4 days of critical care support. This patient had long-term sensorineural hearing loss following successful treatment of *H. influenzae*. There was a history of recurrent otitis media prior to and after the *H. influenzae* meningitis. The patient discontinued antibiotic prophylaxis at age 7 years and has had no recurrent invasive bacterial infections.

Recurrent *H. influenzae* bacteremia occurred in 1 patient (Case 4) 10 weeks following treatment of the first episode. This was a 2-year-old child with prior recurrent otitis media, who was initially treated for *H. influenzae* bacteremia with 4 days of intravenous ceftriaxone followed by 7 days of high dose oral amoxicillin. Following treatment, the child resumed penicillin prophylaxis. Following the second episode of *H. influenzae* bacteremia which was treated similarly (ceftriaxone for 3 days, then amoxicillin for 7 days), long-term antibiotic prophylaxis was changed to amoxicillin 20 mg/kg/day. Following this case, all subsequent patients with SCD and *H. influenzae* bacteremia at Children's had antibiotic prophylaxis changed from penicillin to amoxicillin.

All but 1 patient received treatment with 10 days of parenteral and oral antibiotics for *H. influenzae* bacteremia. In 1 patient (Case 3), an 11-month old with HbSS on penicillin prophylaxis who presented with fever and human metapneumovirus, only 1 dose of

intravenous ceftriaxone was administered. Due to inadvertent failure to communicate blood culture results to caregivers, no subsequent antibiotic therapy was prescribed, as would have been recommended at the time. The patient was discharged from emergency care and had resolution of fever at home. Penicillin prophylaxis was continued for 18 months then switched to amoxicillin for increased antimicrobial efficacy against *H. influenzae*.

DISCUSSION

Infectious concerns in SCD are primarily related to functional asplenia from an early age.² As such, children with SCD are at increased risk for invasive infection with encapsulated bacteria.³ Invasive infections with *S. pneumoniae* or *H. influenzae* were responsible for the majority of deaths of young children enrolled in the CSSCD from 1978–1988.⁶ Several factors have since led to a decrease in infectious deaths in young children with SCD, including the introduction of penicillin prophylaxis¹² and the introduction of immunizations against *S. pneumoniae*, *H. influenzae*, and *N. meningitidis*.^{3, 13, 14} While the incidence of invasive bacterial infections in young children with SCD has decreased dramatically since these measures became widespread, children with SCD continue to have a higher rate of invasive pneumococcal disease than the general African-American population of children¹⁴ and increases in non-vaccine serotypes of *S. pneumoniae* have been observed.¹⁵ In the U.S., invasive infection with non-typeable *H. influenzae* is nearly 100-times more prevalent than with Hib due to immunization.⁸

This is the first report of the population incidence of invasive *H. influenzae* in children with SCD since the introduction of Hib immunization. In 1983, Powars et al. reported 10 cases of invasive *H. influenzae* in 578 children with HbSS (12.4/1,000 person-years for children less than 5 years) with a 30% mortality rate from infection.⁷ In the same year, Buchanan et al. reported an incidence of invasive *H. influenzae* of 5.4/1,000 person-years in 51 children with HbSC disease.¹⁶ In the infant cohort of the CSSCD, there were 14 cases of invasive *H. influenzae* (4.8/1,000 person-years), with a 20% mortality rate in children with HbSS.⁶ More recently, Ellison et al. reported the frequency of bacteremia in 815 children (ages 0 – 22 years) with SCD followed from 2000 – 2010, with no episodes of *H. influenzae* bacteremia found.¹⁷ Our study examines the subsequent time period, from 2010 – 2017. Notably, there was a period of 5 years (2011 – 2015) with no *H. influenzae* isolates in pediatric SCD patients, but an increase in the number of cases in 2017. Thus, ongoing surveillance of *H. influenzae* in the community and in children with SCD is important, as infection rates may vary from year to year.

While the incidence of *H. influenzae* type b has decreased dramatically since the introduction of the Hib vaccine, increases in non-b and non-typable *H. influenzae* have occurred.¹⁰ In 2016, the Active Bacterial Core Surveillance of the CDC reported 13 cases of invasive *H. influenzae* type b as compared to 855 cases of non-b, non-typeable, or unknown type *H. influenzae*.¹⁸ This trend towards non-vaccine serotypes of infection with *H. influenzae* is similar to the increase in non-vaccine serotype *S. pneumoniae* isolates reported by McCavit et al. in children with SCD after the introduction of the pneumococcal polysaccharide and conjugate vaccines.¹⁵

Asymptomatic nasopharyngeal colonization with bacteria that may be potential pathogens including *H. influenzae* and *S. pneumoniae* is common in young children.¹⁹ Antibiotic prophylaxis may serve to suppress but not eradicate these organisms. Prophylactic penicillin in SCD has been shown to reduce nasopharyngeal carriage of *S. pneumoniae* but not necessarily *H. influenzae* when compared to healthy children.²⁰ Thus, decreases in *H. influenzae* invasive disease over the past few decades may be attributable more to Hib immunization than to prophylactic penicillin. All cases in our series had infection with non-vaccine serotypes of *H. influenzae* and were on penicillin prophylaxis, except for one child on amoxicillin prophylaxis who had missed 1 week of treatment prior to presentation.

In a young child with invasive *H. influenzae* infection, long-term antibiotic prophylaxis with amoxicillin (20 mg/kg/day) rather than penicillin should be considered, with the assumption of probable ongoing nasopharyngeal colonization with *H. influenzae* and the superior antimicrobial activity of amoxicillin for *H. influenzae*. There is insufficient evidence to support indefinite continuation of prophylaxis past age 5 years.

A major strength of the current study was the large number of children with SCD with several years of monitoring through one center's comprehensive clinical database for SCD. Limitations include the retrospective nature of the study. Additionally, fact that cases of *H. influenzae* infection were identified through review of our center's laboratory reporting creates a potential for underestimate of the true incidence of *H. influenzae* infection, as patients may have presented for medical attention at other centers or patients who may have moved from the catchment area. With these limitations in mind, this study demonstrates the ongoing importance of vigilance against invasive bacterial infections in children with SCD, including antibiotic prophylaxis at a young age, immunization against encapsulated organisms, and prompt attention to fever with blood cultures and administration of a parenteral antibiotic with coverage against *S. pneumoniae* and *H. influenzae*.

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ABBREVIATION KEY

CDC	Centers for Disease Control and Prevention
CSF	Cerebrospinal fluid
CSSCD	Cooperative Study of Sickle Cell Disease
Hb	Hemoglobin
Hib	<i>Haemophilus influenzae</i> type b
MALDI-TOF	Matrix assisted laser desorption ionization mass spectrometry time of flight
SCD	Sickle cell disease

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Table 1.

H. Influenzae infections at Children's Healthcare of Atlanta compared to national surveillance data, 2010–2017.

Year	+ <i>H. influenzae</i> cultures in SCD (0–18 yrs)	SCD patients (age 0 – 18 years)	SCD patients (age <5 years)	Incidence rate in SCD age <5 years (cases/100,000 <i>person-years</i>)	U.S. population estimated incidence (cases/100,000)
2010	2	1569	548	365	1.65
2011	0	1639	561	0	1.66
2012	0	1672	569	0	1.66
2013	0	1752	545	0	1.77
2014	0	1738	523	0	1.66
2015	0	1754	510	0	1.90
2016	1	1823	553	181	1.99
2017	5	1869	573	698	N/A
Total	8	2,444 patients 13,816 person-years	1493 patients 4,382 person-years	160	1.76

Incident rates reflect cases in children with SCD <5 years of age. One of the 5 cases of invasive *H. influenzae* infection in 2017 was in a child >5 years.

Table 2.

Invasive *H. influenzae* cases, 2010–2017.

Case	Year	Age (yrs)/SCD	Antibiotic Prophylaxis	Hib immuniz	Splenectomy	Clinical presentation	Presenting WBC ($\times 10^3/\mu\text{L}$), neutrophil differential	Culture source/ <i>H. influenzae</i> serotype	Beta-lactamase	Hospital duration / Treatment duration	Subsequent Prophylaxis
1	2010	3.6 / HbSC	PCN	4 doses	No	Fever, cough	27.47 (84% seg, 5% band)	Blood / non-typeable	Negative	2 days / 10 days	PCN till age 7
2	2010	2.0 / HbSS	PCN	4 doses	No	Fever, lethargy, nuchal rigidity, hypotension, CSF pleocytosis	25.5 (43% seg, 47% band)	Blood / type f	Negative	7 days / 10 days	PCN till age 7
3	2016	0.9 / HbSS	PCN	3 doses	No	Fever, cough, HMPV *	4.16 (67% seg, 8% band)	Blood / type f	Positive	0 days / 1 day	PCN, then Amox
4a	2017	2.2 / HbSS	PCN	4 doses	No	Fever, cough, rhinorrhea, abdominal pain	6.56 (55% seg, 4% band)	Blood / type f	Negative	3 days / 10 days	PCN
4b	2017	2.4 / HbSS	PCN	4 doses	No	Fever, rhinorrhea	5.89 (63% seg, 3% band)	Blood / type f	Negative	3 days / 10 days	Amox
5	2017	1.9 / HbSS	Amox; 1 week missed	4 doses	No	Fever, cough, AOM	17.42 (44% seg, 2% band)	Blood / type f	Negative	2 days / 10 days	Amox
6	2017	1.8 / HbSC	PCN / poor adherence	4 doses	No	Fever, cough, Rhinovirus *	14.35 (51% seg, 10% band)	Blood / non-typeable	Negative	2.5 days / 10 days	Amox
7	2017	7.9 / HbSS	PCN	4 doses	Yes	Fever, cough, headache, arm pain.	14.67 (85% seg)	Blood / type a	Negative	6 days / 10 days	Amox

Amox: amoxicillin; AOM: acute otitis media; HMPV: human metapneumovirus; PCN: penicillin; WBC: white blood cell count; seg: segmented neutrophil; band: band neutrophil.

* Results of respiratory viral PCR testing.