HHS Public Access

Author manuscript

Pediatr Infect Dis J. Author manuscript; available in PMC 2016 April 01.

Published in final edited form as:

Pediatr Infect Dis J. 2015 April ; 34(4): 447–449. doi:10.1097/INF.0000000000000587.

Group A Streptococcal Bacteremia without a Source is Associated with Less Severe Disease in Children

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Abstract

We analyzed characteristics of 86 Group A streptococcal (GAS) bacteremia cases at Boston Children's Hospital from 1992-2012. Twenty-three percent of children had severe disease, using ICU admission (18), disability (7), or death (2) as indicators. Children with bacteremia without a source (30% of cases) were less likely to have severe disease than children with focal infections in adjusted models.

Keywords

Group A streptococcus; Toxic shock syndrome; Bacteremia; Varicella; Necrotizing fasciitis

INTRODUCTION

Group A streptococci (GAS) cause a wide variety of clinical syndromes in the pediatric population, ranging from uncomplicated pharyngitis, skin infections, and otitis media, to severe invasive disease, such as pneumonia, necrotizing fasciitis, and streptococcal toxic shock syndrome (STSS). According to the Centers for Disease Control and Prevention (CDC), invasive GAS cases occur at a rate of 3.4 cases per 100,000 population per year in the U.S. and contribute to approximately 1,100 deaths annually(1). About 9% of these cases occurred in children under 18 years of age in 2012(1).

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Conflicts of Interest: The authors have no conflicts of interest relevant to this article to disclose.

GAS bacteremia is associated with poor outcomes and high risk of mortality(2). “Primary”, “isolated,” “transient,” “uncomplicated,” “cryptogenic”, “occult” bacteremia or bacteremia without a source, have been described as causing significant morbidity and mortality, particularly among adults(2-4). However, limited data is available on children with bacteremia without a source; or the extent to which outcomes for children with GAS bacteremia without a source differ from children with GAS bacteremia and concomitant focal infections. We therefore reviewed cases of GAS bacteremia in children at a tertiary care center, and evaluated whether children with GAS bacteremia without a source demonstrate differences in demographic features, clinical presentation, or outcome, compared to children with GAS bacteremia with associated focal infections.

PATIENTS AND METHODS

We conducted a retrospective chart review of children less than 18 years of age identified with GAS bacteremia from laboratory culture data from January 1, 1992 to July 31, 2012 at Boston Children’s Hospital, Boston, MA, USA. Medical records were reviewed for information on demographics, duration of illness, co-morbid conditions, co-infections, symptoms, possible portals of entry, physical exam findings on presentation, laboratory results, radiologic imaging, antibiotic treatment, and outcomes. Children were considered immunocompromised due to either underlying illness (such as neoplasms, nephrotic syndrome, or prematurity) or medical therapy (such as steroids or chemotherapy). Renal impairment was defined as serum creatinine above 2 times the upper limit for age or a value over 2mg/dl. Hepatic impairment was defined as aspartate aminotransferase (AST), alanine aminotransferase (ALT), or serum bilirubin elevated over 2 times the upper limit of normal for age. Coagulopathy was defined as a platelet count under 100,000/ml, or presence of disseminated intravascular coagulation.

Patients with GAS-positive blood cultures, but no associated focal infection, were categorized as having bacteremia without a source based on the CDC’s definition (2, 4). Children were considered to have severe disease if they were admitted to the intensive care unit (ICU), became disabled, or died as a result of GAS infection. STSS was defined according to the Working Group on Severe Streptococcal Infections (5). Diagnosis of necrotizing fasciitis was based on surgical findings.

Disabilities were defined as residual functional limitation at time of discharge resulting from GAS infection, and included: decreased range of motion of extremities, amputation of extremities, ataxia, or hemiparesis. Death was attributed to GAS based on review of the medical record. This study was approved by the Institutional Review Board of Boston Children’s Hospital.

Study data were collected and managed using REDCap electronic data capture tools hosted at Boston Children’s Hospital(6). Chi-squared tests were used to compare categorical variables and Wilcoxon rank sum for continuous variables. Bivariate and multivariable logistic regression analyses were performed to explore potential predictors of severe disease, including age, gender, presence of co-morbid conditions, immunosuppression, co-infections (including varicella), portal of entry (pharyngitis versus no source identified), type of

syndrome (bacteremia without a source versus bacteremia with associated focal infection), temperature, white blood cell count (WBC), and platelet count on admission. Predictor variables significant on bivariate analysis at a p-value of <0.20 (presence of bacteremia without focal infection) were considered for inclusion in the multivariable model in addition to age and gender using forward and backward stepwise regression. Otherwise, a p-value of <0.05 was considered statistically significant. SAS v9.2 was used for all analyses.

RESULTS

Eighty-six patients under the age of 18 with positive blood cultures for GAS were identified during the study period from 1992 to 2012 at BCH, which has approximately 25,000 admissions and 557,000 outpatient visits per year and serves a population of about 3.5 million. There was a mean of 4.5 cases (range, 1-9 cases) of GAS bacteremia per year. Median age was 3.9 years with a range of 7 weeks to 17 years. Forty-eight percent (n=41) were female. Thirty percent of children had bacteremia without a source, while 70% of children had one or more associated focal infections.

Clinical presentation did not differ significantly among children with or without associated focal infections. Eleven children (13%) developed hypotension, 4 of these children suffered disabilities and 2 died. Probable portal of entry for GAS infection included varicella skin lesions (n=15), pharyngitis (n=13), other skin lesions (n=7), otitis media (n=4), sinusitis (n=2), central venous catheter infection (n=2), and surgical wound infection (n=1). Four patients presented with or developed renal dysfunction, 15 developed hepatic dysfunction, and 16 had coagulopathy. Seven patients developed GAS bacteremia >72 hours after admission, 4 of which had bacteremia without a source.

Preceding varicella infection (occurring within one week prior to presentation with GAS infection) was associated with GAS bacteremia in 15 cases. Varicella infection was associated with 30% of cases during the pre-vaccine era (1992-1995) compared with 12% of cases from 1996-2012 (p=0.07).

Thirty-five percent of children had co-morbid diseases, which was more common among children with bacteremia without a source compared to children with concomitant focal infections (58% vs. 25%, p<0.01). Co-morbid illness was not associated with severe disease in bivariate analyses in our study (OR 1.01; 95% CI: 0.35-2.87, p=0.99). Twenty percent of children were considered immunocompromised due to either disease or ongoing medical therapy. Immunosuppression was more commonly observed in bacteremia patients without a source compared to children with focal infections (35% vs. 14%, p=0.04), and was not significantly associated with severe disease (OR 0.38; 95% CI 0.08-1.82, p=0.22).

Twenty children (23%) with GAS bacteremia had severe disease. Eighteen patients were cared for in the ICU, with a median length of ICU stay of five days (range 1-97). Eleven children admitted to the ICU required mechanical ventilation. Seven patients developed disabilities and 2 died. Among the 60 children with focal infections, 9 met criteria for STSS, and all children with focal infection and STSS were admitted to the ICU. Two suffered permanent disabilities due to necrotizing fasciitis requiring limb amputations, and 2 died. Of

the remaining 51 patients with bacteremia with focal infections without STSS, 15 were admitted to the ICU and 6 were discharged with disabilities.

In contrast, of the 26 children with bacteremia without a source, only one was admitted to the ICU. None of the children with bacteremia without a source died or became disabled due to GAS infection.

Neither age (>1 year vs. < 1 year of age), gender, presence of co-infections, portal of entry (pharyngitis versus no known source), fever (≥ 38.5°C), abnormal WBC (<5,000 or ≥15,000 cells/cm^2 on admission), and abnormal platelet count (<100,000 or ≥400,000 cells/cm^2 on admission) were associated with significant differences in severe disease.

In adjusted models, children with bacteremia without a source were found to have a significantly lower risk of severe disease when compared to children with bacteremia and focal infections (AOR 0.08, 95% CI 0.01-0.67).

DISCUSSION

Bacteremia without a source was fairly common in our hospital, representing nearly one third of cases in children with GAS-positive blood cultures, similar to previous reports (3, 4). Although primary bacteremia in adults has been associated with substantial morbidity and mortality (2-4, 7, 8), we found that children with bacteremia without a source were at considerably lower risk of severe disease compared to children with concomitant focal infections. Overall mortality rate among children with GAS bacteremia was 2.3%, comparable to other pediatric studies of invasive GAS infections (8-11) and consistent with published studies that describe substantially lower case fatality rates (CFR) for children with bacteremia compared to adults(4). None of the children with bacteremia without a source died in our study. The two patients that died met criteria for STSS, which resulted in a 22% mortality rate for patients with STSS, similar to previous reports(4, 8, 9, 11).

Chronic underlying illnesses or co-morbid diseases have been reported to be significant risk factors for invasive GAS infections in adults and children(2, 4, 9), and we observed them in 35% of our children. Co-morbid illness or immunosuppression was not associated with death or severe disease in our study. The absence of an association between immunosuppression and more severe GAS disease was surprising, but could be explained if children with underlying illnesses and on immunosuppressive therapies presented earlier or were more aggressively treated in their hospital course compared to previously healthy children.

This study has several limitations, including the relatively small number of patients with GAS bacteremia from a single large tertiary care referral center. It is likely that the patient population included in this study is skewed toward more severe cases of invasive GAS infections and patients with co-morbid conditions. Also, secular trends in diagnosis or management of GAS infection may have influenced our findings, particularly since the study period was 21 years in length. Nonetheless, this is one of the largest studies describing the clinical characteristics and outcomes of GAS bacteremia, particularly GAS bacteremia without a source, in children to date.

Our study underlines the importance of separating cases of GAS bacteremia in future studies into the subgroups of bacteremia with or without associated focal infections. Stratifying outcomes for children with bacteremia without a source should clarify whether these cases can be regarded as likely having a less severe disease course and better outcomes. This would have prognostic implications, help identify children who will likely be more ill early on, and possibly help guide treatment choices.

ACKNOWLEDGMENTS

We thank Alexander McAdam and Eileen Gorss for their laboratory assistance and for identifying eligible patients for this study. We thank Seung-Yeon Kim and the Clinical Research Center and Program for Patient Safety and Quality at Boston Children's Hospital for help with the statistical analyses.

Source of Funding: This study was supported by the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services Grant, K-08 HS013908 (to G.M.L.) and by the Pediatric Critical Care Scientist Development Program K12 grant number 5K12HD047349-07 (to S.G.).

REFERENCES

1. Centers for Disease Control and Prevention. Active Bacterial Core Surveillance report, Emerging Infections Program Network, Group A Streptococcus, 2012. 2013. 2013. Available at: http://www.cdc.gov/abcs/reports-findings/survreports/gas12.pdf
2. O'Brien KL, Beall B, Barrett NL, et al. Epidemiology of invasive group a streptococcus disease in the United States, 1995-1999. Clin Infect Dis. 2002; 35:268–276. [PubMed: 12115092]
3. Hollm-Delgado MG, Allard R, Pilon PA. Invasive group A streptococcal infections, clinical manifestations and their predictors, Montreal, 1995-2001. Emerg Infect Dis. 2005; 11:77–82. [PubMed: 15705326]
4. O'Loughlin RE, Roberson A, Cieslak PR, et al. The epidemiology of invasive group A streptococcal infection and potential vaccine implications: United States, 2000-2004. Clin Infect Dis. 2007; 45:853–862. [PubMed: 17806049]
5. The Working Group on Severe Streptococcal Infections. Defining the group A streptococcal toxic shock syndrome. Rationale and consensus definition. Jama. 1993; 269:390–391. [PubMed: 8418347]
6. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009; 42:377–381. [PubMed: 18929686]
7. Begovac J, Kuzmanovic N, Bejuk D. Comparison of clinical characteristics of group A streptococcal bacteremia in children and adults. Clin Infect Dis. 1996; 23:97–100. [PubMed: 8816136]
8. Patel RA, Binns HJ, Shulman ST. Reduction in pediatric hospitalizations for varicella-related invasive group A streptococcal infections in the varicella vaccine era. J Pediatr. 2004; 144:68–74. [PubMed: 14722521]
9. Laupland KB, Davies HD, Low DE, Schwartz B, Green K, McGeer A, Ontario Group A Streptococcal Study Group. Invasive group A streptococcal disease in children and association with varicella-zoster virus infection. Pediatrics. 2000; 105:E60. [PubMed: 10799624]
10. Mulla ZD. Clinical and epidemiologic features of invasive group A streptococcal infections in children. Pediatr Int. 2007; 49:355–358. [PubMed: 17532835]
11. Zachariadou L, Stathi A, Tassios PT, Pangalis A, Legakis NJ, Papaparaskevas J. Differences in the epidemiology between paediatric and adult invasive Streptococcus pyogenes infections. Epidemiol Infect. 2013:1–8.

Table 1
Children with Group A Streptococcal bacteremia, 1992-2012

Patient characteristics	Total N=86 (%)
Female	41 (48%)
Age distribution	
<1 year	14 (16%)
1-4 years	35 (41%)
5-9 years	20 (23%)
10-17 years	17 (20%)
Co-morbid disease	30 (35%)
Oncologic*	9 (30%)
Cardiac disease	5 (17%)
Hemangioama/cystic hygroma	4 (13%)
Nephrotic syndrome	3 (10%)
Connective tissue disease	2 (7%)
Other**	7 (23%)
Immunosuppression due to underlying disease or medications	17 (20%)
Syndrome associated with GAS bacteremia	
Bacteremia without a source	26 (30%)
Bacteremia with concomitant focal infections****, including:	51 (59%)
Skin and soft tissue infections	41 (48%)
Cellulitis	24 (28%)
Myositis	10 (12%)
Adenitis	9 (11%)
Abscess/phlegmon	7 (8%)
Thrombophlebitis	4 (5%)
Fasciitis (non-necrotizing)	3 (4%)
Tissue Necrosis	3 (4%)
Bone/Joint infections	22 (26%)
Osteomyelitis	15 (17%)
Septic arthritis	11 (13%)
Pneumonia	8 (9%)
Necrotizing fasciitis (NF)	3 (4%)
Meningitis	2 (2%)
Empyema	2 (2%)

Patient characteristics	Total N=86 (%)
Mediastinitis	1 (1%)
Epiglottitis	1 (1%)
Peritonitis	1 (1%)
Pericarditis	1 (1%)

* Oncologic diagnoses included leukemia (7), rhabdomyosarcoma (1), and myelodysplastic syndrome (1)

** Other diagnoses included Down's syndrome (2), encephalopathy (2), prematurity (1), short gut syndrome (1), recent tonsillectomy (1), and recent spinal rod placement (1)

*** 28 patients had multiple foci of infection and therefore adding the percentages will result in a number greater than 100

**** 9 patients (11%) with focal infections had STSS