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ORIGINAL RESEARCH

Infectious Disease

Risk of serious bacterial infections in pediatric patients with hyperpyrexia

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Abstract

Objectives: Hyperpyrexia has been associated with a greater prevalence of bacterial infections in the pediatric population, which prior to routine childhood vaccinations, has led to invasive testing and empiric antibiotic use for urinary tract infections, bacterial pneumonia, bacteremia, and bacterial meningitis. Since the implementation of routine childhood vaccinations, the prevalence of serious bacterial infections (SBIs) has declined. This study aims to determine if there is an association between hyperpyrexia and serious bacterial infections in well-appearing febrile pediatric patients presenting to the emergency department (ED).

Methods: This is a cross-sectional study conducted between January 1, 2019, and December 31, 2019, at a single urban tertiary care pediatric ED. Patients were included if they were between 61 days and ≤18 years old presenting with a chief complaint of fever. Patients were excluded if they received antibiotics within 3 days of presentation, underwent surgical procedures within 2 weeks of presentation, had an ED visit for febrile illness within 2 weeks of study visit, were transferred from another institution, or were ill appearing. Prevalence of SBI was described and compared by presence of hyperpyrexia, age group, chronic medical condition, gender, and vaccination status. Logistic regression was used to analyze the association between SBIs and hyperpyrexia.

Results: Of the 3862 charts reviewed, 2565 patients were included. The prevalence of SBI was 5.6%. A total of 413 patients presented with hyperpyrexia. Of the patients with hyperpyrexia, 31 (7.5%) had a serious bacterial infection. Hyperpyrexia was not significantly associated with SBIs in our logistic regression models (adjusted Odds Ratio 1.40, 95% confidence interval 0.92–2.12).

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Conclusions: Serious bacterial infections were uncommon in our population. There is no statistically significant association between hyperpyrexia and SBIs in well-appearing pediatric patients presenting to the ED with fever. The lack of a statistically significant association between hyperpyrexia and SBIs argues that clinicians should be cautious using hyperpyrexia as an independent risk factor for SBIs. More research is needed to identify independent and grouped SBI risk factors in well-appearing pediatric patients presenting to the ED.

KEYWORDS
childhood vaccinations, emergency medicine, infectious disease, pediatrics, public health, serious bacterial infection

1 | INTRODUCTION

1.1 | Background

Clinicians have long assumed that hyperpyrexia (temperature ≥ 40.0°C) was associated with a greater incidence of serious bacterial infections (SBIs) in the pediatric population.[1] This assumption was based on multiple studies conducted prior to the implementation of routine childhood vaccinations.[1–4] As a result, clinicians often conducted invasive testing and empiric therapy to evaluate for and treat SBIs.[2,5–6]

Studies conducted prior to the implementation of expanded routine childhood vaccinations demonstrate an association of hyperpyrexia with serious bacterial infections.[1–4] The largest study to date, a retrospective analysis from 1966 to 1974, found that hyperpyrexia was associated with a significantly higher risk of bacterial meningitis.[1] However, that analysis was conducted prior to the implementation of childhood vaccination programs, and seven of 10 cases of bacterial meningitis isolated *Haemophilus influenzae* type B (HiB), which is now routinely vaccinated against.[1] Since the implementation of the HiB-conjugated vaccine in 1988, peripartum maternal Group B streptococcus (GBS) screening in 2002, the meningococcal (ACWY)-conjugated vaccine in 2005, the pneumococcal-conjugated vaccine-13 (PCV-13) in 2010, and the meningococcal B vaccine in 2014, there has been a significant decline in the prevalence of SBIs.[7–13]

Identifying a well-appearing febrile pediatric patient with SBI is challenging given the lack of generalizable and consistent literature on the practice patterns, epidemiology, and clinical value of invasive testing to identify SBIs in US pediatric patients greater than 60 days old.[14] However, it remains crucial in reducing morbidity and mortality in this subset of pediatric patients. A 2017 meta-analysis found only two studies comparing the risk of SBI in children with hyperpyrexia. The authors' analyses demonstrated young infants (under 90 days old) with hyperpyrexia were at an increased risk of SBI compared to infants with a lower degree of fever (odds ratio [OR] 3.21, 95% confidence interval [CI] 1.67–6.22).[14] Older children had a minimal risk of SBI.[14] A 2010 systematic review of European pediatric patients demonstrated that reduced consciousness, convulsions, cyanosis, rapid breathing, slow capillary refill, and a temperature ≥40°C have a positive predictive value for SBI in the setting of low prevalence of SBIs.[15] The lack of population-based data identifying most commonly isolated organisms in SBIs, evaluating practice patterns, assessing clinical value of signs/symptoms, and testing in the United States raises the question of whether invasive testing and empiric antibiotics are warranted in well-appearing pediatrics patients with hyperpyrexia.

1.2 | Importance

Studies investigating the association between hyperpyrexia and rates of SBIs in pediatric patients in the post-vaccine era have been limited by small sample size, narrow inclusion criteria of previously healthy young infants, varying definitions of hyperpyrexia, narrow definitions of bacterial infection, or were conducted outside the United States where there are differing vaccine recommendations.[16,17–20] A recent prospective study in pediatric patients presenting to an emergency department (ED) in the United States with hyperpyrexia found that they were equally at risk for SBIs and viral illness.[20] However, this study was limited to patients with hyperpyrexia and lacked a comparison to non-hyperpyrexic patients.[20] A 2005 retrospective study found that the prevalence of SBIs among hyperpyrexic infants 0–90 days old was 38% compared to 8.8% in non-hyperpyrexic infants.[19] However, this study was limited to infants 0–90 days old with an epidemiology of SBIs different to the general pediatric population.[19]

1.3 | Goals of this investigation

The aim of this study is to determine if there is an association between hyperpyrexia and the presence of SBIs in well-appearing febrile patients 61 days to 18 years old presenting to the ED. We also sought to estimate the prevalence of serious bacterial infections in our patient population. Our findings will build on existing literature regarding the prevalence of serious bacterial infections in the general pediatric population.

2 | MATERIALS AND METHODS

2.1 | Study design, setting and participants

This was a cross-sectional study based on patients visiting the ED between January 1, 2019, and December 31, 2019, at a single urban tertiary care pediatric ED with an annual volume of approximately 20,000 visits.

All patients 61 days old to 18 years old presenting to the ED with a chief complaint of fever were identified in the electronic medical record. Patients were eligible if they had a documented temperature ≥38.0°C by any method of measurement (i.e., temporal, oral, otic, axillary, or rectal) at home, in an outpatient provider's office, or in the ED. Patients younger than 61 days old were excluded because they have unique risks for SBIs resulting in the development and implementation of risk stratification tools and treatment protocols that are outside the scope of this study. Patients were also excluded if they received antibiotics within 3 days prior to presentation because the administration of these medications can lead to misinterpretation of clinical presentation and diagnostic testing. We excluded patients who had a visit to the same ED for a febrile illness within 2 weeks prior to presentation to distinguish between two patient populations, those with prolonged febrile illness, and those with acute febrile illnesses, since there is an inherent difference in the epidemiology of these patient populations.[21] We chose to exclude patients with a recent surgical procedure within 2 weeks prior to initial presentation due to their increased risk of SBIs from recent invasive procedures compared to the general population. To further limit potential confounding variables, we excluded patients transferred from an outside hospital or who were ill-appearing. Patient charts with incomplete data for our variables of interest were excluded.

2.2 | Measures

Fever was defined as a documented temperature ≥38.0°C (100.4°F) at home, in an outpatient clinic, or in the ED obtained via any method (e.g., rectal, axillary, temporal, otic, and oral). Non-hyperpyrexic fever was defined as a documented temperature ≥38.0°C (100.4°F)–<40.0°C (104.0°F). Hyperpyrexic fever was defined as a documented temperature of ≥40.0°C (104.0°F).

Variables considered as potential confounders included age, chronic medical conditions, and vaccination status. These variables were selected based on their clinical relevance among variables that were available for abstraction and universally/comprehensively recorded in medical charts. Age was divided into three categories: newborn to 2 years, 3–10 years, and 11–18 years. Sex was recorded as binary biological sex at birth: male or female. Chronic conditions were defined as medical conditions expected to last ≥12 months, involve one or more organ system, and/or require pediatric specialty care.[22,23] Vaccination status was abstracted from hospital medical records but was based on child/parent self-reported status at the time of ED visit. If it was not documented in the hospital medical record, the New York State Immunization Information System (NYSIS) was cross referenced. Up to date with vaccines was defined as having received all recommended doses of HiB, PCV, DTaP, and meningococcal vaccines for the patient's month (≤12 months old) or year (>12 months old) of age as per Centers for Disease Control and Prevention (CDC) routine childhood vaccine schedule.[7]

Ill appearance was defined as any of the following words documented on the physical examination during any point in the ED: "ill-appearing," "toxic," "limp," "unresponsive," "gray," "cyanotic," "apnea," "weak cry," "poorly perfused," "grunting," "listless," "lethargic," or "irritable."[24] If none of these terms were documented, the infant was classified as not ill-appearing. In cases with contradictory documentation of appearance between the attending physician and a trainee or advanced practice provider, the attending physician's documentation was used.

The Bottom Line

This cross-sectional study reviewed patients with fever to see if hyperpyrexia is associated with greater incidence of significant bacterial infections, but were unable to find an association. Therefore, practitioners should treat hyperpyrexia with caution as an independent risk factor for serious bacterial infections.

2.3 | Outcomes

The outcome of interest was SBIs. This was defined as deep neck space infection (i.e., retropharyngeal abscess, peritonsillar abscess, septic thrombophlebitis, and Ludwig's angina), appendicitis, pneumonia, mastoiditis, lymphadenitis, acute bacterial rhinosinusitis, urinary tract infection (UTI), pyelonephritis, cholecystitis, tubo-ovarian abscess, septic arthritis, osteomyelitis, bacteremia, or bacterial meningitis. This outcome definition aligns with recent research definitions for SBI, which includes bacteremia and bacterial meningitis.[14] UTI was defined as the growth of a pathogenic bacteria from urine culture in conjunction with an antibiotic treatment course that was commiserate with UTI. Bacteremia and bacterial meningitis were defined as the growth of a priori pathogenic bacteria from blood or cerebrospinal fluid (CSF) culture (Appendix 1).[25–28]

2.4 | Procedure

Five abstractors performed manual chart review and data extraction via the electronic health record (Soarian) into the Research Electronic Data Capture (REDCap) Albany Medical College database.[29] The abstractors were second-year medical students trained by Albany Medical Center's required Collaborative Institutional Training Initiative (CITI Program) and by the principal investigator, Dr. Christopher

Woll, in a standardized data extraction process. All variables had clear definitions prior to the data extraction training session and did not require further abstractor interpretation. Monthly meetings were held with the abstractors to review coding rules and conflicts. Data collection included demographics (age, sex, race, ethnicity, and health insurance status), past medical history (vaccination status and presence of a complex chronic condition[22,23]), temperature (at home, in an outpatient clinic, in triage, and highest recorded in the ED), maximum and minimum values of all vital signs while in the ED, clinical appearance, presence of a non-serious or invasive bacterial infection on physical examination, laboratory data (complete blood count, glucose, prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), total bilirubin, C-reactive protein, procalcitonin, lactic acid, urinalysis), viral testing results (respiratory viral panel-PCR film array), bacterial culture results (urine, blood, CSF), final diagnosis (International classification of disease-10th revision codes), class of antibiotics prescribed (penicillin, cephalosporin, trimethoprim, tetracycline, aminoglycoside, vancomycin, and clindamycin), and antibiotic susceptibilities (Appendix 2).

2.5 | Data analysis

The prevalence of SBIs was assessed in well-appearing pediatric patients presenting with fever in the ED. Pearson's chi-square test was used to compare the distribution of SBIs across categories of patient demographic and clinical characteristics. Logistic regression was used to analyze the association between SBIs and hyperpyrexia while controlling for potential confounding variables. Both unadjusted and adjusted effects were reported. Multivariable adjusted analysis was based on the full model including all five potential primary and secondary covariates of interest. Statistical significance was determined as a two-sided p-value < 0.05 and a 95% CI that did not cross 1.0. Statistical analyses were performed using Statistical Software STATA 15.0 (StataCorp, Inc).

A post hoc power analysis was done to estimate the possibility of a type II error for the effect size of interest. This was a retrospective chart review study limited to 1 year of data from our institute. The resulting study sample had patients with and without hyperpyrexia in the ratio of 1:5 approximately, with a SBI rate of 5.5% in the non-hyperpyrexia group. This sample size of 2565 was adequate to provide 83.4% power to detect a difference of at least 4%, that is, an expected SBI rate of 9.5% in the hyperpyrexia patient group, assuming an alpha of 0.05 for a two-sided hypothesis test.

2.6 | Ethics approval

The study was approved by the Albany Medical Center's institutional review board, study 6101.

3 | RESULTS

During the study period, a total of 3862 patient charts were reviewed from patients aged 61 days to 18 years who presented to a single urban tertiary pediatric ED. After applying exclusion criteria, 2565 patient charts met inclusion criteria (Figure 1). In the excluded population, 371 charts were excluded because the patient was transferred from an outside hospital. Three hundred charts were excluded due to a prior visit to the same ED within two weeks for febrile illness. Thirty-four charts were excluded because the patient had a surgical procedure within 2 weeks of initial presentation. Four hundred and one charts were excluded for antibiotic use within 3 days prior to presentation. Ninety-one charts were excluded for ill appearance and 33 charts were missing data for extracted variables. Of the included charts,150 (5.9%) had an SBI. A total of 413 (16.1%) patients had hyperpyrexia (Table 1). The 0- to 2-year-old age group was 47.95% of the cohort with 63 (5.1%) patients having an SBI. The 3- to 10-year-old age group comprised 42.96% of the total study population, and 67 (6.1%) patients in this age group had an SBI. The 11- to 18-year-old age group comprised 9.08% of the cohort, and 20 (8.6%) patients had an SBI. The infection rates differed significantly by age with the highest rate of 8.6% in the older patients. Similarly, a higher proportion of males and those with hyperpyrexia had SBIs. The infection rates did not differ significantly by vaccination status. Table 1 displays additional study sample characteristics.

Hyperpyrexia was not significantly associated with SBI in both the bivariate and multivariable analyses. Unadjusted odds ratios and 95% CIs (Table 2) show the size of associative effect with each of the potential risk factors including hyperpyrexia. In the bivariate regression model, patient characteristics not significantly associated with SBI included hyperpyrexia (OR 1.39, 95% CI 0.92–2.09), vaccination status (OR 1.49, 95% CI 0.68–3.21), chronic medical condition (OR 1.02, 95% CI 0.68–1.53), and the 3- to 10-year-age group (OR 1.20, 95% CI 0.84–1.71). Age 11–18 years and male sex were significantly associated with SBI in the unadjusted analyses (OR 1.74, 95% CI 1.03–2.94) and (OR 2.19, 95% CI 1.55–3.09), respectively (Table 2). Hyperpyrexia remained without a statistically significant association to presence of SBI after multivariable logistic regression analysis (adjusted Odds Ratio [aOR] 1.40, 95% CI 0.92–2.12; Table 2). Vaccination status, chronic medical conditions, and age group 3- to 10-year olds also remained not significantly associated with SBI. Older age (11–18 years) and male sex were significantly associated with an increased likelihood of SBIs (aOR 1.73, 95% CI 1.00–2.98) and (aOR 2.16, 95% CI 1.53-3.06), respectively (Table 2).

3.1 | Limitations

Although our study had limitations, we sought to minimize bias through several mechanisms. It is important to recognize that this was a single-

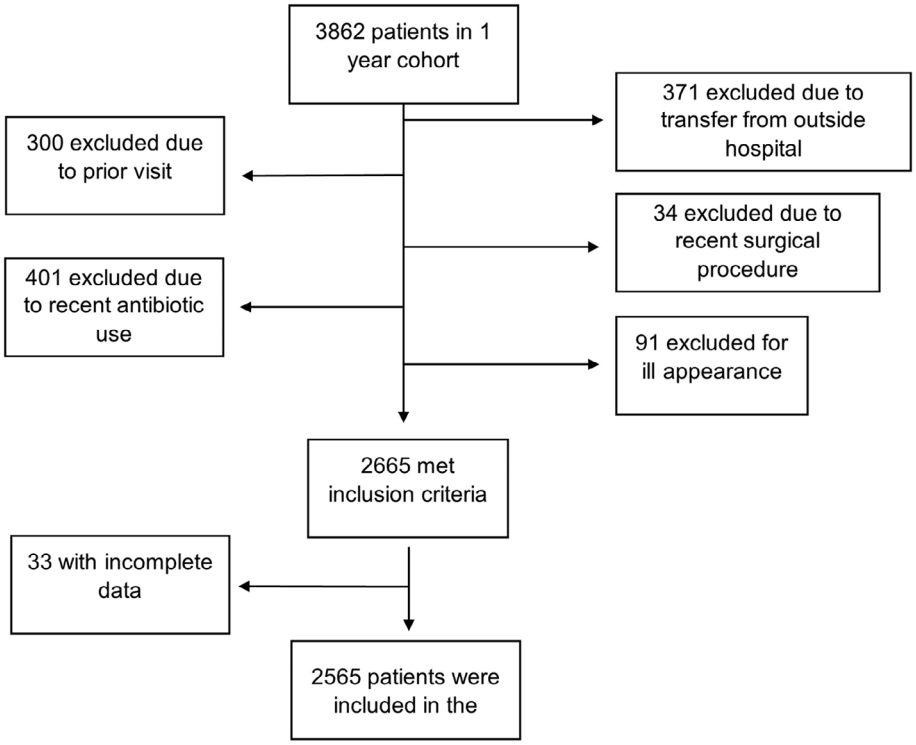

FIGURE 1 Patient inclusion and exclusion criteria. *Exclusion criteria are not mutually exclusive.

site study of an urban pediatric ED, which may limit our study's external validity. Certain patient history features, such as maximum temperature readings at home and vaccination status, relied on self-reporting. To minimize recall bias, we cross referenced vaccine status with the state immunization repository when available. Additionally, we used medical records to obtain historical variables, clinical variables, and diagnostic codes. To minimize interpretation bias, we applied standardized definitions of subjective variables, such as ill appearance, non-serious or invasive bacterial infections, hyperpyrexia, and chronic medical conditions. Similarly, using 40°C as the threshold for hyperpyrexia is not a universally accepted definition and some clinicians may be more inclined to use higher thresholds for "high fever" depending on the age of the patient that may limit the external validity and real-world implications of our findings. Additionally, we used the most senior providers interpretation of subjective variables to adjudicate contradicting assessments within the same ED encounter. Although we did seek to minimize interpretation bias, ill appearance was not interpreted within the context of concurrent fever and therefore resulting in potential selection bias. Limiting inclusion criteria to patients initially presenting to our ED likely results in an under-representation of bacteremia and bacterial meningitis in the general pediatric population who were directly admitted to in-patient units. It is possible that our study design missed cases of SBIs that were diagnosed at subsequent healthcare visits since we did not evaluate if patients were seen at other institutions.

4 | DISCUSSION

In this single-center cross-sectional study of patients aged 61 days to 18 years old presenting to the ED with a chief complaint of fever, there was no statistically significant association between hyperpyrexia and SBIs. This is likely a result of successful childhood vaccination and perinatal screening programs leading to a decreased incidence of SBIs, although further investigation is necessary to fully elucidate this finding.[1–6,10,11,16,30] We found that older age and male sex were significantly associated with an increased risk of SBIs. The reasoning for this finding requires further investigation, which is outside the scope of this study. Our study argues against the association between hyperpyrexia and SBIs cited in studies prior to the implementation of expanded childhood vaccination and universal prenatal GBS screening programs.[1,3]

This finding can add to the knowledge base being used to inform clinicians in their diagnostic and therapeutic strategies for well-appearing pediatric patients with hyperpyrexia. The lack of a statistically significant association between hyperpyrexia and SBIs argues that clinicians should be cautious using hyperpyrexia as an independent risk factor for SBIs. Due to increasing rates of antibiotic resistance and the adverse effects of antimicrobials, clinicians should practice antimicrobial stewardship.[31,32]

To our knowledge, this is the largest study to date evaluating the association between hyperpyrexia and SBIs in pediatric patients

TABLE 1 Distribution of patient characteristics in the overall study sample and by serious bacterial infections.

	Total	Serious bacterial infections present, N (%)		
Variable	N = 2565	Absent, N = 2416	Present, N = 150	*p*-Value
Age	–	–		
0–2 years	1230 (47.95%)	1167 (48.32%)	63 (42.00%)	0.108
3–10 years	1102 (42.96%)	1035 (42.86%)	67 (44.67%)	
11–18 years	233 (9.08%)	213 (8.82%)	20 (13.33%)	
Gender				
Female	1369 (53.37%)	1316 (54.49%)	53 (35.33%)	<0.001
Male	1196 (46.63%)	1099 (45.51%)	97 (64.67%)	
Chronic medical condition				
No	2027 (78.99%)	1909 (79.01%)	118 (78.67%)	0.919
Yes	539 (21.01%)	507 (20.99%)	32 (21.33%)	
Hyperpyrexia				
No	2153 (83.90%)	2034 (84.19%)	119 (79.33%)	0.116
Yes	413 (16.10%)	382 (15.81%)	31 (20.67%)	
Vaccines up to date				
No	170 (6.63%)	163 (6.75%)	7 (4.67%)	0.320
Yes	2396 (93.37%)	2253 (93.25%)	143 (95.33%)	

TABLE 2 Bivariate and multivariable adjusted association of patients' characteristics with the occurrence of serious bacterial infections among pediatric patients presenting to the emergency department with hyperpyrexia.

	Unadjusted		Adjusted	
Variable	Odds ratio (95% CI)	*p*-Value	Odds ratio (95% CI)	*p*-Value
Hyperpyrexia	–		–	
No	Reference		Reference	
Yes	1.39 (0.92–2.09)	0.118	1.40 (0.92–2.12)	0.112
Age	–		–	
0–2 years	Reference		Reference	
3–10 years	1.20 (0.84–1.71)	0.315	1.18 (0.82–1.69)	0.378
11–18 years	1.74 (1.03–2.94)	0.038	1.73 (1.00–2.98)	0.049
Sex	–		–	
Female	Reference		Reference	
Male	2.19 (1.55–3.09)	<0.001	2.16 (1.53–3.06)	<0.001
Chronic medical condition	–		–	
No	Reference		Reference	
Yes	1.02 (0.68–1.53)	0.919	1.01 (0.66–1.54)	0.955
Vaccines up to date	–		–	
No	Reference		Reference	
Yes	1.48 (0.68–3.21)	0.323	1.64 (0.75–3.59)	0.219

in the United States after the implementation of childhood vaccination and universal prenatal GBS screen programs. In comparison to previous studies that excluded patients >3 years of age, patients with chronic medical conditions, and patients without blood cultures obtained during their visit, our study's findings possess greater external validity by incorporating a more representative pediatric population.

There is no statistically significant association between hyperpyrexia and SBIs in pediatric patients presenting to the ED with fever. Future research should focus on identifying historical and clinical fea-

tures that increase patients' risk of SBIs. This could then be used to inform clinicians on which patients would benefit from further testing and empiric antibiotic administration.

AUTHOR CONTRIBUTIONS

Sofia Rachad: Data curation; resources; writing—review and editing. Fiona Berry: Conceptualization; formal analysis; methodology; data curation. Meghan Goddard, Ayesha Khan, and Natalie Muratori: Data curation. Dane Nickel: Conceptualization; formal analysis; methodology; project administration; writing—review and editing. Saul Hymes: Conceptualization; formal analysis; methodology; project administration; writing—review and editing. Ashar Ata: Formal analysis. Christopher Woll: Conceptualization; formal analysis; methodology; project administration; supervision; validation; writing—review and editing.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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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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