
Serious Bacterial Infection in Recently Immunized Young Febrile Infants

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Abstract

Objective: The objective of this study was to investigate the prevalence of serious bacterial infection (SBI) in febrile infants without a source aged 6–12 weeks who have received immunizations in the preceding 72 hours.

Methods: The authors conducted a medical record review of infants aged 6–12 weeks with a fever of $\geq 38.0^{\circ}\text{C}$ presenting to the pediatric emergency department (ED) over 88 months. Infants were classified either as having received immunizations within the 72 hours preceding the ED visit (recent immunization [RI]) or as not having received immunizations during this time period (no recent immunization [NRI]). Primary outcome of an SBI was based on culture results; only patients with a minimum of blood and urine cultures were studied.

Results: A total of 1,978 febrile infants were studied, of whom 213 (10.8%) had received RIs. The overall prevalence of definite SBI was 6.6% (95% confidence interval [CI] = 5.5 to 7.7). The prevalence of definite SBI in NRI infants was 7.0% (95% CI = 5.9 to 8.3) compared to 2.8% (95% CI = 0.6 to 5.1) in the RI infants. The prevalence of definite SBI in febrile infants vaccinated in the preceding 24 hours decreased to 0.6% (95% CI = 0 to 1.9). The prevalence of definite SBI in febrile infants vaccinated greater than 24 hours prior to presentation was 8.9% (95% CI = 1.5 to 16.4). The relative risk of SBI with RI was 0.41 (95% CI = 0.19 to 0.90). All SBIs in the RI infants were urinary tract infections (UTI).

Conclusions: Among febrile infants, the prevalence of SBI is less in the initial 24 hours following immunizations. However, there is still a substantial risk of UTI. Therefore, urine testing should be considered in febrile infants who present within 24 hours of immunization. Infants who present greater than 24 hours after immunizations with fever should be managed similarly to infants without RIs.

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Fever is among the most common reasons for infants to present to an emergency department (ED).¹ Infants less than 3 months of age presenting with fever pose a particular challenge because the prevalence of serious bacterial infection (SBI) in this population is reported between 6% and 10%,^{2,3} and clinical observational scales have been unable to differentiate infants with SBI from those with simple viral infections.^{4,5} In response to this clinical challenge, numerous guidelines have been published about the evaluation of

febrile infants in the ED.^{6–8} However, because these recommendations require invasive procedures, it is desirable to identify patient characteristics that may decrease the risk of SBI in this population, which would allow for a more limited evaluation of those at lower risk.

One possible risk modifier for SBI that has not been investigated is recent vaccination. The prevalence of fever after routine 2-month vaccinations is reported by one recent source to be as high as 27.9%.⁹ Therefore, if a well-appearing young infant presents to the ED with fever after recent immunizations (RIs), physicians may be inclined to attribute the fever to the vaccinations. However, there have not been any published studies assessing the prevalence of SBI in this population, and recommendations for the evaluation of the recently vaccinated infant with fever are nonexistent. Herein, we investigate the prevalence of SBI in young infants presenting to the ED with fever and hypothesize that a history of RI decreases the prevalence of SBI. The objective of this study was to investigate the prevalence

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of SBI in febrile infants aged 6–12 weeks without a source of infection who have received immunizations within the preceding 72 hours.

METHODS

Study Design

This was a medical record review of all infants presenting to the ED. The institutional review board approved this study protocol. Data collection was compliant with the Health Insurance Portability and Accountability Act of 1996.

Study Setting and Population

Febrile infants aged 6–12 weeks who presented to an urban academic pediatric ED between January 2000 and April 2007 were studied. The ED sees approximately 56,000 visits annually. Fever was defined as measured temperature $\geq 38.0^{\circ}\text{C}$ (100.4°F).

Study Protocol

Infants were identified through an electronic dataset of all patients seen in the ED. A query was performed to identify infants aged 6–12 weeks (based on when infants would likely receive their 2-month immunizations). All records were reviewed by the primary author. Records were manually reviewed for documented fever ($\geq 38^{\circ}\text{C}$) measured at home, the pediatrician's office, or the ED. Infants were excluded if the physician note recorded birth at a gestational age less than 32 weeks, a chronic illness, a surgery within 7 days, concurrent antibiotic use, or a focal bacterial infection by examination other than otitis media. All infants were seen by an attending pediatric emergency physician. Data were collected on age, sex, presenting symptoms, fever at home, sick contacts or exposures, and immunization status. Infants were classified as ill-appearing if the physician note described the infant as ill-appearing, cyanotic, apneic, mottled, poorly perfused, unresponsive, or moribund. All other infants were classified as well-appearing. Upper respiratory infection (URI) symptoms were defined as the presence of rhinorrhea, congestion, or cough, or documentation of "URI symptoms" in the physician note. Infants were classified either as having received immunizations within the 72 hours preceding the ED visit (RI), or as not having received immunizations during this time period (no recent immunization [NRI]). The electronic medical record of the study ED has a febrile infant template that prompts physicians to enter immunization status and any RIs. Given the importance of this information in the care of a febrile infant, records that did not specifically comment on RIs were declared to not have RI (knowing that this critical information should be recorded). To support this assumption, electronic immunization records of the patients without explicit documentation of immunization status that received hospital-based primary care were reviewed. For the infants who were recently vaccinated, the time intervals were a priori defined as <12 hours, 12–24 hours, 1–2 days, or 2–3 days.

The Massachusetts Department of Public Health supplied the Centers for Disease Control and Prevention

(CDC) recommended childhood vaccinations for the state during this study period. The vaccines recommended by the CDC during this study period at the 2-month well-child visit were inactivated polio virus, hepatitis B, *Haemophilus influenzae* B, diphtheria-tetanus-acellular pertussis, pneumococcal conjugate (as of November 1, 2000), and rotavirus vaccines (as of December 1, 2006).^{10–12} In July 2004, the Massachusetts Department of Public Health began distributing Pediarix, a pentavalent vaccine, for use at the 2-month well-child visit.¹³

The usual evaluation of a febrile infant ≤ 90 days of age at our institution includes complete blood count, blood culture, urinalysis (UA), urine culture by bladder catheterization, and cerebrospinal fluid (CSF) analysis and culture. Chest radiographs, stool cultures, and point-of-care testing, including respiratory syncytial virus and influenza, were performed at the discretion of the treating physician. Only patients with a minimum of a blood and urine culture performed at the study institution were studied. All laboratory data and radiology reports were directly downloaded from the hospital information systems into the study database.

Outcome Measures

Patients were classified as having a definite SBI, possible SBI, or no SBI. Definite SBI was defined as follows: 1) bacterial pathogen isolated in blood; 2) bacterial pathogen isolated in urine with $\geq 50,000$ colony-forming units (cfu)/mL of a pure pathogen, 10,000–50,000 cfu/mL if the UA was positive (dipstick testing with positive leukocyte esterase and positive nitrite or >5 white blood cells per high-power field on a spun urine); 3) bacterial pathogen isolated in the CSF; 4) pneumonia as identified by an attending radiologist reading of a radiograph as definite pneumonia; or 5) bacterial pathogen isolated in stool culture. Possible SBI was defined as follows: 1) chest radiograph read by an attending radiologist as a possible pneumonia or 2) urine culture yielding a low colony count (10,000–50,000 cfu/mL) of a single pathogen and a negative UA or multiple pathogens with one dominant pathogen ($\geq 50,000$ cfu/mL) regardless of the UA. Urine cultures yielding nonenteric Gram-negative rods, *Streptococcus viridans*, *Staphylococcus saprophyticus*, yeast, and gardenella were considered contaminated. Only cultures and radiologic studies performed at the study institution were included. All other patients were classified as not having an SBI. Febrile infants who did not have laboratory evaluation were reviewed for subsequent ED visits within 1 week of index encounter and are reported separately for completeness of the data set. All cases of definite SBI and possible SBI were reviewed independently by both authors for outcome classification. Although not included in the calculation of SBI prevalence, the records of infants with RI who did not have a complete laboratory evaluation were reviewed for any subsequent visits related to index encounter.

Data Analysis

Prevalence of SBI was compared for patients with and without RI. Infants without specific documentation of immunization status were analyzed separately. Median

and interquartile ranges are used to describe nonnormal distributions, and means and standard deviations (\pm SD) are provided for normal distributions. Continuous variables were analyzed using an independent samples test, and categorical data were analyzed using Fisher's exact test or chi-square analysis where appropriate. Nonparametric variables were analyzed with the Mann-Whitney U-test. Statistical significance was designated at $p \leq 0.05$. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS Version 16.0, SPSS Inc., Chicago, IL).

RESULTS

A total of 2,247 patients between the ages of 6 and 12 weeks with fever of $\geq 38.0^\circ\text{C}$ were identified. A total of 269 patients were excluded for the following reasons: 34 had a chronic disease, 16 had known vesicoureteral reflux, four had surgery in the preceding 7 days, 79 had received antibiotics in the preceding 72 hours, and eight had a focal infection. An additional 128 patients, including 10 patients with RI, were excluded because they did not have the minimum evaluation of a blood and urine culture performed at our institution. The remaining 1,978 patients were studied. Of these, 213 (10.8%) patients had received immunizations in the 3 days prior to the index encounter. Table 1 lists patient characteristics for the study population. The median ages of patients in the RI group and the NRI group were 64 and 65 days, respectively ($p = 0.91$). The mean temperatures of patients with RI and NRI were 38.5 and 38.6°C , respectively ($p = 0.03$). Overall, 86% of the population had explicit documentation regarding immunization status. Of the 276 patients without explicit documentation of immunization status, 51 received primary care at the study institution's primary care center, which has electronic immunization records. None of the 51 patients followed at the primary care center

without ED immunization documentation had received immunizations in the 72 hours preceding the ED visit.

The overall prevalence of SBI (definite and possible) in the study population was 8.0% (95% confidence interval [CI] = 6.8 to 9.2). Table 2 lists the characteristics of infants with and without definite SBI. The prevalence of SBI in the NRI cohort was 8.5% (95% CI = 7.2 to 9.8) including 124 (7.0%, 95% CI = 5.9 to 8.3) with definite SBI and 26 (1.5%, 95% CI = 0.9 to 2.0) with possible SBI. The prevalence of SBI in the RI cohort was 3.7% (95% CI = 1.2 to 6.3) including six (2.8%, 95% CI = 0.6 to 5.1) with definite SBI and two (0.9%, 95% CI = -0.3 to 2.2) with possible SBI. Table 3 lists the recently immunized infants with SBIs.

The remainder of the analysis was performed using only the cases of definite SBI, excluding cases of possible SBI. Table 4 lists the cases of definite SBI in RI and NRI patients. The relative risk of definite SBI with RI was 0.41 (95% CI = 0.19 to 0.90). Among RI patients, 157 (73.7%) presented within 24 hours of immunization, 33 (15.5%) presented 24–48 hours after immunization and 23 (10.8%) presented 48–72 hours after immunization. Among patients presenting within 24 hours of immunization, the prevalence of definite SBI decreased to 0.6% (95% CI = 0 to 1.9) with a relative risk of 0.09 (95% CI = 0.01 to 0.64) compared to the NRI group. The prevalence of definite SBI in febrile infants vaccinated greater than 24 hours prior to presentation was 8.9% (95% CI = 1.5 to 16.4) with a relative risk of 1.25 (95% CI = 0.53 to 2.9). The prevalence of definite SBI in each group is summarized in Table 5. When only cases with explicit documentation of immunization status are considered, the prevalence of definite SBI for RI and NRI infants is 2.8% (95% CI = 0.6 to 5.1) and 7.1% (95% CI = 5.8 to 8.4), respectively.

Patients with RI who did not have a complete laboratory evaluation ($n = 10$) were reviewed. None of these patients returned with SBI. Therefore, if these patients were included in the analysis, the prevalence of definite SBI would decrease from 2.8% (95% CI = 0.6 to 5.1) to 2.7% (95% CI = 0.6 to 4.8) in the febrile infants with RI.

Table 1
Patient Characteristics

	RIs ($n = 213$)	NRIs ($n = 1,765$)
Median age, days (IQR)	64 (62–68)	65 (54–78)
Mean temperature, $^\circ\text{C}$ * (\pm SD)	38.5 (0.7)	38.6 (0.5)
% URI symptoms [†] *	31.0	56.7
% Well-appearing [†]	100	98.7
Mean WBC count, $\times 10^9/\text{L}$ * (\pm SD)	13.5 (4.7)	11.9 (5.7)
Mean ANC, $\times 10^9/\text{L}$ * (\pm SD)	6.8 (2.4)	5.4 (2.7)
% CSF obtained	76.5	77.6
% CXR	14.5	27.4

ANC = absolute neutrophil count; CSF = cerebrospinal fluid; CXR = chest radiograph; NRI = no recent immunization; RI = recent immunization; URI = upper respiratory infection; WBC = white blood cell.

*Statistically different $p < 0.05$

[†]As defined in text.

DISCUSSION

Due to the relatively high prevalence of SBI among young febrile infants compared to older infants, multiple decision rules recommending laboratory evaluations have been developed to guide clinical decision-making.^{2,7,14–16} However, these decision rules have neglected to address the management of the recently immunized febrile infant. This issue is important because fever is a commonly reported adverse event after vaccinations,^{9,17,18} and current immunization schedules recommend vaccinations at 2 months.^{10–12} As a result, studies have shown an increase in medical utilization and procedures following vaccinations in infants.^{18,19} In a study by Lieu et al.,¹⁸ fever after vaccinations in infants resulted in a twofold increase in medical utilization. A recent study by Thompson et al.¹⁹ demonstrated a sevenfold increased risk of receiving a full sepsis evaluation and a threefold increased risk of receiving antibiotics within 7 days for infants receiving a pentavalent vaccination. In addition to the cost

Table 2
Characteristics of Infants With and Without Definite SBIs, Excluding Infants With Possible SBI

	All Infants		Recently Immunized Infants	
	No SBI* (n = 1,820)	SBI* (n = 130)	No SBI* (n = 205)	SBI* (n = 6)
Median age, days (IQR)	65 (54–77)	67 (57–78)	65 (62–69)	67 (63–77)
Mean temperature, °C (±SD)	38.5 (0.5)†	38.7 (0.5) †	38.5 (0.7)	38.6 (0.7)
% URI symptoms*	55.0	41.8	31	16.7
% Well-appearing*	99.1	95.6	100	100
Mean WBC count, ×10 ⁹ /L (±SD)	11.8 (5.3)†	16.0 (7.3) †	13.5 (4.6)	16.3 (5.4)
Mean ANC, ×10 ⁹ /L (±SD)	5.4 (2.6)†	7.3 (3.1) †	6.7 (2.4)	8.7 (0.4)
% CSF obtained	76.8	85.4	75.6	100

ANC = absolute neutrophil count; CSF = cerebrospinal fluid; URI = upper respiratory infection; WBC = white blood cell.
*As defined in text.
†Statistically different p < 0.05.

Table 3
SBI in Recently Immunized Infants

SBI Status	Age (Days)	Sex	Time from Vaccination (Hours)	Maximum Temperature (°C)	Appearance*	URI Symptoms	WBC count (×10 ⁹ /L)	Type of SBI	Culture Data Urine (cfu/mL)
Definite SBI	77	Male	12–24	38.5	Well-appearing	No	26.8	UTI	70,000 <i>E. coli</i>
	68	Male	48–72	38.0	Well-appearing	No	17.7	UTI	>100,000 <i>E. coli</i>
	63	Female	48–72	39.4	Well-appearing	No	10.3	UTI	>100,000 <i>E. coli</i>
	64	Female	48–72	39.9	Well-appearing	No	16.4	UTI	>100,000 <i>E. coli</i>
	67	Male	48–72	38.6	Well-appearing	No	18.2	UTI	>100,000 <i>E. coli</i>
Possible SBI	77	Female	48–72	39.2	Well-appearing	Yes	10.7	UTI	>100,000 <i>E. coli</i>
	71	Male	12–24	38.0	Well-appearing	No	12.3	Possible UTI	30,000 <i>E. coli</i> †
	68	Female	12–24	38.3	Well-appearing	No	18	Possible pneumonia	Negative cultures

cfu = colony-forming units; URI = upper respiratory symptoms; UTI = urinary tract infection; WBC = white blood cell.
*Appearance as defined under Methods.
†Urinalysis negative.

Table 4
Definite SBI in Infants With RI and Infants With NRI, Excluding Infants With Possible SBI

	RI (n = 211), n (%), 95% CI)	NRI (n = 1,739), n (%), 95% CI)
Bacteremia	0 (0, 0–1.8)	15*† (0.9, 0.4–1.3)
UTI	6 (2.8, 0.6–5.1)	99* (5.7, 4.6–6.8)
Bacterial meningitis	0 (0, 0)	3† (0.2, 0–0.4)
Pneumonia	0 (0, 0)	7 (0.4, 0.1–0.7)
Overall SBI	6 (2.8, 0.6–5.1)	124 (7.1, 5.9–8.3)

NRI = no recent immunization; RI = recent immunization; SBI = serious bacterial infection; UTI = urinary tract infection.
*Four infants had UTI and concomitant bacteremia.
†One infant had meningitis and concomitant bacteremia.

Table 5
Summary of Definite SBI in Infants With NRI Compared to Infants With RI

	Prevalence of SBI (95% CI)	Relative Risk (95% CI)
NRI	7.1% (5.9–8.3)	Reference group
RI (all)	2.8% (0.6–5.1)	0.41 (0.19–0.90)
RI < 24 hours	0.6% (0–1.9)	0.09 (0.01–0.64)

Infants with possible SBI were excluded in this analysis.
NRI = no recent immunization; RI = recent immunization; SBI = serious bacterial infection.

associated with performing a sepsis evaluation, there are also risks associated with these procedures²⁰ and the administration of antibiotics. When the results of the diagnostic tests are equivocal or uninterpretable, such as with a traumatic lumbar puncture, the infant may then undergo additional testing or hospitalization.

Published guidelines recommend performing sepsis evaluations on febrile infants given the prevalence of SBI in this age group. However, our study demon-

strates that febrile infants presenting after RIs have a decreased risk of SBI compared to those with fever but NRI. This suggests that these infants may not require routine fever evaluation, although these findings are provisional and need to be confirmed in a larger prospective cohort to guide clinical decision-making. We found the prevalence of definite SBI in the recently immunized infants was 2.8%, whereas the overall prevalence of definite SBI in the study population was 6.6%, which is similar to rates documented in the literature. Urinary tract infection (UTI) was the only SBI occurring

in these recently immunized infants; there were no cases of bacteremia or meningitis, although the number of recently immunized infants was relatively small for these outcomes. In the infants who presented within 24 hours of receiving vaccinations, the prevalence of definite SBI was reduced to 0.6%. Given the possible complications and associated cost of a sepsis evaluation, a modified evaluation may be appropriate in light of the decreased prevalence of SBI in this population. A modified approach to recently immunized infants with fever follows the approach to febrile infants with RSV.²¹

LIMITATIONS

This was a retrospective study, which limited the data available to the information in the medical chart. The exact timing of the immunizations required coding into large blocks of time and was inconsistently recorded. However, given the importance of this information in the care of the febrile infant, it is unlikely that these data would have been excluded from the medical record if the infant had been recently immunized. In addition, review of electronic immunization records at the study institution supported the assumption that infants without documentation of RIs did not have RIs. Another potential limitation due to the retrospective study design is the inability to follow up patient outcomes.

This study population consisted of febrile infants who presented to an academic medical center ED; this may have created a referral bias given the influence of local referral patterns and the opinions of the local pediatricians on ED visits. However, it is unlikely that RI febrile infants who did not present to the ED had SBI. Anecdotally, many pediatricians counsel parents regarding vaccine side effects including fever and advise antipyretic administration. This anticipatory guidance may decrease the rate of visits of these patients to the ED. Therefore, if these infants had presented to the ED, the prevalence of SBI in this population would be lower than demonstrated in this study. Our study is also limited by the relatively small sample size. Although the differences in SBI are significant, the estimates of SBI prevalence should be interpreted cautiously.

These results should be considered in context of the current immunization schedule, as they may change as the immunization schedule changes over time. The immunization schedule during this study included a vaccine with a relatively high rate of fever. If the immunization schedule changes to include immunizations with higher or lower rates of fever, the prevalence of SBI in RI febrile infants presenting to the ED may subsequently change.

CONCLUSIONS

Based on our findings, the prevalence of serious bacterial infections in recently vaccinated infants appears to be lower than in infants with fever and no recent immunization. However, there is still a significant risk of urinary tract infections. Therefore, for

well-appearing infants presenting with fever within 24 hours after immunization, careful examination and consideration of a urine culture and urinalysis might be a reasonable strategy. Young febrile infants presenting greater than 24 hours postimmunization should be managed similarly to those without recent immunization.

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