

# Evaluation, Management, and Outcome of Focal Bacterial Infections (FBIs) in Nontoxic Infants Under Two Months of Age

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**BACKGROUND:** Well-appearing young infants with focal bacterial infections present to the emergency department (ED) and are often admitted for a sepsis evaluation of blood, urine, and spinal fluid. However, the risk of concomitant systemic infections (CSI) in this population is not well reported, specifically comparing febrile to afebrile infants. We hypothesized that afebrile, well-appearing infants under two months of age with a defined focal bacterial infection on exam have a very low risk of CSI.

**METHODS:** This retrospective study was conducted at an urban, academic, tertiary care pediatric hospital ED on patients seen from January 2000-December 2005. Eligible infants were less than 60 days of age, well-appearing on exam, and with normal-for-age vital signs who presented with a focal bacterial infection on exam. Exclusion criteria included immunodeficiency, indwelling catheter, previous admission for bacterial infection, or current use of systemic antibiotics. Main study outcome was risk of CSI in febrile and afebrile groups.

**RESULTS:** One hundred ninety seven patients were included in the study population. Of these, 39 were febrile and 158 were afebrile. Four patients had a documented CSI: one case of *S. pneumoniae* bacteremia and three cases of *E. coli* urinary tract infection. Of these 4 infants, 3 were febrile (7.7% CSI risk) and 1 was afebrile (0.6%). Febrile infants had a significantly higher risk of CSI (OR 13.1, 95% CI 1.3, 129.5).

**CONCLUSIONS:** CSI is very uncommon in afebrile, well-appearing infants under 60 days of age with a focal bacterial infection. *Journal of Hospital Medicine* 2010;5:76-82. © 2010 Society of Hospital Medicine.

**KEYWORDS:** fever/febrile, infants, focal infection, bacteremia, urinary yeast infection.

Focal bacterial infections (FBIs), including otitis media (OM), cellulitis, and lymphadenitis, can occur at any age and are usually treated with oral antibiotics. When patients with focal infections present as a young infant, healthcare providers often worry about the risk of coexisting or concomitant systemic infections (CSIs), often termed serious bacterial infections (SBIs) in the published literature.<sup>1,2</sup> Risk of CSI becomes more worrisome when young infants have fever as part of their presentation, especially within the traditional "rule-out sepsis" age range of less than 2 months. Often, these patients are well-appearing and lack prenatal and neonatal risk factors for systemic infections, but are assumed to be at high risk for CSI based on the presence of focal bacterial infection.<sup>1,3,4</sup>

FBIs have been the subject of multiple studies, especially OM and cellulitis. However, few investigations have looked specifically at infants less than 60 days of age, lending uncertainty to medical decision-making for both community and emergency physicians. Therefore, no standardized evidence-based practice exists for treating young infants with FBIs. While some clinicians treat these infections using systemic antibiotics without performing laboratory tests, others

opt for a full diagnostic evaluation for CSI; including serum blood counts, blood cultures, lumbar punctures (LPs), and bladder catheterizations. Also, some clinicians opt for treatment with oral antibiotics at home, while others choose intravenous (IV) antibiotics and hospitalization.

These decisions are likely due to studies of febrile infants under 60 days of age who present to an emergency department (ED), appear well, and have no focal source of infection on exam, yet are known to have a risk of systemic or occult bacterial infection of roughly 10%.<sup>3-10</sup> There are no such studies documenting the risk of CSI in well-appearing, afebrile patients, as fever is regarded as the main risk factor for CSI in this age.

Based on our clinical experience and review of the literature, we felt that afebrile, well-appearing infants less than 60 days of age with an FBI on exam would have a very low risk of CSI. The primary objectives of this study were to determine the risk of CSI when presented with a well-appearing infant who has an FBI on exam and to examine that risk in relation to the presence of fever. Other objectives were to describe the clinical presentation of FBIs in well-

appearing infants in this age group and to describe the current management and resource utilization of such infections in the ED.

## Patients and Methods

### Study Population

Cincinnati Children's Hospital Medical Center (CCHMC) is a 423-bed tertiary-care hospital located in southwestern Ohio. The medical center serves as the sole pediatric hospital in a 70-mile radius, serving a metropolitan population of roughly 1 million. In addition, CCHMC cares for patients from a wide demographic and socioeconomic spectrum, including the urban, suburban, and rural areas of Cincinnati, southwestern Ohio, northern Kentucky, and southeastern Indiana. The ED sees an average of 90,000 patients annually, with an average of 15,000 admissions.

### Patient Selection

Data were retrospectively collected from a consecutive series of infants age 0 to 59 days who presented to the CCHMC ED between January 1, 2000 and December 31, 2005. Patients met inclusion criteria if they were documented to be well-appearing on exam; had normal-for-age heart rate, respiratory rate, blood pressure, and oxygen saturation (if measured); were discharged from their hospital of birth to home before presentation to the ED; and received a discharge diagnosis consistent with an FBI. Specifically, FBIs included the following diagnoses: soft tissue infection, cellulitis, mastoiditis, abscess, OM, omphalitis, mastitis, mammitis, paronychia, balanitis, posthitis, impetigo, or lymphadenitis. We excluded patients with a history of immunodeficiency, central venous catheter, tracheostomy, gastrostomy tube, chronic lung disease, previous admission for a documented bacterial infection, or if they had been taking systemic antibiotics at the time of evaluation. We also excluded infants noted to be toxic or ill-appearing on examination.

### Definitions

Fever was defined as a temperature greater than or equal to 38°C (100.4°F), recorded by the ED or by parental report. All infants seen in the CCHMC ED had rectal temperatures measured per protocol. A nontoxic infant was defined by chart review as documentation of: nontoxic, well-appearing, or alert infant without signs of respiratory distress or hemodynamic instability. Patients were excluded from the nontoxic category with the following parameters: heart rate >180 beats per minute, respiratory rate >60 breaths per minute, oxygen saturation <90% on pulse oximetry, or systolic blood pressure <60 mmHg on 2 or more measurements. CSIs were defined as any of the following: bacteremia, urinary tract infection (UTI) identified by catheterized urine specimen, meningitis, septic arthritis, or osteomyelitis. Additionally, pneumonia was included as a CSI if confirmed by radiographs, based on final reading by an attending radiol-

ogist. Pneumonia is included as an SBI in a number of prior publications in this age group; therefore, we felt it was important to include it in our definition of CSI.<sup>7,11–15</sup>

### Procedures

The chart review consisted of both electronic and paper medical records. We searched the electronic database for all the infants in this age group receiving a discharge diagnosis of an FBI as defined above. Information from the medical record was entered onto a standardized data sheet by one of the investigators or a research assistant. Data gathered included baseline demographic information (age at ED evaluation, gestational age at birth, gender, race), presence or absence of fever, vital signs on ED presentation, use of diagnostic evaluation (complete blood count [CBC], blood culture, C-reactive protein, erythrocyte sedimentation rate, urinalysis, urine culture, LP, wound culture, radiographic studies), laboratory test results, therapeutic interventions (including antibiotics and subspecialty consultation), initial disposition (home, admission to hospital), and clinical outcome of both admitted and discharged patients. The results of all bacterial cultures were obtained from computerized microbiology records. Bacterial isolates from blood cultures that are considered skin flora, such as *Staphylococcus epidermidis* or Viridans group *Streptococcus*, were considered contaminants unless they were positive for growth within 24 hours of initial culture.<sup>16–18</sup> Radiology results were based on final interpretation by an attending radiologist.

### Statistical Analysis

The primary objectives of this study were to determine the risk of CSI when presented with a well-appearing infant who has an FBI on exam and to examine that risk in relation to the presence of fever. Thus, this study was powered to investigate the difference in CSI between febrile and afebrile patients. Again, we hypothesized that in afebrile, well-appearing infants less than 60 days of age with an FBI on exam there is a very low risk of CSI. For statistical purposes and power calculations we used <1% risk as "very low." Using the approximate risk of 10% CSI in well-appearing, febrile infants this age without CSI, we assumed there would be approximately 10% less CSIs in the afebrile patients compared to the febrile patients. As per consultation with our statistician, for a significance level of  $\alpha = 0.05$  and  $\beta = 0.2$  a 2-sided *t* test required a total of 188 subjects to be enrolled.

Additional outcome measures (such as use of laboratory testing, IV antibiotics, subspecialty consultation, and admission) were reported as descriptive statistics with frequencies. Fisher's Exact test was used for these nominal variables to test significance of relationship between febrile and afebrile patients. The Exact method was used to calculate 95% confidence intervals (CIs) around the primary outcome point estimates. A *P* value < 0.05 was considered significant. All

data were entered into a Microsoft Excel (Microsoft, Redmond, WA) database.

## Results

### Study Population

We identified 246 patients less than 60 days of age who were diagnosed in the ED with an FBI during the study period. Thirty-seven patients met the exclusion criteria, leaving 209 patients for potential enrollment. Twelve (5.7%) charts were not located, resulting in a study population of 197 infants. Of these, 158 patients were afebrile and 39 were febrile. To put these numbers into context, over the study period our ED evaluated 2341 infants less than 60 days of age whose diagnosis included the word fever, febrile, or sepsis. The febrile infants included in our study group were part of these 2341 found in the retrospective search, but the afebrile infants included were not.

The mean age of these 197 infants was 29.6 days, with a standard deviation (SD) of 15.9 days. On average, the febrile patients (mean 40.7 days, SD 15.3 days) were older than the afebrile patients (mean 26.8 days, SD 16.1 days). No statistical differences were found between febrile and afebrile patients in respect to gender, race, and gestational age.

### Primary Study Outcome—Risk of SBI

Four patients had a documented CSI, for an overall risk of CSI in our study population of 2.0% (Table 1). Statistically, febrile infants had a significantly higher risk of CSI (odds ratio [OR], 13.08; 95% CI, 1.32-129.46) than afebrile infants. The febrile infants with a coexisting CSI included the following: a 32-day-old male with a buttock abscess and *E. coli* UTI; a 47-day-old male with periorbital cellulitis and *Streptococcus pneumoniae* bacteremia; and a 21-day-old female with trunk cellulitis and *E. coli* UTI. The afebrile infant with a CSI was an 11-day-old male with acute OM (AOM) and *E. coli* UTI. No cases of bacterial meningitis, septic arthritis, osteomyelitis, radiographic pneumonia, or death occurred.

Eight other patients had positive culture results, all of which were considered contaminants. Four patients had peripheral blood cultures that were deemed contaminants: 2 cases of Viridans group streptococcus and 2 cases of coagulase-negative staphylococcus. Four urine cultures were considered contaminants: 1 staphylococcus species; 1 mixed flora specimen; 1 *Lactobacillus* species, and 1 *E. coli*.

This positive culture for *E. coli* occurred in an 11-day-old female who presented without fever, was diagnosed clinically and by ultrasound with mastitis, and was admitted to the hospital. She underwent a full diagnostic workup for CSI. Initial screening laboratory test results were normal, including a negative urinalysis and 1 to 2 white blood cells (WBCs)/high-powered field on the microscopic exam. The catheterized urine specimen grew the following: (1) 10,000 to 100,000 colony forming units (CFU)/mL of *E. coli*; and (2) normal flora 1000 to 9000 CFU/mL. Her blood and cerebrospinal fluid (CSF) culture were negative. The primary team

TABLE 1. Primary Outcome: Presence of CSI

|                    | CSI | No CSI | Risk (%) | 95% CI (%) |
|--------------------|-----|--------|----------|------------|
| Febrile (n = 39)   | 3   | 36     | 7.69     | 1.62-20.87 |
| Afebrile (n = 158) | 1   | 157    | 0.63     | 0.02-3.48  |
| Total (n = 197)    | 4   | 193    | 2.03     | 0.56-5.12  |

Abbreviations: CI, confidence interval; CSI, concomitant systemic infection.

did not diagnose or treat this patient as a UTI despite the positive culture. According to their documentation, it was a suspected contaminant because of negative chemical and microscopic urinalysis. If this were considered a true positive culture, which seem practical clinically, clinically the overall risk of CSI would be 2.5% (5/197 infants) and the risk of coexisting CSI in afebrile patients would be 1.3% (2/158 infants); however, febrile infants would still had a significantly higher risk of CSI (OR, 6.5; 95% CI, 1.05-40.34) than afebrile infants.

### Secondary Study Outcome—Clinical Presentation of FBI in Well-appearing Infants in This Age Group

Among the 197 study infants, there were multiple types of FBIs found on examination (Table 2). Soft tissue infections were the most common cause in afebrile patients, whereas AOM was the most common cause in the febrile patients. Overall, cellulitis and abscess were the leading causes of focal infections in this age group. A total of 46 patients were diagnosed with abscesses, the buttock being the site in 24 (52%) cases. Abscesses were drained and sent for culture in 13 patients. Methicillin-resistant *Staphylococcus aureus* (MRSA) was found in 4 of these 13 cultures. Of the 55 patients diagnosed with cellulitis, 20 (36%) had cultures drawn from the cellulitis site, of which 5 cultures grew MRSA.

Of note, a 13-day-old male presenting without fever but with a scalp lesion had herpes simplex virus grown from his wound culture. His diagnostic workup was negative for CSI. Omphalitis, uncommon in the United States, was diagnosed in 2 patients in our study and neither of these patients developed necrotizing fasciitis. Mastitis was not a significant focal infection in either group; and no patient was diagnosed with mastoiditis, balanitis, or posthitis.

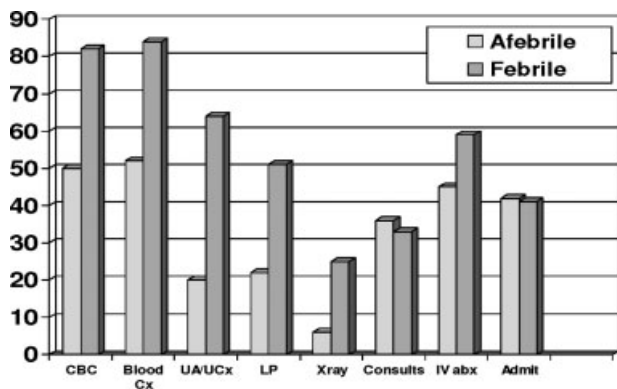
### Secondary Study Outcome—Current Management of FBI in the ED: Resource Utilization

Febrile patients underwent significantly more diagnostic testing procedures than afebrile infants. Specifically, CBCs, peripheral blood cultures, urine analyses with cultures, LPs, and radiographic imaging were performed more often in infants with fever (Figure 1). Fifty-seven infants had urine cultures performed: 32 of 158 afebrile infants and 25 of 39 febrile infants. Among these selected infants, again 3 UTIs occurred: 1 of 32 tested (3.1%) in the afebrile group and 2 of 25 tested (8%) in the febrile group. A total of 115 infants

**TABLE 2. Identification of Focal Bacterial Infections in the ED**

| Focal Infection | Afebrile (n = 158) [n (%)] | Febrile (n = 39) [n (%)] | Totals (n = 197) [n (%)] |
|-----------------|----------------------------|--------------------------|--------------------------|
| AOM             | 19 (12)                    | 22 (56)                  | 41 (21)                  |
| Cellulitis      | 49 (31)                    | 6 (15)                   | 55 (28)                  |
| Abscess         | 40 (25)                    | 6 (15)                   | 46 (23)                  |
| Impetigo        | 20 (13)                    | 1 (3)                    | 21 (11)                  |
| Mastitis        | 11 (7)                     | 2 (5)                    | 13 (7)                   |
| Lymphadenitis   | 4 (3)                      | 1 (3)                    | 5 (3)                    |
| Omphalitis      | 2 (1)                      | 0 (0)                    | 2 (1)                    |
| SSSS            | 2 (1)                      | 0 (0)                    | 2 (1)                    |
| Paronychia      | 1 (1)                      | 0 (0)                    | 1 (0)                    |
| Other           | 10 (6)                     | 1 (3)                    | 11 (6)                   |

**Abbreviations:** AOM, acute otitis media; ED, emergency department; SSSS, staphylococcal scalded skin syndrome.



**FIGURE 1.** Resource utilization for infants with focal bacterial infection (expressed in percentage of infants who underwent diagnostics, therapy, or admission). **Abbreviations:** Admit, infant admitted to hospital for further care; Blood Cx, blood culture;\* CBC, complete blood count;\* Consults, subspecialty consult obtained by ED physician; IV abx, intravenous antibiotics given; LP, lumbar puncture;\* UA/Ucx, urinalysis and urine culture\*; Xray, radiographic study.\* Note: \*denotes statistically significant difference ( $P < 0.05$ ) between febrile and afebrile groups.

had blood cultures performed: 82 of the 158 afebrile infants and 33 of the 39 febrile infants. Among these selected infants, again 1 positive blood culture occurred: 0 of 82 tested (0%) in the afebrile group and 1 of 33 tested (3%) in the febrile group. Fifty-five infants had LP performed: 35 of 158 afebrile infants and 30 of 39 febrile infants. No case of meningitis occurred in these selected infants. Twenty infants had diagnostic radiographs performed, 10 in the febrile group and 10 in the afebrile group. None of the radiographs showed signs of pneumonia on final radiology attending reading.

Overall, 33 of 39 febrile infants had cultures drawn and/or radiographs performed, with 3 CSIs discovered, and 87 of

**TABLE 3. Presence of CSI in Patients Who Underwent Diagnostic Workups**

|                   | CSI | No CSI | Risk (%) |
|-------------------|-----|--------|----------|
| Febrile (n = 33)  | 3   | 30     | 9.1      |
| Afebrile (n = 87) | 1   | 86     | 1.1      |
| Totals (n = 120)  | 4   | 116    | 3.3      |

**Abbreviation:** CSI, concomitant systemic infection.

158 afebrile infants had cultures drawn and/or radiographs performed, with 1 CSI discovered (Table 3). This means that 77 infants diagnosed with FBIs did not have any diagnostic testing for CSI performed while in the ED. The overall risk of CSI in patients who were tested was 3.3%. Comparing febrile and afebrile patients who had diagnostic workups performed, febrile infants had a trend toward increased risk of CSI (OR, 8.6; 95% CI, 0.8613-85.8686).

No significant differences existed in the use of consultants, use of IV antibiotics, or admission rate. Sixty-six (42%) of the 158 afebrile infants were admitted. The average length of stay for these infants was 2.59 days (range, 1-22 days). This included a 22-day-old female with mastitis who required multiple surgeries and a protracted hospital course. Sixteen (41%) of the febrile infants were admitted and had an average stay of 2.87 days (range, 1-6 days).

### Patient Outcomes

Ninety-two (58%) of the afebrile infants were discharged home from the ED, of which 5 (5.4%) returned to the ED within 72 hours after discharge. Three of these were planned ED returns as follow-up with a primary care physician could not be guaranteed. The fourth was a 47-day-old with a buttock abscess who returned for reevaluation because of parental concern. The fifth was the 11-day-old male initially diagnosed with AOM who was called back to the ED when his urine culture grew *E. coli*, at which point he was admitted to the hospital. Twenty-three (59%) of the febrile infants were discharged home from the ED. Two (8.7%) of these 23 returned to the ED within 72 hours; both were initially diagnosed with AOM and had planned follow-ups as no primary care was available. No admitted patients required transfer to the pediatric intensive care unit and no deaths occurred.

### Discussion

This study is the first to investigate the risk of CSI specifically in well-appearing infants under 60 days of age presenting with FBI. Inclusion criteria were not limited to 1 specific infection, ie, OM, but included all FBI. This study demonstrated that the risk of CSI in afebrile infants is small (0.6%), which is similar to what has been shown in the OM literature.<sup>19,20</sup> However, the risk of CSI among febrile infants is not negligible (7.7%), and is similar to the risk of SBIs among young infants presenting with a fever of unknown source.<sup>5-7</sup>

## AOM

A total of 41 infants were diagnosed with AOM. Indeed, AOM was the most common discharge diagnosis among the febrile cohort. No febrile infants with AOM were diagnosed with a CSI. However, as noted above, an 11-day-old afebrile infant with AOM did have a UTI diagnosed. This male underwent blood, urine, and CSF cultures on initial presentation. He was discharged home from the ED, and called back for further evaluation once the urine culture grew *E. coli*.

We relied on the diagnostic skills of the ED attending physician for determination of OM, and no rigorous diagnostic criteria were established for an AOM in this young age group. However, on chart review of those patients with AOM who were admitted, otolaryngology was often consulted and confirmed the diagnosis of OM.

AOM has been the most commonly studied focal infection studied most in this age group.<sup>1,2,11,21-23</sup> More recent studies have investigated the risk of CSI with AOM among febrile and afebrile cohorts. These authors found that in infants under 2 months with AOM, febrile infants had a 6% to 13% risk of CSI, whereas no cases of CSI were found in afebrile patients.<sup>19,20</sup> These results suggest that afebrile, nontoxic infants with AOM could be treated as outpatients without need for further systemic evaluation. Our study strengthens this argument if close follow-up can be assured.

## Cellulitis and Abscess

A total of 106 infants were diagnosed with either abscess and/or cellulitis, with the vast majority of them presenting without fever. Moreover, cellulitis and abscess comprised more than one-half of all infants in the afebrile cohort. The buttocks were the most common site for abscess (23 cases), followed next by the scalp (8 cases). In our study population, there were 29 positive abscess, wound, lesion, or skin aspirate cultures for *Staphylococcus aureus*, with 13 (45%) being MRSA. None of these patients had a CSI.

Community-acquired staphylococcal infections have been studied in the newborn population, with MRSA accounting for up to 69% of soft-tissue infections in one recent study involving 89 neonates.<sup>24</sup> The authors found 4 cases of bacteremia, 3 cases of UTI, and 2 cases of CSF pleocytosis. Application of these results to our patients is difficult, as there was no mention of fever or well-appearance stratification and there is no specific mention of any of the 77 skin and soft-tissue infections having a CSI.

The frequency of bacteremia in pediatric patients with periorbital cellulitis has been studied, with some authors suggested more selective use of LP in patients with these localized soft-tissue infections in the older infant or child.<sup>25,26</sup> Unfortunately, there were not enough patients under 60 days of age in either study from which to draw conclusions. In our study, a total of 5 patients presented with periorbital cellulitis: 2 afebrile and 3 febrile, including the 47-day-old febrile infant with coexisting pneumococcal bacteremia.

Group B streptococcus (GBS) cellulitis-adenitis syndrome has also been identified in neonates, with meningitis occurring in up to 24% of infants in 1 review of 32 cases.<sup>27</sup> These studies only included patients with positive blood cultures, providing no denominator for assessing a true CSI risk in young infants with cellulitis. No infants in our study had GBS infections.

Impetigo was diagnosed in 21 patients, with 17 patients being discharged home from the ED. In addition, 2 infants with staphylococcal scalded skin syndrome were identified. None of these infants had a CSI.

## Other Infections

Mastitis in the young infant has been studied, with the risk of CSI being 3% in 1 review.<sup>28-30</sup> In our study, there were 18 patients diagnosed with either mastitis or breast abscess, of which 4 (22%) had fever and none had positive blood or CSF cultures. Multiple studies, either from older literature in the United States or more contemporary from abroad, have investigated omphalitis and necrotizing fasciitis in the newborn.<sup>31,32</sup> These show that infants presenting with omphalitis have a lower mortality and morbidity than those with necrotizing fasciitis. In our study, we had 2 patients with omphalitis, both were afebrile and neither had a coexisting CSI. We had no patients with necrotizing fasciitis. We also found no patients with mastoiditis, balanitis, or posthitis as the listed diagnosis in our study.

## UTI

Of the 4 cases of CSI in our study, UTI was the most common, occurring in 3 of the 4 cases. This predominance of UTI as the cause of CSI is well-recognized in young febrile infants with OM and infants with fever of unknown origin; however, it has not been reported with other FBIs in this age group.<sup>1,5,9,11,19,33</sup> Specifically, there has not been a reported relationship between UTI and skin or soft tissue infections. However, 2 of our 4 infants with a CSI had a UTI in addition to their skin or soft tissue infection: the 32-day-old male with a buttock abscess and *E. coli* UTI; and the 21-day-old female with truncal cellulitis and *E. coli* UTI.

## Resource Utilization

Young infants with FBI and fever underwent significantly more resource utilization than afebrile infants in our ED (Figure 1). Physicians of febrile infants ordered more serum blood counts and blood cultures, urinalysis and urine cultures, and performed more LPs and radiographic studies. This is not surprising given that fever is a risk factor for CSI in this age group; however, resource utilization is not as well-described in previous reports on infants with FBIs. In 1 retrospective study of 137 infants less than 8 weeks of age with AOM, 88% had diagnostic blood cultures, 66% had LP, and 81% had urine cultures drawn.<sup>19</sup> Additionally, in our study the decision to hospitalize infants, use of IV antibiotics, and hospital length of stay was not statistically different

between febrile and afebrile groups. This potentially suggests that diagnostic testing for infants with FBIs did not affect management and outcome. Another study showed hospital admission is costly and not without safety risks, with a complication rate as high as 19% in infants.<sup>34</sup> Given these results, in addition to the presumption that all FBIs would be treated with antibiotics, one could infer that a number of well-appearing, afebrile infants underwent unwarranted testing.

## Limitations

The main limitation of our study was the retrospective design. A research assistant utilizing a computerized database program of ED patients performed the initial query based upon search criteria. A local expert using an established list of International Statistical Classification of Diseases and Related Health Problems (ICD) codes for any and all of the FBIs performed the chart review. Secondary diagnoses may have been omitted as a result of limited physician charting, which could have resulted in missed patients. CCHMC is currently transitioning from paper records to electronic medical records, which may explain why 12 charts were not found, despite exhaustive searches for them. Ultimately, 94% of all the eligible patients were found. Yet, with so few CSI diagnosed, 1 or 2 could conceivably change our results. As noted above, focal infections in infants under 2 months of age seem to be uncommon, not only in the ED setting, but also in a large cohort of primary care patients.<sup>35</sup> With only a small number FBIs present over 6 years and so few having CSIs, we were limited to a univariate analysis, which limited our potential results and conclusions. Performing this study prospectively would have addressed these limitations, but would have required years of recruitment or multicenter collaboration.

Another potential limitation was the search strategy to identify eligible infants. Specifically, we did not search the records for infants diagnosed with UTI, bacteremia, or meningitis. Infants with these more serious conditions may have been coded as the primary or only problem, even if other problems such as OM were also present. Therefore, we may have underestimated the occurrence of systemic bacterial complications in a systematic way. This form of spectrum bias was a potential limitation. We approached this clinical question from “the eye of the emergency department practitioner” and thus used a search strategy based on the discharge diagnosis from the ED. If we were to look back to see if any patients discharged from the hospital with CSI also had FBI, we doubt our retrospective design would have allowed identification of patients with FBIs.

Other limitations may be our definition of CSI and the potential for missed CSIs. We defined meningitis, bacteremia, and UTI as a positive CSF, blood, or urine culture, respectively. Many studies are now defining culture-negative meningitis or UTI based on WBC findings on a screening cell count or urine microscopy. However, because no

patients were pretreated with antibiotics, we felt that a positive culture from a sterile site was a reasonable definition. Also, not all of the enrolled patients received full diagnostic workups to screen for CSI. In the smaller cohort of infants who received diagnostic testing, febrile infants still seemed to be at higher risk for CSI. To capture all possible CSIs, one would have needed to perform blood culture, suprapubic bladder aspiration, or catheterization for urine culture, LP, and chest radiograph on all patients with an FBI. Given the low risk of CSI in the United States, the previous literature's hinting at low risk for CSI in afebrile patients, and the presence of multiple clinical trials defining low risk characteristics for CSI, such a protocol would not receive support as being standard clinical practice and have difficulty being permitted by an institutional review board.

Another limitation of our study was follow-up. Ideally, every patient would have been contacted to ensure reliable outcomes measurement. Patients may have been seen after their initial evaluation at their primary care provider's office or at another healthcare facility and had more diagnostic studies performed. However, because our institution is the sole admitting pediatric center in the area, particularly in infants, and most CSIs in this age group require admission; we feel that a reasonable degree of reliability for the outcomes of interest was maintained.

Last, we could not establish the rationale of clinical decision making, as our study was retrospective. For example, staff physicians may have foregone diagnostic testing if they had committed to a therapeutic course of antibiotics and felt diagnostic cultures would not change management. Also, we cannot ensure that interpretation of culture results was consistent with national standards. As described previously, 1 afebrile infant in our study potentially had a CSI that was clinically felt to be a contaminant by the inpatient healthcare team. This 11-day-old female was admitted with mastitis and had a negative urinalysis, but grew *E. coli* on urine culture. This was treated as a contaminant by the ward team, despite her age.

## Conclusions

CSI is very uncommon in afebrile, well-appearing infants under 2 months of age with an FBI. However, febrile infants have a greater risk of CSI. UTI is the most common CSI in well-appearing infants less than 2 months of age with an FBI found on examination. Prospective, multicentered studies need to be performed to determine whether diagnostic evaluation should change the management of well-appearing infants with an FBI found on examination.

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