

ORIGINAL ARTICLE

Paediatric emergency departments should manage young febrile and afebrile infants the same if they have a fever before presenting

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Abstract

Aim: Our aim was to evaluate the risk of bacterial meningitis, bacteremia, and urinary tract infection (UTI) in infants ≤ 60 days who presented to paediatric emergency departments (PEDs) after having fever at home. We also investigated any differences between infants who were afebrile or febrile on presentation.

Methods: This was a multicenter retrospective study of infants ≤ 60 days presented to four Swedish PEDs during 2014–2020 with reported fever at home. We used relative risks (RR) to compare the prevalence of UTI, bacteremia, and bacterial meningitis between the infants who were afebrile and the infants who were still febrile when they presented to the PED.

Results: The cohort comprised 1926 infants, and 702 (36%) were afebrile on presentation. The prevalence of UTI in the afebrile and febrile infants was 6.1% [95% confidence interval (CI) 4.5–8.2] versus 14.2% (95% CI 12.3–16.2), corresponding to an RR of 0.43 (95% CI 0.31–0.59). In infants ≤ 28 days, the RR for meningitis was 1.05 (95% CI 0.18–6.23) for afebrile versus febrile infants. Five times more febrile infants underwent a lumbar puncture.

Conclusion: Infants who were afebrile on presentation underwent fewer lumbar punctures, but they had similar rates of bacterial meningitis to febrile infants. Different management approaches are not justified.

KEYWORDS

febrile infant, management, meningitis, prevalence, serious bacterial infection

1 | INTRODUCTION

Febrile infants have a relatively high risk of meningitis, bacteremia, and urinary tract infection (UTI), which are often defined as serious bacterial infections (SBIs). Studies have reported that the prevalence

of SBIs was 9%–25% in febrile infants ≤ 60 days.^{1–6} Because of this high risk, a number of guidelines have been developed to manage febrile infants.^{4,7,8} Previous studies showed that almost 30% of infants brought to paediatric emergency departments (PEDs) due to fever were afebrile during their examination.^{6,9,10} It has been suggested

Abbreviations: CI, confidence interval; IQR, interquartile range; PED, paediatric emergency department; RR, relative risk; SBI, serious bacterial infection; UTI, urinary tract infection.

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that the absence of fever may have influenced whether clinicians adhered to guidelines. This may also partially explain the reported variations in management¹¹⁻¹³ despite the fact that all guidelines recommend the same approach regardless of the absence of fever.

Only few studies have compared the risk of bacterial infections between infants with a history of fever who were still febrile when they presented to PEDs and infants with a history of fever who were afebrile on presentation. Two older studies from 1987 and 2010 showed a significantly lower risk of SBIs in afebrile infants.^{14,15} In contrast, three studies from 2018 to 2019 found no difference¹⁰ or a small risk decrease,^{9,16} which did not justify different management. However, there were important differences in the methodology used in the studies. Mintegi et al.¹⁰ focused on infants ≤ 90 days with fever without source and investigated the risk of invasive bacterial infections, namely bacterial meningitis or bacteremia. Ramgopal et al. included febrile infants in general, not just with fever without source, aged ≤ 28 ⁹ or ≤ 60 days¹⁶ and focused on the risk of SBIs. Also, the overall prevalence of SBIs was 2-3 times higher between the first study (22.4%)¹⁰ and the other two studies (8.6% and 11.5%).^{9,16}

The prevalence of SBIs and risk factors, such as duration of fever, access to healthcare, and socioeconomic characteristics, may differ substantially between countries. However, they are crucial parameters when developing national or local guidelines to optimise patient care. The fact that the recent studies have tended to come from Spain or the USA highlights the need for data from different settings and other countries.

The aim of this study was to evaluate the risk of bacterial meningitis, bacteremia, and UTI in infants ≤ 60 days with reported fever at home. We also wanted to investigate whether there was any difference between the infants who were afebrile when they presented to the PED and infants who were still febrile.

2 | PATIENTS AND METHODS

2.1 | Design

This was a multicenter retrospective study that identified all infants ≤ 60 days with fever registered as contact reason in the electronic registration system of four geographically diverse PEDs in Sweden. The four PEDs were located in Gothenburg, Malmö, Lund, and Stockholm. The study is a continuation of a previously published retrospective study on the prevalence of SBIs in febrile infants ≤ 60 days.⁶ Some of the data from that study, which covered 1 January 2014-31 December 2017, were re-analysed. In two of the PEDs (Malmö and Lund), the end point of the study period was extended to 31 December 2020.

We reviewed the electronic medical records of the infants, and subjects were eligible for the study if they had a temperature of $\geq 38.0^\circ\text{C}$ measured at home. We included term-born infants (born at ≥ 37 weeks of gestation), who did not have comorbidities, such as cardiovascular, neurological, genitourinary, or respiratory tract disorders. Furthermore, we only included infants without an apparent

Key Notes

- The risk of urinary tract infection in infants with a history of fever who were afebrile on presentation at the paediatric emergency department is not so low that urine testing can be omitted.
- The rate of lumbar puncture was 5 times higher in febrile versus afebrile infants ≤ 28 days.
- The risk of meningitis in the febrile and afebrile infants ≤ 28 days was similar, which do not justify a different management.

source of infection, such as gastrointestinal, respiratory, joint, or skin and who had not received antibiotics or been hospitalised in the last 10 days. We identified and reviewed all subsequent visits to the PED in the 10 days after the index visit. Data on demographics, symptoms, clinical findings, and microbiological and biochemical results were registered in the Research Electronic Data Capture program hosted by Lund University, Sweden.

2.2 | Study definitions

Fever without a source was a fever of $\geq 38.0^\circ\text{C}$ without any identifiable source of infection, such as gastrointestinal, respiratory, joint, or skin, after the medical history had been taken and the physical examination had been carried out. An SBI was bacterial meningitis, bacteremia, or UTI. Bacterial meningitis or bacteremia were defined as the growth of a bacterial pathogen in a blood or cerebrospinal fluid culture. Coagulase-negative staphylococci, *Bacillus cereus* species, *Propionibacterium* species, micrococci, alpha hemolytic streptococci, and diphtheroids isolated in blood cultures were considered contaminants. A UTI was an urine culture with growth of the following: First, any amount of a single pathogen in suprapubic aspiration samples; second, more than 10,000 colony forming units (cfu)/ml of a single pathogen if the urine dipstick was positive for nitrite or leukocyte esterase in catheterization or 'clean catch' samples; and third, all samples with $>100,000$ cfu/ml of a single pathogen. We adjusted the UTI definition⁴ of a growth of $\geq 50,000$ cfu/ml for 'clean catch' specimens because the study hospitals reported urine culture results in $<10,000$, 10,000-100,000, and $>100,000$ cfu/ml intervals. Urine bags were not used by any of the study sites and 'clean catch' was the default urine collection method.

2.3 | Data analysis

We used SPSS for Mac, version 27.0 (IBM Corp), for the statistical analyses. The study population was divided into two groups according to the registered temperature on arrival in the PED: The febrile

group had a temperature of $\geq 38.0^{\circ}\text{C}$ and the afebrile group had a temperature of $< 38.0^{\circ}\text{C}$. We then divided the febrile and afebrile groups into two age groups: ≤ 28 and 29–60 days based on the most relevant publications.^{9,15,16} In 2021, the American Academy of Paediatrics⁸ changed the age threshold for routine investigation with lumbar puncture and administration of antibiotics to 21 days. For that reason, we performed separate analyses for infants aged ≤ 21 days. The exact binomial interval method was used to calculate 95% confidence intervals (CIs). We used relative risk (RR) ratios with 95% CIs to compare the rates of SBIs between the febrile and afebrile infants.

3 | RESULTS

We included 1926 infants ≤ 60 days who had a documented temperature of $\geq 38.0^{\circ}\text{C}$ at home with fever without source. Of these, 702 (36%) were afebrile when they presented to the PED and 1224 (64%) were still febrile. These formed the febrile and afebrile groups, respectively. The patients' demographic data, clinical characteristics, and the investigations that were performed are shown in Table 1. Urine dipstick was performed in 92% of the febrile versus 77% of the afebrile infants. Three times as many blood cultures were performed on the febrile group and five times as many lumbar punctures.

The total prevalence of SBI in the afebrile group was 6.6% (95% CI 4.8–8.6) versus 15.4% (95% CI 13–18) in the febrile group, corresponding to an RR of 0.43 (95% CI 0.31–0.58). A UTI was the most common infection and the risk was lower in the afebrile group (RR 0.43, 95% CI 0.31–0.59). The RR of meningitis for the afebrile versus the febrile group was 0.58 (95% CI 0.12–2.87) (Table 2).

The risk of SBIs was lower for the afebrile infants in both age groups (≤ 28 and 29–60 days) with RRs of 0.40 (95% CI 0.25–0.64) and 0.43 (95% CI 0.29–0.65), respectively. This difference was mainly due to the lower UTI risk with RRs of 0.38 (95% CI 0.23–0.62) and 0.46 (95% CI 0.31–0.70), respectively. On the contrary, afebrile and febrile infants aged ≤ 28 days had the same meningitis risk with RR of 1.05 (95% CI 0.18–6.23) (Table 2). We separately analysed the infants aged ≤ 21 days (Table 3). There was also no difference in the risk of meningitis between the afebrile and febrile infants with a RR of 1.06 (95% CI 0.18–6.25).

4 | DISCUSSION

This study evaluated the SBI risk in infants ≤ 60 days with fever at home who were assessed at four Swedish PEDs. We divided the infants into two groups based on their temperature when they presented to the PEDs: Febrile group (temperature $\geq 38.0^{\circ}\text{C}$) and afebrile

TABLE 1 Patient demographics and clinical characteristics in infants ≤ 60 days without and with fever on presentation at the PED

Characteristics	0–28		29–60		0–60	
	Afebrile PED 243 (39)	Febrile PED 382 (61)	Afebrile PED 459 (35)	Febrile PED 842 (65)	Afebrile PED 702 (36)	Febrile PED 1224 (64)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Age (d), median (IQR)	18 (12–23)	18 (12–23)	46 (38–54)	46 (37–54)	38 (22–50)	38 (22–50)
Girls n (%)	103 (42)	157 (45)	206 (45)	363 (41)	309 (44)	520 (42)
Well-appearing n (%)	233 (96)	322 (84)	441 (96)	766 (91)	674 (96)	1088 (89)
Temp home, $^{\circ}\text{C}$ mean (SD)	38.3 (0.4)	38.6 (0.5)	38.3 (0.4)	38.6 (0.5)	38.3 (0.4)	38.6 (0.5)
Temp ED, $^{\circ}\text{C}$ mean (SD)	37.4 (0.4)	38.6 (0.5)	37.4 (0.4)	38.7 (0.5)	37.4 (0.4)	38.6 (0.5)
Duration av feber (h)						
<6	154 (63)	241 (63)	259 (56)	512 (61)	413 (59)	753 (61)
6–12	41 (17)	83 (22)	84 (18)	201 (24)	125 (18)	284 (23)
12–24	25 (10)	45 (12)	46 (10)	86 (10)	71 (10)	131 (11)
>24	9 (4)	12 (3)	54 (12)	28 (3)	63 (9)	40 (3)
Unkown	14 (6)	1 (0)	15 (3)	15 (2)	30 (4)	16 (1)
Investigations performed						
CRP	185 (76)	368 (96)	346 (75)	778 (92)	531 (76)	1146 (94)
WBC	92 (38)	289 (76)	158 (34)	516 (61)	250 (36)	805 (66)
Urine dipstick	177 (73)	356 (93)	365 (80)	774 (92)	542 (77)	1130 (92)
Urine culture	83 (34)	264 (69)	150 (33)	436 (52)	233 (33)	700 (57)
Blood culture	58 (24)	243 (74)	47 (11)	275 (33)	105 (15)	518 (42)
Lumbar puncture	16 (7)	123 (32)	11 (2)	70 (10)	27 (4)	203 (16)

Abbreviations: CRP, C-reactive protein; IQR, interquartile rate; PED, paediatric emergency department; SD, standard deviation; WBC, white blood cell count.

TABLE 2 Prevalence of serious bacterial infections and RR in infants 0–28 days and 29–60 days without and with fever on presentation at the PED

Serious bacterial infections	Afebrile PED	Febrile PED	RR (95% CI)
	N (%; 95% CI)	N (%; 95% CI)	
Infants 0–60 days n (%)	702 (36)	1224 (64)	
Any SBI	46 (6.6; 4.8–8.6)	188 (15.4; 13.4–17.5)	0.43 (0.31–0.58)
UTI all ^a	43 (6.1; 4.5–8.2)	174 (14.2; 12.3–16.3)	0.43 (0.31–0.59)
Bacteremia all ^a	5 (0.7; 0.2–1.7)	21 (1.7; 1.1–2.6)	0.41 (0.16–1.10)
Meningitis all ^a	2 (0.3; 0.0–1.0)	6 (0.5; 0.2–1.1)	0.58 (0.12–2.87)
Infants 0–28 days n (%)	243 (39)	382 (61)	
Any SBI	20 (8.2; 5.1–12.4)	78 (20.4; 16.5–24.8)	0.40 (0.25–0.64)
UTI all ^a	17 (7.0; 4.1–11.0)	71 (18.6; 14.8–22.9)	0.38 (0.23–0.62)
Bacteremia all ^a	3 (1.2; 0.3–3.6)	14 (3.7; 0.2–0.6)	0.34 (0.10–1.16)
Meningitis all ^a	2 (0.8; 0.1–2.9)	3 (0.8; 0.2–2.3)	1.05 (0.18–6.23)
Infants 29–60 days n (%)	459 (35)	842 (65)	
Any SBI	26 (5.7; 3.7–8.2)	110 (13.1; 10.9–15.5)	0.43 (0.29–0.65)
UTI all ^a	26 (5.7; 3.7–8.2)	103 (12.2; 10.1–14.6)	0.46 (0.31–0.70)
Bacteremia all ^a	2 (0.4; 0.1–1.6)	7 (0.8; 0.3–1.7)	0.52 (0.11–2.50)
Meningitis all ^a	0 (0.0; 0.0–0.8)	3 (0.4; 0.1–1.0)	–

Abbreviations: PED, paediatric emergency department; RR, risk ratio; SBI, serious bacterial infection; UTI, urinary tract infection.

^aAll cases, isolated or in any combination, because of the combination the sum of UTI, bacteremia, and meningitis exceeds the number of any SBI.

group (temperature <38.0°C). We found that the prevalence of SBIs was lower in the afebrile group, mainly due to the lower risk of UTI. The risk of meningitis was the same in the infants aged ≤28 days. These findings showed that different management approaches to afebrile and febrile infants could not be justified.

We found that afebrile infants had half the risk of having a UTI as febrile infants. Mintegi et al. and Ramgopal et al. also reported a 30% lower risk in afebrile infants.^{9,10,16} It is worth noting that a urine test was not performed on a quarter of afebrile infants in our cohort. Similar variation has been reported by other studies, where urine testing was as low as in our study.^{11,12,17,18} Although the risk of UTI in afebrile infants was only 6% in our study, this cannot be considered negligible and our data do not justify omitting urine testing in afebrile infants. Thus, this finding highlights the importance of urine test for all infants with reported fever, as recommended by all the current guidelines.^{7,8}

The prevalence of meningitis in our study was the same in the afebrile and the febrile infants ≤28 days. Ramgopal et al. reported similar results,¹⁶ while a study from Spain¹⁰ and one from Israel¹⁵

reported no cases of meningitis in the afebrile infants. At the time of our study, most guidelines recommended lumbar puncture for febrile infants ≤28 days. Despite this, a number of studies have shown variations in the rates of lumbar puncture.^{11–13,17} No studies have investigated the reasons for these different approaches, but it has been speculated that the absence of fever was a possible contributing factor.¹¹ We observed five times lower rate of lumbar punctures in the afebrile than febrile infants ≤28 days. In 2021, the American Academy of Paediatrics lowered the age threshold for routinely performing lumbar puncture to 21 days,⁸ which was previously proposed by Mintegi et al.⁷ Our separate analyses for infants ≤21 days showed similar risks for meningitis in febrile and afebrile infants. Similarly, lumbar puncture was performed less often in the afebrile infants. These differences in management were not supported by the results of our study since the risk of meningitis was the same in febrile and afebrile infants.

In our study, 60% of the infants ≤28 days had a reported fever for up to 6 h and 40% were afebrile when they presented to the PED. These findings were similar to previous studies.^{10,16} Other studies

TABLE 3 Prevalence of serious bacterial infections, RR, and investigations in infants ≤ 21 days without and with fever on presentation at the PED

SBI	Afebrile PED	Febrile PED	RR (95% CI)
	N (%; 95% CI)	N (%; 95% CI)	
Any SBI	161 (39)	255 (61)	
	12 (7.0; 3.9–12.7)	61 (23.9; 18.8–29.6)	0.31 (0.17–0.56)
UTI all ^a	9 (5.6; 2.6–10.3)	55 (21.6; 16.7–27.1)	0.26 (0.13–0.51)
Bacteremia all ^a	3 (1.9; 0.4–5.3)	13 (5.1; 2.7–8.6)	0.37 (0.11–1.26)
Meningitis all ^a	2 (1.2; 0.2–4.4)	3 (1.2; 0.2–3.4)	1.06 (0.18–6.25)
Investigations	N (%)	N (%)	
CRP	123 (76)	246 (96)	
WBC	65 (40)	196 (77)	
Urine dipstick	112 (70)	235 (92)	
Urine culture	50 (31)	168 (66)	
Blood culture	33 (20)	164 (64)	
Lumbar puncture	7 (4)	76 (30)	

Abbreviations: CRP, C-reactive protein; PED, paediatric emergency department; RR, risk ratio; SBI, serious bacterial infection; UTI, urinary tract infection; WBC, white blood cell count.

^aAll cases, isolated or in any combination, because of the combination the sum of UTI, bacteremia, and meningitis exceeds the number of any SBI.

have reported that only 25%–35% of afebrile infants ≤ 28 days with a history of fever developed a fever after admission, with a median time to the first elevated temperature of 5.6 h (interquartile range 3.1–11.4 h) and the risk of SBI and meningitis was high in these infants and very low in those who remained afebrile.^{9,15} In 2019, the Paediatric Emergency Care Applied Research Network proposed a clinical prediction rule for all febrile infants ≤ 28 days. This was based on urinalysis, procalcitonin, and absolute neutrophil count, without routine lumbar puncture and antibiotics.⁴ Maybe, a similar prediction rule combined with watchful observation, and serial biomarkers measurements,¹⁹ could be considered and investigated for afebrile, well-appearing infants. This would mean that lumbar puncture and routine antibiotics could be reserved for infants with persistent fever and/or rising biomarkers.

There were some limitations to this study. First, lumbar punctures and blood cultures were not routinely performed, and this may have resulted in an underestimation of the overall reported prevalence of meningitis and bacteremia. Furthermore, these investigations were much less likely to be performed in the afebrile infants, which may have amplified the reported differences between the afebrile and febrile groups. We reviewed all the patients' medical records, identified all revisits up to 10 days after their discharge, which was longer than the 2–3 days often used by other studies,^{11,12} and registered any new diagnoses. Therefore, we believe that the likelihood of missed cases of bacterial meningitis, which are not self-limiting, and clinically relevant bacteremia, was quite low. Second, we identified infants with fever registered in the electronic registration systems, as the main reason for visiting the PEDs. It is possible that another contact reason was registered on presentation such as vomiting, fatigue, or refusing to feed, especially for the afebrile infants. This may have resulted in an under-representation of afebrile infants in this study. However, the

proportion (36%) of afebrile infants in our study was slightly higher than in similar studies.^{10,16} Third, it is difficult to draw sound conclusions for the age subgroups analyses since the prevalence rates and the 95% CIs of the RRs were quite wide and overlapped. Fourth, we were not able to retrieve information on the administration of antipyretics by caregivers before they visited the PEDs and their possible effect on the infant's body temperature and general condition. Fifth, we did not have robust data on subsequent temperature measurements during the infants' time in the PED or any inpatient ward. These would have allowed us to extend our analyses, especially to investigate the proportion of infants who remained afebrile.

5 | CONCLUSION

Infants with a history of fever who were afebrile when they presented to four Swedish PEDs underwent fewer investigations than those who were still febrile. The SBI risk was lower in the afebrile infants, predominantly due to a lower risk of UTI, but the UTI risk was not low enough to omit urine testing. The risk of meningitis was similar between the afebrile and the febrile infants ≤ 28 days. This means that the results of our study do not justify different management approaches to infants with reported fever who are afebrile when they arrive in the PED.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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