

## Investigation of afebrile neonates with a history of fever

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### ABSTRACT

**Objective:** Our objective was to describe clinically significant infections in a cohort of afebrile neonates who underwent an emergency department (ED) septic workup because of the history of a measured fever at home.

**Methods:** Retrospective medical record review of all infants  $\leq 28$  days of age who presented to our tertiary care pediatric ED between Jan. 1, 1999, and Aug. 22, 2002, underwent lumbar puncture in the ED, had a reported temperature at home of  $\geq 38^{\circ}\text{C}$ , and an ED triage temperature of  $< 38^{\circ}\text{C}$ . Laboratory and radiographic results were tabulated.

**Results:** During the study period, 206 neonates underwent lumbar puncture in our ED. Of these, 108 were excluded because their home temperature was not documented, and 71 were excluded because they were still febrile on presentation to the ED. The study group consisted of the remaining 27 subjects, 4 of whom had received acetaminophen prior to ED arrival. Infections were confirmed in 10 (37%) subjects (3 urinary tract infections, 2 aseptic meningitis, 1 enterovirus meningitis, 1 respiratory syncytial virus bronchiolitis, 1 rotavirus enteritis and 2 pneumonias).

**Conclusions:** Clinically important infections are not uncommon among afebrile neonates undergoing ED septic workup because of a measured fever at home. Some diagnostic testing is warranted in this group, although the clinical utility and indications for specific test modalities remain unclear.

**Key words:** sepsis; occult; meningitis; pyelonephritis; virus

### RÉSUMÉ

**Objectif :** Notre objectif était de décrire les infections cliniquement significatives au sein d'une cohorte de nouveau-nés afebriles ayant subi un bilan septique au département d'urgence (DU) en raison d'antécédents de fièvre mesurée à la maison.

**Méthodes :** Une revue rétrospective fut effectuée des dossiers médicaux de tous les nouveau-nés  $\leq 28$  jours reçus au DU de notre hôpital pédiatrique de soins tertiaires entre le 1<sup>er</sup> janvier 1999 et le 22 août 2002 et qui subirent une ponction lombaire au DU, avaient une fièvre de  $\geq 38^{\circ}\text{C}$  à la maison et une température de triage au DU  $< 38^{\circ}\text{C}$ . Les résultats des radiographies et de laboratoire furent totalisés.

**Résultats :** Au cours de la période à l'étude, 206 nouveau-nés subirent une ponction lombaire à notre DU. Parmi ceux-ci, 108 furent exclus parce que leur température à la maison n'avait pas été notée et 71 furent exclus parce qu'ils étaient encore fébriles au DU. Le groupe à l'étude se composait de 27 sujets, dont quatre avaient reçu de l'acétaminophène avant leur arrivée au DU. Des in-

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fections furent confirmées chez 10 sujets (37 %) (trois infections urinaires, deux méningites à liquide clair, une méningite à entérovirus, une bronchiolite à virus respiratoire syncytial, une entérite à rotavirus et deux pneumonies).

**Conclusions :** Les infections cliniquement importantes ne sont pas rares chez les nouveau-nés afebriles soumis à un bilan septique au DU en raison d'une fièvre mesurée à la maison. Certaines épreuves diagnostiques sont justifiées parmi ce groupe, bien que l'utilité clinique et les indications pour des modalités d'épreuves spécifiques demeurent incertaines.

## Introduction

For the past decade it has been recommended that all neonates (i.e.,  $\leq 28$  days of age) with a temperature  $\geq 38^\circ\text{C}$  undergo diagnostic testing for bacterial infections, receive empiric intravenous antibiotics, and be admitted to the hospital.<sup>1</sup> This straightforward and conceptually simple approach continues to be recommended<sup>2,3</sup> even though more than 80% of febrile neonates do not harbour serious bacterial infections.<sup>4-8</sup> Given the difficulties in using the physical examination by itself to identify neonates who harbour serious bacterial infections<sup>4,5</sup> and the potentially devastating consequences of untreated bacterial infections in febrile neonates, a conservative approach, including laboratory testing, antibiotic administration and hospital admission seems prudent. At the present time the generally accepted approach to the management of a neonate who presents to the emergency department (ED) with a temperature  $\geq 38^\circ\text{C}$  is clear and minimally controversial.

The significance of neonatal defervescence, however, remains controversial. It is unclear what investigations and disposition are indicated for neonates who have a history of fever at home, but are afebrile on arrival at the ED. A single study from 1987 suggested that the incidence of serious bacterial infections (SBIs) in neonates who defer- vesce prior to ED presentation is very low and might even be zero;<sup>9</sup> however, at our institution, many of these neonates undergo a full septic workup, receive antibiotics, and are admitted to hospital. In addition, our ED physicians have incorporated viral testing that was not available in 1987 into the evaluation of afebrile neonates with a history of fever.

If neonates who defer- vesce prior to ED arrival are at extremely low risk of having an identifiable infection, it is conceivable they could be managed without laboratory testing, antimicrobials or hospitalization. This minimalist strategy would avoid exposing these neonates to iatrogenic risks such as nosocomial infections and medication errors,<sup>10</sup> avoid unnecessary testing, treatment and hospitaliza- tion, and relieve the emergency physician of a frequently

time-consuming and technically challenging laboratory evaluation.

The objective of our study was to describe the clinically significant infections identified in a cohort of afebrile neonates who underwent an ED septic workup because of the history of a measured fever at home.

## Methods

### *Setting and patients*

This retrospective medical record review was conducted at Loma Linda University Medical Center and Children's Hospital, Loma Linda, Calif., a tertiary care pediatric ED. Eligible subjects included all neonates  $\leq 28$  days of age who presented between Jan. 1, 1999, and Aug. 22, 2002, with a history of febrile illness, and who underwent lumbar puncture during their ED visit (Fig. 1). Infants were excluded if their reported home fever did not include a numeric value (e.g., the baby "just felt warm"), if their ED triage temperature was  $\geq 38^\circ\text{C}$  or not recorded, or if their medical record was unavailable.

### *Data collection*

A trained data abstractor (T.S.), who was periodically monitored by the principal investigator (L.B.), reviewed the remaining medical records using a standardized data collection form.<sup>11</sup> The abstracted data included date of birth, date of visit, reported home temperature, medications administered at home (including antipyretics), ED triage temperature, bacterial culture results (including blood, urine, cerebrospinal fluid [CSF], stool and wound cultures), CSF bacterial antigen studies, CSF white and red blood cell counts, viral study results (including enterovirus, respiratory syncytial virus, rotavirus and herpes simplex virus [HSV] studies), microscopic urinalysis, the radiologist's final interpretation of a chest radiograph if performed, results of other diagnostic imaging and electroencephalograms, antimicrobial treatment administered, the condition of the patient at discharge and discharge diagnosis. Fahrenheit temperatures were converted to centi- grade using the formula,  $C = (F - 32) \times 0.5556$ .

### Data analysis

Using a random number generator, we selected 22% of the main study group for inter-rater reliability testing. A second trained data abstractor, blinded to the results of the first, reviewed these randomly selected records for selected variables. Results of the 2 reviews were compared using a concordance rate for continuous variables and the kappa statistic for categorical variables. Other analyses were limited to descriptive statistics. Due to non-normal distributions, our data are reported as medians, ranges and interquartile ranges (IQRs). Statistical analyses were performed using Stata 8 (STATA Corporation, College Station, Tex.). This study was approved by our Institutional Review Board.

### Results

We identified 206 neonates  $\leq 28$  days of age who underwent ED lumbar puncture during the study period. Of these, 108 were excluded because they did not have a home temperature documented, and 71 were excluded because they were still febrile on presentation to the ED. The main study group therefore included 27 patients who had a reported temperature at home  $\geq 38^\circ\text{C}$  and who were afebrile at the time of ED arrival. Medical records, ED

triage temperatures, and the home medication listing were available for all subjects.

Table 1 and Table 2 show that the study subjects were from 3 to 27 days of age (median 15 days; IQR 6–23 d) and predominantly male (63%). Reported home temperatures ranged from  $38.0^\circ\text{C}$  to  $40.6^\circ\text{C}$  (median  $38.3^\circ$ ; IQR  $38.2^\circ$ – $38.8^\circ$ ), while ED temperatures ranged from  $35.9^\circ\text{C}$  to  $37.9^\circ\text{C}$  (median  $37.3^\circ$ ; IQR  $36.9^\circ$ – $37.7^\circ$ ). Ten of the subjects (37%) had identifiable infections (Table 1) and 17 subjects did not (Table 2). No cases of bacterial meningitis, *Listeria monocytogenes*, Group B *Streptococcus* or HSV were identified. No subjects had concurrent viral and bacterial infections identified.

Two subjects demonstrated CSF pleocytosis without positive bacterial or viral testing. One of these, a 15-day-old male, underwent lumbar puncture after antimicrobials (ampicillin, cefotaxime and acyclovir) were administered. In this case, CSF culture, CSF bacterial antigen testing, and HSV type 1 and 2 tests were negative despite significant pleocytosis (1440 white blood cells/mm<sup>3</sup> and 6 red blood cells/mm<sup>3</sup>). A brain magnetic resonance imaging revealed edema, and an electroencephalogram demonstrated right temporal lobe spikes suggestive of viral meningoencephalitis. The other subject, a 23-day-old female, underwent lumbar puncture, which demonstrated 485 white

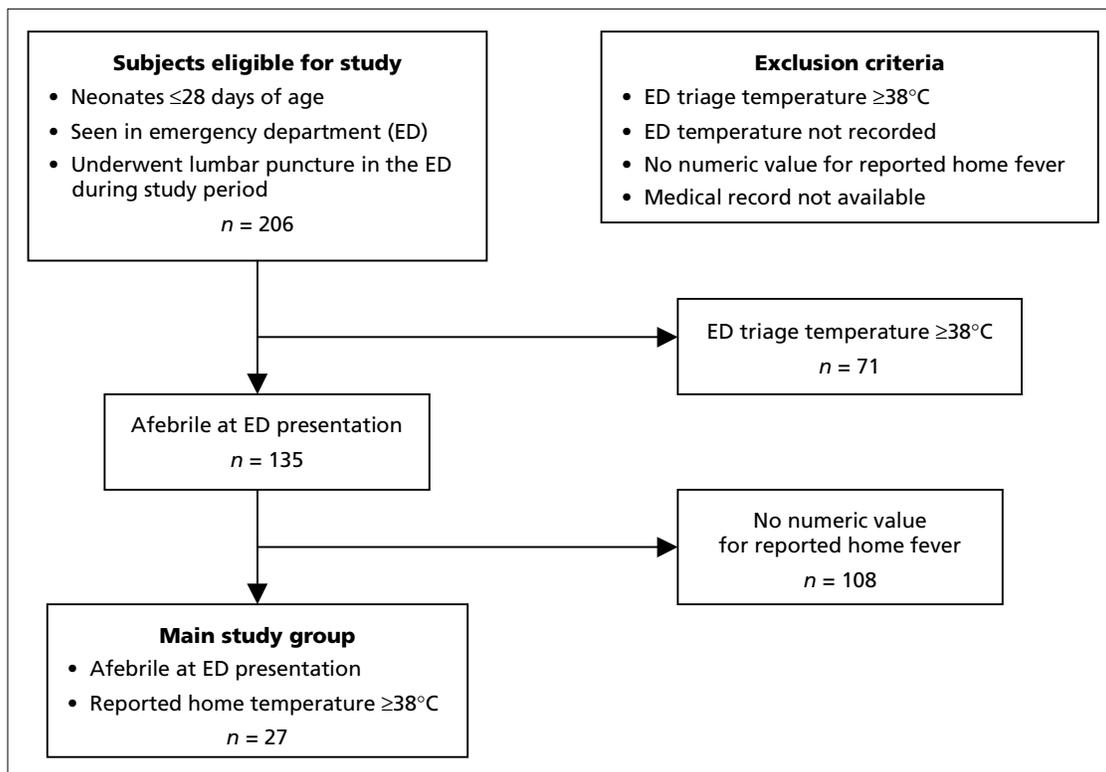


Fig. 1. Subject selection flow diagram

blood cells/mm<sup>3</sup> and 495 red blood cells/mm<sup>3</sup>. Again, CSF cultures, CSF bacterial antigen testing, and HSV type 1 and 2 tests were negative.

Four subjects received home antipyretics (acetaminophen in every case). Three of these 4 had identifiable infections (2 *Escherichia coli* urinary tract infections [UTIs] and one rotavirus diarrhea) (Table 1). All 27 subjects received antimicrobials in the ED. Cefotaxime, ampicillin and acyclovir were the most common antimicrobials administered, given to 25, 24 and 8 subjects respectively. All 27 subjects were ultimately discharged from the hospital in good condition.

Inter-rater reliability testing revealed excellent agreement between the 2 independent data abstractors. The kappa statistic was 1.0, indicating perfect agreement for the following variables: medications administered at home, bacterial culture results, CSF bacterial antigen studies, viral study results, and the radiologist's final interpretation of chest radiography. The concordance rate was 100% for all CSF cell counts and 83% for recorded temperatures.

## Discussion

In this study, identifiable infections were common in afebrile neonates who underwent an ED septic workup because of the history of a fever at home. We are aware of only 1 other study addressing this patient population. In 1987, Bonadio<sup>9</sup> described 109 consecutive previously well full-term neonates who had either a tactile or rectal fever at home, were evaluated in the ED, and underwent lumbar puncture. There are important differences between studies.

Bonadio excluded neonates who had received antipyretics within 4 hours and hypothermic neonates with a temperature <36°C. In the Bonadio study, 54 neonates were febrile at home and afebrile on ED presentation — comparable to the patients described here. Bonadio found no SBIs in

**Table 2. Findings for the 17 afebrile neonates (≤28 days) with a history of fever (≥38°C) who were found to not have an identifiable infection**

Age, days	Gender	Recorded temperature, °C	
		At home	On arrival at ED
3	M	38.2	37.9
3*	M	39.2	37.3
3	F	38.1	37.8
3	M	38.7	37.9
5	F	38.9	35.9
6	M	38.3	37.1
6	F	38.3	37.1
11	M	38.7	37.6
13	F	38.3	36.9
16	M	38.2	36.2
19	F	38.1	37.7
20	M	39.2	35.9
22	M	38.4	37.7
24	M	38.6	37.1
25	F	38.0	37.9
25†	M	38.8	36.9
27	M	40.6	37.9

ED = emergency department

\*This patient had 98 white blood cells per high-powered field in the urinalysis with a negative urine culture.

†The only patient in this group who received an antipyretic, either at home or in the ED.

**Table 1. Findings for the 10 (37% of study subjects) afebrile neonates (≤28 days) with a history of fever (≥38°C) who were found to have an identifiable infection**

Age, days	Gender	Recorded temperature, °C		Neonate was administered antipyretic either at home or in ED	Identified infection
		At home	On arrival at ED		
4	M	38.2	37.6	No	Pneumonia
6	M	38.3	36.9	No	Enterovirus meningitis
14	F	38.2	37.4	Yes	<i>Escherichia coli</i> UTI
15	M	38.7	36.5	No	RSV bronchiolitis
15	M	38.9	36.5	No	Aseptic meningitis
21	M	38.3	37.2	No	Pneumonia
21	F	38.7	37.8	Yes	Rotavirus enteritis
23	F	38.3	37.5	No	Aseptic meningitis
23	M	39.4	37.4	No	<i>E. coli</i> UTI
27	F	38.3	37.2	Yes	<i>E. coli</i> UTI

ED = emergency department; UTI = urinary tract infection; RSV = respiratory syncytial virus

these 54 neonates, but did not report the results of any viral testing.

Assessing Bonadio's data using contemporary methodology,<sup>12</sup> an estimate of the upper limit of the 95% confidence interval (CI) for the incidence of SBIs can be calculated. Although Bonadio's incidence of SBIs was 0%, the upper limit of the 95% CI is 5.5%. In other words, the true incidence of SBIs as defined by Bonadio<sup>9</sup> is most likely between 0% and 5.5%.<sup>13</sup> If the true incidence is 0%, most clinicians would stop testing, treating and admitting these neonates; however, if the true incidence is over 5%, many clinicians would probably test, treat and admit these neonates to avoid a 1 in 20 chance of missing an SBI.<sup>14</sup> This analysis suggests that Bonadio's study has too few subjects to determine if neonates who are febrile at home and afebrile on presentation to the ED can be spared a "full septic workup." In our study, we identified 3 *E. coli* UTIs, suggesting that the incidence of SBIs is not 0% and that testing for UTIs in this group would be prudent.

One major difference between the 2 studies relates to the use of viral testing. In 1987 it was not possible to perform viral testing in any clinically meaningful or timely manner in the ED.<sup>15-21</sup> As viral testing becomes more rapid, more available and less expensive, it will also become more common. Viral infections can present subtly, with only fever and nonspecific signs,<sup>4,22,23</sup> but effective treatments are available for some conditions (e.g., acyclovir for HSV).<sup>24</sup> There is growing evidence that viral testing influences physician behaviour,<sup>18</sup> hence the role of specific viral tests in the ED management of neonates will need to be better defined.

### **Limitations**

Our conclusions are not generalizable to all neonates with a history of "fever at home" because we could not identify all such cases. "Possible fever at home" is not reliably recorded in the medical record and is not computer searchable. Therefore, we chose to select subjects by age and based on the performance of a lumbar puncture (reliably recorded and searchable parameters), the latter being a marker for neonates who underwent a full septic workup. This process eliminated neonates who had no testing or limited testing — those at the "well" end of the spectrum. Unfortunately, because of the retrospective nature of our study, we cannot describe the excluded neonates or their outcomes, and this group may be less likely to harbour clinically significant infections. It is likely that the study subjects, based on having a lumbar puncture, appeared more ill and were

more likely to undergo expanded testing and hospitalization regardless of their temperature. This may not be a substantial limitation, however, as the signs and symptoms of illness in neonates can be subtle and fever may be the only unambiguous sign of serious illness at the time of presentation.<sup>4,5,7,22,23</sup>

Our sample size is small, which limits the ability to estimate the true incidence of clinically significant infections in the population of interest; nevertheless, our study demonstrates that the incidence is not 0%. Further, our sample size precludes drawing any conclusions about the clinical utility of individual tests.

We included neonates who received antipyretics prior to ED arrival. It is possible that neonates who defervesce after antipyretic administration differ from those who defervesce spontaneously. We overcome this limitation by presenting outcomes for both groups of neonates, so readers can determine whether to "lump" or "split" the data, as they see fit.

We excluded infants whose caregivers could not provide a numeric value for temperature at home because of concerns that some of these neonates were actually afebrile. Although Graneto and Soglin reported a sensitivity of 84% and specificity of 76% for maternal detection of fever by palpation,<sup>25</sup> these authors included children up to 10 years of age, and the number of neonates studied is unclear. We are unaware of any study that reports on the parental ability to detect fever by palpation in neonates.

### **Future areas of study**

Although our data suggest that testing for UTIs in this group would be prudent, we cannot conclude that defervescence eliminates the need to look for other serious infections, such as pneumonia, bacteremia or bacterial meningitis. Nor can we identify clinical predictors useful in guiding the use of specific testing modalities such as blood cultures and viral studies. All of these are areas for future prospective study.

### **Conclusion**

Clinically important infections are not uncommon among afebrile neonates undergoing ED septic workup because of a measured fever at home. Some diagnostic testing is warranted in this group, although the clinical utility and indications for specific test modalities remain unclear.

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**Competing interests:** None declared.

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