Invasive bacterial infections in young afebrile infants with a history of fever

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ABSTRACT

Objective  To determine the prevalence of invasive bacterial infections (IBI, pathogenic bacteria in blood or cerebrospinal fluid) in infants less than 90 days old with fever without a source related to the presence or absence of fever on arrival to the emergency department (ED).

Setting  Paediatric ED of a tertiary teaching hospital.

Patients  We included infants less than 90 days old with a history of fever evaluated in the ED from 2003 to 2016.

Main outcomes and measures  The prevalence of IBI in patients with a history of fever who were febrile and afebrile on arrival to the ED.

Results  We included 2470 infants: 678 afebrile and 1792 febrile when evaluated in the ED. Fifty-nine (2.4%) were diagnosed with an IBI (bacteraemia 46, meningitis 7 and sepsis 6): 16 in the group of afebrile infants with a history of fever (2.4%, 95% CI 1.4 to 3.8 vs 43 in the febrile group, 2.4%, 95% CI 1.8 to 3.2). Of the 16 afebrile infants with a history of fever diagnosed with an IBI, 14 were well appearing. The rate of non-IBI (pathogenic bacteria in urine or stools) was similar in both groups (15.5% and 16.7%).

Conclusions  The prevalence of IBI in infants ≤90 days with a history of fever is similar regardless of the presence of fever on the arrival at the ED. The approach to infants with a history of fever who are afebrile in the ED should not differ from that recommended for infants who are febrile in the ED.

INTRODUCTION

Management of febrile infants less than 3 months of age remains challenging. The rate of serious bacterial infections (SBI) is higher among these patients when compared with older children. In addition, it can be difficult to distinguish between a minor febrile illness and one that is life threatening. Thus, a careful assessment and the use of laboratory studies are recommended to identify infants at both high and low risks of invasive bacterial infection (IBI).1–3 Since the classic Rochester,1 Philadelphia2 and Boston6 criteria were published, several studies have tried to find the best set of criteria to identify those infants who are at a low risk of having a bacterial infection.2–6 Nevertheless, regardless of the protocol used, current adherence to any of them in clinical practice is low.9 10 There is a great variation in testing, treatment and overall resource utilisation in the management of these infants.11–14

In young infants with a history of fever, it is not uncommon to be afebrile when evaluated by the physician in the emergency department (ED). Further evaluation according to age and clinical findings has been recommended, even if the infant is afebrile at the time of presentation.15 Nevertheless, this recommendation is not always followed,10 mainly when the afebrile infant appears well in the ED. The prevalence of SBI, and specifically IBI, has been reported to be lower in young afebrile infants with a history of fever when compared with those who are febrile when evaluated by a physician.15 16 In a study conducted by office-based paediatricians in the USA, including 3066 febrile infants less than 3 months of age, the prevalence of IBI was significantly lower in those who were afebrile in the office.16 In the most commonly used set of criteria for the management of these children,4–8 no specific recommendation is given about the management of young afebrile infants with a history of fever.

To our knowledge there is no recent study comparing the prevalence of IBI in febrile infants less than 90 days with fever without a source (FWS) related to the presence or absence of fever on arrival at the ED.

The objectives of the study are to determine the prevalence of IBI and non-IBI in febrile infants less than 90 days with FWS related to the presence or absence of fever on arrival to the ED.
METHODS

Design
We conducted a prospective registry-based cohort study including all the infants less than 90 days of age with FWS evaluated in our paediatric ED over a 13-year period (September 2003 to August 2016). Our ED is in a tertiary hospital and each year receives around 55,000 children less than 14 years of age, including about 2300 infants <90 days. Infants were classified related to the rectal temperature registered on the arrival to the ED:

► febrile group: temperature greater than 38°C
► afebrile group: temperature less than 38°C.

Definitions

► FWS: axillary or rectal temperature measured at home ≥38°C, or rectal temperature measured in the ED ≥38°C in an infant in whom after history and physical exam it is not possible to identify the source of the fever (including normal chest auscultation and an absence of signs of acute otitis media and bone, joint and soft tissue infection).

► Well appearing: normal findings according to paediatric assessment (appearance, work of breathing and circulation to skin), as assessed by the paediatric emergency physician in charge (staff paediatrician with specific training in paediatric emergency medicine).

► Previously healthy infant: born at term, not treated for unexplained hyperbilirubinaemia, not hospitalised longer than the mother, not receiving current or previous antimicrobial therapy, no previous hospitalisation and no chronic or underlying illness.

► SBI:
  – IBI: isolation of a bacterial pathogen in a blood or cerebrospinal fluid (CSF) culture. *Staphylococcus epidermidis, Propionibacterium acnes, Streptococcus viridans* and *Diphtheroids* were considered contaminants.
  – Occult bacteraemia: presence of pathogenic bacteria in the blood of a well-appearing febrile infant in the absence of an identifiable focus of infection.
  – Non-IBI: urinary tract infections (UTI; urine culture with growth of ≥10,000 cfu/mL with leukocyturia associated) and bacterial gastroenteritis (isolation of bacteria in stool culture).
  – Possible bacterial infection: infants classified with possible UTI (positive urine culture without leukocyturia) and those with a final diagnosis of pneumonia or acute otitis media with no positive bacterial culture.
  – Sepsis: we used the sepsis criteria published by Goldstein *et al*17 with only the following modification: well-appearing patients with fever and leucocytosis were not diagnosed with sepsis if they did not have any other sepsis criteria (tachycardia, bradycardia, tachypnoea or signs of organ dysfunction).
  – Urine samples for culture were collected by bladder catheterisation or suprapubic aspiration.

Data collection
In 2003, we started a prospective electronic registry in our ED, including all the infants less than 90 days of age brought to the ED with FWS. Patients afebrile in the ED and in whom fever at home has been only subjectively assessed by parents on touch, without the use of a thermometer, were not included in the registry. The database includes the following: demographic characteristics, medical history, duration of fever, temperature recorded, appearance of the child, findings on physical examination, tests performed, treatment administered, disposition and final diagnosis. In addition, we monitored the progress of the patients: by reviewing the medical records of those who were admitted to ward; and by conducting telephone interviews for those who were managed as outpatients. Interviews were performed within a month after the visit to the ED by medical residents, after a period of training. In all cases, the residents asked specifically about: the final diagnosis, the administration of antibiotics and admission to any hospital after the visit to our ED. If it was not possible to contact the caregivers after three calls, the electronic registries of the ED and the public health system were used to identify and review any subsequent visit to a primary care centre or to any other hospital. The resulting registry contained data entered manually by paediatric residents after training. A paediatric emergency physician reviewed the data after entry.

Exclusion criteria

► patients afebrile at home and in whom fever was first detected at the ED;
► patients in whom the temperature measured at home or on arrival at the ED was not recorded on the medical record;
► patients in whom fever was detected at home exclusively by touch;
► patients with fever with a source.

Local protocol for the management of infants <90 days of age with FWS

Our protocol for the management of infants <90 days of age with FWS recommends the following in all cases: collection of sterile urine sample, urine dipstick test, complete blood cell count, measurement of C-reactive protein (CRP) and procalcitonin (PCT) levels (the latter since 2007), and blood and urine cultures, regardless of the presence of fever in the ED.

We recommend lumbar puncture (LP) to collect CSF in the following cases: all infants who are not well appearing or have clinical manifestations suggestive of bacterial meningitis; all infants <21 days of age; considered in those with abnormal blood test results (absolute neutrophil count >10 000/μL, CRP >20 mg/L and strong if PCT ≥0.5 ng/mL).

Infants who met the low-risk criteria are recommended to stay for up to 24 hours in the short-stay unit of the ED. We do not perform any routine interventions (tests or treatments except for antipyretics) while these infants stay in the short-stay unit. If no clinical deterioration is noted, infants feed well, parents understand the follow-up instructions and a follow-up by the primary care physician is ensured in the next 24 hours, these infants are managed as outpatients without antibiotic therapy. If any of these conditions are not fulfilled, we admit the infant to hospital.

Outcome measures

The primary outcome measure was the proportion of patients diagnosed with an IBI. We compared the prevalence of IBI between febrile and afebrile patients on arrival to the ED.

The secondary outcome measure was the proportion of patients diagnosed with a non-IBI. We compared the prevalence of non-IBI between febrile and afebrile patients on arrival to the ED.
The statistical analysis was carried out using the IBM SPSS Statistics for Windows (V22). Normally distributed data were expressed as mean±SD, non-normally distributed data as median and IQR and categorical variables were reported as percentages. For non-normally distributed data, comparisons were performed by using Mann-Whitney U tests, and comparisons of normally distributed data were performed by using independent samples t-tests. For categorical data, the χ² test was used. A P value less than 0.05 was considered statistically significant.

Ethics/human subjects
Given that all the data were extracted from a database in which the patient identities were anonymised and inclusion in the registry did not imply any additional interventions, informed consent was not required.

RESULTS
During the study period, we registered 3081 episodes corresponding to infants less than 3 months of age with FWS. Of these, 2470 (80.1%) had an axillary or rectal temperature measured at home ≥38°C and both the temperatures registered at home and the ED were recorded. The lowest rectal temperature recorded at the ED was 35.9°C. Of the 2470 infants, 678 (27.4%, 95% CI 25.7 to 29.2) were afebrile on the arrival to the ED and 1792 (72.5%, 95% CI 70.7 to 74.2) were febrile (figure 1).

The characteristics of the patients in both groups are shown in table 1.

Fifty-nine infants (2.4%, 95% CI 1.8 to 3.0) were diagnosed with an IBI (bacteraemia 46, meningitis 7 and sepsis 6) and 405 (16.4%, 95% CI 15.0 to 17.9) with a non-IBI. Of the 678 infants in the afebrile group, 16 were diagnosed with an IBI (2.4%, 95% CI 1.4 to 3.8 vs 43 in the febrile group, 2.4%, 95% CI 1.8 to 3.2) and 105 with a non-IBI (15.5%, 95% CI 12.9 to 18.4 vs 300 in the febrile group, 16.7%, 95% CI 15.1 to 18.5).

The distribution of the IBIs diagnosed is shown in table 2. Bacteria isolated from both groups of patients are shown in table 3. Investigations performed in these infants are described in table 4.

All the patients diagnosed with bacterial meningitis (7) were febrile when evaluated in the ED.

DISCUSSION
Our study found that the prevalence of IBI in infants ≤90 days with a history of fever is not influenced by the presence of fever
when the infant is evaluated in the ED. Our results show that the recommendation for further evaluation according to age and clinical findings of these infants is adequate, even in those afebrile and well appearing when evaluated by the physician. It has been stated that children who are afebrile but have a history of fever should be managed like children who are febrile. In our series, young afebrile infants with a history of fever accounted for around 25% of febrile young infants admitted to the ED.

The rate of SBI and IBI in young afebrile infants with a history of fever has been addressed in two previous studies. In both studies, the prevalence of bacterial infections was lower in young infants with a history of fever who were afebrile at the time of evaluation compared with those who were febrile. The first study was conducted in 1987. Since then, significant changes in the epidemiology of bacterial pathogens have occurred. The use of intrapartum antibiotic prophylaxis has reduced the incidence of early-onset infections caused by group B Streptococcus and the introduction of pneumococcal conjugate vaccines has also decreased SBI rates in these patients. This may explain the differences we found. The second study was conducted outside of the hospital setting.

No recent study has addressed the prevalence of SBI in young afebrile infants with a history of fever in the ED. In our series, the rate of IBI in young infants with a history of fever did not vary related to the presence or absence of fever on the arrival to the ED. Thus, the approach to young infants with a history of fever should not depend on the temperature measured in the ED. In addition, the vast majority of the IBI in young afebrile infants with a history of fever occurred in infants who were well appearing. It has been reported that practitioners relying on their clinical judgements were at least as sensitive as the current guidelines in identifying bacteraemia and bacterial meningitis while sparing many infants unnecessary hospitalisation and tests. Our results differ substantially from this. The rate of IBI in well-appearing young febrile infants is high and justifies laboratory tests in young febrile infants, including those who are afebrile on the arrival to the ED, even when they are well appearing. Furthermore, nowadays, infants are brought very early to the ED increasing the difficulty of distinguishing between a minor febrile illness and one that is life threatening.

The distribution of SBI showed differences between afebrile and febrile children. All infants diagnosed with bacterial meningitis were febrile on the arrival to the ED. There were only seven infants with bacterial meningitis so this finding has to be considered cautiously. The distribution of the bacteria isolated from these children also showed differences between the two groups. Escherichia coli was responsible for the majority of the IBI in afebrile patients. In infants who were febrile on the arrival to the ED, a larger variation of bacteria was noted. Other studies are needed to confirm these findings.

Substantial variability has been observed in the ED management of the febrile young infant. Only two-thirds of febrile neonates ≤28 days old received recommended ED management in a multicentre study. This is particularly worrisome as this is the age group at highest risk for SBI. The reasons some febrile neonates did not receive the recommended ED management are unclear. Nevertheless, the authors argued that there are some potential explanations, specifically the fact that patients may present with ‘fever’ by history but not actually have a fever documented at home or in the ED. In fact, in our study, blood tests and CSF exam were less frequently obtained in infants who were afebrile in the ED.

Finally, it has to be noted that the National Institute for Health and Care Excellence guidelines recommend not to routinely use the oral and rectal routes to measure the body temperature of children aged 0–5 years. Specifically, they recommend for infants under the age of 4 weeks to measure body temperature with an electronic thermometer in the axilla, and for children 4 weeks to 5 years of age to measure by electronic or chemical dot thermometer in the axilla or infrared tympanic thermometer. Nevertheless, to our knowledge, no study has validated routes of fever presentation in young infants when evaluated for SBI and large studies are needed to analyse the adequacy of this recommendation in these children.

The following limitations of our study should be noted. It was not a multicentre study, so the results are difficult to compare with national data. The prevalence of SBI in young afebrile infants with a history of fever is low. In a multicentre study, the rate of IBI in young afebrile infants with a history of fever did not vary related to the presence or absence of fever on the arrival to the ED. Nevertheless, to our knowledge, no study has validated routes of fever presentation in young infants when evaluated for SBI and large studies are needed to analyse the adequacy of this recommendation in these children.

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extrapolate to other populations. Nevertheless, we think that results are likely to be similar to other settings where young febrile infants are brought to the ED to be evaluated early in the course of their illness. We did not record the way the temperature was measured at home and it was impossible for us to analyse the accuracy of different ways to measure temperature. Nevertheless, this was not the objective of the study. We also did not record if caregivers gave an antipyretic to their infants before coming to the ED and if this influenced the temperature and the appearance of the infant when evaluated. Most of the febrile young infants brought to the ED did not receive antipyretics before coming, but we did not specifically record this. We only included children with FWS, and so these results cannot be applied to infants with fever with a focus. Finally, not all the infants got all the laboratory tests, mainly LP. Although this could mean that the prevalence of bacterial meningitis was underestimated, the subsequent monitoring undertaken suggests that it is unlikely that cases were missed. Furthermore, it would not currently be ethical to perform this test on all infants only for research purposes. On the other hand, blood cultures were obtained in more than 90% of the patients, although it was less frequently obtained in infants who were afebrile in the ED. Nevertheless, we do not think that this may bias the results obtained.

We conclude that the prevalence of SBI, and specifically IBI, in infants less than 90 days old with a history of fever at home does not vary depending on the presence of fever on the arrival at the ED. The approach to infants with a history of fever who are afebrile when evaluated in the ED needs to be similar to those infants with fever when evaluated by the physician. The absence of fever in the ED does not place these infants in a low-risk group, even when they are well appearing.

Contributors SM conceptualised and designed the study, supervised data collection, analysed the data, wrote the initial draft of the manuscript and approved the final manuscript as submitted. BG collaborated in the design of the study, supervised data collection, critically revised the manuscript and approved the final manuscript as submitted. AC and HD collaborated in the design of the study, collected data, critically revised the manuscript and approved the final manuscript as submitted. JH collaborated in the design of the study, critically revised the final manuscript and approved the final manuscript as submitted.

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