Outpatient management of selected young febrile infants without antibiotics

Santiago Mintegi, Borja Gomez, Lidia Martinez-Virumbrales, Oihane Morientes, Javier Benito

ABSTRACT

Objective To analyse the outpatient management of selected febrile infants younger than 90 days without systematic lumbar puncture and antibiotics.

Methods A prospective registry-based cohort study including all the infants ≤90 days with fever without a source (FWS) who were evaluated in a paediatric emergency department (ED) over a 7-year period (September 2007–August 2014). We analysed the outcome of those infants with low-risk criteria for serious bacterial infection (SBI) managed as outpatients without antibiotics and without undergoing a lumbar puncture. Low-risk criteria: Well appearing, older than 21 days of age, no leucocyturia, absolute neutrophil count <10 000, serum C reactive protein <20 mg/L, procalcitonin <0.5 ng/mL and no clinical deterioration during the stay in the ED (always <24 hours).

Results 1472 infants with FWS attended the ED. Of these, 676 were classified to be at low risk for SBI without performing a lumbar puncture. After staying ≤24 hours in the short-stay unit of the ED, 586 (86.6%) were managed as outpatients without antibiotics. Two patients were diagnosed with SBI: one occult bacteraemia and one bacterial gastroenteritis. Both were afebrile when evaluated again and did well. No patient returned to the ED due to clinical deterioration. Fifty-one infants (8.7%) returned to the ED mainly due to persistence of fever or irritability. None was diagnosed with definite SBI or non-bacterial meningitis.

Conclusions Outpatient management without antibiotics and systematic lumbar puncture is appropriate for selected febrile infants younger than 3 months of age with close follow-up.

INTRODUCTION

Management of febrile infants <3 months of age is challenging. The rate of serious bacterial infections (SBIs) is higher among these patients when compared with older children, and it is recommended that they are managed more aggressively.

However, there is a great variation in testing, treatment and overall resource utilisation in the management of these infants. Classically, febrile infants <3 months of age would undergo a complete evaluation for sepsis, including a lumbar puncture, and would be admitted to a hospital for intravenous antibiotics for at least 48 hours. This may lead to unnecessary hospitalisations, nosocomial infections, non-judicious use of antibiotics, emergence of resistant bacteria and adverse effects of antibiotics. Currently, it is accepted that not all febrile infants <3 months of age have to be admitted or have to receive antibiotics.

What this study adds?

▸ Young febrile infants, classified as low risk for SBI, can be adequately managed as outpatients without antibiotics and lumbar puncture, if close follow-up is available.

▸ In these selected infants the negative effects associated with empirical use of antibiotics and hospitalisations can be avoided.

addition, omitting lumbar puncture may be considered in selected febrile young infants.

In fact, most of these infants have a benign viral disease. Thus, selected febrile young infants can be included in a low-risk group for SBI, be observed and thereby avoid unnecessary hospitalisation and antibiotic administration.

In the last decades, there have been substantial changes in this group of patients. Most of them are brought to the emergency department (ED) very early, the main bacterial pathogens involved in invasive infections have changed and new blood tests are available to help detect patients with SBI.

Different approaches for these patients including C reactive protein (CRP) and procalcitonin (PCT) have been developed. A sequential approach to these children, including both these biomarkers, has been shown to be highly sensitive in identifying those patients who are suitable for management as outpatients, including those coming to the ED early in the course of their disease.

This approach evaluates sequentially the general appearance of the infant, the age and result of the blood biomarkers, has been shown to be highly sensitive in identifying those patients who are suitable for management as outpatients, including those coming to the ED early in the course of their disease.

What’s already known on this topic?

▸ A sequential approach to young febrile infants, including C reactive protein and procalcitonin can identify those at low risk for SBI.

▸ These low-risk infants could be managed as outpatients.
outpatients whose treatment did not include the use of antibiotics or a lumbar puncture in the last decade.

The aim of the study is to analyse the outpatient management of selected febrile infants younger than 3 months of age with low risk criteria for SBI without performing a lumbar puncture and without receiving empirical antibiotics.

METHODS

Design of the study

We conducted a prospective registry-based cohort study that included all the infants <90 days of age with fever without source (FWS) who were evaluated in our paediatric ED over a 7-year period (September 2007–August 2014). Our ED is in a tertiary hospital and each year receives around 55 000 children under 14 years of age, including about 2300 infants <90 days.

Data collection

In 2003, we started a prospective electronic registry in our ED, including all the infants <90 days of age brought to the ED with FWS. In 2007, we included PCT as part of the routine assessment of these patients.

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, destination and final diagnosis.

In addition, we monitored the outcome of the patients: for those who were admitted to the ward by reviewing their medical records; and for those who were managed as outpatients, by conducting telephone interviews; the latter were performed by medical residents (after a period of training), within a month of the visit to the 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 the Primary Care Center 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.

The decision tree used to manage these patients was published in a previous study. Definitions:

- SBI: isolation of a bacterial pathogen from the blood, cerebrospinal fluid (CSF), urine or stools.
- Definite cases of SBI:
  - Invasive bacterial infection (IBI): isolation of a bacterial pathogen from the blood, CSF or any other sterile fluid.
  - Non-IBI: urine culture yielding growth of ≥10 000 cfu/mL, obtained by an aseptic method, mainly bladder catheterisation, with associated leucocyturia.
- Possible SBI:
  - Infants with a urine culture yielding mixed growth or growth of >10 000 cfu/mL of a single bacterial species without leucocyturia.
  - Infants with a pneumonia with negative blood culture.

The other definitions can be seen in the online supplementary material file.

To be considered to be at low risk for SBI, the febrile infant had to fulfil all the following included in the ‘step by step’ approach when evaluated in the ED:

- Well appearing
- Older than 21 days of age.

No leucocytes on the urine dipstick.
- ANC ≤10 000
- Serum CRP ≤20 mg/L
- Serum PCT <0.5 ng/mL
- No clinical deterioration during the stay in the ED (always <24 hours).

Exclusion criteria

Patients without urine dipstick, white blood cell count (WBC), ANC, CRP, PCT or blood culture performed were excluded from the study.

Patients undergoing a lumbar puncture or those given antibiotics were excluded.

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 count, measurement of CRP and PCT levels (the latter since 2007), and white blood cell count. We recommend lumbar puncture 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.
- Consider in those with abnormal blood test results (ANC>10 000/μL, CRP>20 mg/L and strongly if PCT ≥0.5 ng/mL).

When infants are included in the group of low-risk criteria we recommend they stay for up to 24 hours in the short-stay unit of the ED. We do not perform any intervention systematically (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 all of these conditions are not fulfilled, we admit the infant to hospital.

Outcome measures

The primary outcome measure was the proportion of infants managed as outpatients who returned to the ED due to a clinical deterioration.

The secondary outcome measure was the proportion of infants managed as outpatients later diagnosed with a SBI.

Statistical analysis

The statistical analysis was carried out using IBM SPSS Statistics for Windows (V22, Armonk, New York, USA). Normally distributed data were expressed as mean±SD, non-normally distributed data as median and IQR, and categorical variables were reported as percentages. Given that all the data were extracted from a database in which the patient identities were anonymous and inclusion in the registry did not imply any additional interventions, informed consent was not required.

RESULTS

During the period of the study, we evaluated 1472 infants younger than 90 days of age with FWS. Of these, we performed urine dipstick, ANC, CRP, PCT and blood culture in 1416 (96.2%). Of these, 767 infants (54.1%, CI 95% 51.5% to 56.7%) were classified to be at low risk for SBI (figure 1). The
Of the 767 infants classified to be at low risk for SBI, 91 were excluded due to them obtaining a lumbar puncture. The lumbar puncture was performed due to the persistence of high fever or irritability of the infants when admitted to the observation unit of the ED. None were diagnosed with SBI, but 44 had non-bacterial meningitis (48.3%). Of the 676 low-risk febrile infants without a lumbar puncture performed on them 586 (86.6%, 95% CI 84.0% to 89.1%) were finally managed as outpatients without receiving antibiotics. The percentage of low-risk patients managed as outpatients increased slightly with age (51/63 of those aged 21–28 days old, 80.9%; 326/382 of those aged 29–60 days old, 85.3%; 209/231 of those aged 61–90 days old, 90.4%).

Eighty-one low-risk infants were admitted due to concerns about the suitable management of these children at home, persistence of high fever or not feeding well. Thirty-four received antibiotics. None was finally diagnosed with definite SBI, 71 with non-SBI (87.6%) and 10 possible SBI (12.3%).

The clinical characteristics of the 586 patients classified to be at low risk for SBI and managed as outpatients without empirical antibiotics and lumbar puncture are shown in table 2.

Final diagnoses of the 586 patients classified to be at low risk for SBI and managed as outpatients are shown in table 3.

Two patients were diagnosed with a SBI, one an occult bacteremia due to *Staphylococcus aureus*. This was a 31-day-old girl brought to the ED as a result of her feeding poorly and in whom fever was first detected in the ED. The patient was recalled 24 hours after discharge, when the blood culture became positive, and again evaluated in the ED. The parents

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**Table 1** Final diagnoses of the infants related to their risk for serious bacterial infection (SBI)

<table>
<thead>
<tr>
<th>Final diagnosis</th>
<th>Low risk (n=767)</th>
<th>High risk (n=649)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-SBI</td>
<td>674 (87.8%, 85.4% to 90.1%)</td>
<td>276 (42.5%, 38.7% to 46.3%)</td>
</tr>
<tr>
<td>Non-bacterial meningitis SBI</td>
<td>44 (5.7%, 4.0% to 7.3%)</td>
<td>69 (10.6%, 8.2% to 12.9%)</td>
</tr>
<tr>
<td>Definite SBI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive bacterial infection</td>
<td>1 (0.1%, 0% to 0.3%)</td>
<td>44 (6.8%, 4.8% to 8.7%)</td>
</tr>
<tr>
<td>Non-invasive bacterial infection</td>
<td>1 (0.1%, 0% to 0.3%)</td>
<td>229 (35.2%, 31.5% to 38.8%)</td>
</tr>
<tr>
<td>Possible SBI</td>
<td>47 (6.1%, 4.4% to 7.8%)</td>
<td>31 (4.7%, 3.0% to 6.3%)</td>
</tr>
</tbody>
</table>

Data expressed as n, % and 95% CIs.

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**Figure 1** Flow chart of the patients. CSF, cerebrospinal fluid; ED, emergency department; SBI, serious bacterial infection.
reported her to be afebrile since discharge and blood tests and lumbar puncture performed in the second visit were normal and cultures negative. The patient received intravenous cloxacillin for 5 days and did well. The other patient diagnosed with a possible urinary tract infection (UTI, positive urine culture without associated leucocyturia). None of them returned to the ED due to clinical deterioration. Three of these children were given antibiotics and two were admitted to hospital.

**DISCUSSION**

The outpatient management of selected febrile young infants at low risk for SBI using a sequential approach including PCT, but without a lumbar puncture and antibiotics is adequate and can avoid the admission to hospital of a large number of patients, when close follow-up is ensured.

The adequacy of the outpatient management of selected infants was reported in prior studies. Nevertheless, in contrast with one of these studies, we do not perform a lumbar puncture on these infants before discharge and, in addition, the criteria to select patients suitable for outpatient management are different. Clinical scenarios and the criteria to select infants suitable for an outpatient management without antibiotics have substantially changed in the last decades. The selection of low-risk criteria included a combination of clinical and laboratory data. In the last decade new low-risk criteria have been developed, some of them including CRP and PCT and not systematically performing a lumbar puncture. These new criteria increase the feasibility of selecting young febrile infants at low risk for SBI, and mainly IBI, being an adequate strategy to identify young febrile infants suitable for a safe outpatient management, including those coming to the ED early in the course of their disease. More than 50% of the patients in our series came to the ED in the first 6 hours after detecting fever. With this study, we confirm that the outpatient management of these patients is adequate, when close follow-up is ensured, even in those coming to the ED early in the course of their disease.

A significant percentage of low-risk infants are admitted to the ward. In our study, around 10% of low-risk infants were admitted for a variety of reasons, including persistent high fever, not feeding well or parental concern. Of note, in our sample, none of these low-risk infants admitted to the ward were finally diagnosed with a definite SBI. Nevertheless it has to be taken into account that the management of these infants at home may be more difficult than in older patients, as it may be more difficult to feed them or for the parents to feel comfortable. These aspects have to be considered when discharging the patient.

Table 2

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male)</td>
<td>321 (54.7%)</td>
</tr>
<tr>
<td>Age groups</td>
<td></td>
</tr>
<tr>
<td>21–28 days old</td>
<td>51 (8.7%)</td>
</tr>
<tr>
<td>29–60 days old</td>
<td>326 (56.6%)</td>
</tr>
<tr>
<td>61–90 days old</td>
<td>209 (35.6%)</td>
</tr>
<tr>
<td>Duration of fever</td>
<td></td>
</tr>
<tr>
<td>&lt;6 hours</td>
<td>296 (50.5%)</td>
</tr>
<tr>
<td>6–12 hours</td>
<td>145 (24.7%)</td>
</tr>
<tr>
<td>&gt;12 hours</td>
<td>117 (19.9%)</td>
</tr>
<tr>
<td>&lt;24 hours but not specified</td>
<td>28 (4.7%)</td>
</tr>
<tr>
<td>Temperature</td>
<td></td>
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<tr>
<td>Highest temperature recorded at home</td>
<td></td>
</tr>
<tr>
<td>&lt;38°C</td>
<td>17 (2.9%)</td>
</tr>
<tr>
<td>38°C–38.9°C</td>
<td>410 (69.9%)</td>
</tr>
<tr>
<td>≥39°C</td>
<td>101 (17.2%)</td>
</tr>
<tr>
<td>Not recorded</td>
<td>58 (9.9%)</td>
</tr>
<tr>
<td>Recorded in the ED</td>
<td></td>
</tr>
<tr>
<td>&lt;38°C</td>
<td>154 (26.2%)</td>
</tr>
<tr>
<td>38°C–38.9°C</td>
<td>349 (59.5%)</td>
</tr>
<tr>
<td>≥39°C</td>
<td>76 (12.9%)</td>
</tr>
<tr>
<td>Not recorded</td>
<td>7 (1.2%)</td>
</tr>
<tr>
<td>Length of stay in the ED</td>
<td></td>
</tr>
<tr>
<td>&lt;6 hours</td>
<td>174 (29.7%)</td>
</tr>
<tr>
<td>6–12 hours</td>
<td>132 (22.5%)</td>
</tr>
<tr>
<td>&gt;12 hours</td>
<td>267 (45.5%)</td>
</tr>
<tr>
<td>Not recorded</td>
<td>13 (2.2%)</td>
</tr>
</tbody>
</table>

Table 3

<table>
<thead>
<tr>
<th>Final diagnosis</th>
<th>n (%)</th>
</tr>
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<tbody>
<tr>
<td>Non-SBI</td>
<td>555 (94.7%)</td>
</tr>
<tr>
<td>Non-bacterial meningitis</td>
<td>0</td>
</tr>
<tr>
<td>SBI/</td>
<td></td>
</tr>
<tr>
<td>Definite SBI</td>
<td></td>
</tr>
<tr>
<td>Invasive bacterial infection (occult bacteraemia due to Staphylococcus aureus)</td>
<td>1 (0.17%)</td>
</tr>
<tr>
<td>Non-invasive SBI (acute gastroenteritis due to group C Salmonella)</td>
<td>1 (0.17%)</td>
</tr>
<tr>
<td>Possible SBI</td>
<td>29 (4.9%)</td>
</tr>
</tbody>
</table>
Close follow-up is mandatory for all these patients, as even in this selected group a very small percentage of young febrile infants can be finally diagnosed with an IBI. In our study, one patient was diagnosed with an IBI and no child returned to the ED due to clinical deterioration or was diagnosed with septic shock or bacterial meningitis.

Another controversial issue is whether to perform lumbar puncture or not on these patients before being managed as outpatient. Nowadays, it is accepted that selected patients may be managed without a lumbar puncture.13–15 In a previous manuscript published by our group, among 1975 well-appearing febrile infants between 21 days and 90 days old, none was diagnosed with bacterial meningitis.26 On the other hand, enteroviral meningitis is a frequent diagnosis among young infants presenting with FWS admitted to paediatric EDs,27 even if they are classified as well appearing. Most of the infants with enteroviral meningitis have normal blood test results, and, in addition, pleocytosis is frequently absent in infants younger than 90 days with a positive enteroviral PCR in CSF,28 especially with a short duration of illness.29 In fact, if lumbar puncture was systematically performed in this population, global rate of enteroviral meningitis would increase.16 29 Taking into account that short-term complications of aseptic meningitis in previously healthy infants between 21 days and 90 days are very rare27 it does not seem to be necessary to perform lumbar puncture on well-appearing infants, with no other risk factors. In addition, in our series, no infant was finally diagnosed with bacterial meningitis and no infant had a clinical deterioration compatible with bacterial meningitis.

Another controversial issue is the approach to the infants with a normal urine dipstick and a positive urine culture (collected in and no infant had a clinical deterioration compatible with bac-

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raising difficulties among young infants presenting with FWS admitted to paediatric EDs,27 even if they are classified as well appearing. Most of the infants with enteroviral meningitis have normal blood test results, and, in addition, pleocytosis is frequently absent in infants younger than 90 days with a positive enteroviral PCR in CSF,28 especially with a short duration of illness.29 In fact, if lumbar puncture was systematically performed in this population, global rate of enteroviral meningitis would increase.16 29 Taking into account that short-term complications of aseptic meningitis in previously healthy infants between 21 days and 90 days are very rare27 it does not seem to be necessary to perform lumbar puncture on well-appearing infants, with no other risk factors. In addition, in our series, no infant was finally diagnosed with bacterial meningitis and no infant had a clinical deterioration compatible with bacterial meningitis.

Another controversial issue is the approach to the infants with a normal urine dipstick and a positive urine culture (collected in an aseptic method), as they may not have a true UTI. Thus, admission and antibiotic treatment may not be necessary for all these patients.30 31 Most of our patients were well when the result of the urine culture arrived and were managed without antibiotics, on the assumption they were not suffering from a true UTI. Urine dipstick testing has been described to be an adequate stand-alone screen for UTI in febrile infants while awaiting urine culture results.32 Nevertheless, UTI is the most common SBI in infants33 34 and when receiving the result of a positive urine culture, a prompt evaluation of the infant is needed. Our public health electronic system allows the primary care paediatrician to know the result of the urine culture at the same time as the paediatric emergency physician. This makes it easier to offer appropriate follow-up to all the young febrile infants discharged home.

Our study has several limitations. This was a single-centre study and, in the vast majority of cases, the assessment of the appearance of the infant was made by the resident and a paediatric emergency physician in the first 15 min after the child arrived in the ED. The experience of the physician in charge is relevant when assessing the appearance of a febrile infant and, this fact has to be taken into account when our approach is applied in an emergency setting without paediatric emergency physicians. On the other hand, a large amount of the patients stayed more than 6 hours in the short-stay unit of the ED. This also has to be considered in those emergency settings without an observation unit.

In conclusion, the outpatient management without antibiotics and lumbar puncture of selected febrile infants younger than 3 months of age with low-risk criteria for SBI with an ensured close follow-up was adequate for this group of infants as the vast majority did not experience SBI. In these infants the negative effects associated with empirical use of antibiotics and hospitalisations can be avoided.

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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 and the data collection system, coordinated and supervised data collection, and reviewed and suggested revisions to the manuscript, and approved the final manuscript as submitted. LM-V and OM collaborated in the design of the study, were responsible for data collection, carried out the initial analyses and reviewed and suggested revisions to the manuscript, and approved the final manuscript as submitted. JB revised the design of the study and reviewed and suggested revisions to the manuscript, and approved the final manuscript as submitted.

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Patient consent Parental/guardian consent obtained.

Ethics approval Ethical Committee of the Cruces University Hospital.

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