ORIGINAL ARTICLE

Quick identification of febrile neonates with low risk for serious bacterial infection: an observational study

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Objective: To examine the possible usefulness of simple and quick criteria for identifying febrile neonates with low risk for serious bacterial infection (SBI).

Design: All febrile neonates who were admitted between August 1998 and August 2003 to the Pediatric Emergency Department, HaEmek Medical Center, Afula, Israel, and to the Poriya Hospital, Tiberias, Israel, were included in the study. The recommended evaluation of each neonate included details of medical history and a complete physical examination, including blood culture, erythrocyte sedimentation rate (ESR), white cell count (WBC), and analysis and culture of urine and cerebrospinal fluid. Other tests were carried out as necessary. Patients who met all the following criteria were considered to have low risk for SBI: (1) unremarkable medical history; (2) good appearance; (3) no focal physical signs of infection; (4) ESR $<$30 mm at the end of the first hour; (5) WBC 5000–15 000/mm^3; (6) a normal urine analysis by the dipstick method.

Results: Complete data were available for 386 neonates. SBI was documented in 108 (28%) neonates, of whom 14% had a urinary tract infection, 9.3% had acute otitis media, 2.3% had pneumonia, 1.3% had cellulitis, 0.5% had bacterial meningitis and 0.5% had bacterial gastroenteritis. The overall incidence of SBI was 1 in 166 (0.6%) neonates who fulfilled the criteria compared with 107 in 220 (48.6%) in the neonates who did not fulfil the criteria ($p<0.001$). The negative predictive value for SBI of the combination of the low-risk criteria was 99.4% (95% confidence interval 99.35% to 99.45%).

Conclusions: Fulfilment of the criteria for low risk might be a reliable and useful tool for excluding SBI in febrile neonates.

Between 3% and 20% of febrile infants aged $<$3 months are reported to have serious bacterial infection (SBI); however, the presenting symptoms and signs are often subtle and non-specific. Several studies have shown that a combination of patient history, physical examination and laboratory criteria can be used to identify febrile infants who are at low risk for SBI.[1–4]

Practice guidelines for the management of infants and children aged 0–36 months with fever without a source were published in 1993 and recently revised. These guidelines state that febrile neonates should be presumed to have SBI, indicating that sepsis evaluation and admission are more appropriate for this group.[5] This is the policy currently in use in Israel, and infants are empirically treated with antibiotics until bacterial infection is excluded.

Only a minority of febrile neonates would have SBI. This suggests that routine hospitalisation and antibiotic use are not always necessary. Moreover, hospitalisation of these infants may be associated with iatrogenic complications, emotional and financial burdens on the family, and rising costs for healthcare services. Studies assessing the various strategies or protocols for identifying neonates at low risk for SBI have been reported and compared in the paediatric literature.[1–4] However, although the negative predictive value (NPV) of these criteria for SBI has been as high as 95–100%, no protocol has been universally adopted.

When evaluating criteria for use in the Pediatric Emergency Department, HaEmek Medical Center, Afula, Israel, we looked for a combination that would be simple, quick, easy to implement and reliable for identification of a febrile neonate who is at low risk for SBI. In a prior study, we found that the combination of an unremarkable medical history (no history of prematurity, illness or previous antibiotics), no focal infection (including no acute otitis media (AOM)), erythrocyte sedimentation rate (ESR) $<$30 mm at the end of the first hour, white cell count (WBC) 5000–15 000/mm^3 and a normal urine analysis by the dipstick method had an NPV of 98% (95% confidence interval (CI) 96% to 100%) for SBI in febrile infants aged 1–2 months.[6] We chose the dipstick method for urine analysis because it is simple to carry out and because the results of a recent meta-analysis showed that Gram stain and the dipstick analysis for nitrite and leucocyte esterase perform similarly in detecting urinary tract infection (UTI) in children and were superior to microscopical analysis for pyuria.[7] We found this combination of criteria to be simple, inexpensive and quick (within an hour). The aim of the present study was to test the usefulness of these criteria in evaluating febrile neonates and determining a treatment plan.

PATIENTS AND METHODS

The study was prospective and was conducted between August 1998 and August 2003 at the HaEmek Medical Center, Afula, Israel, and at the Poriya Hospital, Tiberias, Israel. Human investigation review boards in both hospitals approved the study and informed consent was obtained from parents of all babies before inclusion. Together, these hospitals have more than 800 beds and serve a population of about 500 000 in northern Israel, including about 150 000 children. There are no ambulatory paediatric units in these hospitals, and febrile neonates are admitted to the paediatric wards.

Abbreviations: AOM, acute otitis media; CSF, cerebrospinal fluid; ESR, erythrocyte sedimentation rate; NPV, negative predictive value; PED, paediatric emergency department; SBI, serious bacterial infection; UTI, urinary tract infection; WBC, white cell count

All neonates who were admitted to the paediatric emergency department (PED) with a rectal temperature of ⩾38℃ were eligible for participation in this study. A complete history was obtained from the infant's parents, and a paediatric resident or senior paediatrician carried out a physical examination. As recommended, febrile neonates received a complete evaluation for sepsis, including blood tests (peripheral WBC, ESR and blood culture), culture and analysis of urine (obtained by suprapubic aspiration or by in-and-out bladder catheterisation) and cerebrospinal fluid (CSF) examination (protein, glucose and cell analysis, Gram staining and culture). Stool cultures were obtained from patients with diarrhoea. Chest radiographs were taken for patients with respiratory signs or symptoms. Other tests were conducted as necessary.

SBI was defined by (1) growth of any bacterial pathogen in one or more of the following cultures: CSF, blood, urine, stool, middle ear fluid or any other aspirated fluid from a sterile location; and (2) any disease commonly associated with bacterial pathogens, including AOM, suppurative arthritis, osteomyelitis, soft-tissue infections (cellulitis, abscess, mastitis or omphalitis), gastroenteritis and pneumonia. AOM was defined by the presence of pus in the middle ear aspirate. A positive urine analysis was defined by a positive test for leucocyte esterase or nitrite by the dipstick method (Multistix, Bayer Corporation, Elkhart, Indianapolis, USA) in uncentrifuged urine. UTI was defined as a growth of any single pathogen in urine obtained by suprapubic aspiration, or growth of ⩾10 000 colony-forming units/ml of a single pathogen in urine obtained by in-and-out bladder catheterisation. Samples of CSF, urine, blood, stool, middle ear fluid and other specimens were cultured by standard microbiological methods. No specimens were processed for viral cultures.

All neonates were hospitalised and empirically treated with ampicillin 100 mg/kg/day and gentamicin 5 mg/kg/day, or ampicillin 200 mg/kg/day and cefotaxime 150 mg/kg/day (for suspected CNS infection) for at least 48–72 h until documentation or exclusion of SBI. Treatment was discontinued at this time for those neonates in whom no SBI or possible SBI was documented, and they were discharged if afebrile and in good health.

Neonates with no documented bacterial infection, including those who had aseptic meningitis, were defined as having presumed viral infection.

Patients who met all the following criteria were considered to have low risk for SBI: (1) unremarkable medical history, (2) good appearance, (3) no focal physical signs of infection, (4) ESR <30 mm at the end of the first hour, (5) WBC 5000–15 000/mm^3 and (6) a normal urine analysis by the dipstick method. All other patients were assumed to have a high risk for SBI.

The χ^2 analysis was used for comparison of nominal variables. Results were considered to be significant if analysis yielded $p<0.05$. The positive predictive value for SBI of at least one abnormal criterion and the NPV for SBI of the low-risk criteria combination were calculated by standard statistical formula.

RESULTS

During the study period, 449 febrile neonates were admitted to the PED in both hospitals. Complete data were available for 86% (n = 386) of the neonates, of whom 53% were boys and 47% were girls. In 63 patients, one or more laboratory tests were not carried out, so they were excluded from the analysis. In 28% (n = 108) of neonates, SBI was documented according to our criteria. Of these, the pathogen was isolated in 66% (n = 71; tables 1, 2). We found no differences between boys and girls with regard to the prevalence of infections. In 12.9% (7/54) of neonates with UTI, the urine analysis was normal. No pathogens were isolated in 19 of 36 children with AOM, or in neonates with pneumonia and cellulitis.

Overall, 43% (n = 166) of the neonates met the definition for low-risk criteria for SBI, in whom the overall incidence of SBI was only 0.6% (1/166) compared with 48.6% (107/220) in neonates who did not meet the definition ($p<0.001$). For neonates in whom a pathogen was isolated, incidence rates were 0.6% (1/166) and 31.8% (70/220), respectively ($p<0.001$). The SBI that was missed in the low-risk group was UTI in a neonate with normal urine analysis, in whom bacterial growth was found on urine culture at 36 h after admission. Treatment was then initiated and the patient had an uneventful hospitalisation.

The NPV for SBI of the combination of low risk-criteria was 99.4% (95% CI, 99.35% to 99.45%).

DISCUSSION

The decision whether to carry out a full investigation for sepsis, admit and treat the infant, or to consider close follow-up at home or as an inpatient without immediate treatment must be made for febrile neonates presenting to the PED. Our comprehensive study shows that the combination of simple and quick low-risk criteria used in the PED has a very high NPV for SBI, and can be relied on to discriminate neonates with SBI from those without SBI, thus avoiding the need for lumbar puncture in some febrile neonates. The only case of SBI that was missed in our study was that of a neonate with UTI. The urine analysis and other criteria were normal at presentation; the diagnosis was hence delayed for 24 h. The prevalence of SBI in our study was higher, most probably because we included patients with AOM, cellulitis and pneumonia, in whom no bacterial pathogen was isolated (tables 1, 2). We used this approach because these patients would be admitted and treated with parenteral antibiotics for at least 48 h until results of cultures were available. In a recent review, McIntosh[8] stated that it would be difficult to differentiate between viral and bacterial pneumonia in children on the basis of clinical presentation and results of non-invasive procedures. Cellulitis is associated with bacterial pathogens, even without bacteraemia.[9] Defining AOM as an SBI is a controversial issue. Along with Chie *et al*,[10 11] we also consider AOM to be an SBI because of the high rate of bacterial pathogens isolated from the middle ear pus, and possible local and systemic complications. Some authors do not agree.[1 2 12 13] Recently, Turner *et al*[14] showed that the presence of AOM does not predict a higher risk for SBI in febrile infants aged <2 months. However, in our opinion, further data are needed before AOM on presentation is eliminated from consideration as a high-risk criterion for SBI.

A Medline search yielded five studies published in the past 15 years in the English literature, assessing low-risk criteria in febrile neonates.[10–13 15] In one study, the same neonate population was examined according to two protocols.[13] Two of the studies were prospective,[10 11] and the remainder were retrospective chart reviews. All studies used the same common low-risk criteria that we used, which included: (1) previously healthy, (2) healthy appearance, (3) no focal infection apparent on physical examination, (4) normal urine analysis and (5) no CSF pleocytosis. The studies had some variability in terms of definition of SBI, determination of WBC cut-off values and performance of urine tests. In these studies, SBI was delayed in 0–6% of the neonates who met the definition of low risk for SBI. The NPV values of the low-risk criteria for SBI were 97–100%, regardless of protocol used.

UTI is the most commonly missed SBI in neonates who meet the definition of low risk for SBI in studies that evaluate low-risk criteria.[10–13 15] In our study, 12% (7/54) of neonates with UTI

Table 1 Discharge diagnosis of all febrile neonates

Diagnosis	Incidence, n (%)
Viral infection	278 (72)
Urinary tract infection	54 (14)
Acute otitis media	36 (9.3)
Pneumonia	9 (2.3)
Cellulitis	5 (1.3)
Bacterial gastroenteritis	2 (0.5)
Bacterial meningitis	2 (0.5)
Total	386 (100)

had normal urine analysis by the dipstick method. Crain *et al*[16] showed that 16 of 32 infants aged <8 weeks with UTI had normal urine analysis. Other studies have shown that standard urine analysis and Gram staining yield a relatively poor sensitivity, ranging from 48% to 65%.[15 16] On the basis of these data, urine culture should be obtained for all febrile neonates with normal urine analysis, even if they fulfil other low-risk criteria.

There have been two reports of bacteraemia and meningitis, which were missed in neonates who met the definition of low risk for SBI. One neonate was 8 days old, in whom lumbar puncture was not carried out on admission. The infant ran a persistent fever, and CSF examination on day 3 of admission proved bacterial meningitis.[10] In another report, Chie *et al*[17] described a 10-day-old girl admitted to the PED with a fever of 39.4℃. She fulfilled low-risk criteria for SBI and was managed as an inpatient under close observation, without receiving antibiotics. On day 3 in hospital, she was re-evaluated because of a continued fever. She looked well and had no physical findings consistent with ear or soft-tissue infection. A follow-up blood test showed WBC 23 200/mm^3 and C reactive protein concentration 92.9 mg/dl. A repeat lumbar puncture was carried out, confirming bacterial meningitis. Both patients recovered after appropriate treatment without sequela.[17] Whether these infections existed on the day of admission is not known.

What should be the approach to manage a febrile neonate who fulfils low-risk criteria? In five studies including ours,[1 12 13] patients were admitted for 48–72 h, with or without treatment. Infants were admitted to the hospital for observation for 24 h without antibiotics, or with oral antibiotics for infants with AOM in only one study.[15] If the infant appeared well, cultures continued to show the absence of bacterial growth and a close follow-up with a primary care provider could be ensured, then the infant was discharged home. Any low-risk infant whose clinical status deteriorated or whose cultures showed bacterial growth was given antibiotics intravenously until culture results were known. None of the infants was found to have SBI. Another, more liberal, approach was suggested by Dagan *et al*,[2] who used the Rochester criteria on a population of infants aged <60 days with suspected infection (not all febrile). Of the 148 infants who fulfilled these criteria, 42% (n = 62) were initially discharged, and 49% (n = 72) were initially followed up for 24 h and subsequently discharged. In none of the 148 infants was SBI diagnosed.

Several conclusions may be drawn on the basis of data from these studies, and in relation to our study. All the suggested combinations of low-risk criteria had a high NPV for SBI. The advantage of the criteria suggested in this study is that they are simple and can be accomplished rapidly, successfully discriminating neonates with SBI from those without SBI within an hour. Data suggest that urine culture should be obtained in every febrile neonate, regardless of urine analysis results.

In conclusion, on the basis of the analysis in this study, we suggest that the combination of criteria for low risk might be a reliable and useful tool for excluding SBI in febrile neonates. However, for verification, further studies are needed on babies who fulfil the combination of low-risk criteria, observed in hospital, under research conditions, without antibiotic treatment in the first instance.

Table 2 Pathogens causing serious bacterial infections in febrile neonates

SBI	n (% of all neonates with SBI)
Urinary tract infection	
Escherichia coli	39 (36)*
Klebsiella sp	7 (5.5)†
Other	8 (7.3)
Acute otitis media	
Streptococcus pneumoniae	5 (4.6)
Haemophilus influenzae	2 (2.3)
Other bacteria	6 (6.7)
Bacterial gastroenteritis	
Campylobacter jejuni	2 (1.8)
Bacterial meningitis	
Listeria monocytogenese	2 (1.8)
Total	71 (66)

SBI, serious bacterial infection.
*Three neonates had bacteraemia.
†One neonate had bacteraemia.

What is already known on this topic

- Only a minority of febrile neonates have serious bacterial infection.
- The approach to manage febrile neonates has been to carry out investigation for sepsis and to treat the infants with antibiotics until results of cultures are available.

What this study adds

- The suggested combination of the low-risk criteria is a reliable and useful tool for excluding serious bacterial infection in febrile neonates.
- Babies who fulfil the combination of low-risk criteria might be observed without antibiotic treatment in the first instance in a hospital.

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IMAGES IN NEONATAL MEDICINE

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Nasal trauma due to nasal continuous positive airway pressure in newborns

We would like to report a preterm baby, who sustained a major nasal injury secondary to nasal continuous positive airway pressure (nCPAP). The baby was extremely low birth weight and needed CPAP for 3 weeks. The baby developed laceration of the alae nasi within a week (fig 1). The laceration was 1 cm in size, causing division of the alae nasi on the medial side. The tear took 4 weeks to heal after nCPAP. This baby had recovered well from the nasal injuries at the time of discharge.

nCPAP is a common mode of respiratory support used in neonatal intensive care units. Elective use of nCPAP has helped to reduce the incidence of failed extubation. The nasal trauma was caused by nasal prongs and has been reported as 20%.[1] A recent randomised control study by Yong *et al*[2] found a higher incidence of nasal trauma due to CPAP and also found that that there was no significant difference in nasal trauma between prongs and mask. The nasal injuries reported in the literature range from redness, erythema, crusting and excoriation to scaling. The common sites for injuries are the base of the septum, where it meets the philtrum, caused by the mask, and the medial aspect of the septum, caused by the prongs. Duration of nCPAP is a definite risk factor for nasal trauma. Birth weight, gestation and type of nasal device are not significant.

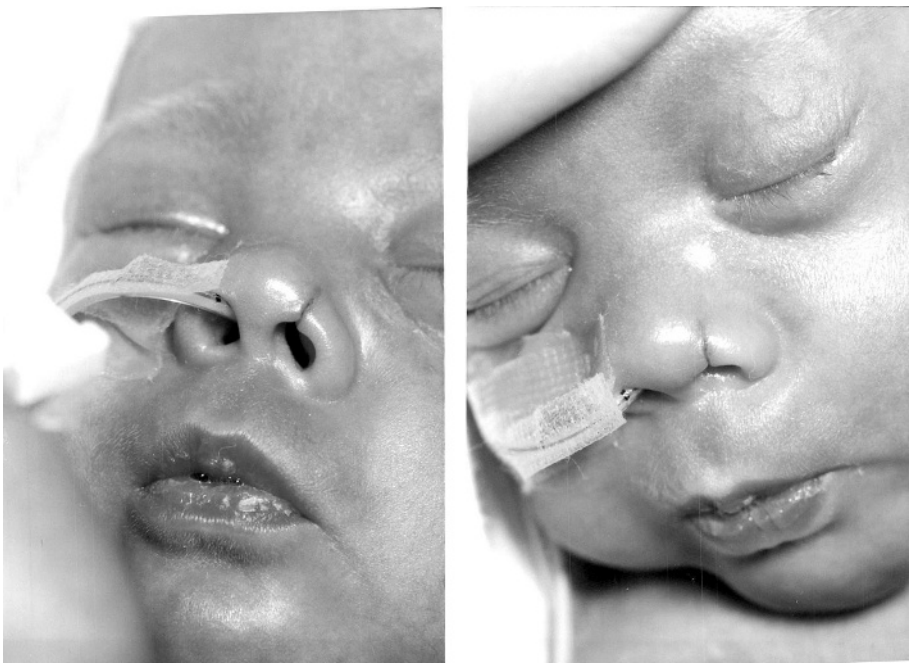

Figure 1 Baby with laceration of alae nasi. Informed parental consent was obtained for publication of this figure.

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