Is 15 Days an Appropriate Cut-off Age for Considering Serious Bacterial Infection in the Management of Febrile Infants?

Silvia Garcia, MD, Santiago Mintegi, PhD,*† Borja Gomez, MD,* Jorge Barron, MD,‡ Mari Pinedo, MD,* Nerea Barcena, MD,* Elena Martinez, MD,* and Javier Benito, PhD**

Introduction: Febrile infants <3 months of age have a greater risk for serious bacterial infection (SBI). The risk is inversely correlated with age. Most protocols recommend admitting to hospital all febrile infants <28 days of age. However, as the prevalence of SBI is not homogenous in this age group, some authors have considered decreasing this cut-off age, allowing ambulatory management of selected patients meeting low-risk criteria.

Objective: To determine whether 15 days is a suitable cut-off age for different approaches to the management of infants with fever.

Patients and Methods: Cross-sectional descriptive study of infants <3 months of age with fever without a source seen between September 1, 2003 and August 30, 2010 in the pediatric emergency department of a tertiary teaching hospital. All infants <3 months of age with fever without a source (≤38°C) were included. The following data were collected: age, sex, temperature, diagnosis, management in pediatric emergency department, and outcome.

Results: Data were collected for 1575 infants; of whom, 311 (19.7%, 95% confidence intervals [CI]: 17.7–21.7) were found to have an SBI. The rate of SBI in the patients who were 15 to 21 days of age was 33.3% (95% CI: 23.7%–42.9%), similar to that among infants who were 7 to 14 days of age (31.9%, 95% CI: 21.1%–42.7%) and higher than among those older than 21 days of age (18.3%, 95% CI: 16.3–20.3%).

Conclusions: Febrile infants 15 to 21 days of age had a rate of SBI similar to younger infants and higher than older age infants. It is not appropriate to establish the approach to management of infants with fever based on a cut-off age of 2 weeks.

Key Words: fever, neonate, young infants, serious bacterial infection

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Fever is one of the most common reasons for children to be brought to a pediatric emergency department (PED), especially in the case of young infants.[1,2] Normally, fever is caused by self-limiting viral infections, but some infants with fever who appear well and with no relevant findings on physical examination have a bacterial infection that could potentially be serious.[3] The rate of serious bacterial infection (SBI) among those <3 months of age is higher than that reported in other age groups, its incidence being inversely correlated with age, with up to 20% of those <1 month of age with fever without a source (FWS) having an SBI.[4] This, together with there being fewer signs associated with this type of infection, in particular at early stages, means that we must take a more cautious and interventionist approach in these patients than in older children.[5–10] In recent years, however, the rates of SBI in infants <3 months of age has decreased, due to improvements in detecting abnormalities in the kidney and urinary tract using prenatal ultrasound and use of intrapartum antibiotic prophylaxis for group B streptococcal infection.[11-13] Further, the development of new diagnostic is causing the management of febrile infants to be reviewed, moving toward less interventionist approaches.[3,14–18] Several different protocols recommend admission of all infants <28 days of age with fever,[4,19,20] while considering ambulatory management for selected patients older than 1 month of age meeting low-risk criteria.[3,21–23] Some authors have suggested lowering the cut-off age for ambulatory management of selected low-risk patients, although they point out that there should be follow-up for these individuals managed as outpatients.[24]

The objective of this study was to identify whether 15 days of age is a suitable cut-off point for higher risk of SBI.

PATIENTS AND METHODS

This was a cross-sectional descriptive study of infants <3 months of age with FWS (see definition later) seen in the PED of a tertiary teaching hospital, during 7 consecutive years (September 2003–August 2010). This PED manages an average of 63,000 children <14 years of age annually.

Study Design

Data were collected from our registry of infants less than 3 months with FWS. We include all the infants of this age with FWS. Every year, between 270 and 280 episodes are entered into this database. The following variables were collected: age, sex, temperature, diagnosis, complementary tests, and patient outcome (follow-up by the primary care Pediatrician - PCP-, revisits to the PED, antibiotic treatment, and final diagnosis).

Management in the PED

The management algorithm for infants <3 months of age with FWS used in our PED, recommends to obtain an urine dipstick test, complete blood count, C-reactive protein (CRP) and procalcitonin (PCT) tests (the latter being added to our protocol in November 2007), and blood and urine cultures for all cases. We recommend to perform a cerebrospinal fluid (CSF) examination in those <15 days of age, in older than 15 days of age who do not well-appear well, and in those with abnormal result in blood tests (same cutoffs as low-risk criteria, see later). During the influenza season, we also carry out a rapid diagnostic test for influenza.

For infants older than 15 days of age who appear well and meet low-risk criteria (previously healthy, well appearance, urine dipstick result negative for leukocyturia and nitrituria, leukocyte levels between 5000 and 15,000 per mm^3, <10,000 neutrophils/mm^3, PCT < 0.5 ng/mL [since November 2007], CRP < 20 mg/L with no pleocytosis in lumbar puncture if performed,

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From the *Pediatric Emergency Department, Cruces University Hospital, Bilbao, Basque Country, Spain; †Department of Paediatrics, University of the Basque Country, Basque Country, Spain; and ‡Microbiology Service, Cruces University Hospital Hospital, Bilbao, Basque Country, Spain.
The authors have no funding or conflicts of interest to disclose.
Address for correspondence: Santiago Mintegi, PhD, Pediatric Emergency Department, Cruces University Hospital, Plaza de Cruces s/n, Bilbao, Basque Country, Spain. E-mail: santiago.mintegi@osakidetza.net.
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and with normal findings on clinical examination after several hours, <24 hours, in the observation unit), we recommend discharge without antibiotic treatment and evaluation in the following 24 hours by the PCP. By contrast, we recommend hospital admission for those <15 days of age, those with abnormal laboratory results and when there is worsening in clinical status.

Every month, a pediatrician of the PED reviews the electronic registry concerning all the cases seen in the department to ensure that data have been correctly entered for all the infants with fever.

Definitions

FWS: Axillary or rectal temperature at home, or rectal temperature in the PED, of ≤38°C, without catarrhal or respiratory symptoms/signs (such as tachypnea) or a diarrheal process, in patients with normal physical examination, according to the diagnostic codes issues by the Spanish Society of Pediatric Emergencies.[25] Infants were excluded if fever was assessed by parents at home without using a thermometer, although the degree of sensitivity in terms of subjective fever assessments carried out by parents ranges between 74% and 84%, with a specificity of 76% to 96%.[26,27]

Well-appearing: Defined by a normal pediatric assessment after being evaluated by a Pediatric emergency physician during the first hour after attending the PED. Appearance (mental status), work of breathing and circulation to the skin had to be normal for infants to be classified as well-appearing, and data had to be reflected on the patient's charts.

SBI: Isolation of a bacterial pathogen in the CSF, blood, or urine or posterior diagnosis of a focal infection is considered to be severe in this age group of patients.

Positive blood culture: Blood culture in which a true pathogenic bacteria has been isolated (*Streptococcus pneumoniae*, *Neisseria meningitidis*, *Enterococcus* sp., *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, group A and B *Streptococcus*, *Listeria monocytogenes*, or *Salmonella* sp.) The growth of *Staphylococcus epidermidis*, Propionibacterium acnes, and diphtheroids in blood cultures of previously healthy immunocompetent children (with no history of heart problems, or of placement of catheters, ventriculoperitoneal shunt, or other prostheses) were classified as contaminated samples.

Occult bacteremia: Positive blood culture in well-appearing infants diagnosed with FWS.

Bacterial meningitis: (a) Positive CSF culture or CSF gram, (b) CSF pleocytosis with a positive blood culture.

Urinary tract infection: Growth of more than 50,000 colony-forming units per mL of a bacterial species from a single urine sample collected by catheterization of the bladder. Additionally, the growth of 10,000 to 50,000 colony-forming units per mm^3 was considered to indicate a urinary tract infection when there was also leukocyturia and/or nitrituria.

Previously healthy infant: To be classified as such, the patient must have been born at term (≤37 weeks of gestation), no chronic or underlying disease, not treated for unexplained hyperbilirubinemia, not hospitalized longer than the mother, not receiving current or prior antimicrobial therapy and no previous hospitalization.

Exclusion Criteria

Patients in whom it was possible to identify the cause of the fever, from their medical history or physical examination on admission to the PED, were not included in study, nor were those with diarrhea or respiratory signs, such as tachypnea, difficulty breathing, wheezing, stridor, nasal flaring, chest retraction, rhonchi, rales, and areas of decreased breath sounds. On the other hand, infants with fever and whose parents reported only mild nasal congestion were included in the study.

Data Collection

The electronic medical records of the PED were reviewed and the following data were collected for each patient: demographic variables (age and sex), medical history, the time that elapsed between the fever being detected and the child being seen in the hospital, body temperature measured at home and in the PED, the general appearance of the infant on arrival, signs and clinical findings in the physical examination, results of any tests performed, treatment received, diagnosis, site of care, and clinical progression.

In the cases in which the child was admitted, the patients' charts at discharge were checked. On the other hand, when the child was not admitted to hospital, a follow-up telephone call was made to the patient's home by a pediatrician resident, after receiving suitable training, to assess the clinical progression of the child. Further, the hospital database was reviewed to determine whether there had been any additional visits to the emergency department, after the initial consultation.

Statistical Analysis

The statistical analysis was carried out using SPSS software (version 19, Chicago, IL). Data are expressed as means, confidence intervals (CIs), and standard deviations for quantitative variables and as numbers and percentages for categorical variables. Continuous variables were compared using the Student *t* test, whereas categorical variables were analyzed using the χ^2 or the Fisher exact tests. The level of significance was set at $P \leq 0.05$.

This study was approved by the Research Committee of the PED. Given that the data were taken from a database, on which entries are anonymous, and no interventions were performed on or withheld from any patients; it was not considered necessary to obtain informed consent.

RESULTS

During the study period, 1575 infants <3 months of age with FWS were included. Table, Supplemental Digital Content 1, http://links.lww.com/INF/B83 lists the general characteristics of these patients. Of the total, 307 patients were ≤28 days of age. Table, Supplemental Digital Content 2, http://links.lww.com/INF/B84 reports the use of these tests by age group.

Of the total, 311 (19.7%, 95% CI: 17.7–21.7) infants were found to have an SBI. The diagnoses of these patients are shown in Table, Supplemental Digital Content 1, http://links.lww.com/INF/B83. The rate of SBI in 15- to 21-day-old patients was 33.3% (95% CI: 23.7%–42.9%), similar to that among those 7- to 14-day-old patients (31.9%, CI 95% 21.1–42.7%), and higher than that in infants older than 21 days of age (18.3%, CI 95% 16.3–20.3%). By age, Table, Supplemental Digital Content 2, http://links.lww.com/INF/B84, and Fig., Supplemental Digital Content 3, http://links.lww.com/INF/B85 show the overall rate of SBI, whereas Table 1 lists the types of SBI diagnosed. Patients with cellulitis and AOM had a normal physical examination when they arrived to the ED.

In total, 66.5% of the patients <3 months of age were managed as outpatients after several hours of observation (15 ± 7 hours, always <24 hours) and without receiving antibiotic treatment. This rate was lower in younger patients, −27% in infants 15 to 21 days of age; however, as many as 53% of infants 21 to 28 days of age managed as outpatients.

During the study period, 988 infants were initially diagnosed with FWS and 599 met low-risk criteria. Of these, 449 (74.9%) were managed as outpatients without CSF examination or antibiotic therapy. Of these, we registered 34 (7.5%) unscheduled visits because of

TABLE 1. Type of Serious Bacterial Infection by Age Group

Age	Serious Bacterial Infection					
	UTI	Bacteremia	Sepsis	Meningitis	Others	Total
≤7 d (25)	4 (16%)	—	—	—	—	16%
8–14 d (72)	19 (26.3%)	1 (1.4%) with associated UTI	1 (1.4%)	2 (2.7%)	—	31.9%
15–21 d (93)	26 (28%)	2 (2.1%) with associated UTI	2 (2.1%)	1 (1.1%)	—	33.3%
22–28 d (117)	25 (21.3%)	—	—	1 (0.9%)	—	22.2%
29–60 d (641)	100 (15.6%)	13 (2%) 6 with associated UTI	1 (0.1%)	1 (0.1%)	2 (0.3%)	18.2%
61–90 d (627)	100 (15.9%)	7 (1.1%) 2 with associated UTI	2 (0.3%)	—	1 (0.1%)	17.5%

UTI indicates urinary tract infection.

persistence of fever or new symptoms and 16 scheduled visits (arrival of a positive culture, mainly positive urine culture without leukocyturia or nitrituria). No patient managed as an outpatient returned to the PED due to a clinical deterioration or referred a clinical deterioration at home, when they were contacted by phone. Complete follow-up of the patients was made in 92%

DISCUSSION

According to our results, the prevalence of SBI is not homogenous among febrile infants <3 months of age. Specifically, the prevalence is higher among those <3 weeks of age. Further, 15- to 21-day-old febrile infants have a rate of SBI that is similar to younger infants but higher than that among older groups. For this reason, we do not believe that it is appropriate to adopt different approaches to the management of febrile infants using 15 days of life as the cut-off point. If we accept that febrile infants <3 months of age do not constitute an homogeneous group, according to our data and regarding the SBI rate, the most adequate age cut-off point for a different approach should be 21 days.

Although the CIs for the SBI in neonates 3 weeks of age show overlap when compared with neonates 4 weeks of age, it seems reasonable to establish the age cut-off for higher risk of SBI at 3 weeks and not at 2 or 4 weeks of age.

Traditionally, febrile infants have been classified into various age groups for different management strategies: neonates (0–28 days); young infants (usually corresponding to 1–3 months of age, although some authors only include those 1–2 months of age); and older infants (3–36 months).The management of febrile infants still is controversial for those <3 months of age and, even more so, for those less than 1 month of age.[3,10,14–16] This latter group has been considered to be at high risk because of relatively high prevalence of SBI, to the difficulty of making a clinical assessment, and because of their weak immune response.[5–10] The fewer clinical signs of infection in this age group makes it more difficult to use classic assessment scales to classify them into groups at higher and lower risk of having an SBI.[28,29] Kadish et al[24] report rates of SBI of up to 3% among patients 1 to 28 days of age who meet low-risk criteria according to the Boston and Philadelphia protocols and who were managed as outpatients. In addition, such infants tend to arrive at the emergency unit early—in our hospital more than 50% of children <3 months are brought in within 6 hours of onset of the fever.

In a recent study, Schwatz et al[4] report figures of SBI in children ≤28 days of age of 19.4%, stratifying the prevalence of SBI by age (in weeks). They observed that the prevalence of SBI in neonates >15 days of age was significantly lower than those in younger infants. However, they did not established different management strategies as a function of age in weeks. We found that the rate of SBI in 15- to 21-day-old patients (33.3%) was similar to that in 7- to 14-day-old infants (31.9%) and higher than in those 21 days of age or older (18.1%). Therefore, our study shows that using 2 weeks of age as the cut-off point to adopt different management strategies for febrile infants is not appropriate. Notably, the rate of SBI in infants ≤7 days of age in our study was 16%, lower than in the other age groups. This pattern of a lower rate of SBI in the first week of life has also been described in other series.[4] In our case, it could be attributed to the fact that our registry did not include any infants <3 days of age. This is because, in line with our hospital's protocols, newborns are routinely discharged between 48 and 72 hours after birth, and if during their hospital stay they have a fever, they are admitted to the neonatal unit directly from the maternity ward.

In recent years, several studies have aimed to identify low-risk infants using the modified versions of the classic Rochester and Philadelphia criteria. These scales take into account not only clinical findings but also results for CRP, the presence of leukocytosis or immature cells, and more recently PCT values, among others.[3,14,16,24,30] There is, however, no consensus with regards to the usefulness of these criteria to identify children at low risk of a SBI. Baker et al[29] classified neonates in low- and high-risk groups of having an SBI according to the Philadelphia criteria. Of those classed in the high-risk group 18.6% were found to have an SBI, but up to 4.6% of those classified in the low-risk group also developed this type of infection. Chiu et al[31] studied 250 febrile patients <28 days of age and, using their own criteria for low risk, concluded that hospital observation without antibiotic therapy was a safe option for the management of these patients. More recently, Maron et al[32] indicated that meeting low-risk criteria may be a useful tool for identifying neonates at high risk of an SBI, so that low-risk infants can be managed as outpatients without antibiotic therapy after some hours less than observation in hospital. In our PED, we are moving toward a less aggressive management with regard to complementary tests, hospitalization, and antibiotic therapy for infants <1 month of age, specifically for the subgroup between 21 days and 1 month of age. A more conservative management of low-risk patients is relevant in terms of sparing health care costs, emerging antibiotic resistance and potential complications associated with hospitalization.

This study has several limitations. A prospective study would have allowed greater rigor in the collection of data concerning these patients. However, data were extracted from a prospective registry with good quality data. Further, the telephone follow-ups, carried out by trained physicians, help to minimize this limitation. Second, it was not a multicenter study, so the results are difficult to extrapolate to other populations. Third, in our hospital, discharge of newborns occurs in the first 48 to 72 hours after birth, so that febrile infants of 2 to 3 days of age are admitted to the neonatal unit directly. Finally, not all the tests were performed on all patients. However, a close follow-up was made as it is exposed in the Results section and no patient with complete or incomplete testing went on to become sicker and wound up having SBIs.

REFERENCES

1. Nelson DS, Walsh K, Fleisher GR. Spectrum and frequency of pediatric illness presenting to a general community hospital emergency department. *Pediatrics.* 1992;90(1 pt 1):5–10.
2. Massin MM, Montesanti J, Gerard P, et al. Spectrum and frequency of illness presenting to a pediatric emergency department. *Acta Clin Belg.* 2006;61:161–165.
3. Ishimine P. Fever without source in children 0 to 36 months of age. *Pediatr Clin North Am.* 2006;53:167–194.
4. Schwartz S, Raveh D, Toker O, et al. A week by week analysis of the low risk criteria for serious bacterial infection in febrile neonates. *Arch Dis Child.* 2009;94:287–292.
5. Baker MD, Bell LM. Unpredictability of serious bacterial illness in febrile infants from birth to 1 month of age. *Arch Pediatr Adolesc Med.* 1999;153:508–511.
6. Bachur RG, Harper MB. Predictive model for serious bacterial infections among infants younger than 3 months of age. *Pediatrics.* 2001;108:311–316.
7. Bema k, ChB M, Harper MB. Identifying febrile young infants with bacteremia: is the peripheral white blood cell count an accurate screen? *Ann Emerg Med.* 2003;42:216–225.
8. Gomez B, Mintegi S, Benito J, et al. Blood culture and bacteremia predictors in infants less than three months of age with fever without source. *Pediatr Infect Dis J.* 2010;29:43–47.
9. Bressan S, Andreola B, Cattelan F, et al. Predicting severe bacterial infections in well-appearing febrile neonates. *Pediatr Infect Dis J.* 2010;29:227–232.
10. Baker MD, Bell LM. Unpredictability of serious bacterial illness in febrile infants from birth to 1 month of age. *Arch Pediatr Adolesc Med.* 1999;153:508–511.
11. Centers for Disease Control and Prevention (CDC). Early- onset and late-onset neonatal group B streptococcal disease—United States, 1996–2004. *Morb Mortal Wkly Rep*. 2005;54:1205–1208.
12. Phares CR, Lynfield R, Farley MM. Epidemiology of invasive group B streptococcal disease in the United States, 1999–2005. *JAMA.* 2008;299:2055–2065.
13. Eberly M, Rajnik R. The effect of universal maternal screening on the incidence of neonatal early- onset Group B Streptococcal disease. *Clin Pediatr.* 2009;48:369–375.
14. Kourtis AP, Sullivan DT, Sathian U. Practice guidelines for the management of febrile infants less than 90 days of age at the ambulatory network of a large pediatric health care system in the United States: summary of new evidence. *Clin Pediatr.* 2004;43:11–16.
15. Mintegi S, García-García JJ, Benito J et al. Rapid influenza test in young febrile infants for the identification of low-risk patients. *Pediatr Infect Dis J.* 2009;28:1026–1028.
16. Maniaci V, Dauber A, Weiss S, et al. Procalcitonin in young febrile infants for the detection of serious bacterial infections. *Pediatrics.* 2008;122:701–710.
17. Olaciregui I, Hernández U, Muñoz JA, et al. Markers that predict serious bacterial infection in infant under 3 months of age presenting with fever of unknown origin. *Arch Dis Child.* 2009;94:501–505.
18. Dagan R, Powell KR, Hall CB, et al. Identification of infants unlikely to have serious bacterial infection although hospitalized for suspected sepsis. *J Pediatr.* 1985;107:855–860.
19. Baraff L. Management of fever without source in infants and children. *Ann Emerg Med.* 2000;36:602–614.
20. Steere M, Sharieff GQ, Stenklyft PH. Fever in children less than 36 months of age: questions and strategies for management in the emergency department. *J Emerg Med.* 2003;25:149–157.
21. Dagan R, Sofer S, Phillip M, et al. Ambulatory care of febrile infants younger than 2 months of age classified as being at low risk for having serious bacterial infections. *J Pediatr.* 1988;112:355–360.
22. Baskin MN, O'Rourke EJ, Fleisher GR. Outpatient treatment of febrile infants 28 to 89 days of age with intramuscular administration of ceftriaxone. *J Pediatr.* 1992;120:22–27.
23. Baker MD, Bell LM, Avner JR. The efficacy of routine outpatient management without antibiotics of fever in selected infants. *Pediatrics.* 1999;103:627–631.
24. Kadish HA, Loveridge B, Tobey J, et al. Applying outpatient protocols in febrile infants 1–28 days of age: can the threshold be lowered? *Clin Pediatr (Phila).* 2000;39:81–88.
25. Benito J. Grupo de trabajo de Codificación diagnóstica de la SEUP. Codificación diagnóstica en urgencias de Pediatría. *An Esp Pediatr.* 2000;53:261–262.
26. Hooker EA, SmithSW, Miles T, et al. Subjective assessment of fever by parents: comparison with measurement by noncontact tympanic thermometer and calibrated rectal glass mercury thermometer. *Ann Emerg Med.* 1996;28:313–317.
27. Graneto JW, Soglin DF. Maternal screening of childhood fever by palpation. *Pediatr Emerg Care.* 1996;12:183–184.
28. Jaskiewicz JA, McCarthy CA, Richardson AC, et al. for the Febrile Infant Collaborative Study Group. Febrile infants at low risk for serious bacterial infection- an appraisal of the Rochester criteria and implications for management. *Pediatrics.* 1994;94:390–396.
29. Baker MD, Bell LM, Avner JR. Outpatient management without antibiotics of fever in selected infants. *N Engl J Med.* 1993;329:1437–1441.
30. Bachur RG, Harper MB. Predictive model for serious bacterial infections among younger than 3 months of age. *Pediatrics.* 2001;108: 311–316.
31. Chiu C, Lin T, Bullard M. Identification of febrile neonates unlikely to have bacterial infections. *Pediatr Infect Dis J.* 1997;16:59–63.
32. Marom R, Sakran W, Antonelli J, et al. Quick identification of febrile neonates with low risk for serious bacterial infection: an observational study. *Arch Dis Child Fetal Neonatal Ed.* 2007;92:F15–F18.