Predictors of Adverse Clinical Outcome in Young Infants with Septicemia or Meningitis

***Source Citation**:* Pruitt CM, Neuman M, Shah SS, Shabanova V, Woll C, Wang ME, *et al*. Factors associated with adverse outcomes among febrile young infants with invasive bacterial infections. J Pediatr. 2019;204:177-82.
***Section Editor**:* ABHIJEET SAHA

SUMMARY

This retrospective cohort study aimed to determine factors associated with adverse outcomes among febrile young infants with invasive bacterial infections (*i.e*, bacteremia and/or bacterial meningitis). Febrile infants ≤60 days of age, with pathogenic bacterial growth in blood and/or cerebrospinal fluid were identified by query of local microbiology laboratory and/or electronic medical record systems, and clinical data were extracted by medical record review. Logistic regression analysis was employed to determine clinical factors associated with 30-day adverse outcomes, which were defined as death, neurologic sequelae, mechanical ventilation, or vasoactive medication receipt. Of the 350 included infants, 279 (79.7%) had bacteremia without meningitis, and 71 (20.3%) had bacterial meningitis. Forty-two (12.0%) infants had a 30-day adverse outcome: 29 of 71 (40.8%) with meningitis *vs* 13 of 279 (4.7%) with bacteremia without meningitis (36.2% difference, 95% CI 25.1%, 48.0%; *P* <0.001). On adjusted analysis, bacterial meningitis (aOR 16.3, 95% CI 6.5, 41.0; *P*<0.001), prematurity (OR 7.1, 95% CI 2.6, 19.7; *P* <0.001), and ill appearance (aOR 3.8, 95% CI 1.6, 9.1; *P*=0.002) were associated with adverse outcomes. The authors concluded that among febrile infants ≤60 days old with invasive bacterial infection, prematurity, ill appearance, and bacterial meningitis (*vs* bacteremia without meningitis) were associated with adverse outcomes.

COMMENTARIES

Evidence-based Medicine Viewpoint

Relevance: The "Febrile Young Infant Research Collaborative" comprises a group of researchers based in leading pediatric/neonatal healthcare research institutions across the United States of America. In recent years, the group has published several important studies related to epidemiology, clinical features, management issues and outcomes of young infants presenting with fever. In this publication [1], the group examined the clinical records of young infants (age ≤ 60 d) with bacteremia/bacterial meningitis to identify one of four outcomes within 30 days of presentation *viz* mortality, neurologic sequelae, mechanical ventilation, or vasoactive therapy. Those with any of these were categorized as 'adverse outcome' and designated 'cases.' Those without any of these were 'controls.' A set of characteristics encompassing demographic (age), clinical (gestation at birth, presence of a chronic medical condition, sick appearance at presentation), diagnosis (presence or absence of meningitis) and management (antibiotic therapy) parameters were evaluated as potential predictors of outcome.

Critical appraisal: This retrospective analysis [1] included several methodological refinements. Most of the terms used in the study were very well defined through objective criteria. Even 'ill appearance' was sought to be determined objectively through identification of one or more of 13 subjective terms from the clinical records. Although, the precise validity of these terms can be argued, the terms themselves convey a state requiring medical attention.

Since the starting point was the identification of positive bacterial culture in infants who had fever as a symptom (at home) or sign (at presentation), the diagnosis of bacteremia is not in doubt. Similarly bacterial meningitis was defined by CSF culture showing organisms deemed *a priori* to be 'pathogens.' If CSF culture was sterile (due to empiric antibiotic therapy), meningitis was defined by the presence of both bacteremia and CSF pleocytosis. However, the term 'pleocytosis' was not defined. This is important although most studies use a cut-off of 10 cells/μL in infants 1-2 mo of age and 20 cells/μL in neonates [2,3]. Again, since the starting point was a positive culture, the investigators did not mention how traumatic lumbar taps were dealt with.

One important issue with this study [1] is the narrow population group under consideration *viz* infants <60 days old, presenting to the Emergency Room (ER), with fever and culture-proven invasive bacterial infection. Each of these phrases limits the generalizability of the study findings to the specific population group considered. For example, the term 'invasive bacterial infection' is defined by the presence of positive blood culture (bacteremia) or positive CSF culture (bacterial meningitis) [4,5]. Further the term is distinct from 'serious bacterial infection' which is a wider term that includes urinary tract infection [6,7], although some authors include pneumonia [8] and bacterial enteritis [9] or positive stool culture [10] as well. The distinction is more than semantic because it limits the generalizability of this study to only infants having bacteremia and/or bacterial meningitis. Invasive bacterial infection exists in one-seventh [10] to one-fifth [11] cases of serious bacterial infection. Further, serious bacterial infection itself accounts for only 2-15% of young infants having fever without a focus [12,13]. Hence the findings of the study [1] are valid only for the specific population group, rather than broader groups such as febrile infants, infants with suspected sepsis, or suspected meningitis. Further, all infants presented from home, and thus the study findings are applicable only to presumably well infantswho subsequently reported to the hospital.

In this study [1], the investigators considered only those infants who had fever as a symptom (*i.e.*,on history) or sign (*i.e.*, on examination in the ER). Thus, the study findings are not even extendible to all infants with positive blood/CSF culture. This distinction is especially important because 93 of 497 (18.7%) infants with positive blood/CSF culture were not included in the analysis[1] because of the absence of fever. In a previous report by the same research group also, 17.6% infants did not have fever [14].

On the plus side, the inclusion of fever either as a symptom or (rather than and) sign widened the scope of inclusion. It has been shown previously that many infants (<3mo old) with a history of fever (at home) are in fact afebrile when examined in the ER. However, one study [15] reported that the frequency of invasive bacterial infection in those with, and without fever on examination was exactly the same. In contrast, another study examining the same issue concluded that infants with fever on examination in the ER (compared to those with only a history of fever at home) had a greater frequency of severe as well as invasive bacterial infection [6]. These data suggest that it is prudent to include fever at home or at the hospital, as was done in this study [1]. The more serious issue in clinical practice is that hypothermia or normothermia (rather than fever) may be the presenting symptom or sign in young infants with invasive bacterial infection [16,17]. The results of this study are obviously not applicable to such infants.

Among the four criteria for 'adverse events' [1], one *viz* 'neurologic sequelae' is likely to occur more frequently in CNS infections than non-CNS infections. Therefore, it is not surprising that this outcome was 19 times more frequent in infants with meningitis than those with only bacteremia (as shown in Table I of the study). Therefore, the investigators' conclusion that meningitis was associated with more frequent adverse events (compared to bacteremia) could be due to the selection of an outcome skewed towards CNS infection. This is especially likely since mortality rate was not significantly different between infants with meningitis versus those with bacteremia. This aspect was not discussed by the authors [1].

In this retrospective analysis [1] based on examination of laboratory and clinical records (in that order), the criteria used by ER physicians for ordering blood or CSF culture are unclear. Although this does not directly impact the internal validity of the study, the investigators previously reported variations in the criteria adopted for performing CSF analysis across hospitals in the USA [18]. These variations were more significant in the age group 29-60 days than neonates [19]. There are also significant inter patient variations in clinical protocols within hospitals, with progressive decline in the proportion of febrile young infants undergoing laboratory testing (of blood, CSF, urine) with each month of age [20]. Such variations are observed in other countries also [21]. Further, many centres use biomarkers (CRP, procalcitonin) and/or viral PCR studies to try and limit the use of investigations and/or therapy for bacterial infections [22]. In fact, in young infants presenting with clinical features of 'sepsis', examination of blood and CSF for viruses such as enterovirus or human parechovirus yielded significant positive results [23]. Even CSF pleocytosis was present in a significant proportion with these viruses [23]. It has been reported that young infants with RSV antigenemia can also have serious bacterial infections, especially urinary tract infection [24]. Other studies have confirmed that infants <60d old with fever having documented viral infections can have bacteremia as well as bacterial meningitis as co-infections [25]. These observations necessitate a clear understanding of which infants underwent blood or CSF culture testing to make better sense of the findings.

One important observation that the authors [1] did not sufficiently highlight is that the small number of

TABLE I CRITICAL APPRAISAL OF THE STUDY METHODOLOGY

Criteria	*Appraisal*
Did the study address a clearly focused issue?	The investigators focused on a very specific issue neatly summarized in the first sentence of the Abstract viz identification of predictors of adverse outcome (within 30 days of presentation) in young infants (<60d) with fever (at home or at presentation to the ER) who had a positive blood or CSF culture (*i.e*., invasive bacterial infection). However, a research question in the usual PICOT format was not presented.
Did the authors use an appropriate method to answer their question?	The clinical question described above can be answered either through a prospective cohort study or a case control study. The former is more cumbersome, permits a limited number of risk factors to be explored and also more time consuming, whereas the latter overcomes these challenges.
Were the cases recruited in an acceptable way?	The cases in this analysis were infants whose records showed one of the four *a priori* features. However, it is unclear whether any infants developing these outcomes (during the 30 days following presentation) could have been missed through migration, accessing other institutions, or failure to report to the healthcare system. The authors did not comment on this.
Were the controls recruited in an acceptable way?	Controls were infants whose records did not have any of the four chosen outcomes. The same issue described for cases is applicable here also.
Was the exposure accurately measured to minimize bias?	The risk factors assessed included age ≤28d, premature birth, existence of a complex chronic condition (standard published definition), ill appearance (based on presence of any one of 13 words in the ER record), bacterial meningitis, and empiric antibiotic therapy. Each of these 'risk factors' was ascertained through the clinical records, hence could be considered reliable except through mis-identification, mis-classification, etc. A sound definition of bacterial meningitis was used for the purpose of the analysis.
What confounding factors have the authors accounted for?	None were described.
What are the results of this study? How precise are the results?	(Cases, *n*=42 *vs* Controls, *n*=308): Age <28d: aOR1.3 (95% CI 0.7, 2.4); Premature birth: aOR6.8 (95% CI 3.3, 14.2); Complex chronic condition: aOR2.1 (95% CI 0.9, 4.8); Ill appearance: aOR6.7 (95% CI 3.3, 13.5); Bacterial meningitis: aOR 14.1 (95% CI 6.8, 29.3); No empiric antibiotic therapy: aOR 1.1 (95% CI 0.2, 5.1)
Do you believe the results?	The results are valid and hence believable. However, several issues affectin gexternal validity and generalizability are highlighted in the text.
Can the results be applied to the local population?	No. Please see details in main text.
Do the results of this study fit with other available evidence?	Please see details in main text.

infants who were not initially administered antibiotic therapy, ultimately required antibiotics as well as hospitalization. This is interesting because presumably antibiotics were initially withheld based on one or more clinical algorithms designed for the purpose [12,26-28]; although this was not specified. The data suggest that more accurate criteria are required for withholding antibiotics in young infants with fever.

In this study [1], the authors did not report data by study site. This can be important not only to identify inter-institution variations but also determine whether the criteria for labelling cultures positive were uniform. In general, inoculation of culture media for 36 hours is deemed adequate to identify all positive cultures in young infants [29]. However, the Febrile Young Infant ResearchCollaborative investigators previously reported that less than 90% cultures became positive within 24 hours and only about 95% cultures were positive by 36 hours [30]. Likewise it is unclear how cultures showing fungus were dealt with.

Extendibility: The setting where this study [1] was undertaken, the socio-economic (*i.e*., home setting) and demographic profile of infants, and the characteristics of the healthcare system are quite different from our setting. The organisms identified on culture and their frequency are also different. Further, the criteria for starting empiric antibiotic therapy, criteria for undertaking investigations, and interpretation of results have not been clarified. For

these reasons, the data from the study [1] cannot be directly extended to our setting.

Conclusion: This case-control study suggested that among young infants (<60d) with fever (on history or examination) who later turn out to have invasive bacterial infection (*i.e.*, bacteremia or bacterial meningitis), some factors reflecting a sicker state are associated with development of adverse events within 30 days of presentation; although mortality rate is unaffected.

Funding: None; *Competing interests*: None stated.

JOSEPH L MATHEW
Department of Pediatrics, PGIMER, Chandigarh, India.
dr.joseph.l.mathew@gmail.com

REFERENCES

1. Pruitt CM, Neuman M, Shah SS, Shabanova V, Woll C, Wang ME, *et al*. Factors associated with adverse outcomes among febrile young infants with invasive bacterial infections. J Pediatr.2019;204:177-82.
2. Schnadower D, Kuppermann N, Macias CG, Freedman SB, Baskin MN, Ishimine P, *et al*. Sterile cerebrospinal fluid pleocytosis in young febrile infants with urinary tract infections. Arch PediatrAdolesc Med. 2011;16:635-41.
3. Lyons TW, Cruz AT, Freedman SB, Neuman MI, Balamuth F, Mistry RD, *et al.* Interpretation of cerebrospinal fluid white blood cell counts in young infants with a traumatic lumbar puncture. Ann Emerg Med. 2017;69:622-31.
4. Chiu IM, Huang LC, Chen IL, Tang KS, Huang YH. Diagnostic values of C-reactive protein and complete blood cell to identify invasive bacterial infection in young febrile infants. Pediatr Neonatol. 2018.pii: S1875-9572(18)30027-5.
5. Cruz AT, Mahajan P, Bonsu BK, Bennett JE, Levine DA, Alpern ER, *et al*. Accuracy of complete blood cell counts to identify febrile infants 60 days or younger with invasive bacterial infections. JAMA Pediatr. 2017;171:e172927.
6. Ramgopal S, Janofsky S, Zuckerbraun NS, Ramilo O, Mahajan P, Kuppermann N, *et al.* Risk of serious bacterial infection in infants aged ≤60 days presenting to emergency departments with a history of fever only. J Pediatr. 2019;204:191-5.
7. Lee IS, Park YJ, Jin MH, Park JY, Lee HJ, Kim SH, *et al.* Usefulness of the procalcitonin test in young febrile infants between 1 and 3 months of age. Korean J Pediatr. 2018;61:285-90.
8. Vujevic M, Benzon B, Markic J. New prediction model for diagnosis of bacterial infection in febrile infants younger than 90 days. Turk J Pediatr. 2017;59:261-8.
9. Dotan M, Ashkenazi-Hoffnung L, Yarden-Bilavsky H, Amir J, Tirosh N, Mor M, *et al*. Using the Rochester criteria to evaluate infantile fever is more effective in males than females. Acta Paediatr. 2016;105:e356-9.
10. Milcent K, Faesch S, Gras-Le Guen C, Dubos F, Poulalhon C, Badier I, *et al.* Use of procalcitonin assays to predict serious bacterial infection in young febrile infants. JAMA Pediatr. 2016;170:62-9.
11. Nigrovic LE, Mahajan PV, Blumberg SM, Browne LR, Linakis JG, Ruddy RM, *et al.* The Yale observation scale score and the risk of serious bacterial infections in febrile infants. Pediatrics. 2017;140:pii:e20170695.
12. Esposito S, Rinaldi VE, Argentiero A, Farinelli E, Cofini M, D'Alonzo R, *et al.* Approach to neonates and young infants with fever without a source who are at risk for severe bacterial infection. Mediators Inflamm. 2018;2018: 4869329.
13. Powell EC, Mahajan PV, Roosevelt G, Hoyle JD Jr, Gattu R, Cruz AT, *et al*. Epidemiology of bacteremia in febrile infants aged 60 days and younger. Ann Emerg Med. 2018;71:211-6.
14. Woll C, Neuman MI, Pruitt CM, Wang ME, Shapiro ED, Shah SS, *et al.* Epidemiology and etiology of invasive bacterial infection in infants ≤60 days old treated in emergency departments. J Pediatr. 2018;200:210-7.
15. Mintegi S, Gomez B, Carro A, Diaz H, Benito J. Invasive bacterial infections in young afebrile infants with a history of fever. Arch Dis Child. 2018;103:665-69.
16. Ahmad MS, Ali N, Mehboob N, Mehmood R, Ahmad M, Wahid A. Temperature on admission among cases of neonatal sepsis and its association with mortality. J Pak Med Assoc. 2016;66:1303-06.
17. Miller AS, Hall LE, Jones KM, Le C, El Feghaly RE. Afebrile infants evaluated in the emergency department for serious bacterial infection. Pediatr Emerg Care. 2017;33:e15-20.
18. Chua KP, Neuman MI, McWilliams JM, Aronson PL; Febrile Young Infant Research Collaborative. Association between clinical outcomes and hospital guidelines for cerebrospinal fluid testing in febrile infants aged 29-56 Days. J Pediatr. 2015;167:1340-6.
19. Aronson PL, Thurm C, Williams DJ, Nigrovic LE, Alpern ER, Tieder JS, *et al.* Association of clinical practice guidelines with emergency department management of febrile infants ≤56 days of age. J Hosp Med. 2015;10: 358-65.
20. Aronson PL, Thurm C, Alpern ER, Alessandrini EA, Williams DJ, Shah SS, *et al.* Variation in care of the febrile young infant <90 days in US pediatric emergency departments. Pediatrics. 2014;134:667-77.
21. Mintegi S, Gomez B, Martinez-Virumbrales L, Morientes O, Benito J. Outpatient management of selected young febrile infants without antibiotics. Arch Dis Child. 2017;102:244-9.
22. Vachani JG, McNeal-Trice K, Wallace SS. Current evidence on the evaluation and management of fever without a source in infants aged 0-90 Days: A review. Rev Recent Clin Trials. 2017;12:240-5.
23. de Jong EP, van den Beuken MGA, van Elzakker EPM, Wolthers KC, Sprij AJ, LoprioreE, *et al.* Epidemiology of sepsis-like illness in young infants: Major role of enterovirusand human parechovirus. Pediatr Infect Dis J. 2018;37:113-8.
24. Levine DA, Platt SL, Dayan PS, Macias CG, Zorc JJ, Krief W, *et al.* Risk of serious bacterial infection in young febrile

infants with respiratory syncytial virus infections. Pediatrics.2004;113:1728-34.
25. Mahajan P, Browne LR, Levine DA, Cohen DM, Gattu R, Linakis JG, *et al.* Risk of bacterial co-infections in febrile infants 60 days old and younger with documented viral infections. J Pediatr. 2018;203:86-91.
26. Gomez B, Mintegi S, Bressan S, Da Dalt L, Gervaix A, Lacroix L, *et al*. Validation of the "step-by-step" approach in the management of young febrile infants. Pediatrics. 2016;138:pii:e20154381.
27. Aronson PL, Wang ME, Shapiro ED, Shah SS, DePorre AG, McCulloh RJ, *et al*. Risk stratification of febrile infants ≤60 days old without routine lumbar puncture. Pediatrics. 2018;142:pii:e20181879.
28. For Academic College of Emergency Experts in India (ACEE-INDIA) – INDO US Emergency and Trauma Collaborative, Mahajan P, Batra P, Thakur N, Patel R, Rai N,Trivedi N, *et al*. Consensus Guidelines on Evaluation and Management of the Febrile Child Presentingto the Emergency Department in India. Indian Pediatr. 2017;54:652-60.
29. Lefebvre CE, Renaud C, Chartrand C. Time to positivity of blood cultures in infants 0 to 90 days old presenting to the emergency department: Is 36 hours enough? J Pediatr Infect Dis Soc.2017;6:28-32.
30. Aronson PL, Wang ME, Nigrovic LE, Shah SS, Desai S, Pruitt CM, *et al*.Time to pathogen detection for non-ill versus ill-appearing infants ≤60 days old withbacteremia and meningitis. Hosp Pediatr. 2018;8:379-84.

Pediatric Emergency Medicine Expert's Viewpoint

Pruitt and colleagues share a well conducted study on the important topic of adverse outcomes with invasive bacterial infections in infants aged below 60 days. The authors of this large retrospective project, conducted at 11 large children's hospitals in USA, study several important variables in the 350 eligible infants. The association of meningitis, prematurity and ill-appearance with 30-day adverse outcome is certainly important knowledge. It is particularly interesting to note that neither age <28 days nor the presence of a complex chronic condition were significantly associated with adverse outcomes.

The study makes a compelling argument to – (*i*) emphasize thorough examination and documentation of the often subjective 'ill-appearance'; (*ii*) understand that although invasive bacterial infections are more common in neonates, the adverse outcomes may not follow that trend. This may alter the rigor of the work-up of febrile infants 28-60 days of age. This knowledge would also be useful in discharge planning and follow-up of infants with high-risk factors.

The authors thoughtfully note some limitations, and some warrant emphasis – including the study methodology and associated data quality, and the fact that the patients could have presented at another hospital and so the outcomes may have been underestimated. Since the authors gathered information on the location of fever, it would be good to know if the adverse outcomes differed based on whether the infant was febrile only at home or home and the Emergency Department.

The reader must also consider that the generalizability may be poor in other settings and geographical locations where the leading bacterial pathogens are different.In summary, this is a well conducted and informative study with potential for practice changes, albeit with some limitations inherent to its retrospective nature.

Funding: None; *Competing interests*: None stated.

SHOBHIT JAIN
Department of Peditrics,
Children's Mercy, Kansas City, MO, USA.
sjain@cmh.edu