

Things We Do for No Reason – The “48 Hour Rule-out” for Well-Appearing Febrile Infants

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The “Things We Do for No Reason” (TWDFNR) series reviews practices that have become common parts of hospital care but may provide little value to our patients. Practices reviewed in the TWDFNR series do not represent “black and white” conclusions or clinical practice standards but are meant as a starting place for research and active discussions among hospitalists and patients. We invite you to be part of that discussion.

Fever, defined as a rectal temperature of $\geq 38^{\circ}\text{C}$ (100.4°F), is a common reason for hospital admission of infants aged ≤ 90 days. Febrile infants are often admitted to the hospital due to risk for serious bacterial infections, such as urinary tract infection, bacteremia, and meningitis. The traditional observation time is 48 hours following the collection of blood, urine, and cerebrospinal fluid cultures. In the majority of these infants, bacterial infection is not the source of fever. When a bacterial source is identified, less than 0.3% of the bacteria will be detected more than 24 hours after the cultures were obtained in low-risk infants.¹ Recent studies show that the traditional 48 hour hospital observation period is unnecessary for infants aged ≤ 90 days who are at low risk for serious bacterial infection based on available scoring systems.

CASE PRESENTATION

A 3-week-old, full-term term male febrile infant was evaluated in the emergency department (ED). On the day of admission, he was noted to feel warm to the touch and was found to have a rectal temperature of 101.3°F (38.3°C) at home.

In the ED, the patient was well appearing and had normal physical exam findings. His workup in the ED included a normal chest radiograph, complete blood count (CBC) with differential count, cerebrospinal fluid (CSF) analysis (cell count, protein, and glucose), and urinalysis. Blood, CSF, and catheterized urine cultures were collected, and he was admitted to the hospital on parenteral antibiotics. His provider

informed the parents that the infant would be observed in the hospital for 48 hours while monitoring the bacterial cultures. Is it necessary for the hospitalization of this child to last a full 48 hours?

INTRODUCTION

Evaluation and management of fever ($T \geq 38^{\circ}\text{C}$) is a common cause of emergency department visits and accounts for up to 20% of pediatric emergency visits.²

In infants under 90 days of age, fever frequently leads to hospitalization due to concern for bacterial infection as the cause of fever.³ Serious bacterial infection has traditionally been defined to include infections such as bacteremia, meningitis, pneumonia, urinary tract infection, skin/soft tissue infections, osteomyelitis, and septic arthritis.⁴ (Table 1) The incidence of serious bacterial infection in febrile infants during the first 90 days of life is between 5%-12%.⁵⁻⁸ To assess the risk of serious bacterial infections, clinicians commonly pursue radiographic and laboratory evaluations, including blood, urine, and cerebrospinal fluid (CSF) cultures.³ Historically, infants have been observed for at least 48 hours.

Why You Might Think Hospitalization for at Least 48 Hours is Necessary

The evaluation and management of fever in infants aged less than 90 days is challenging due to concern for occult serious bacterial infections. In particular, providers may be concerned that the physical exam lacks sensitivity.⁹

There is also a perceived risk of poor outcomes in young infants if a serious bacterial infection is missed. For these reasons, the evaluation and management of febrile infants has been characterized by practice variability in both outpatient¹⁰ and ED³ settings.

Commonly used febrile infant management protocols vary in approach and do not provide clear guidelines on the recommended duration of hospitalization and empiric antimicrobial treatment.¹¹⁻¹⁴ Length of hospitalization was widely studied in infants between 1979 and 1999, and results showed that the majority of clinically important bacterial pathogens can be detected within 48 hours.¹⁵⁻¹⁷ Many textbooks and online references, based on this literature, continue to support 48 to 72 hours of observation and empiric antimicrobial treatment for febrile infants.^{18,19} A 2012 AAP Clinical Report advocated for limiting the antimicrobial treatment in low-risk infants suspected of early-onset sepsis to 48 hours.²⁰

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TABLE 1. Rate of Serious Bacterial Infections by Age

Age (months)	Blood	CSF	All SBI
0–1	2.1% (1.4, 3.1)	0.9% (0.4, 1.6)	8.8% (7.2, 10.6)
1–2	1.0% (0.6, 1.5)	0.2% (0.1, 0.5)	7.3% (6.2, 8.5)
2–3	0.8% (0.4, 1.5)	0.2% (0.1, 0.7)	7.1% (6.0, 8.4)
Total	1.4% (0.9, 1.6)	0.4% (0.2, 0.7)	7.6% (6.9, 8.3)

All SBI group data were published; however, the specific rates of bacteremia and bacterial meningitis were unpublished but derived from the same data set and calculated as rate of positive cultures per total cultures obtained per group. Numbers in parentheses are the 95% confidence intervals.

Abbreviations: CSF, cerebral spinal fluid; SBI, serious bacterial infections.

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TABLE 2. Rates of Blood Culture Positivity

Observation period (hours)	Percentage of pathogenic blood cultures positive	Number needed to evaluate to capture 1 additional bacteremic infant beyond this period
24	91%	556–1,235
36	96%	1250–2,778
48	99%	5000–11,111

Why Shorten the Period of In-Hospital Observation to a Maximum of 36 Hours of Culture Incubation

Discharge of low-risk infants with negative enhanced urinalysis and negative bacterial cultures at 36 hours or earlier can reduce costs²¹ and potentially preventable harm (eg, intravenous catheter complications, nosocomial infections) without negatively impacting patient outcomes.²² Early discharge is also patient-centered, given the stress and indirect costs associated with hospitalization, including potential separation of a breast-feeding infant and mother, lost wages from time off work, or childcare for well siblings.²³

Initial studies that evaluated the time-to-positivity (TTP) of bacterial cultures in febrile infants predate the use of continuous monitoring systems for blood cultures. Traditional bacterial culturing techniques require direct observation of broth turbidity and subsequent subculturing onto chocolate and sheep blood agar, typically occurring only once daily.²⁴ Current commercially available continuous monitoring bacterial culture systems decrease TTP by immediately alerting laboratory technicians to bacterial growth through the detection of ¹⁴CO₂ released by organisms utilizing radiolabeled glucose in growth media.²⁴ In addition, many studies supporting the evaluation of febrile infants in the hospital for a 48-hour period include those in ICU settings,²⁵ with medically complex histories,²⁴ and aged < 28 days admitted in the NICU,¹⁵ where pathogens with longer incubation times are frequently seen.

Recent studies of healthy febrile infants subjected to continuous monitoring blood culture systems reported that the TTP for 97% of bacteria treated as true pathogens is ≤36 hours.²⁶ No significant difference in TTP was found in infants ≤28 days old versus those aged 0–90 days.²⁶ The largest study conduct-

ed at 17 sites for more than 2 years demonstrated that the mean TTP in infants aged 0–90 days was 15.41 hours; only 4% of possible pathogens were identified after 36 hours. (Table 2)

In a recent single-center retrospective study, infant blood cultures with TTP longer than 36 hours are 7.8 times more likely to be identified as contaminant bacteria compared with cultures that tested positive in <36 hours.²⁶ Even if bacterial cultures were unexpectedly positive after 36 hours, which occurs in less than 1.1% of all infants and 0.3% of low-risk infants,¹ these patients do not have adverse outcomes. Infants who were deemed low risk based on established criteria and who had bacterial cultures positive for pathogenic bacteria were treated at that time and recovered uneventfully.^{7, 31}

CSF and urine cultures are often reviewed only once or twice daily in most institutions, and this practice artificially prolongs the TTP for pathogenic bacteria. Small sample-sized studies have demonstrated the low detection rate of pathogens in CSF and urine cultures beyond 36 hours. Evans et al. found that in infants aged 0–28 days, 0.03% of urine cultures and no CSF cultures tested positive after 36 hours.²⁶ In a retrospective study of infants aged 28–90 days in the ED setting, Kaplan et al. found that 0.9% of urine cultures and no CSF cultures were positive at >24 hours.¹ For well-appearing infants who have reassuring initial CSF studies, the risk of meningitis is extremely low.⁷ Management criteria for febrile infants provide guidance for determining those infants with abnormal CSF results who may benefit from longer periods of observation.

Urinary tract infections are common serious bacterial infections in this age group. Enhanced urinalysis, in which cell count and Gram stain analysis are performed on uncentrifuged urine, shows 96% sensitivity of predicting urinary tract infection and

TABLE 3. Commonly Used Criteria for Management of Febrile Infants

Children with the following criteria are defined as low risk

Criteria	Rochester ³⁶	Boston ¹⁵	Philadelphia ¹³
Age (days)	0–60	28–89	29–56
Clinical Appearance	Well	Well	Well by infant observation score
Peripheral WBC/mm ³	5,000–15,000	5,000–20,000	<15,000
Bands	<1500 cells per mm ³	NA	<0.2 ratio bands: pmn
UA	<10wbc/hpf	<10wbc/hpf	<10wbc/hpf; negative gram stain
CSF	N/A	<10wbc/mm ³	<8wbc/mm ³ ; nonbloody
Stool if diarrhea present	<10wbc/hpf	<5wbc/hpf	<5wbc/hpf; no hematochezia
CXR		Not required	Required for all

NOTE: Abbreviations: CSF, cerebral spinal fluid; CXR, chest x-ray; pmn (polymorphonuclear cell); UA, urinalysis; WBC, white blood cell; wbc/hpf (white blood cells per high-powered field).

can provide additional reassurance for well-appearing infants who are discharged prior to 48 hours.²⁷

When a Longer Observation Period May Be Warranted

An observation time of >36 hours for febrile infants can be considered if the patient does not meet the generally accepted low-risk clinical and/or laboratory criteria (Table 2) or if the patient clinically deteriorates during hospitalization. Management of CSF pleocytosis both on its own²⁸ and in the setting of febrile urinary tract infection in infants remains controversial²⁹ and may be an indication for prolonged hospitalization. Incomplete laboratory evaluation (eg, lack of CSF due to unsuccessful lumbar puncture,³⁰ lack of CBC due to clotted samples) and pretreatment with antibiotics³¹ can also affect clinical decision making by introducing uncertainty in the patient’s pre-evaluation probability. Other factors that may require a longer period of hospitalization include lack of reliable follow-up, concerns about the ability of parent(s) or guardian(s) to appropriately detect clinical deterioration, lack of access to medical resources or a reliable telephone, an unstable home environment, or homelessness.

What You Should Do Instead: Limit Hospitalization to a Maximum of 36 Hours

For well-appearing febrile infants between 0–90 days of age hospitalized for observation and awaiting bacterial culture results, providers should consider discharge at 36 hours or less, rather than 48 hours, if blood, urine, and CSF cultures do not show bacterial growth. In a large health system, researchers implemented an evidence-based care process model for febrile infants to provide specific guidelines for laboratory testing, criteria for admission, and recommendation for discontinuation of empiric antibiotics and discharge after 36 hours in infants with negative bacterial cultures. These changes led to a 27% reduction in the length of hospital stay and 23% reduction in inpatient costs without any cases of missed bacteremia.²¹ The reduction in the in-hospital observation duration to 24 hours of

culture incubation for well-appearing febrile infants has been advocated³² and is a common practice for infants with appropriate follow up and parental assurance. This recommendation is supported by the following:

- Recent data showing the overwhelming majority of pathogens will be identified by blood culture <24 hours in infants aged 0-90 days³² with blood culture TTP in infants aged 0-30 days being either no different²⁶ or potentially shorter³²
- Studies showing that infants meeting low-risk clinical and laboratory profiles further reduce the likelihood of identifying serious bacterial infection after 24 hours to 0.3%.¹

RECOMMENDATIONS

- Determine if febrile infants aged 0-90 days are at low risk for serious bacterial infection and obtain appropriate bacterial cultures.
- If hospitalized for observation, discharge low-risk febrile infants aged 0–90 days after 36 hours or less if bacterial cultures remain negative.
- If hospitalized for observation, consider reducing the length of inpatient observation for low-risk febrile infants aged 0–90 days with reliable follow-up to 24 hours or less when the culture results are negative.

CONCLUSION

Monitoring patients in the hospital for greater than 36 hours of bacterial culture incubation is unnecessary for patients similar to the 3 week-old full-term infant in the case presentation, who are at low risk for serious bacterial infection based on available scoring systems and have negative cultures. If patients are not deemed low risk, have an incomplete laboratory evaluation, or have had prior antibiotic treatment, longer observation in the hospital may be warranted. Close reassessment of the rare patients whose blood cultures return positive after 36 hours is necessary, but their outcomes are excellent, especially in well-appearing infants.^{7,33}

What do you do?

Do you think this is a low-value practice? Is this truly a “Thing We Do for No Reason”? Let us know what you do in your practice and propose ideas for other “Things We Do for No Reason” topics. Please join in the conversation online at Twitter (#TWDFNR)/Facebook and don't forget to “Like It” on Facebook or retweet it on Twitter. We invite you to propose ideas for other “Things We Do for No Reason” topics by emailing TWDFNR@hospitalmedicine.org.

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