

LEARNING OBJECTIVES

- Describe the use of viral immunoassay in screening for serious bacterial infection (SBI) in the febrile infant younger than 90 days
- Discuss the benefit of enhanced urinalysis as a specific marker for urinary tract infection
- Review the studies of other biochemical markers that may be useful in the identification of SBI

New diagnostic tools for managing the febrile infant

The latest advances in diagnosing the cause of fever in infants younger than 90 days old include viral immunoassays, enhanced urinalysis, and biochemical markers.

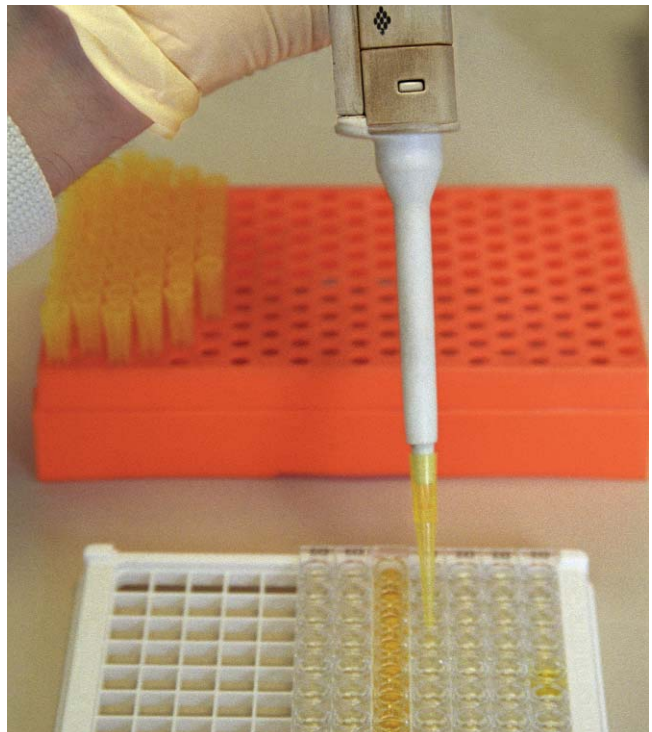
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Every day, a large number of infants 90 days old or younger are taken to emergency departments (EDs) and other health care settings exhibiting only a fever. Physicians and PAs are faced with the challenge of determining the cause of the fever when no other localizing signs or symptoms are present. How to manage these infants remains an ongoing debate among clinicians. Pantell and colleagues demonstrated that experienced outpatient pediatricians use individualized clinical judgment to treat febrile infants.¹ Some clinicians prefer to start antibiotics immediately and send the patient home. Others admit the patient and perform a detailed workup. Two of the more common workups involve using the Rochester criteria² and the Philadelphia criteria.³ Part 1 of this article, published in the February issue, described the current standard of care for managing febrile infants younger than 90 days. This article reviews recent advances that help clinicians to identify the etiology of fever in these infants and to differentiate serious bacterial infection (SBI) from viral illness. The most promising of these advances include viral immunoassays, enhanced urinalysis (EUA), and tests to measure biochemical markers. These tests have the potential to eliminate unnecessary use of antimicrobials, lower the number of invasive procedures performed, and decrease costly hospitalizations.

VIRAL IMMUNOASSAYS

Viral immunoassays are designed to identify the presence of a virus. The ability to diagnose viral infections has improved dramatically in recent years, and the role of viral diagnostic tests is becoming more prevalent. Studies have shown that infections in approximately 8.5% to 13% of

febrile infants aged 90 days or younger have a bacterial source; the remaining infections are presumed to have a viral source alone or to have concomitant viral and bacterial sources.⁴⁻⁷ Several studies have compared febrile infants with a known viral infection and febrile infants with no viral infection. The results demonstrated that infants with a viral infection are less likely to have an SBI than infants who do not have a viral infection.



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Byington and colleagues used polymerase chain reaction, culture, enzyme-linked immunosorbent assay (ELISA), and direct fluorescent assay to identify a variety of viral infections, including infection with enterovirus; respiratory syncytial virus (RSV); influenza A and B; parainfluenza 1, 2, and 3; rotavirus; herpes simplex virus; varicella; and adenovirus in 1,385 febrile infants aged 1 to 90 days.⁴ The researchers compared the rate of SBI in infants with at least one virus with that of infants with no virus. Of the 1,385 enrolled patients who underwent testing for viral and bacterial infections, 491 (35%) infants tested positive for one or more viruses, of which 21 (4.2%) had an SBI. On the other hand, an SBI was found in 110 (12.3%) of the 894 infants with no viral infection. Worth noting, none of the patients with a viral infection had meningitis, but six patients (0.67%) with no viral infection had meningitis. In addition, bacteremia was diagnosed in only five patients (1%) with a viral infection but in 24 (2.7%) patients without a viral infection. Byington's group concluded that SBIs are much less likely to occur in infants with a viral infection than in infants without a viral infection.⁴

Smitherman and colleagues compared the incidence of SBI in febrile children up to 36 months old with influenza A virus with SBI in similarly aged children without influenza A virus, determined by rapid antigen test (RAT) or a positive viral culture.⁶ Of the 705 children, 163 (23%) were positive for influenza A (IP) and 542 (77%) were negative for influenza A (IN). The study reported that the prevalence of bacteremia, urinary tract infection (UTI), meningitis, and pneumonia was lower in the IP group than in the IN group (see Table 1, page 46). Smitherman's team concluded that SBIs occur much less frequently in children with influenza A virus than in those without the virus and that RAT testing can be a cost-effective tool for screening.⁶

Titus and Wright compared SBI rates in febrile infants with RSV with SBI rates in febrile infants without RSV, identified by ELISA test.⁷ A total of 174 previously healthy febrile infants 8 weeks old and younger with a positive RSV antigen test were matched with 174 previously healthy febrile infants similarly aged without RSV. Only two (1.4%) patients in the RSV-positive group had an SBI, both of which were UTIs. In the RSV-negative group, 22 (15%) patients had an SBI, 17 (77.3%) of which were a UTI. The authors concluded that

febrile infants younger than 8 weeks with RSV have a low risk of having an SBI compared with febrile infants younger than 8 weeks without RSV. This study also indicated that a complete septic workup may not be necessary in previously healthy infants with an RSV. The researchers noted that the risk of bacteremia and meningitis are particularly low when an RSV is present, but the risk of UTI still warrants urine studies in all febrile infants.⁷

Levine and team studied febrile infants younger than 60 days presented to any of eight pediatric EDs from October 1998 to March 2001.⁵ Similar to the Titus study, this study compared the risk of SBI in febrile infants with RSV with those not infected with RSV, as determined by an antigen test. Of the 1,248 enrolled patients, 269 were positive for RSV and 979 were negative for RSV. The authors reported an overall SBI incidence of 7% in the RSV-positive group and 12.5% in the RSV-negative group. The incidence of UTI was 5.4% in patients with RSV versus 10.1% in the control group. The authors concluded that febrile infants younger than 60 days with RSV are at a lower risk of having an SBI than those infants without RSV, but they recommend urine testing even in RSV-positive infants.⁵

These studies suggest that nontoxic-appearing infants with a positive viral test are at low risk for an SBI. However, several studies suggested that UTIs are still a major concern, even in infants with a viral infection. Although a full septic workup may not be necessary in the presence of positive viral findings, urinalysis appears to be prudent for all febrile infants.

ENHANCED URINALYSIS

Because UTIs are the most commonly diagnosed and misdiagnosed SBI in febrile infants, a test that easily diagnoses or rules out these infections is an important diagnostic tool. EUA was first described by Dukes in 1927 as a more specific marker for UTI than standard urinalysis. EUA is defined as the combination of hemocytometer cell count and Gram's stain on uncentrifuged urine.⁸

Shaw and colleagues compared the outcomes of several UTI screening tools, in terms of both sensitivity and cost.⁹ The authors found that EUA had the highest sensitivity (94%) but the lowest specificity (84%); they compared EUA with standard urinalysis, dipstick urinalysis, cell count, and

KEY POINTS

- Use of viral immunoassays, enhanced urinalysis (EUA), and biochemical marker levels has the potential to eliminate unnecessary use of antimicrobials, lower the number of invasive procedures performed, and decrease costly hospitalizations in febrile infants.
- Studies have shown that infections in approximately 8.5% to 13% of febrile infants younger than 90 days old have a bacterial source; the remaining infections are presumed to have a viral source alone or concomitant viral and bacterial sources.
- EUA is defined as the combination of hemocytometer cell count and Gram's stain on uncentrifuged urine.
- The biochemical markers C-reactive protein, endogenous pyrogens, and procalcitonin are potentially effective predictors of the presence of an SBI.

COMPETENCIES

●●●● Medical knowledge

● Interpersonal & communication skills

● Patient care

● Professionalism

●●●● Practice-based learning and improvement

●●●● Systems-based practice

Gram's stain. The authors concluded that although standard urinalysis may be the most cost-effective method for detecting UTIs, EUA is the best test for detecting UTI in situations where high sensitivity and early treatment are necessary.⁹

Herr and colleagues evaluated a set of criteria that would identify febrile infants at low risk for acquiring an SBI.⁸ Previous studies used standard urinalysis as one factor in the low risk criteria, but this study used EUA because of its greater sensitivity and negative predictive value (NPV). Of the 434 infants enrolled in the study, 344 were classified as low risk based on a number of laboratory criteria. Of the infants found to have an SBI, none came from the low risk group (NPV = 100%). The researchers found that EUA correctly identified 24 out of 25 infants who had a positive urine culture, resulting in a 96.7% sensitivity and a 99.7% NPV. Although EUA alone would have falsely categorized one infant as low risk, the additional laboratory tests used were stringent enough to correctly categorize that infant as a high-risk patient. The authors concluded that EUA, because of its increased sensitivity, is superior to standard urinalysis in the evaluation of febrile infants. The test identified 100% of infants with a positive urine culture and 100% of infants with an SBI.⁸

The results of these studies establish a strong case for replacing standard urinalysis with EUA to identify febrile infants at low risk for an SBI. Such a step would more accurately categorize febrile infants into the proper risk group and reduce the overall number of missed SBIs. Although the availability of EUA is limited, the results of these studies warrant further investigation and expanded use of EUA.

BIOCHEMICAL MARKERS

Several studies examined a number of biochemical markers that may prove useful in identifying SBIs in febrile infants. C-reactive protein (CRP), endogenous pyrogens (EPs), and procalcitonin (PCT) are just a few of the biomarkers being studied for their potential effectiveness in predicting or ruling out the presence of an SBI.

CRP is released in response to inflammation and tissue damage. Elevated levels of this protein are currently used by some clinicians to diagnose bacterial infections. van Rossum and team reviewed 10 studies published between 1998 and 2003. Their findings questioned the usefulness of CRP because the reported ranges of CRP sensitivity, specificity, and NPV varied widely.¹⁰ EPs, such as cytokines or interleukins, tissue necrosis factor (TNF), and interferons, are released by the body and cause a febrile response to certain infectious toxins. Of the EPs, interleukin-6 (IL-6) may be the most useful in differentiating bacterial from viral infections. A study of febrile children aged 0 to 36 months with a small sample size concluded that IL-6 levels may be helpful in predicting occult bacteremia, but TNF and IL-1 levels are not helpful. The addition of an absolute neutrophil count (ANC) with IL-6 was more predictive of occult bacteremia than traditional tests and clinical signs. The combination of IL-6 and ANC had a sensitivity of 100% and a specificity of 78% with an NPV of 100%. These results indicate a possible future role for IL-6 in predicting occult bacteremia.¹⁰

Levels of PCT, a calcitonin precursor produced by the thyroid gland and released only in response to infection, are widely used in risk assessment of critically ill adults. However, PCT levels elevate immediately after birth and return to normal on approximately the third day of life. This natural occurrence is an obstacle when using this marker to evaluate febrile neonates aged 4 days and younger.

Prat and colleagues conducted a study of children, aged 1 month to 12 years, evaluated at a pediatric ED for fever of more than 12 hours' duration.¹¹ The children were assigned to one of four groups, based on their condition. The first group (n = 25) of children had bacterial sepsis or meningitis. In the second group (n = 18), aseptic meningitis was diagnosed based on presenting signs and symptoms; blood and CSF cultures were negative for bacteria. The third group (n = 22) had a localized infection such as sinusitis, otitis media, or cellulitis. The last group was the control

TABLE 1. Prevalence of SBIs with influenza A virus

Number of infants (N = 705)	Positive for influenza A virus (n = 163 [23%])	Negative for influenza A virus (n = 542 [77%])
Total SBIs (excluding pneumonia) ^a	3 (1.8%)	63 (11.6%)
Total SBIs (including pneumonia) ^a	16 (9.8%)	153 (28.2%)
Bacteremia	1 (0.6%)	23 (4.2%)
UTI	2 (1.8%)	38 (9.9%)
Meningitis	0	4 (2.2%)
Pneumonia	13 (25.5%)	99 (41.9%)

Key: SBI, serious bacterial infection; UTI, urinary tract infection.

^a Investigators were not sure whether to classify pneumonia as an SBI. Results are reported as excluding pneumonia as an SBI and including pneumonia as an SBI.

Data from Smitherman HF et al.⁶

group (n = 25) of similarly aged, healthy children. The PCT levels of every child in the first group were higher than 2 ng/mL. In all of the remaining groups, the PCT levels were 2 ng/mL or lower. This study's findings indicated that a PCT cutoff of 2 ng/mL has a sensitivity, specificity, positive predictive value, and NPV of 100% for bacterial sepsis and meningitis.¹¹

Hatherill and team studied children younger than 3 months (n = 46) and 3 months to 3 years (n = 64) (overall median age, 16 months).¹² However, this study only included children admitted to the ICU, which possibly contributed to selection bias. Based on a PCT level higher than 2 ng/mL, all the patients with bacterial meningitis and sepsis were identified, producing the same results as Prat's study.¹²

Enguix and colleagues conducted a study including neonates aged 3 to 30 days (n = 46) and children 2 months to 12 years (n = 70).¹³ Again, the researchers included only those admitted to the NICU and PICU. This study set a higher cutoff concentration (8.1 ng/mL); however, the results were the same as results for the Prat and Hatherill studies: all cases of bacterial sepsis were correctly diagnosed.¹³

Some limitations of the aforementioned studies were small sample size, wide range of patient ages, and insufficient data regarding the amount of time from onset of signs and symptoms to when diagnostic tests were performed. Many other studies also report high sensitivity and NPV when using PCT as a general screening tool for SBI. Most of the studies reported that 2 ng/mL was the best cutoff value for distinguishing between invasive and localized bacterial infections. Even though the findings of these studies look promising, additional large, multicenter randomized, controlled trials using PCT specifically in febrile neonates are needed to determine the optimal role of this biomarker in screening for SBIs.

CLINICAL JUDGMENT

Private practitioners and clinicians in academic health settings differ in their clinical approach to the febrile infant. In a study of 3,066 infants aged 3 months or younger with a temperature of 38°C or higher and seen within the Pediatric Research in Office Settings (PROS) network, the PROS clinicians hospitalized 35% of the infants, laboratory tests were performed for 75%, and 57% were initially treated with antibiotics.¹ The majority of the infants (64%) were treated exclusively outside of the hospital. Practitioners followed current guidelines in 43% of the cases. Antibiotic treatment was initiated in 61 of the 63 cases of bacteremia/bacterial meningitis during the initial visit. The authors suggested that adhering to the current guidelines may not have improved care but would have resulted in more hospitalizations and laboratory tests.¹ Physicians and PAs in academic centers follow established guidelines of full septic evaluation to avoid missing any cases of SBI because a missed SBI is potentially lethal.

Establishing the cause of fever in the infant and initiating the appropriate treatment are elusive without the availability

of more sensitive diagnostic tests. Although clinical judgment improves with experience, it does not have 100% sensitivity and specificity. A combination of clinical judgment and more sensitive laboratory assessments may achieve this level of diagnostic accuracy. Viral immunoassays and EUA have proven to be helpful. Biochemical markers, such as PCT, show considerable promise but further studies are needed.

CONCLUSION

Determining the source of fever in infants younger than 90 days continues to pose special challenges to health care providers. As evidenced by the literature, community practitioners rely more on their clinical judgment than on published guidelines, which is a very different approach than that used by clinicians in academic settings. Because of these discrepancies, it is important to find new ways to detect SBI in these infants. The most promising developments are viral immunoassays and EUA. Studies show that identifying a viral source of fever points away from a concomitant bacterial source. The addition of EUA is valuable in ruling out UTI, the most common SBI. Biochemical markers may have a role in screening for SBI as well, but more comprehensive studies are necessary to confirm the usefulness of these laboratory tests in the management of febrile infants younger than 90 days. **JAAPA**

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