PERSPECTIVE

Identifying Serious Bacterial Infections in Febrile Young Infants

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Fever is one of the most common presenting complaints among infants brought to pediatric emergency. Although most of the infants have benign, self-limiting viral infections, approximately 10% of all may have serious bacterial infection. Clinical examination alone is insufficient to detect serious bacterial infection in well appearing infants, and a standardized approach is always sought for. However, guidelines used in the United States or European countries may not be applicable in a tropical country like India. Deviation from these guidelines leads to challenges of unwarranted hospitalization and antibiotic usage, extra cost of care and risk of antimicrobial resistance. Various prediction rules can detect a low risk infant with negative predictive values ranging from 93.7-100%. While use of biomarkers such as C reactive protein and procalcitonin can be reliable, it is costly and may not be applicable to the local population. Validation studies over varied population are needed in future.

Keywords: *Blood culture, Diagnosis, Investigations, Management, Procalcitonin*.

Fever is one of the most common presenting complaints of children brought to pediatric emergency. Data from developing countries is lacking, but in the United States, fever accounts for almost 20% of the visits to the pediatric emergency department [1]. Fever may result from infectious (bacterial, viral, parasitic) or non-infectious (autoimmune, environmental, drugs) causes. Young infants (0-90 days) are particularly at risk of serious bacterial infections (SBI) that include bacteremia, meningitis, pneumonia and urinary tract infections, owing to their immature immune system and absence of localizing signs [2]. The incidence of SBI in young infants is reported to be 7-11% [3]. Our focus of discussion here includes neonates (0 to 28 days) and infants aged 29 to 90 days old, in whom the diagnosis and management of SBI is challenging, with a battery of tests being conducted alongwith administration of empirical antibiotics. The authors present a perspective on the dilemmas and current advances in the evaluation and management of febrile young infants.

GUIDELINES FOR IDENTIFICATION

Diagnosis of SBIs in young febrile infants has been challenging for years for clinicians and researchers globally. Clinical examination alone is insufficient to detect SBI as many infants appear well and do not show any localizing symptoms or signs. Results of many of the laboratory tests, like culture, take time. Thus, a standardized approach to identify these cases early, simultaneously avoiding over-investigation and over-treatment in this vulnerable age group is desirable.

Protocols for management of sick or toxic looking infants (defined as clinical picture consistent with the sepsis syndrome including lethargy, signs of poor perfusion, marked hypoventilation or hyperventilation or cyanosis) are relatively well defined, but there is a lack of consensus regarding guidelines for well looking febrile young infants [4]. Further, differentiating well appearing young infants with SBI from those having a benign viral infection remains a diagnostic challenge. Given the incidence of meningitis in neonatal age group is as high as 0.8-6 per 1000 live births [3], American College of Emergency Physicians (ACEP) recommended performing lumbar puncture even in well looking young infants (< 28 days) [5]. Updated ACEP guidelines in the year 2016 focused on key issues pertaining to well appearing febrile child less than 2 years of age and gave evidence-based recommendations after performing systematic review [2].

Guidelines used in the United States or European countries may not be applicable in a tropical country like India. Immunization status of infants also affects the differential diagnosis of fever in this age group. Mahajan, et al. [6] proposed an algorithmic approach for evaluation and management of a febrile child, applicable in India. These guidelines focused on the triage, assessment and management of a child presenting with fever in the emergency department. They recommended that, in all toxic looking infants and well appearing infants aged <28 days, comprehensive severe sepsis evaluation is to be, including complete blood count, quantitative C-reactive protein

(CRP), peripheral smear, blood culture, chest *X*-ray, urinary analysis including culture and lumbar puncture. For well appearing infants aged 29 days to 90 days, lumbar puncture was not advocated. Also, chest *X*-ray had to be performed only if TLC >20,000/cumm, temperature >39^{0}C or respiratory symptoms were present. These guidelines are consensus based, but reasonable to use in absence of strong evidence. However, more research is needed to understand the epidemiology of febrile children ≤90 days of age in India and for validation of the algorithm countrywide. Introduction of newer immunization policies incorporating *H. influenzae* and pneumococcal vaccines and development of antigen-based point-of-care rapid diagnostic tests for various bacterial and viral diseases, for example lateral flow immunochromatographic tests (LFIA) for *Gp A Strepto-coccus*, respiratory syncytial virus (RSV), nucleic acid amplification tests (NAAT) and nicking enzyme ampli-fication reaction (NEAR) for influenzae A and B, have led to a perceived need for change in these guidelines [7].

Although globally, pediatric emergency medicine physicians report following a set of published guidelines for the management of a well-appearing febrile infant, there is a wide variation in diagnostic testing and hospitalization across different sites for young infants aged less than 60 days, with rates of lumbar puncture and hospitalization ranging from 40-90% [8-12]. Non-adherence to these guidelines, results in unwarranted hospitalization, antibiotic usage, extra cost of care and risk of antimicrobial resistance.

CLINICAL PREDICTION CRITERIA

Various prediction rules or criteria have been established in the past to detect infants who do not require hospital admission or parenteral antibiotics. Boston [9], Philadelphia [10] and Rochester criteria [11] are few such well-established prediction rules with negative predictive values ranging from 93.7% to 100%. Application of Boston criteria [9] in 503 infants (28 to 89 days), having fever without focus, showed that 94.6% infants had no SBI if total leucocyte counts were < 20,000/cumm, CSF cell counts were < 10 cells/cumm, with normal urinalysis and normal chest *X*-ray (if done). Philadelphia rule [10] utilized clinical assessment and a set of extensive laboratory evaluation to categorize infants (29 to 56 days) as 'low risk' for SBI, who could be managed on out-patient basis without antibiotics. Rochester criteria were applied to infants who were term-born, without perinatal complications, nor any underlying disease and had not received antibiotics previously, excluding those who were 'too ill' to wait evaluation. Negative predictive value (NPV) of Rochester criteria for ruling out SBI was close to 99% [11]. These rules were created to safely identify infants who are at low risk of having a serious or invasive bacterial infection as the cause of their fever. However, these prediction rules have not been validated across cultural, geographic, socio-economic environ-ments and thus may not be applicable in all clinical settings. A comparison of these three commonly used criteria is given in **Table I**.

Cerebrospinal Fluid Examination

Missing SBIs like meningitis or bacteremia, may lead to serious consequences. The risk of missing SBI must be weighed against the cost of hospitalization, risk of hospital-acquired infections and probable misuse of antibiotics. A large study of 3,246 infants observed bacterial meningitis in only 0.2% of the well-appearing febrile infants >28 days old [13], thus raising doubts regarding the need for routine cerebrospinal fluid (CSF) examination in infants less than 60 days of age. [14,15], In

Table I Comparison of Different Clinical Prediction Criteria to Identify Febrile Young Infants at Low Risk of Serious Bacterial Infections

	Philadelphia criteria [10]	*Rochester criteria [11]*	*Boston criteria [9]*
Age (d)	29-60	<60	28-89
Laboratory parameters (for low risk status)	WBC <15,000/µL Band-neutrophil ratio <0.2 Urine analysis <10 WBC/hpf CSF <8 WBC/µL CSF Gram stain-negative Chest *X* ray – without infiltrates Stool-without blood, few/no WBCs	WBC >5000 and <15,000/µL Absolute band count <1500/µL Urine analysis <10 WBC/HPF Stool <5 WBC/HPF Chest *X*-ray negative	WBC <15,000/µL Urine analysis <10 WBC/HPF CSF <10 WBC/µL Chest *X*-ray negative
Recommendations for low-risk patients	Home care No antibiotics Follow-up	Home care No antibiotics Follow-up	Home care Antibiotics administered Follow-up

WBC: White blood cells; UA –, CSF: Cerebrospinal fluid; hpf: High power field.

another study, in infants with UTI, probable bacterial meningitis was seen in 0.8%, while none had confirmed bacterial meningitis, thereby prompting the authors to recommend a tier-based approach for the evaluation of febrile infants [16]. Such results were reiterated in a systematic review of low-risk febrile young infants with UTI, thus making lumbar puncture (LP) questionable in such infants [17]. Despite growing evidence, centers still perform CSF testing in this age group, because of risk of neurologic sequelae and mortality associated with bacterial meningitis [18,19]. The frequently used Rochester and modified Philadelphia criteria [14] do not require routine lumbar puncture to classify febrile infants as being at low or high risk for SBI. Aronson, et al. [20], found that the modified Philadelphia criteria had higher sensitivity than that of Rochester criteria (91.9% vs 81.5%; P=0.01), but the specificity was lower (34.5% vs 59.8%; P<0.001) to stratify apparently well febrile infants with invasive bacterial infection, without the use of LP. Thus, there is minimal risk of missing a child with meningitis or SBI if these criteria are used judiciously, avoiding unnecessary LP. Yale Observation Scale (YOS), an easily applied observational scale, without any investigations, compiled three decades back [21], was not found to reliably predict SBI in infants< 60 days [22]. On the contrary, a large number of infants aged 29-60 days old, were misclassified as having invasive bacterial infection using modified Boston and modified Philadelphia criteria [23].

In view of the low risk of meningitis, ACEP (2016) recommends that CSF examination can be deferred in full-term, well-appearing, febrile infants, between 29 and 90 days, diagnosed with a viral illness. Antibiotics are to be avoided, unless another bacterial source is identified. Admission, or quick follow-up visits is advisable. [2]. Previous guidelines by ACEP (1993) recommended giving single dose of parenteral ceftriaxone and outpatient management with re-evaluation in OPD 24 hours later, in low-risk febrile infants aged 29 to 60 days, after documenting normal CSF cytology and sepsis screen. In low-risk febrile infants between 61-90 days, additionally, the more conservative approach of withholding lumbar puncture and re-evaluation is to be considered [5]. In a recent study, Kuppermann, et al. [24] as a part of the 'Febrile infant working group of the pediatric emergency care applied research network (PECARN)' derived and validated a clinical prediction rule to identify febrile infants <60 days at low risk of SBI. They concluded that negative urinalysis result, absolute neutrophil count (ANC) of ≤4090/µL, and serum procalcitonin of ≤1.71 ng/mL can rule out SBI with 97.7% sensitivity and 99.6% negative predictive value [24]. The advantage of this rule is that it averts the need for CSF analysis.

Role of Biomarkers

Literature suggests promising role of newer biomarkers in early, reliable identification of children with SBI. Studies have suggested that markers like C-reactive protein (CRP), and procalcitonin (PCT) are useful in predicting SBI [25-30]. Procalcitonin had a greater area under curve than CRP in febrile infants with more invasive disease i.e. sepsis, bacteremia, and bacterial meningitis [31].

STEP-BY-STEP APPROACH

With the objective of avoiding unnecessary investigations, without the risk of missing cases of SBI, a middle path combining clinical criteria and statistically derived cut-offs of standard laboratory tests and newer biomarkers can be used to risk stratify infants and derive prediction rules. The 'step by step' approach is one such algorithmic approach developed by European group of pediatric emergency physicians [32]. This approach sequentially evaluates the general appearance, age, urinalysis and lastly, biomarkers, to identify a low-risk infant who could safely be managed as outpatient without the need of lumbar puncture or empirical antibiotic therapy. Gomez, et al. [33] validated the 'step-by-step' approach and concluded that the sensitivity and NPV of this approach to rule out SBI in infants <90 days was 92% and 99.3%, respectively, which was better than Rochester criteria and lab-score alone. Galleto Lacour, et al. [34] developed and validated a laboratory index score that utilized PCT, CRP and urinary dipstick and found it to be a reliable tool for identifying infants at risk of SBIs. However, prior to application of prediction rules such as the Step-by-Step rule or the PECARN Febrile Infant prediction rule, a robust analysis of the epidemiology of febrile infants as well as feasibility of implementation in the local population needs to be undertaken, because even robustly derived and validated rules may be difficult to apply/implement if found to be irrelevant to the local population.

FUTURE DIRECTIONS

Whenever any decision is taken regarding the management of a febrile child, parents or guardians must be included in the decision-making process. This includes, but is not limited to, clearly informing the risk of including or excluding components of evaluation (like lumbar puncture) and management, so that an informed, responsible decision can be taken. Since neither isolated clinical nor laboratory criteria can absolutely rule in or rule out SBIs in febrile young infants, development of prediction rules seem to be a promising option. Viral infections especially herpes simplex virus and respiratory

Box I Key Points for Identifying Serious Bacterial Infections in Febrile Young Infants

- Neither clinical examination nor individual investigations alone are sufficient to detect serious bacterial infections in well appearing febrile young infants.
- Derivation of prediction rules incorporating clinical prediction rules and investigations including quantitative C-reactive protein and procalcitonin are promising options.
- Multicentric validation studies are required to prove efficacy of these rules.

syncytial virus should also be considered as possible etiologies. Validation studies over varied population and derivation of the age-specific cut-offs of laboratory tests like quantitative CRP, procalcitonin and other biomarkers should be conducted to provide a definite plan for identification of SBI in febrile young infants.

The key messages are listed in **Box I**. Quantifying host immune response to presence of bacterial or viral pathogen using RNA bio-signatures forms an exciting area of future research, which has the potential to replace cultures as the reference standard [35].

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