PRACTICAL SUMMARIES IN
ACUTE CARE
A Focused Topical Review of the Literature for the Acute Care Practitioner

Updates on the Management of Pediatric Fevers in Patients 4–12 Weeks of Age

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Introduction

HISTORICALLY, ALL FEBRILE infants younger than 90 days of age were aggressively evaluated and treated with empiric antibiotics until culture results were available. Although this approach ensured the highest level of sensitivity in the detection of serious bacterial infection (SBI), such evaluations were time- and labor-intensive, and created a risk for unnecessary adverse reactions to medications.

In the 1990s, well-published guidelines (Philadelphia Protocol and Rochester Criteria) suggested a full sepsis evaluation should be pursued in all febrile infants < 28 days old.[1,2] The recommended evaluation included blood cultures, urinalysis, urine cultures, and cerebral spinal fluid (CSF) analysis. The recommendation in a 28- to 90-day-old patient with fever and no source might be abbreviated if the patient was clinically "low-risk" and had received appropriate vaccinations.

Dr. Baker and colleagues (Philadelphia Protocol) enrolled 747 infants age 29 days to 56 days old with temperatures >38.1°C.[3] SBI was diagnosed in 65 (8.7%) of these infants, 64 of which were identified by their screening criteria. The criteria had a 100% negative predictive value for SBI and identified low-risk patients who could safely be discharged home with close follow-up.

Dr. Jaskiewicz and colleagues (Rochester Criteria) also developed criteria for the identification of febrile infants at "low risk" for serious bacterial infection.[4,5] They enrolled 1,057 infants, 437 of whom met the criteria for "low-risk." These criteria had a negative predictive value of 98.9% for any SBI and 99.5% for bacteremia.

This review will focus on studies published since 2004, highlighting the issues that remain controversial in the management of febrile infants, and will discuss the search for biomarkers that may help identify infants with SBI.

Can We Identify Infants at Low Risk for Serious Bacterial Infection (SBI)?

Source: Marom R, 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.

THIS PROSPECTIVE STUDY SOUGHT to delineate criteria to identify neonates at "low-risk" for SBI. All febrile neonates presenting to two hospitals in Israel had a blood culture, erythrocyte sedimentation rate, white blood cell (WBC) count, and urine and CSF analyses and culture

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performed. SBI was defined as bacterial pathogen isolated from blood, urine, CSF, middle ear, stool, and in patients who were diagnosed with any disease commonly associated with bacterial infection, including acute otitis media or soft tissue infection.

"Low-risk" criteria for SBI were defined as follows:

Well-appearing;

No focal signs of infection;

Unremarkable medical history;

ESR < 30mm at the end of the first hour;

WBC between 5,000/mm^3 and 15,000/mm^3; and

Normal urinalysis by dipstick.

During the study period, 449 children were admitted to the study sites, with complete data available for 386 (86%). Of the 386 neonates in the study, 108 (28%) had an SBI. Fifty-four neonates (14%) had a urinary tract infection (UTI), 36 (9.3%) had acute otitis media, 9 (2.3%) had pneumonia, 5 (1.3%) had cellulitis, 2 (0.5%) had bacterial meningitis, and 2 (0.5%) had bacterial gastroenteritis.

Using the criteria above, 166 (43%) of the neonates were stratified as "low-risk" for SBI. The incidence of SBI in these children was 0.6% (1/166). The single child in whom bacterial infection was missed had a UTI with an initially negative dipstick urinalysis and a positive urine culture 36 hours later. The child was treated and recovered uneventfully.

The incidence of SBI in the neonates who did not meet "low-risk" criteria was 48.6% (107/220). A pathogen was isolated in 31.8 % (70/220) of these cases. The negative predictive value (NPV) for SBI using these criteria is 99.4%. The authors concluded that neonates that are at "low risk" for SBI can be identified using these criteria, but even these infants need urinalysis and urine cultures, which should be checked at the time of follow-up.

Commentary

This prospective study correlates well with prior data indicating the relative safety of treating select low-risk febrile infants with careful observation rather than empiric antibiotics. The interesting point of this study was that it examined all neonates who presented with a fever and was therefore more inclusive than the Philadelphia protocol which only applied to children > 28 days of age. These criteria differ from those in the Rochester Criteria, including fewer specific pre- and perinatal history questions, and excluding band counts, stool studies, and microscopic urine analysis.

The NPV of these low-risk criteria was 99.4%, which compared with 98.9% and 97.3% in two studies of the Rochester Criteria. While the sample size was moderate (386), it was large enough to provide statistically significant results. Of note, the infants from this study were from a demographic group that potentially differs somewhat from many pediatric practices in the United States. However, the results were similar to prior studies suggesting low-risk criteria similar to these are likely generalizable to infants in all developed countries where rapid evaluation and close outpatient follow-up are possible.

Can Existing Criteria for Identification of Infants at Low Risk for SBI Be Applied to Other Populations?

Source: Garra G, et al. Reappraisal of criteria used to predict serious bacterial illness in febrile infants less than 8 weeks of age. *Acad Emerg Med* 2005; 12:921-925.

DR. GARRA AND COLLEAGUES sought to test the Philadelphia Protocol and Rochester Criteria in a new population. They performed a prospective validation study at an urban public hospital with a pediatric emergency department (ED) and an annual census of approximately 40,000 patients.

Infants 56 days of age or younger with a rectal temperature of ≥100.6°F were enrolled in the study

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Questions & Comments

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over a 4.5-year period. Prior to laboratory evaluation, physicians recorded an Overall Impression of Sepsis, and an Infant Observation Score.[6] Laboratory evaluation included the acquisition and interpretation of a CBC, CSF studies, urinalysis, serum glucose concentration, and cultures of blood, urine, and CSF. Chest radiograph, respiratory syncytial virus (RSV) testing, and stool studies were obtained at the discretion of the physician.

Investigators blinded to the final culture results and diagnosis assigned a risk category based on the Philadelphia Protocol and the Rochester Criteria.[3,4] Only infants age 29–56 days were included in the Philadelphia Protocol analysis since the protocol was not originally applied to children 1–29 days of age.

SBI was defined as infants with UTIs, bacteremia, bacterial meningitis, pneumonia, or bacterial enteritis. Infants with an identifiable source of a likely bacterial infection on physical exam such as acute otitis media, cellulitis, or septic arthritis were considered to have a SBI and were excluded from analysis.

There were 302 children enrolled in the study, but only the 259 with complete data were analyzed. The median age was 36 days. Sixty-five infants were diagnosed with an SBI, 8 with bacteremia, 51 with UTI, 5 with combined UTI and bacteremia, and 1 with bacteremia and bacterial meningitis. Out of 259 infants, 181 were assigned for Philadelphia Protocol risk stratification, and of those 181, 34 were designated low-risk. One infant of those 34 had a serious bacterial infection with a blood culture positive for *E. faecalis*.

All 259 infants were eligible for risk stratification using the Rochester Criteria. Of those, 73 were considered "low-risk" for serious bacterial infection. Two infants in that group were diagnosed with bacterial infection, both with bacteremia (*S. agalactiae* and *E. faecalis*).

The authors then compared the performance of the Philadelphia Protocol and the Rochester Criteria in this study to the previously published studies from other settings. The Philadelphia Protocol had a sensitivity of 97.4% (compared to 98.5%), specificity of 23.2% (compared to 41.9%), a positive predictive value (PPV) of 25.9% (compared to 13.9%), and an NPV of 97.1% (compared to 99.7%). The Rochester Criteria had a sensitivity of 96.7% (compared to 92.4%), specificity of 39.4% (compared to 49.9%), a PPV of 35.1% (compared with 12.3%) and a NPV of 97.3% (compared with 98.9%). The authors concluded that both criteria sets are useful and valid for identifying infants at "low-risk" for SBI.

Commentary

This is a well-designed prospective study that validated the Philadelphia Protocol and the Rochester Criteria in a new population of febrile infants ≤ 56 days of age in an urban setting. This study confirmed the utility of risk stratification of febrile infants such that "low-risk" infants may avoid invasive testing, inpatient management, and empiric antibiotics. The reproducible high NPVs led the authors of this study to accurately conclude that low-risk criteria for febrile infants are useful clinical decision tools that may be applied to larger populations of infants.

Are Clinicians in Pediatric Office Practice Following the Published Practice Guidelines?

Source: Pantell RH, et al. Management and outcomes of care of fever in early infancy. *JAMA* 2004;291:1203-1212.

THIS PROSPECTIVE COHORT STUDY enrolled 3,066 patients through the Pediatric Research in Office Settings (PROS) network in 573 pediatric offices. The course of care was analyzed for each febrile infant less than 3 months of age that presented to participating facilities over the course of three years. Data were analyzed looking for predictors of SBI.

The pre-laboratory testing demographic correlates ($p<0.05$) of increased likelihood of bacteremia/ bacterial meningitis included: patients enrolled in Medicaid, patients rated as "very ill" appearing by the pediatrician, those with an ill family member, patients with an abnormal cry, and those with temperatures of 38.5°C–38.9°C or >39.5°C.

Post-laboratory testing analysis demonstrated that patients were at increased likelihood of bacteremia/bacterial meningitis if they met the following criteria: age less than 30 days, insured by Medicaid, were "very ill" appearing, had temperatures 38.5°C–38.9°C or >39.5°C, demonstrated an abnormal cry, or had abnormal WBC counts (<5,000/µl or >15,000/µl).

Of the 3,066 total infants enrolled, 5.4% had UTI, 0.5% had bacterial meningitis, and 1.8% had bacteremia detected. There were 63/3,066 cases of bacteremia/ bacterial meningitis. The authors compared age, clinical assessment and temperature and found that only 4 in 1,056 infants 25 days of age or older who had temperatures < 38.6°C and who appeared minimally ill ended up having bacteremia/bacterial meningitis.

Clinical appearance alone had a sensitivity of 58% for detecting bacteremia/bacterial meningitis. An ill appearing child with an abnormal WBC count yielded a sensitivity of

84%, while urinalysis + an abnormal WBC count + an ill clinical appearance was 87% sensitive. When compared with the composite guidelines which yielded 95% sensitivity, the decision tree analysis in this study was 94% sensitive.

Overall, the sensitivity of the actual treatment of patients with antibiotics at the initial visit was 97% in this study. From their data, the authors concluded that office practitioners are able to use clinical judgment to identify infants with serious bacterial infection as effectively as those using published guidelines.

Commentary

This study shows that while practitioners are deviating from published guidelines, their detection levels and initiation of antibiotics are at the same frequency as if they adhered strictly to published guidelines. The authors suggest that guidelines have not replaced clinical judgment and many infants can be spared invasive testing based on their clinical appearance.

The rate of bacterial meningitis in this study was only 0.5%, which is similar to rates found in other recent studies which identified rates of 0.5%,[7] 0.3%,[8] and 1.2%.[9] The rate of bacteremia in this study was 1.8% compared with 7% and 1.2% in other studies.[7,8] While the number of infants with bacteremia was lower in this study, the authors appropriately point out that the other studies were conducted in urban EDs whereas this study involved patients being seen by primary care pediatricians in their offices.

Another interesting point is that patients receiving Medicaid were significantly more likely to be hospitalized and receive laboratory evaluations. The authors attribute this to perceived differences in adequate follow-up. This highlights the point that all of the studies advocating for less invasive management of "low-risk" febrile infants maintain close follow-up as a critical criterion in the decision for outpatient management.

Can WBC Count Be Used as a Predictor of Bacterial Illness?

Source: Brown L, et al. Does leucocytosis identify bacterial infections in febrile neonates presenting to the emergency department? *Emerg Med J* 2005; 22:256-259.

THIS WAS A RETROSPECTIVE RECORD review which attempted to determine whether peripheral WBC may be used to identify febrile neonates 1–28 days of age with bacterial infections. The available records were analyzed, recording the following variables: WBC count, blood culture, CSF analysis and culture, viral study results, urinalysis and culture, stool culture, and chest radiographs. Complete records were available for 69 febrile infants.

Neonates eligible for the study were divided into the following categories: bacterial infections (8/69), pneumonia (3/69), viral infections (10/69), or completely negative evaluations (48/69). Bacterial infections were defined as either positive cultures for urine, blood, stool, CSF, or a clinical diagnosis of a tissue infection such as cellulitis. Viral infections include positive viral cultures or positive polymerase chain reaction tests. Pneumonia was defined as an infiltrate on chest x-ray without meeting the criteria for bacterial or viral infection.

The WBC counts for neonates in these groups showed significant overlap. While neonates with WBC sounds $>17\times10^9$ cells/L were 3.8 times more likely to have a bacterial infection than those with lower cell counts, a WBC of that magnitude alone was only 38% sensitive for detecting bacterial infection. A WBC of 10×10^9 cells/L retained 100% sensitivity for identifying bacterial infection, but the specificity was only 31%. The authors conclude that WBC alone cannot be used to identify febrile neonates with a bacterial infection.

Commentary

This study was restricted to neonates ≤ 28 days of age and included a modest number of patients (69 infants). However, it adds to a growing body of literature which agrees that WBC counts cannot be used to identify febrile infants with SBI. Like other studies, this report revealed that WBC count cutoffs that are low enough to be sensitive are not highly specific, and cutoffs that are high enough to be specific are not sensitive enough to be utilized in a conservative clinical setting.[10-12] A WBC count cannot be used as a clinical indicator of SBI.

Can WBC Counts Differentiate Which Patients Have a Co-existent SBI?

Source: Purcell K, et al. Lack of usefulness of an abnormal white blood cell count for predicting a concurrent serious bacterial infection in infants and young children hospitalized with respiratory syncytial virus lower respiratory tract infection. *Ped Inf Dis J* 2007;26: 311- 315.

HEALTHCARE PRACTITIONERS ARE often faced with a febrile infant with a viral source such as RSV infection, and the question arises as to how invasive the work-up should be to identify possible concurrent bacterial infections. Purcell, et al sought to determine whether WBC counts might distinguish between infants

with uncomplicated RSV infections and those at risk for concurrent SBI.

This study was a review of records of patients diagnosed with RSV with lower respiratory tract disease during five sequential RSV seasons. Records were analyzed from 1,920 patients ranging in age from 6 days to 6.5 years of age, with 93% of them being < 2 years of age and median age of 142 days. Of the records reviewed, 672 patients had fever, CBC, and a culture of blood, urine, and/or CSF. Of these 672 patients, 34 had a positive culture. One hundred-sixty (160) of these 672 patients had elevated WBC counts, 10 of whom had a positive culture from blood, urine, or CSF. Most of the children in the study had UTIs. Two had UTIs with blood cultures positive for the same organism, one child had isolated bacteremia, and none had positive cultures of CSF. The authors also compared band counts, as well as degree of WBC count elevation, but they concluded that while patients with bacteremia tended to have higher WBC counts, there was no statistically significant discriminator identified that could distinguish between children with RSV infection alone and those with concurrent bacterial infections.

Commentary

This study, like the article previously mentioned, adds to a large body of evidence that indicates that WBC counts cannot be used to reliably identify patients with serious bacterial infection.[11] This study specifically focused on febrile infants with documented RSV infection and attempted to determine if WBC counts or band counts could be used to identify infants with concurrent bacterial infections. Neither was an effective discriminator.

In addition, these data support other studies indicating that all infants with RSV should be evaluated with urinalysis, and practitioners should consider a full sepsis evaluation in febrile or ill-appearing infants regardless of the presence of RSV infection.[13-17]

If an Infant Has an Identifiable Source of Fever, What Is the Risk for SBI?

Source: Purcell K, et al. Concurrent serious bacterial infections in 912 infants and children hospitalized for treatment of respiratory syncytial virus lower respiratory tract infection. *Ped Inf Dis J* 2005;23:267-269.

THIS RETROSPECTIVE STUDY WAS A review of medical records of 912 infants with RSV infection at the time of admission. Of the 912 patients, 574 were older than 90 days, 234 were 30–90 days old, and 104 were younger than 30 days of age.

Per the medical records, 470 patients had blood cultures drawn, while CSF analysis and cultures were performed in 101 patients. All of the infants identified as having bacterial infection were documented to be febrile.

Of the 104 infants less than 30 days of age, 6 of the 45 tested had UTIs. None of 63 tested had positive blood cultures, and none of the 38 tested had positive CSF cultures.

Of the 234 infants between 30–90 days old, 14 of the 94 who were tested had a UTI. None of 135 tested had positive blood cultures, and none of 45 tested had positive CSF cultures.

Of 574 infants older than 90 days of age, 8 of the 95 tested had UTIs, all of which were febrile. Two of the 272 tested had positive blood cultures, and none of the 18 tested had positive CSF cultures.

The authors concluded that there is a low rate of bacteremia and meningitis in infants with documented RSV infections, and that a full sepsis workup and empiric antibiotics are therefore not necessary. However, they point out that the relatively high percentage of infants with UTIs suggests that febrile infants with RSV should still have a urinalysis and culture performed.

Commentary

This study revealed a low rate of bacteremia and meningitis in infants with RSV infection and the authors conclude that a complete evaluation for sepsis may be unnecessary in febrile infants with RSV infection as an identified source of the fever. Their data support this conclusion in neonates as well as older infants.

Limitations to this study include the retrospective design, which meant that all infants were not necessarily evaluated via the same protocol and that laboratory testing was per the treating physician's discretion. It is not possible to determine the overall rate of bacteremia, since blood cultures were not obtained on every patient. Also, this study was performed at a single facility in an urban ED.

The authors of this study carefully point out the high rate of UTIs in infants with an RSV infection. Their data support that of other studies indicating that febrile infants with an RSV infection also need a urinalysis performed, regardless of results from other laboratory studies.[13-17]

While these data suggest that febrile infants with RSV infection might be spared a more invasive complete sepsis evaluation, the limitations of the study are significant, and indicate further studies are needed before physicians abandon current accepted practices in the evaluation of the febrile infant.

An Opposing View of Evaluation for SBI in Infants with RSV Infection

Source: Levine DA, et al. Risk of serious bacterial infection in young febrile infants with respiratory syncytial infections. *Pediatrics* 2004;113:1728-1734.

DR. LEVINE AND COLLEAGUES PERformed a prospective cross-sectional study in eight pediatric emergency departments over the course of three years. Infants enrolled in the study were less than 60 days old and had temperatures >38°C by rectal measurement at the time of presentation or by history. Infants were evaluated with the Yale Observational Scale, and RSV status was determined by antigen testing of nasopharyngeal secretions. Blood, urine, and CSF cultures were obtained and SBI was defined as growth of a pathogenic specimen from any of these cultures.

During their study, 1,248 infants were enrolled and bacterial infection status could be reliably determined in 1,169 patients based on available blood and urine cultures and the availability of follow-up data. The overall rate of SBI was 11.4% (133/1,169), with 269 infants (22%) demonstrating a positive RSV swab. In their study population, 8 infants had bacterial meningitis, 112 had UTIs, 2 had bacterial enteritis, and 25 infants had bacteremia. Of the 112 with UTIs, 9 also had bacteremia, and 1 had bacteremia with bacterial meningitis.

Of the 269 patients with a positive RSV swab, not all had complete culture data available. Overall, 17/244 (7%) had SBI, compared to 116/925 (12.5%) in the RSV-negative group. No infant with RSV had bacterial meningitis and only 3/267 (1.1%) had bacteremia. However, 14/261 (5.4%) infants with RSV also had a UTI.

From their data, the authors concluded that infants with RSV infection have significantly lower rates of SBI, but the rates are not low enough to negate the need for evaluation for a concurrent bacterial infection. They recommend that infants younger than 28 days who present with an RSV infection undergo a full septic work-up. Of the infants < 28 days of age, 5/82 had UTIs and 3/82 had bacteremia. This rate of SBI was not statistically different than the rate of SBI in infants that were not infected with RSV.

Furthermore, the authors concluded that infants age 29–60 days should still, at minimum, have a urinalysis performed, and that practitioners strongly consider performing more invasive testing if the child appears ill. Nine of the RSV-positive infants > 28 days of age had UTIs, and none had bacteremia. No distinction was made between male and female or those who were circumcised.

Commentary

This is a large, multicenter study spanning three years and enrolling 1,248 patients. Their results indicate that the RSV-positive infants had lower rates of bacterial infection than febrile infants who were RSV-negative. No RSV-positive infant had bacterial meningitis and only 1.1% had bacteremia compared with 2.3% in the RSV-negative group.

RSV-positive infants in this study did have UTIs at concerning frequencies suggesting that RSV-positive infants should have a urinalysis to rule out a co-existent UTI. The authors conclude that infants less than 28 days of age need a complete evaluation for sepsis and the clinicians' approach should not be altered by the presence of an RSV infection. However, infants 28–60 days of age may potentially be evaluated less aggressively, but their rates of concurrent UTIs remain significant.

Conclusion

THERE IS A GROWING BODY OF evidence that indicates all febrile infants do not require a complete sepsis workup; however, the exact criteria for determining which infants may not require a complete work-up remains a source of controversy. Studies that have focused on identifying febrile infants at low-risk for SBI have many common features. All "low-risk" criteria for febrile infants have included the following: the infant must have been previously healthy; the infant must be well-appearing; there cannot be a focal infection apparent on clinical exam; and the infant cannot have evidence of infection by urinalysis. In addition, all infants deemed to be low-risk for SBI require close, reliable follow-up as part of any outpatient management strategy.

Considerable efforts have been made to identify a single laboratory value as an indicator of serious bacterial infection. Several studies have focused on the WBC count, but these studies have demonstrated that the WBC count cannot be used as a discriminator in febrile infants to identify those with bacterial infection versus those with other sources of fever.[10-12] While not discussed in this review, recent studies have also examined procalcitonin and C-reactive protein as possible biomarkers for bacterial infection. These studies have not yet reached the point of generalized clinical utility, but early results are promising.[18-23]

Studies consistently demonstrate the need for careful attention to urinalysis and urine cultures from febrile infants, regardless of other sources of infection.[3,4,13,15-17,24,25] The co-infection rate and risk for UTI are high even in infants with RSV

infection and those fitting low-risk criteria.

In summary, multiple studies support the utilization of criteria to determine if a patient is at "low-risk" for SBI. Such patients may be managed as an out-patient following the acquisition and accurate interpretation of laboratory and urine tests. If a patient does not undergo a lumbar puncture, antibiotics should not be administered empirically for fear of subjecting patients to the risks associated with an undiagnosed meningitis that may be partially treated on re-evaluation. Large-scale, randomized studies are still needed to validate current findings, but until then, these criteria can provide useful guidelines in the management of febrile infants.

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CME QUESTIONS

1. **Febrile infants with documented RSV infection need, at minimum, the following laboratory test:**
   a) Blood culture
   b) Cerebral spinal fluid analysis
   c) White blood cell count
   d) Urinalysis and urine culture

2. **Which of the following is a reliable indicator of serious bacterial infection in febrile infants?**
   a) Degree of hyperthermia
   b) White blood cell count
   c) Ill appearance of infant
   d) None of the above

3. **Which of the following is a necessary component of all strategies for identifying febrile infants at "low-risk" for serious bacterial infection?**
   a) Normal band count
   b) Readily available follow-up in 24 hours
   c) Urinalysis showing zero white blood cells
   d) Clear chest radiograph

4. **Which of the following is NOT an appropriate management strategy of a 30-day-old, well-appearing febrile infant?**
   a) Obtain blood, urine, and cerebral spinal fluid cultures, admit the patient to the hospital, and treat empirically with antibiotics until cultures are negative.
   b) Obtain blood, urine, and cerebral spinal fluid cultures, treat empirically with antibiotics, and have the patient follow up in 24 hours.
   c) Obtain blood and urine cultures, treat empirically with antibiotics, and have the patient follow up in 24 hours.
   d) Obtain blood, urine, and cerebral spinal fluid cultures, avoid empiric antibiotic therapy, and have the patient follow up in 24 hours.

5. **Which of the following is included in all of the published "low-risk" criteria sets?**
   a) Well-appearing infant
   b) Temperature < 37°C
   c) Mother's GBS negative at birth

Answers: 1.d 2.d 3.b 4.c 5.a