Clinical Policy for Well-Appearing Infants and Children Younger Than 2 Years of Age Presenting to the Emergency Department With Fever

From the American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Pediatric Fever:
Sharon E. Mace, MD (Subcommittee Chair)
Seth R. Gemme, MD
Jonathan H. Valente, MD
Barnet Eskin, MD, PhD
Katherine Bakes, MD
Deena Brecher, MSN, RN, APN, ACNS-BC, CEN, CPEN (ENA Representative)
Michael D. Brown, MD, MSc (Committee Chair)

Approved by the ACEP Board of Directors, January 27, 2016

Endorsed by the Emergency Nurses Association, February 29, 2016

Policy statements and clinical policies are the official policies of the American College of Emergency Physicians and, as such, are not subject to the same peer review process as articles appearing in the journal. Policy statements and clinical policies of ACEP do not necessarily reflect the policies and beliefs of *Annals of Emergency Medicine* and its editors.

0196-0644/$-see front matter

http://dx.doi.org/10.1016/j.annemergmed.2016.01.042

[Ann Emerg Med. 2016;67:625-639.]

ABSTRACT

This clinical policy from the American College of Emergency Physicians addresses key issues for well-appearing infants and children younger than 2 years presenting to the emergency department with fever. A writing subcommittee conducted a systematic review of the literature to derive evidence-based recommendations to answer the following clinical questions: (1) For well-appearing immunocompetent infants and children aged 2 months to 2 years presenting with fever (≥38.0°C [100.4°F]), are there clinical predictors that identify patients at risk for urinary tract infection? (2) For well-appearing febrile infants and children aged 2 months to 2 years undergoing urine testing, which laboratory testing method(s) should be used to diagnose a urinary tract infection? (3) For well-appearing immunocompetent infants and children aged 2 months to 2 years presenting with fever (≥38.0°C [100.4°F]), are there clinical predictors that identify patients at risk for pneumonia for whom a chest radiograph should be obtained? (4) For well-appearing immunocompetent full-term infants aged 1 month to 3 months (29 days to 90 days) presenting with fever (≥38.0°C [100.4°F]), are there predictors that identify patients at risk for meningitis from whom cerebrospinal fluid should be obtained? Evidence was graded and recommendations were made based on the strength of the available data.

INTRODUCTION

Fever is the most common chief complaint among infants and children presenting to an emergency department (ED), accounting for 15% of all ED visits in a given year for patients younger than 15 years.[1] The majority of febrile children will have a benign, self-limited viral infection. However, a small number of pediatric patients, especially those younger than 3 months because of their relatively immature immune system, will have a serious infection. The management of the toxic or ill-appearing pediatric patient is straightforward; however, the dilemma for the health care provider is to differentiate the well-appearing febrile infant or child with a serious bacterial infection (SBI) from the febrile infant or child with a benign, usually viral infection. In a study of more than 3,000 febrile infants, only 58% of those with bacteremia or bacterial meningitis appeared clinically ill.[2]

There are multiple considerations in the initial assessment of the febrile pediatric patient younger than 2 years: infants and children may have a serious infection and be hypothermic or have a normal temperature; antipyretic use in the previous 4 hours may result in a normal or lower temperature when the infant or child presents to the ED or other health care setting; there should be a determination of the accuracy or validity of the temperature obtained with a home measuring device; fever may be the result of a bacterial or nonbacterial infection (eg, viral infection) or have a noninfectious cause; some viral infections, such as herpes simplex virus, can have devastating consequences in this age group; and the presence of a viral infection does not preclude the coexistence of a bacterial infection.

In terms of management, other complex issues to consider include immunization status (ie, fully, partially, or not immunized) and the capacity of the parent or caregiver to continuously monitor the infant or child if discharged home, or to return within 12 to 24 hours.

Fever without a source, or fever without a focus, has the following criteria: acute onset, duration of less than 1 week, and absence of localizing signs. In the prepneumococcal vaccine era, even after a thorough history and physical examination, a source of infection was not identified in 27.1% of children.[3]

There are many difficulties inherent in developing an evidence-based clinical policy for the management of infants and children with fever. This includes the heterogeneity of definitions, age groups, clinical settings, patient populations, types of diagnostic studies, inclusion or exclusion criteria, thresholds for positive or negative test results, and endpoints or outcomes. Even the definition of fever varies between studies, although the generally used definition is a rectal temperature of greater than or equal to 38.0°C (100.4°F), documented in the clinical setting or at home within the past 24 hours. The definitions (and thus incidence, outcomes, etc) of SBI vary greatly. In some studies, SBI includes bacteremia, bacterial meningitis, urinary tract infection, pneumonia, septic arthritis, osteomyelitis, cellulitis, and enteritis, whereas others include only bacteremia, bacterial meningitis, and urinary tract infection. In the majority of studies, the reference standard for the diagnosis of SBI is a positive culture result from a sample of blood, urine, cerebrospinal fluid, or stool (typically performed only if diarrhea is present).[4-6]

In the prepneumococcal vaccine era, for febrile infants and children the risk of SBI by age has been reported as 13% in neonates (aged 3 to 28 days),[4] 9% in infants aged 29 to 56 days,[5] and 7% in infants aged 90 days or younger.[6] Also, the risk of a positive blood culture result (ie, bacteremia) in an otherwise well-appearing febrile infant or child, aged 3 months to 36 months, was approximately 12% with a fever (≥40°C [104°F]) or with the combination of a fever (≥39.5°C [103°F]) and WBC count ($\geq$15x10^9/L),[7] and 7% with a fever ($\geq$38°C [100.4°F]) in infants aged 90 days or younger.[6] In 2 of these older studies of occult bacteremia, the most common organisms were *Streptococcus* pneumonia (85%, 85%) and *Haemophilus* influenza b (7.4%, 10%).[7,8] Other organisms included group B streptococcus, *Neisseria meningitidis*, and salmonella.[6,7]

Since the advent of vaccines against *Streptococcus* pneumonia (7-valent conjugate pneumococcal vaccine, licensed, and recommended in 2000 in the United States) and *Haemophilus* influenza type b vaccine, licensed in the United States in 1985 and replaced by licensed conjugate vaccine in 1990), the incidence of occult bacteremia has declined to 0.004%, 0.9%, 0.17%, 1.6%, and 2% according to various studies.[3,9-12] Pneumococcal disease has declined by nearly 80% and the prevalence of pathogens has changed.

In the postpneumococcal and *Haemophilus* influenza type b vaccine era, although there has been a decrease in the incidence of occult bacteremia, pneumococcal meningitis, and pneumococcal pneumonia, bacterial infections, including meningitis from organisms other than pneumococcus and type B *Haemophilus* influenza, have emerged. In a large study from Kaiser Permanente in California of full-term infants from whom 5,396 blood cultures, 4,599 urine cultures, and 1,796 cerebrospinal fluid cultures were obtained, the SBIs were urinary tract 17.9% (823/4,599 urine cultures), bacteremia 2% (129/5,396 blood cultures), and bacterial meningitis 0.9% (16/1,796 cerebrospinal fluid cultures).[12] *Escherichia coli* was the leading cause of bacteremia (60%), urinary tract infection (87.4%), and bacterial meningitis (43.7%).[12] Multiple sites of infection occurred in 9% of patients, 10% of urinary tract infections were associated with bacteremia, and 52% of bacteremia was associated with urinary tract infections. Of occult infections, 92% were associated with urinary tract infections.[12] The most common SBI is now urinary tract infection in febrile infants younger than 24 months with a prevalence of 5% to 7% and even higher among certain high-risk subgroups (eg, 20% for uncircumcised male infants).[13] The optimal method for the detection of urinary tract infections in infants and children has not been determined. The diagnosis and management of pneumonia continues to be a significant challenge (cough is the second most common reason for a visit to the ED).[1] Whether concurrent viral infections affect the incidence, severity, and type of bacterial infections also remains to be determined.

Various clinical decision rules for risk stratification of febrile infants have been published, including the Rochester, Philadelphia, Boston, and Pittsburgh criteria, and the Yale Observation Scale.[5,14-17] The Agency for Healthcare Research and Quality reviewed these well-known risk stratification schemes,[18] and there is no consensus about the most useful clinical prediction rule for identifying the infant or young child with SBI. In addition, a variety of biological markers such as the WBC count, absolute neutrophil count, band count, C-reactive protein, interleukins, and procalcitonin have been suggested for use in the identification of SBI, but the results have been mixed. Although no single screening test or algorithm for identifying young febrile children or infants with SBIs has been universally accepted, the use of a combination of diagnostic tests along with procalcitonin has potential.[19,20]

Since the previous American College of Emergency Physicians' (ACEP) clinical policy on children presenting with fever,[21] much has changed, especially since the advent of the newer vaccines and the introduction of diagnostic technologies, such as rapid antigen testing for bacteria and viruses. However, questions and controversies remain about the optimal management of the infant and young child presenting to the ED with fever. This clinical policy was selected for review because of the frequent occurrence of fever in infants and children, the difficulty in diagnosis and management of pediatric patients with fever, especially those younger than 2 years, and the potential for serious adverse outcomes. Many of the early SBI studies included children up to aged 36 months; however, with the more recent focus on the identification of specific pathogens and the changing epidemiology among the various age groups, this clinical policy focuses on children and infants younger than 2 years but specifically excludes neonates (aged $\leq$28 days). Although there are many clinical questions that could be asked, the areas of focus in this policy were selected based on ACEP member feedback.

METHODOLOGY

This clinical policy was created after careful review and critical analysis of the medical literature and was based on a systematic review of the literature. Searches of MEDLINE, MEDLINE InProcess, Scopus, Web of Science, and the Cochrane Database were performed. All searches were limited to English-language sources and human studies. Specific key words/phrases, years used in the searches, dates of searches, and study selection are identified under each critical question. In addition, relevant articles from the bibliographies of included studies and more recent articles identified by committee members and reviewers were included.

This policy is a product of the ACEP clinical policy development process, including expert review, and is based on the existing literature; when literature was not available, consensus of emergency physicians was used. Expert review comments were received from emergency physicians, members of the American Academy of Pediatrics (AAP) and American Academy of Family Physicians, and ACEP's Pediatric Emergency Medicine Committee. Comments were received during a 60-day open comment period, with notices of the comment period sent in an e-mail to ACEP members, published in *EM Today*, and posted on the ACEP Web site. The responses were used to further refine and enhance this policy; however, the responses do not imply endorsement of this clinical policy. Clinical policies are scheduled for revision every 3 years; however, interim reviews are conducted when technology, methodology, or the practice environment changes significantly. ACEP was the funding source for this clinical policy.

Assessment of Classes of Evidence

All articles used in the formulation of this clinical policy were graded by at least 2 methodologists and assigned a Class of Evidence. Each article was assigned a design class with design 1 representing the strongest study design and subsequent design classes (ie, design 2, design 3) representing respectively weaker study designs for therapeutic, diagnostic, or prognostic clinical reports, or meta-analyses (Appendix A). Articles were then graded on dimensions related to the study's methodological features, such as randomization processes, blinding, allocation concealment, methods of data collection, outcome measures and their assessment, selection and misclassification biases, sample size, and generalizability. Using a predetermined process related to the study's design, methodological quality, and applicability to the critical question, articles received a final Class of Evidence grade (ie, Class I, Class II, Class III, or Class X) (Appendix B). Articles identified with fatal flaws or that were ultimately not applicable to the critical question received a Class of Evidence grade "X" and were not used in formulating recommendations for this policy. Grading was done with respect to the specific critical questions; thus, the level of evidence for any one study may vary according to the question for which it is being considered. As such, it was possible for a single article to receive different Classes of Evidence as different critical questions were answered from the same study. Question-specific Classes of Evidence grading may be found in the Evidentiary Table (available online at www.annemergmed.com).

Translation of Classes of Evidence to Recommendation Levels

Strength of recommendations regarding each critical question were made by subcommittee members using results from strength of evidence grading, expert opinion, and consensus among subcommittee members according to the following guidelines:

Level A recommendations. Generally accepted principles for patient care that reflect a high degree of clinical certainty (eg, based on evidence from 1 or more Class of Evidence I or multiple Class of Evidence II studies).

Level B recommendations. Recommendations for patient care that may identify a particular strategy or range of strategies that reflect moderate clinical certainty (eg, based on evidence from 1 or more Class of Evidence II studies or strong consensus of Class of Evidence III studies).

Level C recommendations. Recommendations for patient care that are based on evidence from Class of Evidence III studies or, in the absence of any adequate published literature, based on expert consensus. In instances where consensus recommendations are made, "consensus" is placed in parentheses at the end of the recommendation.

There are certain circumstances in which the recommendations stemming from a body of evidence should not be rated as highly as the individual studies on which they are based. Factors such as heterogeneity of results, uncertainty about effect magnitude and consequences, and publication bias, among others, might lead to such a downgrading of recommendations.

When possible, clinically oriented statistics (eg, likelihood ratios [LRs], number needed to treat) are presented to help the reader better understand how the results may be applied to the individual patient. For a definition of these statistical concepts, see Appendix C.

This policy is not intended to be a complete manual on the evaluation and management of young pediatric patients with fever but rather a focused examination of critical issues that have particular relevance to the current practice of emergency medicine.

It is the goal of the Clinical Policies Committee to provide an evidence-based recommendation when the medical literature provides enough quality information to answer a critical question. When the medical literature does not contain adequate empirical data to answer a critical question, the members of the Clinical Policies Committee believe that it is equally important to alert emergency physicians to this fact.

This clinical policy is not intended to represent a legal standard of care for emergency physicians. Recommendations offered in this policy are not intended to represent the only diagnostic or management options available to the emergency physician. ACEP recognizes the importance of the individual physician's judgment and patient preferences. This guideline defines for the physician those strategies for which medical literature exists to provide support for answers to the critical questions addressed in this policy.

Scope of Application. This guideline is intended for physicians working in EDs.

Inclusion Criteria. This guideline applies to previously healthy term infants and children, appropriately immunized for age, with ages as described in each critical question.

Exclusion Criteria. This guideline excludes neonates, prematurely born infants, and pediatric patients considered to be at high risk such as those with significant congenital abnormalities, with serious illnesses preceding the onset of fever, and in an immunocompromised state.

For potential benefits and harms of implementing the recommendations, see Appendix D.

CRITICAL QUESTIONS

1. For well-appearing immunocompetent infants and children aged 2 months to 2 years presenting with fever (≥38.0°C [100.4°F]), are there clinical predictors that identify patients at risk for urinary tract infection?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. Infants and children at increased risk for urinary tract infection include females younger than 12 months, uncircumcised males, nonblack race, fever duration greater than 24 hours, higher fever (≥39°C), negative test result for respiratory pathogens, and no obvious source of infection. Although the presence of a viral infection decreases the risk, no clinical feature has been shown to effectively exclude urinary tract infection. Physicians should consider urinalysis and urine culture testing to identify urinary tract infection in well-appearing infants and children aged 2 months to 2 years with a fever ≥38°C (100.4°F), especially among those at higher risk for urinary tract infection.

Key words/phrases for literature searches: immunocompetence, immunocompetent, febrile, fever, urinary tract infections, clinical predictors, risk assessment or risk factors, all infant, and variations and combinations of the key words/phrases. Searches included January 2003 through search dates of February 6, 2015 and March 2, 2015.

Study Selection: Three hundred seventy-three articles were identified in the search. Twenty-six articles were selected from the search results for further review, with 2 studies included for this critical question.

Based on study selection criteria, 2 Class III studies were included to answer this critical question.[22,23] In a prospective study of infants aged 57 to 180 days presenting to a tertiary pediatric ED with rectal temperatures (≥38.0°C [100.4°F]), Hsiao et al[22] described clinical and laboratory features associated with serious SBI. All infants received the following testing: CBC count with differential, C-reactive protein, blood cultures, urine for urinalysis and urine culture, and direct fluorescent antibody for respiratory syncytial virus (RSV), influenza, parainfluenza, and adenovirus. Urine culture results were considered positive if they grew more than 10,000 bacterial colonies of a single organism. Urethral catheterization was used for all patients except for 2 infants for whom suprapubic needle aspiration was performed because of failed catheterization.

Of 429 consecutive infants enrolled from February 2003 to February 2004, 41 had positive urine culture results (9.6%; 95% confidence interval [CI] 6.9% to 12.7%) and 4 had positive blood culture results (0.9%; 95% CI 0.3% to 2.4%); 1 infant (0.2%) had *E coli* in both the urine and blood. Of the 58 infants who underwent lumbar puncture, none had positive cerebrospinal fluid bacterial culture results.[22] Six infants were diagnosed with sterile pyuria (>11 WBCs per high-power field [hpf]). An obvious source of fever (presumed viral upper respiratory infection, otitis media, or bronchiolitis) was identified in 264 patients (61.5%). Of 163 infants with positive direct fluorescent antibody test results, 8 (4.9%; 95% CI 2.1% to 9.4%) had an SBI. Although the authors noted that 1 of these patients had bacteremia and bacteriuria, there was no further description of positive urine versus blood bacterial culture results in this subgroup. The rate of SBI in infants with positive direct fluorescent antibody test results was lower than that for infants with negative direct fluorescent antibody test results (13.5%; 95% CI 9.6% to 18.4%). Infants with an obvious source of fever had a lower rate of SBI than those without an obvious source (6.1% versus 18.1%).

The mean Yale Observation Scale score for infants with an SBI was 1.4 points higher (indicating more ill-appearing) than for those without an SBI (9.4 [SD 4.6] versus 8.1 [SD 3.6], respectively). Patients with an SBI had a significantly longer duration of fever (26.5 hours [SD 41.5]) than those without SBI (18.6 hours [SD 21.7]). Infants with a Yale Observation Scale score of greater than or equal to 21 ("very ill-appearing") had the highest rate of SBI (40%) versus those with scores of less than 10 (10.0%;

"not ill-appearing") and 11 to 20 (13.1%; "ill appearing"). Uncircumcised male patients had a substantially higher rate of bacteriuria (36%; 95% CI 22.9% to 50.8%) compared with circumcised male patients (1.6%; 95% CI 0.2% to 5.5%). Height of fever, sex, and age were not associated with increased risk of SBI.[22]

In summary, of infants aged 2 to 6 months with rectal temperatures (≥38°C [100.4°F]), the following clinical variables were associated with a greater rate of SBI: ill appearance, longer duration of fever, uncircumcised male infants, negative direct fluorescent antibody results for common viral pathogens, or no obvious source of fever (such as upper respiratory tract infection, otitis media, or bronchiolitis).[22] The following laboratory variables were associated with a greater rate of SBI: elevated mean WBC count, elevated mean absolute neutrophil count, and elevated mean C-reactive protein. All but 4 of the SBIs identified were due to positive urine culture results. Although these clinical variables increased the risk of SBI, the absence of any single measure was insufficient to identify patients who could avoid urine testing to identify a potential SBI. For example, 10% of infants with an SBI were identified as not ill-appearing and almost 5% of infants with a positive direct fluorescent antibody result had an SBI. Of note, 3 of the 4 cases of bacteremia were prospectively identified as not ill-appearing based on clinical examination and the Yale Observation Scale score.[22]

A Class III meta-analysis included studies that contained data on signs or symptoms of urinary tract infection in infants and children aged 18 years or younger with a fever.[23] The meta-analysis included 12 prospective cohort or cross-sectional studies from 1973 to 2006, with a total of 8,837 febrile infants and children aged 15 years or younger. Findings that were most useful for identifying urinary tract infection were temperature greater than 40°C (LR 3.2 to 3.3), history of a urinary tract infection (LR 2.3 to 2.9), uncircumcised male patient (LR 2.8; 95% CI 1.9 to 4.3), and suprapubic tenderness (LR 4.4; 95% CI 1.6 to 12.4). For the combination of temperature greater than 39°C and fever duration greater than 48 hours, the LR was 4.0 (95% CI 1.2 to 13.0).[23]

Data from the 2011 AAP Clinical Practice Guideline on Urinary Tract Infections[24] indicated that otherwise well-appearing patients aged 2 to 24 months with fever (≥38°C) can be stratified according to clinical risk factors for urinary tract infections. Risk factors for female patients include white race, age (<12 months), temperature (≥39°C), fever (≥2 days), and absence of another source of infection (sensitivity=88%; specificity=30%).[25-27] The Level C recommendation for question 1 identifies the same risk factors for urinary tract infection as the AAP guideline.[24]

Future Research

Future investigations should focus on the ability to accurately estimate the risk of urinary tract infections based on clinical predictors among patients aged 2 months to 2 years.

2. For well-appearing febrile infants and children aged 2 months to 2 years undergoing urine testing, which laboratory testing method(s) should be used to diagnose a urinary tract infection?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. Physicians can use a positive test result for any one of the following to make a preliminary diagnosis of urinary tract infection in febrile patients aged 2 months to 2 years: urine leukocyte esterase, nitrites, leukocyte count, or Gram's stain.

Level C recommendations.

(1) Physicians should obtain a urine culture when starting antibiotics for the preliminary diagnosis of urinary tract infection in febrile patients aged 2 months to 2 years.

(2) In febrile infants and children aged 2 months to 2 years with a negative dipstick urinalysis result in whom urinary tract infection is still suspected, obtain a urine culture.

Key words/phrases for literature searches: urine specimen collection, urinary tract infections, urinalysis, all infant, and variations and combinations of the key words/phrases. Searches included January 2003 through search dates of February 6, 2015 and March 13, 2015.

Study Selection: Four hundred ninety-two articles were identified in the search. One hundred nine articles were selected from the search results for further review, with 10 studies included for this critical question.

There were 2 Class II studies[28,29] and 8 Class III studies[30-37] that evaluated urine testing to diagnose a urinary tract infection and included infants and children aged 2 months to 2 years. A subset of a larger study, the Pediatric Research in Office Settings febrile infant study[28] of 3,066 infants aged 0 to 3 months with a fever (≥38°C [100.4°F]) in a pediatric office setting, compared diagnostic testing between urine collected by bag or catheterization, with urinary tract infection defined as pure growth of a single pathogen with greater than or equal to 100,000 colony-forming units (CFU)/mL (bag sample) and greater than or equal to 20,000 CFU/mL (catheterization sample). Of the 1,482 infants who had both urinalysis and urine cultures, 1,384 specimens were bag or catheterization. For all specimens (bag or catheterization), nitrites had better specificity (99% nitrites versus 91% leukocyte esterase), whereas leukocyte esterase had higher sensitivity (84% leukocyte esterase versus 39% nitrites). Although sensitivity and specificity were higher in catheterized specimens versus bag specimens for both leukocyte esterase and nitrite, the only significant difference was leukocyte esterase specificity with bag urine of 84% versus catheterization urine at 94%. For urine WBC/hpf as a diagnostic test for urinary tract infection for all specimens, LR=19 for WBC count greater than 20/hpf, LR=18.2 for 11 to 20 WBCs/hpf, LR=2.8 for 6 to 10 WBCs/hpf, LR=1 for 3 to 5 WBCs/hpf, and LR=0.3 for 0 to 2 WBCs/hpf. The authors found that the relative risk of an ambiguous culture result for specimens obtained by bag was 2.7 (95% CI 1.7 to 4.5), although the absolute risk was small (7.4% bag urine versus 2.7% catheterization urine). Moreover, 21 cultures (95% CI 13 to 53) would have to be obtained by catheterization to avoid 1 ambiguous culture obtained by bag.[28] In the technical report from the AAP,[38] given a 5% prevalence of urinary tract infection and a bagged urine specificity of 70%, the positive predictive value of a urinary culture obtained from a bag is only 15%. Therefore, among positive bagged urine results, it would be expected that 85% would be false positives.[38] Although a negative urinalysis result from a bagged specimen may be useful for clinical decisionmaking, a positive bagged urinalysis result should prompt a urine culture obtained by catheterization or suprapubic aspiration.

A Class II meta-analysis of diagnostic tests for urinary tract infection evaluated 95 studies in 95,703 children aged 18 years or younger.[29] Summary estimates for sensitivity and specificity, respectively, were nitrite only 49% (95% CI 41% to 57%) and 98% (95% CI 96% to 99%); leukocyte esterase or nitrite 88% (95% CI 82% to 91%) and 79% (95% CI 69% to 87%); urine WBC counts ($>10/\mu L$) 74% (95% CI 67% to 80%) and 86% (95% CI 82% to 90%), unstained bacteria 88% (95% CI 75% to 94%) and 92% (95% CI 84% to 96%), and Gram's-stained bacteria 91% (95% CI 80% to 96%) and 96% (95% CI 92% to 98%). These rapid diagnostic tests were negative in about 10% of children with urinary tract infections and "cannot replace urine culture."

A Class III retrospective review of 375 pediatric ED patients aged 0 to 10 years from Australia defined a negative urinalysis result as a urine dipstick negative for all blood, protein, leucocytes, and nitrites, and a positive urine culture result as greater than 10^5 organisms/mm^3 of an isolated organism deemed not to be a contaminant.[30] Urine was obtained by bag or clean catch except for 4 cases in which suprapubic aspirate was conducted. For all patients, the researchers found a prevalence of urinary tract infections of 10.7%, urine dipstick sensitivity of 92.5% (95% CI 84.3% to 100%), and specificity 39.4% (95% CI 34.2% to 44.6%). In the 0- to 2-year age group (160 patients), the prevalence of urinary tract infection was higher at 15%, sensitivity lower at 87.5% (95% CI 74.3% to 100%), and specificity about the same at 39.7% (95% CI 31.5% to 47.9%), whereas in the 2- to 10-year age group, the prevalence was lower at 7.0%, sensitivity greater at 100% (95% CI 100% to 100%), and specificity similar at 39.2% (95% CI 32.4% to 46%).

In another Class III study, 321 urine samples from febrile patients younger than 2 years (mean age 9.3 months) presenting to a pediatric ED in the United Kingdom were evaluated by dipstick urinalysis and urine culture.[31] A test that was positive for nitrite, leukocyte esterase, and blood was 97.12% specific (95% CI 94.17% to 98.6%) and had a positive LR of 15.13 (95% CI 6.99 to 32.76), whereas a test negative for nitrite, leukocyte esterase, blood, and protein had a sensitivity of 97.44% (95% CI 91.12% to 99.29%) and a negative LR of 0.10 (95% CI 0.02 to 0.39).

One Class III study that evaluated a subgroup of infants (N=649) with a positive urine culture result ($\geq$50,000 CFU/mL) of a single pathogen collected by a sterile method (ie, catheterization or suprapubic aspiration) was part of a larger febrile ($\geq$38°C [100.4°F]) infant (<90 days of age) multicenter study from Spain.[32] For leukocyte esterase, there was a mean sensitivity of 82.1%, mean specificity of 92.4%, mean negative predictive value of 97.8% for female patients (N=176) and 94.1% for male patients (N=473), and a mean positive predictive value of 58% for female patients and 79.4% for male patients.

A pediatric ED Class III study of febrile patients younger than 5 years (half the patients were $\leq$12 months) with a urinary tract infection prevalence of 17.6% reported lower sensitivities for diagnostic testing compared with other studies.[33] Urine samples were obtained by catheterization. For all patients, the sensitivities and negative predictive values were nitrite 20% and 85%, hemoglobin 44% and 88%, leukocyte esterase 48% and 90%, 2 to 5 or more WBCs/hpf in sediment 48% and 90%, centrifuge Gram's stain 60% and 92%, and unspun WBC count greater than $10/\mu L$ 68% and 92%, respectively. For infants aged 12 months or younger versus older than 12 months, the respective sensitivities were nitrite 17% and 23%, hemoglobin 33% and 53%, leukocyte esterase 42% and 53%; 2 to 5 or more WBCs/hpf in sediment 42% and 53%, centrifuge Gram's stain 42% and 76%, and unspun WBC count greater than $10/\mu L$ 67% and 69%, respectively.

A Class III study by Reardon et al[34] of 435 patients who had both a urinalysis and urine culture from a larger registry of febrile patients (<3 months and temperature

≥38°C, or 3 to 24 months of age with temperature ≥39°C) (mean age 12.6 months) seen at a tertiary care general ED reported 10.3% positive culture results (≥10,000 CFU). Urine samples were obtained by catheterization in all female patients, male patients younger than 6 months, and uncircumcised male patients younger than 12 months. A positive urinalysis result was any one of the following: pyuria (≥5 WBCs/hpf) or positive leukocyte esterase result or positive nitrite result. The results for urinalysis were sensitivity 64% (95% CI 49% to 78%), specificity 91% (95% CI 88% to 94%), positive predictive value 46% (95% CI 31% to 53%), and negative predictive value 96% (95% CI 93% to 97%).

A Class III retrospective chart review by Waseem et al[35] of 749 children aged 2 months to 2 years, assessed the diagnostic performance of urinalysis among those who presented to the ED with fever (temperature >38°C [100.4°F]) and a positive urine culture result. Of these 749 children, 141 were excluded because of incomplete urinalysis results, incomplete antibiotic sensitivity data, and polymicrobial infection, leaving 608 children for analysis. They were divided into those with *E coli* (82.1%) versus non–*E coli* (17.9%) groups. Thirty percent of children with a positive urine culture result had a negative urinalysis result as defined by negative leukocyte esterase result, negative nitrite result, and urine WBC count less than 5/hpf. Of the 183 negative urinalysis results, 59% were due to non–*E coli* organisms. Positive leukocyte esterase result had a LR=2.5 (95% CI 1.5 to 4.2), whereas positive nitrite result had an LR=2.8 (95% CI 1.4 to 5.5) and urine WBC count LR=1.8 (95% CI 1.3 to 2.4) in predicting *E coli* versus non–*E coli* infections.

A Class III study by Tosif et al[36] evaluated contamination rates in 599 urine specimens obtained from 599 children younger than 2 years. Sample collection methods were 34% clean catch urine, 16% catheter specimen urine, 14% suprapubic aspiration, 2% bag specimen urine, and 34% unknown. Urine contamination was mixed growth and a colony count greater than or equal to 10^4 CFU/mL for suprapubic aspiration or catheter specimen urine; greater than or equal to 10^6 for clean catch urine, indwelling catheters, and unspecified samples; and greater than or equal to 10^8 for bag specimen urine. The contamination rates were 26% clean catch urine, 12% catheter specimen urine, and 1% suprapubic aspiration.

Point-of-care urine dipstick and automated urinalysis were compared in a Class III prospective study of febrile (temperature ≥38.0°C [100.4°F]) infants and children younger than 48 months who underwent urethral catheterization.[37] Urine cultures were positive if they had urinary bacterial growth greater than or equal to 50,000/mL. Twelve percent (42/346) of the children and infants had urinary bacterial growth. Point-of-care urine dipstick with greater than or equal to 1+ leukocyte esterase or positive nitrite had a sensitivity of 95% and a specificity of 98%. Sensitivities and specificities were 86% and 98% for automated leukocyte counts greater than or equal to 100/μL and 98% and 98% for bacterial counts greater than or equal to 250/μL.

Automated microscopy also showed promising results in a study by Shah et al.[39] The study was of catheterized specimens from ED patients, of whom 81% were younger than 2 years of age and 80% had fever (either by history or physical examination). For automated microscopy (finding both pyuria and bacteriuria), positive LR=16 and negative LR=0.4, whereas conventional nonautomated results were positive LR=78 and negative LR=0.23. In patients of all ages, flow cytometry has been shown to have an excellent negative LR of 0.015.[40]

The level B recommendation about the use of diagnostic tests (eg, leukocyte esterase, nitrites, leukocyte count, Gram's stain) for a preliminary diagnosis of urinary tract infection and the level C recommendation that a urine culture should be obtained when urinary tract infection is suspected even with a negative urinalysis result are consistent with the AAP guideline.[24] The AAP guideline further recommends that the specimen be obtained through catheterization or suprapubic aspirate; however, the different methods for obtaining urinalysis were not evaluated for this ACEP clinical policy.

Future Research

Future research should include a comparison of dipstick urinalysis diagnostic findings with the standard criterion of urine culture for the different urine collection methods, especially for clean catch versus catheter urine, and an evaluation of automated microscopy and flow cytometry with standard techniques of urinalysis.

3. For well-appearing immunocompetent infants and children aged 2 months to 2 years presenting with fever (≥38.0°C [100.4°F]), are there clinical predictors that identify patients at risk for pneumonia for whom a chest radiograph should be obtained?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. In well-appearing immunocompetent infants and children aged 2 months to 2 years presenting with fever (≥38°C [100.4°F]) and no obvious source of infection, physicians should consider obtaining a chest radiograph for those with cough, hypoxia, rales, high fever (≥39°C), fever duration greater than 48 hours, or tachycardia and tachypnea out of proportion to fever.

Level C recommendations. In well-appearing immunocompetent infants and children aged 2 months to 2 years presenting with fever (≥38°C [100.4°F]) and wheezing or a high likelihood of bronchiolitis, physicians should not order a chest radiograph.

Key words/phrases for literature searches: pneumonia, radiography thoracic, chest radiography, chest x-ray, fever, febrile, infant/child, all infant, and variations and combinations of the key words/phrases. Searches included January 2003 through search dates of February 6, 2015, and March 13, 2015.

Study Selection: Four hundred seventy-three articles were identified in the search. Sixty-four articles were selected from the search results for further review, with 9 studies included for this critical question.

Based on study selection criteria, 1 Class II study[41] and 8 Class III studies[42-49] were included to answer this critical question.

Obtaining a chest radiograph in a well-appearing child presenting with fever has potential benefits in terms of making the diagnosis and initiating appropriate treatment, but the decision must be balanced against potential harms such as radiation exposure and cost. Although there is less diagnostic dilemma in the ill-appearing child, the need to obtain a chest radiograph may be unclear for the more commonly presenting well-appearing febrile pediatric patient. This is especially true given the greater likelihood of benign viral illnesses in this age group, which can produce respiratory symptoms that mimic more serious bacterial pneumonias.

A critical limitation related to the study of pediatric pneumonia is the lack of a reference standard for the diagnosis of bacterial pneumonia, which was defined as a consolidation on radiograph plus a positive blood culture result, pleural fluid culture or antigen, or serologic marker.[41] All other studies graded for this clinical question defined bacterial pneumonia as a radiographic finding, thus likely overestimating the true incidence of bacterial pneumonia.

In a Class II study, Craig et al[41] found that physician diagnosis of bacterial infection overall had low sensitivity (10% to 50%) and high specificity (90% to 100%). In an effort to develop a multivariable model to predict SBIs, including pneumonia, patients with high fever (≥102.2°F), cough, rales (crackles) on auscultation, tachycardia, tachypnea, or long duration of fever were more likely to have bacterial pneumonia. Bilkis et al[42] in a Class III study also concluded that having decreased breath sounds, rales, or tachypnea was predictive of radiographic pneumonia, with a sensitivity of 94%. Hypoxia was not addressed in either of these studies.

With regard to negative predictors, the presence of any one of the following 3 reduced the likelihood of having bacterial pneumonia: wheezing, stridor, or an abnormal ear, nose, and throat examination result.[41] In a prospective Class III study by Mathews et al,[43] none of the 126 patients aged 2 months to 2 years who presented with wheezing had radiographic pneumonia. However, this study did not specify which children in this group had fever, thus providing only indirect evidence related to the critical question.[43]

In a Class III study by Cardoso et al,[44] tachypnea and lower chest indrawing (retractions) were found to be a predictor of radiographic pneumonia in patients aged 2 months to 2 years with associated sensitivity of 92% (95% CI 80% to 98%) and specificity 44% (95% CI 40% to 53%). The limitation to this study is the application to our question, given that these clinical features could be argued to indicate the ill-appearing child.

Oxygen saturation has been shown to be lower in subjects with radiographic pneumonia in 4 Class III studies; however, these studies did not agree on a specific cutoff value.[45-48] In a study by Simon et al,[45] hypoxia was found to be predictive of radiographic pneumonia but had inadequate sensitivity and specificity to recommend a specific cutoff value for oxygen saturation; in fact, radiographic pneumonia was found in half of patients with an oxygen saturation of 96% or higher. Therefore, the absence of hypoxia in their study group did not rule out radiographic pneumonia. Neuman et al[46] found hypoxia (oxygen saturation ≤92%) to be the single best predictor of radiographic pneumonia in a subset of children younger than 5 years; however, this finding cannot be directly applied to our clinical question, given the inclusion of children older than 2 years. Ayalon et al[47] and Mahabee-Gittens et al,[48] using a cutoff of 95% and 96%, respectively, found a higher likelihood of radiographic pneumonia among hypoxic patients.

In children with bronchiolitis, Ecochard-Dugelay et al[49] (Class III study) found that a temperature greater than or equal to 38°C (100.4°F) was the only positive predictor of radiographic pneumonia. Furthermore, rales (crackles) and SpO_2 less than 95% did not predict radiographic pneumonia in their study population.

Future Research

Large prospective studies are needed to better assess historical information and physical examination findings to more accurately determine which children should undergo a chest radiograph to determine the diagnosis and optimal management for bacterial pneumonia. The development and validation of an accurate clinical decision tool would also be helpful.

4. For well-appearing immunocompetent full-term infants aged 1 month to 3 months (29 days to 90 days) presenting with fever (≥38.0°C [100.4°F]), are there predictors that identify patients at risk for meningitis from whom cerebrospinal fluid should be obtained?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations.

(1) Although there are no predictors that adequately identify full-term well-appearing febrile infants aged 29 to 90 days from whom cerebrospinal fluid should be obtained, the performance of a lumbar puncture may still be considered.

(2) In the full-term well-appearing febrile infant aged 29 to 90 days diagnosed with a viral illness, deferment of lumbar puncture is a reasonable option, given the lower risk for meningitis. When lumbar puncture is deferred in the full-term well-appearing febrile infant aged 29 to 90 days, antibiotics should be withheld unless another bacterial source is identified. Admission, close follow-up with the primary care provider, or a return visit for a recheck in the ED is needed. (Consensus recommendation)

Key words/phrases for literature searches: meningitis, cerebrospinal fluid, fever, febrile, all infant, *Haemophilus influenzae*, pneumococcal vaccines, conjugate vaccines, bacterial infections, and variations and combinations of the key words/phrases. Searches included January 2003 through search dates of February 6, 2015, March 13, 2015, April 9, 2015, and April 13, 2015.

Study Selection: Six hundred sixty-one articles were identified in the search. Sixty-eight articles were selected from the search results for further review, with 1 study included for this critical question. Studies that did not report subgroup analysis of the specific age groups noted in the question were not included.

Laboratory evaluation for fever in the young infant is frequently performed in the ED setting. This often includes lumbar puncture to obtain cerebrospinal fluid to assess for meningitis. Although concern is greatest for bacterial meningitis, the diagnosis of viral meningitis often leads to an admission disposition for observation and treatment, pending bacterial cultures. Routine lumbar puncture in the young infant younger than 90 days has been an area of extensive debate and controversy, as noted in many studies showing variation of practice and nonadherence to guidelines.[50-54] Treatment with antibiotics without lumbar puncture may lead to concerns about partially treated or delayed recognition of meningitis; however, lumbar puncture is a procedure that is invasive and not without risk. Prediction of well-appearing healthy young infants with fever who should have a lumbar puncture would be very helpful in potentially limiting parental anxiety, invasive testing, cost, exposure to antibiotics, and/or hospital admission.

The challenge and difficulty in assessing the literature revolves around the fact that most studies defined SBI as bacterial infection resulting in meningitis, urinary tract infection, or bacteremia, whereas other studies included infections such as pneumonia or soft tissue infections within the definition of SBI. In addition, many trials had very small numbers of patients with the outcome of interest, particularly meningitis. Heterogeneity among trials, including age subsets, fever or temperature thresholds, and other clinical assessment strategies, limited the number of studies that directly addressed this clinical question. Cerebrospinal fluid pleocytosis without meningitis is relatively common in young infants with enterovirus or urinary tract infection.[55,56] Even in a well-appearing infant who has a lumbar puncture, cerebrospinal fluid pleocytosis rarely equates to a diagnosis of bacterial meningitis. Approximately 20% of all infants younger than 90 days with fever will have enterovirus, and roughly 50% of enterovirus-positive infants will have cerebrospinal fluid pleocytosis.[55] Clearly, for the ill-appearing patient or infant with concerning examination findings for meningitis, a lumbar puncture should be performed; however, the challenge lies in assessing this need in the well-appearing infant.

One Class III trial by Meehan and Bachur[57] was identified in this systematic review. This 2008 retrospective study assessed 2,820 immunocompetent infants aged 90 days or younger with rectal fever (≥38°C [100.4°F]) for presence of cerebrospinal fluid pleocytosis, which was defined as cerebrospinal fluid WBC count greater than or equal to 25 cells/µL for those aged 0 to 28 days or greater than or equal to 10 cells/µL for those aged 29 to 90 days. A cerebrospinal fluid WBC count correction factor for the number of RBCs was used at a ratio of 500:1. Of the 2,197 patients from whom cerebrospinal fluid was obtained, 182 had a traumatic lumbar puncture (defined as ≥10,000 RBCs/µL), and 12 patients (9 pretreated with antibiotics and 3 with ventriculoperitoneal shunts) were excluded, leaving 2,003 patients for analysis. The study outcome was cerebrospinal fluid pleocytosis and not specifically bacterial meningitis. In this study, 176 of 2,003 patients (8.8%; 95% CI 7.6% to 10.1%) aged 90 days or younger had cerebrospinal fluid pleocytosis (8.4% aseptic meningitis and 0.4% bacterial meningitis). Another purpose of this study was to create a decision tree model using recursive partitioning to predict which infants were most likely to have cerebrospinal fluid pleocytosis, using age, WBC counts, absolute neutrophil count, temperature, and season of presentation. There were 2 strong predictors: seasonal presentation and temperature greater than 38.4°C (101.1°F) with a WBC count greater than 6,100/µL. Cerebrospinal fluid pleocytosis risk was 5.0% (69/1,387; 95% CI 4.0% to 6.3%) in the nonsummer months (October through May) versus 17.4% (107/616; 95% CI 14.6% to 20.6%) during the summer months (June through September). Patients with a temperature greater than 38.4°C (101.1°F) and WBC count greater than 6,100/µL were categorized as being at higher risk for cerebrospinal fluid pleocytosis (49/673; 95% CI 5.6% to 9.5%). Overall, 7 patients (0.35%; 95% CI 0.17% to 0.72%) had bacterial meningitis and 2 of these patients did not have cerebrospinal fluid pleocytosis; however, only 1 of these patients would not have been classified in either of the high-risk groups discussed above. This patient was 2.5 months old and described as "ill appearing, lethargic, with mottled skin and poor perfusion, full anterior fontanelle" and had a temperature of 38.8°C with WBC count 2,200/µL. Five of 7 (71%) of the patients with bacterial meningitis had positive blood culture results.

Several studies have evaluated infants for the presence of SBI in the setting of a viral illness such as influenza, RSV, or the clinical diagnosis of bronchiolitis. In these trials, overall risk of SBI was lower in the setting of a clinically diagnosed viral illness or positive viral test result; however, these studies did not provide adequate power to discern statistical differences between viral and nonviral subgroups for meningitis.[54,58-60] A multicenter prospective cross-sectional study of 1,091 febrile infants aged 60 days or younger with fever evaluated during 3 consecutive influenza seasons showed a significantly decreased risk of overall SBI in patients testing positive for influenza.[59] In this study, 844 of 1,091 infants (77.4%) were tested for influenza, 123 of 844 (14.6%) tested positive, and there were no cases of meningitis in the influenza-positive group (0/119=0% [95% CI 0% to 2.5%]). Study interpretation in the context of the critical question is limited because all patients with fever were included (ie, not just well-appearing infants), and outcomes assessing meningitis were not statistically significant.[59]

A 3-year multicenter prospective cross-sectional trial sought to compare the risk of SBI in febrile infants aged 60 days or younger from October through March diagnosed with RSV by nasopharyngeal antigen testing versus those without RSV.[60] RSV-positive testing was noted in 269 of 1,248 enrolled infants (22%), but overall SBI status was determined from 1,169 of 1,248 (94%) because these patients had either all 3 cultures performed (urine, blood, and cerebrospinal fluid; N=1,135 [91%]) or 2 cultures (blood and urine) performed with clinical follow-up (N=34 [3%]). The rate of SBI in the RSV-positive group compared with the RSV-negative group was 7.0% (17/244; 95% CI 4.1% to 10.9%) versus 12.5% (116/925; 95% CI 10.5% to 14.8%), respectively, (risk difference 5.5%; 95% CI 1.7% to 9.4%). No RSV-positive infant had bacterial meningitis (0/251; 95% CI 0% to 1.2%).[60]

The Pediatric Research in Office Settings network trial[54] was a prospective cohort of 3,066 febrile infants younger than 3 months. Practitioners made the diagnosis of bronchiolitis clinically, using a predefined definition from the Febrile Infant Study manual before obtaining laboratory results. A clinical diagnosis of bronchiolitis was given to 218 of 3,066 infants (7.1%); 35 of 218 (16%) had cerebrospinal fluid obtained and none of these patients had an SBI or meningitis. The authors also noted that meningitis has rarely been reported, complicating a concomitant diagnosis of bronchiolitis with only sporadic case reports in the literature.[54]

Future Research

Future research should focus on the improved availability of early detection or point-of-care viral and bacterial testing to quickly assess identifiable causes to better risk stratify the well-appearing febrile infant population for meningitis. Large multicenter prospective trials are needed to improve power, with more robust sample sizes. Future studies should report on meningitis as a separate outcome rather than combining several outcomes under the general umbrella of SBI. Studies assessing the risks of overtesting should be developed to improve patient-centered decisionmaking.

Relevant industry relationships: There were no relevant industry relationships disclosed by the subcommittee members for this topic. One Clinical Policies Committee member was recused from voting on recommendations due to a spousal relationship with industry.

Relevant industry relationships are those relationships with companies associated with products or services that significantly impact the specific aspect of disease addressed in the critical question.

REFERENCES

1. National Center for Health Statistics. 2011 National Hospital Ambulatory Medical Care Survey, ED summary table 10– Ten leading principal reasons for emergency department visits, by patient age and sex: United States, 2011. Available at: http://www.cdc.gov/nchs/data/ahcd/nhamcs_emergency/2011_ed_web_tables.pdf. Accessed September 2, 2015.
2. Pantell RH, Newman TB, Bernzweig J, et al. Management and outcomes of care of fever in early infancy. *JAMA*. 2004;291:1203-1210.
3. Lee GM, Harper MB. Risk of bacteremia for febrile young children in the post–*Haemophilus influenzae* type b era. *Arch Pediatr Adolesc Med*. 1998;152:624-628.
4. Baker MD, Bell LM. Unpredictability of serious bacterial illness in febrile infants from birth to 1 month of age. *Arch Pediatr Adolesc Med*. 1999;153:508-511.
5. Baker MD, Bell LM, Avner JR. Outpatient management without antibiotics of fever in selected infants. *N Engl J Med*. 1993;329:1437-1441.
6. Bachur RG, Harper MB. Predictive model for serious bacterial infections among infants younger than 3 months of age. *Pediatrics*. 2001;108:311-316.
7. Bass JW, Steele RW, Wittler RR, et al. Antimicrobial treatment of occult bacteremia: a multicenter cooperative study. *Pediatr Infect Dis J*. 1993;12:466-473.
8. Jaffe DM, Tanz RR, Davis AT, et al. Antibiotic administration to treat possible occult bacteremia in febrile children. *N Engl J Med*. 1987;317:1175-1180.
9. Waddle E, Jhaveri R. Outcomes of febrile children without localising signs after pneumococcal conjugate vaccine. *Arch Dis Child*. 2009;94:144-147.
10. Wilkinson M, Bulloch B, Smith M. Prevalence of occult bacteremia in children aged 3 to 36 months presenting to the emergency department with fever in the postpneumococcal conjugate vaccine era. *Acad Emerg Med*. 2009;16:220-225.
11. Mintegi S, Benito J, Sanchez J, et al. Predictors of occult bacteremia in young febrile children in the era of heptavalent pneumococcal conjugated vaccine. *Eur J Emerg Med*. 2009;16:199-205.
12. Greenhow TL, Hung YY, Herz AM, et al. The changing epidemiology of serious bacterial infections in young infants. *Pediatr Infect Dis J*. 2014;33:595-599.
13. Baraff LJ, Oslund SA, Schriger DL, et al. Probability of bacterial infections in febrile infants less than three months of age: a meta-analysis. *Pediatr Infect Dis J*. 1992;11:257-264.
14. Baskin MN, O'Rourke EJ, Fleisher GR. Outpatient treatment of febrile infants 28 to 89 days of with intramuscular administration of ceftriaxone. *J Pediatr*. 1992;120:22-27.
15. Herr SM, Wald ER, Pitetti RD, et al. Enhanced urinalysis improves identification of febrile infants ages 60 days and younger at low risk for serious bacterial illness. *Pediatrics*. 2001;108:866-871.
16. Jaskiewicz JA, McCarthy CA, Richardson AC, et al; Febrile Infant Collaborative Study Group. Febrile infants at low risk for serious bacterial infection — an appraisal of the Rochester criteria and implications for management. *Pediatrics*. 1994;94:390-396.
17. Baker MD, Avner JR, Bell LM. Failure of infant observation scales in detecting serious illness in febrile, 4- to 8-week-old infants. *Pediatrics*. 1990;85:1040-1043.
18. Hui C, Neto G, Tsertsvadze A, et al. *Diagnosis and Management of Febrile Infants (0-3 Months)*. Rockville, MD: Agency for Healthcare Research and Quality; 2012. Evidence Report/Technology Assessments, No. 205. Available at: http://www.ncbi.nlm.nih.gov/books/NBK92690/. Accessed September 2, 2015.
19. Mahajan P, Grzybowski M, Chen X, et al. Procalcitonin as a marker of serious bacterial infections in febrile children younger than 3 years old. *Acad Emerg Med*. 2014;21:171-179.
20. Kuppermann N, Mahajan P, Casper TC, et al. A clinical prediction rule for identifying febrile infants 60 days and younger with serious bacterial infections. *Acad Emerg Med*. 2015;22:S4.
21. American College of Emergency Physicians. Clinical policy for children younger than three years presenting to the emergency department with fever. *Ann Emerg Med*. 2003;42:530-545.
22. Hsiao AL, Chen L, Baker MD. Incidence and predictors of serious bacterial infections among 57- to 180-day-old infants. *Pediatrics*. 2006;117:1695-1701.
23. Shaikh N, Morone NE, Lopez J, et al. Does this child have a urinary tract infection? *JAMA*. 2007;298:2895-2904.
24. American Academy of Pediatrics Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics*. 2011;128:595-610.
25. Gorelick MH, Hoberman A, Kearney D, et al. Validation of a decision rule identifying febrile young girls at high risk for urinary tract infection. *Pediatr Emerg Care*. 2003;19:162-164.
26. Gorelick MH, Shaw KN. Clinical decision rule to identify febrile young girls at risk for urinary tract infection. *Arch Pediatr Adolesc Med*. 2000;154:386-390.
27. Shaw KN, Gorelick M, McGowan KL, et al. Prevalence of urinary tract infection in febrile young children in the emergency department. *Pediatrics*. 1998;102:e16.
28. Schroeder AR, Newman TB, Wasserman RC, et al. Choice of urine collection methods for the diagnosis of urinary tract infection in young, febrile infants. *Arch Pediatr Adolesc Med*. 2005;159:915-922.
29. Williams GJ, Macaskill P, Chan SF, et al. Absolute and relative accuracy of rapid urine tests for urinary tract infection in children: a meta-analysis. *Lancet Infect Dis*. 2010;10:240-250.
30. Doley A, Nelligan M. Is a negative dipstick urinalysis good enough to exclude urinary tract infection in paediatric emergency department patients? *Emerg Med*. 2003;15:77-80.
31. Ramlakhan SL, Burke DP, Goldman RS. Dipstick urinalysis for the emergency department evaluation of urinary tract infections in infants aged less than 2 years. *Eur J Emerg Med*. 2011;18:221-224.
32. Velasco R, Benito H, Mozun R, et al; Group for the Study of Febrile Infant of the RiSEUP-SPERG Network. Using a urine dipstick to identify a positive urine culture in young febrile infants is as effective as in older patients. *Acta Paediatr*. 2015;104:e39-e44.
33. Novak R, Powell K, Christopher N. Optimal diagnostic testing for urinary tract infection in young children. *Pediatr Dev Pathol*. 2004;7:226-230.
34. Reardon JM, Carstairs KL, Rudinsky SL, et al. Urinalysis is not reliable to detect a urinary tract infection in febrile infants presenting to the ED. *Am J Emerg Med*. 2009;27:930-932.
35. Waseem M, Chen J, Paudel G, et al. Can a simple urinalysis predict the causative agent and the antibiotic sensitivities? *Pediatr Emerg Care*. 2014;30:244-247.
36. Tosif S, Baker A, Oakley E, et al. Contamination rates of different urine collection methods for the diagnosis of urinary tract infections in young children: an observational cohort study. *J Paediatr Child Health*. 2012;48:659-664.
37. Kanegaye JT, Jacob JM, Malicki D. Automated urinalysis and urine dipstick in the emergency evaluation of young febrile children. *Pediatrics*. 2014;134:523-529.
38. Finnell SME, Carroll AE, Downs SM, et al. Technical report — diagnosis and management of an initial UTI in febrile infants and young children. *Pediatrics*. 2011;128:e749-e770.
39. Shah AP, Cobb BT, Lower DR, et al. Enhanced versus automated urinalysis for screening of urinary tract infections in children in the emergency department. *Pediatr Infect Dis J*. 2014;33:272-275.
40. De Rosa R, Grosso S, Bruschetta G, et al. Evaluation of the Sysmex UF1000i flow cytometer for ruling out bacterial urinary tract infection. *Clin Chim Acta*. 2010;411:1137-1142.

41. Craig JC, Williams GJ, Jones M, et al. The accuracy of clinical symptoms and signs for the diagnosis of serious bacterial infection in young febrile children: prospective cohort study of 15,781 febrile illnesses. *BMJ*. 2010;340:c1594.
42. Bilkis MD, Gorgal N, Carbone M, et al. Validation and development of a clinical prediction rule in clinically suspected community-acquired pneumonia. *Pediatr Emerg Care*. 2010;26:399-405.
43. Mathews B, Shah S, Cleveland RH, et al. Clinical predictors of pneumonia among children with wheezing. *Pediatrics*. 2009;124:e29-e36.
44. Cardoso MR, Nascimento-Carvalho CM, Ferrero F, et al. Adding fever to WHO criteria for diagnosing pneumonia enhances the ability to identify pneumonia cases among wheezing children. *Arch Dis Child*. 2011;96:58-61.
45. Simon LV, Carstairs KL, Reardon JM, et al. Oxygen saturation is not clinically useful in the exclusion of bacterial pneumonia in febrile infants. *Emerg Med J*. 2010;27:904-906.
46. Neuman MI, Monuteaux MC, Scully KJ, et al. Prediction of pneumonia in a pediatric emergency department. *Pediatrics*. 2011;128:246-253.
47. Ayalon I, Glatstein MM, Zaidenberg-Israeli G, et al. The role of physical examination in establishing the diagnosis of pneumonia. *Pediatr Emerg Care*. 2013;29:893-896.
48. Mahabee-Gittens EM, Grupp-Phelan J, Brody AS, et al. Identifying children with pneumonia in the emergency department. *Clin Pediatr*. 2005;44:427-435.
49. Ecochard-Dugelay E, Beliah M, Perreaux F, et al. Clinical predictors of radiographic abnormalities among infants with bronchiolitis in a paediatric emergency department. *BMC Pediatr*. 2014;14:143.
50. Jones RG, Bass JW. Febrile children with no focus of infection: a survey of their management by primary care physicians. *Pediatr Infect Dis J*. 1993;12:179-183.
51. Goldman RD, Scolnik D, Chauvin-Kimoff L, et al; Fever in Infants Group Research, Pediatric Emergency Research of Canada. Practice variations in the treatment of febrile infants among pediatric emergency physicians. *Pediatrics*. 2009;124:439-445.
52. Ferguson CC, Roosevelt G, Bajaj L. Practice patterns of pediatric emergency medicine physicians caring for young febrile infants. *Clin Pediatr (Phila)*. 2010;49:350-354.
53. Oray-Schrom P, Phoenix C, St Martin D, et al. Sepsis workup in febrile infants 0-90 days of age with respiratory syncytial virus infection. *Pediatr Emerg Care*. 2003;19:314-319.
54. Luginbuhl LM, Newman TB, Pantell RH, et al. Office-based treatment and outcomes for febrile infants with clinically diagnosed bronchiolitis. *Pediatrics*. 2008;122:947-954.
55. Rittichier KR, Bryan PA, Bassett KE, et al. Diagnosis and outcomes of enterovirus infections in young infants. *Pediatr Infect Dis J*. 2005;24:546-550.
56. Adler-Shohet FC, Cheung MM, Hill M, et al. Aseptic meningitis in infants younger than six months of age hospitalized with urinary tract infections. *Pediatr Infect Dis J*. 2003;22:1039-1042.
57. Meehan WP, Bachur RG. Predictors of cerebrospinal fluid pleocytosis in febrile infants aged 0 to 90 days. *Pediatr Emerg Care*. 2008;24:287-293.
58. Bilavsky E, Shouval DS, Yarden-Bilavsky H, et al. A prospective study of the risk for serious bacterial infections in hospitalized febrile infants with or without bronchiolitis. *Pediatr Infect Dis J*. 2008;27:269-270.
59. Krief WI, Levine DA, Platt SL, et al. Influenza virus infection and the risk of serious bacterial infections in young febrile infants. *Pediatrics*. 2009;124:30-39.
60. Levine DA, Platt SL, Dayan PS, et al. Risk of serious bacterial infection in young febrile infants with respiratory syncytial virus infections. *Pediatrics*. 2004;113:1728-1734.

Appendix A. Literature classification schema.*

Design/ Class	Therapy[†]	Diagnosis[‡]	Prognosis[§]
1	Randomized, controlled trial or meta-analysis of randomized trials	Prospective cohort using a criterion standard or meta-analysis of prospective studies	Population prospective cohort or meta-analysis of prospective studies
2	Nonrandomized trial	Retrospective observational	Retrospective cohort Case control
3	Case series Case report Other (eg, consensus, review)	Case series Case report Other (eg, consensus, review)	Case series Case report Other (eg, consensus, review)

*Some designs (eg, surveys) will not fit this schema and should be assessed individually.
[†]Objective is to measure therapeutic efficacy comparing interventions.
[‡]Objective is to determine the sensitivity and specificity of diagnostic tests.
[§]Objective is to predict outcome, including mortality and morbidity.

Appendix B. Approach to downgrading strength of evidence.

	Design/Class		
Downgrading	**1**	**2**	**3**
None	I	II	III
1 level	II	III	X
2 levels	III	X	X
Fatally flawed	X	X	X

Appendix C. Likelihood ratios and number needed to treat.*

LR (+)	LR (−)	
1.0	1.0	Does not change pretest probability
1-5	0.5-1	Minimally changes pretest probability
10	0.1	May be diagnostic if the result is concordant with pretest probability
20	0.05	Usually diagnostic
100	0.01	Almost always diagnostic even in the setting of low or high pretest probability

LR, likelihood ratio.
*Number needed to treat (NNT): number of patients who need to be treated to achieve 1 additional good outcome; NNT=1/absolute risk reduction×100, where absolute risk reduction is the risk difference between 2 event rates (ie, experimental and control groups).

Appendix D. Potential benefits and harms of implementing the recommendations

1. For well-appearing immunocompetent infants and children aged 2 months to 2 years presenting with fever (≥38.0°C [100.4°F]), are there clinical predictors that identify patients at risk for urinary tract infection?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. Infants and children at increased risk for urinary tract infection include females younger than 12 months, uncircumcised males, nonblack race, fever duration greater than 24 hours, higher fever (≥39°C), negative test result for respiratory pathogens, and no obvious source of infection. Although the presence of a viral infection decreases the risk, no clinical feature has been shown to effectively exclude urinary tract infection. Physicians should consider urinalysis and urine culture testing to identify urinary tract infection in well-appearing infants and children aged 2 months to 2 years with a fever ≥38°C (100.4°F), especially among those at higher risk for urinary tract infection.

Potential Benefit of Implementing the Recommendations: A decreased risk of missing a urinary tract infection with its associated morbidity and mortality in this vulnerable population.

Potential Harm of Implementing the Recommendations: Potential complications associated with obtaining a urine sample using sterile techniques by catheterization or suprapubic aspiration, and the increased financial costs associated with diagnostic testing.

2. For well-appearing febrile infants and children aged 2 months to 2 years undergoing urine testing, which laboratory testing method(s) should be used to diagnose a urinary tract infection?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. Physicians can use a positive test result for any one of the following to make a preliminary diagnosis of urinary tract infection in febrile patients aged 2 months to 2 years: urine leukocyte esterase, nitrites, leukocyte count, or Gram's stain.

Level C recommendations.

(1) Physicians should obtain a urine culture when starting antibiotics for the preliminary diagnosis of

urinary tract infection in febrile patients aged 2 months to 2 years.

(2) In febrile infants and children aged 2 months to 2 years with a negative dipstick urinalysis result in whom urinary tract infection is still suspected, obtain a urine culture.

Potential Benefit of Implementing the Recommendations: If the urine test result is positive, it decreases further testing and allows more rapid decisionmaking in regard to disposition.

Potential Harm of Implementing the Recommendations: If the urine test result is negative, it increases uncertainty about the source of the fever, which may lead to further testing and delays to disposition.

3. For well-appearing immunocompetent infants and children aged 2 months to 2 years presenting with fever (≥38.0°C [100.4°F]), are there clinical predictors that identify patients at risk for pneumonia for whom a chest radiograph should be obtained?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. In well-appearing immunocompetent infants and children aged 2 months to 2 years presenting with fever (≥38°C [100.4°F]) and no obvious source of infection, physicians should consider obtaining a chest radiograph for those with cough, hypoxia, rales, high fever (≥39°C), fever duration greater than 48 hours, or tachycardia and tachypnea out of proportion to fever.

Level C recommendations. In well-appearing immunocompetent infants and children aged 2 months to 2 years presenting with fever (≥38°C [100.4°F]) and wheezing or a high likelihood of bronchiolitis, physicians should not order a chest radiograph.

Potential Benefit of Implementing the Recommendations: The benefits of obtaining a chest radiograph in patients at higher risk for pneumonia will decrease the incidence of complications associated with missed cases of pneumonia and allow the initiation of treatment that may lead to earlier resolution of symptoms.

Potential Harm of Implementing the Recommendations: The primary harm associated with obtaining chest radiographs in children at higher risk of pneumonia is the exposure to radiation, yet the radiation dose associated with a standard chest radiograph is much lower than that of advanced imaging modalities such as computed tomography of the thorax. Another potential harm is overdiagnosis from false-positive radiographs. This can lead to overtreatment and subsequent potential harms without any potential benefit.

4. For well-appearing immunocompetent full-term infants aged 1 month to 3 months (29 days to 90 days) presenting with fever (≥38.0°C [100.4°F]), are there predictors that identify patients at risk for meningitis from whom cerebrospinal fluid should be obtained?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations.

(1) Although there are no predictors that adequately identify full-term well-appearing febrile infants aged 29 to 90 days from whom cerebrospinal fluid should be obtained, the performance of a lumbar puncture may still be considered.

(2) In the full-term well-appearing febrile infant aged 29 to 90 days diagnosed with a viral illness, deferment of lumbar puncture is a reasonable option, given the lower risk for meningitis. When lumbar puncture is deferred in the full-term well-appearing febrile infant aged 29 to 90 days, antibiotics should be withheld unless another bacterial source is identified. Admission, close follow-up with the primary care provider, or a return visit for a recheck in the ED is needed. (Consensus recommendation)

Potential Benefit of Implementing the Recommendations: Potential for less invasive testing, reduced resource use, and costs (ie, potential reduction in iatrogenic injury, traumatic lumbar punctures with unclear results or cerebrospinal fluid pleocytosis, patient pain, and parental anxiety), reduced exposures to other infectious diseases associated with hospital admission, and decreased exposure to unnecessary empiric antibiotic treatment.

Potential Harm of Implementing the Recommendations: Potential for delayed diagnosis and/or treatment if lumbar puncture is deferred.

Evidentiary Table.

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Question 1					
Hsiao et al[22] (2006)	III	Prospective cohort; tertiary children's hospital 2003 to 2004	57 to 180 days with rectal temperature ≥38°C, urine obtained by catheter or suprapubic needle aspiration in 2; positive urine culture definition: >10,000 colonies of single organism per milliliter	N=429; 424 (98.8%) had urine available; SBI in 44 (10.3%); 41 (9.7%) positive urine culture, 6 with sterile pyuria; 4 (0.9%) positive blood culture; 0 positive CSF culture; predictive of positive urine culture among 217 male patients: uncircumcised (36%) vs circumcised (1.6%), compared to overall 9.7% of positive urine culture in female patients; WBC, CRP, and Yale Observation Scale score increased in positive SBI	Included those with obvious source of illness in 264 (61.5%), such as URI or otitis; although most of the cases of SBI are positive urine culture, there are 4 cases of SBI that are from positive blood cultures
Shaikh et al[23] (2007)	III	Systematic review and meta-analysis of both prospective and cross-sectional observational studies from 1966 to 2007; multiple different clinical settings, including EDs and clinics	Inclusion criteria: children <18 y with structured search for UTI; standardized systematic review, including comprehensive literature search and meta-analysis methods including blinded abstraction and use of pooled estimates	N=12 studies; N=8,837 patients; pooled prevalence of UTI: 0- to 3-mo male: 9% (95% CI 5% to 12%); 0- to 3-mo female: 8% (95% CI 6% to 9%); 3- to 12-mo male: 2% (95% CI 1% to 3%); 3- to 12-mo female: 2% (95% CI 1% to 4%); history of UTI: LR range 2.3 to 2.9; temperature >40°C: LR range 3.2 to 3.3; suprapubic tenderness: LR 4.4 (95% CI 1.6 to 12.4); among males lack of circumcision: LR 2.8 (95% CI 1.9 to 4.3); in verbal children: abdominal pain LR 6.3 (95% CI 2.5 to 16); back pain LR 3.6 (95% CI 2.1 to 6.1); dysuria, frequency, or both LR range 2.2 to 2.8; temperature >39°C without other source for infection: LR 4.0 (95% CI 1.2 to 13)	Included 12 studies with patients <18 y, although only 4 studies included those 0 to 3 mo and another 4 included those 0 to 24 mo; method of urine collection varied from catheterization to bagged specimens; no mention of heterogeneity, although results were pooled

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Question 2					

Schroeder et al[28] (2005)	II	Prospective cohort study from PROS, the practice-based research network of the AAP; the Febrile Infant Study involved 573 practitioners from 219 practices from within the PROS network; practitioners represented 44 states, the District of Columbia, and Puerto Rico	All children: (1) age ≤93 days, (2) axillary, rectal, or tympanic temperature of 38°C or higher in the office or in the previous 24 h at home; and (3) initial examination by a PROS practitioner; 4 had both urinalysis and urine culture; data collected 1995 to 1998; urine analysis by catheter and bag compared to urine culture; outcome: for bag specimens, at least 100,000 CFU/mL of a single pathogenic organism was required; 20,000 CFU/mL for catheter	N=1,482 of 3,066 patients had both urinalysis and culture (48.3%); bag 273, catheter 716; 21 cultures (95% CI 13 to 53) would have to be obtained by catheter to avoid 1 ambiguous culture obtained by bag;
				bag LE: SN 76; SP 84;
				cath LE: SN 86; SP 94;
				bag nitrites: SN 25; SP 98;
				cath nitrites: SN 43; SP 99;
				
				bag WBC 6 to 10: LR=0;
				bag WBC 11 to 20: LR=7;
				bag WBC >20: LR=13.5;
				area under ROC curve=0.71 (95% CI 0.61 to 0.82);
				
				cath WBC 6 to 10: LR=3.7;
				cath WBC 11 to 20: LR=23.9;
				cath WBC >20: LR=26.3;
				area under ROC curve=0.86 (95% CI 0.82 to 0.91)
					Indirectly applicable: included ages <2 mo; likely a secondary analysis of data from the PROS network; only captured 48.3% of the cohort; few bag specimens; CIs not reported for SN and SP

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Question 2					
Williams et al[29] (2010)	II	Meta-analysis of prospective controlled trials published 1966 to July 2009	Study inclusion criteria: involved children ≤18 y; compared urine culture (reference standard) with 1 or more rapid tests (index test) for the diagnosis of UTI; contained sufficient information for 2x2 contingency table	N=95 studies involving 95,703 children (94,664 urine samples); microscopy and Gram's-stained bacteria: SN 91% (95% CI 80% to 96%) SP 96% (95% CI 92% to 98%); microscopy and unstained bacteria: SN 88% (95% CI 75% to 94%) SP 92% (95% CI 84% to 96%) urine microscopy for WBCs: SN 74% (95% CI 67% to 80%) SP 86% (95% CI 82% to 90%); leucocyte esterase or nitrite positive dipstick: SN 88% (95% CI 82% to 91%) SP 79% (95% CI 69% to 87%); nitrite-only positive dipstick: SN 49% (95% CI 41% to 57%) SP 98% (95% CI 96% to 99%); rapid tests are negative in approximately 10% of children with a UTI and cannot replace urine culture	Indirectly applicable: included children <2 mo and >2 y; unclear whether some studies were retrospective; articles combined differing definitions of urine culture results indicating an infection and means for collecting urine samples (catheter vs. bag); studies often had poor explanations for methods; definitions of positives highly heterogeneous; 7 thresholds reported for WBC count, 5 for bacterial microscopy, and 3 for LE; included studies before new vaccines; regression models adjusted for these minor limitations
Doley and Nelligan[30] (2003)	III	Retrospective chart review over 8 mo; unclear setting; unclear year	Aged 0 to 10 y (stratified <2 y) with those who had a printed microscopy and culture; urine collected by bag or clean catch; positive urine culture definition=10^5	N=375; 0 to 2 y=160; UTI prevalence=15%; SN=87.5% (95% CI 74.3% to 100%); SP=39.7% (95% CI 31.5% to 47.9%); PPV=20.4% (95% CI 12.6% to 28.2%); NPV=94.7% (95% CI 88.9% to 100%)	Included <2 mo and 2 to 10 y; urine collected by bag or clean catch (not catheter); subjects could be afebrile

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Question 2					
Ramlakhan et al[31] (2011)	III	Retrospective cohort in United Kingdom; pediatric ED	All children aged <2 y with fever and urine dipstick and quantitative culture as criterion standard	N=321 samples; mean age=9 mo; 63% female; test positive for nitrite, LE, and blood resulted in SP=97% (LR+=15); negative for nitrite, LE, blood, and protein has SN of 97% (LR-=0.1)	Minor methodological downgrading for convenience sampling, no blinding, and unclear assessment of the outcome
Velasco et al[32] (2015)	III	Subgroup analysis of prospective cohort multicenter 19 hospitals, 2011 to 2013	Aged <90 days with temperature ≥38°C and no source; outcome: positive urine culture, defined as ≥50,000 CFU/mL, catheter	N=3,401; mean age 46.6 days; female=176 (12.8%); urine dipstick abnormal in 766 (22.5%); 496 (14.6%) LE+; 14 (0.7%)+nitrites; 649 (19.1%) positive urine culture; LE SN=82.1% (95% CI 79 to 85), SP=92.4 (95% CI 91.4 to 93.4); LR+ 10.8, LR- 0.2; nitrites SN=37.1 (95% CI 33 to 41); nitrites SP=98.9 (95% CI 98.5 to 99.3); *E coli* in 550 (84.8%); SN and SP differ by sex: LE increased SN in female=86.4% vs 80.5% in male; SP lower in female=90.8% vs 93.6% in males	All <90 days (unable to determine who was aged 60 to 90 days); all had CRP, WBC count, urine dip, urine and blood culture (selection bias); subgroup analysis of previously collected data

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Question 2					
Novak et al[33] (2004)	III	Retrospective cohort of urban pediatric ED over 4 mo; unclear year	Aged <5 y who had catheter urinalysis and sent for unspun leukocyte, Gram's stain, urine dipstick for blood, LE, nitrite, and standard spun sediment; positive urine culture definition: $>10^3$ colonies of a single organism plus unspun leukocyte count >10 or positive Gram's stain	N=142; half are ≤1 y; 34% male; 25 (17.6%) positive urine culture; best test characteristics were cytocentrifuge Gram's stain with SN=80% and NPV 92%; unspun leukocyte count >10/µL with SN=68% and NPV=92%	Included all <5 y and stratified only by <1 y or greater; frequency of low volumes of urine or dilute urine far more common in <1 y

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Question 2					
Reardon et al[34] (2009)	III	Retrospective cohort study; single academic center naval hospital	All children ≤2 y included with fever urinalysis and urine culture included; sterile catheterized urinalysis was obtained on all females, on all males younger than 6 mo, and on uncircumcised males younger than 12 mo; fever defined as younger than 3 mo and had a temperature of at least 38°C or if they were between 3 and 24 mo and had a temperature of at least 39°C; the urinalysis was considered positive if there was presence of pyuria (≥5 WBCs per high-power field), LE on the urine dipstick, or nitrites on the dipstick; outcome: urine culture considered positive if they contained at least 10,000 CFU	N=435 patients having both urinalysis and urine culture from same specimen; median age 12 mo; 45 (10.3%) positive urine culture results; female patients accounted for 33 (73%) of 45 positive results; urinalysis: SN: 64% (95% CI 49% to 78%); SP: 91% (95% CI 88% to 94%); PPV 46% (95% CI 31% to 53%); NPV 96% (95% CI 93% to 97%)	Indirect; infants 0 to 3 mo and 3 mo to 2 y; 78% of eligible patients captured; included both catheter and bag specimens; few outcomes to support conclusions; no a priori sample size calculation; unclear whether blinded abstraction

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Question 2					
Waseem et al[35] (2014)	III	Retrospective cohort	Children 2 mo to 2 y with fever, presenting to an ED and who had urine sample obtained; positive urine culture as the criterion standard	N=608 (culture-proven UTIs); 70% with positive urinalysis; LE+: 84% *E coli*; 16% non–*E coli*; nitrite+: 91% *E coli*; 9% non–*E coli*	Only those with positive urine culture were included
Tosif et al[36] (2012)	III	Retrospective cohort from tertiary children's hospital	Children <2 y	N=599 samples; mean age 7 mo; 54% male; contamination: 26% clean catch; 12% catheter; 1% suprapubic aspiration	Excellent chart abstraction methodology; unclear sampling, likely convenience, resulting in minor downgrading
Kanegaye et al[37] (2014)	III	Prospective enrollment; cross-sectional study; tertiary children's hospital	Convenience sample of children <48 mo who presented to the ED with fever and with evaluation for UTI; outcome included UTI defined as urinary bacterial growth ≥50,000/mL	N=342; 42 (12%) had UTI; median age 8 mo (IQR: 4 to 14); point-of-care tests: nitrites LR+ 79 (95% CI 19 to 322); LE ≥trace: LR+ 27 (95% CI 15 to 50%); LE ≥2+: LR+ 83 (95% CI 27 to 259); automated tests: WBC ≥10 cells/µL: LR+ 1.7 (95% CI 1.5 to 1.8); WBC ≥25 cells/µL: LR+ 5.2 (95% CI 4 to 6.7); WBC ≥50 cells/µL: LR+ 17 (95% CI 10 to 29); WBC ≥100 cells/µL: LR+ 43 (95% CI 19 to 96)	Convenience sampling; single institution with experience with point-of-care testing; unclear blinding

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Question 3					
Craig et al[41] (2010)	II	Prospective cohort from a pediatric ED	Included children <5 y presenting with fever; outcome: pneumonia by committee	N=15,781 (3%) with pneumonia; physician diagnosis of infection had low sensitivity (10% to 50%) and high specificity (90% to 100%), depending on the characteristic	Criterion standard diagnosis by committee; large sample
Bilkis et al[42] (2010)	III	Prospective cohort, 4 hospitals 2006 to 2007	Included 1 to 16 y with fever and clinically suspected pneumonia; outcome=pneumonia with pulmonary consolidation on CXR; 2 pediatric radiologists (K=0.7) or clinical pneumonia without chest radiograph	N=257; 179 (69%) + CXR pneumonia, 78 (30%) with clinical pneumonia; multivariable model — grunting, cough, rales, decreased breath sounds, and vomiting had sensitivity of 94% and specificity of 33%; also validated Lynch prediction rule with 4 predictors: fever, localized rales, decreased breath sounds, or tachypnea with 93.8% SN and SP of 19%	Excluded <1 y; difficult to tell who was 1 to 2 y
Mathews et al[43] (2009)	III	Prospective cohort; single pediatric ED	Included patients <21 y of age but included appropriate subgroup (2 mo to 2 y); outcome=pneumonia by infiltrate on CXR; assessed by 2 radiologists blinded, independent	N=526; median age 1.9 y; 36% hospitalized; wheezing in 47%, 5% with pneumonia; afebrile children with wheezing had pneumonia prevalence of 2%	CXR used as criterion standard to define pneumonia as outcome, resulting in minor downgrading

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Question 3					
Cardoso et al[44] (2011)	III	Prospective cohort from pediatric ED in 5 public Brazilian hospitals	Included children 2 to 59 mo with acute lower respiratory tract disease; defined signs and symptoms were wheezing, rales, tachypnea, and/or dyspnea; assessed pneumonia risk using WHO criteria (rapid breathing or lower chest indrawing) with and without addition of fever; outcome radiographic diagnosis of pneumonia or clinical diagnosis by chest physician	N=390; 153 (39%) had CXR; 265 (68%) between 2 mo to 2 y; all children: WHO SN 84% (95% CI 74% to 92%) SP 19% (95% CI 15% to 24%) WHO+fever SN 81% (95% CI 70% to 90%) SP 46% (95% CI 40% to 52%) children 2 mo-2 y: WHO SN 94% (95% CI 83% to 99%) SP 20% (95% CI 15% to 26%) WHO+fever SN 92% (95% CI 80% to 98%) SP 44% (95% CI 40% to 53%) children without wheezing: WHO SN 76% (95% CI 56% to 89%) SP 62% (95% CI 46% to 75%) WHO+fever SN 76% (95% CI 56% to 89%) SP 70% (95% CI 55% to 82%) children with wheezing: WHO SN 90% (95% CI 76% to 97%) SP 12% (95% CI 8% to 16%) WHO+fever SN 85% (95% CI 70% to 94%) SP 42% (95% CI 36% to 48%)	Limited number of outcomes; only 70 cases of pneumonia; unclear whether chart abstraction was blinded; no agreement reported about radiologic outcomes

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Question 3					
Simon et al[45] (2010)	III	Retrospective cohort; tertiary care military hospital 2002 to 2003	Febrile infant registry; included children <3 mo with temperature >38°C and those 3 mo to 2 y with temperature >39°C	N=985; median age 12 mo; 55% male; 790 with CXR and 10% pneumonia prevalence; oxygen saturation was lower in subjects with pneumonia (*P*<.001) but with a poor SN/SP profile	Retrospective registry study; CXR used as criterion standard for pneumonia
Neuman et al[46] (2011)	III	Prospective cohort; urban pediatric ED between 2006 and 2009	Enrolled children <21 y, who had a CXR for clinical suspicion of pneumonia; excluded patients having preexisting medical conditions with increased risk for pneumonia (eg, sickle cell disease, immunodeficiency), or radiograph for other conditions (eg, trauma); assessed pneumonia risk using logistic regression models and recursive partitioning; outcome: final radiology report in the electronic medical record — definitive or pneumonia included in differential diagnosis	N=2,574, 1,189 <2 y (46.2%); median age=2.3 y; definite pneumonia=199 (7.7%); radiographic pneumonia=422 (16.4%); 576 admitted to hospital (22.4%); multivariable for pneumonia: oxygen saturation <92%=OR 3.7 (95% CI 2 to 6.8); chest pain=OR 2.9 (95% CI 1.9 to 4.4); focal rales=OR 2.3 (95% CI 1.3 to 3.9); fever >72 h=OR 3.6 (95% CI 2.1 to 6.4); temperature ≥38°C=OR 1.4 (95% CI 1.0 to 2.0); CART 5 software: oxygen saturation ≤92%=high risk; intermediate risk if oxygen saturation >92% but fever, focal decreased breath sounds, rales; if oxygen saturation >92%, no fever, no focal decreased breath sounds, no focal rales, then radiographic pneumonia in only 7.6%	Indirectly applicable: study included all children <21 y; separate rule for children <5 y; minor methodological limitations: only 51% eligible were enrolled; all children had to have a CXR (spectrum bias); in the <2 y cohort, could have included those <2 mo; in the subgroup analysis of <5 y, cannot tell who was <2 y; children did not need to have a fever; no interrater reliability of radiographic findings; no interrater reliability of chart review part or prospective questionnaire

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Question 3					
Ayalon et al[47] (2013)	III	Prospective cohort urban academic pediatric ED, Tel Aviv 2007 to 2010	Included children 1 mo to 16 y for children with fever, suspicion of pneumonia, and a CXR was ordered; excluded suspected hospital-acquired pneumonia (positive radiographic results within 10 days of hospital discharge) or suspected aspiration pneumonia; assessed pneumonia risk with signs and symptoms recorded on a questionnaire; outcome clearly visible and obvious findings of air-space disease on CXR interpreted by board-certified radiologist	N=525 patients; 181 (34%) with pneumonia or with 95% CIs for history and physical examination findings: increased age 1.09 (95% CI 1.013 to 1.164); higher fever 2.14 (95% CI 1.208 to 2.138); ill appearance 2.3 (95% CI 1.406 to 3.781); lower oxygen saturation 2.4 (95% CI 1.035 to 5.645); accessory breath muscles 2.17 (95% CI 1.126 to 4.203); presence of rales 1.96 (95% CI 1.046 to 3.683); presence of crackles 2.2 (95% CI 1.312 to 3.694)	Indirectly applicable: included children 1 to 2 mo; no stratification for 2 mo to 2 y; study included ill-appearing children; no reliability assessments for clinical findings, only for radiology interpretations; unclear attrition; sample size not reported

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Question 3					
Mahabee-Gittens et al[48] (2005)	III	Prospective cohort; tertiary care pediatric ED between 2000 and 2002	Included 2 to 59 mo with cough and 1 more symptom of tachypnea, noisy breathing, chest or abdominal pain, or fever; 5 pediatric ED study physicians examined subjects for findings and were asked pretest probability of pneumonia; they piloted 50 subjects for interobserver agreement, K=0.8; CXR reviewed by 2 radiologists, blinded to physical examination and symptoms, K=0.84	N=510; 44 (8.6%) had radiographic pneumonia; multivariable for pneumonia: age >12 mo (OR=1.4, 95% CI 1.1 to 1.9); RR ≥50 (OR=3.5, 95% CI 1.6 to 7.5); oxygen saturation ≤96% (OR=4.6, 95% CI 2.3 to 9.2); nasal flaring (OR=2.2, 95% CI 1.2 to 4.0) if ≤12 mo	All children had to have a CXR (spectrum bias); unable to tell who was 2 mo to 24 mo; subjects did not have to have a fever
Ecochard-Dugelay et al[49] (2014)	III	Prospective cohort; urban pediatric ED, France between 2006 and 2007	Included <2 y with clinical bronchiolitis; outcome=CXR abnormality; CXR reviewed by 2 pediatric radiologists, K=0.8; multivariable analysis	N=821; 171 (21%) <3 mo; 427 had CXR, 40/427 (9.7%) abnormal and 39 with lobar or alveolar consolidation; multivariable predictor of CXR abnormality=only temperature ≥38° C (OR=2.4, 95% CI 1.1 to 5.1) predictive; age <3 mo, feeding difficulties, rales, and retractions not predictive of CXR plus pneumonia	Included <2 mo and cannot tell who was <2 mo; all had to have clinical bronchiolitis; subjects did not need to have fever; CXR conducted in 52% and diagnosis of pneumonia made by CXR

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Question 4					
Meehan and Bachur[57] (2008)	III	Retrospective cohort; single urban pediatric medical center 4-y period; unclear actual years	Infants ≤90 days with temperature ≥38°C; outcome: pleocytosis; no CSF obtained in 623 (22%); excluded 182 traumatic LP (8.3%); stratified by age <30 days, 31 to 60 days, 61 to 90 days; used CART (age, WBC, ANC, temperature, and season entered based on a priori criteria)	N=2,003; mean age 1.6 mo; 176 (8.8%) with CSF pleocytosis (8.4% with aseptic meningitis and 0.4% with bacterial meningitis); pleocytosis increased risk in summer; if nonsummer months, then temperature >38.4°C and WBC count >6,100/μL increased risk of CSF pleocytosis in 38/500 (7.6%) of ≤30 days, 86/813 (10.4%) of 31 to 60 days, and 52/680 (7.7%) of 61 to 90 days	Outcome was CSF pleocytosis, not meningitis; only 78% of patients underwent an LP; excluded traumatic LPs; very small number with actual bacterial meningitis

AAP, American Academy of Pediatrics; *ANC*, absolute neutrophil count; *CART*, classification and regression trees; *Cath*, catheterization; *CFU/mL*, colony-forming units/milliliter; *CI*, confidence interval; *CRP*, C-reactive protein; *CSF*, cerebrospinal fluid; *CXR*, chest radiograph; *E coli*, *Escherichia coli*; *ED*, emergency department; *h*, hour; *IQR*, interquartile range; *LE*, leukocyte esterase; *LP*, lumbar puncture; *LR-*, negative likelihood ratio; *LR+*, positive likelihood ratio; *mo*, month; *N*, number; *NPV*, negative predictive value; *OR*, odds ratio; *PPV*, positive predictive value; *PROS*, Pediatric Research in Office Settings; *ROC*, receiver operating characteristic; *RR*, respiratory rate; *SBI*, serious bacterial infection; *SN*, sensitivity; *SP*, specificity; *URI*, upper respiratory infection; *UTI*, urinary tract infection; *vs*, versus; *WBC*, white blood cell; *WHO*, World Health Organization; *y*, year.