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Diagnosis and Management of Febrile Infants (0–3 months)

Executive Summary

Introduction

The febrile infant is a common clinical problem that accounts for a large number of ambulatory care visits. Young febrile infants (ages 0– 3 months) often present with nonspecific symptoms and it is difficult to distinguish between infants with a viral syndrome and those with early serious bacterial illness (e.g., meningitis, bacteremia, urinary tract infection (UTI), and pneumonia).

The definitions of serious bacterial illness (SBI) vary across published literature. SBI typically includes the diagnoses of meningitis, bacteremia, and UTI. Some studies have also included pneumonia, bone and joint infections, skin and soft tissue infections, and bacterial enteritis in the definition. Invasive herpes simplex virus (HSV) infections are grouped into meningoencephalitis; disseminated; or skin, eyes, and mouth. There is some overlap in these presentations.

Febrile illness in infancy is often due to viral infections and is likely to be self-limiting. Although SBI is relatively uncommon among febrile infants, if it is not promptly diagnosed and managed, serious consequences may result. The clinical dilemma that practitioners often face is how to avoid missing a case of SBI versus how to avoid the risks and harms of investigating, observing, and potentially treating a febrile infant with no SBI.

The most common bacterial pathogen for SBI in the young infant is *Escherichia coli,* with Group B *Streptococcus, Staphylococcus aureus, Listeria monocytogenes*, and other

Evidence-based Practice Program

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

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Evidence-Based Practice

gram-negative enteric bacteria being the other likely pathogens in this age group. Although uncommon, HSV infections are a major cause of morbidity and mortality among neonates (ages 0–28 days) with a case fatality rate of 15.5 percent.[1] The prevalence of neonatal HSV infection has been reported to be between 25 and 50 per 100,000 live births in the United States.[2] The prevalence of HSV infection in a febrile neonate is 0.3 percent which is similar to the prevalence of bacterial meningitis in this age group.[3]

Historically, febrile infants less than 3 months of age would undergo a complete evaluation for sepsis, including a lumbar puncture, and would be admitted to a hospital for intravenous antibiotics for at least 48 hours pending culture results.[15] The rationale for this approach is based on the high prevalence of SBI in this group and the difficulty with the clinical assessment for sepsis in the young infant where clinical signs of sepsis are often subtle.[4] Although this approach minimizes the risk of infectious complications, it leads to unnecessary hospitalization and treatment, resulting in potential iatrogenic harms to infants. In recent decades, increasing awareness of these trade-offs has led to efforts to discriminate better which young infants with fever might really need more versus less intensive management. Technical advances have been part of the impetus. For example, with the availability of longer-acting antibiotics that can be administered intramuscularly (e.g., ceftriaxone in the 1980s) and newer diagnostic tests that do not require 48-hour incubation, the reasons for the "rule-out sepsis" hospitalization may seem less compelling, and practice patterns may have evolved.

Infant observation scales were developed to help define infants who have severe illness, but they failed to predict reliably which infants were likely to have sepsis.[4-7] Several studies focused, conversely, on the development of low-risk criteria to help select infants who were unlikely to have SBI and could therefore be managed as outpatients. These studies developed low-risk criteria such as the Philadelphia, Rochester, and Boston criteria to predict the absence of SBI. These criteria are comprised of clinical (appearance, past medical history) and laboratory features such as white blood cell count (WBC), C-reactive protein (CRP), urinalysis (UA), cerebrospinal fluid (CSF), erythrocyte sedimentation rate (ESR), absolute band counts (ABC), and procalcitonin (PCT). The application of clinical assessments combined with laboratory criteria classifies infants into low-risk and not low-risk groups for having SBI. The identification of febrile infants with low risk of SBI helps to minimize unnecessary costs and harmful consequences associated with the treatment.[8-13] There are a small number of infants who will be classified as low risk who are subsequently found to have SBI and there may be harm in these infants from the delay in diagnosis and treatment.

The recommended management of febrile neonates, infants under 28 days of age, is controversial. Given that the overall prevalence of SBI is higher in the neonate, most experts would advocate for a full sepsis evaluation and hospitalization.[14,15] There are studies that have attempted to apply low-risk criteria in infants less than 1 month of age but because of the higher baseline rates of serious bacterial illness in the neonate the overall rates of SBI in the low-risk group are higher than in older infants.[10,16,17]

The current recommendations for the evaluation and management of the young febrile infant are based on studies conducted in the late 1980s and early 1990s.[18] An up-to-date systematic review of the diagnostic tests and harms of the management strategies for febrile infants is warranted. This evidence report is designed to review the literature to answer Key Questions (KQs) about the management of the febrile infant and to identify needs for future research.

Methods

Literature Search

Studies were identified through electronic searches in MEDLINE (1950 to September Week 2 2010, OVID interface), MEDLINE in Process (September 29, 2010), CINAHL (1982–2008, OVID Interface), Embase (1980 to 2010 Week 37, OVID interface), PsycINFO (1806 to September Week 2 2010 OVID interface), EBM Reviews, Cochrane Central Register of Controlled Trials (2nd Quarter 2010), the Cochrane Database of Systematic Reviews (2nd Quarter 2010), and PubMed (1973 to September 22, 2010). The Web sites of relevant organizations were searched to identify any unpublished materials. Additional studies were sought through contacting experts. The searches were combined into a single Reference Manager database and duplicate records were manually deleted, providing a database of unique citations.

Study Selection

The English-language studies that reported the diagnosis and/or management of infants (0–3 months of age for KQ1–KQ5 and 0–6 months of age for KQ6) with no history of major diseases predisposing to fever (rectal temperature ≥ 38°C) and/or SBI (including bacterial meningitis, bacteremia, UTI) or HSV infection admitted to an emergency department of a hospital, evaluated in an outpatient office practice or an acute care walk-in clinic were eligible. Studies conducted in North America,

Australia, New Zealand, Western Europe (i.e., Belgium, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Switzerland, and United Kingdom), Northern Europe (i.e., Denmark, Finland, Norway, Sweden), Israel, Hong Kong, Japan, Taiwan, and Singapore were eligible for inclusion in the review. The inclusion was not restricted by study design (e.g., randomized or nonrandomized controlled trials, case-series, cohort, case-control, or cross-sectional/prevalence studies). Case reports, systematic reviews, cost-effectiveness analyses, editorials, or letters were excluded.

Two reviewers independently screened titles and abstracts of all identified bibliographic records and afterwards full-text reports of potentially relevant records. Discrepancies were resolved by discussion.

Data Extraction and Assessment of Study and Reporting Quality

Two reviewers independently extracted relevant information from the included studies using a data extraction form, which was verified by a third independent reviewer. Abstracted data included study and population characteristics (e.g., first author, country, design, age, ethnicity, demographics, setting). Information was extracted on index tests (e.g., criteria, laboratory thresholds) used to identify or screen bacterial or herpetic infection with treatment outcomes as well as diagnostic methods or reference standards (e.g., bacterial culture growth in blood, urine, or cerebral spinal fluid, viral culture). The test results (i.e., sensitivity and specificity), positive and negative predictive values (PPV, NPV), and area under the curve (AUC) were directly abstracted when reported or derived whenever possible. Other extracted information included prevalence (i.e., proportion) of SBI or HSV infection in febrile infants and parents' compliance with followup examination visits. Efforts were made to extract relevant data separately for each age strata (i.e., 0–28; 28–60; 60–90 days), where possible.

The included studies were classified with respect to design (e.g., randomized controlled trial, cohort study, case-series). The studies reporting diagnostic accuracy data and those for which this data could be derived were classified as diagnostic accuracy studies. Two independent reviewers assessed the risk of bias of the included studies. The diagnostic test accuracy studies were assessed using a validated 14-item quality assessment of diagnostic accuracy studies (QUADAS) tool.[19]

Synthesis of the Evidence

The index tests (i.e., criteria, protocols, clinical symptoms, and laboratory thresholds) used for classifying febrile infants into low- or high-risk groups (for having SBI or HSV infection) were categorized in three groups: (1) combined clinical and laboratory criteria, (2) clinical criteria alone, and (3) laboratory criteria alone. We did not specify the definition of SBI (or HSV infection) in this report. Instead, the definitions from original studies were presented. For each study, a two-by-two table was constructed and diagnostic accuracy parameters with the corresponding 95 percent confidence intervals (95 percent CI) were calculated, if possible. Where data allowed, the diagnostic accuracy parameters were calculated for total SBI and for bacteremia and meningitis separately. The prevalence of SBI or HSV infection in virus-positive and virus-negative febrile infants was ascertained and compared using odds ratios or prevalence ratios. The potential sources of clinical and methodological heterogeneity (e.g., population, study quality, different index tests and their thresholds) were considered. Sensitivity and specificity were pooled using the DerSimonian and Laird random effects model if they were based on the application of the same criteria/protocol in similar populations of infants for predicting total or the specific type of bacterial infection (e.g., total serious bacterial infection, UTI, and bacteremia). The degree of statistical heterogeneity was examined graphically by plotting values of sensitivity and specificity and guided by I^2 and Chi-squared statistics.[20]

Results

In total, 84 unique studies (92 records) were included in this review.

KQ1A. In infants < 3 months old who present with a fever, what are the sensitivity, specificity, and predictive values of individual or combinations of clinical features (history including information on the mother's history and previous testing, risk factors, findings on clinical exam, laboratory tests, and formal scoring instruments based on clinical features) for identifying those with serious bacterial illness (SBI)?

This section included 62 studies. The reviewed studies reported an extensive array of classification methods (i.e., index tests) for predicting risk of SBI in febrile infants. We found no evidence relating to other possibly relevant factors such as the clinical history of the mother.

Combined clinical and laboratory criteria. This review identified studies using the following criteria/protocols: Boston, Philadelphia, Rochester, Milwaukee, and Young Infant Observation Scale (YIOS). (Table A.) Other criteria were different combinations of clinical (e.g., ill or toxic appearance, impression of sepsis, age, rectal temperature) and laboratory features with varying thresholds (e.g., serum WBC, ESR, CRP, ABC, urine microscopy). The presence of SBI was determined by confirming bacterial growth in blood, CSF, stool, and/or urine.

The Rochester, Philadelphia, Milwaukee, and Boston protocol/criteria were similar for correctly identifying febrile infants with SBI (sensitivity range: 84.4 percent to 100.0 percent; NPV range: 93.7 percent to 100.0 percent). These four criteria demonstrated lower specificity (range: 26.6 percent to 69.0 percent). The YIOS compared to the other four criteria demonstrated lower sensitivity for correctly identifying total SBI (76.0 percent), but similar specificity (81.9 percent) and NPV values (96.0 percent).[21]

The sensitivities and NPVs of Boston,[22] Rochester,[23-27] and Philadelphia criteria[9,11,12,22,25] in identifying bacteremia overlapped and ranged from 75.0 percent to 100.0 percent and 97.1 percent to 100.0 percent, respectively. The corresponding specificity for bacteremia was more variable across these criteria, ranging from 19.1 percent to 51.1 percent for Philadelphia, 26.3 percent to 64.9 percent for Rochester criteria, and 63.3 percent for Boston criteria. The probability of being free of bacteremia among test-negative infants (i.e., NPV) for the Philadelphia, Boston, and Rochester criteria was 97.0 percent or greater.

The Philadelphia protocol demonstrated high sensitivity and NPV (100.0 percent) but lower specificity (24.2 percent[9] to 50.7 percent[22]) in correctly identifying meningitis.

Several studies reported diagnostic accuracy data which combined various clinical (e.g., clinical/good/toxic/ill appearance, impression of sepsis, age, rectal temperature, unremarkable medical history) and laboratory criteria (e.g., serum and urine WBC, ABC, ESR, CRP, urine dipstick result) with sensitivity values ranging from 68.3 percent[28] to 99.1 percent.[29] The combination of clinical appearance (e.g., well, ill, good) and laboratory values (WBC, ESR, UA: Leukocyte esterase [LE]/nitrite) tended to demonstrate a higher sensitivity for identifying infants with total SBI compared to criteria that combined infant age (< 13 days), rectal temperature (> 39.6°C) and laboratory values WBC, LE/nitrites) or the combination of infant sex and laboratory values (WBC, CRP). The combination of clinical appearance and laboratory values (WBC: 5,000-15,000/mm3, ESR < 30 mm/h, normal UA: LE/nitrites) had the highest overall accuracy in correctly classifying infants with and without SBI (sensitivity 99.1 percent, specificity 59.3 percent, and NPV 99.4 percent).[29] The NPVs for the criteria that combined clinical and laboratory features ranged from 90.0 percent28 to 99.4 percent.[29,30]

The criteria that combined clinical impression of sepsis/toxic appearance with one or more laboratory features (WBC, ABC, ESR, and/or CRP)[31-33] ruled out the presence of sepsis/meningitis or bacteremia with greater sensitivity (i.e., 100.0 percent) but lower specificity (17.0 percent to 75.0 percent) compared to the criteria that combined ill appearance and WBC ≥ 15,000/mm^3 (sensitivity: 28.5 percent to 75.0 percent; specificity: 50.0 percent to 95.8 percent).[5,34]

The sensitivity values were greater for identifying bacteremia (84.0 percent to 100.0 percent)[5,31-33] than total SBI (68.3 percent to 99.1 percent).[28,29]

Table A. Commonly used combined clinical and laboratory criteria				
	Boston Criteria	**Milwaukee Criteria**	**Philadelphia Protocol**	**Rochester Criteria**
Age range	28-89 d	28-56 d	29-60 d	≤60 d
Temperature	≥ 38.0°C	≥ 38.0°C	≥ 38.2°C	≥ 38.0°C
History*	No immunizations within last 48 hours No antimicrobial within 48 hours Not dehydrated	Not defined	Not defined	Term infant No perinatal antibiotics No underlying disease Not hospitalized longer than the mother
Physical examination*	Well appearing no sign of focal infection (middle ear, soft tissue, bone/joint)	Well appearing (normal breathing, alert, active, normal muscle tone) Not dehydrated No sign of focal infection (middle ear, soft tissue, bone/joint)	Well appearing Unremarkable examination	Well appearing no sign of focal infection (middle ear, soft tissue, bone/joint)
Laboratory parameters*	CSF < 10 /mm^3 WBC < 20,000/mm^3 UA < 10 WBC/hpf Chest radiograph: no infiltrate (if obtained)	CSF < 10/mm^3 WBC < 15,000/ mm^3 UA < 5-10 WBCs/hpf (no bacteria, negative LE/nitrite) Chest radiograph: no infiltrate (if obtained)	CSF < 8/mm^3 WBC < 15,000/mm^3 UA < 10 WBC/hpf Urine Gram stain negative CSF Gram stain negative Chest radiograph: no infiltrate Stool: no blood, few or no WBCs on smear (if indicated) Band-neutrophil ratio < 0.2	CSF: NA (no lumbar puncture is indicated) WBC > 5,000 and <15,000/mm3 ABC < 1,500 UA ≤ 10 WBC/hpf Stool: WBC ≤ 5 /hpf smear (if indicated)
Management strategy for low risk	Home/outpatient Empiric antibiotics Followup required	Reliable caretaker followup required IM ceftriaxone 50 mg/kg followed by re-evaluation within 24 hours	Home/outpatient No antibiotics Followup required	Home/outpatient No antibiotics Followup required
Management strategy for high risk	Hospitalize Empiric antibiotics	Not defined	Hospitalize Empiric antibiotics	Hospitalize Empiric antibiotics

*The evaluation algorithms rate patients as normal/low risk versus high/not low risk for serious bacterial infection based on information in each of these domains. The example values in the table represent low risk.

ABC = absolute band count; C = Celsius; CSF = cerebrospinal fluid; D = day(s); hpf = high power field; UA = urinalysis; WBC = white blood cells

Clinical criteria. The identified studies reported data on diagnostic accuracy for different clinical criteria used for predicting risk of SBI. These criteria were the following: temperature ≥ 40°C,[30,35,36] ill appearance (i.e., presence of at least tachypnea, dyspnea, tachycardia, bradycardia, lethargy, decrease in activity/appetite),[30,37,38] age (different categories),[30] not ill appearance, gender (male vs. female),[30] clinical impression of sepsis (based on physical examination, complete history, laboratory results),[32-34,39,40] and no history of recent immunization.[41] We found no evidence reporting on other possibly relevant factors such as the clinical history of the mother.

The criteria based on clinical history (i.e., no history of recent immunization or rapid influenza test-negative result) demonstrated higher sensitivity (range: 94.0 percent to 95.4 percent) but lower specificity (11.3 percent to 33.2 percent)[41,42] compared with criteria based on age (≤ 30 days; sensitivity: 35.0 percent, specificity: 76.4 percent),[30] gender (sensitivity: 74.0 percent, specificity: 42.9 percent),30 and the degree of fever (≥ 39.5°C; range of sensitivity: 7.3 percent to 26.1 percent, range of specificity: 90.5 percent to 99.0 percent)[30,35,36] The only exception for the criteria based on clinical history was not previously healthy which demonstrated lower sensitivity (21.7 percent) and higher specificity (88.5 percent).[30]

The criteria based on clinical appearance for identifying bacteremia tended to yield higher sensitivity (range: 80.0 percent to 100.0 percent) and lower specificity (40.0 percent to 80.0 percent)[32-34,39,40] than criteria based on the degree of fever > 40°C (range of sensitivity: 5.1 percent to 12.5 percent, range of specificity: 96.1 percent to 98.3 percent).[35,36]

Laboratory criteria. The reviewed studies reported data on diagnostic accuracy for different laboratory measures by using various thresholds of the following tests: UA (microscopy, dipstick), WBC, ESR, ABC, absolute neutrophil count (ANC), and PCT. Across and within studies, the sensitivity for identifying total SBI tended to decrease (16.0 percent to 100.0 percent) and the corresponding specificity increase (31.0 percent to 95.2 percent) with higher thresholds of WBC (≥ 8,000/mm3 to ≥ 20,000/mm).[43-46] Similar pattern of trade off between sensitivity and specificity was observed for ANC thresholds (>4,650/µL to >12,500/µL),[45] and ABC thresholds (> 250/mm3 to > 3,000/mm3).[44]

The overall accuracy of ANC (AUC: 78.0 percent)[43,47] and ABC (AUC: 81.0 percent)44 was greater than that for WBC (AUC range: 59.0 percent to 69.0 percent).[43,44,47] The use of CRP demonstrated higher overall accuracy (AUC: 74.0 percent to 84.0 percent) than WBC (AUC range: 68.0 percent to 70.0 percent), ANC (AUC: 71.1 percent), or PCT (AUC: 77.0 percent) in correctly identifying infants with and without SBI.[30,46,48]

The sensitivity of UA (LE, nitrite or both) was 71.0 percent in one study.[49] In another study,[30] UA had a sensitivity of 43.5 percent, specificity of 82.8 percent, and NPF of 98.4 percent. The sensitivity of UA (dipstick; the presence of LE or nitrite, or both) for identifying infants with UTI across the studies[13,49-52] ranged from 81.0 percent[49] to 85.0 percent.[13] The corresponding specificity for UA ranged from 92.0 percent[52] to 100.0 percent.[13] The microscopy of spun urine (WBC ≥ 5/hpf) yielded lower sensitivity of 59.0 percent,[53] 65.0 percent,[13] and 40.0 percent.[54] The corresponding specificities for these three studies were 85.0 percent,[54] and 94.0 percent.[13,53]

KQ1B. How do these findings vary by age within the age range 0–3 months?

Comparison of the diagnostic test characteristics across age groups (neonates: age ≤ 28 days vs. older infants: age > 29 days) was possible for few selected criteria (Boston, Philadelphia, Rochester, combined laboratory and clinical) reported in 14 studies. We found no evidence relating to other possibly relevant factors such as the clinical history of the mother.

The Boston criteria[22,55] and Philadelphia protoco[l9,11,12,22] demonstrated higher sensitivity, lower specificity, smaller PPV, and similar NPV when applied to older infants (age > 28 days)[9,12,55] compared to neonates (age: 0–28 days)[11,22] for total SBI or bacteremia. In contrast, the application of Rochester criteria[10,24,56,57] was more accurate (higher sensitivity, specificity, and PPV) in neonates[24,57] than in older infants[10,56] for total SBI or bacteremia. The false positive rate for SBI (i.e., percentage of infants with SBI classified as low risk) tended to be higher for neonates (1.0 percent to 6.25 percent)[11,22,24,57] versus older infants (0 percent to 5.4 percent).[9,10,12,23,25,26,55,56,58-60]

In one study,[28] the sensitivity of the combined clinical and laboratory criteria (well appearance without focal infection, WBC: 5,000–15,000/mm^3, ABC ≤ 1,500/mm^3, enhanced UA, cerebrospinal fluid WBC < 5/mm^3 and negative gram stain) was 100.0 percent and did not change across the age groups (0–14, 15–28, 29–45, and 46–59 days of age). In contrast, these criteria demonstrated greater specificity in infants 29 days of age or older (36.0 percent to 39.0 percent) than in neonates 28 days or younger (26.3 percent to 28.0 percent).[28]

The overall diagnostic accuracy of PCT for predicting SBI was better for older infants (AUC: 85.0 percent; age > 28 days) compared with neonates (AUC: 73.0 percent; age ≤ 28 days).[61]

KQ1C. In infants < 3 months old who present with a fever, what are the sensitivity, specificity, and predictive values of individual or combinations of clinical features (history including information on the mother's history and previous testing, risk factors, findings on clinical exam, laboratory tests, and formal scoring instruments based on clinical features) for identifying those with invasive herpes simplex virus infection (HSV)? How do these findings vary by age within the age range 0 to 3 months?

The reported data on the presence of HSV in febrile infants 3 months or younger was scarce. Only four studies reported the prevalence of HSV (total of seven cases). We found no evidence relating to other possibly relevant factors such as the clinical history of the mother. None of these infants had a concurrent bacterial infection. The prevalence of HSV amongst the febrile infants admitted across these studies (admission period range: 2–6 years) were 2.0 percent,[60] 1.7 percent,[62] and 0.3 percent.[39,63] The diagnostic accuracy of any given criteria in predicting the risk of HSV could be calculated only for one study.[63] In this study, CSF pleocytosis (≥ 20 WBCs/mm3 and > 1 WBC per 500 red blood cells s/mm^3) predicted the risk of HSV in neonates with sensitivity of 66.6 percent (95 percent CI: 12.5, 98.2) and specificity of 74.6 percent (95 percent CI: 71.4, 77.6). The positive and negative predictive values in this study were 1.0 percent (95 percent CI: 0.2, 3.9) and 99.8 percent (95 percent CI: 98.9, 99.9), respectively. There were insufficient data to compare the findings in neonates and infants in older age groups.

KQ 2A. What is the evidence that clinical features alone, basic laboratory tests alone, or the combination are sufficient to identify febrile infants < 3 months who are at low risk of having a serious bacterial illness (i.e., have a high negative predictive value)?

The evidence indicated that the reviewed criteria were able to correctly classify most or all of the infants truly without SBI into low-risk groups. The probability of a low-risk infant (< 3 months old) for being free of total SBI (i.e., NPV) for the majority of the criteria ranged from 90.0 percent to 100.0 percent.

Generally, combined clinical and laboratory criteria (Boston,[22,55] Rochester,[10,23-26,57,60] Milwaukee,[10] Philadelphia,[9,11,12,22,25,58,59] YIOS,[21] but not Yale,[64,65] and other combined criteria[28-30,37,49,66-68]) as well as clinical criteria alone (not well appearing infants, age < 1 month, gender, fever > 40°C)[30] demonstrated high NPVs (> 90.0 percent) in correctly identifying infants without SBI. In other words, the percent of missed SBI cases in these studies was 10.0 percent or less. The evidence regarding NPV for identifying infants without SBI using laboratory criteria alone was available for eight studies.[30,43,44,47,48,61,63,69] Of these, several criteria (WBC < 5000–> 15,000/mm^3 [47], PCT ≥ 0.5 ng/mL,[48] CRP ≥ 30 mg/L,[48] and presence of CSF-pleocytosis,[63,69]) showed relatively lower NPVs (78.1 percent to 91.0 percent).

KQ 2B. What is the evidence for the potential risks resulting from a delay in the diagnosis and treatment of patients who appear low risk but have a serious bacterial illness?

Overall, outcomes related to recovery, harms, and complication associated with delayed diagnosis/management of febrile infants 0–3 months of age was poorly reported. There were nine studies that reported the management (e.g., antibiotics, inpatient/outpatient observation) of febrile infants 0–3 months of age who had been classified as being at low risk for SBI.[5,10,23,47,55,57,58,67,70] In these studies 32 out of 4,497 infants who were classified as low risk, had SBI (0.7 percent). Three studies (both including neonates) did not provide any information on outcomes related to recovery or complications for seven neonates with SBI.[47,57,70] The remaining six studies indicated no complications and uneventful recovery of the 25 low-risk infants (0–3 months) with SBI who had delayed diagnosis and/or treatment.

KQ3A. What is the evidence that clinical features alone, basic laboratory tests alone, or the combination are sufficient to identify febrile infants < 3 months who are at high risk of having a serious bacterial illness (i.e., have a high positive predictive value)?

For the majority of the criteria (combined clinical and laboratory, clinical only, and laboratory only), the probability for a "high risk" infant (< 3 months old) of having total SBI (i.e., PPV) was low. The low PPVs are indicative of high false-positive rates or low specificity for SBI (i.e., high percentage of febrile infants without SBI classified as high risk).

Only the minority of the criteria demonstrated PPVs greater than 50.0 percent for SBI.[47,48,68,71] These criteria were combined, 68 clinical alone (ill appearance),[71] and selected laboratory alone criteria (ANC, CRP, PCT-Q).[47,48]

The remaining combined clinical and laboratory criteria such as Boston, Milwaukee, Philadelphia, Rochester, YIOS, Yale observational scale, and other combined criteria showed PPVs below 50.0 percent (range 3.3 percent[10] to 48.6 percent[29]). The PPVs for laboratory criteria alone were similar to those of the combined criteria, ranging from 6.3 percent (CRP at 20 g/L)30 to 43.8 percent (WBC 5,000–15,000/mm^3 [47]).The corresponding PPVs for clinical alone

criteria were lower than those for combined or laboratory only criteria, ranging from 3.3 percent (age ≤ 30 days versus > 30 days)[30] to 17.5 percent (rapid influenza test results).[30]

In general, the PPVs for predicting bacteremia were low, ranging from 0.5 percent (Rochester Criteria in age range 29-60)[10] to 40.0 percent (ESR ≥ 30 mm/h).[33]

The PPV for predicting meningitis across the combined clinical and laboratory criteria ranged from 0.5 percent[10] to 5.4 percent.[63]

KQ 3B. What are the benefits and harms of immediate antibacterial, antiviral therapy, and/or hospitalization (vs. delaying until diagnostic workup is complete) in patients at high risk of serious bacterial illness?

We identified 10 studies reporting on immediate antibiotic (or antiviral) therapy administered to infants at high risk of SBI (or HSV). There was no evidence directly comparing outcomes in the immediate versus delayed treatment groups. No treatment outcomes were reported for three studies.[10,47,56] Overall, the benefits and harms of immediate antibiotic/antiviral therapy (vs. delaying until diagnostic workup is complete) in patients at high risk of SBI (or HSV) were poorly reported.

Febrile infants classified as being at high risk for SBI were administered immediate antibiotic therapy (vs. delaying until diagnostic workup is complete). In one study, 0.4 percent of the included infants developed drug-related rash and 18.9 percent had infiltration of an intravenous line.[12] In another study,[32] immediate intravenous antibiotic therapy administered to 13 toxic appearing infants 2 months or younger was reported to be without any complications. Another study reported minor intravenous access problems that had occurred in 15.6 percent of the 51 high-risk infants (most of them diagnosed with UTI) treated with intravenous antibiotics for 4 days. About 67.0 percent of these infants were transferred to an outpatient day treatment center to complete their antibiotic treatment course.[72]

KQ 4. What is the evidence that the presence of an identified viral infection predicts against a serious bacterial infection?

This section included 11 studies in which the association between the status of viral infection and the risk of SBI in febrile infants was explored. There was no evidence to assess the probability of having SBI with respect to the presence of HSV infection in febrile infants. The most frequent types of SBI in these studies were UTI (range: 5.6 percent to 11.3 percent)[41,73] and bacteremia (range: 1.4 percent to 3.8 percent).[27,73] The types of virus reported in most of these studies were influenza A/B and respiratory syncytial virus (RSV). Four studies reported data on enterovirus.[27,60,73,74]

Overall, the study results indicated significantly higher prevalence (or risk) of SBI in infants without viral infection or clinically diagnosed bronchiolitis (prevalence range: 10.0 percent[75] to 20.0 percent[27]) compared to infants with viral infection or clinically diagnosed bronchiolitis (prevalence range: 0 percent[5,76] to 7.0 percent[65,73]). The estimate of odds ratio across the studies ranged from 0.08[77] to 0.58.[65]

Similarly, the reviewed evidence indicated significantly lower prevalence of UTI in infants with viral infection or bronchiolitis versus infants free of viral infection or bronchiolitis.[65,78-80] The evidence was insufficient or inconclusive (i.e., statistically nonsignificant due to imprecision of the estimates) regarding the prevalence of bacteremia (range: 0 percent to 2.3 percent) and meningitis (range: 0 percent to 0.9 percent) due to small counts.[78-80]

The data on comparison of the prevalence of SBI between virus-positive and virus–negative neonates (age: 0–28 days) was scarce. In one study,[65] the prevalence of SBI did not significantly differ between RSV positive and negative groups of neonates (10.1 percent vs. 14.2 percent; RR: 0.71; 95 percent CI: 0.35, 1.5).[65]

KQ 5. What is the evidence that the prevalence of serious bacterial illness varies among febrile infants presenting to primary care and emergency practice? What is the evidence that prevalence affects the predictive value of clinical and laboratory findings?

This section included 70 studies reporting the prevalence of SBI (and/or HSV). In order to compare the prevalence of SBI, the studies were divided by the setting (i.e., emergency department vs. primary care) and place of conduct (North America, Taiwan, Spain, Israel, and Italy).

For studies conducted in North America in the emergency departments (n = 40), the prevalence of total SBI ranged from 4.1 percent[10] to 25.1 percent.[25] For more than half of the studies, the prevalence of total SBI in emergency departments was 10.0 percent or greater. One study[81] reported increased prevalence of SBI for the period of 2002–2006 compared to 1997–2001 (14.4 percent vs. 6.5 percent, p = 0.001). Of the three primary care setting study reports,[5,27,34] two reported the prevalence of total SBI of 9.9 percent[27] and 10.3 percent.[5]

For Taiwanese studies (n = 3),[57,66,82] the prevalence of total SBI was numerically similar in emergency departments versus primary care setting (17.7 percent to 25.2 percent vs. 16.4 percent).

All three Spanish studies[41,83,84] reported prevalence of SBI in the emergency departments. In two of these studies, the prevalence of SBI were 13.1 percent[41] and 18.9 percent.[83] The third study[84] reported that the prevalence of SBI was significantly greater in infants younger than 29 days than in those older than 29 days (20.1 percent vs. 12.6 percent, p = 0.04). This study did not report the crude prevalence of SBI based on the total sample.

Three studies conducted in Israel, in the emergency departments, reported prevalence of total SBI ranging from 10.8 percent[45] to 19.4 percent.[37] One of these studies[37] reported an estimate of the prevalence of SBI of 19.4 percent in neonates (0–28 days). In this study, the prevalence of SBI did not differ for infants aged 3–7 days (21.6 percent), 8–18 days (26.1 percent), 15–21 days (17.9 percent), and 22–28 days (12.1 percent).[37]

In one Italian study,[47] the prevalence of SBI amongst neonates (0–28 days of age) was 25.3 percent.

The effect of prevalence of total SBI on the PPVs was possible to be examined only for the Philadelphia protocol[9,11,12,22,25] and the Rochester criteria[23,24,27,56,57,60] regardless of the setting. For the Philadelphia protocol, the prevalence of total SBI did not appear to contribute to the difference observed in the PPVs. For the Rochester criteria, higher prevalence of total SBI corresponded to higher PPVs.

KQ6. Clinicians base decisions about initial diagnostic workup and treatment of febrile infants not solely on the infants' medical status but also on their assessments of non-clinical factors (e.g., parental understanding, parents' ability to monitor the patient, access to care). A strategy of initial observation without extensive diagnostic tests or hospitalization depends on confidence that parents will reliably bring the baby back for a timely followup appointment if conditions warrant. How likely are parents whose infants are less than 6 months of age and have fever or other potentially serious medical condition to comply with a provider's recommendation that the parent bring the infant back (to that provider or another) for a return appointment to reassess the condition(s) of concern?

KQ6A. What is the evidence that identifiable parental factors (e.g., education, insurance status, living situation, history of previous visits with the provider, time/distance required to travel to an appointment, etc.) allow a provider to judge the likelihood that a parent will adhere to treatment recommendations such as returning for followup if circumstances warrant?

KQ6B. What is the evidence that the clinical setting (community practice vs. emergency department and/or hospital outpatient clinic) in which care is sought independently influences the likelihood of compliance with a return appointment?

This section included four studies conducted in North America. These studies included children with age range of 0–3 months. All studies reported at least some information on the degree of parental compliance to followup (range: 12 hours to 14 days after initial examination or discharge) with telephone or return visits to reassess the condition. The proportion of successful followup across these studies ranged from 77.4 percent[59] to 99.8 percent.[56] For example, one study[80] reported that telephone followups were completed for 78.0 percent of the 132 infants 4–7 days after they were discharged. In another study,[72] the parental compliance for the day treatment center followups was 98.3 percent. The parental compliance for the day treatment center followups did not differ between the two groups of younger (age $\leq$ 2 months) and older infants (ages 2–3 months).[72] In the same study, the parental compliance to the day treatment center followups was greater than that to antibiotic treatment (98.3 percent vs. 80.4 percent). In one study,[59] the reported success rates for followup calls 2, 7, and 14 days after discharge were 77.4 percent, 85.4 percent, and 83.9 percent, respectively. In this study, most parents preferred discharge rather than hospitalization.[59]

None of the studies reported any evidence regarding the influence of parental factors (e.g., age, education, distance/time to travel to an appointment, living situation) or clinical settings (emergency department vs. primary care office) on parental compliance to telephone or return visit followups. The full report reviews the results of nine studies that were excluded from KQ6B, some of which potentially have data that could be extrapolated to the relevant patient population.

Discussion and Future Research

The clinical dilemma is how to balance the risk of missing an SBI (with potentially a devastating outcome) with the risks and costs associated with diagnostic and management strategies for febrile infants 3 months or younger. To date, a tremendous amount of resources and effort has been focused on the development of tests, protocols, and criteria to attempt to minimize the risk of missing an SBI. However, there has been less research exploring risks associated with diagnosis and treatment of febrile infants.

The evidence synthesis for the diagnosis of SBI and invasive HSV infection in infants less than 3 months of life has been challenging. In general, there was a lack of standard definitions across the reviewed evidence. For

example, the definitions for fever and SBI across studies varied. There was very little evidence on HSV in febrile infants aged 3 months or younger to allow any definitive conclusions. This review sought to summarize evidence on harms in the evaluation and management of febrile infants 0–3 months of age, to evaluate the role of viral infections or clinical bronchiolitis in the risk of SBI, and to identify the factors that influence parental compliance to followup visits. Moreover, we attempted to calculate the test accuracy characteristics from raw data for the different types of SBI (UTI, bacteremia, meningitis) and for the neonatal period, when possible.

The risks for the specific types of SBI (e.g., UTI, bacteremia, and meningitis) were not uniform either. There was insufficient data to definitively determine the accuracy of detecting the rarer and more devastating bacterial meningitis. The majority of SBI were due to UTIs (> 70.0 percent).

In general, the combined clinical and laboratory criteria/protocol (Rochester, Philadelphia, Milwaukee, Boston), and selected clinical criteria alone (not well appearing infants, age < 30 days, gender, fever > 40°C) reported better test accuracy performance (high sensitivity and negative predictive values) compared with selected laboratory criteria only (e.g., PCT ≥ 0.5 ng/mL, WBC < 5000 - > 15,000/mm^3, CRP ≥ 30 mg/L, and presence of CSF-pleocytosis). In other words, the proportion of missed SBI cases in these studies was 10.0 percent or less. The specificity of combined criteria was generally lower indicating high false-positive rates for SBI. Although many studies had high negative predictive values, these should be interpreted with caution as predictive values vary based on prevalence.

It was difficult to compare the test characteristics between detecting bacteremia and meningitis due to small counts and wide confidence intervals.

Due to the heterogeneity across studies, meta-analysis was possible to be performed only for the Rochester criteria and Philadelphia protocol. There was no clear difference in the study quality (QUADAS scores) between the studies reporting combined clinical and laboratory criteria such as Rochester, Boston, Philadelphia criteria/protocol and those reporting clinical or laboratory criteria alone.

There remains controversy about the need for lumbar puncture in infants with fever. In our review, six studies reported to have misclassified 8 (out of 42) cases of meningitis into low risk for SBI (total number of meningitis were reported only in five studies). Using the Rochester criteria (four missed cases), a data-derived model of combined clinical and laboratory (one missed case), clinical only (one missed case), and a laboratory test (two missed cases). None of these criteria included a lumbar puncture and CSF analysis. Our review does not answer the question of whether a lumbar puncture is required in all febrile infants or what parameter can predict for the need for a lumbar puncture.

Contrary to the approach of ruling out a SBI, studies attempting to rule in an infection have not been as successful (low positive predictive values, and low specificity rates). Lower PPVs for bacteremia and meningitis compared to PPVs for SBI are reflective of lower prevalence of the former among febrile infants 0–3 months of age. In the absence of better data on harms and the costs of diagnostics and therapeutics or improved positive predictive values, many clinicians will continue to opt to treat a large group of SBI negative patients. There is little reported evidence on what factors are associated with variations in practice patterns among different individual providers.

Neonates (0–28 days of life) have a higher prevalence of SBI compared with older children. When separately evaluated, neonates did not have the same test characteristics as the older children or whole group of less than 3 months of age. In only one study evaluating the Rochester criteria in neonates the testing in the neonatal age group showed better numerical accuracy than in the older age group. The rest of the combined, laboratory, or clinical criteria demonstrated lower sensitivity in the neonate as compared to older groups. Likewise, false-positive rate for SBI (i.e., proportion of infants with SBI classified as low risk) tended to be higher for neonates compared to older infants.

There is very little evidence on the risks of delayed diagnosis and management of low-risk infants who were later found to have SBI. Several studies reported that such infants were subsequently hospitalized and treated with antibiotics without adverse events. Although reassuring, the absence of adverse events in these studies may be partially explained by underreporting and/or lack of followup data.

The harms and costs of immediate therapy or management in high-risk patients have been poorly reported. Burdens on families and possible lasting psychological harms of testing have not been explicitly considered in the studies.

Unnecessary testing may have had the unexpected consequence of the parents viewing the infant as more fragile or have more anxiety around the chance of a serious bacterial infection, although the literature has not well delineated the presence or absence of such factors. Byington and Paxton reported on a survey of parents of infants undergoing a “rule-out sepsis” evaluation months

after admission. The majority of the 60 parents who interviewed reported finding the evaluation very stressful, and some reported breastfeeding, financial stress, and iatrogenic problems.

With the advent of rapid testing for viral pathogens, many clinicians now have the ability to quickly diagnose viral infections in children less than 3 months of age. This review has shown a significantly reduced risk of SBI amongst infants who tested positive for the presence of viral infection or clinical bronchiolitis compared to infants who tested negative for the presence of viral infection or bronchiolitis. Note that this finding may not be applicable to neonates.

The majority of studies were conducted in North American emergency department settings.

There appears to be a somewhat higher prevalence of SBI in the emergency department vs. primary care setting. The difference in prevalence may reflect a difference in the patient population that seeks care in the emergency department. The patients seen in the emergency department may be a sicker group than those who those who see their primary care provider. Alternatively, these patients may have been referred from their office-based primary care providers or sent for further testing that is not readily available in the office setting.

Followup and reassessment of the febrile infant is an important component of their care. A clinician's decisionmaking can be highly influenced by his/her assessment that the patient's caregivers are likely to comply with followup or further testing. Very little is known about the factors that affect compliance for followup in this area. Although the followup was reported in four studies, it was not the primary focus. The high rate of followup for therapy and telephone followup in these studies could in part be explained by the increased motivation of patients that are enrolled in a study. Although there were no included studies in this review on parental factors or clinical setting influencing followup, a review of the broader literature reveals some potential factors that need to be further studied in the 0–3 month febrile infant population. In some studies Hispanic patients were less likely to comply with followup. The other identified parental factors such as lack of parental ability to speak English, having to make their own appointment, self-pay, lack of a primary care provider, and followup greater than 24 hours seem self-evident but require further study.

To move the field further, there is a need to further delineate the risks associated with the alternative approaches to testing and treatment of this group. Well conducted studies reporting age-stratified (e.g., 0–28, 29–60, 61–90 days) outcomes are needed. Consideration should be given to exclude from such studies infants 0–6 days of age, as they are likely to represent another clinical syndrome of early onset sepsis related to perinatal factors. The focus should be on the clinical conundrum of febrile infants with no apparent source of infection.

The group of low-risk patients needs to be defined by incorporating risks associated with age group and viral or clinical syndrome status. Detailed reporting of the harms associated with the patient diagnosis and followup observations (in or outpatient) of the low-risk group would be crucial.

Besides documenting numbers of infants with SBI, followup should be done to determine the long-term consequences of "missed" or "delayed" diagnosis of SBI such as decreased renal function with UTI, progression from UTI to bacteremia, and complications of meningitis. Integrated into these studies should be evaluations of the factors or interventions that increase parental compliance with return assessments in febrile infants. Optimally, these studies should be multi-centered and they should evaluate both outpatient and emergency department settings. Better data on harms of diagnostic and observation protocols would be helpful to determine the risk-benefit balance.

Conclusion

Overall, the focus of the literature has been on ruling out SBI. Harms associated with testing or management strategies have been poorly reported. Attempts to identify high-risk groups, as described in the minority of reports, were not accurate. The Boston, Philadelphia, Rochester, and Milwaukee were fairly accurate in identifying a low-risk group for SBI in infants younger than 3 months of age. The diagnosis of a viral infection or clinical bronchiolitis significantly decreased the chances of a serious bacterial illness. Invasive herpes simplex virus infection is a significant differential diagnosis in the febrile infant, yet the relevant literature is presented from the diagnosis rather than from the syndrome point of view, making it difficult to draw conclusions of test accuracy or management efficacy in an undifferentiated febrile infant. Although crucial to the management strategies in the low-risk group, there is very little literature on factors associated with compliance in this population. Future studies should focus on identifying the risks associated with testing and management strategies and on factors that influence compliance to followup care.

Table B. Summary table for executive summary	
Key Question (KQ) N of studies	**Resluts/Conclusions**
KQ1A 54 studies	Combined clinical/laboratory criteria Rochester criteria for SBI (pooled sensitivity: 94%; specificity range: 36%-69%)[23-27,57,60] Philadelphia protocol for SBI (pooled sensitivity: 93%; specificity range: 27%-67%)[9,11,12,22,25,58] Boston for SBI (sensitivity: 88.5%, specificity: 56.2%)[22,55] Milwaukee for SBI (sensitivity: 96.0%, specificity: 28.0%)[10] Rochester and Philadelphia for meningitis (sensitivity range: 50.0%-100.0%)[10,11,22] Rochester and Philadelphia for bacteremia (sensitivity range: 33.3%, 83.3%)[10,11,22] Other combined clinical (e.g., clinical/good/toxic/ill appearance, impression of sepsis, age, rectal temperature) and laboratory (e.g., serum and urine WBC, ABC, ESR, CRP, urine dipstick) criteria for SBI (sensitivity range: 68.3%[28]-99.1%,[29], specificity range: 37.6%[28]-77.8%[82]) [5,28-34,37,49,66-68,70,82,85] Other combined clinical and laboratory criteria for bacteremia (sensitivity range: 84.0%-100.0%, specificity range: 17.0%-54.0%).[5,31-33] Clinical criteria The criteria of temperature ≥ 40°C or > 39.5°C for SBI (sensitivity range: 7.3%-26.1%, specificity range: 90.5%-98.8%)[30,35,36] Clinical impression of sepsis for bacteremia (sensitivity range: 80.0%[40]-100.0%[33,39]) Laboratory criteria UA (dipstick; the presence of LE or nitrite, or both) for UTI (sensitivity range: 40.0%[54]- 85.0%,[13] specificity range: 63.6%[50]–94.0%[52]) UA of urine collected by catheterization (AUC: 86.0%, sensitivity: 86.0% or 43.0%, and specificity: 94.0% or 99.0%)[5,51] UA of urine collected by bag (AUC: 71.0%, sensitivity: 76.0% or 25.0%, and specificity: 84.0% or 99.0%)[5,51] AUC-WBC for UTI (61.0%, 69.0%)[44,45] AUC-ANC for UTI (77.0%)[44,45] AUC-ABC for UTI (81.0%)[44,45] AUC-CRP for SBI (range: 74.0%-84.0%)[30,46,48] AUC-WBC for SBI (range: 68.0%-70.0%)[30,46] AUC-ANC for SBI (71.1%)[30] AUC-PCT for SBI (77.0%)[48] CRP for bacteremia (AUC-CRP: 68.0%, sensitivity: 69.9%, specificity: 93.8%)[46] Urine dipstick for bacteremia (sensitivity: 43.5%, specificity: 82.8%)[30] PCT for bacteremia (AUC-PCT: 84.0%)[48]

Table B. Summary table for executive summary (continued)	
Key Question (KQ) N of studies	**Results/Conclusions**
KQ1B 14 studies	The Boston criteria for SBI Age > 28 days: sensitivity (88.5%), specificity (56.2%), PPV (16.2%), NPV (98.1%)[55] Age 0–28 days: sensitivity (82.0%), specificity (68.0%), PPV (26.0%), NPV (97.0%)[22] The Philadelphia protocol for SBI Age > 28 days: sensitivity (98.0%, 100.0%), specificity (26.6%, 42.0%)[9,12] Age 0 – 28 days: sensitivity (84.4%, 87.9%), specificity (46.8%, 55.0%)[11,22] The Philadelphia protocol for bacteremia Age > 28 days: sensitivity (100.0%)[9,12] Age 0–28 days: sensitivity (75.0%, 83.3%)[11,22] The Rochester criteria for SBI Age > 28 days: sensitivity (52.0%, 59.0%), specificity (26.3%)[10,56] Age 0–28 days: sensitivity (97.6%, 86.4%), specificity (62.2%, 46.4%), PPV (33.6%, 26.8%), and NPV (99.2%, 93.8%)[24,57] The Rochester criteria for bacteremia Age > 28 days: sensitivity (55.0%)[56] Age 0–28 days: sensitivity (86.4%)[24] PCT for SBI Age > 28 days: sensitivity (AUC: 85.0%)[61] Age: 0–28 days (AUC: 73.0%)[61]
KQ1C 4 studies	The data on HSV was scarce[39,60,62,63] CSF pleocytosis (≥ 20 WBCs/mm^3 and > 1 WBC per 500 red blood cells s/mm^3) for HSV: sensitivity of 66.6% (95% CI: 12.5, 98.2) and specificity of 74.6% (95% CI: 71.4, 77.6)[63] Insufficient data to compare the findings across age groups
KQ2A 23 studies	Several low-risk criteria/protocols (e.g., Boston, Philadelphia, Rochester, Milwaukee, good appearance, WBC: 5,000-15,000/mm3, ESR < 30 mm/h, normal urinalysis)[5,9-12,22-30,37,55,57-60,66,67,70] NPV for SBI (range: 90.0%[28]-100.0%[9]) Sensitivity for SBI (range: 82.0%[22,66]-100.0%[9,26]) Specificity for SBI (range: 27.0%[9]-69.0%[26])
KQ3A 10 studies	Several high-risk criteria (e.g., ill appearance, WBC < 5,000/mm^3 or WBC > 15,000/mm^3 and WBC ≥ 5/high powered field) for SBI[30-34,49,54,68,71,85] Sensitivity: 61.0%[68] and 82.0%[49] Specificity: 90.0%[68] and 76.0%[49] PPV: 21.0%[49] and 60.0%[68]

Table B. Summary table for executive summary (continued)	
Key Question (KQ) N of studies	**Results/Conclusions**
KQ4 11 studies	Significantly higher risk of SBI in infants without viral infection compared to infants with viral infection[27,41,60,73-79,86] The ORs ranged from 0.08[77] to 0.58[65]
KQ5 70 studies	Prevalence of SBI (emergency vs. primary care) <u>North America</u> Prevalence of SBI in emergency for all infants (range): 4.1%[10]-25.1%[25] Prevalence of SBI in emergency for neonates 0-28 days (range): 11.5%[87]–23.8[62] Prevalence of SBI in emergency for infants > 28 days (range): 4.1%[10]–11.2%[88] Prevalence of SBI in primary care for all infants: 9.9%[27] and 10.3%[5] <u>Taiwan</u> Prevalence of SBI in emergency for all infants: 17.7%[66] and 25.2%[82] Prevalence of SBI in emergency for all infants: 16.4%[57]
KQ6A 4 studies	4 studies reported at least some information on the degree of parental compliance to followup with telephone or return visits to reassess the condition[56,59,72,80] The range of followup (12 hours to14 days after initial examination or discharge): 77.4%[59]-99.8%[56]
KQ6B 0 studies	No evidence was identified

Table C. Abbreviations used in this section			
Definition	**Abbreviation**	**Definition**	**Abbreviation**
Absolute band counts	ABC	Negative predictive values	NPV
Absolute neutrophil count	ANC	Positive predictive values	PPV
Area under the curve	AUC	Procalcitonin	PCT
Cerebrospinal fluid	CSF	Quality assessment of studies of diagnostic accuracy included in systematic reviews	QUADAS
Confidence interval	CI	Respiratory syncytial virus	RSV
C-reactive protein	CRP	Serious bacterial illness	SBI
Erythrocyte sedimentation rate	ESR	Urinalysis	UA
Invasive herpes simplex virus	HSV	Urinary tract infection	UTI
Key Question	KQ	White blood cell count	WBC
Leukocyte esterase	LE	Young Infant Observation Scale	YIOS

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