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

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Preface

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 and strategies.

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. To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review and public comment prior to their release as a final report.

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.

We welcome comments on this evidence report. Comments may be sent by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Structured Abstract

Objectives. To review the evidence for diagnostic accuracy of screening for serious bacterial illness (SBI) and invasive herpes simplex virus (HSV) infection in febrile infants 3 months or younger; ascertain harms and benefits of various management strategies; compare prevalence of SBI and HSV between different clinical settings; determine how well the presence of viral infection predicts against SBI; and review evidence on parental compliance to return for followup assessments (infants less than 6 months).

Data Sources. MEDLINE, CINAHL, Embase, Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, abstracts, and unpublished materials.

Review Methods. Two independent reviewers screened the literature and extracted data on population characteristics, index/diagnostic test characteristics. Diagnostic test accuracy studies were assessed using Quality Assessment of Diagnostic Accuracy Studies.

Results. Eighty-four original studies were included. The combined clinical and laboratory criteria (Rochester, Philadelphia, Boston, and Milwaukee) demonstrated similar overall accuracy (sensitivity: 84.4 percent to 100.0 percent; specificity: 26.6 percent to 69.0 percent; negative predictive value: 93.7 percent to 100.0 percent; and positive predictive value: 3.3 percent to 48.6 percent) for identifying infants with SBI. The criteria based on history of recent immunization or rapid influenza test demonstrated higher sensitivity but lower specificity compared with criteria based on age, gender, and the degree of fever. The overall accuracy of C-reactive protein was greater than that for absolute neutrophil count and absolute band counts , white blood cell, and procalcitonin.

For correctly identifying infants with and without SBI (or bacteremia), the Boston, Philadelphia, and Milwaukee criteria/protocol showed better overall accuracy when applied to older infants versus neonates. The Rochester criteria were more accurate in neonates than in older infants.

Evidence on HSV was scarce.

Most of the criteria/protocols demonstrated high negative predictive values and low positive predictive values for correctly predicting the absence or presence of SBI.

In studies reporting outcomes of delayed treatment for infants with SBI initially classified as low risk, all infants recovered uneventfully. The reported adverse events following immediate antibiotic therapy were limited to drug related rash and infiltration of intravenous line.

There was a higher prevalence of SBI in infants without viral infection or clinical bronchiolitis compared to infants with viral infection or bronchiolitis.

The prevalence of SBI tended to be higher in the emergency departments versus primary care setting offices.

The parental compliance to followup for return visits/reassessment of infants after initial examination across four studies ranged from 77.4 percent to 99.8 percent. There was no evidence

to determine the influence of parental factors and clinical settings on the degree of parental compliance.

Conclusions. Overall, the focus of the literature has been on ruling out SBI. Harms associated with testing or management strategies have been less well studied. Combined criteria showed fairly high sensitivity and (therefore) reliability in not missing possible cases of SBI. Attempts to identify high-risk groups specifically, described in a minority of reports, were not as successful. There is very little literature on factors associated with compliance to followup care, although that information could be crucial to improving management strategies in the low-risk group. Future studies should focus on identifying the risks associated with testing and management strategies and factors that predict compliance.

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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 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 percent[28] 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 $\geq$ 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/mm^3 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/mm^3 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/mm^3 to > 3,000/mm^3).[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 $\leq$ 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 protocol[9,11,12,22] 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 $\leq$ 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 $\leq$ 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 ($\geq$ 20 WBCs/mm^3 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	Results/Conclusions
KQ1A **54 studies**	<u>Combined clinical/laboratory criteria</u> 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] <u>Clinical criteria</u> 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]) <u>Laboratory criteria</u> 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/mm^3, 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]

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

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Introduction

The febrile infant is a common problem that accounts for a large number of ambulatory care visits. Young infants (0 to 3 months of age) often present with nonspecific symptoms, and it is difficult to distinguish between infants with a viral syndrome and those with bacterial diseases. In the majority of cases febrile illness in infancy is secondary to viral infections and is self-limited. Although serious bacterial illness (SBI) is relatively uncommon, if it is not promptly diagnosed and treated, serious consequences may result. The clinical dilemma that practitioners face is how to avoid missing a case of serious bacterial illness versus how to avoid the risks and harms of investigating, observing, and potentially treating a febrile infant with no SBI.

Definitions

Fever in an infant is usually defined as a rectal temperature >38 degrees Celsius.[89] For infants <3 months old, this value is approximately two standard deviations above the mean. The majority of studies that focus on the febrile infant have used this definition.

A young infant is an infant less than 3 months old. Neonates are infants from birth to 28 days of age.[90]

The definitions of SBI vary across published literature. The identification of SBI typically includes the diagnoses of meningitis, bacteremia, and urinary tract infection. 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.

Epidemiology

The prevalence of SBI in young infants with fever is about 8.0 percent overall and is higher in infants aged 0–28 days (9.0 percent–13.0 percent) than in infants aged 2- 3 months (7.1 percent)[11,12,22,23,27,49] The prevalence of SBI is highest in infants < 2 weeks old (25.0 percent). The most common SBI is urinary tract infection, which is found in 3.0–11.0 percent of febrile infants in various reports.[85,91,92]

In the first month of life, the predominant bacterial infections involved are those acquired from the birth canal. The most common are Group B *Streptococcus* and *Escherichia coli*, with *Staphylococcus aureus*, *Listeria monocytogenes* and other Gram-negative enteric bacteria occurring less commonly. These organisms remain the common bacterial pathogens for the infant 1–3 months of age, but other organisms such as *Streptococcus pneumoniae* and *Neisseria meningitidis* may be seen in these older infants. *Haemophilus influenzae* type b infection is now uncommon due to widespread immunization. *Escherichia coli* is the most frequent pathogen in urinary tract infections. *Salmonella* spp. and *Shigella* spp. are the common causes of bacterial enteritis. In the past few years, the widespread use of intrapartum antibiotics prophylaxis led to decreased prevalence of Group B *Streptococcal* infections.[93]

The HSV infections are a major cause of morbidity and mortality among neonates with a case fatality rate of 15.5 percent.[94] 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 that of bacterial meningitis in this

age group.[3][95] The HSV is transmitted to the newborn infant at the time of delivery and symptoms usually develop within the first 2 weeks of life. The risk of transmission is highest if the mother has primary disease, however the majority of women are asymptomatic at the time of delivery. Other risk factors include vaginal delivery, prolonged rupture of membranes, and the use of fetal scalp monitors. The HSV type 1 and type 2 are causes of disease in 30.0 percent and 70.0 percent of the infants, respectively.[95]

Clinical Assessment

The history and physical examination is the first step in the evaluation of the febrile infant. The initial clinical assessment of the infant involves deciding if the child appears unwell or "toxic." The clinical features that define toxicity include irritability, lethargy, and decreased social interaction. There may be signs of compromised circulation with poor perfusion and cyanosis or respiratory distress.

The clinical diagnosis of SBI in young infants is difficult; infants at this age may have SBI in the absence of signs of toxicity. There is a limited range of behavior in the young infant and signs of serious bacterial infection may be subtle. In addition, in the young infant with meningitis, there are often nonspecific symptoms with no meningeal signs.

Several studies have used observation scales to help predict SBI. In young infants, clinical observation scales have low sensitivity for the diagnosis of SBI. Although clinical assessment cannot adequately predict SBI, it may help define a group of infants who are at low risk for SBI due to their high sensitivity in identifying SBI.[4-7]

There are several published protocols which combine clinical and laboratory criteria in an attempt to identify young infants at low risk of SBI who can be safely managed as outpatients. Laboratory testing includes blood testing with white blood cell count, absolute band count or band to neutrophil ratio and blood culture. Urine testing is performed by catheterization or suprapubic aspiration with urinalysis and urine culture obtained. If the infant has diarrhea, stool microscopic testing and cultures are added. Some of the protocols include cerebrospinal fluid testing. Although this is the only test that will diagnose meningitis, lumbar puncture is the most invasive test.

The most commonly used criteria in practice are the Rochester criteria. Two modified versions of the Rochester criteria have been subsequently developed with the addition of either stool white blood cell (in presence of diarrhea) or normal inflammatory markers (erythrocyte sedimentation rate or C-reactive protein levels).[96] The Rochester criteria aims to identify a low-risk group of infants who are well appearing, previously healthy, with no evidence of bacterial illness on examination, and with normal laboratory testing. In the Rochester criteria, if the infant is considered low risk, no lumbar puncture is performed and antibiotics are not routinely used.

Other commonly used low risk criteria are the Boston criteria [8] and the Philadelphia protocol (original and modified versions).[9,96] For these criteria, all infants require to have an analysis of cerebrospinal fluid as part of the laboratory criteria. Low risk infants identified with these criteria receive intramuscular ceftriaxone and are treated as outpatients. Other criteria- the Milwaukee [10] also include lumbar puncture as part of the assessment but no antibiotics are given. See Appendix F.

The use of above-mentioned criteria are recommended for different age groups of infants (Philadelphia: 29–60 days; Rochester: 60 days or younger; Boston: 28–89 days).[25]

Infants who present with a recognizable viral illness or who have a confirmed viral infection by laboratory testing may have a different rate of serious bacterial illness than those with no viral

symptoms. The various low risk protocols do not include viral testing in the assessment of the febrile infant.

Large studies have not been performed on the diagnostic accuracy of clinical assessment for invasive HSV infection in an infant who presents with fever. The literature has been focused on patients with confirmed infections, thereby not allowing better understanding of the diagnostic accuracy of clinical and/or laboratory assessments.

Historical Context and Current Practice

As techniques for administering antibiotics to infants and for culturing bacteria from clinical specimens improved during the 1950s to 1970s, it became orthodox pediatric practice that all febrile infants <3 months of age undergo a complete evaluation for sepsis, including lumbar puncture, be admitted to hospital, and receive intravenous antibiotics for at least 48 hours as a precaution 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 conservative approach minimizes the risk of infectious complications, it leads to unnecessary hospitalization and treatment, with potential for iatrogenic harm to many 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.

In the well appearing infant with no clear source of infection, the current approach is to use a combination of clinical and laboratory criteria to decide which infants are likely at low risk for infection and can be managed as outpatients with or without antibiotics. With this approach there will be a small number of infants classified as low risk but who would subsequently be found to have serious bacterial illness. The delay in diagnosis and treatment may be potentially harmful for these infants.

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]

Regardless of guidelines or published protocols, a considerable number of clinicians do not adhere to them and manage the patient based on their own clinical judgment.[5,76,97,98] Many infants are managed by community pediatricians and are not seen in the emergency department where most of the studies are based. It is not clear if infants seen in the emergency department have a different risk of infection than those managed in the office. In the community practice setting, clinicians who are familiar with the families may be better able to predict the parents who are likely to comply with followup instructions.

The current recommendations for the evaluation and management of the young febrile infant are based on studies conducted in the late 1980's and early 1990's. 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 about the management of the febrile infant and to identify needs for future research.

Methods

Key Questions Addressed in This Report

The University of Ottawa EPC's evidence report on Diagnosis & Management of Febrile Infants (0–3 months) is based on a systematic review of the scientific literature. A technical expert panel helped revise the Key Questions and provide expertise to the review team during the review process.

The Key Questions (KQ) are:

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)?

KQ1b. How do these findings vary by age within the age range 0 to 3 months?

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? How do these findings vary by age within the age range 0 to 3 months?

KQ2a. What is the evidence that clinical features alone, basic laboratory tests (e.g., complete blood count [CBC], urinalysis) 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)?

KQ2b. 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?

KQ3a. What is the evidence that clinical features alone, basic laboratory tests (e.g., complete blood count [CBC], urinalysis) 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)?

KQ3b. What is the evidence on the benefits and harms of immediate antibiotic (antibacterial and antiviral) therapy and or hospitalization (vs. delaying until diagnostic workup is complete) in patients at high risk of serious bacterial illness?

KQ4. What is the evidence that the presence of an identified viral infection predicts against a serious bacterial infection?

KQ5. 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?

KQ6. Clinicians base decisions about initial diagnostic work-up and treatment of febrile infants not solely on the infants' medical status but also on their assessments of nonclinical 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 follow-up 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?

Data Sources and Search Strategy

Studies were identified through electronic searches in MEDLINE (1950 to September Week 2 2010, OVID interface), MEDLINE in Process (September 29, 2010, OVID interface), CINAHL (1982 to July Week 2 2008, OVID interface), Embase (1980 to 2010 Week 37, OVID interface), EBM Reviews, Cochrane Central Register of Controlled Trials (2nd Quarter 2010, OVID interface), the Cochrane Database of Systematic Reviews (2nd Quarter 2010, Wiley interface), PsycINFO (1806 to September Week 2 2010) and PubMed (Updated to September 22nd, 2010). Whenever possible, the electronic searches were limited to 1973 onwards, as this was the year that the first study examining bacteremia in a walk-in clinic was published.[99]

We searched for abstracts in the websites of relevant organizations (i.e., Society of Academic Emergency Medicine, American College of Emergency Physicians, Canadian Association of Emergency Physicians, American Academy of Pediatrics and the Pediatric Academic Societies) to identify any unpublished materials. Additional studies were sought from the authors' personal files and by contacting experts.

The search strategies are presented in Appendix A. The electronic search strategies were developed and executed by two experienced information specialists. The main electronic search strategy (MEDLINE) was also peer reviewed using PRESS (Peer Review of Electronic Search Strategies.[100] The searches were combined into a single Reference Manager database and duplicate records were manually deleted, providing a database of unique citations (i.e., titles and abstracts). An update search of the electronic databases was run on October 6th, 2008.

Study Eligibility and Screening

Studies were eligible if they reported the diagnosis of serious bacterial infection (e.g., bacterial meningitis, bacteremia, urinary tract infection) or herpes and/or management of infants (0-3 months of age) with no history of major disease(s), presenting with fever (rectal temperature ≥ 38°C) to a hospital clinic, an emergency department, an acute care clinic, or an outpatient office. Given the lack of relevant evidence found for KQ6 with respect to infants 0–3 months of age, the eligibility criteria were expanded to include children aged 0–6 months. The diagnostic test accuracy results for infants older than 3 months of age reported in some studies were not considered in this review (KQ1a). Such studies were included in the review only if they reported other relevant data (e.g., prevalence of SBI, outcomes related to management of febrile infants).

Reports of studies examining participants from 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 to be included.

The eligibility for 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, articles with no patient data specific to our inclusion criteria (e.g., editorials without any data, decision analyses), and those written in languages other than English were excluded. A list of the citations (i.e., titles and abstracts) that were potentially relevant but written in languages other than English was retained and provided to the technical expert panel for their review and is available upon request. Studies were included regardless of their publication status.

Two reviewers (GN, ACT) independently screened titles and abstracts of all identified bibliographic records by using a study relevance form. Two reviewers (CH, ACT) independently screened full-text reports of potentially relevant records. Discrepancies were resolved by discussion or the involvement of a third reviewer (DM).

Data Extraction

Initially, a draft standardized data extraction form was developed by the review team and circulated to the technical expert panel members who provided additional expert input after which the form was accordingly modified. Then, two reviewers (ACT, AT) piloted the modified version of the data extraction form before the actual data extraction process began. Two reviewers (ACT, AT) independently extracted relevant information from the included study reports. Afterwards, a third independent reviewer (FY) verified the extracted data.

Abstracted data included study characteristics (e.g., first author, country of research origin, study design), population examined (e.g., age, ethnicity, mother's demographics), methods used to identify or screen for bacterial or herpetic infection, and treatment or management outcomes of the febrile infants. The diagnostic test results (i.e., sensitivity, specificity, positive and

negative predictive values) were directly abstracted when reported. Where possible, the test results were derived from the information provided in studies.

The primary outcome was the set of accuracy indices of an index test (e.g., various laboratory and/or clinical criteria, protocols, laboratory thresholds) against a reference standard (e.g., bacterial culture growth in blood, urine or cerebral spinal fluid, viral culture, molecular testing) in predicting the presence of serious bacterial or herpes simplex virus infections. Secondary outcomes were any events or potential risks associated with a delayed diagnosis/treatment of infants with serious bacterial or herpes simplex virus infection or those associated with immediate treatment (antibacterial or antiviral) for infants classified at a high risk for having a serious bacterial or herpes simplex virus infection. Another outcome of interest was the prevalence of serious bacterial infection in febrile infants stratified by the status of viral infection and a clinical setting of presentation (emergency department vs. outpatient clinic). The proportion of parents' compliance in followup examination visits was also one of the relevant outcomes.

Risk of Bias (Study and Reporting Quality)

The study reports were categorized by study design as follows: randomized controlled trial (including quasi-randomized trials), controlled clinical trial, quasi-experimental (e.g., prepost study), cohort, nested case-control, case-control, cross-sectional, case series, and chart review. Studies reporting diagnostic accuracy data, as well as those for which this data could be derived were classified as diagnostic accuracy studies. Two independent reviewers (ACT, AT) assessed the risk of bias (i.e., study and reporting quality) for the included studies. The reviewers were not blinded to any study details.[101]

The diagnostic test accuracy studies were assessed using the QUADAS tool.[19] This validated instrument consists of 14 items (i.e., questions) asking if a study reported information on the applicability, description of selection criteria, and explanation of study withdrawals. The QUADAS items are rated as "Yes," "No," or "Unclear." For potential convenience and to efficiently summarize the quality data, the reviewers for each study assigned a score of 1 to 'Yes' rating and score of 0 to 'No' or 'Unclear' rating across all 14 items. For example, a study that reported or described information for seven out of 14 QUADAS items received a score of seven. We did not assess the study quality of single arm/single cohort studies (for Q2b and Q3b) and chart reviews, as we could not identify a validated way of conducting such appraisals.

Data Synthesis and Analysis

The identified studies were grouped according to the criteria/protocols (i.e., classification methods, index test) used to predict the risk of serious bacterial infection (or herpes simplex virus) in febrile infants. We did not specify the definition of SBI in this report. Instead, the definitions from original studies were presented. The classification criteria were categorized into the following groups: (1) combined (clinical and laboratory) criteria (Boston, Philadelphia, Rochester, Milwaukee, Yale Observational Score), (2) clinical criteria, and (3) laboratory criteria. Further, the identified formal protocols and criteria were categorized as "Low-Risk" and "Not Low-Risk."

For each study, two by two tables (i.e., cross-tabulation of infant counts classified by index tests and reference standards used for the diagnosis of serious bacterial or herpes simplex virus infection) were constructed in order to calculate all the necessary diagnostic accuracy parameters (i.e., sensitivity, specificity, negative and positive predictive values) with 95 percent confidence

intervals (95 percent CI). Where possible, these parameters were ascertained and calculated for separate types of serious bacterial infection (e.g., bacteremia, meningitis, and bacteremia plus meningitis). The sensitivity of a test may be defined as the probability of an infant being classified in high-risk group given the presence of SBI. Specificity - the probability of an infant being classified in low-risk group given the absence of SBI. Two types of error may occur: one when infants with SBI are classified into low-risk groups (false negatives) and the other when infants without SBI are classified into high-risk groups (false positives). Although it is desirable to have both highly sensitive and specific test, it is not feasible because of the tradeoff between the two indices. Predictive values (negative, positive) of a test are probabilities of having or not having SBI given the risk group an infant was classified into. For example, positive predictive value may be defined as a chance of an infant having SBI given the index test classified this infant into high-risk group. The sensitivity, specificity, negative and positive predictive values for clinical different clinical criteria and/or laboratory thresholds were assembled in tables and were qualitatively compared across studies.

The prevalence with 95 percent CIs of serious bacterial infection in virus-positive and virus-negative febrile infants were ascertained, calculated, and compared by means of prevalence ratios and odds ratios with accompanying 95 percent CIs. The prevalence proportions of serious bacterial infection (or herpes simplex virus infection) were qualitatively compared between the two types of setting (i.e., emergency department vs. primary care) through matching the studies by the country of conduct.

The diagnostic accuracy parameters 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 the specific type of bacterial infection (e.g., total serious bacterial infection, urinary tract infection, and bacteremia). The degree of heterogeneity across the study results was examined graphically by plotting values of sensitivity and specificity. The assessment of heterogeneity was guided by I^2 and Chi-squared statistics and corresponding p-values.[20] The potential sources of heterogeneity considered a priori were patient population age (0–28 days vs. > 28 days), prevalence of serious bacterial infection (or herpes simplex virus infection), different index tests (i.e., laboratory/clinical criteria, protocols), and different thresholds for any given index test.

The statistical analyses were performed using Meta-Disc (version 1.4).[102]

Results

Literature Search

A total of 2,440 records were identified using the search strategy designed for KQs 1–5. Of these, 1,918 records were excluded based on title and abstract screening, leaving 522 records for full text assessment.

The search strategy for KQ6 returned 236 records to be screened for title and abstract (including 15 reviewer-nominated studies). Of these, 43 records passed to full text screening, and 4 records were included in the review.

In total, 84 unique studies (published in 92 papers) were included in this review. The study flow process is depicted in Figure 1 (PRISMA flow chart). The included studies were 21 chart reviews, 10 case series, 21 cohort studies, 21 cross sectional studies, four quasi experimental studies, and 6 case-control/nested case control studies.

Five studies were reported in multiple publications: Bilavsky et al. (2009/2010),[45,103] Levine et al. (2004/2005/2009),[65,79,80] Maniaci et al. (2008),[61,104] Chen et al. (2008 and 2009),[71,105] and the PROS study by Pantell, et al., (2002/2004/2005/2008).[5,51,76,106] In this report we referred to only one of the publications judged as the primary publication, however relevant data extracted from all publications pertaining to any given study have been presented. Where unique data by any secondary publications was reported, the appropriate citations have been indicated.

Study Populations

Total number of included infants with laboratory and culture results could be verified in 78/84 studies (n = 53,873). The percentage of infants with confirmed total SBI could be obtained from in 70 studies. (4,273/45,639, 9.4 percent)

The reviewed studies included febrile infants aged 0–3 months with fever (rectal temperature ≥ 38°C measured at home or on arrival at emergency department) and with no history of major disease(s) who had been admitted and assessed in an emergency department, an outpatient clinic, or a primary care physician's office. The source of fever for most of these infants was described as not known (fever without a source or FWS). These studies excluded infants who had a current or previous antibiotic treatment. Of the 83 included studies, 58 (69.9 percent) were conducted in North America, eight (9.6 percent) in Western Europe, and seven (8.4 percent) in Asia (Taiwan or Korea). Information on ethnicity and socioeconomic status were poorly reported in majority of reports. The span of data collection for these studies ranged from 1974 to 2009. Twelve of the studies included more than one hospital/office sites, including the Pediatric Research in Office Settings (PROS) study, which included 219 physicians' office practice sites.[5] The remaining studies were conducted at a single site. Twenty-two studies reported information on neonates (0–28 days old). The detailed information for all included studies is presented in Appendix C (Evidence Tables 1–8).

Methods for Classification (i.e., Screening Tests to Predict SBI) and Diagnosis of SBI and Viral Infection

The reviewed studies reported a wide array of index tests (i.e., criteria) for predicting the risk of serious bacterial infection in febrile infants assessed in emergency departments or outpatient clinics. These criteria were comprised of either clinical or laboratory features alone or

represented a variety of combinations of clinical features and laboratory thresholds which were tested in febrile infants in order to predict serious bacterial infection. Some of these tests were commonly used criteria such as the Boston criteria,[22,55] Philadelphia protocol,[9,11,12,22,25,58,59] Rochester criteria, and [10,23-27,35,56,57,60] Milwaukee protocol[10](Table 1). Other criteria also used were Yale scoring criteria,[64,65] and Young Infant Observational Scale (YIOS).[21](Appendix F) Other reported criteria were various of clinical (e.g., ill or toxic appearance, impression of sepsis, age, rectal temperature) and/ or laboratory features using different techniques with varying thresholds such as serum WBC counts, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), absolute band count (ABC), cerebrospinal fluid (CSF) (e.g., presence of pleocytosis), Procalcitonin levels (PCT), and urine analysis (e.g., microscopy: WBC of spun urine, dipstick: leukocyte esterase/nitrite).[5,26-29,31-36,38-40,46,49,66,67,70,82,85]

Table 1. 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/mm^3 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 reevaluation 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; ° = degrees C = Celsius; CSF = cerebrospinal fluid; d=day(s); hpf = high power field; UA = urinalysis; WBC = white blood cells

The presence of serious bacterial infection was determined by confirming bacterial growth in blood, cerebrospinal fluid, stool, and/or urine. The definition of urinary tract infection was based on supra-pubic tap > 1,000 colony forming units/mL or catheterization > 10,000 colony forming units/mL) although one report employed the higher threshold of > 20,000 colony forming units/mL with a single organism.[5] Although serious bacterial infection studies consistently reported on bacteremia, meningitis and urinary tract infection, some other studies chose to include osteomyelitis, suppurative arthritis, soft tissue infections (cellulites, abscess, mastitis), gastroenteritis, and pneumonia. The following bacterial isolates were considered as pathogens: *Streptococcus pneumoniae*, Neisseria meningitidis, Klebsiella species, *Salmonella* species, Group A *Streptococcus*, Group B *Streptococcus*, *Haemophilus influenzae* type b, *Staphylococcus aureus*, Moraxella catarrhalis, *Escherichia coli*, Listeria monocytogens, or other enteric gram-negative rods. Urine cultures were thought contaminated if the symptoms of febrile infants disappeared without appropriate treatment or if the isolated bacteria were not regarded as a pathogen.

The diagnosis of UTI accounted for the greatest proportion of all types of SBI (bacteremia, meningitis, pneumonia, cellulitis, gastroenteritis, others). For example, the prevalence of diagnosis of UTI across studies ranged from 15.0 percent to 94.0 percent. In contrast, the ranges for this prevalence for bacteremia and meningitis were 0 percent to 41.0 percent and 0 percent to 25.9 percent, respectively (with the exception of one study reporting the prevalence of 34.0 percent for bacterial meningitis in infants 0–2 months of age.[21]

In total, *E. coli* was found in 60.0 percent of total SBI cases (1136/1890). The same organism was responsible for 68.0 percent (range: 37.5 percent to 100.0 percent) of all UTI cases, 24.3 percent (range 0 percent to 55.5 percent) of all bacteremia, and 8.0 percent (range: 0 percent to 40.0 percent) of all bacterial meningitis. *Group B streptococcus* was the second most prevalent organism found in bacteremia, and bacterial meningitis cases (25.0 percent).

The presence of influenza A was confirmed by documented positive direct antigen Flu A testing or positive viral culture. Enterovirus (EV) was diagnosed using polymerase chain reaction or culture (blood, cerebrospinal fluid, nasopharyngeal and throat swabs). The diagnosis of respiratory syncytial virus (RSV) was documented by rapid immunoassay or viral culture.[27,74,78,79,86,107]

Study Outcomes

The outcomes of reviewed studies were performance characteristics (i.e., accuracy indices: sensitivity, specificity, positive and negative predictive value, the area under receiver operating curve, likelihood ratios) of variety of classification methods in predicting the risk of serious bacterial infection in febrile infants (KQs 1a, 1b, 2a, 3a) or herpes simplex virus (HSV) infection (KQ1c). Other studies compared prevalence of serious bacterial infection in febrile infants between those with or without viral infection (prevalence ratios, odds ratios) (Question 4).[27,60,74,76,78,79,86]

Several studies in "low-risk" or "not low-risk" groups of infants (as classified by index tests or criteria) explored and reported outcomes such as hospitalization, total health care costs associated with hospitalization, incidence of serious bacterial infection and treatment-related harms (e.g., infiltrated intravenous lines, drug-related rush, diarrhea), parents' compliance, and culture contamination (blood, urine, cerebrospinal fluid).[5,9,10,12,23,26,28,29,55-58,67,70,108]

Risk of Bias (Study and Reporting Quality)

The study and reporting quality of the included in the review studies were assessed using the Quality Assessment of Studies of Diagnostic Accuracy Included in Systematic Reviews (QUADAS). (Appendix G)

The mean (range) 14-item QUADAS score for included studies was 9.0 ($3^{43,109}$-$14^{9,67}$). For example, the study with lowest quality score of 3 was rated "Yes" on only 3 items and the study with the highest score was rated "Yes" on all 14 items. About 86.9 percent of the studies clearly described selection criteria, 91.3 percent used a valid reference standard for the diagnosis, and in 68.1 percent of studies there was a short period of time between reference standard and index test. The reference standard and index tests were reported to be independent in about 75.4 percent of the studies. Only 28.9 percent of the studies explicitly reported that test results were interpreted without knowledge of either reference standard, or index test results (33.3 percent). The withdrawals were explained in 54.7 percent of the studies.

Based on qualitative assessment, study quality did not seem to account for the observed discrepancies in the diagnostic accuracy parameters for a specific criteria or protocol across the studies. For Boston, Rochester, Philadelphia, Milwaukee criteria, comparison of results according to QUADAS score was not possible due to: (a) relative lack of variability in quality, (b) different combinations of clinical criteria used, (c) various laboratory criteria (or thresholds) used, and/or (d) various target conditions for which a given index test was evaluated (e.g., serious bacterial infection, bacteremia, meningitis).

Figure 1. PRISMA flow chart - Febrile infant (0–3 months)

Key Questions 1 – 5   Key Question 6

Identification

| 3367 records identified from bibliographic searches | 223 records identified from bibliographic searches |

| 19 records nominated by reviewers | 946 duplicates and review articles removed | 2 duplicates and review articles removed | 15 records nominated by other sources |

Screening

| 2440 screened at Level 1 | 236 screened at Level 1 |

1918 excluded
(284) Not an English language publication
(1534) Primary objective is not relevant to topic of review
(80) Is a systematic or narrative review, clinical guidelines or cost-effectiveness analysis

193 excluded
(0) Not an English language publication
(188) Primary objective is not relevant to topic of review/ does not include eligible population
(5) Not from geographic locations specified for this review

Eligibility

| 522 eligible for further assessment (Full Text) | 43 eligible for further assessment (Full Text) |

430 excluded (N)
(8) Not English language publication
(338) Primary objective not diagnosis or management of infants 0 – 90 d, and or
(60) Not referring to infants presenting to ED or primary care, and or
(5) Not from geographic locations specified for this review
(19) A narrative or systematic review

39 excluded (N)
(30) Did not address key question or ineligible population/ study design
(9) Addressed Key questions but did not meet the age/condition criteria of this review

Included

| 84 studies (92 publications) included | 4 studies excluded |

84 studies were included for evidence synthesis
All Questions: (0) Randomized controlled trial
(21) Chart review
(10) Case Series
(21) Cohort
(21) Cross-sectional
(4) Quasi-experimental
(6) Case control/Nested case control

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)?

In this section, the classification criteria (i.e., index tests) for predicting the risk of SBI were divided into the following three broad groups: (1) Combined clinical and laboratory criteria, (2) clinical criteria alone, and (3) laboratory criteria alone.

Key Findings

The most commonly used combined criteria (Philadelphia, Rochester, Boston, and Milwaukee protocol/criteria) demonstrated similar degree of overall accuracy (i.e., sensitivity and specificity) in correctly classifying febrile infants with and without total SBI with high sensitivity (range: 84.4 percent–100.0 percent), but lower specificity (range: 26.6 percent–69.0 percent). The application of Young Infant Observation Scale and Yale Observation Score was associated with lower sensitivity (76.0 percent and 33.3 percent, respectively) for total SBI. The corresponding range of sensitivity for the other combined clinical (e.g., well, ill, good appearance) and various laboratory features (e.g., WBC, ESR, CRP, ABC, and/or urine dipstick test) was from 68.3 percent to 99.1 percent. We found no evidence relating to other possibly relevant factors such as the clinical history of the mother.

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–95.4 percent) for total SBI compared with criteria based on age ($\leq$ 30 days; sensitivity: 35.0 percent), gender (sensitivity: 74.0 percent), the degree of fever ($\geq$ 39.5°C; range of sensitivity: 7.3 percent-26.1 percent), and ill appearance (range of sensitivity: 21.0 percent-33.3 percent). Criteria based on clinical appearance (ill, toxic, impression of sepsis) alone or criteria that combined age (> 30 days) with clinical ill-appearance tended to yield higher sensitivity (range: 80.0 percent-100.0 percent) than criteria based on the degree of fever > 40°C (range: 5.1 percent-12.5 percent) for identifying infants with bacteremia.

Across and within studies, the sensitivity for identifying total SBI tended to increase with lower thresholds of WBC (e.g., from $\geq$ 5,000/mm3 to $\geq$ 20,000/mm3), ABC (from ABC>250/mm3 to ABC>3,000/mm3), and absolute neutrophil count (ANC) (from 4,650/μL to 12,500/μL). The overall accuracy of ANC (AUC: 78.0 percent) and ABC (AUC: 81.0 percent) was greater than that for WBC (AUC range: 59.0 percent-69.0 percent). The use of C-reactive protein (CRP) demonstrated the highest sensitivity in correctly identifying infants with and without SBI (AUC: 84.0 percent).

Detailed Presentation

This review included 62 studies that reported data on the performance characteristics (i.e., accuracy indices: sensitivity, specificity, PPV, NPV) of variety of criteria used in predicting the

risk of SBI in febrile infants admitted to emergency departments or outpatient clinics (Tables 2–5).

Combined Clinical and Laboratory Criteria/Protocols (Philadelphia, Boston, Rochester, Milwaukee, and Young Infant Observation Scale).

Total serious bacterial infection. The performance characteristics of the Philadelphia, Boston, Rochester, Milwaukee protocol/criteria, and Young Infant Observation Scale (YIOS) for predicting the risk of total SBI in febrile infants was reported and/or ascertained from 19 studies (Table 2).[9-12,21-27,35,55-60,64]

Based on results from 17 studies, the Philadelphia, [9,11,12,25,58,59] Rochester,[23-27,35,57,60] Boston, [35,55] and Milwaukee criteria [10] demonstrated similar degree of overall accuracy (i.e., sensitivity and specificity) in correctly classifying febrile infants with and without SBI (e.g., UTI, bacteremia, meningitis, pneumonia, and gastroenteritis). Specifically, these four criteria showed high sensitivity (range: 84.4 percent–100.0 percent), and as expected, lower specificity (range: 26.6 percent–69.0 percent) for identifying infants without SBI. The probability of being free of SBI among test-negative infants (i.e., NPV) across these 4 criteria was also high (> 94.0 percent).

The pooling of sensitivity values was possible for only Rochester (94.0 percent; 95.0 percent CI: 91.0, 96.0) [23-27,57,60] and Philadelphia criteria (93.0 percent; 95 percent CI: 89.0, 95.0). [9,11,12,22,25,58] The specificity for Rochester (range: 36.0 percent to 69.0 percent) and Philadelphia criteria (range: 27.0 percent to 67.0 percent) could not be pooled due to high degree of statistical heterogeneity (Rochester: I^2 = 95.9 percent, Chi-squared = 147.0, p<0.01 and Philadelphia: I^2 = 96.8 percent, Chi-squared = 157.2, p<0.01). The forest plots for sensitivity and specificity of Rochester and Philadelphia protocol/criteria are given in Figures 2–5.

Three studies reporting lowest sensitivity values for the Rochester (52.0 percent and 59.0 percent) [10,56] and Boston criteria (82.0 percent) [22] were not considered in the analyses. The included infants in the first study,[56] were older (up to 89 days) than it is specified in the Rochester criteria (≤ 2 months). The second study [10] did not report the inclusion/exclusion criteria and baseline characteristics of the included infants. The third study,[22] included infants 28 days or younger, that is, outside the age eligibility of the Boston criteria (28 - 89 days).

In one study of febrile infants 2 months or younger,[21] the Young Infant Observation Scale (YIOS) was evaluated for predicting risk of total SBI. The YIOS included three factors (affect, respiratory status, and peripheral perfusion which were scored as 1 (no compromise), 3 (intermediate level of compromise), or 5 (severe compromise). For predicting the risk of total SBI, the YIOS score ≥7 yielded the sensitivity, specificity, and NPV of 76.0 percent, 75.0 percent, and 96.0 percent, respectively.

In two studies of infants 2 months or younger,[64,65] the application of Yale Observation Score (YOS > 10 denoting a high risk of SBI given ill appearance) demonstrated low sensitivity in correctly identifying infants with UTI (4.4 percent, 95 percent CI: 1.4, 11.5)[65] or total SBI (33.3 percent, 95 percent CI: 11.3, 64.5).[64]

Specific types of serious bacterial infection. The accuracy indices of Boston,[22] Philadelphia,[9,11,12,22,25,58] and Rochester [10,23-27,56,57] protocols/criteria for identifying febrile infants with bacteremia, meningitis, and/or bacteremia/meningitis were ascertained for 14 studies. This information could not be ascertained for the Milwaukee criteria.[10]

The sensitivities 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. The corresponding specificity for bacteremia was more variable across these criteria, ranging from 19.1 percent– 51.1 percent for Philadelphia, 26.3 percent–64.9 percent for Rochester criteria, and 63.3 percent for Boston criteria. In one study, for the Rochester criteria, the sensitivity value for correctly identifying bacteremia was 33.3 percent (see SBI subsection for more detail about this study).[10] 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 sensitivity of Yale Observation Score (YOS) test in predicting bacterial sepsis was 75.0 percent (95 percent CI: 21.9, 98.6).[64]

The Philadelphia protocol demonstrated high sensitivity (100.0 percent) and high NPV (100 percent) but lower specificity (24.2 percent[9]–50.7 percent[22]) in correctly identifying meningitis.

There was insufficient data to compare the validity indices across these criteria with respect to the identification of infants with meningitis. The use of Rochester criteria,[10] reported to have misclassified two cases of bacterial meningitis (total of four cases) into the category of low risk for SBI.

Figure 2. Sensitivity plots (Rochester criteria)

	Sensitivity (95% CI)	
Byington 2004	0.92	(0.85 - 0.96)
Chiu 1997	0.98	(0.87 - 1.00)
Ferrera 1997	0.86	(0.65 - 0.97)
Garra 2005	0.97	(0.89 - 1.00)
Jaskiewicz 1994	0.92	(0.83 - 0.97)
Dagan 1988	1.00	(0.84 - 1.00)
Dagan 1985	0.96	(0.78 - 1.00)

Pooled Sensitivity = 0.94 (0.91 to 0.96)
Chi-square = 7.94; df = 6 (p = 0.2423)
Inconsistency (I-square) = 24.5 %
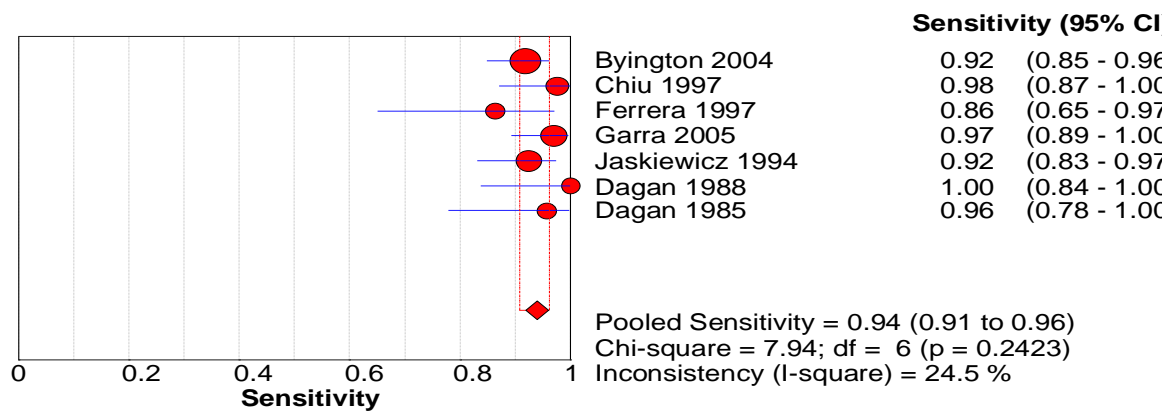
Sensitivity

Figure 3. Specificity plots (Rochester criteria)

	Specificity (95%CI)	
Byington 2004	0.36	(0.33 - 0.39)
Chiu 1997	0.62	(0.55 - 0.69)
Ferrera 1997	0.46	(0.36 - 0.57)
Garra 2005	0.37	(0.30 - 0.44)
Jaskiewicz 1994	0.50	(0.47 - 0.53)
Dagan 1988	0.69	(0.62 - 0.75)
Dagan 1985	0.68	(0.61 - 0.74)

Pooled Specificity = 0.49 (0.47 to 0.51)
Chi-square = 147.05; df = 6 (p = 0.0000)
Inconsistency (I-square) = 95.9 %

Specificity

20
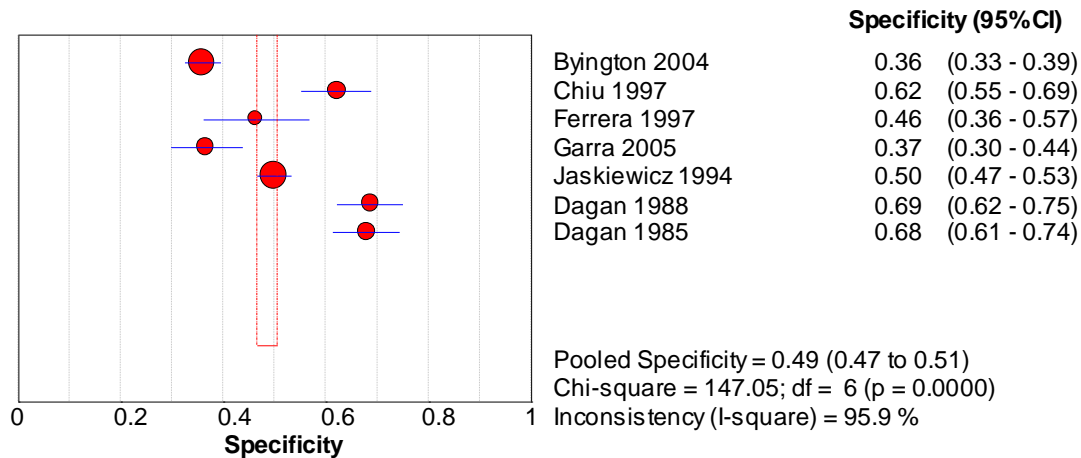
Figure 4. Sensitivity plots (Philadelphia protocol)

	Sensitivity (95% CI
Baker 1993	0.98 (0.92 - 1.0(
Baker 1999a	1.00 (0.92 - 1.0(
Baker 1999b	0.84 (0.67 - 0.9!
Brik 1997	0.87 (0.75 - 0.9
Garra 2005	0.97 (0.89 - 1.0(
Kadish 2000	0.87 (0.73 - 0.9!

Pooled Sensitivity = 0.93 (0.89 to 0.95)
Chi-square = 20.41; df = 5 (p = 0.0010)
Inconsistency (I-square) = 75.5 %
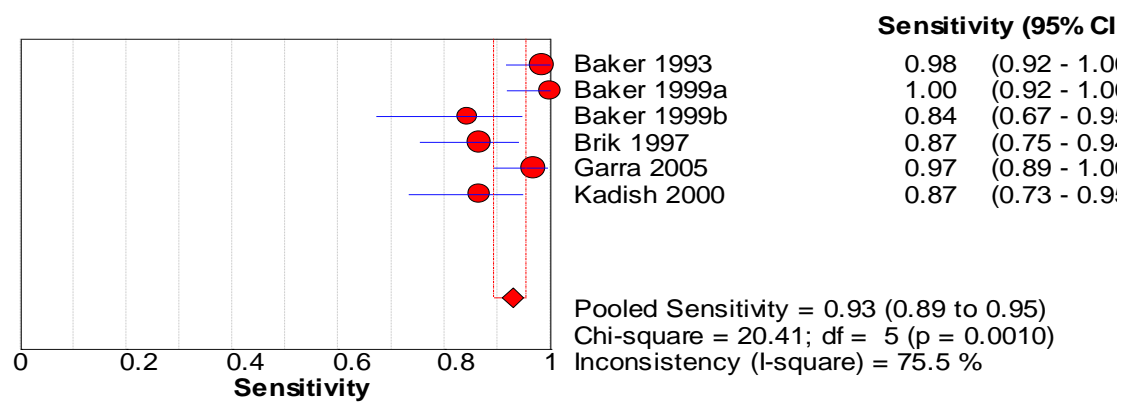
Figure 5. Specificity plots (Philadelphia protocol)

	Specificity (95% CI)
Baker 1993	0.42 (0.38 - 0.46)
Baker 1999a	0.27 (0.22 - 0.31)
Baker 1999b	0.47 (0.40 - 0.54)
Brik 1997	0.67 (0.62 - 0.71)
Garra 2005	0.37 (0.30 - 0.44)
Kadish 2000	0.55 (0.49 - 0.61)

Pooled Specificity = 0.46 (0.44 to 0.48)
Chi-square = 157.18; df = 5 (p = 0.0000)
Inconsistency (I-square) = 96.8 %

Table 2. Test results – Combined clinical & laboratory criteria I (Boston criteria, Milwaukee protocol, Philadelphia protocol, Rochester criteria, and Yale observation score)

Study ID QUADAS Total Score	N/n* Age Range	N (%) with SBI	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]	Other
Boston Criteria							
Kadish (2000)[22] [12]	394/372 1–28 d	Total: 45 (12.1) UTI: 32 Bacteremia: 12 Meningitis: 5 Cellulitis: 3 Septic arthritis: 1 Gastroenteritis: 1 Pneumonia: 1	82.0 [67.4, 91.5]	68.0 [62.8, 73.1]	26.0 [19.4, 34.4]	97.0 [93.0, 98.4]	LR^+=2.58 LR-= 0.26
		Bacteremia: 12	75.0 [42.8, 93.3]	63.3 [58.1, 68.3]	6.4 [3.1, 12.1]	98.7 [96.0, 99.6]	LR^+=2.04 LR-= 0.39
Kaplan (2000)[55] [8]	3,166/2,190 28–90 d	Total: 191 (8.7) Types of SBI: NR	88.5 [82.8, 92.5]	56.2 [54.0, 58.4]	16.2 [14.0, 18.6]	98.1 [97.0, 98.7]	LR^+= 2.02 LR-= 0.20
Stanley (2005)[35] [13]	5,279/5,279 0–90 d	Total: 480 (9.1) UTI: 305 Meningitis: 10 Bacteremia: 39 Bacteremia/meningitis: 8 Bacteremia/UTI: 11 Pneumonia: 70 Cellulitis: 26 Bacterial enteritis: 11	99.5 [98.3, 99.9]	NR	NR	NR	NR

Table 2. Test results – Combined clinical & laboratory criteria I (Boston criteria, Milwaukee protocol, Philadelphia protocol, Rochester criteria, and Yale observation score) (continued)

Study ID QUADAS Total Score	N/n* Age Range	N (%) with SBI	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]	Other
				Milwaukee Protocol			
Bonadio (1993)[10] [5]	534/534 29–60 d	Total: 24 (4.5) UTI: 11 Bacterial meningitis: 4 Bacteremia: 6 Bacterial enteritis: 2 Pneumonia: 1	96.0 [88.0, 100.0]	28.0 [23.0, 36.0]	5.9 [3.6, 8.2]	99.3 [98.0, 100.0]	LR$^+$= 1.33 LR-= 0.15
				Philadelphia Protocol			
Baker (1999)[11] [13]	254/254 3–28 d	Total: 32 (12.5) UTI: 17 Bacteremia: 8 Meningitis: 4 Cellulitis: 1 Gastroenteritis: 2 Peritonitis: 1 Osteomyelitis: 1	84.4 [67.0, 95.0]	46.8 [40.0, 53.0]	18.6 [12.0, 25.0]	95.4 [90.0, 99.0]	LR$^+$=1.58 LR-= 0.33
		Bacteremia: 8	75.0 [35.6, 95.5]	43.5 [37.2, 49.9]	4.1 [1.7, 9.1]	98.1 [92.7, 99.7]	LR$^+$=1.32 LR-= 0.57
		Meningitis: 4	100.0 [39.6, 100.0]	43.6 [37.4, 49.9]	2.7 [0.9, 7.3]	100.0 [95.7, 100.0]	LR$^+$=1.77 LR-= 0
Baker (1999)[9] [14]	422/422 29–60 d	Total: 43 (10.2) UTI: 17 Bacteremia: 9 Meningitis: 5 Gastroenteritis: 5 Cellulitis: 5 Chlamydia pneumonia: 2 Enterocolitis: 1 Osteomyelitis: 1 Septic arthritis: 1	100.0 [89.7, 100.0]	26.6 [22.3, 31.4]	14.0 [10.0, 17.7]	100.0 [96.0, 100.0]	LR+= 1.36 LR-= 0
		Bacteremia: 9	100.0 [62.9, 100.0]	24.4 [20.4, 28.9]	2.8 [1.4, 5.4]	100.0 [95.4, 100.0]	LR+= 1.32 LR-= 0
		Meningitis: 5	100.0 [46.3, 100.0]	24.2 [20.3, 28.7]	1.5 [0.6, 3.8]	100.0 [95.4, 100.0]	LR+= 1.31 LR-= 0

Table 2. Test results – Combined clinical & laboratory criteria I (Boston criteria, Milwaukee protocol, Philadelphia protocol, Rochester criteria, and Yale observation score) (continued)

Study ID QUADAS Total Score	N/n* Age Range	N (%) with SBI	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]	Other
Baker (1993)[12] [11]	747/747 29–56 d	Total: 65 (8.7) UTI: 24 Bacteremia: 19 Meningitis: 9 Cellulitis: 6 Gastroenteritis: 13 Adenitis: 1	98.0 [92.0, 100.0] 100.0‡ [93.0, 100.0]	42.0 [38.0, 46.0] 42.0‡ [38.3, 45.9]	14.0 [11.0, 17.0] 14.1‡ [11.1, 17.7]	99.7 [98.0, 100.0] 100.0‡ [98.3, 100.0]	LR+=1.69 LR-= 0.03 LR+=1.72 LR-= 0
		Bacteremia: 19	100.0‡ [79.0, 100.0]	39.4‡ [35.8, 43.0]	4.1‡ [2.5, 6.5]	100.0‡ [98.3, 100.0]	LR+=1.65 LR-= 0
		Meningitis: 9	100.0‡ [62.8, 100.0]	38.9‡ [35.4, 42.5]	2.0‡ [0.9, 3.8]	100.0‡ [98.3, 100.0]	LR+=1.63 LR-= 0
Brik (1997)[58] [12]	492/492 0–90 d	Total: 60 (12.3) UTI: 40 Meningitis: 2 Bacteremia: 10 Gastroenteritis: 4 Cellulitis: 2 Adenitis: 1	86.6 [74.8, 93.6]	66.6 [62.0, 71.0]	26.5 [20.6, 33.4]	97.3 [94.5, 98.7]	LR+= 2.60 LR-= 0.20
Condra (2010)[59] [7]	1,672/240 29–60 d	*Data on only low risk infants (n=62)* Total: 2 (NR) UTI: 2	NR	NR	NR	96.7 [NR]	NR
Garra (2005)[25] [12]	302/259 0–56 d	Total: 65 (25.1) UTI: 51 Bacteremia/UTI: 5 Bacteremia: 8 Bacteremia/Meningitis:1	98.5 [92.0, 100.0]	41.9 [38.0, 46.0]	13.9 [11.0, 17.0]	99.7 [98.0, 100.0]	LR+= 1.70 LR-= 0.03
		Bacteremia: 8	87.5 [46.7, 99.3]	19.1 [13.6, 25.9]	4.7 [2.1, 9.9]	97.0 [82.9, 99.8]	LR+= 1.08 LR-= 0.65

Table 2. Test results – Combined clinical & laboratory criteria I (Boston criteria, Milwaukee protocol, Philadelphia protocol, Rochesterter criteria, and Yale observation score) (continued)

Study ID QUADAS Total Score	N/n* Age Range	N (%) with SBI	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]	Other
Kadish (2000)[22] [12]	394/372 1–28 d	Total: 45 (12.1) UTI: 32 Bacteremia: 12 Meningitis: 5 Cellulitis: 3 Septic arthritis: 1 Gastroenteritis: 1 Pneumonia: 1	87.0 [72.5, 94.4]	55.0 [49.5, 60.5]	21.0 [15.5, 27.6]	97.0 [92.8, 98.7]	LR+=1.92 LR-= 0.24
		Bacteremia: 12	83.3 [50.8, 97.0]	51.1 [45.8, 56.3]	5.3 [2.7, 9.9]	98.9 [95.6, 99.8]	LR+=1.70 LR-= 0.32
		Meningitis: 5	100.0 [46.3, 100.0]	50.7 [45.5, 55.9]	2.6 [0.9, 6.5]	100.0 [97.4, 100.0]	LR+=2.03 LR-= 0
Rochester Criteria†							
Baskin (1992)[56] [11]	503/501 28–89 d	Total: 27 (5.4) Bacteremia: 8 UTI + bacteremia: 1 UTI: 8 Gastroenteritis: 10	52.0 [31.7, 71.6]	NR	NR	NR	NR
		Bacteremia: 8	55.5 [22.6, 84.6]	NC	NC	NC	NC
Bonadio (1993)[10] [5]	534/532 29–60 d	Total: 22 (4.1) UTI: 11 Meningitis: 4 Bacteremia: 6 Klebsiella pneumoniae: 1	59.0 [36.6, 78.5]	26.3 [22.5, 30.3]	3.3 [1.9, 5.8]	93.7 [88.0, 96.9]	LR+=0.80 LR-= 1.55
		Bacteremia: 6	33.3 [6.0, 75.9]	26.3 [22.5, 30.3]	0.5 [0.09, 2.1]	97.1 [92.3, 99.0]	LR+=0.45 LR-= 2.53
		Meningitis: 4	50.0 [9.1, 90.8]	26.7 [23.0, 30.7]	0.5 [0.08, 2.1]	98.6 [94.5, 99.7]	LR+=0.68 LR-= 1.87
Byington (2004)[60] [10]	894/888 (infants without viral infections) 1–90 d	Total: 109 (12.3) Types of SBI: bacteremia, UTI, meningitis, pneumonia	91.7 [84.5, 95.9]	36.0 [32.6, 39.4]	16.6 [13.8, 20.0]	96.9 [94.0, 98.5]	LR+= 1.43 LR-= 0.23

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Table 2. Test results – Combined clinical & laboratory criteria I (Boston criteria, Milwaukee protocol, Philadelphia protocol, Rochester criteria, and Yale observation score) (continued)

Study ID QUADAS Total Score	N/n* Age Range	N (%) with SBI	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]	Other
Chiu (1997)[57] [12]	250/250 4–28 d	Total: 41 (16.4) UTI: 16 Bacteremia/Meningitis: 7 Bacteremia/Enteritis: 3 Enteritis: 2 Bacteremia/Osteomyelitis: 1 Others: NR	97.6 [92.9, 100.0]	62.2 [55.6, 68.8]	33.6 [25.1, 42.1]	99.2 [97.7, 100.0]	LR+= 2.58 LR-= 0.04
		Bacteremia/Meningitis: 7 Bacteremia/Enteritis: 3 Bacteremia/Osteomyelitis: 1	100.0 [67.8, 100.0]	54.8 [48.2, 61.2]	9.2 [4.9, 21.2]	100.0 [96.4, 100.0]	LR+= 2.21 LR-= 0
Dagan (1988)[26] [11]	237/236 < 60 d	Total: 22 (9.3) Bacteremia: 8 UTI: 6 Otitis media: 6 Gastroenteritis: 1 Bacteremia: 1 (not included)	100.0 [80.7, 100.0]	68.8 [62.1, 74.8]	23.8 [15.7, 34.3]	100.0 [96.8, 100.0]	LR+= 3.20 LR-= 0
		Bacteremia: 8	100.0 [59.7, 100.0]	64.9 [58.3, 71.0]	9.0 [4.3, 17.6]	100.0 [96.8, 100.0]	LR+= 2.85 LR-= 0
Dagan (1985)[27] [12]	233/233 < 60 d	Total: 23 (9.8) Bacteremia: 9 UTI: 6 Other: NR	96.0 [78.0, 100.0]	68.0 [61.0-74.0]	24.7 [19.9, 25.8]	99.3 [96.3, 100.0]	LR+= 2.99 LR-= 0.06
Ferrera (1997)[24] [12]	188/134 0–28 d	Total: 22 (16.4) UTI: 13 UTI/meningitis: 1 Bacteremia: 4 Bacteremia/UTI: 1 Bacteremia/meningitis: 1 Listeria meningitis: 1 Pneumonia: 1	86.4 [64.0, 96.4]	46.4 [36.3, 56.7]	26.8 [17.2, 38.8]	93.8 [81.8, 98.4]	LR+=1.61 LR-= 0.29
		Bacteremia: 4	100.0 [39.5, 100.0]	41.7 [32.7, 51.3]	5.6 [1.8, 14.3]	100.0 [90.2, 100.0]	LR+=1.71 LR-= 0

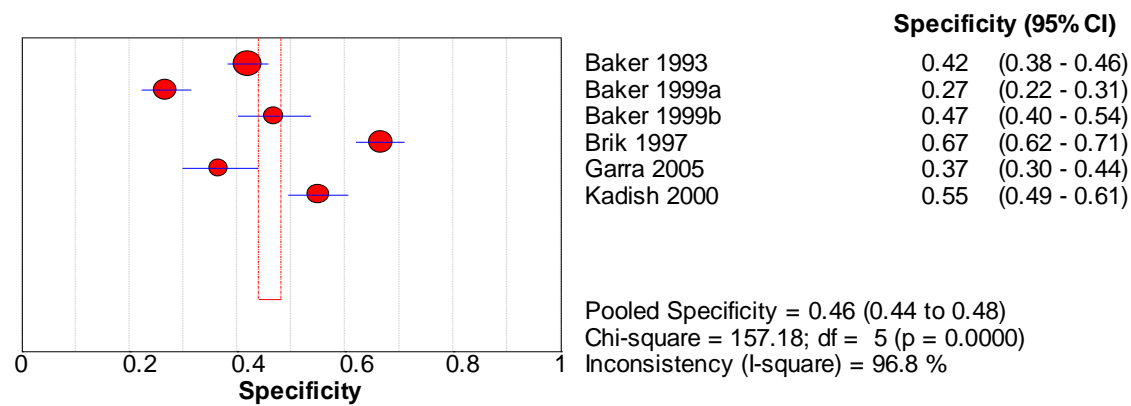**Table 2. Test results – Combined clinical & laboratory criteria I (Boston criteria, Milwaukee protocol, Philadelphia protocol, Rochesterter criteria, and Yale observation score) (continued)**

Study ID QUADAS Total Score	N/n* Age Range	N (%) with SBI	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]	Other
Garra (2005)[25] [12]	302/259 0–56 d	Total: 65 (25.1) UTI: 51 Bacteremia/UTI: 5 Bacteremia: 8 Bacteremia/Meningitis: 1	96.9 [89.3, 99.6]	36.6 [29.8, 43.8]	33.9 [31.1, 34.8]	97.3 [90.3, 99.5]	LR+=1.52 LR-= 0.08
		Bacteremia: 8	75.0 [35.5, 95.5]	28.3 [22.9, 34.3]	3.2 [1.3, 7.3]	97.3 [89.6, 99.5]	LR+=1.04 LR-= 0.88
		Bacteremia/UTI: 5	100.0 [46.3, 100.0]	28.7 [23.3, 34.8]	2.6 [0.9, 6.5]	100.0 [93.6, 100.0]	LR+=1.40 LR-= 0
Jaskiewicz (1994)[23] [10]	1057/931 0–60 d	Total: 66 (7.0) UTI: 34 Skin/soft tissue infection: 18 Bacteremia: 16 Gastroenteritis: 4 Pneumonia: 1	92.4 [82.5, 97.2]	50.0 [46.5, 53.3]	12.3 [9.6, 15.6]	98.9 [97.2, 99.6]	LR+=1.84 LR-= 0.15
		Bacteremia: 16 (1.7)	87.5 [60.4, 97.8]	47.5 [44.2, 50.8]	2.8 [1.6, 4.8]	99.5 [98.2, 99.9]	LR+= 1.66 LR-= 0.26
Stanley (2005)[35] [13]	5,279/5,279 0–90 d	Total: 480 (9.1) UTI: 305 Meningitis: 10 Bacteremia: 39 Bacteremia/meningitis: 8 Bacteremia/UTI: 11 Pneumonia: 70 Cellulitis: 26 Bacterial enteritis: 11	99.8 [98.6, 99.9]	NR	NR	NR	NR
YIOS score ≥ 7 (affect, respiratory status/effort, peripheral perfusion)							
Bonadio (1993)[21] [13]	242/233 0–29 d	Total: 29 (12.4) Meningitis: 10 Bacteremia: 12 UTI: 7	76.0 [56.0, 88.9]	81.9 [75.7, 86.7]	37.3 [25.3, 50.8]	96.0 [91.6, 98.2]	ROC given

Table 2. Test results – Combined clinical & laboratory criteria I (Boston criteria, Milwaukee protocol, Philadelphia protocol, Rochester criteria, and Yale observation score) (continued)

Study ID QUADAS Total Score	N/n* Age Range	N (%) with SBI	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]	Other
		Yale Observation Scale (YOS) > 10					
Baker (1990)[64] [8]	126/126 29–56 d	Total: 12 (9.5%) UTI: 5 Bacterial sepsis: 4 Other: 3	33.3 [11.3, 64.5]	72.8 [63.5, 80.5]	11.4 [3.7, 27.6]	91.2 [82.9, 95.8]	LR+= 1.22 LR-= 0.91
		Bacterial sepsis: 4	75.0 [21.9, 98.6]	73.7 [64.8, 81.1]	8.5 [2.2, 24.1]	98.9 [93.1, 99.9]	LR+= 2.85 LR-= 0.33
Zorc (2005)[65]	1,513/995 1–60 d	Total: 91 (9.0%) UTI	4.4 [1.4, 11.5]	92.6 [90.6, 94.1]	5.6 [1.8, 14.5]	90.5 [88.5, 92.3]	LR+=0.60 LR-= 1.03

d=day(s); LR=likelihood ratio; NPV= negative predictive value; NR=not reported; PPV= positive predictive value; SBI=serious bacterial infection; UTI=urinary tract infection; YIOS=Young Infant Observation scale

‡ Values based on Philadelphia protocol + no immunodeficiency syndrome, band-to-neutrophil ratio < 0.2

* N/n: number of infants enrolled/ number of infants with culture and test results

† The Rochester Criteria does not require cerebrospinal fluid (CSF) testing through lumbar puncture (LP)

Combined clinical and laboratory criteria (other). The data on the diagnostic accuracy of different combinations of clinical (e.g., clinical/good/toxic/ill appearance, impression of sepsis, age, rectal temperature, unremarkable medical history) and laboratory features such as serum and urine WBC (with different thresholds), ABC ≥ 5,000/μL, ESR < 30 (or 20) mm/h, C-reactive protein (CRP) < 20 mg/L, or urine dipstick result (leukocyturia and/or nitrituria) were reported for 16 studies (Table 3).[5,28-34,37,49,66-68,70,82,85]

Total serious bacterial infection. Criteria that combined infant appearance (e.g., well, ill, good) with various laboratory features (e.g., WBC: 5,000–15,000/mm^3, ESR < 30 mm/h, CRP < 20 mg/L, UA-WBC < 10/hpf, ABC ≤ 1,500/mm^3, CSF-WBC < 23/hpf, and/or urine dipstick test for the presence of leukocyturia/ nitrituria), reported across 6 studies,[28-30,37,66,67] were able to rule out the presence of total SBI with sensitivity ranging from 68.3 percent[28] to 99.1 percent.[29] The same criteria yielded specificity values ranging from 37.6 percent[28] to 60.3 percent.[66] The NPVs for these criteria ranged from 90.0 percent[28] to 99.4 percent.[29,30] The combination of clinical appearance and laboratory values (WBC: 5,000-15,000/mm^3, 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).[29]

Criteria that combined infant age (< 13 days) and rectal temperature of 39.6°C with WBC < 4,100/mm^3 or WBC > 20,000/mm^3 and test positive for LE or nitrate demonstrated similar accuracy (sensitivity: 82.0 percent, specificity: 76.0 percent, and NPV=98.3 percent)[49] to criteria that combined infant sex (male) with spun urine WBC count ≥ 10/hpf and CRP ≥3.6 mg/L (sensitivity: 78.0 percent, specificity: 78.0 percent, NPV=not available).[82] One of these criteria misclassified one case of bacterial meningitis into low risk.[49]

Criteria consisting of the lack of mild upper respiratory tract infection symptoms (URI) and no URI symptoms in the patient's sibling combined with CRP ≥ 1.87 mg/dL yielded relatively lower sensitivity (61.0 percent) but higher specificity (90.0 percent) in correctly identifying the absence or presence of SBI.[68]

Specific types of serious bacterial infection. Criteria that combined clinical impression of sepsis/toxic appearance with one or more laboratory features (e.g., WBC ≥ 15,000/mm^3, ABC ≥ 5,000/μL, ESR ≥ 30 mm/h, CRP positive) reported in 3 studies ruled out the presence of sepsis/meningitis[31] or bacteremia[32,33] with sensitivity of 100.0 percent and specificity ranging from 17.0 percent[33] to 75.0 percent.[31] The NPV reported in these studies was 100.0 percent. The ill appearance combined with WBC ≥ 15,000/mm^3 reported in two studies demonstrated lower sensitivity for identifying bacteremia (75.0 percent in infants aged 1-2 months and 28.5 percent in neonates 30 days or younger)[34] or bacteremia/meningitis (83.9 percent; infants aged 0-3 months).[5] In one of these studies,[5] age ≤ 30 days, very ill appearance, and abnormal WBC count (WBC ≥ 15,000/mm^3 or WBC < 5,000/mm^3) were the strongest predictors of bacteremia/meningitis (p = 0.001) in a logistic regression model. This model had the AUC of 80.0 percent, which was an increase from the AUC of 76.0 percent after the addition of abnormal WBC count (≥ 15,000/mm^3 or < 5,000/mm^3) as a dichotomized variable.[5]

In one study,[66] the criteria that combined infant appearance (no findings consistent with soft tissue, skeletal, ear, or eye infection) and laboratory values (UA-WBC: < 10/hpf, WBC: 5,000-15,000/mm3, CRP < 20 mg/L, and ABC ≤ 1,500/mm3) showed a higher sensitivity for correctly identifying infants with bacteremia/meningitis (92.3 percent, 95 percent CI: 62.0, 99.6) than for total SBI (82.2 percent, 95 percent CI: 67.4, 91.5). In this study, there were 13 cases of bacteremia/meningitis one of which was misclassified as low risk for SBI. Another study,[70] using similar criteria reported to have misclassified one infant who was later hospitalized with

diagnosis of Neisseria meningitidis. This study included 86 infants younger than 2 months of age who were classified as low risk for SBI. The total number of infants with SBI or Neisseria meningitidis could not be ascertained.

Table 3. Test results –combined clinical & laboratory criteria II (Other combinations)

Criteria	Study ID QUADAS total score	N/n* Age range	N (%) with SBI	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]	Other
Clinical Impression of Sepsis/ Appearance of Infant + Laboratory Markers								
Toxic appearance (↑ irritability, ↓ eye contact, unwillingness to feed, and the state of alertness) and ABC ≥ 5,000 /µL	Broner (1990)[32] [9]	NR/52 4–56 d	Total: 5 (9.6) (bacteremia)	100.0 [46.3, 100.0]	49.0 [34.3, 63.7]	17.2 [6.5, 36.5]	100.0 [82.2, 100.0]	LR+=1.95 LR-= 0
Toxic appearance and CRP positive				*100.0 [46.3, 100.0]*	48.0 [32.4, 61.7]	16.6 [6.3, 35.4]	100.0 [81.5, 100.0]	LR+=1.88 LR-= 0
Toxic appearance and ABC ≥ 5,000 ABC/µL and WBC ≥ 15,000 /µL				100.0 [46.3, 100.0]	49.0 [34.3, 63.7]	17.2 [6.5, 36.5]	100.0 [81.5, 100.0]	LR$^+$=1.96 LR$^-$=0
Ill appearance WBC ≥ 15,000/mm^3	Caspe (1983)[34] [11]	305/1070 0–30 d	Total: 7 (6.5) (bacteremia)	28.5 [5.1, 69.7]	NR	NR	NR	NR
		305/198 30–60 d	Total: 4 (2.0) (bacteremia)	75.0 [21.9, 98.6]	95.8 [91.7, 98.0]	27.3 [7.3, 60.6]	99.4 [96.6, 99.9]	LR$^+$=18.1 LR$^-$=0.26
No findings consistent with soft tissue, skeletal, ear, eye, or umbilical infection and UA: WBC < 10 /hpf, ESR < 30 mm/h, CRP < 20 mg/L, WBC: 5,000-15,000/mm^3, 1,500 band forms/ mm^3	Chiu (1994)[66] [9]	254/254 4–31 d	Total: 45 (17.7) UTI: 16 Bacteremia/men ingitis: 13 Enterocolitis: 2 Abscess: 2 Peritonitis: 1 Omphalitis: 10 Pustulosis: 1 Purulent conjunctivitis: 1	60.3 [53.3, 66.9]	82.2 [67.4, 91.5]	30.8 [22.9, 40.0]	94.0 [88.2, 97.2]	LR$^+$= 2.07 LR$^-$= 0.29
			Bacteremia/men ingitis: 13	55.2 [48.6, 61.5]	92.3 [62.0, 99.6]	10.0 [5.5, 17.1]	99.2 [95.3, 99.9]	LR$^+$= 2.06 LR$^-$= 0.13

Table 3. Test results –combined clinical & laboratory criteria II (Other combinations) (continued)

Criteria	Study ID QUADAS total score	N/n* Age range	N (%) with SBI	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]	Other
Clinical Impression of Sepsis/ Appearance of Infant + Laboratory Markers								
Low risk: -ve or ambivalent impression of sepsis and both WBC < 15,000/mm^3 and ESR < 30 mm/h High risk: 1) strong, or ambivalent *impression* of sepsis with either WBC ≥ 15,000 /mm^3, or ESR ≥ 30 mm/h, or 2) -ve impression of sepsis and both WBC and ESR criteria	Crain (1988)[31] [9]	46/35 0–15 d	Total: 3 (8.5) Sepsis/meningitis	100.0 [31.0, 100.0]	75.0 [56.2, 87.9]	27.3 [7.3, 60.7]	100.0 [82.8, 100.0]	LR$^+$=4.0 LR$^-$=0
Clinical impression of sepsis [-ve] (infant's level of activity, irritability, responsiveness, ability to be consoled, feeding pattern) and WBC ≥ 15,000/mm^3 + ESR ≥ 30 mm/h	Crain (1982)[33] [11]	134/134 0–60 d	Total: 5 (3.7) (bacteremia)	100.0 [46.3, 100.0]	17.0 [11.2, 24.9]	4.5 [1.6, 10.6]	100.0 [81.5, 100.0]	LR$^+$=1.20 LR$^-$= 0
Clinical impression of sepsis [strong or ambivalent] and WBC ≥ 15,000/mm^3 or ESR ≥ 30 mm/h				100.0 [46.3, 100.0]	17.0 [11.2, 24.9]	4.5 [1.6, 10.6]	100.0 [81.5, 100.0]	LR$^+$=1.20 LR$^-$=0
Impression of sepsis + either WBC > 15,000 /mm^3 or ESR > 30 mm/h, or both; or –ve impression of sepsis + both WBC > 15,000 /mm^3 and ESR > 30 mm/h	Crain (1990)[85] [12]	442/442 8–57d	Total: 33 (7.4) (UTI)	46.0 [31.1, 66.1]	98.0 [95.7, 98.9]	64.0 [42.6, 81.3]	95.9 [93.4, 97.5]	LR$^+$=22.0 LR$^-$=0.52
General appearance (well appearing versus not well appearing) and Urine - UA: dipstick (LE$^+$, nitrite, $^+$ or both versus normal)	Gomez (2010)[30] [9]	1,125/ 1,018 0–90 d	Total: 23 (2.2) Bacteremia: 9 UTI/bacteremia: 8 Meningitis: 4 Sepsis: 2	87.0 [67.9, 95.5]	NR/NC	NR/NC	99.4 [98.2, 99.8]	NR/NC

Table 3. Test results –combined clinical & laboratory criteria II (Other combinations) (continued)

Criteria	Study ID QUADAS total score	N/n* Age range	N (%) with SBI	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]	Other
			Clinical Impression of Sepsis/ Appearance of Infant + Laboratory Markers					
Well appearance without focal infection, full term, no underlying illness, no previous hospitalization, no perinatal antibiotics (if < 14 days old), no sibling with group GBS disease; WBC: 5,000-15,000/ mm^3, ABC ≤ 1,500/mm^3, enhanced UA (WBC ≤ 9 mm^3; -ve Gram stain), CSF WBC ≤ 5/mm^3 and –ve Gram stain	Herr (2001)[28] [13]	434/344 < 59 d	SBI: 41 (12.0) UTI: 25 Pneumonia: 8 Bacteremia: 3 Meningitis: 2 Gastroenteritis: 1 Chlamydia: 1	68.3 [51.7, 81.4]	37.6 [32.2, 43.3]	12.9 [8.8, 18.2]	89.7 [82.8, 94.2]	LR+=1.09 LR-=0.84
		434/42 0–14 d	SBI: 3 (7.1)	100.0 [31.0, 100.0]	28.2 [15.5, 45.1]	9.6 [2.5, 26.9]	100.0 [67.8, 100.0]	LR$^+$=1.39 LR$^-$=0
		434/104 15–28 d	SBI: 9 (8.6)	100.0 [62.8, 100.0]	26.3 [18.0, 36.5]	11.3 [5.6, 21.0]	100.0 [83.0, 100.0]	LR$^+$=1.35 LR$^-$=0
		434/138 29–45 d	SBI: 19 (13.7)	100.0 [79.0, 100.0]	39.5 [30.7, 48.9]	20.8 [13.3, 30.9]	100.0 [90.5, 100.0]	LR$^+$=1.65 LR$^-$=0
		434/113 46–59 d	SBI: 10 (8.7)	100.0 [65.5, 100.0]	35.9 [26.8, 46.0]	13.1 [6.8, 23.3]	100.0 [88.2, 100.0]	LR$^+$=1.56 LR$^-$=0
Unremarkable medical history, good appearance, no focal/physical signs of infection + ESR < 30 mm/h, WBC 5,000-15,000/mm^3, normal UA (dipstick: LE, nitrites)	Marom (2007)[29] [10]	449/386 0–90 d	Total: 108 (28.0) UTI: 54 Acute OM: 13 Gastroenteritis: 2 Meningitis: 2 Others: NR	99.1 [94.2, 99.9]	59.3 [53.3, 65.1]	48.6 [41.8, 55.4]	99.4 [99.3, 99.5]	LR$^+$=2.43 LR$^-$=0.01
Previously healthy infants without physical finding of OM, skin or musculoskeletal infection + WBC: 5,000-15,000/mm^3, ABC ≤ 1,500/mm^3, UA- WBC ≤ 10/hpf, and stool- WBC ≤ 5 /hpf (in infants with diarrhea)	McCarthy (1990)[70] [5]	86/NR 0–60 d	SBI: 1 (NR) (data given only on 1 infant with SBI out of 86 infants classified as 'low risk')	NR	NR	NR	98.8 [92.7, 99.9]	NR
Clinical appearance; WBC < 5,000/ mm^3 or WBC >15,000/mm^3	Pantell (2004)[5] [10]	3,066/ 1,746 0–90d	Total: 63 (3.6) (Bacteremia/bacterial meningitis	83.9 [NC]	54.0 [NC]	NR	NR	LR$^+$=1.82 LR$^-$=0.29

Table 3. Test results –combined clinical & laboratory criteria II (Other combinations) (continued)

Criteria	Study ID QUADAS total score	N/n* Age range	N (%) with SBI	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]	Other
Clinical Impression of Sepsis/ Appearance of Infant + Laboratory Markers								
Clinical appearance; WBC < 5,000/mm^3 or WBC >15,000/mm^3; UA- WBC ≥ 5/hpf		3,066/ 1,746 0–90d	Total: 63 (3.6) (Bacteremia/bac terial meningitis)	87.1 [NC]	50.7 [NC]	NR	NR	LR$^+$=1.75 LR$^-$=0.25
Not ill appearing + WBC 5000–15,000/mm^3; absence of LE in noncentrifuged urine on dipstick test CSF-WBC < 23 /hpf	Schwartz (2009)[37] [9]	449/449 0–28 d	SBI: 87 (19.4)	83.9 [75.6, 90.0]	58.6 [56.6, 60.0]	32.7 [29.5, 35.1]	93.8 [90.6, 96.1]	LR$^+$= 2.02 LR$^-$=0.27
Low risk: not ill appearing, no bacterial illness + benign laboratory screening findings (undefined)	Wasserman (1990)[67] [14]	NR/443 < 90 d	Total: 53 (12.0) Bacteremia: 8 Meningitis: NR Soft tissue infection: NR UTI: NR Enteritis: NR	90.5 [78.6, 96.5]	55.4 [50.3, 60.3]	21.6 [16.5, 27.7]	97.7 [94.5, 99.1]	LR$^+$=2.10 LR$^-$=0.17

Table 3. Test results –combined clinical & laboratory criteria II (Other combinations) (continued)

Criteria	Study ID QUADAS total score	N/n* Age range	N (%) with SBI	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]	Other
			Other Clinical Criteria + Laboratory Markers					
Age < 13 d; T > 39.6°C UA (LE+ or nitrite+) WBC < 4,100/mm^3, > 20,000/mm^3	Bachur (2001)[49] [12]	5,279/ 5,279 0–90 d	Total: 373 (7.0) UTI: 297 Meningitis: 17 Bacteremia: 40 Bacteremia/ meningitis: 8 Bacteremia/UTI: 11	82.0 [78.0, 86.0]	76.0 [75.0, 77.0]	21.0 [19.0, 23.0]	98.3 [97.8, 98.7]	LR+=3.48 LR-=0.23
			Bacteremia or meningitis: 48	NR	NR	NR	99.6 [99.4, 99.8]	LR+=2.36 LR-= 0.48
Sex of infant (male) spun urine + WBC ≥ 10/hpf, and CRP ≥ 3.6 mg/L (probability > 0.265 based on logistic regression model)	Chen (2009) [82] [6]	135/135 0–90 d	Total: 34 (25.2)	77.8 [NR]	77.8 [NR]	NR	NR	NR
Lack of mild upper respiratory tract infection symptoms, and no upper respiratory tract infection symptoms in the patient's siblings + CRP ≥ 1.87 mg/dL,	Shin (2009) [68] [7]	NR/211 0–90 d	Total: 51 (23.0) UTI: 28 Bacteremia: 6 Meningitis: 4 UTI/ bacteremia: 3 Other: 10	61.0 [NR]	90.0 [NR]	60.0 [NR]	91.0 [NR]	NR
Lack of mild upper respiratory tract infection symptoms+ CRP ≥ 1.87 mg/dL		NR/183 (excludin g 28 infants with UTI) 0–90 d	Total: 23 (10.4) Bacteremia: 6 Meningitis: 4 UTI/bacteremia: 3 Miscellaneous: 10	38.5 [NR]	93.5 [NR]	31.3 [NR]	95.2 [NR]	NR

ABC = absolute band count; CRP = C-reactive protein; CSF = cerebrospinal fluid; d = day(s); ESR = erythrocyte sedimentation rate; GBS = group B streptococcal disease; h = hour; LE = leukocyte esterase; LR = likelihood ratio; NC = not calculable; NPV = negative predictive value; NR = not reported; OM = otitis media; PPV = positive predictive value; T = temperature; UA = urinalysis; UTI = urinary tract infection; WBC = white blood cell count; ↑ = increased; ↓ = decreased; -ve = negative;
* N/n: number of infants enrolled/number of infants with test and culture results

Clinical criteria alone. The use and performance characteristics of clinical criteria for predicting the risk of SBI in febrile infants was reported in and/or ascertained from 15 studies (Table 4).[5,30,32-42,71,110]

Total serious bacterial infection. Criteria based on clinical history, namely 'no history of recent immunization'(inactivated polio virus, hepatitis B, Haemophilus influenzae B, diphtheria-tetanus-acellular pertussis, pneumococcal conjugate, and rotavirus vaccines)[41] or rapid influenza test-negative result[42] demonstrated higher sensitivity (range: 94.0 percent–95.4 percent) but lower specificity (11.3 percent–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-26.1 percent, range of specificity: 90.5 percent–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 association between grunting respiration and the presence of SBI was assessed in one observational study,[110] in which 40 cases (infants with grunting) and 40 controls (infants with no grunting) admitted to a hospital were matched on age, day of hospitalization, and fever. The association between grunting and SBI was not significant with 3 infants with SBI in the case group versus two infants with SBI in the control group (7.5 percent vs. 5.0 percent; OR=1.54, 95 percent CI: 0.19, 14.1).

Specific types of serious bacterial infection. Criteria based on clinical appearance (ill, toxic, impression of sepsis) alone[32-34,39,40] was available for identifying bacteremia which tended to yield higher sensitivity (range: 80.0 percent-100.0 percent) and lower specificity (40.0 percent–80.0 percent) than criteria based on the degree of fever > 40°C (range of sensitivity: 5.1 percent-12.5 percent, range of specificity: 96.1 percent– 98.3 percent).[35,36] The use of rectal temperature ≥ 40°C criterion was reported to have missed one of six cases of infants with bacterial meningitis.[36]

Table 4. Test results – Clinical criteria alone

Criteria	Study ID	N/n* Age range	N (%) with SBI	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV % [95% CI]	Other
Appearance at Presentation								
Ill appearance	Bonadio (1994)[38] [9]	367/356 60–90 d	Total: 33 (9.3) UTI: 17 Meningitis: 5 Bacteremia: 8 Salmonella: 3	33.3 [18.5, 51.9]	NR	NR	NR	NR
			Bacteremia: 8 (2.2)	37.5 [10.2, 74.1]	NR	NR	NR	NR
			UTI: 17 (4.7)	17.6 [4.6, 44.2]	NR	NR	NR	NR
			Salmonella: 3 (0.8)	0.0 [NA]	NR	NR	NR	NR
			Meningitis: 5 (1.4)	100.0 [46.3,100.0]	NR	NR	NR	NR
Toxic appearance (i.e., increased irritability, decreased eye contact, unwillingness to feed, and the state of alertness)	Broner (1990)[32] [9]	NR/52 4–56 d	Total: 5 (9.6) (bacteremia)	80.0 [29.8, 98.9]	80.0 [66.2, 90.3]	30.7 [10.3, 61.1]	97.4 [84.5, 99.8]	LR+=4.17 LR-=0.24
Ill appearance (inconsolable when held or fed or unresponsive to their environment)	Caspe (1983)[34] [11]	305/305 0–90 d	Total: 11 (3.6) (bacteremia)	91.0 [57.1, 99.5]	56.6 [49.3, 63.5]	10.4 [5.4, 18.7]	99.1 [94.4, 99.9]	LR+=2.10 LR-=0.16
		305/107 0–30 d	Total: 7 (6.5) (bacteremia)	85.7 [42.0, 99.2]	73.2 [63.4, 81.3]	18.2 [76.1, 36.0]	98.6 [91.8, 99.9]	LR+=3.20 LR-=0.19
		305/198 30–60 d	Total: 4 (2.0) (bacteremia)	100.0 [39.6,100.0]	69.6 [62.5, 75.9]	6.3 [2.0, 16.2]	100.0 [96.5, 100.0]	LR+=3.28 LR-=0
		305/305 0–90 d	UTI 7 (2.3)	42.8 [11.8, 79.8]	NR	NR	NR	NR

Table 4. Test results – Clinical criteria alone (continued)

Criteria	Study ID	N/n* Age range	N (%) with SBI	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV % [95% CI]	Other
			Appearance at Presentation					
Ill appearance (at least one of the following: tachypnea, dyspnea, tachycardia, bradycardia, decrease of activity, lethargy, and decrease of appetite)	Chen (2008)[71]	44/NR 0–90 d	Total: 23 (NR) UTI: 17 Bacteremia: 2 Meningitis: 2 Other: 2 (data given only on 23 infants with SBI out of 44 infants classified as 'high risk')	NR	NR	52.3 [36.8, 67.3]	NR	NR
Clinical impression of sepsis (infant's level of activity, irritability, responsiveness, ability to be consoled, feeding pattern)	Crain (1982)[33] [9]	134/134 0–60 d	Total: 5 (3.7) (bacteremia)	100.0 [46.3,100.0]	58.1 [49.1, 66.6]	8.5 [3.1, 19.4]	100.0 [93.9, 100.0]	LR+=2.38 LR-=0
Ill appearing (based on appearance, respiratory, and circulatory functioning)	Gomez (2010)[30] [9]	1,125/ 1,018 0–90 d	Total: 198 (19.4) UTI: 172 Bacteremia: 9 UTI/bacteremia: 8 Meningitis: 4 Sepsis: 2 Cellulitis: 2 Otitis media: 1	NR/NC	NR/NC	NR/NC	NR/NC	NR/NC
Not well appearing (based on appearance, respiratory, and circulatory functioning) versus well- appearing			Total: 23 (2.2) Bacteremia: 9 UTI/bacteremia: 8 Meningitis: 4 Sepsis: 2	26.1 [11.3, 47.2]	95.8 [95.4, 96.3]	12.5 [5.4, 22.6]	98.2 [97.9, 98.7]	LR+=6.18 LR-=0.77
Septic appearance (yes, no, unsure) based on physical examination, complete history, initial laboratory results	King (1987)b[39] [6]	NR/97 < 60 d	Total: 4 (5.4) Bacteremia or meningitis	100.0 [39.6,100.0]	66.0 [54.9, 74.9]	11.1 [3.6, 27.0]	100.0 [92.6, 100.0]	LR+=2.90 LR-=0

Table 4. Test results – Clinical criteria alone (continued)

Criteria	Study ID	N/n* Age range	N (%) with SBI	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV % [95% CI]	Other
Appearance at Presentation								
Clinical appearance (well or minimally ill)	Pantell (2004)[5] [10]	3,066/ 3,066 0–90d	Total: 63 (3.6) (Bacteremia/bacterial meningitis)	58.1 [NC]	68.1 [NC]	NR	NR	LR+=1.82 LR-=0.61
Clinical impression of sepsis (irritable, toxic, lethargic)	Rosenberg (1985)[40] [6]	122/122 0–60 d	Total: 5 (4.0) (bacteremia)	80.0 [29.9, 98.9]	37.5 [28.7, 47.2]	5.4 [1.7, 13.9]	97.6 [86.2, 99.8]	LR+=1.28 LR-=0.53
Not ill appearing	Shwartz (2008)[37] [9]	644/449 0–28 d	Total: 87 (19.4) Bacteremia + meningitis + UTI: 2 Bacteremia + meningitis: 1 Bacteremia + UTI: 10 UTI: 70 Pneumonia: 2 Omphalitis: 1	21.0 [NR]	NR	NR	82.5 [78.5, 86.0]	NR
Age/ Gender of Infant Alone or in Combination with Other Clinical Criteria								
Age ≤ 30 days versus > 30 days	Gomez (2010)[30] [9]	1,125/ 1,018 0–90 d	Total: 23 (2.2) Bacteremia: 9 UTI/bacteremia: 8 Meningitis: 4 Sepsis: 2	34.8 [17.3, 56.9]	76.4 [76.0, 76.9]	3.3 [1.6, 5.4]	98.1 [97.5, 98.7]	LR+=1.47 LR-=0.85
Gender (male versus female)		1,125/ 1,018 0–90 d	Total: 23 (2.2) Bacteremia: 9 UTI/bacteremia: 8 Meningitis: 4 Sepsis: 2	73.9 [51.6, 88.9]	42.9 [42.4, 43.3]	2.9 [2.0, 3.5]	98.6 [97.4, 99.4]	LR+=1.29 LR-=0.60

Table 4. Test results – Clinical criteria alone (continued)

Criteria	Study ID	N/n* Age range	N (%) with SBI	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV % [95% CI]	Other
Age/ Gender of Infant Alone or in Combination with Other Clinical Criteria								
High risk: age < 30 d and ill-appearing Low risk: age > 30 d and well-appearing	Pantell (2004)[5] [10]	3,066/ 1,746 0–90d	Total: 63 (3.6) (Bacteremia/bacterial meningitis)	95.2 [NC]	35.49 [NC]	NR	NR	LR+=1.47 LR-=0.13
Well or minimally ill appearance, Temperature < 38.6°C, age < 25 d		3,066/ 3,066 0–90 d		93.6 [NC]	27.3 [NC]	NR	NR	LR+=1.28 LR-=0.23
Well or minimally ill appearance, Temperature < 38.6°C, age ≥ 25 d		3,066/ 3,066 0–90 d	Total: 14 (0.7) (Bacteremia/bacterial meningitis)	71.4 [42.0, 90.4]	56.8 [54.5, 59.1]	1.2 [0.6, 2.4]	99.6 [98.9, 99.8]	LR+=1.65 LR-=0.50

Table 4. Test results – Clinical criteria alone (continued)

Criteria	Study ID	N/n* Age range	N (%) with SBI	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV % [95% CI]	Other
			Fever Temperature					
Temperature > 40.0°C	Bonadio (1991)[36] [12]	683/683 30–60 d	Total: 34 (5.0) Meningitis: 6 Bacteremia: 8 UTI: 16 Enteritis: 4	21.0 [9.3, 38.4]	97.0 [95.2, 98.0]	26.0 [11.8, 46.6]	95.8 [94.0, 97.2]	LR+=6.68 LR-=0.81
			Bacteremia: 8	12.5 [0.6, 53.3]	96.1 [94.3, 97.4]	3.7 [0.2, 20.8]	98.9 [97.7, 99.5]	LR+=3.24 LR-=0.91
			Meningitis: 6	33.3 [5.9, 75.9]	96.3 [94.5, 97.5]	7.4 [1.3, 25.7]	99.4 [98.3, 99.8]	LR+=9.02 LR-=0.69
	Stanley (2005)[35] [13]	5,279/ 5,279 0–90 d	Total: 480 (9.1) UTI: 305 Meningitis: 10 Bacteremia: 39 Bacteremia/meningitis: 8 Bacteremia/UTI: 11 Pneumonia: 70 Cellulitis: 26 Bacterial enteritis: 11	7.3† [5.2, 10.1]	98.8 [98.4, 99.1]	38.0 [28.3, 48.8]	91.4 [90.6, 92.1]	LR+=6.13 LR-=0.93
			Bacteremia: 39	5.1 [0.9, 18.6]	98.3 [97.8, 98.6]	2.1 [0.3, 8.3]	99.3 [99.0, 99.5]	LR+=2.98 LR-=0.96
			Bacteremia/meningitis: 8	25.0 [4.4, 64.4]	98.3 [97.8, 98.6]	2.2 [0.4, 8.4]	99.8 [91.6, 99.6]	LR+=0 LR-=0.76
			Meningitis: 10	0 [0, 34.4]	98.2 [97.8, 98.6]	0 [0, 5.0]	99.8 [99.6, 99.9]	LR+=14.6 LR-=1.01
Temperature ≥ 39.5°C versus 38°C–39.4°C	Gomez (2010)[30] [9]	1,125/1018 0–90 d	Total: 23 (2.2) Bacteremia: 9 UTI/bacteremia: 8 Meningitis: 4 Sepsis: 2	26.1 [11.2, 48.0]	90.5 [90.2, 91.0]	6.1 [2.6, 11.3]	98.1 [97.7, 98.7]	LR+=2.75 LR-=0.81

Table 4. Test results – Clinical criteria alone (continued)

Criteria	Study ID	N/n* Age range	N (%) with SBI	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV % [95% CI]	Other
Clinical History								
Not previously healthy versus previously healthy	Gomez (2010)[30]	1,125/ 1,018 0–90 d	Total: 23 (2.2) Bacteremia: 9 UTI/bacteremia: 8 Meningitis: 4 Sepsis: 2	21.7 [8.4, 43.6]	88.5 [88.2, 89.0]	4.2 [1.6, 8.4]	98.0 [97.7, 98.6]	LR+=1.89 LR-=0.88
Rapid influenza test (negative versus positive)	Mintegi (2009)[41] [3]	520/381 0–90 d	Total: 50 (13.1) UTI: 34 Bacteremia: 8 Meningitis: 5 Other: 3	94.0 [83.1, 98.4]	33.2 [31.6, 33.9]	17.5 [15.5, 18.4]	97.3 [92.5, 99.3]	LR+=1.4 LR-=0.18
No history of recent immunization (72 hrs preceding the ED visit)£	Wolff (2009) [42] [10]	2,247/1,978 45–90 d	Total: 130 (6.6) UTI: 105 Bacteremia: 11 Bacteremia/UTI: 4 Meningitis: 3 Pneumonia: 7	95.4µ [90.0, 98.1]	11.3 [10.9, 11.5]	7.1 [6.7, 7.3]	97.2 [93.8, 98.8]	LR+=1.07 LR-=0.4

d = day(s); hpf = high-power field; LR = likelihood ratio; NC = not calculable; NPV = negative predictive value; NR = not reported; PPV = positive predictive value; T = temperature; UTI = urinary tract infection

*N/n: number of infants enrolled/ number of infants with test and culture results

£ Inactivated polio virus, hepatitis B, Haemophilus Influenzae B, diphtheria-tetanus-acellular pertussis, pneumococcal conjugate, rotavirus, and Pediarix (pentavalent vaccine) vaccines; µ 28 cases of possible SBI were excluded from the calculations of the test accuracy indices

Laboratory criteria alone. The use and performance characteristics of laboratory thresholds for predicting the risk of SBI or bacteremia in febrile infants was reported in and/or ascertained from the reports of 27 studies (Table 5).[5,13,30,32-34,37,39,40,43-50,52-54,61,63,69,91,109,111,112]

A wide variety of laboratory variables and thresholds were applied alone or combination across the reviewed studies. Some of the examples are UA (microscopy, dipstick),[5,13,30,30,49,50,52-54] WBC,[32,34,39,40,43-47,53,109,111,112] ESR,[33,39,53] ABC,[32,44,109,112] and procalcitonin (PCT).[48,61,104]
Blood cell count (WBC; ABC; ANC) Across and within studies, the sensitivity for identifying total SBI tended to decrease (16.0 percent-100.0 percent) and the corresponding specificity increase (31.0 percent–95.2 percent) with higher thresholds of WBC ($\geq$8,000/mm3 to $\geq$20,000/mm).[43-46] Similar pattern of trade off between sensitivity and specificity was observed for absolute neutrophil count thresholds (>4,650/μL to >12,500/μL),[45] and ABC thresholds (>250/mm3 to >3,000/mm3).[44]

Two studies calculating the AUCs,[43,47] demonstrated numerically better overall accuracy of ANC compared to WBC in correctly classifying infants with and without total SBI. In the first study,[47] the areas under ROC for ANC and WBC were 0.78 (95 percent CI: 0.69, 0.86) and 0.59 (95 percent CI 0.49, 0.69), respectively. In the second study,[43] corresponding AUCs for ANC and WBC were 0.77 (95 percent CI: 0.67, 0.78) and 0.69 (95 percent CI: 0.61, 0.73), respectively. Similarly, in one study,[44] the AUC for ABC was greater than that for WBC (81.0 percent versus 61.0 percent).

In three studies,[30,46,48] the value of blood CRP levels (C-reactive protein) was shown to be greater than those of WBC, ANC, and PCT levels in predicting risk of SBI (AUC-CRP: 74.0 percent-84.0 percent vs. AUC-WBC: 68.0 percent-70.0 percent vs. AUC-ANC: 71.1 percent vs. AUC-PCT: 77.0 percent).

One study concluded that laboratory markers are more accurate and reliable predictors of SBI when performed after 12 hours of initiation of fever.[47]
Erythrocyte sedimentation rate (ESR). All three studies,[33,39,53] that tested criterion of ESR > 30 mm/h demonstrated high values of specificity (range: 75.7 percent - 93.6 percent) for bacteremia or UTI. The sensitivity values for bacteremia (or meningitis) differed in two studies: 80.0 percent[33] and 25.0 percent.[39] In the third study, ESR > 30 mm/h predicted the risk of UTI with sensitivity of 73.0 percent (95 percent CI: 50.0, 88.4).[53]
C-reactive protein (CRP). In one study,[46] the predictive ability of blood CRP levels (> 2 mg/dL, > 4 mg/dL, > 8 mg/dL) was shown to be better than WBC levels (> 15 K/μL, > 20 K/μL, > 15 or < 5 K/ μL) in terms of sensitivity, specificity, and the values of likelihood ratio. The areas under the ROC curve (AUC) for CRP and WBC in predicting SBI were 74.0 percent (95 percent CI: 67.0 percent, 80.0 percent) and 70.0 percent (95 percent CI: 64.0 percent, 76.0 percent), respectively. In one study,[30] the use of CRP (at 70 g/L) resulted in higher sensitivity and specificity (69.6 percent and 93.8 percent, respectively) for predicting bacteremia compared to urine dipstick (43.5 percent and 82.8 percent, respectively) in 1,018 febrile infants ($\geq$ 38.0°C) aged 3 months or younger. Likewise, the AUC for CRP (84.7 percent) was significantly greater than AUCs for WBC (67.9 percent) and absolute neutrophil count (ANC; 71.1 percent).[30] In one study,[47] CRP (> 20 mg/L) was used to predict SBI in 99 febrile neonates (7–28 days) at admission (duration of fever < 12 hours). Serious bacterial infection (UTI, bacteremia, meningitis, pneumonia, cellulitis, osteomyelitis, septic arthritis) was found in 25 (25.3 percent) of the neonates. The area under ROC for CRP was 0.77 (95 percent CI: 0.67, 0.85).
Procalcitonin (PCT). In a study by Maniaci (2008),[61,104] the performance of procalcitonin (PCT) for identifying SBI (bacteremia, UTI, meningitis, pneumonia, bacterial GI) or possible SBI (UTI

with urine culture of 10,000 to 49,000, or bacterial pneumonia as a chest radiograph interpreted by an attending radiologist) for febrile infants ≤ 3 months of age was examined. Overall, 30/234 (12.8 percent), and 12 /234 (5.12 percent) of infants were identified with definite SBI and possible SBI, respectively. At a cut off value of 0.13 ng/mL, procalcitonin had a sensitivity of 96.7 percent (95 percent CI: 81.0 percent–99.8 percent), specificity of 30.3 percent (95 percent CI: 24.0, 37.5), and NPV of 98.3 percent (95 percent CI: 89.7, 99.9). In discriminating definite plus possible SBIs and no SBI, a cutoff value of 0.12 ng/mL yielded a sensitivity of 95.2 percent (95 percent CI: 83.0, 99.0), specificity of 25.5 percent (95 percent CI: 20.0, 32.0), and NPV of 96.1 percent (95 percent CI: 85.4, 99.3).

A recent study,[48] compared the ability of C-reactive protein, and procalcitonin (PCT) to predict SBI in 347 febrile infants younger than 3 months of age. Serious bacterial infection (bacteremia; meningitis; sepsis such as hemodynamic instability, tissue perfusion; UTI; pneumonia by chest x ray; gastroenteritis; cellulitis) was diagnosed in 82 (23.6 percent) of infants (65 UTI, 4 UTI + bacteremia, 5 bacteremia, 2 cellulitis, 4 sepsis, 1 acute bacterial gastroenteritis, and 1 pneumonia). In this study, the area under the ROC curve (AUC) for PCT was 0.77 (95 percent CI: 0.72, 0.81) and for CRP it was 0.79 (95 percent CI: 0.75, 0.84). In 15 infants with more invasive infection (sepsis, bacteremia, bacterial meningitis), the diagnostic value of PCT (AUC 0.84, 95 percent CI: 0.79, 0.88) was higher than CRP (AUC 0.68, 95 percent CI: 0.63, 0.73).

Cerebrospinal fluid (CSF). In two studies, the presence of CSF pleocytosis as a criterion was evaluated to predict total SBI, bacteremia and bacterial meningitis in neonates[63] and infants aged 0–3 months.[69] The definition of CSF pleocytosis for neonates differed in these studies. In the first study,[63] the definition of pleocytosis was ≥ 20 WBC/mm^3 and > 1 WBC per 500 red blood cells/mm^3.[63] In the second study,[69] the WBC thresholds used in neonates was ≥ 25 cells/ μL, and in infants aged 29 days–3 months was ≥ 10 cells/μL The sensitivity values for detecting total SBI in the two studies were 31.1 percent[63] and 12.5 percent.[69] Since one of these studies[69] reported sensitivity for the entire group of infants (0–3 months), these results were not comparable. In both studies the use of CSF pleocytosis resulted in a better sensitivity for detecting bacteremia (range: 28.0 percent- 34.5 percent) and bacterial meningitis (71.4 percent- 91.6 percent) compared to total SBI (12.5 percent- 31.1 percent). In these two studies,[63,69] three of 19 cases of bacterial meningitis had no CSF pleocytosis.

Urine analysis (UA). The ranges of sensitivity and specificity values of UA (dipstick; the presence of LE or nitrite, or both) for identifying infants with UTI across the studies were 81.0 percent[49]- 85.0 percent[13] and 63.6 percent[50]– 94.0 percent,[52] respectively.[5,13,49,50,52] In one study, the sensitivity of urine dipstick was lower in identifying UTI in neonates (73.2 percent) with NPV of 94.1 percent (95 percent CI: 91.7, 96.3).[37] For three studies, the microscopy of spun urine (WBC ≥ 5/hpf) yielded sensitivity of 59.0 percent,[53] 65.0 percent,[13] and 40.0 percent.[54] The specificity values for the same studies were 92.4 percent[13] 93.0 percent,[53] and 85.0 percent.[54]

In one study,[5,51] two methods of urine collection (gold standard of >100 000 cfu/mL for a bag specimen; >20 000 cfu/mL for catheterization specimen), catheterization and bag were compared in terms of specificity and sensitivity of UA (the presence of LE or nitrite) in identifying infants with UTI. Regardless of the criteria used (LE or nitrites), the UA of urine collected by catheterization had a better sensitivity (86.0 percent or 43.0 percent) and specificity (94.0 percent or 99.0 percent) compared to sensitivity (76.0 percent or 25.0 percent) and specificity (84.0 percent or 99.0 percent) for urine collected with bag. In general, the presence of nitrites taken as a criterion had a lower sensitivity for both collection methods (catheterization: 43.0 percent and

bag: 25.0 percent) than LE taken alone (catheterization: 94.0 percent and bag: 84.0 percent). Similarly, the area under the curve (AUC) of ROC based on sensitivity and specificity values for different thresholds of urine microscopy (WBC: 0-2, 3-5, 6-10, 11-20, > 20/hpf) was numerically greater for the collection method using catheterization (AUC: 86.0 percent, 95 percent CI: 82.0, 91.0) vs. bag (AUC: 71.0 percent, 95 percent CI: 61.0, 82.0).[5,51] In another study,[30] the use of urine dipstick result (leukocyturia and/or nitrituria vs. normal) yielded a sensitivity of 43.5 percent and specificity of 82.8 percent in correctly identifying bacteremia in 1,018 febrile infants (≥ 38.0°C) aged 3 months or younger.

Table 5. Test results - Laboratory criteria

Criteria	Study ID QUADAS total score	N/n Age range	N (%) with SBI	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV (%) [95% CI]	Other
Blood Markers in Neonates (0–28 d)								
WBC > 15,000/mm^3	Bonadio (1987)[112] [7]	55/55 0–28 d	Total: 8 (14.5) UTI: 3 Gastroenteritis: 2 Meningitis: 2 Bacteremia: 1	0.0 [NA]	NR	NR	NR	NR
ABC >1,500/mm^3				50.0 [17.4, 82.5]	NR	NR	NR	NR
CBC Differential Ratio < 1 (Low risk)				87.5 [46.6, 99.3]	NR	NR	NR	NR
WBC < 5,000, or > 15,000 (fever < 12 hours duration)	Bressan (2010)[47] [7]	99/99 7–28 d	Total: 25 (25.3) UTI: 15 Meningitis: 3 Bacteremia: 3 Bacteremia + UTI: 2 Pneumonia: 1 Osteomyelitis: 1	28.0 [14.3, 47.6]	87.7 [78.2, 93.4]	43.75 [23.1, 66.8]	78.1 [68.0, 85.6]	LR$^+$ = 2.3 LR$^-$ = 0.8
WBC < 5,000, or > 15,000/mm^3 (fever > 12 hours duration)		99/58 7–28 d	Total: 5 (8.6) only low risk infants determined by the same criteria	80.0 [37.6, 96.4]	90.6 [79.7, 95.9]	44.4 [18.9, 73.3]	98.0 [89.3, 99.6]	LR$^+$ = 8.5 LR$^-$ = 0.2
ANC > 10,000/mm^3 (fever < 12 hours duration)		99/99 7–28 d	Total: 25 (25.3)	20.0 [8.9, 39.1]	97.3 [90.6, 99.3]	71.4 [35.9, 91.8]	78.0 [68.5, 85.3]	LR+ = 7.3 LR- = 0.8
ANC > 10,000/mm^3 (fever > 12 hours duration)		99/58 7–28 d	Total: 5 (8.6) only low risk infants determined by the same criteria	80.0 [37.6, 96.4]	100.0 [93.2, 100.0]	100.0 [51.0, 100.0]	98.2 [90.2, 99.7]	LR$^+$ = NR LR$^-$ = 0.2
CRP > 20 mg/L (fever < 12 hours duration)		99/99 7–28 d	Total: 25 (25.3)	48.0 [30.3, 66.5]	93.2 [85.1, 97.1]	70.6 [46.9, 86.7]	84.2 [74.7, 90.5]	LR$^+$ = 7.1 LR$^-$ = 0.6
CRP > 20 mg/L (fever > 12 hours duration)		99/58 7–28 d	Total: 5 (8.6) only low risk infants determined by the same criteria	100.0 [56.6, 100.0]	96.2 [87.2, 99.0]	71.4 [35.9, 91.8]	100.0 [93.0, 100.0]	LR$^+$ = 0.2 LR$^-$ = 0

Table 5. Test results - Laboratory criteria (continued)

Criteria	Study ID QUADAS total score	N/n Age range	N (%) with SBI	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV (%) [95% CI]	Other
WBC 10,000/mm^3	Brown (2005)[43] [3]	71/69 < 28 d	Total: 8 (12.0) UTI: 4 Bacteremia: 2 Other: NR	100.0 [60.0, 100.0]	31.0 [19.9, 44.7]	17.0 [8.0, 30.7]	100.0 [78.1, 100.0]	LR$^+$ = 1.40 LR$^-$ = 0
WBC 12,000/mm^3				75.0 [35.5, 95.5]	53.0 [41.6, 68.0]	18.0 [7.8, 37.0]	94.0 [78.9, 98.9]	LR$^+$ = 1.60 LR$^-$ = 0.50
WBC 15,000/mm^3				50.0 [17.4, 82.5]	74.0 [64.4, 87.0]	21.0 [7.8, 50.2]	91.0 [79.5, 97.3]	LR$^+$ = 1.90 LR$^-$ = 0.70
WBC 17,000/mm^3				38.0 [9.0, 76.0]	89.0 [78.1, 95.7]	33.0 [9.0, 69.0]	91.0 [80.0, 96.7]	LR$^+$ = 3.80 LR$^-$ = 0.70
WBC 5,000/mm^3				100.0 [NC]	2.0 [NC]	12.0 [NC]	100.0 [NC]	LR$^+$ = 1.00 LR$^-$ = 0
WBC within 5,000 - 10,000; 12,000 - 15,000; 17,000 - 20,000; 22,000 - 25,000/mm^3				NA	NA	NA	NA	ROC (AUC) = 72.3, 95% CI: 56.6, 87.9
WBC ≥ 15,000/mm^3	Caspe (1983)[34] [11]	305/107 0–30 d	Total: 7 (6.5) (bacteremia)	28.6 [5.1, 69.7]	NR	NR	NR	NR
Blood Markers in Infants 0–60 d								
PMN ≥ 10,000/mm^3	Berkowitz (1985)[109] [3]	434/239 < 60 d	Total: 10 (4.2) Sepsis/meningitis	38.0 [NC]	93.0 [NC]	NR	NR	LR$^+$ = 5.42 LR$^-$ = 0.66
WBC ≥ 15,000/mm^3				50.0 [NC]	77.0 [NC]	NR	NR	LR$^+$ = 2.17 LR$^-$ = 0.64
WBC ≥ 15,000/mm^3 + PMN ≥ 10,000/mm^3				38.0 [NC]	94.0 [NC]	NR	NR	LR$^+$ = 6.33 LR$^-$ = 0.65
WBC ≥ 15,000/mm^3 + ABC ≥ 500/mm^3				63.0 [NC]	84.0 [NC]	NR	NR	LR$^+$ = 3.93 LR$^-$ = 0.44
ABC ≥ 500/mm^3				88.0 [NC]	61.0 [NC]	NR	NR	LR$^+$ = 2.25 LR$^-$ = 0.19

Table 5. Test results - Laboratory criteria (continued)

Criteria	Study ID QUADAS total score	N/n Age range	N (%) with SBI	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV (%) [95% CI]	Other
Total WBC/mm^3 (3,000, 10,000, 12,000, 18,000, 20,000)				NA	NA	NA	NA	ROC (AUC): 61.0 (SE: 0.038)
WBC >10,000/mm^3				69.0 [57.7, 78.6]	52.0 [48.2, 54.7]	11.0 [8.5, 14.2]	95.0 [92.6, 96.7]	LR$^+$ = 1.43 LR$^-$ = 0.59
WBC >12,000/mm^3				51.0 [39.6, 61.8]	72.0 [68.9, 74.8]	14.0 [10.0, 18.1]	94.0 [92.3, 95.9]	LR$^+$ = 1.82 LR$^-$ = 0.68
WBC >15,000/mm^3				31.0 [21.3, 42.2]	88.0 [85.5, 89.8]	18.0 [12.3, 25.7]	94.0 [91.6, 95.0]	LR$^+$ = 2.58 LR$^-$ = 0.78
WBC >20,000/mm^3				16.0 [9.1, 26.2]	97.0 [96.2, 98.3]	35.0 [20.7, 52.6]	93.0 [91.1, 94.5]	LR$^+$ = 5.33 LR$^-$ = 0.86
WBC >8,000/mm^3				74.0 [62.9, 82.9]	28.0 [25.4, 31.4]	8.0 [6.4, 10.6]	93.0 [88.7, 95.2]	LR$^+$ = 1.02 LR$^-$ = 0.92
ABC (250, 500, 1,000, 2,000, and 3,000/mm^3)	Bonadio (1992)[44] [10]	1,009/ 1,009 4–60 d	Total: 81 (8.0) Meningitis: 21 UTI: 29 Bacteremia: 23 Enteritis: 8	NA	NA	NA	NA	ROC (AUC): 81 .0 (SE: 0.025)
ABC > 250/mm^3				93.0 [82.4, 96.1]	44.0 [40.8, 47.3]	13.0 [9.9, 15.4]	99.0 [96.4, 99.3]	LR$^+$ = 1.66 LR$^-$ = 0.15
ABC > 500/mm^3				80.0 [76.5, 92.7]	61.0 [55.5, 63.0]	16.0 [12.3, 19.2]	98.0 [96.4, 99.0]	LR$^+$ = 2.05 LR$^-$ = 0.32
ABC >1,000/mm^3				74.0 [62.9, 82.9]	80.0 [76.9, 82.1]	24.0 [19.0, 30.0]	97.0 [95.7, 98.2]	LR$^+$ = 3.70 LR$^-$ = 0.32
ABC>2,000/mm^3				42.0 [31.2, 53.4]	93.0 [91.2, 94.6]	35.0 [25.5, 45.0]	96.0 [93.1, 96.1]	LR$^+$ = 6.00 LR$^-$ = 0.62
ABC>3,000/mm^3				19.0 [11.0, 29.0]	98.0 [97.0, 98.9]	47.0 [29.5, 64.9]	93.0 [91.4, 94.7]	LR$^+$ = 9.50 LR$^-$ = 0.82
ABC>1,500/mm^3				50.0 [17.4, 82.5]	NR	NR	NR	NR
CBC Differential Ratio < 1 (Low risk)				87.5 [46.6, 99.3]	NR	NR	NR	NR

Table 5. Test results - Laboratory criteria (continued)

Criteria	Study ID QUADAS total score	N/n Age range	N (%) with SBI	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV (%) [95% CI]	Other
WBC > 15,000/μL				38.8 [31.0, 47.3]	84.6 [82.4, 86.6]	NR	NR	LR[+] = 2.5 LR[-] = 0.7
WBC > 20,000/μL				16.4 [11.1–23.6]	95.6 [94.3, 96.7]	NR	NR	LR[+] = 3.8 LR[-] =0.9
WBC < 4,100 or > 20,000/μL			Total SBI: 134 (10.7%)	17.2 [11.7, 24.4]	93.2 [91.6, 94.6]	NR	NR	LR[+] = 2.5 LR[-] = 0.9
WBC < 5,000 or > 15,000/μL			UTI: 104 Bacteremia + UTI: 9	42.5 [34.5, 51.0]	79.3 [76.9, 81.6]	NR	NR	LR[+] = 2.1 LR[-] = 0.7
ANC >4.650/μL	Bilavsky (2010)[45] [9]	1,257/ 1,257 0–60 d	Isolated bacteremia: 4 Bacteremia + enteritis: 3	70.9 [62.7, 77.9]	63.3 [60.5, 66.1]	NR	NR	LR[+] = 1.9 LR[-] = 0.5
ANC>10,000/μL			Bacteremia + enteritis: 3	28.4 [21.4, 36.5]	95 [93.6, 96.0]	NR	NR	LR[+] = 5.7 LR[-] = 0.8
ANC>12.500/μL			Pneumonia: 13 Enteritis: 1	11.9 [7.5, 18.5]	97.8 [96.7, 98.5]	NR	NR	LR[+] = 5.4 LR[-] =0.9
ANC/WBC > 20%			Bacterial meningitis: 0	98.5 [94.7, 99.6]	7.2 [5.8, 8.9]	NR	NR	LR[+] = 1.0 LR[-] =0.2
ANC/WBC > 40%				76.1 [68.2, 82.6]	50.0 [47.0, 52.9]	NR	NR	LR[+] = 1.5 LR[-] = 0.5
ANC/WBC > 60%				27.6 [20.1, 35.7]	89.6 [87.7, 91.2]	NR	NR	LR[+] = 2.7 LR[-] = 0.8
WBC ≥ 15,000 /μL				20.0 [1.0, 70.0]	80.0 [66.2, 90.3]	10.0 [0.5, 45.8]	90.4 [76.4, 96.9]	LR[+] = 1.00 LR[-] = 1.00
ABC ≥ 5,000 /μL	Broner (1990)[32] [9]	NR/52 4–56 d	Total: 5 (9.6) (bacteremia)	80.0 [29.8, 98.9]	57.0 [42.2, 71.4]	16.6 [5.4, 38.1]	96.4 [79.7, 99.8]	LR[+] = 1.86 LR[-] = 0.35
CRP [+]ve				64.0 [17.0, 92.7]	67.0 [52.7, 80.4]	16.6 [4.4, 42.2]	94.1 [78.9, 98.9]	LR[+] = 1.93 LR[-] = 0.53
ESR ≥ 30 mm/h				25.0 [1.0, 70.1]	87.0 [73.5, 94.7]	14.3 [0.7, 58.0]	91.1 [77.8, 97.1]	LR[+] = 1.92 LR[-] = 0.86
WBC ≥ 15,000/mm^3	Caspe (1983)[34] [11]	305/198 30–60 d	Total: 4 (2.0) (bacteremia)	75.0 [21.9, 98.7]	NR	NR	NR	NR
ESR ≥ 30 mm/h	Crain (1982)[33] [11]	134/99 0–60 d	Total: 5 (5.0) (bacteremia)	80.0 [29.8, 98.9]	93.6 [86.0, 97.3]	40.0 [13.7, 72.6]	99.0 [93.0, 99.9]	LR[+] =12.50 LR[-] = 0.21
Bacteriuria (Any number of bacteria by hpf)	Hoberman (1993)[91] [11]	NR/306 0–59 d	Total: 14 (UTI)	64.0 [35.6, 86.0]	NR	NR	NR	NR

Table 5. Test results - Laboratory criteria (continued)

Criteria	Study ID QUADAS total score	N/n Age range	N (%) with SBI	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV (%) [95% CI]	Other
% Immature neutrophils ≥ 20%	King (1987)a[39] [6]	NR/321 < 60 d	Total: 16 (5.0) Bacteremia or meningitis	69.0 [41.5, 87.9]	75.0 [69.7, 79.7]	12.6 [6.8, 21.9]	97.0 [94.8, 99.2]	LR+ = 2.76 LR- = 0.41
WBC ≤ 5,000 /mm³		NR/342 < 60 d		44.0 [20.7, 69.4]	96.0 [93.1, 97.7]	35.0 [16.3, 59.0]	97.0 [94.5, 98.6]	LR+ = 11.00 LR- = 0.58
ESR ≥ 30 mm/h		NR/74 < 60 d	Total: 4 (5.4) Bacteremia or meningitis	25.0 [1.3, 78.0]	75.7 [63.7, 84.8]	5.5 [0.2, 29.3]	94.6 [84.2, 98.6]	LR+ = 1.04 LR- = 0.99
WBC > 15,000 / µL	Lin (2000)[53] [10]	223/162 < 60 d	Total: 22 (13.5) (UTI)	36.0 [18.0, 59.1]	80.0 [72.2, 86.0]	22.2 [10.7, 39.6]	88.9 [81.7, 93.5]	LR+ = 1.80 LR- = 0.80
CRP > 20 mg/L				59.0 [36.6, 78.5]	90.0 [83.5, 94.2]	48.1 [29.1, 67.6]	93.3 [87.3, 96.7]	LR+ = 5.90 LR- = 0.40
ESR > 30 mm/h				73.0 [49.5, 88.4]	78.0 [69.9, 84.2]	34.0 [21.3, 49.4]	94.7 [88.5, 97.8]	LR+ = 3.30 LR- = 0.30
Blood Markers in Infants 0–90 d								
WBC > 15,000/µL	Bilavsky (2009)[46] [8]	892/892 0–90 d	Total: 102 (11.3) UTI: 84 Bacteremia: 6 Pneumonia: 11 Meningitis: 1	48.0 [38.6, 57.6]	84.1 [81.4, 86.5]	NR	NR	LR+ = 3.00 LR- = 0.60
WBC > 20,000/µL		892/892 0–90 d	Total: 102 (11.3) UTI: 84 Bacteremia: 6 Pneumonia: 11 Meningitis: 1	21.6 [14.7, 30.5]	95.2 [93.5, 96.5]	NR	NR	LR+ = 4.50 LR- = 0.80
WBC > 15,000/µL or WBC < 5,000/µL		892/892 0–90 d	Total: 102 (11.3) UTI: 84 Bacteremia: 6 Pneumonia: 11 Meningitis: 1	50.0 [40.5, 59.5]	78.1 [75.0, 80.8]	NR	NR	LR+ = 2.30 LR- = 0.60
CRP > 8 mg/dL	Bilavsky (2009)[46] [8]	892/892 0–90 d	Total: 102 (11.3) UTI: 84 Bacteremia: 6 Pneumonia: 11 Meningitis: 1	23.5 [16.4, 32.6]	98.2 [97.1, 98.9]	NR	NR	LR+ = 13.30 LR- = 0.80
CRP > 4 mg/dL				44.1 [34.9, 53.8]	92.2 [90.1, 93.8]	NR	NR	LR+ = 5.60 LR- = 0.60
CRP > 2 mg/dL				55.9 [46.2, 65.1]	82.2 [79.3, 84.7]	NR	NR	LR+ = 3.10 LR- = 0.50

Table 5. Test results - Laboratory criteria (continued)

Criteria	Study ID / QUADAS total score	N/n Age range	N (%) with SBI	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV (%) [95% CI]	Other
WBC < 5,000/mm^3	Bonsu (2003)[111] [9]	3,961/ 3,810 0–89 d	Total: 38 (1.0) (bacteremia)	-	-	-	-	LR = 3.90
WBC < 5,000 or WBC ≥ 15,000/mm^3				66.0 [49.0, 80.0]	72.0 [71.0, 74.0]	2.3 [1.5, 3.5]	99.5 [99.1, 99.7]	LR$^+$ = 2.37 LR$^-$ = 0.47
WBC < 5,000 or WBC 20,000/mm^3				45.0 [29.0, 62.0]	88.0 [87.0, 89.0]	3.6 [2.2, 5.8]	99.3 [99.0, 99.6]	LR$^+$ = 3.70 LR$^-$ = 0.62
WBC ≥ 10,000/mm^3				61.0 [43.0, 76.0]	42.0 [40.0, 44.0]	1.0 [0.6, 1.5]	99.0 [98.4, 99.4]	LR$^+$ = 1.04 LR$^-$ = 0.94
WBC ≥ 15,000/mm^3				45.0 [29.0, 62.0]	78.0 [76.0, 79.0]	2.0 [1.2, 3.2]	99.3 [98.9, 99.5]	LR$^+$ = 2.00 LR$^-$ = 0.71
WBC ≥ 20,000/mm^3		3,961/ 3,810 0–89 d	Total: 38 (1.0) (bacteremia)	24.0 [11.0, 40.0]	93.0 [92.0, 94.0]	3.4 [1.6, 6.6]	99.1 [98.8, 99.4]	LR$^+$ = 3.50 LR$^-$ = 0.81
WBC ≥ 5,000/mm^3				79.0 [63.0, 90.0]	5.0 [4.0, 6.0]	0.8 [0.6, 1.2]	96.2 [92.3, 98.2]	LR$^+$ = 0.83 LR$^-$ = 3.95
WBC ≤5,000 - ≤15,000/mm^3				NA	NA	NA	NA	LR = 0.40
ANC ≥ 10,000/mm^3	Gomez (2010)[30] [9]	1,125/1018 0–90 d	Total: 23 (2.2) Bacteremia: 9 UTI/bacteremia: 8 Meningitis: 4 Sepsis: 2	NR/NC	NR/NC	NR/NC	NR/NC	AUC=71.1% [58.5, 83.8]
WBC ≥ 15,000/mm^3				NR/NC	NR/NC	NR/NC	NR/NC	AUC=67.9% [55.3, 80.4]
CRP at 70 g/L	Gomez (2010)[30] [9]	1,125/ 1,018 0–90 d	Total: 23 (2.2) Bacteremia: 9 UTI/bacteremia: 8 Meningitis: 4 Sepsis: 2	69.6 [49.1, 89.4]	93.8 [92.1, 95.1]	20.5 [14.1, 25.3]	99.3 [98.5, 99.6]	LR$^+$ = 11.17 LR$^-$ = 0.32 AUC=84.7% [75.4, 94.0]
CRP at 20 g/L				73.9 [53.5, 87.5]	74.8 [72.0, 77.5]	6.3 [4.4, 7.6]	99.2 [98.5, 99.7]	LR$^+$ = 2.93 LR$^-$ = 0.34 AUC=84.7% [75.4, 94.0]
PCT at 0.13 ng/mL	Maniaci (2008)[61] [11]	435/234 0–90 d	Total: 30 (12.8) Bacteremia: 4 Bacteremia + UTI: 2 UTI: 24	96.7 [81.0, 99.8]	30.3 [24.0, 37.5]	NR	98.3 [89.7, 99.9]	NR

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Table 5. Test results - Laboratory criteria (continued)

Criteria	Study ID QUADAS total score	N/n Age range	N (%) with SBI	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV (%) [95% CI]	Other
PCT-Q (semi-quantitative PCT) ≥ 0.5 ng/mL	Olaciregui (2008)[48] [10]	375/347 0–90 d	Total: 82 (23.6) UTI: 69 (4 with bacteremia) Bacteremia: 5 Cellulitis: 2 (1 with bacteremia) Sepsis: 4 (2 with bacteremia) Gastroenteritis: 1 with bacteremia	63.0 [52.0, 74.0]	87.0 [83.0, 91.0]	59.0 [48.0, 70.0]	89.0 [85.0, 93.0]	LR+ = 4.8 LR- = 0.42
Leucocyte count (5,000–15,000), CRP (<30), PCT (<0.5), good general state and –ve urine dipstick				96.0 [88.0, 99.0]	35.0 [29.0, 42.0]	32.0 [25.0, 38.0]	96.0 [92.0, 100]	LR+ = 1.48 LR- = 0.11
PCT-Q (semi-quantitative PCT) > 0.5 ng/mL			Bacteremia: 5 (1.4)	86 .0 [58.0, 100.0]	93.0 [90.0, 96.0]	35.0 [19.0, 51.0]	99.0 [98.0, 100.0]	LR+ = 12.3 LR- = 0.15
Leucocyte count (5,000–15,000), CRP (<30), PCT (<0.5), good general state and –ve urine dipstick				100 [74.0, 100.00]	29 [24.0, 35.0]	6 [3.0, 9.0]	100 [96.0, 100.0]	LR+ = 1.4 LR- = 0
CRP ≥ 30 mg/L	Olaciregui (2008)[48] [10]	375/347 0–90 d	Total: 82 (23.6) UTI: 69 (4 with bacteremia) Bacteremia: 5 Cellulitis: 2 (1 with bacteremia) Sepsis: 4 (2 with bacteremia) Gastroenteritis + bacteremia: 1	59.0 [48, 70]	89.0 [85.0, 93]	63.0 [52.0, 74.0]	87.0 [83.0, 91.0]	LR+ = 5.4 LR- = 0.46
CRP ≥ 20 mg/L				64.0 [54.0, 74.0]	84.0 [80.0, 88.0]	55 [45.0, 65.0]	88.0 [84.0, 92.0]	LR+ = 4.0 LR- = 0.43
CRP > 30 mg/L			Bacteremia: 5 (1.4)	56.0 [32.0, 80]	74.0 [69.0, 79.0]	9.6 [4.0, 16.0]	97 [95.0, 99.0]	LR+ = 2.15 LR- = 0.59
Cerebro-Spinal Fluid (CSF) Markers								
CSF pleocytosis (≥ 20 WBC/mm^3 and > 1 WBC per 500 red blood cells/mm^3)	Caviness (2008)[63] [8]	960/800 0–28 d	Total: 119 (14.8) UTI: 78 Bacteremia: 29 Meningitis: 12	31.1 [23.1, 40.3]	75.5 [72.0, 78.6]	18.1 [13.2, 24.2]	86.2 [83.1, 88.8]	LR+ = 1.26 LR- = 0.91
			Bacteremia: 29	34.5 [18.6, 54.3]	74.8 [71.6, 77.8]	4.9 [2.5, 9.1]	96.8 [95.0, 98.0]	LR+ = 1.37 LR- = 0.87

Table 5. Test results - Laboratory criteria (continued)

Criteria	Study ID QUADAS total score	N/n Age range	N (%) with SBI	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV (%) [95% CI]	Other
			Meningitis: 12	91.6 [59.7, 99.5]	75.5 [72.3, 78.4]	5.4 [2.8, 9.6]	99.8 [98.9, 99.9]	LR[+] = 3.74 LR[-] = 0.11
CSF pleocytosis (neonates: WBC ≥ 25 cells/ µL; age 29–90 d: WBC ≥ 10 cells/ µL)	Meehan (2008)[69] [9]	2,820/ 2,003 0–90 d	Total: 192 UTI: 160 Bacteremia: 25 Meningitis: 7	12.5 [8.3, 18.2]	91.6 [90.2, 92.8]	13.6 [9.1, 19.8]	90.8 [89.3, 92.0]	LR[+] = 1.48 LR[-] = 0.95
			Bacteremia: 25	28.0 [12.8, 49.6]	91.4 [90.1, 92.6]	3.9 [1.7, 8.3]	99.0 [98.4, 99.4]	LR[+] = 3.27 LR[-] = 0.78
			Meningitis: 7	71.4 [30.2, 94.8]	91.4 [90.1, 92.6]	2.8 [1.0, 6.8]	99.9 [99.5, 99.9]	LR[+] = 8.33 LR[-] = 0.31
Urine Markers								
Urine - UA: dipstick (LE[+], nitrite, [+] or both) and microscopy (pyuria: ≥ 5 WBC/hpf)	Bachur (2001)[52] [8]	NR/868 0–29 d	UTI: 73 (8.4)	82.0 [71.0, 90.0]	92.0 [90.0, 94.0]	48.4 [39.4, 57.5]	98.2 [96.9, 99.0]	LR[+] = 10.25 LR[-] = 0.19
Urine - UA: dipstick (LE[+], nitrite, [+] or both) and microscopy (pyuria: ≥ 5 WBC/hpf)	Bachur (2001)[52] [8]	NR/2,283 29–89 d	UTI: 172 (7.5)	82.0 [75.0, 87.0]	94.0 [93.0, 95.0]	52.6 [46.4, 58.7]	98.4 [97.8, 98.9]	LR[+] = 13.60 LR[-] = 0.20
Urine – UA (LE[+] or nitrite[+])	Bachur (2001)[49] [12]	5,279/ 5,279 0–90 d	Total: 373 (7.0) UTI: 297 Meningitis: 17 Bacteremia: 40 Bacteremia/meningitis: 8 Bacteremia/UTI: 11	71.0 [66.0, 76.0]	NR	NR	NR	NR
			UTI: 297 (5.6)	81.0 [76.0, 85.0]	NR	NR	NR	NR
Urine – UA (LE,[+] nitrite,[+] or protein)	Bonsu (2007)[50] [11]	3,765/ 3,765 0–89 d	UTI: 307 (8.1) (UTI with sepsis)	84.0 [79.3, 87.8]	63.6 [62.0, 65.2]	17.0 [15.1, 19.0]	97.8 [97.1, 98.3]	LR[+] = 2.31 LR[-] = 0.25

Table 5. Test results - Laboratory criteria (continued)

Criteria	Study ID QUADAS total score	N/n Age range	N (%) with SBI	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV (%) [95% CI]	Other
Urine - Any LE alone	Dayan (2002)[13] [11]	246/193 1 - 60 d	UTI: 27(14.0)	80.0 [62.5, 97.5]	94.2 [90.7, 97.7]	67.7 [48.5, 82.6]	96.3 [91.7, 98.5]	LR⁺ = 13.80 LR⁻ = 0.21
Urine - Any nitrite alone				35.0 [14.1, 55.9]	97.7 [95.4, 99.9]	69.2 [38.8, 89.6]	90.0 [84.4, 93.8]	LR⁺ = 15.10 LR⁻ = 0.67
Urine - Gram stain, any organisms				80.0 [62.5, 97.5]	99.4 [93.8, 100.0]	95.6† [76.0, 99.8]	96.8 [92.9, 98.9]	LR⁺ = 138.40 LR⁻ = 0.20
Urine - Nitrite + LE				30.0 [10.0, 50.0]	100.0 [98.3, 100.0]	100.0 [60.0, 100.0]	89.7 [84.2, 93.5]	LR⁺ = ∞ LR⁻ = NA
Urine - UA (LE⁺ or nitrite⁺)				85.0 [69.4, 100.0]	91.9 [87.8, 96.0]	62.1 [44.8, 77.0]	97.4 [93.1, 99.1]	LR⁺ = NA LR⁻ = 0.16
Urine –Microscopy of spun urine (≥ 5 WBC/hpf)				65.0 [44.1, 85.9]	92.4 [88.6, 96.4]	56.6 [37.6, 74.0]	93.8 [88.7, 96.8]	LR⁺ = 8.60 LR⁻ = 0.38
Urine –Microscopy of spun urine (≥ 10 WBC/hpf)				45.0 [23.2, 66.8]	97.6 [95.4, 99.9]	75.0 [47.4, 91.6]	91.5 [86.1, 95.0]	LR⁺ = 19.50 LR⁻ = 0.56
Urine - UA: dipstick (LE⁺, nitrite, ⁺ or both)	Gomez (2010)[30] [9]	1,125/1,018 0–90 d	Total: 23 (2.2) Bacteremia: 9 UTI/bacteremia: 8 Meningitis: 4 Sepsis: 2	43.5 [24.1, 64.8]	82.8 [82.3, 83.3]	5.6 [3.1, 8.4]	98.4 [97.9, 99.0]	LR⁺ = 2.52 LR⁻ = 0.68
Urine –UA Microscopy (hemocytometer; ≥ 10 WBC/μL)	Lin (2000)[53] [10]	223/162 < 60 d	UTI: 22 (13.5)	82.0 [59.0, 94.0]	94.0 [88.6, 97.3]	69.2 [48.1, 84.9]	97.0 [92.2, 99.0]	LR⁺ = 12.70 LR⁻ = 0.20
Urine – UA Microscopy (spun urine; ≥ 5 WBC/hpf)				59.0 [36.7, 78.5]	93.0 [86.9, 96.3]	56.5 [34.8, 76.1]	93.5 [87.7, 96.8]	LR⁺ = 8.30 LR⁻ = 0.40
Urine – UA Microscopy (spun urine; ≥ 5 WBC/hpf, LE⁺ or nitrite⁺)	Reardon (2009)[54] [8]	NR/51 < 90 d	Total: NR (UTI)	40.0 [7.0, 83.0]	85.0 [71.0, 93.0]	NR	NR	NR

Table 5. Test results - Laboratory criteria (continued)

Criteria	Study ID QUADAS total score	N/n Age range	N (%) with SBI	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV (%) [95% CI]	Other
Urine –UA (LE[+]) by bag	Schroeder (2005)[5,51]	3,066/ 1,482 0–90 d	UTI: 152 (10.2) UTI/bacteremia: 16	76.0 [NC]	84.0 [NC]	NR	NR	LR[+] = 4.75 LR[-] = 0.28
Urine - UA (LE[+]) by CATH				86.0 [NC]	94.0 [NC]	NR	NR	LR[+] = 14.33 LR[-] = 0.14
Urine – UA (LE[+]) combined both methods: bag/CATH				84.0 [NC]	91.0 [NC]	NR	NR	LR[+] = 9.33 LR[-] = 0.17
Urine – UA\ (Nitrites[+]) by bag				25.0 [NC]	98.0 [NC]	NR	NR	LR[+] = 17.50 LR[-] = 0.76
Urine - UA (Nitrites[+]) by CATH				43.0 [NC]	99.0 [NC]	NR	NR	LR[+] = 43.00 LR[-] = 0.57
Urine - UA (Nitrites[+]) combined both methods: bag/CATH				39.0 [NC]	99.0 [NC]	NR	NR	LR[+] = 39.00 LR[-] = 0.61
Urine microscopy (0-2, 3-5, 6-10, 11-20, > 20 WBC/hpf) combined both methods: bag/CATH		3,066/ 1,056 0–90d		NR	NR	NR	NR	ROC (AUC): 83.0%, 95% CI: 79.0, 87.0
Urine microscopy (0-2, 3-5, 6-10, 11-20, > 20 WBC/hpf) by bag		3,066/273 0–90d		NR	NR	NR	NR	ROC (AUC): 71.0%, 95% CI: 61.0, 82.0
Urine microscopy (0-2, 3-5, 6-10, 11-20, > 20 WBC/hpf) by CATH		3,066/716 0–90d		NR	NR	NR	NR	ROC (AUC): 86.0%, 95% CI: 82.0, 91.0

Table 5. Test results - Laboratory criteria (continued)

Criteria	Study ID QUADAS total score	N/n Age range	N (%) with SBI	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV (%) [95% CI]	Other
Urine dipstick– UA (absence of LE)	Schwartz (2009) [37]	644/449 0–28 d	Total: 87 (19.4) UTI: 82	73.2 [NR]	NR	NR	94.1 [91.7, 96.3]	NR

ABC = absolute band count; ANC = absolute neutrophil count; CATH = catheterization; CBC = complete blood count; CRP = C-reactive protein; CSF = cerebrospinal fluid; d = day(s); ESR = erythrocyte sedimentation rate; hpf = high-power field; LE = leukocyte esterase; LR = likelihood ratio; NA = not applicable; NC = not calculable; NPV = negative predictive value; NR = not reported; PCT = Procalcitonin; PMN = polymorphonuclear count; PPV = positive predictive value; ROC (AUC) = receiver operating characteristic (area under the curve); SBI = serious bacterial infection; SE = standard error; UA = urinalysis; UTI = urinary tract infection; WBC = white blood cell count; +ve = positive

* N/n: number of infants enrolled/number of infants with test and culture results

KQ1b. How do these findings vary by age within the age range 0 to 3 months?

The diagnostic test accuracy characteristics for criteria were compared qualitatively within and across studies where possible.

Key Findings

Overall most combined clinical and laboratory criteria demonstrated higher sensitivity for SBI in older infants (28–90 days) compared to neonates with the exception of Rochester criteria which is designed for younger infants and therefore had better sensitivity for SBI in neonates compared with older infants (four studies). The false positive rate for SBI tended to be higher for neonates compared to older infants.

Similarly, one study using laboratory criterion alone (PCT) demonstrated better diagnostic accuracy for older infants compared with neonates in predicting SBI. The Philadelphia protocol demonstrated lower specificity for correctly identifying infants without SBI when applied to older infants (1–2 months) compared to neonates. Combined clinical and laboratory (ill appearance and WBC > 15,000 mm^3) criteria and laboratory criteria alone (WBC > 15,000 mm^3) demonstrated greater sensitivity in identifying infants with bacteremia among older infants (1–3 months) compared to neonates. Clinical appearance alone or combined with WBC $\geq$ 15,000/mm^3 across two studies demonstrated better sensitivity in infants aged 2–3 months (75.0 percent and 100.0 percent) compared to neonates (28.5 percent and 85.7 percent).We found no evidence relating to other possibly relevant factors such as the clinical history of the mother.

Detailed Presentation

The diagnostic test characteristics were compared for selected criteria across age groups (neonates vs. older infants) using the data from 15 studies (Table 6). [9-12,22,24,28,34,38,52,55-57,59,61]
Combined clinical and laboratory criteria. For the Boston criteria,[22] the estimates of sensitivity, specificity, PPV, and NPV for total SBI in neonates were 82.0 percent (95 percent CI: 67.4, 91.5), 68.0 percent (95 percent CI: 62.8, 73.1), 26.0 percent (95 percent CI: 19.4, 34.4), and 97.0 percent (95 percent CI: 93.0, 98.4), respectively. In infants aged 28 - 90 days, these parameters had the following values: 88.5 percent (95 percent CI: 82.8, 92.5), 56.2 percent (95 percent CI: 54.0, 58.4), 16.2 percent (95 percent CI: 14.0, 18.6), and 98.1 percent (95 percent CI: 97.0, 98.7), respectively.[55]

With respect to total SBI, the Philadelphia protocol in neonates,[11,22] sensitivity values were 84.4 percent[11] and 87.9 percent[22] and specificity values were 46.8 percent[11] and 55.0 percent [22]). In infants aged 29–60 days,[9,12] higher sensitivity (98.0 percent and 100.0 percent) and lower specificity values (26.6 percent and42.0 percent) were reported. For detecting bacteremia, the Philadelphia protocol demonstrated higher sensitivity (i.e., 100.0 percent) in older infants (age: 29-60 days)[9,12] compared to sensitivity of 75.0 percent and 83.3 percent in neonates (age: 0-28 days).[11,22]

The two studies that tested Rochester criteria for total SBI in infants 28 days or younger,[24,57] showed the following estimates of sensitivity (97.6 percent and 86.4 percent), specificity (62.2 percent and 46.4 percent), PPV (33.6 percent and 26.8 percent), and NPV (99.2 percent and 93.8 percent). In two other studies the application of Rochester criteria in infants aged 28 days–90 days[56] and 28 days–60 days[10] yielded sensitivities of 52.0 percent (95 percent CI: 31.7, 71.6) and

59.0 percent (95 percent CI: 36.6, 78.5), respectively. The corresponding specificity value was reported only for one study (26.3, 95 percent CI: 22.5, 30.3).[10] In identifying bacteremia, the Rochester criteria in neonates demonstrated sensitivity of 86.4 percent[24] as opposed to 55.5 percent in older infants (age: 28 days-90 days).[56]

The results for combined criteria (clinical and laboratory) for predicting total SBI in neonates and older infants were reported in two studies.[28,34] The authors in the first study[28] examined the effect of age on the accuracy indices of the criteria in correctly identifying total SBI. Overall, there was no discernable numerical trend in the values of sensitivity and specificity across the age groups (0–14, 15–28, 29–45, and 46 - 59 days). In the second study,[34] the classification of infants aged 0–1 month and 1–2 months with respect to risk of bacteremia, using a similar criteria of ill appearance and WBC $\geq$ 15,000/mm^3, resulted in sensitivity values of 28.5 percent (95 percent CI: 5.1, 69.7) and 75.0 percent (95 percent CI: 21.9, 98.6), respectively.

Clinical criteria alone. One study reported the result for identifying risk of bacteremia using ill appearance as a criterion in neonates with sensitivity of 85.7 percent (95 percent CI: 42.0, 99.2) and specificity of 73.2 percent (95 percent CI: 63.4, 81.3).[34] The value for sensitivity in another study in infants 2–3 months using the same criteria for predicting bacteremia was 37.5 percent (95 percent CI: 10.2, 74.1).[38] No specificity was reported for the latter study.

Laboratory criteria alone. In one study,[34] the application of WBC $\geq$ 15,000/mm^3 for identifying bacteremia in neonates was associated with a sensitivity value of 28.6 percent. In the same study, the sensitivity was 75.0 percent when the criterion WBC $\geq$ 15,000/mm^3 was used in older infants aged 1-2 months.

One study reported sensitivity of 82.0 percent (95 percent CI: 71.0, 90.0) and specificity of 92.0 percent (95 CI: 90.0, 94.0) for urinalysis (dipstick, microscopy) in detecting UTI in neonates.[52] In the same study this test criteria was applied to older infants (29–89 days) and yielded similar estimates of sensitivity (82.0 percent, 95 percent CI: 75.0, 87.0) and specificity (94.0 percent, 95 percent CI: 93.0, 95.0).

In one study,[61] nine of 30 infants with SBI were younger than 28 days of age. The overall performance of Procalcitonin (PCT) levels in this study to identify SBI (definite and possible SBI) in ROC curve analysis had an AUC of 0.85 for patients >28 days of age compared with an AUC of 0.73 for patients $\leq$ 28 days of age.

Table 6. Test characteristic variations within age range 0 – 3 months

Study ID	N/n* Age range	N (%) with SBI	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]	Other
		Boston Criteria					
Kadish (2000)[22]	394/372 1 – 28 d	SBI: 45 (12.1)	82.0 [67.4, 91.5]	68.0 [62.8, 73.1]	26.0 [19.4, 34.4]	97.0 [93.0, 98.4]	LR+=2.58 LR-= 0.26
		Bacteremia: 12	75.0 [42.8, 93.3]	63.3 [58.1, 68.3]	6.4 [3.1, 12.1]	98.7 [96.0, 99.6]	LR+=2.04 LR-= 0.39
Kaplan (2000)[55]	3,166/2,190 28 – 90 d	SBI: 191 (8.7)	88.5 [82.8, 92.5]	56.2 [54.0, 58.4]	16.2 [14.0, 18.6]	98.1 [97.0, 98.7]	LR+= 2.02 LR-= 0.20
		Philadelphia Protocol					
Baker (1999)[11]	254/254 3 – 28 d	SBI: 32 (12.5)	84.4 [67.0, 95.0]	46.8 [40.0, 53.0]	18.6 [12.0, 25.0]	95.4 [90.0, 99.0]	LR+=1.58 LR-= 0.33
		Bacteremia: 8	75.0 [35.6, 95.5]	43.5 [37.2, 49.9]	4.1 [1.7, 9.1]	98.1 [92.7, 99.7]	LR+=1.32 LR-= 0.57
		Meningitis: 4	100.0 [39.6, 100.0]	43.6 [37.4, 49.9]	2.7 [0.9, 7.3]	100.0 [95.7, 100.0]	LR+=1.77 LR-= 0
Baker (1993)[12]	747/747 29 – 56 d	SBI: 65 (8.7)	98.0 [92.0, 100.0]	42.0 [38.0, 46.0]	14.0 [11.0, 17.0]	99.7 [98.0, 100.0]	LR+=1.69 LR-= 0.03
			100.0‡ [93.0, 100.0]	42.0‡ [38.3, 45.9]	14.1‡ [11.1, 17.7]	100.0‡ [98.3, 100.0]	LR+=1.72 LR-= 0
		Bacteremia: 19	100.0‡ [79.0, 100.0]	39.4‡ [35.8, 43.0]	4.1‡ [2.5, 6.5]	100.0‡ [98.3, 100.0]	LR+=1.65 LR-= 0
		Meningitis: 9	100.0‡ [62.8, 100.0]	38.9‡ [35.4, 42.5]	2.0‡ [0.9, 3.8]	100.0‡ [98.3, 100.0]	LR+=1.63 LR-= 0
Baker (1999)[9]	422/422 29 – 60 d	SBI: 43 (10.2)	100.0 [89.7, 100.0]	26.6 [22.3, 31.4]	14.0 [10.0, 17.7]	100.0 [96.0, 100.0]	LR+= 1.36 LR-= 0
		Bacteremia: 9	100.0 [62.9, 100.0]	24.4 [20.4, 28.9]	2.8 [1.4, 5.4]	100.0 [95.4, 100.0]	LR+= 1.32 LR-= 0
		Meningitis: 5	100.0 [46.3, 100.0]	24.2 [20.3, 28.7]	1.5 [0.6, 3.8]	100.0 [95.4, 100.0]	LR+= 1.31 LR-= 0
Condra (2010) [59]	1,672/240 29 – 60 d	*Data on low risk infants (n=62)* UTI: 2 (NR)	NR	NR	NR	96.7 [NR]	NR

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Table 6. Test characteristic variations within age range 0 – 3 months (continued)

Study ID	N/n* Age range	N (%) with SBI	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]	Other
Kadish (2000)[22]	394/372 1 – 28 d	SBI: 45 (12.1)	87.0 [72.5, 94.4]	55.0 [49.5, 60.5]	21.0 [15.5, 27.6]	97.0 [92.8, 98.7]	LR+=1.92 LR-= 0.24
		Bacteremia: 12	83.3 [50.8, 97.0]	51.1 [45.8, 56.3]	5.3 [2.7, 9.9]	98.9 [95.6, 99.8]	LR+=1.70 LR-= 0.32
		Meningitis: 5	100.0 [46.3, 100.0]	50.7 [45.5, 55.9]	2.6 [0.9, 6.5]	100.0 [97.4, 100.0]	LR+=2.03 LR-= 0
Rochester Criteria							
Baskin (1992)[56]	503/501 28 - 89 d	SBI: 27 (5.4)	52.0 [31.7, 71.6]	NR	NR	NR	NR
		Bacteremia: 8	55.5 [22.6, 84.6]	NC	NC	NC	NC
Bonadio (1993)[10]	534/532 29 – 60 d	SBI: 22 (4.1)	59.0 [36.6, 78.5]	26.3 [22.5, 30.3]	3.3 [1.9, 5.8]	93.7 [88.0, 96.9]	LR+=0.80 LR-= 1.55
		Bacteremia: 6	33.3 [6.0, 75.9]	26.3 [22.5, 30.3]	0.5 [0.09, 2.1]	97.1 [92.3, 99.0]	LR+=0.45 LR-= 2.53
		Meningitis: 4	50.0 [9.1, 90.8]	26.7 [23.0, 30.7]	0.5 [0.08, 2.1]	98.6 [94.5, 99.7]	LR+=0.68 LR-= 1.87
Chiu (1997)[57]	250/250 4 – 28 d	SBI: 41 (16.4)	97.6 [92.9, 100.0]	62.2 [55.6, 68.8]	33.6 [25.1, 42.1]	99.2 [97.7, 100.0]	LR+= 2.58 LR-= 0.04
		Bacteremia/Meningitis: 7 Bacteremia/Enteritis: 3 Bacteremia/Osteomyelitis: 1	100.0 [67.8, 100.0]	54.8 [48.2, 61.2]	9.2 [4.9, 21.2]	100.0 [96.4, 100.0]	LR+= 2.21 LR-= 0
Ferrera (1997)[24]	188/134 0 – 28 d	SBI: 22 (16.4)	86.4 [64.0, 96.4]	46.4 [36.3, 56.7]	26.8 [17.2, 38.8]	93.8 [81.8, 98.4]	LR+=1.61 LR-= 0.29
		Bacteremia: 4	100.0 [39.5, 100.0]	41.7 [32.7, 51.3]	5.6 [1.8, 14.3]	100.0 [90.2, 100.0]	LR+=1.71 LR-= 0

Table 6. Test characteristic variations within age range 0 – 3 months (continued)

Study ID	N/n* Age range	N (%) with SBI	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]	Other
Clinical Impression of Sepsis/ Appearance of Infant + Laboratory Markers							
Herr (2001)[28]	434/344 < 59 d	SBI: 41 (12.0)	68.3 [51.7, 81.4]	37.6 [32.2, 43.3]	12.9 [8.8, 18.2]	89.7 [82.8, 94.2]	LR^+=1.09 LR^-=0.84
	434/42 0 – 14 d	SBI: 3 (7.1)	100.0 [31.0, 100.0]	28.2 [15.5, 45.1]	9.6 [2.5, 26.9]	100.0 [67.8, 100.0]	LR^+=1.39 LR^-=0
	434/104 15 – 28 d	SBI: 9 (8.6)	100.0 [62.8, 100.0]	26.3 [18.0, 36.5]	11.3 [5.6, 21.0]	100.0 [83.0, 100.0]	LR^+=1.35 LR^-=0
	434/138 29 – 45 d	SBI: 19 (13.7)	100.0 [79.0, 100.0]	39.5 [30.7, 48.9]	20.8 [13.3, 30.9]	100.0 [90.5, 100.0]	LR^+=1.65 LR^-=0
	434/113 46 – 59 d	SBI: 10 (8.7)	100.0 [65.5, 100.0]	35.9 [26.8, 46.0]	13.1 [6.8, 23.3]	100.0 [88.2, 100.0]	LR^+=1.56 LR^-=0
Clinical Criteria Alone: Ill Appearance							
Bonadio (1994)[38]	367/356 60 – 90 d	SBI: 33 (9.3)	33.3 [18.5, 51.9]	NR	NR	NR	NR
		Bacteremia: 8 (2.2)	37.5 [10.2, 74.1]	NR	NR	NR	NR
Caspe (1983)[34]	305/305 0 – 90 d	Bacteremia: 11 (3.6)	91.0 [57.1, 99.5]	56.6 [49.3, 63.5]	10.4 [5.4, 18.7]	99.1 [94.4, 99.9]	LR^+=2.10 LR^-=0.16
	305/107 0 – 30 d	Bacteremia: 7 (6.5)	85.7 [42.0, 99.2]	73.2 [63.4, 81.3]	18.2 [76.1, 36.0]	98.6 [91.8, 99.9]	LR^+=3.20 LR^-=0.19
	305/198 30 – 60 d	Bacteremia:: 4 (2.0)	100.0 [39.6,100.0]	69.6 [62.5, 75.9]	6.3 [2.0, 16.2]	100.0 [96.5, 100.0]	LR^+=3.28 LR^-=0
	305/305 0 – 90 d	UTI: 7 (2.3)	42.8 [11.8, 79.8]	NR	NR	NR	NR
Laboratory Criteria Alone: WBC > 15,000/mm³							
Caspe (1983)[34]	305/107 0 – 30 d	Bacteremia: 7 (6.5)	28.6 [5.1, 69.7]	NR	NR	NR	NR
Caspe (1983)[34]	305/107 30 - 60 d	Bacteremia: 4 (2.0)	75 [21.9, 98.7]	NR	NR	NR	NR
d=day(s); UTI=urinary tract infection; NR=not reported; WBC=white blood cell count; mm³= millimeter; LR=likelihood ratio; PPV= positive predictive value; NPV= negative predictive value							

*N/n: number of infants enrolled/ number of infants with test and culture results

‡ Values based on Philadelphia protocol + no immunodeficiency syndrome, band-to-neutrophil ratio < 0.2

Table 6. Test characteristic variations within age range 0–3 months (continued)

Study	N	Condition					
Kadish (2000)[22]	394/372 1–28 d	SBI: 45 (12.1)	87.0 [72.5, 94.4]	55.0 [49.5, 60.5]	21.0 [15.5, 27.6]	97.0 [92.8, 98.7]	LR+=1.92 LR-= 0.24
		Bacteremia: 12	83.3 [50.8, 97.0]	51.1 [45.8, 56.3]	5.3 [2.7, 9.9]	98.9 [95.6, 99.8]	LR+=1.70 LR-= 0.32
		Meningitis: 5	100.0 [46.3, 100.0]	50.7 [45.5, 55.9]	2.6 [0.9, 6.5]	100.0 [97.4, 100.0]	LR+=2.03 LR-= 0
Rochester Criteria							
Baskin (1992)[56]	503/501 28 - 89 d	SBI: 27 (5.4)	52.0 [31.7, 71.6]	NR	NR	NR	NR
		Bacteremia: 8	55.5 [22.6, 84.6]	NC	NC	NC	NC
Bonadio (1993)[10]	534/532 29–60 d	SBI: 22 (4.1)	59.0 [36.6, 78.5]	26.3 [22.5, 30.3]	3.3 [1.9, 5.8]	93.7 [88.0, 96.9]	LR+=0.80 LR-= 1.55
		Bacteremia: 6	33.3 [6.0, 75.9]	26.3 [22.5, 30.3]	0.5 [0.09, 2.1]	97.1 [92.3, 99.0]	LR+=0.45 LR-= 2.53
		Meningitis: 4	50.0 [9.1, 90.8]	26.7 [23.0, 30.7]	0.5 [0.08, 2.1]	98.6 [94.5, 99.7]	LR+=0.68 LR-= 1.87
Chiu (1997)[57]	250/250 4–28 d	SBI: 41 (16.4)	97.6 [92.9, 100.0]	62.2 [55.6, 68.8]	33.6 [25.1, 42.1]	99.2 [97.7, 100.0]	LR+= 2.58 LR-= 0.04
		Bacteremia/Meningitis: 7 Bacteremia/Enteritis: 3 Bacteremia/Osteomyelitis: 1	100.0 [67.8, 100.0]	54.8 [48.2, 61.2]	9.2 [4.9, 21.2]	100.0 [96.4, 100.0]	LR+= 2.21 LR-= 0
Ferrera (1997)[24]	188/134 0–28 d	SBI: 22 (16.4)	86.4 [64.0, 96.4]	46.4 [36.3, 56.7]	26.8 [17.2, 38.8]	93.8 [81.8, 98.4]	LR+=1.61 LR-= 0.29
		Bacteremia: 4	100.0 [39.5, 100.0]	41.7 [32.7, 51.3]	5.6 [1.8, 14.3]	100.0 [90.2, 100.0]	LR+=1.71 LR-= 0
Clinical Impression of Sepsis/ Appearance of Infant + Laboratory Markers							
Herr (2001)[28]	434/344 < 59 d	SBI: 41 (12.0)	68.3 [51.7, 81.4]	37.6 [32.2, 43.3]	12.9 [8.8, 18.2]	89.7 [82.8, 94.2]	LR+=1.09 LR-=0.84
	434/42 0–14 d	SBI: 3 (7.1)	100.0 [31.0, 100.0]	28.2 [15.5, 45.1]	9.6 [2.5, 26.9]	100.0 [67.8, 100.0]	LR+=1.39 LR-=0
	434/104 15–28 d	SBI: 9 (8.6)	100.0 [62.8, 100.0]	26.3 [18.0, 36.5]	11.3 [5.6, 21.0]	100.0 [83.0, 100.0]	LR+=1.35 LR-=0
	434/138 29–45 d	SBI: 19 (13.7)	100.0 [79.0, 100.0]	39.5 [30.7, 48.9]	20.8 [13.3, 30.9]	100.0 [90.5, 100.0]	LR+=1.65 LR-=0
	434/113 46–59 d	SBI: 10 (8.7)	100.0 [65.5, 100.0]	35.9 [26.8, 46.0]	13.1 [6.8, 23.3]	100.0 [88.2, 100.0]	LR+=1.56 LR-=0
Clinical Criteria Alone: Ill Appearance							
Bonadio	367/356	SBI: 33 (9.3)	33.3	NR	NR	NR	NR

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Table 6. Test characteristic variations within age range 0–3 months (continued)

Kadish (2000)[22]	394/372 1–28 d	SBI: 45 (12.1)	87.0 [72.5, 94.4]	55.0 [49.5, 60.5]	21.0 [15.5, 27.6]	97.0 [92.8, 98.7]	LR+=1.92 LR-= 0.24
		Bacteremia: 12	83.3 [50.8, 97.0]	51.1 [45.8, 56.3]	5.3 [2.7, 9.9]	98.9 [95.6, 99.8]	LR+=1.70 LR-= 0.32
		Meningitis: 5	100.0 [46.3, 100.0]	50.7 [45.5, 55.9]	2.6 [0.9, 6.5]	100.0 [97.4, 100.0]	LR+=2.03 LR-= 0
(1994)[38]	60–90 d		[18.5, 51.9]				
		Bacteremia: 8 (2.2)	37.5 [10.2, 74.1]	NR	NR	NR	NR
Caspe (1983)[34]	305/305 0–90 d	Bacteremia: 11 (3.6)	91.0 [57.1, 99.5]	56.6 [49.3, 63.5]	10.4 [5.4, 18.7]	99.1 [94.4, 99.9]	LR$^+$=2.10 LR$^-$=0.16
	305/107 0–30 d	Bacteremia: 7 (6.5)	85.7 [42.0, 99.2]	73.2 [63.4, 81.3]	18.2 [76.1, 36.0]	98.6 [91.8, 99.9]	LR$^+$=3.20 LR$^-$=0.19
	305/198 30–60 d	Bacteremia:: 4 (2.0)	100.0 [39.6,100.0]	69.6 [62.5, 75.9]	6.3 [2.0, 16.2]	100.0 [96.5, 100.0]	LR$^+$=3.28 LR$^-$=0
	305/305 0–90 d	UTI: 7 (2.3)	42.8 [11.8, 79.8]	NR	NR	NR	NR
Laboratory Criteria Alone: WBC > 15,000/mm^3							
Caspe (1983)[34]	305/107 0–30 d	Bacteremia: 7 (6.5)	28.6 [5.1, 69.7]	NR	NR	NR	NR
Caspe (1983)[34]	305/107 30 - 60 d	Bacteremia: 4 (2.0)	75 [21.9, 98.7]	NR	NR	NR	NR

d = day(s); LR = likelihood ratio; mm^3 = millimeter; NPV = negative predictive value; NR = not reported; UTI = urinary tract infection; PPV = positive predictive value; WBC = white blood cell count

*N/n: number of infants enrolled/ number of infants with test and culture results

‡ Values based on Philadelphia protocol + no immunodeficiency syndrome, band-to-neutrophil ratio < 0.2

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 Herpes Simplex Virus (HSV) in febrile infants 3 months or younger was very scarce. For example, there were only four studies [39,60,62,63] in which the prevalence of Herpes Simplex Virus (HSV) was reported. In total, there were seven infants diagnosed with HSV in these studies and none of them had a concurrent bacterial infection. The prevalence of HSV amongst the febrile infants admitted across these studies (period range: 2 years[62]-6 years[60]) 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 (defined as $\geq$ 20 WBCs/mm^3 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/protocols were able to correctly classify most or all of the infants truly without SBI into low-risk groups (Tables 2–5).

Generally, all 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] 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, UTI, bacteremia, and bacterial meningitis. In other words, the proportion of infants misclassified to the low risk category (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 $\geq$ 0.5 ng/mL,[48] CRP $\geq$ 30 mg/L,[48] and presence of CSF-pleocytosis,[63,69]) showed relatively lower NPVs (78.1 percent- 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?

Key Findings

Nine studies reported that all low risk infants later found to have SBI were subsequently hospitalized and treated with full term antibiotics without adverse events or complications.

Detailed Presentation

We identified nine studies reporting outcomes related to delayed treatment of febrile infants initially classified as low risk and later diagnosed with SBI. [5,10,23,47,55,57,58,67,70] Studies reporting immediate antibiotic treatment for management of low risk infants[29,72] as well as studies in which none of the low risk infants was diagnosed with SBI were excluded.[9,12,26,84]

Nine studies reported on management of 4,497 infants 0–3 months of age managed according to low risk criteria (Table 7).[5,23,47,55,57,58,67] In these studies, 32 infants from those initially classified at low risk (0.70 percent) had SBI. All infants with SBI were eventually treated with antibiotics after the diagnoses were made. Outcomes on recovery or complications of six neonates initially classified as low risk and later diagnosed with SBI were not reported in two studies.[47,57] The infants in the remaining five studies were aged 0–3 months.

In two studies, majority of infants were monitored as outpatients in accordance with Philadelphia protocol,[58] and a combined clinical and laboratory criteria (not ill appearing, no bacterial illness, undefined benign laboratory screening findings).[67] In these studies, 14 out of 517 infants (2.7 percent) initially classified as low risk and later diagnosed with SBI were subsequently treated with full dose antibiotics, and recovered without any complications. In one study,[23] various management strategies (initial treatment with or without antimicrobial agents; hospitalization with or without parenteral antimicrobial agents) were used. In this study, a total of five infants initially classified as low risk using Rochester criteria were diagnosed with SBI, four of whom were not initially treated with antibiotics. All four infants recovered without complications.

In the PROS study,[5] using practitioner guidelines two of the total of 63 infants with SBI were initially treated as low risk and later received delayed diagnosis/treatment. None of these infants had complications.

In the remaining one study,[55] three infants (age 28 days–3 months) out of 1,146 initially classified as low risk using Boston criteria were subsequently diagnosed with SBI, treated with antibiotics and recovered without complications.

In the study by Bonadio, [10] 26.8 percent (143/534) of the included infants were considered low risk.[10] The low risk infants according to Milwaukee protocol were managed by injection of ceftriaxon (50mg/kg) before being discharged. Eight of them were hospitalized within 72 hours due to bacteremia (n=1), gastroenteritis (n=4), and paediatrician's preference (n=3). Only 0.7 percent (1/143) of the infants were diagnosed as having SBI (Moraxella catarrhalis bacteremia with a negative repeat blood culture) and were treated with parenteral antibiotics for 72 hours. No complications occurred in these infants.

In the study by McCarthy, [70] 86 low risk (well appearing with WBC: 5,000-15,000/mm3, ABC ≤ 1,500/mm3, UA ≤ 10 WBC/hpf, and stool ≤ 5 WBC/hpf) for SBI infants younger than 2 months were enrolled and treated as outpatients with cefriaxone (50 mg/kg). All infants returned

at day 2 (24 hours for follow up). There were no serious complications. Twelve (14.0%) infants developed transient problems possibly related to intramuscular cefriaxone therapy. Six infants were hospitalized, one for SBI (Neisseria meningitidis bacteremia) and five others for medical and social reasons. The infant with SBI was a 4 week-old female who received ceftriaxone for 7 days. No further data were reported.

Table 7. Management and outcomes of delayed diagnosis and treatment of SBI infants initially classified as low risk of having SBI

Author (year)	Criteria Age of Infants	Early management detail	n/N (delayed SBI diagnosis/total infant at low risk)	Complications
Bonadio, WA (1993)[10]	Combined clinical and laboratory (Milwaukee protocol) 28–56 d	Discharged after injection of ceftriaxon (50mg/kg)	1/143 (0.7%) Bacteremia	None occurred
Bressan, S (2010)[47]	Well appearing + repeated lab test > 12 hrs of fever neonates	All infants were hospitalized upon admission.	5/62 (8.1%) 3 bacteremia; 2 meningitis	No data
Brik, R (1997)[58]	Combined clinical and laboratory (Philadelphia protocol) 0 - 30 d	Low risk infants were treated as outpatient treatment without antibiotics	9/296 (3.04%) 1 bacteremia; 7 UTI	No data
Chiu C (1997)[57]	Combined clinical and laboratory (Rochester criteria) neonates	All low risk infants were hospitalized and closely monitored without antibiotics; 44.3% of infants were reclassified as high risk on 2nd or 3rd day and were given antibiotics	1/131 (0.8%) UTI	7 day course antibiotics Recovered with no complications
Jaskiewicz, J (1994)[23] Combined clinical and laboratory	Combined clinical and laboratory criteria (Rochester criteria) 0 - 60 d	203 (39.7%) of infants were treated without antibiotics (this included 4/5 infants with SBI) Remaining infants were treated with IM ceftriaxone and discharged home	5/437 (1.1%) 2 bacteremia; 3 UTI	None occurred
Kaplan, R (2000)[55]	Combined clinical and laboratory criteria (Boston criteria) 28 - 90 d	NR	3/1146 (0.3%)	None occurred
McCarthy, CA (1990)[70]	Combined clinical and laboratory 11–59 d	Discharged after injection of ceftriaxon (50mg/kg)	1/86 (1.2%)	No data
Pantell, R (2005)[5] The PROS study (office setting)	Laboratory (75%) and clinical criteria (PROS practitioner guidelines) 0 - 90 d	1264 (64%) were treated as outpatients; initially treated 57% of infants with antibiotics unclear how many of these infants had SBI;	2/1975 (0.1 %)	None occurred
Wasserman, G (1990)[67]	Combined clinical and laboratory criteria 0 - 30 d	All infants were hospitalized, 222 (high risk) were treated with antibiotics and 221 (low risk) received no antibiotics	5/221 (2.3%) 3 infants < 2 weeks of age with Bacteremia or bacterial meningitis 2 infants > 2 weeks of age	None occurred

d = day(s); hr(s) = hours; NR = not reported; PROS = Pediatric Research in Office Settings; UTI = urinary tract infection

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)?

Key Findings

Generally, the reviewed criteria tended to show poor predictive values in identifying the presence of SBI (or other sub-types of SBI) amongst high risk infants. This was demonstrated by low positive predictive values (PPVs) across the studies. The PPVs for total SBI varied markedly and ranged from 3.3 percent to 71.4 percent.

Detailed Presentation

For 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).

SBI. The PPVs for total SBI across the combined clinical and laboratory criteria ranged from 3.3 percent[10] to 71.4 percent.[47] Only the minority of the criteria demonstrated PPVs greater than 50.0 percent.[47,48,68,71] These criteria were combined (lack of mild upper respiratory tract infection symptoms in infants or siblings and CRP ≥ 1.87 mg/dL, [68] clinical alone (ill appearance)[71] 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 (Table 2), and other combined criteria (Table 3) showed PPVs below 50.0 percent (range 3.3 percent[10]–48.6 percent[29])[9-12,21-26,28,29,37,49,55,58,60,64,66-68] 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[347]).[30,43,44,47,48,63] The corresponding PPVs for clinical alone criteria were lower than those for combined or laboratory only criteria, ranging from 3.3 percent (age ≤ 1 month versus > 1 month) [30] to 17.5 percent (rapid influenza test results).[30]

Bacteremia/Bacterial meningitis. 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]

Bacterial Meningitis. 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?

Key Findings

The amount of data on harms of immediate antibiotics was limited. In one study, three deaths occurred in neonates with enteroviral infection (two infants) and viral infection (one infant). In two studies, minor intravenous access problems or drug related rash occurred following administration of antibiotics. We found no data on other possibly relevant outcomes such as loss of work time, or effects on quality of life of caregivers.

Detailed Presentation

There was no evidence directly comparing outcomes in the immediate versus delayed treatment groups. We identified 10 studies reporting on immediate antibiotic (or antiviral) therapy administered to infants at high risk of SBI (or HSV) (Table 8). No treatment outcomes were reported for three studies.[10,47,56] The remaining studies reported that febrile infants classified as being at high risk for SBI were administered immediate antibiotic therapy (versus 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 centre to complete their antibiotic treatment course.[72]

In one study,[83] the immediate antibiotic treatment was administered to six infants aged 28 days or younger, of whom three infants had enterovirus and three infants had sepsis/meningitis. Two of the six infants with enterovirus died. None of the two infants who died had SBI. In one study,[47] 51 infants with suspected viral encephalitis (based on clinical findings) were treated with intravenous acyclovir (antiviral drug primary used for treatment of HSV). At admission, none of the tested 47 infants had renal dysfunction. Fifty infants were prescribed antibiotics (cefotaxime). No death and no clinical relapses occurred.

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Table 8. Effects of immediate antibacterial/antiviral therapy in infants at high risk for SBI

Author (year)	Criteria Age of Infants	Management strategy	N/n at high risk n with SBI or HSV	Effect of antibiotic therapy (AEs)
Baker (1993)[12]	Yale Observation Scale 29–56 days	High risk infants were treated with antibiotics for 72 hours	HR: 460/747 SBI: 65/460 (14.1%)	Infiltration of intravenous line 87 (18.9%) Suspected drug-related rash 2 (0.4%)
Baker (1999)[9]	Philadelphia protocol 29–60 days	High risk infants were treated with unspecified antibiotics as inpatients	HR: 321/422 (21/422 pts also at high risk were treated without antibiotics, 3 had SBI) SBI: 43/321 (13.4%)	No complications occurred
Baskin (1991)[56]	Rochester Criteria 28–90 d	All infants were treated with intramuscular ceftriaxone (50 mg/kg) and discharged. infants were followed for 2 to 7 days	HR: NR (13/25 with SBI were at high risk) SBI: 25/NR	NR
Bonadio (1993)[10]	Milwaukee Protocol 29–60 d	High risk infants were treated with ampicillin 50 mg/kg/day or cefotaxime 50 mg/kg/day	HR: 391/534 SBI: 22/391 (5.6%)	NR
Bressan (2010)[47]	Clinical criteria (ill appearance and laboratory tests) 7–28 days	High risk infants were treated with antibiotics (69/156) - but not included in the analysis immediately after admission	HR: 69/156 SBI: 38/69 (55.0%)	NR
Broner (1990)[32]	Clinical (toxic appearance) 4–56 days	High risk infants were treated with intravenous antibiotics	HR: 13 (toxic appearance)/52 SBI: NR (5 total SBI)	No complications occurred
Dore-Bergeron (2009)[72]	Combined clinical and laboratory criteria 30–90 days	High risk infants were treated with intravenous antibiotics	51/NR	Minor intravenous access problems 7 (15.6%)
Dore-Bergeron (2008)[72]	Clinical and laboratory criteria 0–90 days	High risk infants were hospitalized and treated with intravenous antibiotics	HR: 51/118 SBI: 45/51 (88.2%) (UTI)	Minor intravenous access problems occurred in 7/51 (13.7%)

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Table 8. Effects of immediate antibacterial/antiviral therapy in infants at high risk for SBI (continued)

Author (year)	Criteria Age of Infants	Management strategy	N/n at high risk n with SBI or HSV	Effect of antibiotic therapy (AEs)
Jordan (2009)[83]	NR 3–28 days	Parenteral antibiotics for all febrile infants upon admission (no information on antiviral treatment was provided)	NR (this was not a diagnostic accuracy study and the number of infants with high or low risk was not determined) SBI: 62/328 (18.9%) Enterovirus infection (EI): 10/328 (0.3%); 50% of EI infants were < 10 days of age	Death 3/328 (< 0.1%) One with fulminant *S. agalactiae* sepsis (SBI) 2 with enteroviral infection: one developed severe meningitis (PCR testing of CSF for enterovirus) and cardiomyopathy; the other infant with EI was confirmed for positive enterovirus on liver biopsy with molecular diagnostic method
Kneen (2010)[108]	NA 0–28 days (infants under treatment with antiviral agent acyclovir)	Antiviral treatment with intravenous acyclovir; 26 (51%) were admitted to the intensive care unit	NA HSV: 2/51 (3.9%)	No death occurred. No renal dysfunction occurred in 47/51 infants tested for renal function

AE= adverse effects; HR= high risk; HSV= herpes simplex virus infection; NA= not applicable; NR= not reported; SBI=serious bacterial infection; UTI= urinary tract infection

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

This review identified and included 11 studies in which the association between the status of viral infection and the risk of SBI in febrile infants was explored (Table 9).[5,27,41,60,65,73-75,77,78,86]

Key Findings

There was a 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. This finding may not be applicable to neonates.

Detailed Presentation

There was no evidence to assess the probability of having SBI with respect to the presence of HSV infection in febrile infants. We identified four studies reporting prevalence of HSV in febrile infants, however, none of these studies reported concurrent SBI.[39,60,62,63]

The most frequent types of SBI across the reviewed studies were UTI (range: 5.6 percent[73] - 11.3 percent[41]) and bacteremia (range: 1.4 percent[73]–3.8 percent[27]). The types of virus studied were: influenza A/B,[41,60,80,86] RSV,[5,27,60,65,75,77,78,80] nonpolio EV,[27,74] and EV.[60,73] In these studies, the prevalence (or odds) of SBI were compared between the two groups of virus-positive and virus-negative infants. For two studies,[73,86] the number of infants with SBI was not reported for one or two groups, and therefore the prevalence ratios (or risk ratios) could not be calculated. The authors of one study, however, provided the estimates of odds ratio by age groups (Table 9).[86]

Overall, based on the study results, there was an inverse statistically significant association between the status of viral infection and the prevalence (or risk) of SBI. Specifically, there were higher prevalence (or risk) of SBI in infants without viral infection or clinically diagnosed bronchiolitis compared to infants with viral infection or clinically diagnosed bronchiolitis. The observed differences were statistically significant,[27,41,60,65,74,75,77,79,86] regardless of relatively smaller samples and event counts for some of these studies. The prevalence of SBI in virus-positive infants across the studies ranged from 0 percent[78] to 7.0 percent.[65,73,79] The prevalence of SBI in virus-negative infants ranged from 9.6 percent[75] to 19.8 percent.[27] The estimate of odds ratio ranged from 0.08[77] to 0.41[74] (Table 9).

In the study by Byington and colleagues, the prevalence of SBI in low and high risk groups (classified using Rochester criteria) was compared in febrile infants with and without viral infections.[60] All infants in this study were tested for at least one virus. Of the 1,385 infants, 491 (35 percent) were found to have one or more viral infections (EV, RSV, Influenza A or B, Parainfluenza 1, 2, or 3, Rotovirus, Adernovirus, HSV, and Varicella). The rate of concurrent SBI in infants with viral infection was 21/491 (4.2 percent) compared with 110/894 (12.3 percent) in infants without a viral infection. The lowest prevalence of SBI was in the low risk group with a documented viral infection (1.8 percent). In the high risk group, the prevalence of SBI was 5.5 percent when a viral infection was present compared to 16.7 percent when there was negative viral testing.

For infants with RSV,[27,60,65,77,79] the odds ratios for having an SBI ranged from 0.08[77] to 0.58.[65] The odds ratios for those with influenza A/B,[41,60,86] were similar: 0.28 (95 percent CI: 0.16, 0.48),[86] 0.32 (95 percent CI: 0.19, 0.52),[60] and 0.13 (95 percent CI: 0.03, 0.44).[41] Levine

and colleagues reported on a prospective 3 year multicentre study on SBI in infants 0–2 months of life who presented to the emergency department with fever. Based on rapid Respiratory Syncytial Virus (RSV) testing they were able to assess the impact of RSV status on the prevalence of SBI. Consistent with all the viral studies, there was a significant overall decrease in prevalence of SBI when RSV was identified (7.0 percent vs. 12.5 percent; risk difference 5.5 percent: 1.7, 9.4). Although the majority of the SBI were UTI, bacteremia did occur in the RSV positive group. Only 38.0 percent of RSV positive infants had clinical bronchiolitis. The most important observation from this study was the fact that in the young infant subpopulation (<or equal to 28 days) the prevalence of SBI did not differ between RSV positive or negative groups (10.1 percent vs. 14.2 percent; RR: 0.71; 95 percent CI: 0.35, 1.5).[65] In the same study (analyzed data from 5 centers),[80] the prevalence of both SBI (RR=0.19, 95 percent CI: 0.06, 0.59) and UTI (RR=0.23, 95 percent CI: 0.07, 0.70) were significantly lower amongst infants with influenza- or RSV-positive test as compared to those with negative test result. There were no significant differences between the two groups of infants with regards to bacteremia (0 percent vs. 2.2 percent, p=0.15) and meningitis (0 percent vs. 0.9 percent, p=0.6).

Clinical bronchiolitis was also found to be a significant predictor against SBI in three studies.[5,75,78] In the PROS research network study 0/125 (0 percent) cases of SBI in infants with bronchiolitis versus 212/1933 (10.9 percent) in infants without bronchiolitis were reported.[5,76] This study did not provide specific data for the various age groups (within 0-3 months), so it was not clear whether the observed prediction against SBI would apply to the neonatal age group. These results were consistent with data from one study reporting higher prevalence of bacteremia and UTI in infants without bronchiolitis (2.0 percent and 12.0 percent respectively) compared to infants with bronchiolitis (0 percent). Similar results were reported in another prospective study in two pediatric departments from 2005-2007, infants less than 3 months of age who had clinical bronchiolitis versus no clinical bronchiolitis had a significantly decreased chance of SBI 3/136 (2.2 percent) versus 30/312 (9.6 percent) (p = 0.005).[75] The three cases of SBI in the clinical bronchiolitis group were UTI, which clinically resolved with antimicrobial therapy.[75]

In two studies[27,74] of infants with nonpolio EV, the odds of having an SBI relative to those without this virus were 0.41 (95 percent CI: 0.15, 0.95)[74] and 0.12 (95 percent CI: 0.03, 0.40).[27]

Table 9. Concurrent viral and bacterial infection

Study ID	Viral Infection [SBI]	Viral infection +			Viral infection -			Prevalence ratio (%) [95% CI]	OR* [95% CI]
		SBI+ n	Total N	Prevalence (%) [95% CI]	SBI+ n	Total N	Prevalence (%) [95% CI]		
Neonates 0–28 days									
Smitherman (2005)[86]	Influenza A	NR	13	NA	NR	49	NA	NA	NR
Infants 0–60 days									
Kuppermann (1997)[78]	RSV [Bacteremia]	0	36	0	1	50	2.00 [1.88, 5.88]	-	-
	RSV [UTI]	0	33	0	6	50	12.0 [3.00, 21.00]	-	-
Krief (2009)[80]	RSV, influenza [SBI]	3	119	2.5 [0.5, 7.2]	92	690	13.3 [10.9, 16.1]	0.19 [0.06, 0.59]	0.16 [0.04, 0.56]
	RSV, influenza [UTI]	3	123	2.4 [0.5, 6.9]	77	712	10.8 [8.6, 13.3]	0.23 [0.07, 0.70]	0.20 [0.05, 0.69]
	RSV, influenza [Bacteremia]	0	123	0	16	715	2.2 [1.3, 3.6]	-	p=0.15
	RSV, influenza [Meningitis]	0	119	0	6	698	0.9 [0.3, 1.9]	-	p=0.6
Levine (2004)[65]	RSV [SBI]	17	244	7.00 [4.10, 10.90]	116	925	12.50 [10.50, 14.80]	0.60 [0.30, 0.90]	0.58 [0.33, 0.99] [ζ δ]
	RSV [UTI]	14	261	5.4 [3.0, 8.8]	98	966	10.1 [8.3, 12.2]	0.50 [0.30, 0.90]	-
	RSV [Bacteremia]	3	267	1.1 [0.2, 3.2]	22	968	2.3 [1.4, 3.4]	0.5 [0.1, 1.6]	-
	RSV [Meningitis]	0	251	0	8	938	0.9 [0.4, 1.7]	-	-
Titus (2003)[77]	RSV [SBI]	2	174	1.15 [0.43, 2.73]	22	174	12.60 [7.70, 17.60]	0.09 [0.02, 0.38]	0.08 [0.01, 0.36]
Infants 29–90 days									
Smitherman (2005)[86]	Influenza A [SBI]	NR	45	NA	NR	185	NA	NA	0.21 [0.05, 0.93] [ψ] 0.19 [0.03, 1.44] [ζ]

Table 9. Concurrent viral and bacterial infection (continued)

Study ID	Viral Infection [SBI]	Viral infection +			Viral infection -			Prevalence ratio (%) [95% CI]	OR* [95% CI]
		SBI+ n	Total N	Prevalence (%) [95% CI]	SBI+ n	Total N	Prevalence (%) [95% CI]		
Infants 0–90 days									
Bilavsky (2008)[75]	RSV [SBI]	3	136	2.20 [0.60, 6.00]	30	312	9.62 [6.35, 12.89]	0.23 [0.05, 0.76] [θ]	0.21 [0.05, 0.74]
Byington (1999)[74]	Nonpolio EV [SBI]	6	89	6.70 [2.8, 13.3]	38	256	14.84 [10.5, 19.20]	0.45 [0.17, 0.96]	0.41 [0.15, 0.95]
Byington (2004)[60]	EV, RSV, Influenza A/B, parainfluenza, rotavirus [SBI]	21	491	4.30 [2.80, 6.20]	110	894	12.30 [10.15, 14.45]	0.34 [0.21, 0.55]	0.32 [0.19, 0.52]
Dagan (1985)[27]	Nonpolio EV RSV, influenza [SBI]	4	137	2.92 [0.10, 5.34]	19	96	19.79 [11.82, 27.76]	0.14 [0.04, 0.44]	0.12 [0.03, 0.40]
Luginbuhl (2008)[5,76]	RSV [SBI]	0	125	0	212	1933	10.96 [9.62, 12.46]	-	-
Mintegi (2009)[41]	Influenza A/B [SBI]	3	113	2.65 [0.0, 5.6]	47	268	17.5 [13.0, 22.0]	0.15 [0.04, 0.48]	0.13 [0.03, 0.44]
Rittichier (2005)[73]	EV [SBI]	15	214	7.00 [3.59, 10.43]	NR	847	NA	NA	NA
Smitherman (2005)[86]	Influenza A [SBI]	NR	58	NA	NR	234	NA	NA	0.28 [0.16, 0.48] [ψ] 0.14 [0.04, 0.46] [ζ]

EV = enterovirus; NA = not applicable; NR = not reported; RSV = respiratory syncytial virus; SBI = serious bacterial infection; UTI = urinary tract infection; WBC = white blood cell; YOS = Yale Observation Score;

*The odds of SBI in viral infection-positive infants divided by the odds of SBI in viral infection-negative infants

ψ including pneumonia

ζ excluding pneumonia

δ adjusted for age, temperature, YOS, and WBC count

θ relative risk (i.e., rate ratio)

KQ 5. What is the evidence that the prevalence of SBI 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?

Key Findings

The majority of studies were conducted in North American emergency department settings. The prevalence of SBI tended to be higher in the emergency departments versus primary care setting offices. The effect of prevalence of total SBI on the PPVs was possible to be examined only for the Philadelphia protocol and the Rochester criteria. For the Philadelphia protocol, the prevalence of total SBI did not appear to affect the observed PPVs. For the Rochester criteria, higher prevalence of total SBI corresponded to higher PPVs.

Detailed Presentation

In order to assess whether the prevalence of total SBI (and/or HSV) varied depending on the setting (i.e., emergency department vs. primary care) of the study, the included studies reporting the prevalence of total SBI (and/or HSV) were divided by the setting and were matched by the country of conduct. Overall, there were 70 studies included in this section.

Although in one study conducted in the U.S., nine SBI cases had been identified amongst infants 3 months or younger, the prevalence of SBI could not be calculated due to lack of the appropriate denominator (i.e., the number of infants with culture results).[113] There was insufficient data to compare the prevalence of bacteremia or meningitis between emergency and primary care settings.

For the studies conducted in North America (Table 10), the prevalence of total SBI in the emergency departments ranged from 4.1 percent[10] to 25.1 percent.[25] More than half of the studies conducted in emergency departments of North America reported the prevalence of total SBI ≥10.0 percent. One U.S. study,[81] reported an increase in the rate of SBI for the period of 2002–2006 compared to 1997–2001 (14.4 percent 6.5 percent, p = 0.001). This increase was reported to be due to an increase in *E. coli* UTI particularly in infants 31–3 months of age. Of the 3 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 (Table 11), the prevalence of total SBI was numerically similar in emergency departments versus primary care setting (17.7 percent–25.2 percent vs. 16.4 percent).[57,66]

The prevalence of total SBI in the two Spanish studies (both emergency departments) were 13.1 percent[41] and 18.9 percent (Table 11).[83] In the third Spanish study, the prevalence of SBI was significantly higher in infants younger than 29 days than in those older than 29 days (20.1 percent vs. 12.6 percent, p=0.04).[84] This study did not report the crude prevalence of SBI based on the total sample.

In two prospective studies conducted at a hospital emergency department in Israel (Table 11), the prevalence of total SBI were 10.8 percent (infant age: 0 - 2 months)[45] and 11.3 percent (infant age: 0–3 months).[46] In one of these studies,[45] the prevalence of UTI, bacteremia, and pneumonia amongst febrile infants 2 months or younger were 10.8 percent (90/833), 8.1 percent (68/833), 1.3 percent (11/833), and 1.2 percent (10/833), respectively. Another Israeli study,[37]

reported an estimate of the prevalence of SBI in neonates (0–28 days) of 19.4 percent The prevalence of SBI in this study 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) admitted to emergency departments was 25.3 percent.

Across all studies, the prevalence of total SBI was higher in the neonates (age: 0–28 days) ranging from 11.5 percent[87] to 25.3 percent[47] compared to the older infants (age: > 28 days) in whom it ranged from 4.1 percent[10] to 13.0 percent.[113]

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 whether a study was conducted in an emergency department or primary care setting in North America or Taiwan (Tables 10–11). 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. The enrollment rate (n analyzed/N enrolled) in the 11 studies of Philadelphia protocol [9,11,12,22,25] and Rochester criteria [23,24,27,56,57,60] was uniformly high (> 70.0 percent). For example, the enrollment rate in six studies was 100.0 percent,[9,11,12,27,56,57] and in four studies > 80.0 percent.[22,23,25,60] The enrollment rate was less likely to affect the differences in prevalence of SBI across studies.

Table 10. Prevalence of serious bacterial infection by setting for studies across North America

Author (year)	Study Period	Age Range	Prevalence n/ N (%) SBI (or SBI type)	PPV (%) [95% CI]
Emergency Setting				
Andreola (2007)[87]	2004- 2005	< 30 d	6/52 (11.5) SBI	NR
		< 90 d	20/175 (11.4) SBI	NR
Bachur (2001)[49]	1993–1999	0–90 d	373/5,279 (7.0) SBI	21.0 [19.0, 23.0]
Bachur (2001)[52]	1993–1999	0–29 d	73/868 (8.4) UTI	48.4 [39.4, 57.5]
Baker (1993)[12]	1987–1992	29–56 d	65/747 (8.7) SBI	14.0 [11.0, 17.0]
Baker (1999)[9]	1994–1996	29–60 d	43/422 (10.2) SBI	14.0 [10.0, 17.7]
Baker (1999)[11]	1994–1996	3–28 d	32/254 (12.5) SBI	18.6 [12.0, 25.0]
Baker (1990)[64]	1987–1988	29–56 d	12/126 (9.5) SBI	11.4 [3.7, 27.6]
Baskin (1992)[56]	1987–1990	28–89 d	27/501 (5.4) SBI	NR
Berkowitz (1985)[109]	1978–1979	< 60 d	10/239 (4.2) sepsis/meningitis	NR
Bonadio (1993)[10]	1991–1992	29–60 d	22/532 (4.1) SBI	5.9 [3.6, 8.2]
Bonadio (1993)[21]	1991–1992	0–29 d	29/233 (12.4) SBI	37.3 [25.3, 50.8]
Bonadio (1991)[36]	1986–1990	30–60 d	34/683 (5.0) SBI	26.0 [11.8, 46.6]
Bonadio (1987)[112]	1986–1987	0–28 d	8/55 (14.5) SBI	NR
Bonadio (1994)[38]	1989–1993	60–90 d	33/356 (9.3) SBI	NR
Bonadio (1992)[44]	1985–1991	4–60 d	81/1,009 (8.0) SBI	NR
Bonadio (1987)[114]	1984–1985	0–60 d	12/159 (7.5) UTI	NR
Bonadio (1991)[88]	January–November 1990	28–60 d	18/161 (11.2) SBI	NR
Bonsu (2007)[50]	1993–1999	0–89 d	307/3,765 (8.1) UTI/sepsis	17.0 [15.1, 19.0]
Bonsu (2003)[111]	1992–1999	0–89 d	38/3,810 (1.0) bacteremia	2.0 [1.2, 3.2]

Table 10. Prevalence of serious bacterial infection by setting for studies across North America (continued)

Author (year)	Study Period	Age Range	Prevalence n/ N (%) SBI (or SBI type)	PPV (%) [95% CI]
Broner (1990)[32]	NR	4- 56 d	5/52 (9.6) Bacteremia	10.0 [0.5, 45.8]
Brown (2005)[43]	1999–2002	< 28 d	8/66 (12.0) SBI	21.0 [7.8, 50.2]
Byington (2004)[60]	1996-2002	1- 90 d	109/888 (12.3) SBI	16.6 [13.8, 20.0]
Byington (2003)[93]	1999-2002	1- 90 d	105/1,298 (8.0) SBI	NR
Byington (1999)[74]	1996–1997	0–90 d	44/345 (12.8) SBI	NR
Caviness (2008)[63]	2001–2005	0–28 d	119/800 (14.8) SBI	18.1 [13.2, 24.2]
Crain (1988)[31]	NR	0- 15 d	3/35 (8.5) sepsis/meningitis	27.3 [7.3, 60.7]
Crain (1990)[85]	1982–1987	8- 57 d	33/442 (7.4) UTI	64.0 [42.6, 81.3]
Crain (1982)[33]	1979–1981	0–60 d	5/134 (3.7) bacteremia	4.5 [1.6, 10.6]
Dayan (2002)[13]	1998–2000	1–60 d	27/193 (14.0) UTI	56.6 [37.6, 74.0]
DeAngelis (1983)[115]	1978–1981	0–60 d	39 /290 (13.4) SBI	NR
Ferguson (2008)[116]	2004–2005	30–60 d	9/90 (10.0) SBI	NR
		60–90 d	10/100 (10.0) SBI	NR
Ferrera (1997)[24]	1990–1994	0–28 d	22/134 (16.4) SBI	26.8 [17.2, 38.8]
Filippine (2001)[62]	1995–1997	0–30 d	27/113 (23.8) SBI	NR
Garra (2005)[25]	1998–2004	0–56 d	65/259 (25.1) SBI	13.9 [11.0, 17.0]
Gomez (2010)[30]	2003–2008	0–90 d	198/1,018 (19.4) SBI	NR
		0–90 d	23/1,018 (2.2) bacteremia	12.5 [5.4, 22.6]
Grover (1999)[117]	1992–1993	0–60 d	7/48 (14.6) SBI	NR
Herr (2001)[28]	1999–2000	< 59 d	41/344 (12.0) SBI	12.9 [8.8, 18.2]
Hoberman (1993)[91]	1990-1991	0–59 d	306/14 (4.6) UTI	NR
Hsiao (2006)[118]	2003-2004	57–90 d	NR (8.8) SBI	NR
Jaskiewicz (1994)[23]	1984–1992	0–60 d	66/931 (7.0) SBI	12.3 [9.6, 15.6]
Kadish (2000)[22]	1993–1996	1–28 d	45/372 (12.1) SBI	21.0 [15.5, 27.6]
Kaplan (2000)[55]	1993–1997	28–90 d	191/2,190 (8.7) SBI	16.2 [14.0, 18.6]

Table 10. Prevalence of serious bacterial infection by setting for studies across North America (continued)

Author (year)	Study Period	Age Range	Prevalence n/ N (%) SBI (or SBI type)	PPV (%) [95% CI]
King (1987)[39]	1978–1982	< 60 d	4/97 (5.4) bacteremia or meningitis	5.5 [0.2, 29.3]
Kuppermann (1997)[78]	1993–1995	0–60 d	6/86 (7.0) UTI	NR
Kuppermann (1999)[119]	1994–1995	0–60 d	7/30 (23.3) SBI	NR
Krief (2009) [80] Levine (2004)[65]	1998–2001	0–60 d	123/1,169 (11.4) SBI	NR
Maniaci (2008)[61]	2005–2007	0–90 d	30/234 (12.8)	NR
Meehan (2008)[69]	NR (4 Years study)	0–90 d	192/2003 (9.6%) SBI	4.9 [2.5, 9.1]
Rittichier (2005)[73]	1996-2002	0–90 d	15/214 (7.0) SBI	NR
Rosenberg (1985)[40]	1981–1982	0–60 d	5/122 (4.1) bacteremia	NR
Stanley (2005)[35]	1993–2000	0–90 d	480/5,279 (9.1) SBI	NR
Titus (2003)[77]	1997–2001	0–60 d	24/348 (6.9) SBI	NR
Wasserman (1990)[67]	NR	< 60 d	22/236 (9.3) SBI	21.6 [16.5, 27.7]
Watt (2010)[81]	2002–2006	0–90 d	52/361 (14.4) SBI [UTI: 45/52 (86.0%); 38 cases in infants 31-90 d]	NR
	1997–2001	0–90 d	20/307 (6.5) SBI [UTI: 13/20 (65%), 9 cases in infants 31–90 d]	NR
Wolff (2009) [42]	2000–2007	45–90 d	130/1,950 (6.6) SBI	7.1 [6.7, 7.3]
Zorc (2005)[65]	1999–2001	1–60 d	91/995 (9.0) UTI	5.6 [1.8, 14.5]
Primary Care Setting				
Caspe (1983)[34]	1974–1979	0–30 d	7/107 (6.5) bacteremia	NR
		30–60 d	4/198 (2.0) bacteremia	27.3 [7.3, 60.6]
Dagan (1985)[27]	1982–1984	0–90 d	23/233 (9.9) SBI	24.7 [16.4, 35.2]
Pantell (2004)[5]	PROS Study: 1995–1998	0–90 d	63/3066 (3.6) bacteremia/meningitis	NR
			212/2058 (10.3) SBI (excluding Gastroenteritis)	NR

d=days; PPV = positive predictive value; PROS = Pediatric Research in Office Setting; SBI = Serious Bacterial Infection; UTI= urinary tract infection;

Table 11. Prevalence of serious bacterial infection by setting for studies conducted in other countries (Taiwan, Israel, Spain)

Study ID	Study period	Age range	Prevalence n/ N (%) SBI (or SBI type)	PPV(%) [95% CI]
Emergency Setting In Taiwan				
Chen (2009)[82]	2003–2004	0–90 d	34/135 (25.2) SBI	NR
Chiu (1994)[66]	1992–1993	4–31 d	45/254 (17.7) SBI	30.8 [22.9, 40.0]
Lin (2000)[53]	1997–1998	< 60 d	22/162 (13.5) UTI	34.0 [21.3, 49.4]
Emergency Setting In Israel				
Jordan (2008)[83]	2003–2004	0–29 d	62/328 (18.9) SBI	NA
Mintegi (2009)[41]	2003–2008	0–90 d	50/381 (13.1) SBI	2.7 [0.7, 7.5]
Mintegi (2010)[84]	2003–2007	0–29 d	26/124 (20.1) SBI (UTI, bacteremia, pneumonia)	NA
		30 d–90 d	71/561 (12.6) SBI	NA
Emergency Setting In Spain				
Bilavsky (2009) [46]	2005–2008	0–90 d	102/892 (11.3) SBI	NR
Yarden-Bilavsky (2009/2010) [45]	2006–2008	0–60 d	134/1257 (10.7) SBI	NA
			68/833 (8.1) UTI	NA
			11/833 (1.3) bacteremia	NA
			10/833 (1.2) pneumonia	NA
Shwartz (2008) [37]	1997–2006	< 28 d	87/449 (19.4) SBI	32.7 [29.5, 35.1]

Table 11. Prevalence of serious bacterial infection by setting for studies conducted in other countries (Taiwan, Israel, Spain) (continued)

Study ID	Study period	Age range	Prevalence n/ N (%) SBI (or SBI type)	PPV(%) [95% CI]
Primary Care Setting (only for Taiwan)				
Chiu (1997)[57]	1994–1995	4–28 d	41/250 (16.4) SBI	33.6 [25.1, 42.1]

d=days; PPV = positive predictive value; SBI = serious bacterial infection; UTI= urinary tract infection;

KQ6. Clinicians base decisions about initial diagnostic work-up and treatment of febrile infants not solely on the infants' medical status but also on their assessments of nonclinical 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 follow-up 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?

Key Findings

Four studies conducted in North America that included children 0–3 months of age reported the degree of parental compliance to the followup visits/telephone calls which ranged from 77.4 percent to 99.8 percent. There was no evidence on parental compliance to the followup visits/telephone calls for infants 3–6 months. Similarly, there was a lack of evidence regarding the influence of parental factors or clinical setting on the degree of parental compliance to the followup visits/telephone calls.

Detailed Presentation

Four studies were included in this section.[56,59,72,80] The study by Krief,et al., was reported in 3 publications.[65,79,80] Three studies were conducted in the United States (1987–2001),[56,59,80] and one study was conducted in Canada (2005)[72] (Table 12). All studies were prospective in design and included 4,593 children aged of 0–3 months.[56,59,72,80]

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 rates of parental compliance to telephone or return visit followups.

In the study by Baskin (1992) conducted in the U.S.,[56] outpatient treatment of febrile infants (28–89 days) and adherence to strict follow up protocol was investigated as an alternative to hospital admission during the period of 39 months (1987–1988). The included 503 infants were

febrile well appearing (≥ 38° C) with peripheral leukocyte count < 20 x 109 cells/L, cerebrospinal fluid leukocyte count < 10 x106/L, and without any urinary leukocyte esterase. All infants were required to have a caretaker available by telephone. Follow up was obtained for all except one infant (99.8 percent). Infants were initially treated with intramuscular injection of ceftriaxone (50 mg/kg) and then discharged from the emergency department. A second injection of ceftriaxone was administered on return visit in 24 hours. Follow up calls were conducted at 12 hours, 2 days, and 7 days later after first entry to ED. When culture results became available, patients with bacterial growth in cultures of blood, CSF, urine, or stool were immediately recalled to the emergency department for appropriate antimicrobial therapy.

Twenty seven of 503 (5.4 percent) infants were identified with SBI. A 24 hour visit and administration of 2nd dose of ceftriaxone was documented for 494 (98.0 percent) of infants. A 48 hour telephone call was made for 475 (94.0 percent) and a 7 day call for 482 (96.0 percent). Overall some follow up was obtained for all but one infant. All infants without SBI 453 (95.2 percent) were treated successfully as outpatient. Twenty three infants without SBI (4.8 percent) were hospitalized due to concerns documented during follow ups. Two of these infants were hospitalized more than 24 hours due to concerns about parental supervision.

In a prospective multicenter U.S. study by Krief et al (2009)[65] during the period of 1998 - 2001, the risk of SBI in infants with or without influenza virus infections in 1091 infants ≤ 2 months of age was compared. The Yale observation scale (YOS) score was determined by the examining physician upon admission to ED (prior to laboratory evaluations). Eighty five percent (n=712) of infants tested for influenza virus were admitted to the hospital. Telephone follow ups on patients discharged from the ED (n=132) within 4–7 days were performed and were successfully completed for 103 (78.0 percent) infants. No other information about noncompliant infants was reported.

In one Canadian study by Dore-Bergeron (2008),[72] the feasibility of ambulatory treatment of 67 febrile infants (aged 33-85 days) with presumed UTI presented to ED of a tertiary hospital was investigated. The diagnosis of UTI was confirmed for 86.6 percent of infants treated in a Day Treatment Center (DTC). Seven infants were subsequently admitted to hospital due to confirmed bacteremia or other complications. The treatment protocol for ambulatory patients included a single dose of intravenous gentamicin, a single dose of ampicillin and 2 or 3 doses of oral amoxicillin until the next visit to DTC in 24 hours. Parents were instructed to monitor the fever every 4 hours during 24 hours after initial visit to ED. Daily administration of intravenous antibiotics was continued at DTC until the infant was afebrile or diagnosed with SBI (UTI) in which case full course of antibiotic treatment would follow. Four infants were hospitalized because of parents' refusal to follow up with the DTC protocol. Parental compliance with DTC visits and with antibiotic treatment at home was 98.3 percent and 80.4 percent, respectively. There were no differences in rate of compliance with DTC treatment between parents of younger infants (≤ 2 months) and those of older infants (2-3 months).

Adherence of ED physicians to patient referral to the appropriate setting (DTC or hospital ward) was somewhat lower for younger infants, but this association was not statistically significant (comparing <2 month -old children with older children: crude OR: 0.5; 95 percent CI: 0.2–1.5). The authors conclude that ambulatory treatment of infants 1-3 months of age with febrile UTI is a feasible option.

One U.S. study by Condra (2010),[59] investigated the costs and complications involved in the inpatient treatment with antibiotic therapy for 62 febrile infants aged 29–60 days. This study included infants meeting Philadelphia criteria for low risk for SBIs during a 16 months study

period. Six (9.7 percent) of the 62 low risk subjects were discharged from the ED by the physician after a full evaluation for sepsis. Five (83.3 percent) discharged infants required reevaluation, and two (33.3 percent) required reevaluation and hospitalization within 24 hours of discharge (one for an erroneous positive blood culture and one for continued fever and newly documented pneumonia). Despite meeting low-risk criteria, all remaining 56 febrile infants were hospitalized and received intravenous antibiotics.

Followup calls were scheduled and were successful on days 2 (77.4 percent), 7 (85.4 percent), and 14 (83.9 percent) after discharge. All six subjects (100.0 percent) discharged directly from the ED did have medical followups within 48 hours. Medical followup with primary care provider was not made for one third (27.4 percent) of infants discharged after hospitalization. This study also reported that after the experience of hospitalization most parents preferred discharge rather than admission.

There was a lack of evidence regarding the influence of parental factors or clinical setting on the degree of parental compliance to the followup visits/telephone calls.

Table 12. KQ6 Factors influencing the likelihood of parental adherence to followup schedule and treatment recommendations for febrile infants 0–6 months of age

Author, (year) RefID Country	Study Design/objective Setting Study period	Population characteristics	Treatment characteristics	Followup details	Results
Baskin, MN (1992)[56] US	-Prospective -ED -1987–1997	N=503 infants 28–89 d (67% 28-60 d, 33% 61-89 d); with fever without a source–476 were treated as outpatients and were followed Age: mean 55 (SD 17) d No other characteristic reported	IMI of Ceftriaxone (2 doses within 24 hrs) pending culture results	3 phone calls (1–12 hrs; 2–48 hrs; 3–7 d post discharge) and 1 return visit to the ED in 24 hrs post initial visit	Infants with fu at 24 hrs: 494 (98%) who had a 2nd dose of ceftriaxone Infants with fu at 48 hrs: 482 (96%) There was concern about 2/476 (0.42%) parents of infants without SBI about parental supervision — These infants were hospitalized > 24 hrs of initial entry
Condra SC (2010)[59] US	Prospective observation/ evaluation of cost and complications in inpatient treatment of febrile infants 29-60 d of age Period: NR – total length of study was 16 months	N = 62 infants 29–60 d; fever without a source; met a criteria derived from Philadelphia for Low Risk for SBI 55% male median age: 44 d 39 (63%) White; 18 (29%) African American, 5 (8%) Hispanic (range 29 -60 d) White (63%), African American (29%), Hispanic (8%). 8 (12.9%) Group B Streptococcus +ve or unknown (the mothers treated with peripartum antibiotics)	Despite meeting LR criteria, 56/62 (90.3%) infants were admitted and received IVI antibiotics 6/62 (9.7%) were LRI and discharged from the ED after a full sepsis workup.	3 phone followups with parent and primary care provider (PCP) within the 2 wks after discharge + contact with PCP at 14 d post discharge Questionnaire on 1-Intants' health status 2-compliance 3-hospital charges	Compliance with phone calls after initial discharge (reported for FI who were managed as inpatients 56 (90.32%)]: d 2: 77.4%; d 7: 85.4%; d 14: 83.9% All 6 subjects (100%) discharged directly from the ED did have medical followup within 48 hours with PCP Parents preferred discharge to admission (66%-70%) 5/6 (83.3%) discharged infants required reevaluation and 2/6 (33.3%) were hospitalization within 24 hrs of discharge-one for a +ve blood culture (later determined to be a contaminant) and one for continued fever & newly documented pneumonia. Complications in outpatients:

Table 12. KQ6 Factors influencing the likelihood of parental adherence to followup schedule and treatment recommendations for febrile infants 0–6 months of age (continued)

Author, (year)RefID Country	Study Design/objective Setting Study period	Population characteristics	Treatment characteristics	Followup details	Results
Dore-Bergeron, MJ (2009)[72] (10351 commentary) Canada	Prospective cohort/ to investigate feasibility of ambulatory tx at day treatment centre (DTC) One tertiary-care pediatric ED Period: 2005	N=118 FI 30–90 d with presumed UTI Age: median age for 67 FI admitted to DTC = 66 d (range: 33– 85 d)	Inpatient tx (protocol not described) if any: abnormal CSF, toxic appearance, underlying medical problems, abnormal creatinine levels, parental refusal to fu in DTC, or outpatients tx Ambulatory tx protocol: single IVI gentamicin (5 or 2.5 mg/kg)+ 1 dose IVI ampicillin, & 2 or 3 doses oral amoxicillin, to be taken until the 1st visit to DTC in 24 hrs. At DCT IVI gentamicin daily until the child was afebrile. If UTI was confirmed tx with antibiotics were started.	In outpatient tx, monitoring the fever every 4 hrs + return the child after 24 hrs	67/118 (56.8%) of FI were admitted to DTC. Rate of parental compliance with DTC visits: 98.3%. Successful tx in the DTC (attendance at all visits, normalization of temperature within 48 hrs, -ve control urine & BC results, & absence of hospitalization): 86.2% of pts with confirmed UTI Compliance with guidelines of antibiotic tx: 80.4%; hospitalization during the course of tx in DTC: 12.1% Adherence of ED physicians to patient referral to the appropriate setting (DTC or hospital ward): lower but not statistically-significant for younger infants, [crude OR, comparing < 60-day-old children with older children: 0.5 (95% CI: 0.2, 1.5)]

Table 12. KQ6 Factors influencing the likelihood of parental adherence to followup schedule and treatment recommendations for febrile infants 0–6 months of age (continued)

Author, (year)RefID Country	Study Design/objective Setting Study period	Population characteristics	Treatment characteristics	Followup details	Results
Krief (2008)[65,79,80] US	Prospective cross sectional/ to determine the risk of SBIs in FI with or without influenza virus infections 5 pediatric ED clinics (original report of this trial include 8 ED hospitals) 3 consecutive influenza seasons 1998-2001	N=844 FI ≤ 60 d, n=844 FI +ve for influenza virus (original report included 1025 infants) Age: mean 35.8 d, 55% male, median YOS score (IQR 6-8)	Yale Observation Scale (YOS) was used as a tool to determine infants' status. Antibiotic therapy and/or hospitalization, were at the discretion of the responsible physician & not determined by study protocol	One telephone fu on patients discharged from the ED within 4 to 7 d	Compliance with phone fu: 103/132 (78.0%) of discharged infants. 7 (1%) (patients without CSF cultures were determined not to have bacterial meningitis by telephone fu) No information about characteristics of compliant or noncompliant parents/infants was reported.

BC= blood culture; CPT-4=Current Procedural Terminology, Forth Revision CSF=cerebrospinal fluid; d=day/s; FI=febrile infant; fu=follow up; HR= high risk for SBI; hr/s = hour/s; ICD-9-CM=International Classification of Diseases, Ninth Revision, Clinical Modification; IMI = intramuscular injection; IQR=interquartile range; IVI=intravenous injection; LP=lumbar puncture; LR= low risk for SBI; LRI=low risk infants; mo/s= month/s; N = number of participants; #, n, N=number; NR= not reported; RefID=Reference Identification; SBI= serious bacterial infection; tx=treatment; US = United States; UTI= urinary tract infection; wks = weeks; YOS= Yale Observational Scale; yrs = years;

Excluded Studies- Qualitative Description

Nine studies reported somewhat relevant outcomes in pediatric population (age 0–6 months) but data was not stratified by age.[120-128] A brief summary of these studies is provided in this section.

In a U.S. quasi-experimental study by O'Neill-Murphy (2001),[124] education (interactive fever education program and the standard written fever pamphlet) on fever and its effect on parental anxiety in parents of febrile ($> 38.4°$ C) children 3 months to 5 years of age was investigated. Outcomes included correct use of a thermometer, fever home management skills, and appropriate fever telephone follow up. Both intervention programs were equally effective in improving all outcomes. This information was not reported for parents of children less than 6 months of age.

In another study by Sarrell (2003),[123] impact of a single session education program on parental knowledge and approach to low grade childhood fever ($< 38.5°$ C) was investigated. This study included parents of children with a broad age range (mean age of youngest child 53.5 months). This study indicates that parental knowledge of fever management in children can be improved by reinforced educational session. The outcomes were not stratified by age groups.

One study by Hemphill (1998),[125] reported compliance rates in 423 febrile children aged 3 months - 10 years. In this study, the follow up rates during the period of 1993-1994 were compared between two medical systems in U.S. with preset appointments after ED release and free medical care (WHMC); or one in which parents must arrange follow up appointments after ED release (FFX). One to 7 days telephone follow ups were conducted. Variables associated with poor followup compliance for the entire study population were: Hispanic children (OR: 2.5, 95 percent CI 1.3-4.8), children within the FFX system of follow ups (OR: 2.5, 95 percent CI: 1.1-5.3), children whose parents did not speak English (OR: 2.8, 95 percent CI 1.2-6.6), and children who were told to follow up in 2–3 days after the ED visit rather than in 1 day (OR 1.7, 95 percent CI 1.3-2.2). Compliance to follow up in the WHMC system was better compared with that in the FFX system (92.0 percent vs. 67.0 percent, p < 0.001). For FFX alone the following factors were associated with poor follow up: Hispanic ethnicity, self-payer status, lack of a primary physician for follow up, the diagnosis of otitis media, and follow up in > 24 hours.

In one study by Crane (2000)[121] parents' compliance to after-hours telephone advice given by pediatric residents in a continuity clinic in U.S. was investigated. Study population consisted of 412 consecutive patients enrolled in the resident-staffed pediatric continuity clinic with access to a telephone triage system. Only 21.0 percent of chief complaint of children was fever. No specific outcomes for the febrile children were reported. Overall 412 (87.0 percent) of caregivers complied with the advice given over the telephone by resident. The study reports no discrepancy in caregiver compliance based on the child's age. Most of the 474 calls were about children younger than 1 year. Only slightly higher levels of compliance were noted among parents of children younger than 3 months, whereas lower levels of compliance were found in parents of children aged 1–3 years.

In one U.S. study by Baker (2009),[122] the impact of a brief educational video shown to parents during an emergency department visit for minor febrile illness was investigated. 280 caregivers of febrile children 3–36 months were enrolled into two intervention groups (either an 11 minutes fever education video or a control child safety video). There was no difference between the rates of return visit to ED for fever for intervention or control groups. The consensus among the three blinded independent ED physician reviewers was that 30/81 visits (37.0 percent) were medically necessary in the intervention group compared with 21/81 (25.9 percent) in the

control group (statistically not significant, p = 0.07). The overall rate of medical necessity was found to be 31.5 percent.

In a prospective cohort study by Gauthier (2004),[126] feasibility and complications of outpatient management with IV antibiotics among 212/291 episodes of UTI (72.9 percent) in 275 febrile infants and children (3 months to 5 years) treated at a day treatment center of a tertiary care pediatric hospital was investigated. This study was conducted in the U.S. in 2002-2003. In this study children who appeared nontoxic were treated with IV ampicillin and three doses of oral amoxicillin to be taken until the visit at the day treatment centre within the next 24 hrs. Parents were asked to measure the child's temperature every 4-6 hrs during IV treatment. In total there were 202 children treated at the DTC, 65 children treated as inpatient, and eight who were discharged from the ED with oral treatment. In 9/71 hospital admissions, the child was admitted due to parents refusal or inability to comply with day treatment center treatment protocol. Overall, the adherence to protocol for both physicians and parents were described as excellent. The data for infants and children under 6 months of age was not presented.

Baker (1999),[127] in a U.S. survey of three private practices, and one urban hospital based nonprivate practice during a 2 week period in 1996 compared compliance with recommended ED or office visit referrals in the two settings. Pediatric telephone triage and advice system (developed by Barton D. Schmitt) was used to evaluate medical complaints and suggest appropriate management including referral for physician evaluation (immediate, 4 hours, 24 hours, 48 hours, 72 hours, 2 weeks) and/or advice for caregiver for management in the home. In total 663 calls were received from 377 nonprivate practice patients (age range 1–192 months; mean 39 months) and 286 for private practice patients (age range 1–242 months; mean age 58 months). Only six percent of all calls were based on a primary complaint of fever. Other complaints included respiratory complaints (21.0 percent), trauma (14.0 percent), rash (10.0 percent) and miscellaneous (36.0 percent). Significantly more nonprivate practice patients were referred to their primary care physician for an office visit (p = 0.005) or were referred to an ED or urgent care facility for immediate evaluation (p=0.01). There were no differences between compliance rates of the two settings. Data was not stratified for infants with fever.

In one retrospective study by Vidwan, G (2010),[128] conducted in U.S. at an urban academic tertiary care pediatric hospital ED during the period of 2000-2005, management and outcome of focal bacterial infections in nontoxic infants under 2 months of age was investigated. In this study febrile (39) and afebrile infants (158) were included. Twenty-three (59.0 percent) of the febrile infants were discharged home from the ED. Two (8.7 percent) of these infants were returned to the ED within 72 hours; both were initially diagnosed with acute otitis (AOM) media and had planned followups as no primary care was available. No other information regarding the follow up visits or mode of contact was provided.

Discussion

The synthesis of the literature on the diagnosis of serious bacterial illnesses (SBI) and invasive herpes simplex virus infection in infants less than 3 months of life has been challenging. In general, there is a lack of standard definitions in this field. Even simple issues such as what constitutes a fever or what should be included in the definition of SBI vary widely. The increase in precision of testing over time (i.e., aseptic meningitis vs. enteroviral meningitis), and emergence of different types of testing make it difficult to standardize the above mentioned definitions.

The evaluation of a patient is not always a one-time event and experienced clinicians value the ability to followup a patient over time for serial reassessment. Only the minority of studies report on reassessment and reassignment of the clinical status [26,57] and variable or no followup durations are reported. Additionally, only a fraction of studies reported to have employed lumbar puncture to diagnose bacterial meningitis. Similarly, majority of studies reporting the use of lumbar puncture did not employ this test on all included infants, thereby raising the possibility of incorrect test interpretations. Also, the vast majority of the studies did not report on long-term followup where partially treated meningitis might have been identified.

The heterogeneity of studies has precluded meta-analysis; therefore, simple summary statistics were not available except 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. Moreover, the diagnostic test accuracy results for infants older than 3 months of age reported in some studies were not considered in this review (KQ1a). Such studies were included in the review only if they reported other relevant data (e.g., prevalence of SBI, outcomes related to management of febrile infants).

The clinical conundrum is how to balance the risk of missing an SBI (with potentially a devastating outcome) with the risks associated with diagnostic and management strategies. To date, a tremendous amount of resources and effort has been focused on developing tests, protocols, and criteria to attempt to minimize the first while almost ignoring the latter. The literature has revealed that the field of febrile infants less than 3 months is not homogenous and there are factors that either increase (i.e., neonatal age group) or decrease (i.e., viral syndrome) the risk and also the testing strategy accuracy. Equally heterogeneous are the risks associated with the specific types of SBI (e.g., urinary tract infections, bacteremia, and meningitis). A clinician fears the consequences of missing a case of meningitis much greater than missing a urinary tract infection; however the data are lacking to determine the accuracy of detecting the rarer and more devastating meningitis.

This systematic review has several strengths. We were able to calculate the test accuracy characteristics from raw data when possible; we provided test accuracy characteristics on the different types of SBI (UTI, bacteremia, meningitis) and for the neonatal period. To our knowledge, this is the first systematic review to seek the 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 prevalence of SBI, and to identify the factors that influence compliance in febrile infants or other infants with serious medical problems in infants 0–6 months of age.

KQ 1a. 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)?

KQ 1b. How do these findings vary by age within the age range 0–3 months?

The formal scoring instruments were the most evaluated standard approach used across multiple sites, with the Rochester criteria being tested the most. These criteria reported a higher sensitivity and negative predictive value compared with clinical criteria or only laboratory criteria. The use of other combined clinical and laboratory criteria also yielded high sensitivity and negative predictive values. Since these criteria were developed for having a high sensitivity, specificity across these criteria tended to be fairly low. There was a consistent trend of similar test characteristics between total SBI and bacteremia and meningitis across the criteria and various other tests, however reflecting the small numbers, the confidence intervals were large.

Generally, the studies evaluating clinical criteria alone revealed test characteristics (i.e., tendency towards higher specificity and lower sensitivity) that were not appreciably different from laboratory testing. Both types of tests demonstrated lower sensitivity and higher specificity values compared to combined criteria. Therefore, clinical or laboratory criteria alone may have limited ability to rule out the presence of SBI.

The pooled sensitivity estimates for the Rochester criteria and Philadelphia protocol were similar. Given the similar test accuracy between the two criteria, attention should be paid to the differences. Where the Philadelphia protocol requires the evaluation of the cerebrospinal fluid by lumbar puncture and a chest x-ray in the 1-2 month old group to define the low risk group, the Rochester criteria identifies the low risk group in 0 to 2 month old infants without using LP and CXR.

The neonatal period (0–28 days of life) was shown to 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 correctly identifying the presence of SBI in the neonates than in older groups of infants.

There remains controversy about the need for lumbar puncture in infants with fever. In our review, six studies reported to have misclassified eight (out of 42) cases of meningitis into low-risk for SBI (total number of meningitis were reported only in fives 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.

KQ 1c. 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 herpes simplex virus infection (HSV)? How do these findings vary by age within the age range 0 to 3 months?

Little evidence on invasive herpes simplex virus infection in febrile infants included in this systematic review does not indicate the lack of clinical cases. The literature mainly focused on the end diagnosis of HSV,[129] rather than the clinical syndrome of a febrile infant. When invasive herpes simplex virus infection is reported in large series of febrile infants, the numbers are very small. In a recent study, Caviness et al. reported that during the season, enterovirus infection was 20 times more likely and a serious bacterial illness was 23 times more likely to occur in hospitalized febrile neonates as compared with HSV in febrile infants.[63] This lack of evidence is likely due to the fact that HSV does not routinely present with fever (3/10 in Caviness 2008 study[63]) and the fact that herpes simplex infection due to skin eyes and mouth infection were likely excluded from other studies as they represent a focus of infection. Given the lack of evidence of diagnostic accuracy and the inability to target and adequately screen mothers,[130,131] we are left only with expert opinion.[132]

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)?

There were several studies that used clinical and laboratory criteria to identify infants at low risk for SBI. The first study to use this approach used the Rochester criteria and showed a high negative predictive value of 99.3 percent in infants < 3 months of age.27 Other studies that used the Rochester criteria showed similar negative predictive values (93.7–99.2 percent). The other low risk criteria (Philadelphia, Boston, and Milwaukee) also had high NPV for SBI indicating relatively low proportion of missed SBI cases in these studies (10.0 percent or less).

The prevalence of SBI in the low risk group is about 1.0–2.0 percent compared to the prevalence of ~10.0 percent overall. Low risk criteria can identify infants unlikely to have SBI and who can be managed less aggressively. We found no information on variability among clinicians in terms of competence in assessing risk.

Infants < 1 month of age have been treated differently based on a higher baseline risk of SBI and the difficulty of clinical assessment. Several studies have shown that although the overall risk of SBI is higher, the Rochester criteria may be able to identify low risk infants in this age group. The negative predictive values for the Rochester criteria in this younger age group were 93.0–97.0 percent. The prevalence of SBI in the low risk group of neonates is 3.0–5.0 percent. The low risk criteria can identify infants < 1 month old who are unlikely to have SBI but a small number of infants with SBI will be missed. Although many studies had high negative predictive values, these should be interpreted with caution as predictive values vary based on prevalence.

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?

There is very little evidence on the risks of delay in diagnosis and management in low risk infants who were later found to have SBI. Several studies reported the outcomes of infants in which the diagnosis of SBI was initially missed. Most infants were subsequently hospitalized and treated with antibiotics. Although somewhat reassuring, the fact that there were no adverse outcomes in these infants may have been due to underreporting and/or lack of followup in these studies. Of note, several of the studies reported on contaminated urine, blood and cerebrospinal fluid cultures. The added management and harms associated with these false positive results were not reported.

Indirect evidence comes from the PROS research network febrile infant study. In the office based study by Pantell,[5] many practitioners did not adhere to the most conservative approach for management of febrile infants (i.e., full sepsis workup on each febrile infant <3 months of age presenting to physician's office). In this study, only 54.0 percent of the infants had a urinalysis and 24.0 percent had no testing of blood, urine or cerebrospinal fluid. The prevalence of UTI and bacteremia in the overall group were 5.4 percent and 1.8 percent, respectively; in the infants that actually had testing, these rates were 9.7 percent and 2.4 percent, respectively. It is possible that cases of SBI were missed because many infants had no investigations. There were no adverse outcomes observed. It should be noted that many infants had either office or telephone followup which may enable the practitioner to have a less aggressive management approach. Note that most of the results of this study are based on suburban setting and may not accurately reflect the febrile infant risks present in the primary care urban settings.

Additionally, Newman reported results on UTIs from the same study.[106] It was modeled so that in the 807 infants not initially tested or treated with antibiotics, there should have been 61 UTIs based on predictors of UTIs, whereas only two cases were diagnosed at followup. No adverse outcomes were reported with office and telephone followup, suggesting that some acute UTIs may have spontaneously resolved. The study was not designed to look at the long-term renal function of these patients; the findings of this study do not support the concern that all untreated UTIs lead to bacteremia.

The low risk criteria have been used in practice for over 10 years and yet there is minimal data on the morbidity and mortality of infants with SBI who are missed by the low risk criteria. As the literature and field has been focused exclusively on avoiding missed SBI, the consequences of iatrogenic harms have not been evaluated. To truly balance the risks and benefits of management strategies, the risks need to be fully delineated.

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)?

A confusing aspect of the literature on SBI in febrile infants is the focus on either identifying high risk patients or identifying low risk patients. It is important that studies reporting on indentifying low risk infants emphasize that that infants not meeting the low risk criteria are not necessarily high risk, and therefore are more appropriate to be labeled as not low risk.

In general, most studies demonstrated higher sensitivity and lower specificity. The low PPV values reported for the selected combined criteria (e.g., Boston, Milwaukee, Philadelphia, Rochester) are indicative of high false positive rates for SBI (i.e., high proportion of febrile infants without SBI classified as high risk). 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.

There is little reported evidence on what factors are associated with variations in practice patterns among different individual providers. 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 "overtreat" a large group of SBI negative patients.

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?

The realm of this question should encompass medical harms as well as cost associated with immediate hospitalization and treatment with antibiotics. Additionally, the psychological harms of the testing have not been explicitly stated 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 delineated the presence or absence of such factors.

Byington and Paxton reported on a survey of parents of infants undergoing a 'rule-out sepsis' (ROS) evaluation months after admission. The majority of the sixty parents who interviewed reported finding the ROS evaluation very stressful with 28.0 percent believing their infant was to die. Additionally, 36.0 percent of mothers reported breastfeeding problems with 18.0 percent stopping breastfeeding, 35.0 percent perceived their child to be less healthy on followup, 43.0 percent reported financial stress, and 33.0 percent reported perceived iatrogenic problems.[133]

Overall, the reporting of harms for this area has been very poor.

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

There seems to be some confusion surrounding SBI evaluation in a child with a recognized viral syndrome. [134-136] Advent of rapid testing for viral pathogens has given many clinicians the ability to diagnose viral infections in children less than 3 months of age. This review has shown a consistent statistically significant inverse relationship between viral testing positive or clinical bronchiolitis and the presence of SBI among infants with fever. Most of the SBI were UTI, although there were some cases of bacteremia, but no meningitis.

For the clinician in an office or with no access to rapid viral testing a clinical diagnosis is more applicable. Some of the studies enrolled patients with positive viral culture results due to their retrospective nature. As rapid antigen testing is not 100.0 percent sensitive (87.0 percent),[86] some patients with rapid testing negative, who subsequently have viral culture that is positive would not benefit from this information. More concerning is the issue of false positives, where 3/135 were rapid testing positive, but viral culture negative, thereby providing the clinician with a false sense of security and potentially mislabeling the patient as being low-risk for SBI.[86] This area is further confused by the development of PCR testing which is more sensitive than the previous "gold standard" of viral culture.

However, even in the absence of rapid testing, the clinician is able to obtain significant information that decreases the chance of SBI. The three studies by Lubinghl, Bilavsky and Kuppermann demonstrate a similar inverse relationship between clinically diagnosed bronchiolitis and SBI.

The sample sizes of the studies did not answer the clinical dilemma regarding the need for lumbar puncture in infants with clinical bronchiolitis or a positive viral test. The study by Levine et al. reported zero cases of meningitis in the RSV positive group. Although bacteremia and meningitis were lower in the RSV positive group, the difference did not reach the statistical significance. Luginbuhl's publication for the PROS study also could not answer this question due to the sample size (only 35 patients [16.0 percent] of the bronchiolitis group had a lumbar puncture). Bilavsky et al. reported no cases of meningitis or bacteremia in the bronchiolitis group compared with one and four in the no-bronchiolitis group respectively. The rarity of the entity of bacterial meningitis in RSV or bronchiolitis positive patients likely means that this question will not be answered without an enormous effort. Indeed, only a few cases of meningitis have been described in the literature in febrile infants with a viral infection.[136,137]

The lack of reporting of the age-specific sub-groups does not provide information on whether the group of infants 0-3 months of age is homogenous in terms of risk of SBI in the bronchiolitis or virus positive patient. However, given our understanding that the prevalence of SBI is significantly higher in the 0-28 day group and that the diagnostic tests differ in their accuracy in this age group compared with the entire 0-3 month group, it seems logical that the neonatal time period should be viewed differently. This is supported by the only study by Levine et al. that provided the prevalence of specific SBI in neonates and demonstrated no significant difference in prevalence of SBI between patients with and without proven RSV.

Overall, evidence in this review indicates that bronchiolitis or a positive result for a virus significantly predicts against SBI. The majority of cases of SBI were UTI. Caution should be used when evaluating neonates with these findings as the presence of bronchiolitis or virus in this sub-population may not be as predictive against an SBI as in older groups of infants.

KQ 5. What is the evidence that the prevalence of SBI 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?

The majority of studies were conducted in an emergency department setting. The reported prevalence of SBI in North American emergency department settings varied from 4.0 percent to 25.0 percent. The prevalence of SBI in the primary care studies varied about 9.0 percent-10.0 percent. There appears to be a somewhat higher prevalence of SBI in the emergency department population. 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 wait to see their primary care provider.

There is considerable practice variation between emergency department and office settings. These differences bring up the following questions: in the emergency department, are infants being over-investigated or does this reflect a difference in their level of acuity? In office practice, are infants with bacterial infections being missed and is there any associated morbidity and long-term consequences?

Given the low prevalence of serious bacterial illness and very low prevalence of bacteremia and meningitis, many clinicians, especially physicians who evaluate low volumes of febrile

infants less than 3 months of age, may never see a significant adverse outcome regardless of what their practice of diagnostics and management is. This may provide a "false" sense of security that the clinician is correctly managing these infants. Conversely, habitually adhering to more rigorous protocols for diagnosis and treatment may instill a "false" belief that they are necessary. The small numbers of bacteremia and meningitis in all the cited studies do not allow an accurate experienced-based understanding of the accuracy of current testing strategies for these more serious outcomes.

KQ6. Clinicians base decisions about initial diagnostic work-up 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 follow-up appointment if conditions warrant. How likely are parents whose infants are less than six 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 re-assess 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?

The dearth of studies in this area led us to expand our inclusion criteria to up to 6 months of age and to include infants with fever or other potentially serious medical condition. The lack of focus in this area is evidenced by the identification of only four studies with this expanded inclusion criteria. Although the followup was reported in these studies, they were not the primary focus. The high rate of success for outpatient therapy and telephone followup in these studies could in part be explained by the increased motivation of parents whose infants were enrolled in the studies.

Follow up and reassessment of the febrile infant is an important component of their care. A clinician's decision making 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 follow up in this population and it is an area where more research is needed.

There was a lack of 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 rates of parental compliance to telephone or return visit followups.

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.

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 sparse literature on factors associated with compliance in this population. Future studies should focus on identifying the risks associated with testing and observation strategies and on factors that influence compliance to followup care.

Research Needs and Future Directions

To move the field further, there is a need to delineate the risks associated with testing and also management options in this group. Rigorous studies need to be done with separate reporting for infants 0-28 days, 1-2 months, 2-3 months of age (see QUADAS in Appendix G).

Consideration should be given not to include the 0-6 day old group as these infants likely represent another clinical syndrome of early onset sepsis related to perinatal factors. Most clinicians when faced with a febrile infant 3 days of age would perform a full evaluation including lumbar puncture and admit the infant for intravenous antibiotics. 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 determined by incorporating risks associated with age group and viral or clinical syndrome status and observed as outpatient or inpatient at followup. Detailed reporting of the harms associated with the diagnosis and in/outpatient observation of this low-risk group would be crucial. This should include management changes associated with contaminated specimens, parental anxiety, breastfeeding cessation, a long-term concern over "vulnerable child syndrome," and financial costs. The outcomes should not only be numbers of SBI, but followup should be done to determine the long-term consequences of 'missed' or 'delayed' diagnosis of SBI such as decreased renal function with urinary tract infection, progression from UTI to bacteremia, and complications of meningitis.

Efforts of future research should also be directed towards the development of new constellations of those clinical and laboratory criteria that were shown in previous research to have better sensitivity for various sub-types of SBI (e.g., bacteremia, meningitis).

Integrated into these studies should be evaluations on the factors or interventions that increase parental compliance and/or clinicians' ability to predict compliance. Optimally, these studies should be multi-centered and evaluate both outpatient and emergency department settings. Once there are better data on harms of diagnostic and observation protocols a consensus expert panel could be struck to define the risk balance.

Furthermore, a registry or surveillance network should be developed to describe the changing pathogens and resistance over time as there is increasing concern over these shifts and their potential clinical significance.[81,93,138] Effects of vaccination and other interventions may be appropriately studied on a population basis. Although the majority of the SBI cases are due to gram negative UTIs, bacteremia occurred predominantly due to *Streptococcus pneumoniae,* Group B *Streptococcus* and *Haemophilus influenzae* type b – all pathogens that have changed significantly over time due to vaccinations or interventions. Additionally, there is some evidence of resistance and different pathogens in more recent studies.[93,138,139]

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Acronyms/Abbreviations

Clinical

ABC	absolute band count
CATH	catheterization
CBC	complete blood cell
CI	confidence interval
CRP	C-reactive protein
CSF	cerebrospinal fluid
CT	computer tomography
CXR	chest x-ray
DAS	diagnostic accuracy study
ESR	erythrocyte sedimentation rate
EV	enteroviral
GBS	group B streptococcal disease
hpf	high power field
HR	high risk (+: positive or -: negative)
HSV	herpes simplex virus
IV/I	intravenous/ injection
HSV	rare invasive herpes simplex virus infection
LE	leukocyte esterase
LR	low risk (+: positive or -: negative)
PCMC	primary children's medical center
PCR	polymerase chain reaction
PCT	procalcitonin
PMN	polymorphonuclear count
RSV	respiratory syncytial virus
SBI	serious bacterial infection/ illness
T	temperature
UA	urinalysis
UTI	urinary tract infection
WBC	white blood cell
YIOS	Young Infant Observation Scale
YOS	Yale Observation Score

Units

µg	micrograms
µg /L	micrograms per liter
µg /mL	micrograms per milliliter
µg/dL	micrograms per deciliter
µm	micromolar
µmol/L	micromoles per liter
cm	centimeters
cm/s	centimeters/second

Ibs	pounds
IU/L	international units per liter
IU/L	international units per liter
kg	kilograms
kg/m^2	kilograms per meter squared
m	meters
mg	milligrams
mg/d	milligrams per day
mL	millilitre
mmol/L	millimoles per liter
N	sample size
ng/dL	nanogram per deciliter
ng/L	nanogram per liter
ng/mL	nanograms per milliliter
nmol/L	nanomoles per liter
pg/mL	picograms per milliliter
pmol/L	picomoles per liter
˚F	degrees Fahrenheit
˚C	degrees Celsius

Statistics

ARD	absolute risk difference
CCT	controlled clinical trial
CI	confidence interval
IQR	interquartile range
LS	least square
NS	not significant
RCT	randomized controlled trial
S/sign.	significant
SD	standard deviation
SE/SEM	standard error
WMD	weighted mean difference
ROC (AUC)	receiver operating characteristic (area under the curve)
LR	likelihood ratio
PPV	positive predictive value
NPV	negative predictive value

Commonly Used Abbreviations

#	number
%	percent
<	less than
< or </=+	less than or equal to and
>	greater than
> or >/=	greater than or equal to
▲/↑ or ▼/↓	increased, or decreased,
CG	control group

grp	group/s
ctrls	controls
d	day
Deg or ˚	degrees
Dept.	department
F	female
f/u	followup
FHx	family history
hr	hour
Hx	history
IG	intervention group
M	male
max	maximum
min	minimum
mo	month
NA	not applicable
NIH	National Institutes of Health
NR	not reported
Q	question
Tx	treatment
vs.	versus
wks	weeks
y	year

Appendix A. Search Strategies

Appendix A lists the exact search strings used for each database included in the search of the literature for this review. This search strategy was divided into two separate searches. Key questions 1-5 were combined in one search and Key question 6 was searched separately due to the different databases targeted.

Key Questions 1–5

MEDLINE (1950 to September 21 2010)

1. exp fever/
2. (fever$ or febrile or pyrexi$).tw.
3. 1 or 2
4. exp bacteremia/
5. exp meningitis, bacterial/.
6. exp urinary tract infections/
7. exp herpes simplex/
8. (bacteremia or bacteraemia).tw.
9. (bacteria$ adj3 meningitis).tw.
10. (urinary adj2 tract$ adj3 infection$).tw.
11. (herpes adj2 simplex).tw.
12. ((severe or serious) adj3 bacteria$ adj4 (infection$ or illness$)).tw.
13. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. exp "sensitivity and specificity"/
15. exp diagnostic errors/
16. predicti$.tw.
17. sensitivity.tw.
18. specificity.tw.
19. (roc adj curve$).tw.
20. (false adj2 negative$).tw.
21. (false adj2 positive$).tw.
22. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. exp "signs and symptoms"/
24. exp physical examination/
25. exp medical history taking
26. (ill adj2 appear$).tw.
27. (clinical adj2 examin$).tw.
28. (medical adj2 histor$).tw.
29. (rochester adj4 criteri$).tw.
30. (philadelphia adj4 protocol$).tw.

31. (milwaukee adj3 protocol$).tw.

32. exp Clinical Protocols/

33. "Severity of Illness Index"/

34. (scoring adj2 instrument$).tw.

35. exp risk/

36. risk$.tw.

37. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36

38. 3 and 13 and 22 and 37

39. limit 38 to (yr="1973 - 2008" and "all infant (birth to 23 months)")

40. (infant$ or newborn$ or neonate$).tw.

41. 38 and 40

42. limit 41 to (english language and yr="1973 - 2008")

43. 39 or 42

44. exp clinical laboratory techniques/

45. exp "laboratory techniques and procedures"/

46. exp diagnostic tests, routine/

47. (complete adj2 blood adj3 count$).tw.

48. urine.tw.

49. Urinalysis/

50. urinalysis.tw.

51. (diagnosis or blood or urine or cerebrospinal fluid).fs,sh.

52. 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51

53. 37 or 52

54. 3 and 13 and 22 and 53

55. limit 54 to (yr="1973 - 2008" and "all infant (birth to 23 months)")

56. 40 and 54

57. limit 56 to (english language and yr="1973 - 2008")

58. 55 or 57

59. exp time/

60. ((diagnos$ or therap$ or treatment$) adj3 (interval$ or delay$)).tw.

61. (immediate adj3 (treatment$ or therap$ or diagnos$)).tw.

62. (diagnosis or drug therapy or therapy).fs,sh.

63. 59 and 62

64. 60 or 61 or 63

65. 3 and 13 and 64

66. limit 65 to (yr="1973 - 2008" and "all infant (birth to 23 months)")

67. 40 and 65

68. limit 67 to (english language and yr="1973 - 2008")

69. 66 or 68

70. Harm Reduction/

71. harm$.tw.

72. benefi$.tw.

73. exp prognosis/

74. ((treatment or therap$) adj2 outcome$).tw. 75. no-observed-adverse-effect level/

76. adverse effects.fs.

77. adverse.tw.

78. contraindications.fs.

79. Medication Errors/

80. 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79

81. exp anti-bacterial agents/

82. exp antiviral agents/

83. Antibiotic Prophylaxis/

84. (antibacteria$ or antivirus$ or antiviral$).tw.

85. 81 or 82 or 83 or 84

86. 3 and 13 and 80 and 85

87. limit 86 to (yr="1973 - 2008" and "all infant (birth to 23 months)")

88. limit 87 to english language

89. 40 and 86

90. limit 89 to (english language and yr="1973 - 2008")

91. 88 or 90

92. Mothers/

93. (mother$ or maternal).tw.

94. ((medical or clinical) adj2 histor$).tw.

95. 93 and 94

96. 53 or 95

97. 3 and 13 and 22 and 96

98. limit 97 to (yr="1973 - 2008" and "all infant (birth to 23 months)")

99. limit 98 to english language

100. 40 and 97

101. limit 100 to yr="1973 - 2008"

102. limit 101 to english language

103. 99 or 102

104. Ambulatory Care/

105. Outpatients/

106. ambulatory.tw.

107. outpatient$.tw.

108. exp primary care/

109. Physicians' Offices/

110. Physicians, Family/

111. (primary adj2 care).tw.

112. (doctor$ adj2 office$).tw.

113. (doctor$ adj2 office$).tw.

114. exp Community Health Services/

115. Emergencies/

116. exp Emergency Medical Services/

117. emergenc$.tw.

118. 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117

119. prevalence/

120. prevalen$.tw.

121. Epidemiology/

122. epidemiology.fs,tw.

123. exp epidemiologic studies/

124. 119 or 120 or 121 or 122

125. 3 and 13 and 118 and 124

126. limit 125 to (yr="1973 - 2008" and "all infant (birth to 23 months)")

127. limit 126 to english language

128. 40 and 125

129. limit 128 to (english language and yr="1973 - 2008")

130. 127 or 129

131. 3 and 13 and 53 and 124

132. limit 131 to (yr="1973 - 2008" and "all infant (birth to 23 months)")

133. limit 132 to english language

134. 40 and 131

135. limit 134 to (english language and yr="1973 - 2008")

136. 133 or 135

137. 43 or 58 or 69 or 91 or 103 or 130 or 136

138. 3 and 13

139. limit 138 to (english language and yr="1973 - 2008" and "all infant (birth to 23 months)")

140. 40 and 138 (656)

141. limit 140 to (english language and yr="1973 - 2008") (539)

142. 139 or 141 (1470)

143. from 137 keep 1-757 (757

EMBASE (1980 to September 21 2010)

1. exp fever/

2. (fever$ or febrile or pyrexi$).tw.

3. 1 or 2

4. exp bacteremia/

5. exp meningitis, bacterial/

6. exp urinary tract infections/

7. exp herpes simplex/

8. (bacteremia or bacteraemia).tw.

9. (bacteria$ adj3 meningitis).tw.

10. (urinary adj2 tract$ adj3 infection$).tw.

11. (herpes adj2 simplex).tw.

12. ((severe or serious) adj3 bacteria$ adj4 (infection$ or illness$)).tw.

13. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12

14. exp "sensitivity and specificity"/

15. exp diagnostic errors/

16. predicti$.tw.

17. sensitivity.tw.

18. specificity.tw.

19. (roc adj curve$).tw.

20. (false adj2 negative$).tw.

21. (false adj2 positive$).tw.

22. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21

23. exp "signs and symptoms"/

24. exp physical examination/

25. exp medical history taking/

26. (ill adj2 appear$).tw.

27. (clinical adj2 examin$).tw.

28. (medical adj2 histor$).tw.

29. (rochester adj4 criteri$).tw.

30. (philadelphia adj4 protocol$).tw.

31. (milwaukee adj3 protocol$).tw.

32. exp Clinical Protocols/

33. "Severity of Illness Index"/

34. (scoring adj2 instrument$).tw.

35. exp risk/

36. risk$.tw.

37. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36

38. 3 and 13 and 22 and 37

39. limit 38 to (english language and yr="1980 - 2008" and infant <to one year>)

40. (infant$ or newborn$ or neonate$).tw.

41. 38 and 40

42. limit 41 to (english language and yr="1980 - 2008")

43. 39 or 42

44. exp "diagnosis, measurement and analysis"/

45. (complete adj2 blood adj3 count$).tw.

46. urine.tw.

47. urinalysis.tw.

48. diagnosis.sh.

49. blood.sh.

50. urine.sh.

51. cerebrospinal fluid.sh.

52. 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51

53. 37 or 52

54. 3 and 13 and 22 and 53

55. limit 54 to (english language and yr="1980 - 2008" and infant <to one year>)

56. 40 and 54

57. limit 56 to (english language and yr="1980 - 2008")

58. 55 or 57

59. exp time/

60. ((diagnos$ or therap$ or treatment$) adj3 (interval$ or delay$)).tw.

61. (immediate adj3 (treatment$ or therap$ or diagnos$)).tw.

62. (diagnosis or drug therapy or therapy).sh,tw.

63. 59 and 62

64. 60 or 61 or 63

65. 3 and 13 and 64

66. limit 65 to (english language and yr="1980 - 2008" and infant <to one year>)

67. 40 and 65

68. limit 67 to (english language and yr="1980 - 2008")

69. 66 or 68

70. harm reduction/

71. harm$.tw.

72. prognosis/

73. ((treatment or therap$) adj2 outcome$).tw.

74. exp Adverse Drug Reaction/

75. Side Effect/

76. adverse.tw.

77. contraindicat$.tw.

78. exp Medication Error/

79. benefi$.tw.

80. 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79

81. Antiinfective Agent/

82. (antibacteria$ or antiviral or antivirus or antibiotic$).tw.

83. 81 or 82

84. 3 and 13 and 80 and 83

85. limit 84 to (english language and yr="1980 - 2008" and infant <to one year>)

86. 40 and 84

87. limit 86 to (english language and yr="1980 - 2008")

88. 85 or 87

89. mother/

90. (mother$ or maternal).tw.

91. ((medical or clinical) adj2 histor$).tw.

92. 89 or 90

93. 91 and 92

94. 53 or 93

95. 3 and 13 and 22 and 94

96. limit 95 to (english language and yr="1980 - 2008" and infant <to one year>)

97. 40 and 95

98. limit 97 to (english language and yr="1980 - 2008")

99. 96 or 98

100. exp ambulatory care/

101. outpatient/

102. ambulatory.tw.

103. outpatient$.tw.

104. outpatient care/ or primary medical care/ or private practice/

105. general practitioner/

106. (primary adj2 care).tw.

107. (doctor$ adj2 office$).tw.

108. Community Care/

109. Emergency/

110. emergency health service/

111. emergenc$.tw.

112. 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111

113. prevalen$.tw.

114. exp epidemiology/

115. epidemiology.tw.

116. 113 or 114 or 115

117. 3 and 13 and 112 and 116

118. limit 117 to (english language and yr="1980 - 2008" and infant <to one year>)

119. 40 and 117

120. limit 119 to (english language and yr="1980 - 2008")

121. 118 or 120

122. 43 or 58 or 69 or 88 or 99 or 121

123. 3 and 13

124. limit 123 to (english language and yr="1980 - 2008" and infant <to one year>)

125. 40 and 123

126. limit 125 to (english language and yr="1980 - 2008")

127. 124 or 126

128. from 122 keep 1-268

EBM Reviews – Cochrane Central Register of Controlled Trials (1st Quarter 2008)

1. exp fever/

2. (fever$ or febrile or pyrexi$).tw.

3. 1 or 2

4. exp bacteremia/

5. exp meningitis, bacterial/

6. exp urinary tract infections/

7. exp herpes simplex/

8. (bacteremia or bacteraemia).tw.

9. (bacteria$ adj3 meningitis).tw

10. (urinary adj2 tract$ adj3 infection$).tw.

11. (herpes adj2 simplex).tw.

12. ((severe or serious) adj3 bacteria$ adj4 (infection$ or illness$)).tw.

13. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12

14. exp "sensitivity and specificity"/

15. exp diagnostic errors/

16. predicti$.tw.

17. sensitivity.tw.

18. specificity.tw.

19. (roc adj curve$).tw.

20. (false adj2 negative$).tw.

21. (false adj2 positive$).tw.

22. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21

23. exp "signs and symptoms"/

24. exp physical examination/

25. exp medical history taking/

26. (ill adj2 appear$).tw.

27. (clinical adj2 examin$).tw.

28. (medical adj2 histor$).tw.

29. (rochester adj4 criteri$).tw.

30. (philadelphia adj4 protocol$).tw.

31. (milwaukee adj3 protocol$).tw.

32. exp Clinical Protocols/

33. "Severity of Illness Index"/

34. (scoring adj2 instrument$).tw.

35. exp risk/

36. risk$.tw.

37. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36

38. 3 and 13 and 22 and 37

39. limit 38 to (yr="1973 - 2008" and "all infant (birth to 23 months)")

40. (infant$ or newborn$ or neonate$).tw.

41. 38 and 40

42. limit 41 to (english language and yr="1973 - 2008")

43. 39 or 42

44. exp clinical laboratory techniques/

45. exp "laboratory techniques and procedures"/

46. exp diagnostic tests, routine/

47. (complete adj2 blood adj3 count$).tw.

48. urine.tw.

49. Urinalysis/

50. urinalysis.tw.

51. (diagnosis or blood or urine or cerebrospinal fluid).fs,sh.

52. 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51

53. 37 or 52

54. 3 and 13 and 22 and 53

55. limit 54 to (yr="1973 - 2008" and "all infant (birth to 23 months)")

56. 40 and 54

57. limit 56 to (english language and yr="1973 - 2008")

58. 55 or 57

59. exp time/

60. ((diagnos$ or therap$ or treatment$) adj3 (interval$ or delay$)).tw.

61. (immediate adj3 (treatment$ or therap$ or diagnos$)).tw.

62. (diagnosis or drug therapy or therapy).fs,sh.

63. 59 and 62

64. 60 or 61 or 63

65. 3 and 13 and 64

66. limit 65 to (yr="1973 - 2008" and "all infant (birth to 23 months)")

67.40 and 65

68. limit 67 to (english language and yr="1973 - 2008")

69. 66 or 68

70. Harm Reduction/

71. harm$.tw.

72. benefi$.tw.

73. exp prognosis/

74. ((treatment or therap$) adj2 outcome$).tw.

75. no-observed-adverse-effect level/

76. adverse effects.fs.

77. adverse.tw.

78. contraindications.fs.

79. Medication Errors/

80. 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79

81. exp anti-bacterial agents/

82. exp antiviral agents/

83. Antibiotic Prophylaxis/

84. (antibacteria$ or antivirus$ or antiviral$).tw.

85. 81 or 82 or 83 or 84

86. 3 and 13 and 80 and 85

87. limit 86 to (yr="1973 - 2008" and "all infant (birth to 23 months)")

88. limit 87 to english language

89. 40 and 86

90. limit 89 to (english language and yr="1973 - 2008")

91. 88 or 90

92. Mothers/

93. (mother$ or maternal).tw.

94. ((medical or clinical) adj2 histor$).tw.

95. 93 and 94

96. 53 or 95

97. 3 and 13 and 22 and 96

98. limit 97 to (yr="1973 - 2008" and "all infant (birth to 23 months)")

99. limit 98 to english language

100. 40 and 97

101. limit 100 to yr="1973 - 2008"

102. limit 101 to english language

103. 99 or 102

104. Ambulatory Care/

105. Outpatients/

106. ambulatory.tw.

107. outpatient$.tw.

108. exp primary care/

109. Physicians' Offices/

110. Physicians, Family/

111. (primary adj2 care).tw.

112. (doctor$ adj2 office$).tw.

113. (doctor$ adj2 office$).tw.

114. exp Community Health Services/

115. Emergencies/

116. exp Emergency Medical Services/

117. emergenc$.tw.

118. 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117

119. prevalence/

120. prevalen$.tw.

121. Epidemiology/

122. epidemiology.fs,tw.

123. exp epidemiologic studies/

124. 119 or 120 or 121 or 122

125. 3 and 13 and 118 and 124

126. limit 125 to (yr="1973 - 2008" and "all infant (birth to 23 months)")

127. limit 126 to english language

128. 40 and 125

129. limit 128 to (english language and yr="1973 - 2008")

130. 127 or 129

131. 3 and 13 and 53 and 124

132. limit 131 to (yr="1973 - 2008" and "all infant (birth to 23 months)")

133. limit 132 to english language

134. 40 and 131

135. limit 134 to (english language and yr="1973 - 2008")

136. 133 or 135

137. 43 or 58 or 69 or 91 or 103 or 130 or 136

138. 3 and 13

139. limit 138 to (english language and yr="1973 - 2008" and "all infant (birth to 23 months)")

140. 40 and 138

141. limit 140 to (english language and yr="1973 - 2008")

142. 139 or 141

Pubmed

#55 OR #56 Limits: Entrez Date from 1973 to Current

#55 OR #56

#46 AND #53 Limits: Humans, All Infant: birth-23 months

#46 AND #53

(Multicenter Study[ptyp] OR Randomized Controlled Trial[ptyp] OR Controlled Clinical Trial[ptyp]) OR (random*[tiab] OR RCT[tiab] OR RCTs[tiab] OR sham*[tiab] OR placebo*[tiab]) OR (single blind*[tiab] OR single dumm*[tiab] OR single mask*[tiab]) OR

#49 OR #51

#48 AND #50

infant [mesh] OR infant [tiab] OR infants [tiab] OR newborn* [tiab] OR neonate* [tiab]

#48 Limits: Humans, All Infant: birth-23 months

#46 AND #47

((meta-analysis[ptyp] OR Meta-Analysis[MeSH]) OR (meta analy*[tiab] OR metaanaly*[tiab] OR met analy*[tiab] OR metanaly*[tiab] OR integrative research[tiab] OR integrative review*[tiab] OR integrative overview*[tiab] OR reintegration*[tiab] OR reoverview*[tiab] OR collaborative review*[tiab] OR collaborative overview*[tiab]) OR (quantitative review*[tiab] OR quantitative overview*[tiab] OR quantitative synthes*[tiab] OR systematic literature review*[tiab] OR systematic review*[tiab] OR systematic overview*[tiab] OR methodologic literature review*[tiab] OR methodologic review*[tiab] OR methodologic overview*[tiab]) OR ("technology assessment, biomedical"[MeSH Terms]) OR (health technology assessment*[tiab] OR biomedical technology assessment*[tiab] OR HTA[tiab] OR HTAs[tiab]) OR (systematic[sb]))

#21 AND #45

#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44

Urinalysis [mesh] OR Spinal Puncture [mesh] OR urinalysis [tiab] OR spinal puncture* [tiab] OR lumbar puncture [tiab]

Diagnostic Errors [mesh] OR diagnostic error* [tiab] OR diagnostic mistake* [tiab] OR mistaken diagnos* [tiab] OR "error in diagnosis" [tiab] OR "error in diagnoses" [tiab] OR "errors in diagnosis" [tiab] OR "errors in diagnoses" [tiab] OR incorrect diagnosis [tiab] OR incorrect diagnoses [tiab]

diagnostic test [tiab] OR diagnostic tests [tiab] OR diagnostic procedure* [tiab] OR diagnostic evaluation* [tiab] OR diagnostic investigation* [tiab] OR diagnostic work* [tiab] OR diagnostic workup* [tiab] OR diagnostic work-up* [tiab] OR diagnostic result* [tiab]

laboratory test [tiab] OR laboratory tests [tiab] OR lab test [tiab] OR lab tests [tiab] OR laboratory work* [tiab] OR lab work* [tiab] OR laboratory workup* [tiab] OR laboratory work-up* [tiab] OR lab workup* [tiab] OR lab work-up* [tiab] OR laboratory investigation* [tiab] OR laboratory evaluation* [tiab] OR laboratory result* [tiab] OR lab result* [tiab] OR Culture method* [tiab] OR culturing method* [tiab] OR sepsis workup [tiab] OR sepsis work-up* [tiab]

Practice Guideline Field: Publication Type

Practice Guidelines as Topic [mesh] OR Algorithms [mesh] OR Decision Trees [tiab] OR cpg [tiab] OR cpgs [tiab] OR practice guideline* [tiab] OR practice protocol* [tiab] OR clinical guideline* [tiab] OR clinical protocol* [tiab] OR algorithm* [tiab] OR decision tree* [tiab] OR decision-making [tiab] OR clinical decision* [tiab]

(Test [tiab] OR tests [tiab] OR testing [tiab] OR culture* [tiab] OR specimen* [tiab] OR workup* [tiab] OR work-up* [tiab]) AND (cerebrospinal fluid* [tiab] OR CSF [tiab] OR spinal fluid* [tiab] OR blood [tiab] OR WBC [tiab] OR CBC [tiab] OR c-reactive protein* [tiab] OR CRP [tiab] OR procalcitonin [tiab] OR PCP [tiab] OR interleukin-6 [tiab] OR IL-6 [tiab] OR urine [tiab] OR stool [tiab])

"Sensitivity and Specificity" [mesh] OR sensitivity [tiab] OR specificity [tiab] OR "predictive value of tests" [tiab] OR false negative* [tiab] OR false positive* [tiab] OR ROC curve* [tiab] OR Receiver Operating Characteristic* [tiab] OR ROC analys* [tiab]

Risk [mesh] OR risk [tiab] OR risks [tiab] OR predicti* [tiab]

Diagnosis, Differential [mesh] OR differential diagnosis [tiab] OR differential diagnoses [tiab] OR delayed diagnosis [tiab] OR delayed diagnoses [tiab]

Laboratory Techniques and Procedures [mesh]

Severity of Illness Index [mesh] OR "Severity of Illness Index" [tiab] OR "severity of illness indexes" [tiab] OR "severity of illness indices" [tiab]

Philadelphia Criteri* [tiab] OR Rochester criteri* [tiab] OR Yale Observation Scale [tiab] OR Young Infant Observation Scale [tiab]

medical history [tiab] OR clinical history [tiab] OR physical examination* [tiab] OR physical exam [tiab] OR physical exams [tiab] OR clinical exam [tiab] OR clinical exams [tiab] OR clinical examination* [tiab] OR medical exam [tiab] OR medical exams [tiab] OR medical examination* [tiab] OR clinical evaluation* [tiab] OR medical evaluation* [tiab] OR physical evaluation* [tiab] OR clinical symptom* [tiab] OR medical symptom* [tiab] OR physical symptom* [tiab]

Physical Examination [mesh]

Medical History Taking [mesh]

"Herpes Simplex/diagnosis" [mesh]

"Osteomyelitis/diagnosis" [mesh]

"Bacterial Infections/diagnosis" [mesh]

"Meningitis, Bacterial/diagnosis" [mesh]

"sepsis/diagnosis"[mesh]

("fever/diagnosis"[MeSH Terms] OR "fever/etiology"[MeSH Terms])

Diagnosis [mesh]

#3 AND #20

#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19

Herpesvirus hominis [tiab] AND (serious [tiab] OR severe [tiab] OR invasive [tiab])

(HSV* [tiab] OR herpes simplex [tiab]) AND (serious [tiab] OR severe [tiab] OR invasive [tiab])

IHI [tiab]

Herpes Simplex [mesh] AND (serious [tiab] OR severe [tiab] OR invasive [tiab])

osteomyelitis [mesh] OR osteomyelitis [tiab]

Listeria Infection* [tiab] AND (serious [tiab] OR severe [tiab] OR invasive [tiab])

Gram negative [tiab] AND bacteria* [tiab] AND infection* [tiab]

Gram-Negative Bacterial Infections [mesh]

Gram positive [tiab] AND bacteria* [tiab] AND infection* [tiab]

Gram-Positive Bacterial Infections [mesh]

meningitis [tiab] AND (bacteria* [tiab] OR listeria* [tiab] OR escherichia [tiab] OR Haemophilus [tiab] OR Hemophilus [tiab] OR meningococc* [tiab] OR pneumococc* [tiab] OR tuberculo* [tiab])

Meningitis, Bacterial [mesh]

sepsis [tiab] OR septicemia [tiab] OR septicaemia [tiab]

urinary tract infections [mesh] OR UTI [tiab] OR UTIs [tiab] OR urinary tract infection* [tiab] OR urinary infection* [tiab] OR urinary tract inflammation* [tiab]

serious bacterial infection* [tiab] OR severe bacterial infection* [tiab] OR invasive bacterial infection* [tiab] OR rare bacterial infection* [tiab] OR SBI [tiab] OR SBIs [tiab] OR serious infection* [tiab] OR severe infection* [tiab] OR invasive infection* [tiab] OR rare infection* [tiab]

Sepsis [mesh]

#1 OR #2

Fever [tiab] OR fevers [tiab] OR feverish [tiab] OR febril* [tiab] OR febricity [tiab] OR pyrexi* [tiab]

Fever [MeSH]

Key Question 6

CINAHL (1982 to May 13 2008)

1. exp FEVER/

2. (Fever or fevers or feverish or febril$ or febricity or pyrexi$).ti,ab.

3. exp SEPSIS/

4. (sepsis or septicemia or septicaemia).ti,ab.

5. (serious bacterial infection$ or severe bacterial infection$ or invasive bacterial infection$ or rare bacterial infection$ or SBI or SBIs or serious infection$ or severe infection$ or invasive infection$ or rare infection$).ti,ab.

6. (serious illness* or serious condition* or serious medical illness* or serious medical condition*).ti,ab.

7. exp Urinary Tract Infections/

8. (UTI or UTIs or urinary tract infection$ or urinary infection$ or urinary tract inflammation$).ti,ab.

9. exp Meningitis, Bacterial/

10. ((meningitis or meningitides or meningeal) adj3 (bacteria$ or listeria$ or escherichia or Haemophilus or Hemophilus or meningococc$ or pneumococc$ or tuberculo$)).ti,ab.

11. exp Gram-Positive Bacterial Infections/

12. (Gram positive adj2 bacteria$ infection$).ti,ab.

13. exp Gram-Negative Bacterial Infections/

14. (Gram negative adj2 bacteria$ infection$).ti,ab.

15. (listeria infection$ adj3 (serious or severe or invasive)).ti,ab.

16. exp OSTEOMYELITIS/

17. osteomyelitis.ti,ab.

18. exp Herpes Simplex/

19. (Herpes Simplex or HSV or Herpesvirus hominis).ti,ab.

20. (serious or severe or invasive).ti,ab.

21. 18 or 19

22. 20 and 21

23. IHI.ti,ab.

24. exp pneumonia/

25. (pneumonia or pneumonitis or pulmonary inflammation* or lung inflammation or bronchopneumonia or pleuropneumonia).ti,ab.

26. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 22 or 23 or 24 or 25

27. limit 26 to (newborn infant <birth to 1 month> or infant <1 to 23 months>)

28. (infant or infants or newborn$ or neonate$).ti,ab.

29. 26 and 28

30. 28 or 29

31. exp CAREGIVERS/

32. exp PARENTS/

33. (Caregiver$ or care giver$ or caretaker$ or care-taker$ or parent$ or stepparent$ or step-parent$ or father$ or mother$ or stepmother$ or stepfather$ or step-mother$ or step-father$).ti,ab.

34. 31 or 32 or 33

35. exp Office Visits/ or exp "Continuity of Patient Care"/

36. ((visit or visits or appointment$ or clinic or clinics or outpatient) and (repeat$ or return$ or recommend$)).ti,ab.

37. (reassessment* or recall* or follow-up or followup or watchful waiting or expectant management).ti,ab.

38. (continuity adj3 care).ti,ab.

39. or/35-38

40. exp Patient Compliance/

41. (comply or complies or compliant or compliance or noncomply or noncompliant or noncompliance or non-compliant or non-compliance or adherent or adherence or nonadherence or non-adherence).ti,ab.

42. (caregiver$ acceptance or caregiver$ attitude$ or caregiver$ responsibilit$ or caregiver$ behavi$ or caretaker$ acceptance or caretaker$ attitude$ or caretaker$ responsibilit$ or caretaker$ behavi$ or care-giver$ acceptance or care-giver$ attitude$ or care-giver$ responsibilit$ or care-giver$ behavi$ or care-taker$ acceptance or care-taker$ attitude$ or care-taker$ responsibilit$ or care-taker$ behavi$).ti,ab.

43. (parent$ acceptance$ or parent$ attitude$ or parent$ responsibilit$ or parent$ behavi$ or patient$ acceptance or patient$ attitude$ or patient$ responsibilit$ or patient$ behavi$).ti,ab.

44. exp Attitude to Health/

45. ((Health adj3 attitude$) or health belief$).ti,ab.

46. 40 or 41 or 42 or 43 or 44 or 45

47. 30 and 34 and 39 and 46

Embase (1980 to September 22 2010)

1. exp FEVER/

2. (Fever or fevers or feverish or febril$ or febricity or pyrexi$).ti,ab.

3. exp SEPSIS/

4. (sepsis or septicemia or septicaemia).ti,ab.

5. (serious bacterial infection$ or severe bacterial infection$ or invasive bacterial infection$ or rare bacterial infection$ or SBI or SBIs or serious infection$ or severe infection$ or invasive infection$ or rare infection$).ti,ab.

6. (serious illness* or serious condition* or serious medical illness* or serious medical condition*).ti,ab.

7. exp Urinary Tract Infections/

8. (UTI or UTIs or urinary tract infection$ or urinary infection$ or urinary tract inflammation$).ti,ab.

9. exp Meningitis, Bacterial/

10. ((meningitis or meningitides or meningeal) adj3 (bacteria$ or listeria$ or escherichia or Haemophilus or Hemophilus or meningococc$ or pneumococc$ or tuberculo$)).ti,ab.

11. exp Gram-Positive Bacterial Infections/

12. (Gram positive adj2 bacteria$ infection$).ti,ab.

13. (Gram negative adj2 bacteria$ infection$).ti,ab.

14. (listeria infection$ adj3 (serious or severe or invasive)).ti,ab.

15. exp OSTEOMYELITIS/

16. osteomyelitis.ti,ab.

17. exp Herpes Simplex/

18. (Herpes Simplex or HSV or Herpesvirus hominis).ti,ab.

19. (serious or severe or invasive).ti,ab.

20. 17 or 18

21. 19 and 20

22. IHI.ti,ab.

23. exp PNEUMONIA/

24. (pneumonia or pneumonitis or pulmonary inflammation* or lung inflammation or bronchopneumonia or pleuropneumonia).ti,ab.

25. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 21 or 22 or 23 or 24

26. limit 25 to to infant <to one year>

27. (infant or infants or newborn$ or neonate$).ti,ab.

28. 25 and 27

29. 26 or 28

30. exp CAREGIVER/

31. exp PARENT/

32. (Caregiver$ or care giver$ or caretaker$ or care-taker$ or parent$ or stepparent$ or step-parent$ or father$ or mother$ or stepmother$ or stepfather$ or step-mother$ or step-father$).ti,ab.

33. 30 or 31 or 32

34. exp Ambulatory Care/

35. exp Patient Care/

36. ((visit or visits or appointment$ or clinic or clinics or outpatient) and (repeat$ or return$ or recommend$)).ti,ab.

37. (reassessment* or recall* or follow-up or followup or watchful waiting or expectant management).ti,ab.

38. (continuity adj3 care).ti,ab.

39. 34 or 35 or 36 or 37 or 38

40. exp Patient Compliance/

41. (comply or complies or compliant or compliance or noncomply or noncompliant or noncompliance or non-compliant or non-compliance or adherent or adherence or nonadherence or non-adherence).ti,ab.

42. (caregiver$ acceptance or caregiver$ attitude$ or caregiver$ responsibilit$ or caregiver$ behavi$ or caretaker$ acceptance or caretaker$ attitude$ or caretaker$ responsibilit$ or caretaker$ behavi$ or care-giver$ acceptance or care-giver$ attitude$ or care-giver$ responsibilit$ or care-giver$ behavi$ or care-taker$ acceptance or care-taker$ attitude$ or care-taker$ responsibilit$ or care-taker$ behavi$).ti,ab.

43. (parent$ acceptance$ or parent$ attitude$ or parent$ responsibilit$ or parent$ behavi$ or patient$ acceptance or patient$ attitude$ or patient$ responsibilit$ or patient$ behavi$).ti,ab.

44. exp Attitude to Health/

45. exp Patient Attitude/

46. ((Health adj3 attitude$) or health belief$).ti,ab.

47. 40 or 41 or 42 or 43 or 44 or 45 or 46

48. 29 and 33 and 39 and 47

PsycINFO (1806 to September 22 2010)

1. exp HYPERTHERMIA/

2. (hyperthermi$ or fever or fevers or feverish or febril$ or febricity or pyrexi$).ti,ab.

3. (sepsis or septicemia or septicaemia).ti,ab.

4. (serious bacterial infection$ or severe bacterial infection$ or invasive bacterial infection$ or rare bacterial infection$ or SBI or SBIs or serious infection$ or severe infection$ or invasive infection$ or rare infection$).ti,ab.

5. (serious illness* or serious condition* or serious medical illness* or serious medical condition*).ti,ab.

6. exp urinary function disorders/

7. (UTI or UTIs or urinary tract infection$ or urinary infection$ or urinary tract inflammation$).ti,ab.

8. exp Bacterial Meningitis/

9. ((meningitis or meningitides or meningeal) adj3 (bacteria$ or listeria$ or escherichia or Haemophilus or Hemophilus or meningococc$ or pneumococc$ or tuberculo$)).ti,ab.

10. (Gram positive adj2 bacteria$ infection$).ti,ab.

11. (Gram negative adj2 bacteria$ infection$).ti,ab.

12. (listeria infection$ adj3 (serious or severe or invasive)).ti,ab.

13. osteomyelitis.ti,ab.

14. exp Herpes Simplex/

15. (Herpes Simplex or HSV or Herpesvirus hominis).ti,ab.

16. (serious or severe or invasive).ti,ab.

17. 14 or 15

18. 16 and 17

19. IHI.ti,ab.

20. exp PNEUMONIA/

21. (pneumonia or pneumonitis or pulmonary inflammation* or lung inflammation or bronchopneumonia or pleuropneumonia).ti,ab.

22. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 18 or 19 or 20 or 21

23. limit 22 to

24. (infant or infants or newborn$ or neonate$).ti,ab.

25. 22 and 24

26. 23 or 25

27. exp CAREGIVERS/

28. exp PARENTS/

29. (Caregiver$ or care giver$ or caretaker$ or care-taker$ or parent$ or stepparent$ or step-parent$ or father$ or mother$ or stepmother$ or stepfather$ or step-mother$ or step-father$).ti,ab.

30. 27 or 28 or 29

31. exp "Continuum of Care"/

32. ((visit or visits or appointment$ or clinic or clinics or outpatient) and (repeat$ or return$ or recommend$)).ti,ab.

33. (reassessment* or recall* or follow-up or followup or watchful waiting or expectant management).ti,ab.

34. (continuity adj3 care).ti,ab.

35. 31 or 32 or 33 or 34

36. exp compliance/

37. (comply or complies or compliant or compliance or noncomply or noncompliant or noncompliance or non-compliant or non-compliance or adherent or adherence or nonadherence or non-adherence).ti,ab.

38. (caregiver$ acceptance or caregiver$ attitude$ or caregiver$ responsibilit$ or caregiver$ behavi$ or caretaker$ acceptance or caretaker$ attitude$ or caretaker$ responsibilit$ or caretaker$ behavi$ or care-giver$ acceptance or care-giver$ attitude$ or care-giver$ responsibilit$ or care-giver$ behavi$ or care-taker$ acceptance or care-taker$ attitude$ or care-taker$ responsibilit$ or care-taker$ behavi$).ti,ab.

39. (parent$ acceptance$ or parent$ attitude$ or parent$ responsibilit$ or parent$ behavi$ or patient$ acceptance or patient$ attitude$ or patient$ responsibilit$ or patient$ behavi$).ti,ab.

40. ((Health adj3 attitude$) or health belief$).ti,ab.

41. 36 or 37 or 38 or 39 or 40

42. 26 and 30 and 35 and 41

Appendix B. Data Extraction Forms

Appendix B outlines in detail all of the questions that were used in screening the literature and ultimately determined whether a study was included or excluded. Furthermore, all data that was extracted from each study are also listed in this appendix.

Key Questions 1–5

Level 1: Broad Screening Form

1. Is the citation an English-language report?
- Yes - include
- No - exclude
- Cannot tell - include

2. Is the **primary objective** of the citation to diagnose and/or manage healthy infants (0-90 days in age) presenting with fever and/or serious bacterial infections (including bacterial meningitis, bacteremia, urinary tract infection) or herpes?
- Yes - include
- No - exclude
- Unclear - include

3. Additional Criteria (Check the most appropriate):
- Is a primary study - include
- Is a systematic review, narrative review, clinical practice guideline or cost-effectiveness analysis - exclude
- Cannot tell - include

4. Citation may be important for the introduction and/or discussion section: (optional)
- Yes

5. Participants included in this study were from at least one of the following locations: North America, Australia/New Zealand, Western Europe, Northern Europe (Norway, Sweden, Finland, Denmark), Japan, Taiwan, or Israel
- Yes - include
- No - exclude
- Unclear - include

Note: We are assuming that Western Europe encompasses the United Kingdom, Ireland, France, Belgium, Germany, Netherlands, Switzerland, Luxembourg, Spain, Italy, Greece and Portugal.

Level 2: Full Text Screening Form

1. Is this an English-language report?
- Yes - include
- No - exclude

2.   Is the **primary objective** of the report to diagnose and/or manage healthy infants (0-90 days in age) presenting with fever and/or serious bacterial infections (including bacterial meningitis, bacteremia, urinary tract infection) or herpes??
- Yes - neutral
- No - neutral
- Cannot Tell -neutral
- Still cannot tell after conflict discussion - exclude

3.   Is the **primary objective** of the report to diagnose and/or manage healthy infants with streptococcus pneumonia, listeria monocytogenes, group b streptococcus, enterococcus sp., and enterobactericiae (including E. Coli and klebsiella sp.)?
- Yes - neutral
- No - neutral
- Cannot Tell - neutral
- Still cannot tell after conflict discussion - exclude

4.   Does this study refer to patients presenting to hospital or to a physician setting (office or community health setting)?
- Yes - include
- No - exclude
- Not clear from the report - exclude
- Still cannot tell after conflict discussion – exclude

Note: In-patients excluded

5.   Participants included in this study were from at least one of the following locations: North America, Australia/New Zealand, Western Europe, Northern Europe (Norway, Sweden, Finland, Denmark), Japan, Taiwan, Singapore, Hong Kong, or Israel
- Yes - include
- No - exclude
- Not clear from the report - exclude
- Still cannot tell after conflict discussion – exclude

6. Is this study a relevant Systematic Review (SR)?
- Yes - exclude
- No – include

Note: All Systematic Reviews will be excluded (however, can be identified from this question)

7. If you answered "No" to both questions 2 & 3, please check this box:
- click here

Level 3: Screening by Study Design Form

1. Please choose the study design that corresponds with this study:
- Randomized controlled trial - include
- Controlled clinical trial - include
- Cohort - include
- Case-control - include
- Nested case control - include

- Cross sectional (includes surveys, ecological studies) - include
- Case series - include
- Quasi-experimental studies - include
- Chart review - include
- Systematic review - exclude
- Other or none of the above - exclude
- Unclear - include

2. Does this study report diagnostic test results and outcomes? (specificity, sensitivity, prevalence, npv, ppv, etc.)
- Yes - include
- No - include

Level 4 – Screening by Key Question Form

1. Is this report related to the following category of questions? Please check all that apply.

Note: Please refer to updated review questions for more information regarding each of the listed items.

Q1a: Test characteristics (sensitivity, specifity, predictive values) in studies using individual or a combination of clinical features or formal scoring systems to identify infants with SBI. – include

Q1b: Test characteristics (sensitivity, specifity, predictive values) in studies using individual or a combination of clinical features or formal scoring systems to identify infants with IHI. - include

Q2a: Study on identifying infants at low risk for SBI or IHI according to clinical features, laboratory tests (alone or in combination), and/or formal scoring systems. - include

Q2b: Data on risks resulting from delay in management (dx and tx) in low risk infants. - include

Q3a: Study on identifying infants at high risk for SBI or IHI according to clinical features, laboratory tests and/or formal scoring systems. - include

Q3b: Data on benefits and harms of immediate versus delayed antibiotic (antibacterial and antiviral) treatment in infants at high risk for SBI or IHI. - include

Q4: Data on co-infection (prediction against SBI or IHI based in case of presence of an identified viral infection). - include

Q5: Data on variation on prevalence rate of SBI and IHI in different settings (primary care vs. emergency practice). - include

Q6: Data on influence of parental or clinical setting on compliance (studies will be crossed checked against compliance silo only). – include

None of the above - exclude

2. Comment Box

Key Question 6

Level 1: Broad Screening Form

1. Is the citation an English-language record?
- Yes- include
- No-exclude
- Cannot tell-include

2. Is this a primary study[1] addressing the influence of non-clinical factors[2] in diagnosis, and management of infants 0-6 months who present with fever or other serious conditions[3]?
- Yes - include
- No - exclude
- Cannot tell – include

Note:

[1]- primary studies do not include systematic reviews, narrative reviews, guidelines, commentaries, and letters

[2]- non-clinical factors include setting or parental factors that affect the likelihood of compliance with follow up visits and physicians' recommendations

[3]- serious conditions (pneumonia, urinary tract infection, bacteremia, meningitis, herpes simplex infection, hyperbilirubinemia, failure to thrive, and anemia)

3. Was the study conducted in at least one of the following locations: North America, Australia/New Zealand, Western Europe, Northern Europe (Norway, Sweden, Finland, Denmark), Japan, Taiwan, Hong Kong, Singapore or Israel?
- Yes - include
- No - exclude
- Cannot tell - include

Note: For articles of interest for the introduction or discussion, please use the flag article feature on the upper right hand corner of screen.

Level 2: Full Text Screening Form

1. Is this an English record?
- Yes - include
- No - exclude

2. Is this a primary study in infants 0-6 months old presenting with fever or other potentially serious conditions?

- Yes - include
- No - exclude

3. Is this a primary study addressing possible influence of parental factors[1], and or clinical setting[2] on likelihood of compliance with return appointments[3]?

- Yes - include
- No – exclude

[1] - education, insurance status, living situation, history of previous visits with the provider, time/distance required to travel to an appointment, etc.

[2]- community practice versus emergency department and/or hospital outpatient clinic

[3]- Excluding routine child health supervision visits and/or immunizations

4. If "No" was answered to questions 2, or 3, is the study important for introduction or discussion section?

- Yes - neutral
- No - neutral

Appendix C. Evidence Tables

The purpose of Appendix C is to provide detailed evidence tables that depict the criteria used to determine validity for each study. Furthermore, the tables summarize the evidence described and reflect specific information discussed in the report. The tables are categorically separated and alphabetized within each category.

Table 1. Studies with combined clinical and laboratory criteria

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Bachur (2001)[1]	Design: Chart review Region: North America Setting: Emergency Department Study period: 1993-1999	N: 5,279/5,279 Age group(s): 0 – 90 d Inclusion / exclusion: Male (%): NR Ethnicity (%): NR ----------------------------------- Information on mother: NR	Clinical appearance, age < 13 d + UA (LE$^+$ or nitrite$^+$); WBC > 20,000/mm^3 WBC < 4,100/mm$^{3;}$ T > 39.6°C	Positive culture of urine, blood or CSF UTI if supra-pubic ≥ 1000; catheterized ≥ 10000 colony forming units/mL (cfu/mL) of a single urinary pathogen) Diagnosis: SBI: 373 (7.0) UTI: 316 Meningitis: 17 Bacteremia: 40 Bacteremia/meningitis: 8 Bacteremia/UTI: 11	SBI: Sensitivity: 82.0 (78.0, 86.0) Specificity: 76.0 (75.0, 77.0) PPV: 21.0 (19.0, 23.0) NPV: 98.3 (97.8, 98.7)

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Broner (1990)[2]	Design: Quasi experimental Region: North America Setting: General ED Study period: NR	N: NR/52 Age group(s): 4 – 56 d Inclusion / exclusion: Infants with rectal temperature ≥ 38.1°C presented to general ED- Exclusion: NR Male (%): NR Ethnicity (%): NR ----------------------------------- Information on mother: NR	Toxic appearance (i.e., increased irritability, decreased eye contact, unwillingness to feed, and the state of alertness) + 1) WBC: ≥ 5,000 ABC/µL or 2) CRP+ or 3) WBC: ≥ 5,000 ABC/µL + ≥ 15,000 WBC/µL	NR Diagnosis: SBI (1): 5 (9.6) (sepsis) SBI (2): 5 (9.6) (sepsis) SBI (3): 5 (9.6) (sepsis)	SBI (1): Sensitivity: 100.0 (46.3, 100.0) Specificity: 49.0 (34.3, 63.7) PPV: 17.2 (6.5, 36.5) NPV: 100.0 (82.2, 100.0) SBI (2): Sensitivity: 100.0 (46.3, 100.0) Specificity: 48.0 (32.4, 61.7) PPV: 16.6 (6.3, 35.4) NPV: 100.0 (81.5, 100.0) SBI (3): Sensitivity: 100.0 (46.3, 100.0) Specificity: 49.0 (34.3, 63.7) PPV: 17.2 (6.5, 36.5) NPV: 100.0 (81.5, 100.0)

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Caspe (1983)[3]	Design: Quasi-experimental Region: North America Setting: Primary care Study period: 1974-1979	N: 305/305 Age group(s): 0 – 30 d 30 – 60 d Inclusion / exclusion: Infants presenting to community based hospital with rectal temperature ≥ 38°C seen in outpatient or well documented fever at home Male (%): 54 Ethnicity (%): White/non-Hispanic: 3 Hispanic: 51 African/American: 45 Asian/ South Pacific: 1.3 ----------------------------------- Information on mother: NR	Ill appearance + WBC ≥ 15,000/mm3	Blood, urine, CSF- also stool and nasopharynx when indicated Diagnosis: SBI (Bacteremia only) - (1) 0 – 30 d: 7 (6.5) SBI (Bacteremia only) - (2) 30 – 60 d: 4 (2.0)	SBI (1)- 0 – 30 d: Sensitivity: 28.5 (5.1, 69.7) Specificity: NR PPV: NR NPV: N SBI (2)- 30 – 60 d: Sensitivity: 75.0 (21.9, 98.6) Specificity: 95.8 (91.7, 98.0) PPV: 27.3 (7.3, 60.6) NPV: 99.4 (96.6, 99.9)

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Condra (2010)[4]	Design: Prospective Quality indicator Region: US Setting: Peadiatric ED Study period: NR (16 months in length)	N: 240/62 Age group(s): 29 – 60 d; median 44 d (SD 9.0) Inclusion / exclusion: Met Low Risk criteria (derived from Philadelphia criteria) with full sepsis evaluation/ ill appearing infants. Lack of fu, evidence of focal infection, hx antibiotic tx. Male (%): 55 Ethnicity (%): 39 (63%) White, 18 (29) African American, 5 (8) Hispanic Other: Group *B Streptococcus* positive or unknown: 8(12.9%); their mothers were treated with Peri-partum antibiotics. ---------------------------------- Information on mother: NR	WBC: $\leq 15,000/mm^3$ UA WBC: ≤ 10/hpf CSF Gram stain negative CSF WBC $< 8/mm^3$, or $\leq 1:500$ WBC-RBC (red blood cells) ratio band neurtophil ratio: ≤ 0.2	NR Diagnosis: SBI: 2 (3.2) all UTI Management: 58 (93.5%) were admitted and 4 (6.5) were discharged	SBI: Sensitivity: NR Specificity: NR PPV: NR NPV: NR (data only for LR infants- test results could not be calculated) Complications: 17 (29.3%) developed a complication during the admission Schedule phone fu were successful on days 2 (77.4%), 7 (85.4%), and 14 (83.9%) after discharge (data on admitted infants) most parents preferred discharge to admission

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Crain (1988)[5]	Design: Chart review Region: North America Setting: Peadiatric ED Study period: Unclear	N: 46/35 Age group(s): 0 – 15 d Inclusion / exclusion: Prospective sample of infants with rectal temperature ≥ 38.1°C Male (%): NR Ethnicity (%): NR ---------------------------------- Information on mother: NR	Either: Impression of sepsis + either WBC > 15,000 /mm3 or ESR > 30 mm/h or both or Negative impression of sepsis + both WBC > 15,000/mm3 and ESR > 30 mm/h	NR Diagnosis: SBI: 3 (8.5) Sepsis/meningitis	SBI: Sensitivity: 100.0 (31.0, 100.0) Specificity: 75.0 (56.2, 87.9) PPV: 27.3 (7.3, 60.7) NPV: 100.0 (82.8, 100.0)

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Crain (1990)[6]	Design: Cohort Region: North America Setting: Peadiatric ED Study period: 1982-1987	N: 442/442 Age group(s): 8 – 57d Inclusion / exclusion: Prospective sample of Febrile infants with rectal temperature ≥ 38°C Male (%): NR Ethnicity (%): NR ---------------------------------- Information on mother: NR	Either: Impression of sepsis + WBC > 15,000 /mm3 or ESR > 30 mm/h, or both; or Negative impression of sepsis + both WBC > 15,000 /mm3 and ESR > 30 mm/h	NR UTI if ≥ 10000 pure growth in bag-collected, or catheter obtained specimen; ≥ 100 pure growth in supra-pubic specimen Diagnosis: SBI (only UTI): 33 (7.4)	SBI: Sensitivity: 46.0 (31.1, 66.1) Specificity: 98.0 (95.7, 98.9) PPV: 64.0 (42.6, 81.3) NPV: 95.9 (93.4, 97.5)

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Dagan (1985)[7]	Design: Quasi-experimental Region: North America Setting: Peadiatric ED Study period: 1982-1984	N: 233/233 Age group(s): 0 – 90 d Inclusion / exclusion: All previously healthy infants with rectal temperature ≥ 38°C Male (%): 58 Ethnicity (%): White/non-Hispanic: 60.9 Hispanic: 12 African/American: 25.3 Asian/ South Pacific: 1.7 ---------------------------------- Information on mother: NR	Findings consistent with soft tissue, ear or skeletal infection + WBC ≥ 15,000/mm3	Bacteremia, meningitis, cellulites, osteomyelitis, gastroenteritis, UTI CSF: ≥ 20 cells/ mm3 in infants younger than 30 days, and > 10 cells/ mm3 in infants > 30 days UTI: >100000 colonies/ml of a single organism in urine Diagnosis: SBI: 23 (9.8) Bacteremia: 9 Others: NR	SBI: Sensitivity: 95.6 (76.0, 99.7) Specificity: 68.0 (61.2, 74.2) PPV: 24.7 (16.4, 35.2) NPV: 99.3 (95.6, 99.9)

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Dagan (1988)[8]	Design: Cohort Region: Israel Setting: Peadiatric ED Study period: 1985-1986	N: 237/236 Age group(s): < 60 d Inclusion / exclusion: Prospective sample of previously healthy (born at term, with no history of perinatal complications, underlying diseases, or antibiotics tx) with rectal temperature ≥ 38°C Male (%): 57 Ethnicity (%): NR ----------------------------------- Information on mother: NR	No findings consistent with soft tissue or skeletal infection + UA: < 25 WBC/hpf, WBC: 5,000-15,000/mm3, and 1,500 band forms/mm3	Bacterial meningitis, cellulites, osteomyelitis, septic arthritis, gastroenteritis, UTI, culture positive purulent OM UTI if > 100000 colonies/mL of a single organism Diagnosis: SBI: 23 (9.8) Bacteremia: 9 Others: NR	SBI: Sensitivity: 95.6 (76.0, 99.7) Specificity: 68.0 (61.2, 74.2) PPV: 24.7 (16.4, 35.2) NPV: 99.3 (95.6, 99.9)

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Gomez (2010)[9]	Design: Retrospective Cross sectional Region: Spain Setting: pediatric ED Study period: 2003 – 2008	N: 1125/1018 Age group(s): 0 – 90 d Inclusion / exclusion: Infants 0 – 90 d days, fever >/=38.0°C at home or on arrival in the Pediatric Emergency Department (blood and urine culture was obtained for all infants) Male (%): 57 Ethnicity (%): NR ---------------------------------- Information on mother: NR	Criteria for discharge without antibiotic tx: well appearing, age > 15 d, negative, normal lab test results (up to 24 hrs of observation in ED). Criteria for hospital admission: age < 15 d, abnormal lab tests (CRP, CBC, urine dipstick)	SBI: isolation of a bacterial pathogen from CSF, blood, or urine. Positive blood culture: growth of a true bacterial pathogen was grown (*Streptococcus pneumoniae*, *Neisseria meningitidis*, *Enterococcus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, group A and B *Streptococcus*, *Listeria monocytogenes*, or *Salmonella* species). Diagnosis: SBI: 198 (19.4) Bacteremia: 9 UTI: 172 Bacterial meningitis: 4 Sepsis:2, OM or Cellulitis: 3 Most frequently pathogens were *Escherichia coli* (9), *Streptococcus pneumonia*.	SBI: Sensitivity: 87.0 (67.9, 95.5) Specificity: NR PPV: NR NPV: 99.4 (98.2, 99.8) Bacteremia: Sensitivity: 26.1 (11.3, 47.2) Specificity: 95.8 (95.4, 96.3) PPV: 12.5 (5.4, 22.6) NPV: 98.2 (97.9, 98.7) Other: increased probability of having bacteremia with respect to general appearance (not well-appearing vs. well appearing; OR=8.01, 95% CI: 2.76, 23.05) and highest temperature detected (≥ 39.5°C vs. 38.0°C to 39.4°C; OR=3.37, 95% CI: 1.16, 9.36). CRP, WBC, and absolute neutrophil count were not good bacteremia predictors.

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Herr (2001)[10]	Design: Chart review Region: North America Setting: Emergency Department Study period: 1999-2002	N: 434/344 Age group(s): < 59 d (subgroups: 0-14; 15-28; 29-45; and 46-59) Inclusion / exclusion: infants presented to the ED for evaluation with temperature ≥ 38°C-excluded infants with focus of infection and those with incomplete data Male (%): 51 Ethnicity (%): NR ---------------------------------- Information on mother: NR	Full term, no underlying illness, no previous hospitalization, no perinatal antibiotics (if < 14 days old), no sibling with group GBS disease; well appearance without focal infection + WBC: 5,000-15,000/mm3, ABC ≤ 1,500/mm3, enhanced UA (WBC ≤ 9 mm3 and negative Gram stain), CSF WBC ≤ 5/mm3 and negative Gram stain	Lobar infiltration on CXR, growth of a bacterial pathogen from CSF, blood, stool or soft tissue (UTI =growth of ≥ 50000 cfu/mL of a single pathogenic organism for urine obtained by catheter) Diagnosis: SBI: 41 (12.0) UTI: 25 Pneumonia: 8 Bacteremia: 3 Meningitis: 2 Gastroenteritis: 1 Chlamydia: 1	SBI: Sensitivity: 68.3 (51.7, 81.4) Specificity: 37.6 (32.2, 43.3) PPV: 12.9 (8.8, 18.2) NPV: 89.7 (82.8, 94.2)

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Marom (2007)[11]	Design: Cross Sectional Region: Israel Setting: Peadiatric ED Study period: 1998-2003	N: 449/386 Age group(s): 0 – 90 d Inclusion / exclusion: Consecutive infants presented to peadiatric EDs, with rectal temperature ≥ 38°C Male (%): 53% Ethnicity (%): NR --------------------------------- Information on mother: NR	Unremarkable medical history, good appearance, no focal/physical signs of infection + ESR < 30 mm/h WBC: 5,000-15,000/mm3, normal UA (dipstick: LE, nitrites)	NR (UTI if supra-pubic ≥ 1000; catheterized ≥ 10000 colony forming units/mL of a single urinary pathogen) Diagnosis: SBI: 108 (28.0) UTI: 54 Acute otitis media: 13 Gastroenteritis: 2 Meningitis: 2 Others: NR	SBI: Sensitivity: 99.1 (94.2, 99.9) Specificity: 59.3 (53.3, 65.1) PPV: 48.6 (41.8, 55.4) NPV: 99.4 (99.3, 99.5)

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Pantell (2004)[12]	Design: Cohort Region: North America Setting: 219 family practices Study period: 1995 – 1998	N: 3,066/1,746 Age group(s): 0 – 90d Inclusion / exclusion: Healthy infants with rectal temperature ≥ 38° C measured at home or office, hospitalized Male (%): 53.2% Ethnicity (%): White/non-Hispanic: 70 Hispanic: 15 African/American: 8 Asian/ South Pacific: 2 Other: 5 --------------------------------- Information on mother: NR	1) Clinical appearance + WBC< 5,000/ mm3 or WBC>15,000/mm3 2) Clinical appearance + WBC< 5,000/ mm3 or WBC>15,000/mm3; WBC ≥ 5/hpf	Bacteremia with pathogenic organisms and bacterial meningitis Bacteremia/bacterial meningitis: (1): 63 (3.6) Bacteremia/bacterial meningitis: (2): 63 (3.6)	SBI - (Bacteremia/bacterial meningitis) (1): Sensitivity: 83.9 (NC) Specificity: 54.0 (NC) PPV: NR NPV: NR SBI - (Bacteremia/bacterial meningitis) (2): Sensitivity: 87.1 (NC) Specificity: 50.7 (NC) PPV: NR NPV: NR

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Schwartz (2008)[13]	Design: Cross sectional Region: Israel Setting: ED Study period: 1997 – 2006	N: 644/449 Age group(s): 0 – 28 d Inclusion / exclusion: neonates with rectal temperature ≥ 38° C measured at home or office, hospitalized/ preterm, prior hospitalization or receipt of antibiotics, known chronic dx and a source of infection apparent on physical exam other than acute OM Male (%): NR Ethnicity (%): NR ---------------------------------- Information on mother: NR	Criteria for LR: not ill appearing, WBC 5,000 – 15,000/ mm^3, absence of LE in none centrifuged urine on dipstick test, and < 23 WBC/hpf on microscopic exam	SBI: positive bacterial growth of pathogens in blood, urine, CSF or stool culture, or a CXR revealing a lobar infiltrate or a bone or soft tissue infection not present on admission or ER after hospitalization Diagnosis: SBI: 87 (19.4%)- 79% male Bacteremia + meningitis + UTI: 2 Bacteremia + UTI: 2 Bacteremia: 1 UTI: 70 Pneumonia: 2 Omphalitis: 1	SBI - Sensitivity: 83.9 (75.6, 90.0) Specificity: 58.6 (56.6, 60.0) PPV: 32.7 (29.5, 35.1) NPV: 93.8 (90.6, 96.1)
Wasserman (1990)[14]	Design: Chart review Region: North America Setting: Army Medical Centre Study period: 1983-1985	N: NR/443 Age group(s): 0 – 90 d Inclusion / exclusion: Consecutive sample of FI with rectal temperature ≥ 38°C Male (%): NR Ethnicity (%): NR ---------------------------------- Information on mother: NR	Clinical judgment for 'low risk' (non-bacterial illness, did not appear ill, benign physical examination + unremarkable initial laboratory screen	Bacteremia, bacterial meningitis, soft tissue infection, UTI and bacterial enteritis Diagnosis: SBI: 53 (12.0) Bacteremia: 8 Meningitis: NR Soft tissue infection: NR UTI: NR Enteritis: NR	SBI: Sensitivity: 90.5 (78.6, 96.5) Specificity: 55.4 (50.3, 60.3) PPV: 21.6 (16.5, 27.7) NPV: 97.7 (94.5, 99.1)

Table 2. Clinical Criteria

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Bilavsky (2008)[15]	Design: Case Control Region: Israel Setting: Peadiatric ED Study period: 2005 – 2006	N: 149 cases/40 cases + 40 controls Age group(s): 0 – 90 d mean 80 d Inclusion / exclusion: Cases= previously healthy infants hospitalized with grunting respirations with fever ≥ 38°C; Controls= matched with cases for age, days of hospitalization and fever only without grunting)/ NR Note: study also included older infants (age >91 d) Male (%): NR Ethnicity (%): NR ---------------------------------- Information on mother: NR	Grunting respiration in cases vs. no grunting	NR SBI: 3 (7.5%) cases and 2 (5.0%) controls, p=1	SBI: Sensitivity: NR Specificity: NR PPV: NR NPV: NR The association between grunting and SBI was not significant with 3 infants with SBI in the case group vs. 2 infants with SBI in the control group (7.5% vs. 5.0%; OR=1.54 (95% CI: 0.19, 14.1).

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Bonadio (1991)[16]	Design: Case series Region: Taiwan Setting: Peadiatric ED Study period: 1986-1990	N: 683/683 Age group(s): 30 – 60 d Inclusion / exclusion: infants with temperature <41°C, and sepsis workup- excluded infants with preadmission antipyretic medication within 4 hours, or antibiotics within 72 hours Male (%): NR Ethnicity (%): NR ---------------------------------- Information on mother: NR	T ≥ 40.0°C	Bacterial meningitis, bacteremia, UTI, salmonella gastroenteritis, septic arthritis, osteomyelitis UTI if ≥ 100000 cfu/hpf Diagnosis: SBI: 34 (5.0) Meningitis: 6 Bacteremia: 8 UTI: 16 Enteritis: 4	SBI: Sensitivity: 21.0 (9.3, 38.4) Specificity: 97.0 (95.2, 98.0) PPV: 26.0 (11.8, 46.6) NPV: 95.8 (94.0, 97.2)

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Bonadio (1994)[17]	Design: Case series Region: North America Setting: Peadiatric ED Study period: 1989-1993	N: 367/356 Age group(s): 60 – 90 d Inclusion / exclusion: All infants with rectal temperature ≥ 38°C excluded infants who were culture negative for bacterial pathogens and received antibiotic treatment within 72 hours; antipyretic medication within 4 hours of presentation Male (%): NR Ethnicity (%): NR ---------------------------------- Information on mother: NR	Ill appearance	Bacterial meningitis, bacteremia, UTI, and salmonella enteritis UTI if ≥ 10000 cfu/mL of a single organism by bladder catheterization Diagnosis: SBI: 33 (9.3) UTI: 17 Meningitis: 5 Bacteremia: 8 Salmonella: 3	SBI: Sensitivity: 33.3 (18.5, 51.9) Bacteremia: Sensitivity: 37.5 (10.2, 74.1) Meningitis: Sensitivity: 100.0 (46.3,100.0) UTI: Sensitivity: 17.6 (4.6, 44.2) Salmonella: Sensitivity: 0
Broner (1990)[2]	Design: Quasi-experimental Region: North America Setting: General ED Study period: Unclear	N: NR/52 Age group(s): 4 – 56 d Inclusion / exclusion: Infants with rectal temperature ≥ 38.1°C Male (%): NR Ethnicity (%): NR ---------------------------------- Information on mother: NR	Toxic appearance (i.e., increased irritability, decreased eye contact, unwillingness to feed, and the state of alertness)	NR Diagnosis: SBI: 5 (9.6) (sepsis)	SBI: Sensitivity: 80.0 (29.8, 98.9) Specificity: 80.0 (66.2, 90.3) PPV: 30.7 (10.3, 61.1) NPV: 97.4 (84.5, 99.8)

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Caspe (1983)[3]	Design: Quasi-experimental Region: North America Setting: Primary care (community based hospital) Study period: July 1974 – December 1979	N: 305/305 Age group(s): 0 – 90 d Inclusion / exclusion: Infants with rectal temperature ≥ 38°C seen in outpatient or well documented fever at home Male (%): 54 Ethnicity (%): White/non-Hispanic: 3 Hispanic: 51 African/American: 45 Asian/ South Pacific: 1.3 ---------------------------------- Information on mother: NR	Ill appearance (inconsolable when held or fed or unresponsive to their environment)	NR Diagnosis: Bacteremia (0-90 d)- (1): 11 (3.6) Bacteremia (0-90 d)- (2): 11 (3.6) UTI: 7 (2.3)	Bacteremia (1): Sensitivity: 91.0 (57.1, 99.5) Specificity: 56.6 (49.3, 63.5) PPV: 10.4 (5.4, 18.7) NPV: 99.1 (94.4, 99.9) Bacteremia (2): Sensitivity: 85.7 (42.0, 99.2) Specificity: 73.2 (63.4, 81.3) PPV: 18.2 (76.1, 36.0) NPV: 98.6 (91.8, 99.9) UTI: Sensitivity: 42.8 (11.8, 79.8) Specificity: NR PPV: NR NPV: NR

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Chen (2008)[18]	Design: Case Series Region: Taiwan Setting: Peadiatric Hospital Study period: October 2005- July 2006	N: NR / 44 Age group(s): 0 – 90 d Inclusion / exclusion: Febrile infants with a clinical suspicion of SBI. Male (%): 68 Ethnicity (%): NR ---------------------------------- Information on mother: NR	Presence of at least one of the following: tachypnea, dyspnea, tachycardia, bradycardia, decrease of activity, lethargy, and decrease of appetite	SBI defined as pathogen in blood, CSF, or urine. Pneumonia was diagnosed as the presence of related clinical symptoms such as tachypnea productive cough with consolidation or fluid in lobar fissure/pleura visible on chest X-ray. UTI diagnosed as pyuria in routine urine exam and two sets or urine culture with a single pathogen growth more than 104 CFU/mL from a bladder catheterization or more than 105 CFU/ML collected from a sterile collection bag after sterile preparation. Diagnosis: Total SBI: 23/NR (all infants at high risk)	SBI: Sensitivity: NR Specificity: NR PPV: 52.3 (95% CI: 36.8, 67.3) NPV: NR

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Crain (1982) [19]	Design: Case series Region: North America Setting: Primary care Study period: 1979-1981	N: 134/134 Age group(s): 0 – 60 d Inclusion / exclusion: infants with rectal temperature ≥ 38°C documented at ED or home Male (%): NR Ethnicity (%): NR ---------------------------------- Information on mother: NR	Clinical impression of sepsis (infant's level of activity, irritability, responsiveness, ability to be consoled, feeding pattern)	NR Diagnosis: SBI (bacteremia): 5 (3.7)	SBI: Sensitivity: 100.0 (46.3,100.0) Specificity: 58.1 (49.1, 66.6) PPV: 8.5 (3.1, 19.4) NPV: 100.0 (93.9, 100.0)
King (1987)b [20]	Design: Cohort Region: North America Setting: Primary care Study period: 1983-1985	N: NR/97 Age group(s): 0 – 60 d Inclusion / exclusion: Outpatient infants with rectal temperature ≥ 38°C Male (%): 50 Ethnicity (%): White/non-Hispanic: 21 African/American: 75 Not known: 4 ---------------------------------- Information on mother: NR	Septic appearance (yes, no, unsure) based on physical examination, complete history, initial laboratory results	Positive culture of blood, CSF, and urine Diagnosis: SBI (Bacteremia or meningitis): 4 (5.4)	SBI: Sensitivity: 100.0 (39.6,100.0) Specificity: 66.0 (54.9, 74.9) PPV: 11.1 (3.6, 27.0) NPV: 100.0 (92.6, 100.0)

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Mintegi (2009)[21]	Design: Prospective Cohort Region: Spain Setting: ED Study period: 5 consecutive influenza seasons during 2003 – 2008	N: 520/381 Age group(s): 0 – 90 d Mean age: 48.8 d (n=88 were neonates) Inclusion / exclusion: Fever without a source ≥ 38°C, with blood culture and rapid influenza test (RIT)/ infants taking antibiotics prior to ED visit were excluded Note: 26 (6.6%) had underlying dx at presentation to ED Male (%): 53 Ethnicity (%): NR (likely to be 100% Hispanic) ----------------------------------- Information on mother: NR	Positive vs. negative influenza test	NR Diagnosis: SBI: Infants with positive RIT: 3/113 (2.65) Infants with negative RIT: 47/268 (17.5) Bacteremia: 8 (4 *Streptococcus agalactiae*; 2 *Neisseria meningitidis*, 1 *streptococcus pneumonia*; 1 *staphylococcus aureus*) UTI: 34 (only 301/381 had urine culture) UTI in positive RIT: 3/72 (4.17%); UTI in negative RIT: 31/229 (13.5%) Meningitis: 5 (only 110/381 had CSF culture) all with negative RIT (2 *S. agalactiae*, 2 *Listeria monocytogenes*, 1 *N. meningitidis*)	SBI: Sensitivity: 94.0 [83.1, 98.4] Specificity: 33.2 [31.6, 33.9] PPV: 17.5 [15.5, 18.4] NPV: 97.3 [92.5, 99.3] Prevalence of SBI in viral positive infants vs. viral negative: 2.65 [0.0, 5.6] vs. 17.5 [13.0, 22.0] Prevalence ratio: 0.15 [0.04, 0.48] OR: 0.13 [0.03, 0.44]

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Pantell (2004)[12]	Design: Cohort Region: North America Setting: 219 family practices Study period: 1995-1998	N: 3,066/1,746 Age group(s): 0 – 90d Inclusion / exclusion: Healthy infants with rectal temperature ≥ 38° C measured at home or office Male (%): 53.2 Ethnicity (%): White/non-Hispanic: 70 Hispanic: 15 African/American: 8 Asian/ South Pacific: 2 Other: 5 ---------------------------------- Information on mother: NR	1) High risk: age < 30 d and ill-appearing Low risk: age > 30 d and well-appearing 2) Moderately or very ill vs. well or minimally ill; age < 25 d; T ≥ 38.6°C 3) Clinical appearance	Bacteremia with pathogenic organisms and bacterial meningitis Diagnosis: SBI (Bacteremia/bacterial meningitis)- (1): 63 (3.6) SBI (Bacteremia/bacterial meningitis)- (2): 63 (3.6) SBI (Bacteremia/bacterial meningitis)- (3): 63 (3.6)	SBI (Bacteremia/bacterial meningitis)- (1): Sensitivity: 95.2 (NC) Specificity: 35.49 (NC) PPV: NR NPV: NR SBI (Bacteremia/bacterial meningitis)- (2): Sensitivity: 93.6 (NC) Specificity: 27.3 (NC) PPV: NR NPV: NR SBI (Bacteremia/bacterial meningitis)- (3): Sensitivity: 58.1 (NC) Specificity: 68.1 (NC) PPV: NR NPV: NR

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Rosenberg (1985)[22]	Design: Case series Region: North America Setting: Peadiatric ED Study period: 1981-1982	N: 122/122 Age group(s): 0 – 60 d Inclusion / exclusion: Infants with auxiliary temperature ≥ 37.8°C Male (%): NR Ethnicity (%): NR ---------------------------------- Information on mother: NR	Clinical impression of sepsis (irritable, toxic, lethargic)	NR UTI if > 100,000 cfu/ml Diagnosis: SBI (bacteremia): 5 (4.0)	SBI: Sensitivity: 80.0 (29.9, 98.9) Specificity: 37.5 (28.7, 47.2) PPV: 5.4 (1.7, 13.9) NPV: 97.6 (86.2, 99.8)
Stanley (2005)[23]	Design: Chart review Region: North America Setting: Peadiatric ED Study period: Unclear	N: 5,279/5,279 Age group(s): 0 – 90 d Inclusion / exclusion: infants with a rectal temperature ≥ 38°C, with complete test and culture records. Male (%): NR Ethnicity (%): NR ---------------------------------- Information on mother: NR	Temperature > 40.0°C	Positive culture of urine, blood or CSF UTI if supra-pubic ≥ 1000; catheterized ≥ 10000 colony forming units/mL (cfu/mL) of a single urinary pathogen Diagnosis: SBI: 480 (9.1) UTI: 305 Meningitis: 10 Bacteremia: 39 Bacteremia/meningitis: 8 Bacteremia/UTI: 11 Pneumonia: 70 Cellulitis: 26 Bacterial enteritis: 11	SBI: Sensitivity: 7.3† (5.2, 10.1) Specificity: 98.8 (98.4, 99.1) PPV: 38.0 (28.3, 48.8) NPV: 91.4 (90.6, 92.1)

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Wolff (2009)[24]	Design: Chart review Region: North America Setting: Peadiatric ED Study period: Unclear	N: 2,247/1978 Age group(s): 45 – 90 d; median age 64 d in recently immunized infants (RI) and 65 d in infants not recently (72 preceding ED visit) immunized (NRI) Inclusion / exclusion: infants with a temperature ≥ 38°C at home, GP office or ED (based on the 2-month immunization record)/ pre-term infants (< 32 week gestational age), chronic illness, surgery within 7 days, concurrent antibiotic use or focal bacterial infection by examination other than OM. Male (%): NR Ethnicity (%): NR ---------------------------------- Information on mother: NR	Ill appearing (excluded): ill appearing on exam , cyanotic, apneic, mottled, poorly perfused, unresponsive or morbibund All other infants were classified as well appearing	Definite SBI: bacterial pathogen isolated in blood or in urine; bacterial pathogen isolated in the CSF; pneumonia; or bacterial pathogen isolated in stool culture (study also reports criteria for possible SBI) Diagnosis: SBI: 130 (6.6) UTI: 105 Bacteremia: 11 Bacteremia/UTI: 4 Meningitis: 3 Pneumonia: 7 Prevalence of SBI in NRI (72 hrs prior to ED visit): 7.0% (95% CI: 5.9, 8.3) In RI: 2.8%, (95% CI: 0.6, 5.1) Prevalence of SBI in RI (24 hrs prior to ED visit): 0.6%,(95% CI: 0, 0.9)	SBI: Sensitivity: 95.4 [90.0, 98.1] Specificity: 11.3 [10.9, 11.5] PPV: 7.1[6.7, 7.3] NPV: 97.2 [93.8, 98.8] RI infants were at lower risk of having SBI compared with NRI infants (RR=0.41, 95% CI: 0.19, 0.90). Infants immunized 24 hr were at a lower risk of having SBI than NRI infants (RR=0.09, 95% CI: 0.01, 0.64).

Table 3. Other studies - Prevalence of SBI/IHI in Febrile Infants

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI/Herpes	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Andreola (2007)[25]	Design: Cohort Region: Western Europe Setting: Peadiatric ED Study period: 2004-2005	N: 107 (26.2% of total sample age 0 – 36 months) Age group(s): 0 – 90 d Inclusion / exclusion: All children younger than 3 years admitted to the ED with fever of certain source- excluded infants with antibiotic use within 48 hours before admission; vaccination during the previous 2 days, known immunodeficiencies; any chronic pathology; fever lasting longer than 5 days Male (%): NR Ethnicity (%): NR --------------------------------- Information on mother: NR	Yale Observation Scale age 7-90 d, and fever >38ºC	SBI by growth of a single pathogen in blood, urine or CSF culture included bacteraemia; UTI, bacterial meningitis; lobar pneumonia, sepsis (UTI: single urinary tract pathogen at ≥ 10^5 cfu/mL in 2 consecutive urine sample and presence of a renal hypocaptation at DMSA scan performed within the fist week after admission) Diagnosis: SBI: 6 (11.5)	SBI: Sensitivity: NA Specificity: NA PPV: NA NPV: NA

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI/Herpes	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Bilavsky (2009)[26]	Design: Region: Israel Setting: Peadiatric Ward Study period: 2005 – 2008	N: 892 Age group(s): 0 – 90 d Inclusion / exclusion: all febrile infants age </=3 months (including those hospitalized)/ excluded were those with chronic disease, or congenital or acquired immune deficiency, preterm birth (<32 wks of gestation), and receipt of antibiotics within 48 hrs Male (%): 57.5 Ethnicity (%): NR ---------------------------------- Information on mother: NR	Only WBC and CRPs were measured upon admission- WBC cut offs: >15,000, > 20,000, > 15,000 or < 5,000/µL CRP cut offs: > 8, >4, or >2 mg/dL	SBI: growth of pathogen in culture of blood, urine or CSF. Cultures with more than one isolate were considered to be contaminated. Diagnosis: SBI: 102/892 (11.3)	SBI: Sensitivity: NR Specificity: NR PPV: NR NPV: NR

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI/Herpes	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Bonadio (1987)[27]	Design: Chart review Region: North America Setting: Paediatric ED Study period: 1984 (July – Nov)	N: 159 (subgroup of larger study, n=265 age 0-12 months) Age group(s): 0 – 60 d Inclusion / exclusion: Febrile infants less than 12 months of age admitted with the diagnosis of rule out sepsis, with no source of infection identified Male (%): NR Ethnicity (%): NR --------------------------------- Information on mother: NR	Urine analysis by bag, catheter or suprapubic aspiration	UTI cultures positive if: Suprapubic aspiration specimen: pure colony count of ≥ 1000 cfu/mL Bladder catheterization: ≥ 1000-10000 cfu/mL Diagnosis: SBI (UTI only): 12/159 (7.5) Note: complete urine culture result by method of collection reported for the larger sample	SBI: Sensitivity: NA Specificity: NA PPV: NA NPV: NA

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI/Herpes	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Bonadio (1991)[16]	Design: Case Series Region: North America Setting: Paediatric ED Study period: 1989 – 1990	N: 161 Age group(s): 30 – 60 d Inclusion / exclusion: All infants with rectal temperature ≥ 38ºC documented at the time of triage in ED Male (%): NR Ethnicity (%): NR --------------------------------- Information on mother: NR	NR	SBI included bacterial meningitis, bacteraemia, UTI and bacterial enteritis Diagnosis: SBI: 18 (11.2)	SBI: Sensitivity: NA Specificity: NA PPV: NA NPV: NA

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI/Herpes	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
DeAngelis (1983)[28]	Design: Chart review Region: North America Setting: Peadiatric hospital (outpatient) Study period: 1978- 1981	N: 290 Age group(s): 0 – 60 d Inclusion / exclusion: Infants with rectal temperature ≥ 38ºC evaluated at outpatient care Male (%): NR Ethnicity (%): NR ---------------------------------- Information on mother: NR	NR	Immobile tympani membrane positive bacterial culture or infiltrate on chest roentgenogram Diagnosis: SBI: 39 (13.4)	SBI: Sensitivity: NA Specificity: NA PPV: NA NPV: NA

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI/Herpes	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Ferguson (2008)[29]	Design: Chart review Region: North America Setting: ED Study period: 2004 – 2005	N: 190 Age group(s): 30 – 60 d: n=90 60 – 90 d: n=100 Inclusion / exclusion: infants with temperature ≥ 38ºC who presented to the ED Male (%): 56% Ethnicity (%): NR ---------------------------------- Information on mother: NR	NR (clinical variables, microbiologic results including rapid viral testing and cultures was extracted from charts)	NR Diagnosis: SBI (total): 30 – 60 d: 9 (10.0) 60 – 90 d: 10 (10.0) Bacteremia: 30 – 60 d: 1 (1.1) 60 – 90 d: 1 (1.0) UTI 30 – 60 d: 6 (6.7) 60 – 90 d: 5 (5.0) Meningitis 30 – 60 d: 0 60 – 90 d: 0 Pneumonia 30 – 60 d: 2(2.2) 60 – 90 d: 4 (4.0)	SBI: Sensitivity: NA Specificity: NA PPV: NA NPV: NA

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI/Herpes	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Filippine (2001)[30]	Design: Chart review Region: North America Setting: Primary care Study period: 1995-1997	N: 242/113 Age group(s): 0 – 90 d Inclusion / exclusion: All febrile infants with virology laboratory results- excluded infants if no presenting fever was documented, there was an obvious source of infection on presentation, had congenital anomaly, hardware predisposing them to infection, or were immunocompromised Male (%): NR Ethnicity (%): NR ---------------------------------- Information on mother: NR	Positive virology results to identify infants with HSV HSV: a) HSV encephalitis as HSV positive brain biopsy or autopsy specimen b) probable case of HSV encephalitis as consistent neurologic picture and virologic evidence of HSV (by culture of PCR). c) definite case of disseminated HSV as evidence of HSV infection and evidence of other affected organs. d) SEM disease as laboratory confirmed HSV infection confined to the skin, eye and/or mouth only	Diagnosis: SBI: 27/113 (23.9%) UTI: 20 UTI + bacteremia: 5 Bacterial meningitis: 2 HSV encephalitis: 2 (one infant died) Note: 14 probable case of HSV encephalitis 12/14 with obvious SEM disease on physical examination 32 infants also were HSV positive but were diagnosed with transplacental maternal antibody	SBI: Sensitivity: NA Specificity: NA PPV: NA NPV: NA

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI/Herpes	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Grover (1999)[31]	Design: Diagnostic accuracy study Region: North America Setting: Peadiatric ED Study period: 1992 – 1993	N: 48 (subgroup in a larger study) Age group(s): 0 – 60 d Inclusion / exclusion: All infants less than 2 moths of age seen in pediatric ED including a subgroup with rectal temperature ≥ 38ºC Male (%): NR Ethnicity (%): NR ---------------------------------- Information on mother: NR	Ill appearance	Blood, urine and CSF culture positives. Stool cultures for bacterial and viral for infants with diarrhea, chest radiograph for infants with respiratory symptoms Diagnosis: SBI: 12 (25.0)	SBI: Sensitivity: NA Specificity: NA PPV: NA NPV: NA

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI/Herpes	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Hsiao (2006)[32]	Design: Diagnostic accuracy study Region: North America Setting: Peadiatric ED Study period: 2003 – 2004	N: NR (subgroup of a large study with n=429 age 57-180 d) Age group(s): 57 – 89 d Inclusion / exclusion: infants with rectal temperature ≥ 37.9ºC who consecutively presented to the ED. Excluded if parent did not sign consent Male (%): NR Ethnicity (%): NR --------------------------------- Information on mother: NR	Yale Observational Scale	NR (UTI: < 10000 colonies of a single organism /mL) Diagnosis: SBI: NR (8.8) Note: results reported for all infants 57-180 d	SBI: Sensitivity: NA Specificity: NA PPV: NA NPV: NA

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI/Herpes	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Kuppermann (1999)[33]	Design: cross sectional Region: North America Setting: Peadiatric ED Study period: 1994 – 1995 & 1995 – 1996	N: 30 (subgroup of larger study n=432 age 0-2 years) Age group(s): 0 – 90 d Inclusion / exclusion: Consecutive sample of febrile infants (0-2 years) Male (%): NR Ethnicity (%): NR --------------------------------- Information on mother: NR	Yale Observation Scale & laboratory (WBC, manual differential count)	Blood, urine and CSF cultures in addition to viral tests Diagnosis: SBI: 7 (23.3)	SBI: Sensitivity: NA Specificity: NA PPV: NA NPV: NA

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI/Herpes	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Mintegi (2010)[34]	Design: Cohort Region: Western Europe Setting: Peadiatric ED Study period: 2003 – 2007	N: 685 Age group(s): 0 – 90 d Inclusion / exclusion: Consecutive previously healthy well appearing infants younger than 3 mo with fever without known source Male (%): NR Ethnicity (%): NR --------------------------------- Information on mother: NR	Routine blood and urine work was performed WBC: >15,000/mm^3, or < 5,000 mm^3	Meningitis: positive CSF culture or positive CSF Gram tincture or CSF pleocytosis with negative CSF culture + positive blood culture LP was recommended for febrile infants under 15 d upon visit, with consideration for LP for infants 15 – 28 d Diagnosis: SBI: 97 (14.2%) SBI in infants 20.1%, in infants < 29 d, 12.6% in infants 29 – 60 d (p=0.04)-	SBI: Sensitivity: NA Specificity: NA PPV: NA NPV: NA 418 infants without LP were discharged without antibiotics. 38 of these had unscheduled return visits to ED due to persistent fever. 7/418 (1.6%) were admitted to ward, 4 of them were diagnosed with aseptic meningitis. No complications occurred. Study conclusion: the decision to perform the LP in healthy, well appearing febrile infants cold be individualized with no subsequent adverse outcomes

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI/Herpes	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Rudinsky (2009)[35]	Design: Case series Region: Western Europe Setting: Peadiatric ED Study period: 2002 – 2003	N: infants 0 – 24 months were included n of infants under 90 d NR Age group(s): 0 – 90 d Inclusion / exclusion: Consecutive previously healthy well appearing infants younger than 3 mo with fever without known source, fever ≥ 38.0ºC Male (%): NR Ethnicity (%): NR --------------------------------- Information on mother: NR	WBC: criteria NR	UTI, bacteremia, pneumonia, and/or meningitis with positive culture of blood, urine, CSF or chest radiographs. Diagnosis: SBI: 9 infants identified with SBI (total n of infants 0 – 3 mo NR)	SBI: Sensitivity: NA Specificity: NA PPV: NA NPV: NA

Table 4. Studies with laboratory criteria

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Bachur (2001)[1]	Design: Chart Review Region: North America Setting: ED Study period: 1993-1999	N: NR/5279 Age group(s): 0–90 d Inclusion / exclusion: Retrospective sample of infants with a rectal temperature ≥ 38°C, with complete test and culture records. Male (%): NR Ethnicity (%): NR -------------------------------- Information on mother: NR	UA (LE$^+$ or nitrite$^+$)	Positive culture of urine, blood or CSF (UTI if supra-pubic ≥ 1000; catheterized ≥ 10000 colony forming units/mL (cfu/mL) of a single urinary pathogen) Test Results: SBI 373 (7.0) UTI: 316 (6.0%) Meningitis: 17 Bacteremia: 40 Bacteremia/meningitis: 8 Bacteremia/UTI: 11	SBI: Sensitivity: 71.0 (66.0, 76.0) Specificity: NR PPV: NR NPV: NR UTI: Sensitivity: 81.0 (76.0, 85.0) Specificity: NR PPV: NR NPV: NR

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Bachur (2001)[36]	Design: Chart Review Region: North America Setting: Peadiatric ED Study period: NR	N: 37450/4539 (from original sample of 8815 who were 0-2 years old) Age group(s): 0–90 d Inclusion / exclusion: Retrospective sample of infants with temperature ≥ 38°C seen at ED with paired UA and urine culture Male (%): NR Ethnicity (%):NR -------------------------------- Information on mother: NR	UA: dipstick (LE,[+] nitrite,[+] or both) and microscopy (pyuria: ≥ 5 WBC/hpf)	UTI only (UTI if supra-pubic ≥ 1000; catheterized ≥ 10000 colony forming units/mL (cfu/mL) of a single urinary pathogen) Test Results: 73 (8.4) (UTI) 172 (7.5) (UTI)	UTI: Sensitivity: 82.0 (71.0, 90.0) Specificity: 92.0 (90.0, 94.0) PPV: 48.4 (39.4, 57.5) NPV: 98.2 (96.9, 99.0) UTI: Sensitivity: 82.0 (75.0, 87.0) Specificity: 94.0 (93.0, 95.0) PPV: 52.6 (46.4, 58.7) NPV: 98.4 (97.8, 98.9)

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Berkowitz (1985)[37]	Design: Chart Review Region: North America Setting: ED Study period: 1978-1979	N: 434/239 Age group(s): 0–60 d Inclusion / exclusion: Retrospective sample of FI with temperature ≥ 38°C evaluated in acute care walk in clinics (1978-1979) Male (%): 58 Ethnicity (%):NR --------------------------------- Information on mother: NR	≥ 15000/mm^3 WBC ≥ 10000/mm^3 PMN ≥ 500/mm^3 ABC ≥ 15000/mm^3 WBC + ≥ 500/mm^3 ABC ≥ 15000/mm^3 WBC + ≥ 10000/mm^3 PMN	NR (culture results of blood, CSF, and viral; culture- positive infants are referred to as category I) (NR) Test Results: SBI (Sepsis/meningitis 1-5): 10 (4.2)	SBI (1): Sensitivity: 50.0 (NC) Specificity: 77.0 (NC) PPV: NR NPV: NR SBI (2): Sensitivity: 38.0 (NC) Specificity: 93.0 (NC) PPV: NR NPV: NR SBI (3): Sensitivity: 88.0 (NC) Specificity: 61.0 (NC) PPV: NR NPV: NR SBI (4): Sensitivity: 63.0 (NC) Specificity: 84.0 (NC) PPV: NR NPV: NR SBI (5): Sensitivity: 38.0 (NC) Specificity: 94.0 (NC) PPV: NR NPV: NR

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Bilavsky (2010)[38]	Design: Case Control Region: Israel Setting: 2 EDs Study periods: 2005 – 2009	N: NR/1,257 Age group(s): 0–60 d Inclusion / exclusion: hospitalized febrile infants/ presence of chronic disease, or congenital or acquired immune deficiency, preterm birth (< 35 weeks of gestation) and receipt of antibiotics within 48 hr of presentation to ED Male (%): 59 Ethnicity (%): NR --------------------------------- Information on mother: NR	absolute neutrophil count (ANC with thresholds: > 4.65, > 10, > 12.5 K/µL), WBC (various thresholds: > 15, >20, > 20 or < 4.1, > 15 or <5 K/µL), and ratio % of ANC/WBC	Growth of a known pathogen in culture of blood, urine or CSF (UTI, meningitis, bacteremia or bacterial enteritis) Test Results: Total SBI: 134 (10.7%) UTI: 104 Bacteremia + UTI: 9 Isolated bacteremia: 4 Bacteremia + enteritis: 3 Pneumonia: 13 Enteritis: 1 Bacterial meningitis: 0 isolated bacteremia was caused by *S. pneumonia*, *S. pyogenes* and *S. group B*	SBI: Sensitivity: 38.8 [31.0, 47.3] Specificity: 84.6 [82.4, 86.6] PPV: NR NPV: NR Isolated Bacteremia: Sensitivity:17.2 [11.7, 24.4] Specificity: 93.2 [91.6, 94.6] PPV: NR NPV: NR AUC for ANC =0.77 (95% CI: 0.67, 0.78) and for WBC = 0.69 (95% CI: 0.61, 0.73). For infants ≤ 28 d, the AUC for % WBC= 0.73 (95% CI: 0.67–0.78), for % ANC = 0.70 (95% CI: 0.65–0.76), for WBC= 0.67 (95% CI: 0.61–0.73).

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)	
Bonadio (1987)[39]	Design: Chart Review Region: North America Setting: Peadiatric ED Study period: 1986-1987	N: 109/55 Age group(s): 0–28 d Inclusion / exclusion: Retrospective sample of Febrile infants with rectal temperature ≥ 38°C evaluated for sepsis in paediatric ED. Excluded: Infants currently receiving antibiotic medication at home, or antipyretic within 4 hours of admission Male (%): NR Ethnicity (%):NR -------------------------------- Information on mother: NR	15000/mm^3 WBC CBC Differential Ratio < 1 (Low risk) ABC/mm^3 > 1500	NR (UTI if > 100000 cfu/ml) Test Results: SBI (1-3): 8 (14.5) UTI: 3 Gastroenteritis: 2 Meningitis: 2 Bacteremia: 1	SBI: Sensitivity: 0.0 (NA) Specificity: NR PPV: NR NPV: NR SBI: Sensitivity: 87.5 (46.6, 99.3) Specificity: NR PPV: NR NPV: NR SBI: Sensitivity: 50.0 (17.4, 82.5) Specificity: NR PPV: NR NPV: NR	
Bonadio (1992)[40]	Design: Case Series Region: North America Setting:	N: NR/1009 Age group(s): 0–60 d Inclusion / exclusion: Retrospective sample of consecutive cases of infants with rectal	ABC/mm^3 (250, 500, 1000, 2000, 3000) Total WBC/mm^3 (3000, 10000, 12000, 18000, 20000)	Bacterial meningitis, bacteremia, TI, salmonella enteritis, osteomyelitis and septic arthritis (UTI if > 100000 cfu/mL of a single organism)	SBI: Sensitivity: 93.0 (82.4, 96.1) Specificity: 44.0 (40.8, 47.3) PPV: 13.0 (9.9, 15.4) NPV: 99.0 (96.4,	SBI: Sensitivity: 74.0 (62.9, 82.9) Specificity: 28.0 (25.4, 31.4) PPV: 8.0 (6.4, 10.6) NPV: 93.0 (88.7,

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)	
	Peadiatric ED Study period: NR	temperature ≥ 38.0°C at the time of triage Male (%): NR Ethnicity (%):NR -------------------------------- Information on mother: NR	ABC/mm^3 > 250 ABC/mm^3 > 500 ABC/mm^3 > 1000 ABC/mm^3 > 2000 ABC/mm^3 > 3000 WBC/mm^3 > 8000 WBC/mm^3 > 10000 WBC/mm^3 > 12000 WBC/mm^3 > 15000 WBC/mm^3 > 20000	Test Results: SBI (1-12): 81(8.0) Meningitis: 21 UTI: 29 Bacteremia: 23 Enteritis: 8	99.3) Bacteremia: Sensitivity: 80.0 (76.5, 92.7) Specificity: 61.0 (55.5, 63.0) PPV: 16.0 (12.3, 19.2) NPV: 98.0 (96.4, 99.0) Meningitis: Sensitivity: 74.0 (62.9, 82.9) Specificity: 80.0 (76.9, 82.1) PPV: 24.0 (19.0, 30.0) NPV: 97.0 (95.7, 98.2) SBI: Sensitivity: 42.0 (31.2, 53.4) Specificity: 93.0 (91.2, 94.6) PPV: 35.0 (25.5, 45.0) NPV: 96.0 (93.1, 96.1)	95.2) SBI: Sensitivity: 69.0 (57.7, 78.6 Specificity: 52.0 (48.2, 54.7) PPV: 11.0 (8.5, 14.2) NPV: 95.0 (92.6, 96.7) SBI: Sensitivity: 51.0 (39.6, 61.8) Specificity: 72.0 (68.9, 74.8) PPV: 14.0 (10.0, 18.1) NPV: 94.0 (92.3, 95.9) SBI: Sensitivity: 31.0 (21.3, 42.2) Specificity: 88.0 (85.5, 89.8) PPV: 18.0 (12.3, 25.7) NPV: 94.0 (91.6, 95.0)

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)	
					SBI: Sensitivity: 19.0 (11.0, 29.0) Specificity: 98.0 (97.0, 98.9) PPV: 47.0 (29.5, 64.9) NPV: 93.0 (91.4, 94.7)	SBI: Sensitivity: 16.0 (9.1, 26.2) Specificity: 97.0 (96.2, 98.3) PPV: 35.0 (20.7, 52.6) NPV: 93.0 (91.1, 94.5)

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Bonsu (2003)[41]	Design: Chart Review Region: North America Setting: Peadiatric ED Study period: NR	N: 6027/3961 Age group(s): 0–89 d Inclusion / exclusion: Consecutive infants presented to paediatric ED with peripheral blood sent concurrently for bacterial culture and total peripheral WBC, with rectal temperature ≥ 38°C at triage-excluded infants with leukemia Male (%): NR Ethnicity (%):NR ------------------------------- Information on mother: NR	≥ 5000/mm^3 WBC ≥ 10000/mm^3 ≥ 15000/mm^3 ≥ 20000/mm^3 < 5000/mm^3 or ≥ 15000/mm^3 < 5000/mm^3 or ≥ 20000/mm^3	Bacteremia coded to be present if standard cultures isolated a pathogen known to cause bacteremia unequivocally in this age group. (NR) Test Results: 38 (1.0) (bacteremia) Same Results for all Lab tests	Bacteremia (1): Sensitivity: 79.0 (63.0, 90.0) Specificity: 5.0 (4.0, 6.0) PPV: 0.8 (0.6, 1.2) NPV: 96.2 (92.3, 98.2) Bacteremia (2): Sensitivity: 61.0 (43.0, 76.0) Specificity: 42.0 (40.0, 44.0) PPV: 1.0 (0.6, 1.5) NPV: 99.0 (98.4, 99.4) Bacteremia (3): Sensitivity: 45.0 (29.0, 62.0) Specificity: 78.0 (76.0, 79.0) PPV: 2.0 (1.2, 3.2) NPV: 99.3 (98.9, 99.5) Bacteremia (4): Sensitivity: 24.0 (11.0, 40.0) Specificity: 93.0 (92.0, 94.0) PPV: 3.4 (1.6, 6.6) NPV: 99.1 (98.8, 99.4) Bacteremia (5): Sensitivity: 66.0 (49.0, 80.0) Specificity: 72.0 (71.0, 74.0) PPV: 2.3 (1.5, 3.5) NPV: 99.5 (99.1, 99.7) Bacteremia (6): Sensitivity: 45.0 (29.0, 62.0) Specificity: 88.0 (87.0, 89.0) PPV: 3.6 (2.2, 5.8) NPV: 99.3 (99.0, 99.6)

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Bonsu (2007)[42]	Design: Cross-Sectional Region: North America Setting: Peadiatric ED Study period: 1993-1999	N: NR/3765 Age group(s): 0–89 d Inclusion / exclusion: Consecutive Febrile infants, temperature in triage ≥ 38°C, presented to paediatric ED Male (%): NR Ethnicity (%):NR ------------------------------ Information on mother: NR	UA (LE,[+] nitrite,[+] or protein)	UTI and SBI (no definition for SBI is provided) (UTI if supra-pubic ≥ 1000; 12.6 [6.8, 21.9]catheterized ≥ 10000 colony forming units/mL (cfu/mL) of a single urinary pathogen) Test Results: UTI with sepsis: 307 (8.1)	SBI: Sensitivity: 84.0 (79.3, 87.8) Specificity: 63.6 (62.0, 65.2) PPV: 17.0 (15.1, 19.0) NPV: 97.8 (97.1, 98.3)
Bresan (2010)[43]	Design: Cohort Region: Europe (Italy) Setting: Peadiatric ED Study period: 2003 – 2007	N: 131/99 Age group(s): 0–28 d; mean age 19.6 d Inclusion / exclusion: Fever(rectal ≥ 38°C, or axillary 37.5°C) without source for less than 12 hrs, good clinical appearance/ underlying diseases, Previously on antibiotics, preterm (<37 weeks gestation)	absolute neutrophil count (ANC: > 10,000/ mm3), or WBC (threshold: <5,000/ mm3 or > 15,000/ mm3), or CRP > 20 mg/L measured for infants with fever duration < 12 hours and also for infants with normal lab test after 12 hrs of fever	UTI, bacteremia, meningitis, pneumonia, cellulitis, osteomyelitis, septic arthritis identified as growth of pathogens in culture of blood, urine or CSF Test Results: Total SBI (< 12 hrs of fever duration): 25 (25.3) (total SBI identified by repeated blood test: 5/25)	SBI for low risk infants determined for fever < 12 hrs vs. > 12 hrs: WBC (threshold: <5,000/ mm3 or > 15,000/ mm3 Sensitivity: 28.0[14.3, 47.6] vs. 80.0 [37.6, 96.4] Specificity: 87.7[78.2, 93.4] vs. 90.6 [79.7, 95.9] PPV: 43.75[23.1, 66.8] vs. 44.4 [18.9, 73.3] NPV: 78.1[68.0, 85.6] vs. 98.0 [89.3, 99.6]

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
		Male (%): NR Ethnicity (%): NR -------------------------------- Information on mother: NR	duration	management: Immediate antibiotic therapy for 37 neonates (7 – 28 days) who were hospitalized upon admission. Twenty (54.0%) of these neonates were diagnosed with SBI. No treatment outcomes were reported.	SBI for low risk infants determined for fever < 12 hrs vs. > 12 hrs: CRP > 20 mg/L Sensitivity: 48.0 [30.3, 66.5] vs. 100.0 [56.6, 100.0] Specificity: 93.2 [85.1, 97.1] vs. 96.2 [87.2, 99.0] PPV: 70.6 [46.9, 86.7] vs. 71.4 [35.9, 91.8] NPV: 84.2[74.7, 90.5] vs. 100.0 [93.0, 100.0] AUC: ANC= 0.78 (95% CI: 0.69, 0.86) WBC =0.59 (95% CI 0.49, 0.69) CRP = 0.77 (95% CI: 0.67, 0.85) * Repeated blood examination (n=58). 5/58 had SBI. AUC for repeated tests resulted in improved values for CRP (0.99, 95% CI: 0.92, 1.0), ANC (0.85, 95% CI: 0.73, 0.93) and WBC (0.79, 95% CI: 0.66, 0.88).

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Broner (1990)[2]	Design: Quasi-Experiments Region: North America Setting: ED Study period: NR	N: NR/52 Age group(s): 0–60 d Inclusion / exclusion: Prospective sample of Febrile infants with rectal temperature ≥ 38.1°C presented to general ED Male (%): NR Ethnicity (%):NR ------------------------------- Information on mother: NR	1) ≥ 15,000 WBC/µL 2) ≥ 5,000 ABC/µL 3) ESR ≥ 30 mm/h 4) CRP [+]	NR (NR) Test Results: SBI (Sepsis 1-4): 5 (9.6)	SBI (1): Sensitivity: 20.0 (1.0, 70.0) Specificity: 80.0 (66.2, 90.3) PPV: 10.0 (0.5, 45.8) NPV: 90.4 (76.4, 96.9) SBI (2): Sensitivity: 80.0 (29.8, 98.9) Specificity: 57.0 (42.2, 71.4) PPV: 16.6 (5.4, 38.1) NPV: 96.4 (79.7, 99.8) SBI (3): Sensitivity: 25.0 (1.0, 70.1) Specificity: 87.0 (73.5, 94.7) PPV: 14.3 (0.7, 58.0) NPV: 91.1 (77.8, 97.1) SBI (4): Sensitivity: 64.0 (17.0, 92.7) Specificity: 67.0 (52.7, 80.4) PPV: 16.6 (4.4, 42.2) NPV: 94.1 (78.9, 98.9)

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Brown (2005)[44]	Design: Chart Review Region: North America Setting: Peadiatric ED Study period: 1999-2002	N: 206/69 Age group(s): 0–28 d Inclusion / exclusion: Retrospective sample of FI presenting to tertiary paediatric ED (1999-2002) with triage temperature ≥ 38°C, and complete sepsis workup record – excluding infants in whom the triage temperature record was not available or ≤ 38°C Male (%): 55 Ethnicity (%):NR ------------------------------- Information on mother: NR	≥ 5000/mm^3 WBC ≥ 10000/mm^3 WBC ≥ 12000/mm^3 WBC ≥ 15000/mm^3 WBC ≥ 17000/mm^3 WBC 5000;10000; 12000; 15000; 17000; 20000; 22000; 25000/mm^3 WBC	Positive culture of blood, urine, CSF, or stool or a clinical diagnosis of cellulitis, fasciitis, omphalitis, osteomyelitis or mastitis- excluded pneumonia Viral: positive viral culture, PCR or immunofluorescence study (NR) Test Results: SBI (1-6): 8 (12.0)	SBI (1): Sensitivity: 100.0 (NC) Specificity: 2.0 (NC) PPV: 12.0 (NC) NPV: 100.0 (NC) SBI (2): Sensitivity: 100.0 (60.0, 100.0) Specificity: 31.0 (19.9, 44.7) PPV: 17.0 (8.0, 30.7) NPV: 100.0 (78.1, 100.0) SBI (3): Sensitivity: 75.0 (35.5, 95.5) Specificity: 53.0 (41.6, 68.0) PPV: 18.0 (7.8, 37.0) NPV: 94.0 (78.9, 98.9) SBI (4): Sensitivity: 50.0 (17.4, 82.5) Specificity: 74.0 (64.4, 87.0) PPV: 21.0 (7.8, 50.2) NPV: 91.0 (79.5, 97.3) SBI (5): Sensitivity: 38.0 (9.0, 76.0) Specificity: 89.0 (78.1, 95.7) PPV: 33.0 (9.0, 69.0) NPV: 91.0 (80.0, 96.7) SBI (6): NR

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Caspe (1983)[3]	Design: Quasi-Experimental Region: North America Setting: Primary Care Study period: 1974-1979	N: 305/198 Age group(s): 0–60 d Inclusion / exclusion: Infants presenting to community based hospital with rectal temperature ≥ 38°C seen in outpatient or well documented fever at home Male (%): 54 Ethnicity (%): White/non-Hispanic: 3 Hispanic: 45 African/American: 51 Asian/ South Pacific: 1.3 Other: 0 ------------------------------- Information on mother: NR	≥ 15,000/mm^3 WBC	NR (blood, urine, CSF- also stool and nasopharynx when indicated) (NR) Test Results: SBI (bacteremia): Age 0 – 30 d: 7 (6.5) Age 30 – 60 d: 4 (2.0)	Bacteremia (age: 0 – 30 d) Sensitivity: 28.6 (5.1, 69.7) Specificity: NR PPV: NR NPV: NR Bacteremia (age 30 – 60 d): Sensitivity: 75.0 (21.9, 98.7) Specificity: NR PPV: NR NPV: NR

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Caviness (2008)[45]	Design: Case Series Region: North America Setting: Peadiatric Emergency Department Study period: 2001-2005	N: NR/960 Age group(s): 0–90 d Inclusion / exclusion: Every infant aged <28 days evaluated in the ED Male (%): NR Ethnicity (%):NR ------------------------------- Information on mother: NR	CSF pleocytosis: ≥ 20 WBC/mm^3 & > 1 WBC per 500 red blood cells/mm^3	HSV infection: a positive HSV test result (HSV DNA detection by PCR, HSV antigen detection by direct fluorescence assay, and viral culture, on any tissue or body fluid obtained before or after death, confirmed with medical record SBI: positive bacterial culture from CSF, blood, or urine; meningitis if CSF bacterial culture was positive, bloodstream infection (bacteremia or septicemia) if blood culture was positive, UTI: >/=10,000 CFU/mL urinary pathogen confirmed with medical record Diagnosis: Total HSV: 3 Total SBI: 119 (12.4) UTI: 78 Bacteremia: 29 Meningitis: 12	HSV: Sensitivity: 66.6% (95% CI: 12.5, 98.2) Specificity: 74.6% (95% CI: 71.4, 77.6) PPV: 1.0% (95% CI: 0.2, 3.9) NPV: 99.8% (95% CI: 98.9, 99.9), SBI: Sensitivity: 31.1 [23.1, 40.3] Specificity: 75.5 (95% CI: 72.0, 78.6) PPV: 18.1 (95% CI: 13.2, 24.2) NPV: 86.2 (95% CI: 83.1, 88.8) Bacteremia: Sensitivity: 34.5 (95% CI: 18.6, 54.3) Specificity: 74.8 (95% CI: 71.6, 77.8) PPV: 4.9 (95% CI: 2.5, 9.1) NPV: 96.8 (95% CI: 95.0, 98.0) Meningitis: Sensitivity: 91.6 (95% CI: 59.7, 99.5) Specificity: 75.5 (95% CI: 72.3, 78.4) PPV: 5.4 (95% CI: 2.8, 9.6) NPV: 99.8 (95% CI: 98.9, 99.9)

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)	
Crain (1982)[19]	Design: Case Series Region: North America Setting: Primary Care Study period: 1979-1981	N: 134/99 Age group(s): 0–60 d Inclusion / exclusion: Prospective sample of Febrile infants presenting to paediatric care with rectal temperature ≥ 38°C documented at ED or home Male (%): NR Ethnicity (%):NR --------------------------------- Information on mother: NR	ESR ≥ 30 mm/h	NR (NR) Test Results: SBI (bacteremia): 5 (5.0)	Bacteremia: Sensitivity: 80.0 (29.8, 98.9) Specificity: 93.6 (86.0, 97.3) PPV: 40.0 (13.7, 72.6) NPV: 99.0 (93.0, 99.9)	
Dayan (2002)[46]	Design: Cross-Sectional Region: North America Setting: Peadiatric ED Study period:	N: 246/232 Age group(s): 1–60 d Inclusion / exclusion: Consecutive sample of infants with temperature ≥ 38°C presenting at paediatric ED (1998-2000)- excluded were infants without completed Gram stain	Gram stain, any organisms Microscopy of spun urine (≥ 5 WBC/hpf) Microscopy of urine (≥ 10 WBC/hpf) Any nitrite alone	UTI only (UTI if supra-pubic ≥ 1000; catheterized ≥ 10000 cfu/ mL (cfu/mL) of a single urinary pathogen) Test Results: SBI (UTI only): 27 (14.0) (%)	UTI (1): Sensitivity: 80.0 (62.5,97.5) Specificity: 99.4 (93.8, 100.0) PPV: 95.6[†] (76.0, 99.8) NPV: 96.8 (92.9, 98.9) UTI (2):	UTI (5): Sensitivity: 80.0 (62.5, 97.5) Specificity: 94.2 (90.7, 97.7) PPV: 67.7 (48.5, 82.6) NPV: 96.3 (91.7, 98.5) UTI (6):

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)	
	1998-2000	Male (%): 49 Ethnicity (%): NR ---------------------------------- Information on mother: NR	Any LE alone Nitrile + LE UA (LE$^+$ or nitrite$^+$)	Same Results for all Lab tests	Sensitivity: 65.0 (44.1, 85.9) Specificity: 92.4 (88.6, 96.4) PPV: 56.6 (37.6, 74.0) NPV: 93.8 (88.7, 96.8) UTI (3): Sensitivity: 45.0 (23.2, 66.8) Specificity: 97.6 (95.4, 99.9) PPV: 75.0 (47.4, 91.6) NPV: 91.5 (86.1, 95.0) UTI (4): Sensitivity: 35.0 (14.1, 55.9) Specificity: 97.7 (95.4, 99.9) PPV: 69.2 (38.8, 89.6) NPV: 90.0 (84.4, 93.8)	Sensitivity: 30.0 (10.0, 50.0) Specificity: 100.0 (98.3, 100.0) PPV: 100.0 (60.0, 100.0) NPV: 89.7 (84.2, 93.5) UTI (7): Sensitivity: 85.0 (69.4, 100.0) Specificity: 91.9 (87.8, 96.0) PPV: 62.1 (44.8, 77.0) NPV: 97.4 (93.1, 99.1)

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)	
Hoberman (1993)[47]	Design: Cohort Region: North America Setting: Peadiatric ED Study period: NR	N: NR/306 Age group(s): 0–60 d Inclusion / exclusion: All febrile infants presented in pediatric ED (1990-1991) with rectal temperature ≥ 38.3°C or auxiliary ≥ 37.4°C recorded in the ED, or recorded within 24 hours- excluded were infants with antibacterial treatment or bladder catheterization Male (%): NR Ethnicity (%):NR ------------------------------ Information on mother: NR	Bacteriuria (Any number of bacteria by hpf)	UTI only (UTI if result of standard quantitative and dipslide culture were considered positive if ≥ 10000 CFLU of a single type of organism/mm.) Test Results: 14 (UTI)	UTI: Sensitivity: NR Specificity: NR PPV: NR NPV: NR	

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
King (1987)a[20]	Design: Chart Review Region: North America Setting: Primary Care Study period: NR	N: 439 / 245 Age group(s): 0–60 d Inclusion/ exclusion: Retrospective sample of Febrile infants with rectal temperature ≥ 38°C who presented to University hospital (1978-1982) Prospective sample of outpatients with rectal temperature ≥ 38°C (1983-1985) Male (%): 50 Ethnicity (%): White/non-Hispanic: 21 Hispanic: 0 African/American:75 Asian/ South Pacific: 0 Other: 4 ------------------------------- Information on mother: NR	≤ 5,000 WBC/mm^3 % Immature neutrophils ≥ 20% ESR ≥ 30 mm/h	NR (blood, CSF, and urine culture results reported) (NR) Test Results: SBI (Bacteremia or meningitis 1):16 (4.6) SBI (Bacteremia or meningitis 2):16 (5.0) SBI (Bacteremia or meningitis 3):4 (5.4)	SBI (1): Sensitivity: 44.0 (20.7, 69.4) Specificity: 96.0 (93.1, 97.7) PPV: 35.0 (16.3, 59.0) NPV: 97.0 (94.5, 98.6) SBI (2): Sensitivity: 69.0 (41.5, 87.9) Specificity: 75.0 (69.7, 79.7) PPV: 12.6 (6.8, 21.9) NPV: 97.0 (94.8, 99.2) SBI (3): Sensitivity: 25.0 (1.3, 78.0) Specificity: 75.7 (63.7, 84.8) PPV: 5.5 (0.2, 29.3) NPV: 94.6 (84.2, 98.6)

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Lin (2000)[48]	Design: Cross-sectional Region: Taiwan Setting: Peadiatric ED Study period: 1997-1998	N: 223/162 Age group(s): 0–60 d Inclusion / exclusion: Infants presenting to ED, with rectal temperature ≥ 38°C. Excluded were infants with past antibiotic treatment, infants in whom urine aspiration was not successful, urine specimens of < mL, and infants with more than one aspiration Male (%): 58 Ethnicity (%):NR ------------------------------- Information on mother: NR	UA microscopy (spun urine; ≥ 5 WBC/hpf) UA microscopy (hemocytometer; ≥ 10 WBC/µL) CRP > 20 mg/L ESR > 30 mm/h > 15,000 WBC/ µL	UTI only (growth of a single pathogen at a concentration of ≥ 100 cfu/mL (cultures with mixed organisms or nonpathogenic Gram-positive cocci were considered contaminated)) Test Results: 22 (13.5) (UTI) Same Results for all Lab tests	UTI: Sensitivity: 59.0 (36.7, 78.5) Specificity: 93.0 (86.9, 96.3) PPV: 56.5 (34.8, 76.1) NPV: 93.5 (87.7, 96.8) UTI: Sensitivity: 82.0 (59.0, 94.0) Specificity: 94.0 (88.6, 97.3) PPV: 69.2 (48.1, 84.9) NPV: 97.0 (92.2, 99.0) UTI: Sensitivity: 59.0 (36.6, 78.5) Specificity: 90.0 (83.5, 94.2) PPV: 48.1 (29.1, 67.6) NPV: 93.3 (87.3, 96.7) UTI: Sensitivity: 73.0 (49.5, 88.4) Specificity: 78.0 (69.9, 84.2) PPV: 34.0 (21.3, 49.4) NPV: 94.7 (88.5, 97.8) UTI: Sensitivity: 36.0 (18.0, 59.1) Specificity: 80.0 (72.2, 86.0) PPV: 22.2 (10.7, 39.6) NPV: 88.9 (81.7, 93.5)

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Dauber (2008)[49,50]	Design: Case Series Region: North America Setting: Peadiatric ED Study duration/ period: 18 months during 2005 – 2007	N: 435/234 Age group(s): 0–90 d median age 51 d Inclusion / exclusion: Infants presenting to paediatric ED (with documented temperature ≥ 38°C Exclusion: Previous identified immunodeficiency, focal infection, on antibiotics, surgery in past 7 d, immunizations in the past 48 hrs, or antibiotic tx within 48 hrs Male (%): 53 Ethnicity (%): NR ------------------------------- Information on mother: NR	Procalcitonin levels (PCT) at 0.13 ng/mL	Definite SBI: bacteremia, UTI (from catheterization with ≥ 50 000 CFUs/ mL of a single pathogen or 10 000 to 49 000 CFUs/ mL with positive UA results; (3) bacterial meningitis, as a positive CSF culture result with a pathogen or bacteremia with CSF pleocytosis (>10 WBCs per μL); bacterial pneumonia, as a positive pleural fluid culture result with a pathogen or a chest radiograph interpreted ;a bacterial pathogen in stool culture. Possible SBIs were also defined result. Diagnosis: Total: 30 (12.8) Bacteremia: 4 Bacteremia + UTI: 2 UTI: 24	PCT at 0.13 ng/mL SBI: Sensitivity: 96.7 [81.0, 99.8] Specificity: 30.3 [24.0, 37.5] PPV: NR NPV: 98.3 [89.7, 99.9] PCT at 0.12 ng/mL Sensitivity: 95.2 Specificity: 25.5 PPV: NR NPV: 96.1 All cases of bacteremia were correctly identified with 0.12 cut off value

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Meehan (2008)[51]	Design: Case Series Region: North America Setting: Peadiatric ED Study duration/ period: 4 years	N: 2003/2820 Age group(s): 0–90 d Inclusion / exclusion: Infants presenting to paediatric ED (with rectal temperature ≥ 38°C Exclusion: Previous antibiotics, immunodeficiency, intracranial surgery Male (%): 55 Ethnicity (%): NR ------------------------------- Information on mother: NR	Laboratory: CSF pleocytosis in neonates: WBC ≥ 25 cells/ µL; in infants aged 29 – 90 d: WBC ≥ 10 cells/ µL)	NR Diagnosis: Total SBI: 192/ 2003 (9.6%) UTI: 160 Bacteraemia: 25 Meningitis: 7	SBI: Sensitivity: 12.5 (95% CI: 8.3, 18.2) Specificity: 91.6 (95% CI: 90.2, 92.8) PPV: 13.6 (95% CI: 9.1, 19.8) NPV: 90.8 (95% CI: 89.3, 92.0) Bacteraemia: Sensitivity: 28.0 (95% CI: 12.8, 49.6) Specificity: 91.4 (95% CI: 90.1, 92.6) PPV: 3.9 (95% CI: 1.7, 8.3) NPV: 99.0 (95% CI: 98.4, 99.4) Meningitis: Sensitivity: 71.4 (95% CI: 30.2, 94.8) Specificity: 91.4 (95% CI: PPV: 2.8 (95% CI: 1.0, 6.8) NPV: 99.9 (95% CI: 99.5, 99.9)
Olaciregui (2008)[52]	Design: Cross Sectional Region: Europe	N: 347 Age group(s): 4–90 d Mean age: 47 d	1) PCT at 0.13 ng/mL 2) Leucocyte count (5,000 – 15,000), CRP	bacteremia; meningitis; sepsis such as hemodynamic instability, tissue perfusion; UTI; pneumonia by chest x ray; gastroenteritis;	SBI: PCT at 0.13 ng/mL Sensitivity: 63.0 [52.0, 74.0] Specificity: 87.0 [83.0, 91.0] PPV: 59.0 [48.0, 70.0] NPV: 89.0 [85.0, 93.0]

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
	(Spain) Setting: Peadiatric ED Study duration/ period: 2004 – 2006	Inclusion / exclusion: Febrile infants (rectal T. ≥ 38°C) with detailed history and physical exam did not reveal a focus of infection with blood test results / exclusion: lack of blood test, fever of more than 7 d duration, antibiotic therapy in the 48 hrs prior to dx and the presence of any type of immunodeficiency Male (%): 52 Ethnicity (%): NR (likely to be Hispanic) -------------------------------- Information on mother: NR	(<30), PCT (<0.5), good general state and –ve urine dipstick 3) CRP ≥ 30 mg/L 4) CRP ≥ 20 mg/L (to detect bacteremia)	cellulitis (blood culture available for 95% of infants) Diagnosis: Total: 82 (23.6) UTI: 69 (4 with bacteremia) Bacteremia: 5 Cellulitis: 2 (1 with bacteremia) Sepsis: 4 (2 with bacteremia) Gastroenteritis: 1 with bacteremia Common organism for bacteremia: *S. agalactiae B*, *S. pneumonia*, and Gram negative *bacilli*.	Bacteremia: Sensitivity: 86 .0 [58.0, 100.0] Specificity: 93.0 [90.0, 96.0] PPV: 35.0 [19.0, 51.0] NPV: 99.0 [98.0, 100.0] SBI: <u>WBC 5,000 – 15,000, CRP <30, PCT <0.5, good general state, –ve urine dipstick</u> Sensitivity: 96.0 [88.0, 99.0] Specificity: 35.0 [29.0, 42.0] PPV: 32.0 [25.0, 38.0] NPV: 96.0 [92.0, 100] Bacteremia: Sensitivity: 100 [74.0, 100.00] Specificity: 29 [24.0, 35.0] PPV: 6 [3.0, 9.0] NPV: 100 [96.0, 100.0] AUC for PCT (for definite and possible SBI) for < 28 d = 0.73 vs. > 28 d = 0.85 AUC for PCT =0.77 (95% CI: 0.72, 0.81) and for CRP = 0.79 (95% CI: 0.75, 0.84). In 15 infants with more invasive infection (sepsis,

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
					bacteremia, bacterial meningitis), the diagnostic value of PCT (AUC 0.84, 95% CI: 0.79, 0.88) was higher than CRP (AUC 0.68, 95% CI: 0.63, 0.73).
Reardon (2009)[53]	Design: Cross Sectional Region: North America Setting: Peadiatric ED Study duration/ period: 2002 - 2003	N: 51 (in total age 0 – 90 and older: n= 985) Age group(s): 0–90 d (mean age of total sample 12.6 months) Inclusion / exclusion: Infants presenting to paediatric ED (with rectal temperature ≥ 38°C / Note: the study also included older infants and the results are reported for the total sample Male (%): 55 Ethnicity (%): NR ------------------------------- Information on mother: NR	UA was considered positive if there was presence of pyuria (≥5 WBC/hpf), leukocyte esterase on the urine dipstick, or nitrites on the dipstick	UTI by urine culture at least 10,000 colony forming units Diagnosis: UTI: NR (total UTI is reported for the total sample of infants	UTI: Sensitivity: 40.0 [7.0, 83.0] Specificity: 85.0 [71.0, 93.0] PPV: NR NPV: NR Study notes: There was no significant difference in the sensitivity or specificity with respect to sex or age of the infants.

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Rosenberg (1985)[22]	Design: Case Series Region: North America Setting: Peadiatric ED Study period: 1981-1982	N: 1655/122 Age group(s): 0–60 d Inclusion / exclusion: Infants presenting to paediatric ED (1981-1982) with auxiliary temperature ≥ 37.8°C Male (%): NR Ethnicity (%): NR ------------------------------- Information on mother: NR	< 5,000/mm^3 or ≥ 15,000/mm^3 WBC	NR (UTI if > 100000 cfu/ml) Test Results: SBI (bacteremia): 5 (4.1)	Bacteremia: Sensitivity: 60.0 (17.0, 92.7) Specificity: NR PPV: NR NPV: NR

Table 5. Formal screening criteria

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results- % (95% CI)
Baker (1990)[54]	Design: Case Series Region: North America Setting: Peadiatric ED Study period: 1987-1988	Enrolled: 126 Age group(s): 29 – 56 d Inclusion / exclusion: Febrile Infants with rectal temperature ≥ 38.2°; Male (%): 53 Ethnicity (%): Black: 84 (67%) White: 42 (33%) ---------------------------------- Information on mother: NR	Yale Observation Scale (YOS) score > 10	Isolation of bacterial pathogens from culture of urine, blood, stool, CSF, joint fluid, pneumonia. The study also considered aseptic meningitis (not included in the analysis of this review) Diagnosis Total SBI: 12 (9.5%) UTI: 5 Bacterial sepsis: 4 Other: 3	SBI: Sensitivity: 33.3% (95% CI: 11.3, 64.5) Specificity: 72.8 (95% CI: 63.5, 80.5) PPV: 11.4 (95% CI: 3.7, 27.6) NPV: 91.2% (95% CI: 82.9, 95.8) Bacteraemia: Sensitivity: 75.0 (95% CI: 21.9, 98.6) Specificity: 73.7 (95% CI: 64.8, 81.1) PPV: 8.5 (95% CI: 2.2, 24.1) NPV: 98.9 (95%CI: 93.1, 99.9) Meningitis: Sensitivity: NR Specificity: NR PPV: NR NPV: NR

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results- % (95% CI)
Baker (1993)[55]	Design: Cohort Region: North America Setting: Peadiatric ED Study period: 1987-1992	N: 747/747 Age group(s): 29 – 56 d Inclusion / exclusion: Immunocompetent infants presenting with rectal temperature ≥ 38.2°C Male (%): 56.2 Ethnicity (%): NR --------------------------------- Information on mother: NR	Philadelphia protocol	Bacterial growth in cultures from blood, CSF, urine or stool (obvious cellulites or abscess were considered SBI) (UTI if > 1000 colony-forming units of a single organism) Test Results: SBI: 65 (8.7) UTI: 24 Bacteremia: 19 Meningitis: 9 Cellulitis: 6 Gastroenteritis: 13 Adenitis: 1	SBI: Sensitivity: 100.0 (93.0, 100.0) Specificity: 42.0 (38.3, 45.9) PPV: 14.1 (11.1, 17.7) NPV: 100.0 (98.3, 100.0)

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results- % (95% CI)
Baker (1999)[56]	Design: Cohort Region: North America Setting: Peadiatric ED Study period: 1994-1996	N: 254/254 Age group(s): 3 – 28 d Inclusion / exclusion: neonates with rectal temperature ≥38°C Male (%): 57.1 Ethnicity (%): NR ---------------------------------- Information on mother: NR	Philadelphia protocol	Bacterial growth in cultures from blood, CSF, urine or stool- including pneumonia, cellulites, osteomyelitis, abscess (negative if blood and spinal fluid were free of bacterial pathogens at 72 hours (considered contaminated if patients symptoms resolved without treatment); UTI, if > 10^3 or more colony forming units/mm of known urinary pathogens) Test Results: SBI: 32 (12.5) UTI: 17 Bacteremia: 8 Meningitis: 4 Cellulitis: 1 Gastroenteritis: 2 Peritonitis: 1 Osteomyelitis: 1	SBI: Sensitivity: 84.4 (67.0, 95.0) Specificity: 46.8 (40.0, 53.0) PPV: 18.6 (12.0, 25.0) NPV: 95.4 (90.0, 99.0) Bacteremia: Sensitivity: NR Specificity: NR PPV: NR NPV: NR Meningitis: Sensitivity: NR Specificity: NR PPV: NR NPV: NR

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results- % (95% CI)
Baker (1999)[57]	Design: Chart Review Region: North America Setting: Peadiatric ED Study period: 1994 - 1996	N: 422/422 Age group(s): 29 – 60 d Inclusion / exclusion: Immunocompetent Febrile infants with rectal temperature ≥ 38°C Male (%): 56 Ethnicity (%): NR --------------------------------- Information on mother: NR	Philadelphia protocol* LR infants: n= (%) Not LR infants (or HR): n= (%)	Test Results: SBI: 43 (10.2) UTI: 17 Bacteremia: 9 Meningitis: 5 Gastroenteritis: 5 Cellulitis: 5 Chlamydia pneumonia: 2 Enterocolitis: 1 Osteomyelitis: 1 Septic arthritis: 1	SBI: Sensitivity: 100.0 (89.7, 100.0) Specificity: 26.6 (22.3, 31.4) PPV: 14.0 (10.0, 17.7) NPV: 100.0 (96.0, 100.0)

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results- % (95% CI)
Baskin (1992)[58]	Design: Cohort Region: North America Setting: ED Study period: 1987-1990	N: 503/501 Age group(s): 28 - 89 d Inclusion / exclusion: Well appearing infants with rectal temperature ≥ 38°; no allergies to ß-lactam, no vaccination within 48 hrs of presentation to unit - no ear, soft tissue, joint or bone infection on physical examination; not source of infection; and normal laboratory screening - no immunization with diphtheria, and tetanus toxoids and pertussis vaccine within 48 hours Male (%): NR Ethnicity (%): NR --------------------------------- Information on mother: NR	Rochester Criteria	Bacterial growth in cultures from blood, CSF, urine or stool (UTI = culture with > 1,000 colonies/ml for supra-pubic samples, and ≥ 10,000 colonies/ml in bladder catheterizations; test done for 479, 95.2%) Results: SBI: 27 (5.4) Occult bacteremia: 8 UTI + bacteremia: 1 UTI: 8 Gastroenteritis: 10 (%)	SBI: Sensitivity: 52.0 (31.7, 71.6) Specificity: NR PPV: NR NPV: NR

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results- % (95% CI)
Bonadio (1993)[59]	Design: Case Series Region: North America Setting: pediatric ED Study period: 1991-1992	N: 242/233 Age group(s): 0 – 29 d Inclusion / exclusion: febrile infants with rectal temperature ≥ 38.0°C. Excluded were infants who were culture-negative for bacterial pathogen and had received antibiotic therapy within 72 hours Male (%): NR Ethnicity (%): NR ------------------------------------ Information on mother: NR	YIOS score ≥ 7 (affect, respiratory status/effort, peripheral perfusion)	Bacterial meningitis, bacteraemia, UTI (UT if ≥ 10000 cfu/ml of a single bacterial specie; CSF positive if pleocytosis present (total blood cell count > 10 mm3) Test Results: SBI: 29 (12.4%) Meningitis: 10 Bacteremia: 12 UTI: 7	SBI: Sensitivity: 76.0 (NC) Specificity: 75.0 (NC) PPV: NR NPV: 96.0 (NC)

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results- % (95% CI)
Bonadio (1993)[60]	Design: Cohort Region: North America Setting: Peadiatric ED Study period: 1991-1992	N: 534/534 Age group(s): 29 – 60 d Inclusion/ exclusion: Previously healthy Febrile infants with fever ≥ 100°F reported by caretaker or ≥ 38° at triage Male (%): NR Ethnicity (%): NR ---------------------------------- Information on mother: NR	1) Milwaukee protocol 2) Rochester criteria (n=532)	NR SBI by Milwaukee Total: 24 (4.5) UTI: 11 Meningitis: 4 Bacteremia: 6 Bacterial enteritis: 2 Klebsiella pneumoniae: 1 SBI by Rochester Total: 22 (4.1) UTI: 11 Meningitis: 4 Bacteremia: 6 Klebsiella pneumoniae: 1	SBI by Milwaukee Sensitivity: 96.0 (88.0, 100.0) Specificity: 28.0 (23.0, 36.0) PPV: 5.9 (3.6, 8.2) NPV: 99.3 (98.0, 100.0) SBI by Rochester Sensitivity: 59.0 (36.6, 78.5) Specificity: 26.3 (22.5, 30.3) PPV: 3.3 (1.9, 5.8) NPV: 93.7 (88.0, 96.9)

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results- % (95% CI)
Brik (1997)[61]	Design: Chart Review Region: Israel Setting: Peadiatric ED Study period: 1988-1994	N: 492/492 Age group(s): 0 – 90 d Inclusion / exclusion: Charts of all hospitalized Febrile infants with rectal temperature ≥ 38°C. Excluded were patient with congenital malformation, metabolic inherited diseases or immunological deficiency Male (%): 60 Ethnicity (%): NR ---------------------------------- Information on mother: NR	Philadelphia protocol	Growth of a known bacterial pathogen in cultures of blood, spinal fluid, urine or stool (including cellulites or abscess) Bacterial meningitis, if a) Infants <4 weeks; leukocyte >30 cell/ mm3, >60% polymorphonuclear cells, a protein concentration >170 mg/dl, a CSF/blood glucose ratio <0.5-0.6 and the presence of microorganisms on Gram stained smears of CSF; b) Infants 4-12 weeks: leukocyte >10 cells/ mm3 in younger infants and 5 cells/ in older infants with >1 polymorphonuclear cell/ mm3 in addition to protein concentration >100 mg/dl, glucose concentration 60% lower in CSF than in blood, and finding of bacteria on Gram stained smears Test Results: SBI: 60 (12.3) UTI: 40 Meningitis: 2 Bacteremia: 10 Gastroenteritis: 4 Cellulitis: 2 Adonitis: 1	SBI: Sensitivity: 86.6 (74.8, 93.6) Specificity: 66.6 (62.0, 71.0) PPV: 26.5 (20.6, 33.4) NPV: 97.3 (94.5, 98.7)

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results- % (95% CI)
Byington (2004)[62]	Design: Case Series Region: North America Setting: primary pediatric medical center Study period: 1996-2002	N: 894/888 (infants without viral infections) Age group(s): 1 – 90 d Inclusion / exclusion: Infants evaluated for sepsis with temperature ≥ 38°C. Excluded infants if received oral polio vaccine, a live EV vaccine, or antibiotics (in last 48 hours) Male (%): 55 Ethnicity (%): White/non-Hispanic: 63 Hispanic: 24 African/American:1 Asian/ South Pacific: <1 Other: 4 --------------------------------- Information on mother: NR	Rochester criteria	Positive bacterial culture: bacteremia, bacterial meningitis, UTI, soft tissue or bone infection, bacterial pneumonia, or bacterial enteritis Test Results: SBI: 109 (12.3) Types of SBI: bacteremia, UTI, meningitis, pneumonia IHI: 2/101 (2%) tested for HSV were positive for virus identified by skin lesion or mucous membrane	SBI: Sensitivity: 91.7 (84.5, 95.9) Specificity: 36.0 (32.6, 39.4) PPV: 16.6 (13.8, 20.0) NPV: 96.9 (94.0, 98.5)

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results- % (95% CI)
Chiu (1997)[63]	Design: Cross sectional Region: Taiwan Setting: Pediatric hospital Study period: 1994-1995	N: 250/250 Age group(s): 4 – 28 d Inclusion / exclusion: Well appearing healthy, (born at term, without any prenatal complications and no underlying disease) with rectal temperature > 38°C Male (%): 53.3 Ethnicity (%): NR ---------------------------------- Information on mother: NR	Rochester criteria	Isolation of a bacterial pathogen from cultures of blood, urine, CSF, joint fluid, stool, pus or other body fluids (UTI if > 100000 colonies/ml of a single pathogen- Enteritis if other foci of infection were excluded and the patient had a diarrhea) Test Results: SBI: 41 (16.4) UTI: 16 Bacteremia/Meningitis: 7 Bacteremia/Enteritis: 3 Enteritis: 2 Bacteremia/Osteomyelitis: 1 Others: NR	SBI: Sensitivity: 97.6 (92.9, 100.0) Specificity: 62.2 (55.6, 68.8) PPV: 33.6 (25.1, 42.1) NPV: 99.2 (97.7, 100.0)

Study ID	Study Characteristics	N (Screened/enrolled) General Information at baseline	Criteria to identify infants at risk for SBI-Outcome	Diagnosis Detail Definition Criteria Patient Diagnosis	Results-% (95% CI)
Ferrera (1997)[64]	Design: Chart Review Region: North America Setting: ED of tertiary referral center Study period: 1990-1994	N: 188/134 Age group(s): 0 – 28 d Inclusion/ exclusion: Chart of infants with temperature (including rectal) ≥ 38°C regardless of chief complaint- Excluded: 1) Incomplete blood, urine, and CSF culture data; 2) Infants with a source for fever on physical examination (septic arthritis, osteomyelitis, cellulites) Male (%): NR Ethnicity (%): NR ---------------------------------- Information on mother: NR	Rochester criteria	Bacterial meningitis, bacteremia, septic arthritis, osteomyelitis, UTI, bacterial enteritis, salmonellosis, or pneumonia (UTI if > 1000 colony forming units/mL of 2 organisms or less in a specimen obtained by catheterization or by supra-pubic aspirate) Test Results: SBI: 22 (16.4) UTI: 13 UTI/meningitis: 1 Bacteremia: 4 Bacteremia/UTI: 1 Bacteremia/meningitis: 1 Listeria meningitis: 1 Pneumonia: 1	SBI: Sensitivity: 86.4 (64.0, 96.4) Specificity: 46.4 (36.3, 56.7) PPV: 26.8 (17.2, 38.8) NPV: 93.8 (81.8, 98.4)

Study ID	Study Characteristics	N (Screened/enrolled) General Information at baseline	Criteria to identify infants at risk for SBI-Outcome	Diagnosis Detail Definition Criteria Patient Diagnosis	Results-% (95% CI)
Garra (2005)[65]	Design: Cohort Region: North America Setting: Peadiatric ED Study period: NR	N: 302/259 Age group(s): 0 – 56 d Inclusion / exclusion: Consecutive term infants with rectal temperature ≥ 38.1°C (100.6° F). Excluded infants with likely bacterial source of fever (cellulites, abscess, mastitis, or omphalitis, otitis media, or septic arthritis) Male (%): 60.2 Ethnicity (%): NR ---------------------------------- Information on mother: NR	1) Philadelphia protocol 2) Rochester criteria	Bacteremia, UTI, bacterial meningitis, pneumonia or bacterial culture positive enteritis (UTI according to Rochester or Philadelphia protocol) SBI by Philadelphia protocol: Total: 65 (25.1) UTI: 51 Bacteremia/UTI: 5 Bacteremia: 8 Bacteremia/Meningitis: 1 SBI by Rochester criteria: Total: 65 (25.1) UTI: 51 Bacteremia/UTI: 5 Bacteremia: 8 Bacteremia/Meningitis: 1	SBI by Philadelphia protocol: Sensitivity: 98.5 (92.0, 100.0) Specificity: 41.9 (38.0, 46.0) PPV: 13.9 (11.0, 17.0) NPV: 99.7 (98.0, 100.0) SBI by Rochester criteria: Sensitivity: 92.4 (84.0, 97.0) Specificity: 49.9 (47.0, 53.0) PPV: 12.3 (10.0, 16.0) NPV: 98.9 (97.0, 100.0)

Study ID	Study Characteristics	N (Screened/enrolled) General Information at baseline	Criteria to identify infants at risk for SBI-Outcome	Diagnosis Detail Definition Criteria Patient Diagnosis	Results-% (95% CI)
Jaskiewicz (1994)[66]	Design: Diagnostic Accuracy Study Region: North America Setting: ED Study period: NR	N: 1057/931 Age group(s): 0 – 60 d Inclusion / exclusion: Infants with rectal temperature ≥ 38°, well-appearing - previously healthy - no evidence of skin, soft tissue, bone, joint, or ear infection - laboratory values and sufficient data to determine level of risk with Rochester Criteria Male (%): NR Ethnicity (%): NR --------------------------------- Information on mother: NR	Rochester criteria LR infants: n= (%) Not LR infants (or HR): n= (%)	Bacteremia, meningitis, osteomyelitis, suppurative arthritis, soft tissue infections (cellulites, abscess, mastitis, omphalitis), UTI, gastroenteritis, pneumonia Test Results: SBI: 66 (7.0) UTI: 34 Skin/soft tissue infection: 18 Bacteremia: 16 Gastroenteritis: 4 Pneumonia: 1	SBI: Sensitivity: 92.4[†] (82.5, 97.2) Specificity: 50.0 (46.5, 53.3) PPV: 12.3 (9.6, 15.6) NPV: 98.9 (97.2, 99.6) Bacteremia: Sensitivity: 87.5 (60.4, 97.8) Specificity: 47.5 (44.2, 50.8) PPV: 2.8 (1.6, 4.8) NPV: 99.5 (98.2, 99.9)

Study ID	Study Characteristics	N (Screened/enrolled) General Information at baseline	Criteria to identify infants at risk for SBI-Outcome	Diagnosis Detail Definition Criteria Patient Diagnosis	Results-% (95% CI)
Kadish (2000)[67]	Design: Chart Review Region: North America Setting: Peadiatric ED Study period: NR	N: 394/372 Age group(s): 1 – 28 d Inclusion / exclusion: Previously healthy Febrile infants with documented rectal temp. ≥38°C. Excluded 1) no sepsis evaluation at time of admission (CBC, UA, CSF, cell count, blood, urine, and CSF cultures); 2) inpatients; 3) with congenital heart disease Male (%): NR Ethnicity (%): NR ---------------------------------- Information on mother: NR	1) Boston protocol 2) Philadelphia protocol	Bacterial growth in cultures from blood, CSF, urine or stool – including pneumonia, septic arthritis, cellulites, osteomyelitis, abscess (UTI, if > 50000 colonies/mL of a single organism was isolated) SBI by Boston protocol: Total: 45 (12.1) UTI: 32 Bacteremia: 12 Meningitis: 5 Cellulitis: 3 Septic arthritis: 1 Gastroenteritis: 1 Pneumonia: 1 SBI by Boston protocol: Total: 45 (12.1) UTI: 32 Bacteremia: 12 Meningitis: 5 Cellulitis: 3 Septic arthritis: 1 Gastroenteritis: 1 Pneumonia: 1	SBI by Boston protocol: Sensitivity: 82.0 (67.4, 91.5) Specificity: 68.0 (62.8, 73.1) PPV: 26.0 (19.4, 34.4) NPV: 97.0 (93.0, 98.4) SBI by Philadelphia protocol: Sensitivity: 87.0 (72.5, 94.4) Specificity: 55.0 (49.5, 60.5) PPV: 21.0 (15.5, 27.6) NPV: 97.0 (92.8, 98.7)

Study ID	Study Characteristics	N (Screened/enrolled) General Information at baseline	Criteria to identify infants at risk for SBI-Outcome	Diagnosis Detail Definition Criteria Patient Diagnosis	Results-% (95% CI)
Kaplan (2000)[68]	Design: Chart Review Region: North America Setting: Peadiatric ED Study period: 1993-1997	N: 3166/2190 Age group(s): 28 – 90 d Inclusion / exclusion: Retrospective sample of infants with rectal temperature ≥ 38°C; excluded Infants without 3 culture results at screening) Male (%): NR Ethnicity (%): NR ---------------------------------- Information on mother: NR	Boston criteria	Positive cultures of blood, CSF or urine (UTI if ≥ 10000 cfu/mL of a single urinary pathogen by supra-pubic aspiration, or bladder catheterization) Test Results: SBI: 191 (8.7)	SBI: Sensitivity: 88.5 (82.8, 92.5) Specificity: 56.2 (54.0, 58.4) PPV: 16.2 (14.0, 18.6) NPV: 98.1 (97.0, 98.7)
Stanley (2005)[23]	Design: Chart Review Region: North America Setting: Peadiatric ED Study period: 1993-2000	N: 5279/5279 Age group(s): 0 – 90 d Inclusion / exclusion: Retrospective sample of infants with a rectal temperature ≥ 38°C, with complete test and culture records Male (%): NR Ethnicity (%): NR ---------------------------------- Information on mother: NR	Rochester or Philadelphia criteria	Positive culture of urine, blood or CSF (UTI if supra-pubic ≥ 1000; catheterized ≥ 10000 colony forming units/mL (cfu/mL) of a single urinary pathogen) Test Results: SBI: 480 (9.1) UTI: 305 Meningitis: 10 Bacteremia: 39 Bacteremia/meningitis: 8 Bacteremia/UTI: 11 Pneumonia: 70 Cellulitis: 26 Bacterial enteritis: 11	SBI: Sensitivity: 99.8 (98.6, 99.9) Specificity: NR PPV: NR NPV: NR

Study ID	Study Characteristics	N (Screened/enrolled) General Information at baseline	Criteria to identify infants at risk for SBI-Outcome	Diagnosis Detail Definition Criteria Patient Diagnosis	Results-% (95% CI)
Zorc (2005)[69]	Design: Cross sectional Region: North America Setting: Peadiatric ED Study period: 1999-2001	N: 1513/995 Age group(s): 1 – 60 d Inclusion / exclusion: Infants with rectal temperature ≥ 38°C. Excluded if taken antibiotics within 48 hours; no consent received Male (%): NR Ethnicity (%): NR ---------------------------------- Information on mother: NR	Yale Observation Scale (YOS) > 10	Test Results: SBI (UTI only): 91 (9.0%)	SBI (UTI only): Sensitivity: 4.4 (1.4, 11.5) Specificity: 92.6 (90.6, 94.1) PPV: 5.6 (1.8, 14.5) NPV: 90.5 (88.5, 92.3)

Table 6. Studies in Febrile infant with delayed (question 2a) or immediate (question 3a) treatment

Study ID	Number of Infants Setting	General Information at Baseline; Infants, Mothers	Criteria and Results of Diagnostic Tests	Management	Treatment Results
Wasserman (1990)[14]	Eligible for screening: NR Screened: NR Enrolled: 443 Number of site(s): 1 Design: Chart Review Region: North America/ U.S. Setting: military medical center Study duration: 28 months	General: 443 Febrile infant with rectal temperature ≥ 38°C; age younger than 3 months Age: mean NR Age groups: a) ≤ weeks: 63 (14.2%) b) 3-4 weeks: 95 (21.4%) c) 5-8 weeks: 198 (44.7%) d) 9-12 weeks: 87 (19.6%) Male (%): NR Ethnicity (%): NR Fever: mean NR Medication: ------------------------------- Information on mother: NR	Clinical criteria (LR): well appearing, no benign physical examination Laboratory criteria (normal): Criteria: WBC, UA (by catheter or suprapubic aspiration) in all patients; CSF in most patients Formal scoring systems: -- LR infants (infants treated without antibiotics): n= 221 (49.9%) [a=20 (32%), b= 50 (53%), c= 113 (57%), d=38 (44%)] Not LR infants (Outcomes in infants treated with antibiotics): n= 222 (51.1%) [a=43 (69%), b= 45 (47%), c= 85 (43%), d=49 (56%)] Sensitivity: NR; Specificity: NR; PPV:NR; NPV:NR Diagnosis: SBI: 53 (12%) [a=16 (25%), b=12 (13%), c=13 (6.6%), d=12 (14%)] UTI: NR [a= 7.9%, b=1.1%), c= 1.5%, d= 3.4%] Bacteremia & or bacterial meningitis: 8 (1.8%) [a= 3 (4.8%), b= 2 (2.1%), c=1 (0.5%), d= 2 (2.3%)] Other: NR	Initial management of LR n: 221 Hospitalized: 100% Discharged: 0 Treatment: No antibiotics: 100% Infants diagnose with SBI (FN): n=5 (2.3%); 1 bacteremia, 3 UTI, 1 Salmonella Management of FN(s) infants: infant with bacteremia: 10 days parenteral antibiotics; UTI and Salmonella infants were treated with antibiotics after culture results Initial management of not LR n: 222 Hospitalized: 100% Discharged: 0 Treatment: Oral antibiotics: 58 (26%) [a= 1 (2%), b= 8 (8%), c=27 (14%), d=22 (25%)] Parenteral antibiotics: 164 (74%) [a= 42 (67%), b= 37 (39%), c= 58 (29%), d= 27 (31%)]	Change in treatment was reported in 28 infants, 5 due to +ve blood or urine results, 10 due to OM, 1 chest infiltrate & 12 for other reasons.

Study ID	Number of Infants Setting	General Information at Baseline; Infants, Mothers	Criteria and Results of Diagnostic Tests	Management	Treatment Results
Wasserman (1990)[14]	Eligible for screening: NR Screened: NR Enrolled: 443 Number of site(s): 1 Design: Chart Review Region: North America/ U.S. Setting: military medical center Study duration: 28 months	General: 443 Febrile infant with rectal temperature ≥ 38°C; age younger than 3 months Age: mean NR Age groups: a) ≤ weeks: 63 (14.2%) b) 3-4 weeks: 95 (21.4%) c) 5-8 weeks: 198 (44.7%) d) 9-12 weeks: 87 (19.6%) Male (%): NR Ethnicity (%): NR Fever: mean NR Medication: ------------------------------- Information on mother: NR	Clinical criteria (LR): well appearing, no benign physical examination Laboratory criteria (normal): Criteria: WBC, UA (by catheter or suprapubic aspiration) in all patients; CSF in most patients Formal scoring systems: -- LR infants (infants treated without antibiotics): n= 221 (49.9%) [a=20 (32%), b= 50 (53%), c= 113 (57%), d=38 (44%)] Not LR infants (Outcomes in infants treated with antibiotics): n= 222 (51.1%) [a=43 (69%), b= 45 (47%), c= 85 (43%), d=49 (56%)] Sensitivity: NR; Specificity: NR; PPV:NR; NPV:NR Diagnosis: SBI: 53 (12%) [a=16 (25%), b=12 (13%), c=13 (6.6%), d=12 (14%)] UTI: NR [a= 7.9%, b=1.1%, c= 1.5%, d= 3.4%] Bacteremia & or bacterial meningitis: 8 (1.8%) [a= 3 (4.8%), b= 2 (2.1%), c=1 (0.5%), d= 2 (2.3%)] Other: NR	Initial management of LR n: 221 Hospitalized: 100% Discharged: 0 Treatment: No antibiotics: 100% Infants diagnose with SBI (FN): n=5 (2.3%); 1 bacteremia, 3 UTI, 1 Salmonella Management of FN(s) infants: infant with bacteremia: 10 days parenteral antibiotics; UTI and Salmonella infants were treated with antibiotics after culture results Initial management of not LR n: 222 Hospitalized: 100% Discharged: 0 Treatment: Oral antibiotics: 58 (26%) [a= 1 (2%), b= 8 (8%), c=27 (14%), d=22 (25%)] Parenteral antibiotics: 164 (74%) [a= 42 (67%), b= 37 (39%), c= 58 (29%), d= 27 (31%)]	

Study ID	Number of Infants Setting	General Information at Baseline; Infants, Mothers	Criteria and Results of Diagnostic Tests	Management	Treatment Results
Watt (2010)[73]	Eligible for screening: NR Screened: 1501 Enrolled: 668 Number of site(s): 1 Design: Cohort (retrospective) Region: US Setting: Paediatric ED Study duration: 1997-2006	General: 668 febrile neonates (age < 90 days) with rectal temperature ≥ 38° without an apparent source Age: 0 – 90 d Male (%): 57.0% Ethnicity (%): NR Fever: mean NR Medication: NR ------------------------------ Information on mother: NR	Clinical criteria (HR): NR Laboratory criteria (HR): NR Formal scoring systems: Not used -- LR infants: NA HR infants: NA Sensitivity: NA Specificity: NA PPV: NA NPV: NA Diagnosis: SBI (total): 72/668 (10.8%) UTI: 52/72 (72.2%) Bacteremia: 11/72 (15.3%) Meningitis: 2/72 (3.0%) UTI/bacteremia: 6/72 (8.3%) Meningitis/bacteremia: 1/72 (1.4%)	Initial management of infants: almost all neonates received a complete blood, urine, and CSF sample/culture workup Hospitalized: Discharged: Treatment: The immediate antibiotic treatment was given to 562 infants (out of 668 infants) over 10 years Infants diagnosed with SBI (FN): NA Management of FN infants: NA Initial management of HR: NR	Outcomes Overall mortality: NR Harms of delayed treatment: NR Infants not treated with antibiotics: NR Outcomes in infants treated with antibiotics: Ampicillin resistance for all infants with SBI was 41.7% over the 10-year period; the corresponding resistance rate for the infants with UTI was 46.6% 6 infants who had ampicillin resistant bacteremia had switched their antibiotics, 4 of which stayed 2 extra days in the

Study ID	Number of Infants Setting	General Information at Baseline; Infants, Mothers	Criteria and Results of Diagnostic Tests	Management	Treatment Results
					hospital and the other two had venous catheters for at least 2 extra days

Table 7. Co-infection in febrile infants (studies assessing risk of SBI in infants with or without other infections)

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Type of infection Method used to identify infection	Results:	Prevalence ratio (%) [95% CI] Odds Ratio (OR) [95% CI]
Bilavsky (2008)[74]	Design: Quasi-experimental Region: North America Setting: NR Study period: 2006-2007	N: NR/448 Age group(s): 0 – 90 d Inclusion / exclusion: All febrile infants who were hospitalized – excluded infants with a chronic disease, pre term infants, infants who received antibiotics within 48 hours of presenting to ED and infants without documented fever Male (%): NR Ethnicity (%): NR --- Information on mother: NR	Type(s) of infection studies: Bronchiolitis Method: Bronchiolitis: acute wheezing or chest retractions in association with an URT infection or by cough or rhinorrhea detected on physical examination RSV: nasopharyngeal aspirates collected from infants with bronchiolitis for RSV antigen detection by rapid enzyme linked immunoassay (results for RSV reported only for patients with bronchiolitis & could not be used for this review)	N with infection: 136 Infection (+) & SBI: 3 Prevalence (%) [95% CI]: 2.20 [0.60, 6.00] N without infection: 312 Infection (-) & SBI: 30 Prevalence (%) [95% CI]: 9.62 [6.35, 12.89]	Prevalence ratio (%) [95% CI]: (rate ratio) 0.23 [0.05, 0.76] OR [95% CI]: 0.21 [0.05, 0.74]

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Type of infection Method used to identify infection	Results:	Prevalence ratio (%) [95% CI] Odds Ratio (OR) [95% CI]
Byington (1999)[75]	Design: Chart review Region: North America Setting: Primary care Study period: 1996-1997	N: NR/ 345 Age group(s): 0 – 90 d Inclusion / exclusion: Healthy infants with documented fever ≥38ºC with complete sepsis evaluation- excluded infants who received polio vaccine Male (%): 51% Ethnicity (%): NR ---------------------------------- Information on mother: NR	Type(s) of infection studies: Nonpolio EV Method: Nonpolio EV: enteroviruses by PCR assay (polio and non polio viruses)	N with infection: 89 Infection (+) & SBI: 6 Prevalence (%) [95% CI]: 6.70 [2.8, 13.3] N without infection: 256 Infection (-) & SBI: 38 Prevalence (%) [95% CI]: 14.84 [10.5, 19.20]	Prevalence ratio (%) [95% CI]: 0.45 [0.17, 1.06] OR*[95% CI]: 0.41 [0.15, 1.07]

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Type of infection Method used to identify infection	Results:	Prevalence ratio (%) [95% CI] Odds Ratio (OR) [95% CI]
Byington (2004)[62] Companion Kuppermann (1999)[33]	Design: Case series Region: North America Setting: Primary care Study period: 1996-2002	N: NR/1385 Age group(s): 1 – 90 d Inclusion / exclusion: Febrile infants with temperature ≥38ºC evaluated for sepsis (bacterial cultures of blood, urine, and CSF)- excluding infants who had received antibiotics in the 48 hours preceding the evaluation; infants who received polio vaccine, a live enterovirus vaccine Male (%): 55% Ethnicity (%): White/non-Hispanic: 63% Hispanic: 24% Black: 1% Asian/Pacific Islander: <1% Other: 4% ---------------------------------- Information on mother: NR	Type(s) of infection studies: EV, RSV, Influenza A/B, parainfluenza, rotavirus Method: EV: PCR; ARUP EV-RT, or by culture on specimens from CSF, stool, nasopharyngeal and throuat swab RSV: enzymed linked immunoabsorbent assay, by PCR, or by direct fluoroscent assay detection perfomed on nasal wash specimens Herpes: culture of skin lesions or mucoous membranes Varicella infection: (in a single infant) dx made by history of exposure and physical exam of vesicular skin rash consistent with varicella	N with infection: 491 Infection (+) & SBI: 21 Prevalence (%) [95% CI]: 4.30 [2.80, 6.20] N without infection: 894 Infection (-) & SBI: 110 Prevalence (%) [95% CI]: 12.30 [10.15, 14.45]	Prevalence ratio (%) [95% CI]: 0.34 [0.21, 0.55] OR*[95% CI]: 0.32 [0.19, 0.52]

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Type of infection Method used to identify infection	Results:	Prevalence ratio (%) [95% CI] Odds Ratio (OR) [95% CI]
Dagan (1985)[7]	Design: Quasi-experimental Region: North America Setting: Primary care Study period: 1982-1984	N: NR/233 Age group(s): 0 – 90 d Age 0 – 30 d 92 (39%) Age 31 – 60 d 107 (46%) Age 61 – 90 d 34 (15%) Inclusion / exclusion: Previously healthy infants suspected of sepsis and hospitalized for sepsis workup Male (%): 58% Ethnicity (%): White/non-Hispanic: 60.9% Hispanic: 12% Black: 25.3% Asian/Pacific Islander: 1.7% ---------------------------------- Information on mother: NR	Type(s) of infection studies: Nonpolio EV RSV, influenza Method: Nonpolio EV RSV, influenza: viral culture on specimens of throat swab, stool or rectal swab, CSF and blood during July to November; nasopharyngeal/ throat swab, stool or rectal swab, and CSF during November through June; nasal wash specimens and nasopharyngeal/ throat swab, stool or rectal swab, and CSF during December through May Concurrent immuno-electrophoresis for rotavirus antigen in stool and viral culture of urine, vesicle, or eye swab specimens performed when indicated.	N with infection: 137 Infection (+) & SBI: 4 Prevalence (%) [95% CI]: 2.92 [0.10, 5.34] N without infection: 96 Infection (-) & SBI: 19 Prevalence (%) [95% CI]: 19.79 [11.82, 27.76]	Prevalence ratio (%) [95% CI]: 0.14 [0.04, 0.44] OR*[95% CI]: 0.12 [0.03, 0.40]

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Type of infection Method used to identify infection	Results:	Prevalence ratio (%) [95% CI] Odds Ratio (OR) [95% CI]
Kuppermann (1997)[76]	Design: Quasi-experimental Region: North America Setting: Peadiatric ED Study period: 1994-1996	N: NR/86 Age group(s): 0 – 60 d Inclusion/ exclusion: All febrile infants with rectal temperature ≥38ºC (≥39ºC for infants 3-24 months)- infants with vaccination or antibiotics within 48 hours of presentation to ED; focal bacterial infection other than otitis media, an identifiable viral infection other than bronchiolitis, known chronic illness, or a known immunodeficiency that would affect the risks of bacterial infections, currently taking immunosuppressive medication including corticosteroids, parent refusal to sign consent Male (%): NR Ethnicity (%): NR ---------------------------------- Information on mother: NR	Type(s) of infection studies: Bronchiolitis Method: Bronchiolitis: clinical evaluation of diffuse wheezing and or retractions in association with a history of rhinorrhea or upper respiratory signs on examination,	N with infection: 36 Infection (+) & SBI: 0 Prevalence (%) [95% CI]: NA N without infection: 50 Infection (-) & SBI: 7 blood culture 1; urine culture 6 Prevalence (%) [95% CI]: Blood culture (+) 2.00 [1.88, 5.88] Urine culture (+) 12.0 [3.00, 21.00]	Prevalence ratio (%) [95% CI]: NA OR*[95% CI]: NA

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Type of infection Method used to identify infection	Results:	Prevalence ratio (%) [95% CI] Odds Ratio (OR) [95% CI]
Rittichier (2005)[77]	Design: Case series Region: North America Setting: Primary care Study period: 1996-2002	N: 1779/1061 Age group(s): 0 – 90 d Inclusion / exclusion: All febrile infants with temperature ≥38ºC, and a completed sepsis evaluation with bacterial cultures of blood, urine, and CSF was perform Male (%): NR Ethnicity (%): NR --- Information on mother: NR	Type(s) of infection studies: enterovirus (EV) Method: <u>enterovirus:</u> PCR of blood, CSF or both in 93% of infants	N with infection: 214 (20%) Infection (+) & SBI: Prevalence (%) [95% CI]: 7.00 [3.59, 10.43] N without infection: 847 Infection (-) & SBI: NA Prevalence (%) [95% CI]: NA	Prevalence ratio (%) [95% CI]: NA OR*[95% CI]: NA

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Type of infection Method used to identify infection	Results:	Prevalence ratio (%) [95% CI] Odds Ratio (OR) [95% CI]
Smitherman (2005)[78]	Design: chart review Region: North America Setting: Peadiatric ED Study period: 1997-2001	N: NR/292 age 0 – 28 d: 62 age 29 – 90 d:230 Age group(s): 0 – 90 d age 0 – 28 d (21.2%) age 29 – 90 d (78.8%) Inclusion / exclusion: infants 0-36 months (including a sub-sample of 0- 90 d) evaluated during 5 consecutive influenza season presenting with fever; documented influenza by rapid antigen testing and or by viral culture – excluded: antibiotic use within the preceding 48 hours; an immuno-compromised host; increased risk for infection secondary to indwelling or foreign bodies; conditions that would increase risk of bacteraemia, UTIs or pneumonia Male (%): NR Ethnicity (%): NR -- Information on mother: NR	Type(s) of infection studies: Influenza A Method: Influenza A: *positive if* documented positive Directigen Flu A rapid antigen testing test or positive VC for influenza A; *negative if:* viral studies were negative for influenza A Viral studies: by nasopharyngeal washes and aspirates (nasopharyngeal and pharyngeal specimens) Pneumonia: possible probable or definite focal parenchymal density on CXR by attending radiologist	N with infection: Influenza A: age 0 – 90 d: 58 (20.0%) age 0 – 28 d: 13 (21.0%) age 29 – 90 d: 45 (19.6%) Infection (+) & SBI: NR Prevalence (%) [95% CI]: NR N without infection: Influenza A: age 0 – 90 d: 234 (80.0%) age 0 – 28 d: 49 (79.0%) age 29 – 90 d: 185 (80.4%) Infection (-) & SBI: NR Prevalence (%) [95% CI]: NR	Prevalence ratio (%) [95% CI]: NR OR*[95% CI]: including pneumonia (age 29 – 90 d) 0.21 [0.05, 0.93] excluding pneumonia (age 29 – 90 d) 0.19 [0.03, 1.44]

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Type of infection Method used to identify infection	Results:	Prevalence ratio (%) [95% CI] Odds Ratio (OR) [95% CI]
Titus (2003)[79]	Design: Case control Region: North America Setting: Peadiatric ED Study period: Unclear	N: NR/358 Age group(s): 0 – 60 d Inclusion / exclusion: Infants admitted with documented fever ≥100ºF- excluded infants with congenital heart disease or other significant medical history Male (%): 51% Ethnicity (%): NR -- Information on mother: NR	Type(s) of infection studies: RSV Method: RSV: nasopharyngal aspirates for rapid RSV antigen detection via enzyme immunoassay	N with infection: 174 Infection (+) & SBI: 2 Prevalence (%) [95% CI]: 1.15% [0.43, 2.73] N without infection: 174 Infection (-) & SBI: 22 Prevalence (%) [95% CI]: 12.60% [7.70, 17.60]	Prevalence ratio (%) [95% CI]: 0.09 [0.02, 0.38] OR*[95% CI]: 0.08 [0.01, 0.36]

Table 8. KQ6 Included studies reporting on relevant outcomes for infants 0 – 6 months of age

Author, (year) Citation No. Country	Study Design/objective Setting Study period	Population characteristics	Treatment characteristics	Followup details	Results
Baskin, MN (1992)[58] US	-Prospective -ED -1987 – 1997	N=503 infants 28 – 89 d (67% 28-60 d, 33% 61-89 d); with fever without a source – 476 were treated as outpatients and were followed Age: mean 55 (SD 17) d No other characteristic reported	IMI of Cefriaxone (2 doses within 24 hrs) pending culture results	3 phone calls (1 – 12 hrs; 2 – 48 hrs; 3 – 7 d post discharge) and 1 return visit to the ED in 24 hrs post initial visit	Infants with fu at 24 hrs: 494 (98%) who had a 2nd dose of cefriaxone Infants with fu at 48 hrs: 482 (96%) There was concern about 2/476 (0.42%) parents of infants without SBI about parental supervision —These infants were hospitalized > 24 hrs of initial entry
Condra SC (2010)[4] US	Prospective observation/ evaluation of cost and complications in inpatient treatment of febrile infants 29-60 d of age Period: NR – total length of study was 16 months	N = 62 infants 29 – 60 d; fever without a source; met a criteria derived from Philadelphia for Low Risk for SBI 55% male median age: 44 d 39 (63%) White; 18 (29%) African American, 5 (8%) Hispanic (range 29 -60 d) White (63%), African American (29%), Hispanic (8%). 8 (12.9%) Group B Streptococcus +ve or unknown (the mothers treated with peripartum antibiotics)	Despite meeting LR criteria, 56/62 (90.3%) infants were admitted and received IVI antibiotics 6/62 (9.7%) were LRI and discharged from the ED after a full sepsis workup.	3 phone follow-ups with parent and primary care provider (PCP) within the 2 wks after discharge + contact with PCP at 14 d post discharge Questionnaire on 1-Intants' health status 2-compliance 3-hospital charges	Compliance with phone calls after initial discharge (reported for FI who were managed as inpatients 56 (90.32%)]: d 2: 77.4%; d 7: 85.4%; d 14: 83.9% All 6 subjects (100%) discharged directly from the ED did have medical follow-up within 48 hours with PCP Parents preferred discharge to admission (66%-70%) 5/6 (83.3%) discharged infants required re-evaluation and 2/6 (33.3%) were hospitalization within 24 hrs of discharge-one for a +ve blood culture (later determined to be a contaminant) and one for continued fever & newly documented pneumonia. Complications in outpatients:

C-89

Author, (year) Citation No. Country	Study Design/objective Setting Study period	Population characteristics	Treatment characteristics	Followup details	Results
Dore-Bergeron, MJ (2009)[70 80] commentary) Canada	Prospective cohort/ to investigate feasibility of ambulatory tx at day treatment centre (DTC) One tertiary-care pediatric ED Period: 2005	N=118 FI 30 – 90 d with presumed UTI Age: median age for 67 FI admitted to DTC = 66 d (range: 33– 85 d)	Inpatient tx (protocol not described) if any: abnormal CSF, toxic appearance, underlying medical problems, abnormal creatinine levels, parental refusal to fu in DTC, or outpatients tx Ambulatory tx protocol: single IVI gentamicin (5 or 2.5 mg/kg)+ 1 dose IVI ampicillin, & 2 or 3 doses oral amoxicillin, to be taken until the 1st visit to DTC in 24 hrs. At DCT IVI gentamicin daily until the child was afebrile. If UTI was confirmed tx with antibiotics were started.	In outpatient tx, monitoring the fever every 4 hrs + return the child after 24 hrs	67/118 (56.8%) of FI were admitted to DTC. Rate of parental compliance with DTC visits: 98.3%. Successful tx in the DTC (attendance at all visits, normalization of temperature within 48 hrs, -ve control urine & BC results, & absence of hospitalization): 86.2% of pts with confirmed UTI Compliance with guidelines of antibiotic tx: 80.4%; hospitalization during the course of tx in DTC: 12.1% Adherence of ED physicians to patient referral to the appropriate setting (DTC or hospital ward): lower but not statistically-significant for younger infants, [crude OR, comparing < 60-day-old children with older children: 0.5 (95% CI: 0.2, 1.5)]

Citation No.=Citation number; US = United States; N = number of participants; yrs = years; mo/s= month/s; wks = weeks; d=day/s; hr/s = hour/s; IMI = intramuscular injection; IVI=intravenous injection; SBI= serious bacterial infection; LRI=low risk infants; FI=febrile infant; =treatment; fu=follow up; #, n, N=number; LR= low risk for SBI; HR= high risk for SBI; SBI=serious bacterial infection; LP=lumbar puncture; BC= blood culture; YOS= Yale Observational Scale; IQR=inter-quartile range; NR= not reported; CSF=cerebrospinal fluid; UTI= urinary tract infection; ICD-9-CM=International Classification of Diseases, Ninth Revision, Clinical Modification; CPT-4=Current Procedural Terminology, Forth Revision

Appendix D. Excluded Studies

Appendix D lists all of the studies that were excluded from this review, separated by the two main searches, and categorized by reason for exclusion and alphabetized.

Key Questions 1–5

Non-English publications

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Primary objective was not the diagnosis or the management of febrile infants aged 0–90 days

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Appendix E. Quality Assessment Forms

Quality Assessment of Diagnostic Accuracy Studies (QUADAS)

Appendix E lists the questions asked to conduct the quality assessment of the included studies using the QUADAS tool.

Total QUADAS score range = 0 – 14

1. Was the spectrum of patients representative of the patients who will receive the test in practice?
- Yes (score = 1)
- No (score = 0)
- Unclear (score = 0)

2. Were selection criteria clearly described?
- Yes (score = 1)
- No (score = 0)
- Unclear (score = 0)

3. Is the reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?
- Yes (score = 1)
- No (score = 0)
- Unclear (score = 0)

4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?
- Yes (score = 1)
- No (score = 0)
- Unclear (score = 0)

5. Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?
- Yes (score = 1)
- No (score = 0)
- Unclear (score = 0)

6. Did patients receive the same reference standard regardless of the index test result?
- Yes (score = 1)
- No (score = 0)
- Unclear (score = 0)

7. Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?

- Yes (score = 1)
- No (score = 0)
- Unclear (score = 0)

8. Was the execution of the index test described in sufficient detail to permit replication of the test?
- Yes (score = 1)
- No (score = 0)
- Unclear (score = 0)

9. Was the execution of the reference standard described in sufficient detail to permit its replication?
- Yes (score = 1)
- No (score = 0)
- Unclear (score = 0)

10. Were the index test results interpreted without knowledge of the results of the reference standard?
- Yes (score = 1)
- No (score = 0)
- Unclear (score = 0)

11. Were the reference standard results interpreted without knowledge of the results of the index test?
- Yes (score = 1)
- No (score = 0)
- Unclear (score = 0)

12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?
- Yes (score = 1)
- No (score = 0)
- Unclear (score = 0)

13. Were uninterpretable/ intermediate test results reported?
- Yes (score = 1)
- No (score = 0)
- Unclear (score = 0)

14. Were withdrawals from the study explained?
- Yes (score = 1)
- No (score = 0)
- Unclear (score = 0)

Appendix F. Protocols and Criteria

Appendix F lists less commonly used criteria (Yale, and Young Infant Observation Scales)

The Yale Observation Scale

ation e		ate rment (3)	hent (5)
Quality of cry	Strong, normal tone *or* content, not crying	Whimpering, sobbing	Weak, moaning, high pitched
Reaction to Parents	Cries briefly, stops *or* content, not crying	Cries off and on	Continual cry *or* hardly responds
State Variation	If awake, stays awake If asleep, arouses easily	Eyes close briefly, awakes with prolonged stimulation	Falls to sleep, cannot be aroused
Color	Pink	Pale extremities Acrocyanosis	Pale, cyanotic mottled ,ashen
Hydration	Skin, eyes normal Mucous membranes moist	Skin, eyes normal Mouth slightly dry	Skin doughy, tented Mucous membranes dry, Sunken eyes
Response to Social Overtures	Smiles Becomes alert	Brief smile Alerts briefly	No smile, anxious, dull, expressionless Can't be alerted

McCarthy PL, Sharpe MR, Spiesel SZ, et al. Observation scales to identify serious illness in young children. Pediatrics 1982; 70: 802-809

The Young Infant Observation Scale

Affect	Smiles *or* not irritable (1)	Irritable, consolable (3)	Irritable, not consolable (5)
Respiratory status/effort	No impairment, vigorous (1)	Mild-moderate compromise (tachypnea, retractions, grunting) (3)	Respiratory distress *or* inadequate effort (apnea, resp failure) (5)
Peripheral perfusion	Pink, warm extremities (1)	Mottled, cool extremities (3)	Pale, shock (5)

Bonadio, W. A., Hennes, H., Smith, D., Ruffing, R., Melzer-Lange, M., Lye, P., and Isaacman, D., Reliability of observation variables in distinguishing infectious outcome of febrile young infants, Pediatric Infectious Disease Journal, 12(2), 1993, p.111 - 114

Appendix G. Quality Assessment of Included Studies

Appendix G lists all of the questions and answers and tabulated total score for each included study using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool.

Table 1. Quality assessment on all QUADAS questions for each included study

Study ID	Q1.Spectrum of patients	Q2. Selection criteria	Q3. Ref stand & index test length of time	Q4. Ref stand vs. index test period of time	Q5. Reference standard?	Q6. Same ref. standard?	Q7. Ref. stand independent of index test	Q8.Details of index test described	Q9. Replication	Q10.Index test interpreted without knowledge of RS	Q11.Ref. stand interpreted without knowledge of RS	Q12.Same Clinical Data Available	Q13. Uninterpretable	Q14. Withdrawals Explained	Total Score
Andreola B, (2007)[25]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Not clear	Yes	12
Bachur R, (2001)[36]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Not clear	Not clear	Yes	Not clear	Not clear	8
Bachur RG, (2001)[1]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	12
Baker MD, (1990)[54]	Yes	no	Yes	Not clear	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes	No	no	8
Baker MD, (1993)[55]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Not clear	Not clear	Yes	Yes	Yes	11
Baker MD, (1999)[56]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	13
Baker MD, (1999)[57]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	14
Baskin (1992)[58]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Not clear	Not clear	Yes	Yes	Yes	11
Berkowitz CD, (1985)[37]	Not clear	Yes	Not clear	Not clear	No	Not clear	Not clear	No	Yes	Not clear	Not clear	Yes	Not clear	Not clear	3
Bilavsky E, (2008)[15]	Not clear	Not clear	Yes	Not clear	Not clear	Yes	Not clear	No	No	Not clear	Yes	Not clear	No	No	3

Study ID	Q1.Spectrum of patients	Q2. Selection criteria	Q3. Ref stand & index test length of time	Q4. Ref stand vs. index test period of time	Q5. Reference standard?	Q6. Same ref. standard?	Q7. Ref. stand independent of index test	Q8.Details of index test described	Q9. Replication	Q10.Index test interpreted without knowledge of RS	Q11.Ref. stand interpreted without knowledge of RS	Q12.Same Clinical Data Available	Q13. Uninterpretable	Q14. Withdrawals Explained	Total Score
Bilavsky E, (2009)[26]	Yes	Yes	Yes	Not clear	Not clear	Yes	Yes	Yes	Yes	Not clear	Yes	Not clear	No	Not clear	8
Bilavsky E, (2010)[38]	Yes	Yes	Yes	Not clear	No	Yes	Yes	Yes	Not clear	Not clear	Not clear	Yes	Yes	Yes	9
Bilavsky E, (2008)[74]	Not clear	Yes	Not clear	Not clear	Yes	Not clear	Not clear	No	No	Not clear	Not clear	Not clear	Not clear	Yes	3
Bonadio WA, (1991)[16]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	Yes	Not clear	Yes	12
Bonadio WA, (1992)[40]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes	Not clear	Not clear	10
Bonadio WA, (1993)[60]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	13
Bonadio WA, (1994)[17]	Not clear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes	Not clear	Not clear	9
Bonadio WA. (1987)[39]	Yes	Yes	Not clear	Not clear	Yes	Yes	Not clear	No	Yes	Not clear	Not clear	Yes	Not clear	Yes	7
Bonsu BK, (2003)[41]	Not clear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Not clear	Not clear	Yes	Not clear	Yes	9
Bonsu BK, (2007)[42]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Not clear	Not clear	11
Bressan S, (2010)[43]	No	Yes	Yes	Not clear	No	Yes	Yes	Yes	Yes	Not clear	Not clear	Not clear	No	Yes	7
Brik R, (1997)[61]	Not clear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	12
Broner CW, (1990)[2]	Not clear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Not clear	Yes	Not clear	Not clear	9
Brown L,	Not	Not	Yes	Not	No	Not	Not	No	No	Not clear	Not clear	Yes	Not	Yes	3

Study ID	Q1.Spectrum of patients	Q2. Selection criteria	Q3. Ref stand & index test length of time	Q4. Ref stand vs. index test period of time	Q5. Reference standard?	Q6. Same ref. standard?	Q7. Ref. stand independent of index test	Q8.Details of index test described	Q9. Replication	Q10.Index test interpreted without knowledge of RS	Q11.Ref. stand interpreted without knowledge of RS	Q12.Same Clinical Data Available	Q13. Uninterpretable	Q14. Withdrawals Explained	Total Score
(2005)[44]	clear	clear		clear		clear	clear						clear		
Byington CL, (1999)[75]	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Not clear	Yes	Not clear	Yes	8
Byington CL, (2004)[62]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Not clear	Yes	Not clear	No	9
Caspe WB, (1983)[3]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Not clear	Yes	Not clear	Yes	11
Caviness AC, (2008)[45]	Yes	Yes	Yes	Not clear	No	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes	No	no	8
Chen C-J, (2009)[81]	Yes	Yes	Yes	Not clear	Not clear	Yes	Yes	No	Yes	Not clear	Not clear	Not clear	No	Not clear	6
Chiu CH, (1994)[82]	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Not clear	Not clear	Not clear	Yes	Yes	9
Chiu CH, (1997)[63]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes	Yes	Yes	12
Condra CS, (2010)[4]	No	Yes	Yes	Not clear	No	Yes	Yes	Yes	Yes	Not clear	Not clear	No	No	Yes	7
Crain EF, (1982)[19]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	Not clear	Not clear	11
Crain EF, (1988)[5]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes	Not clear	Not clear	9
Crain EF, (1990)[6]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	12
Dagan R, (1985)[7]	Not clear	Yes	Yes	Yes	Yes	Yes	Not clear	No	No	Not clear	Not clear	Yes	Not clear	Not clear	6
Dagan R, (1988)[8]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes	Yes	Yes	11

Study ID	Q1.Spectrum of patients	Q2. Selection criteria	Q3. Ref stand & index test length of time	Q4. Ref stand vs. index test period of time	Q5. Reference standard?	Q6. Same ref. standard?	Q7. Ref. stand independent of index test	Q8.Details of index test described	Q9. Replication	Q10.Index test interpreted without knowledge of RS	Q11.Ref. stand interpreted without knowledge of RS	Q12.Same Clinical Data Available	Q13. Uninterpretable	Q14. Withdrawals Explained	Total Score
Dayan PS, (2002)[46]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Not clear	Yes	Yes	No	Yes	11
Ferrera PC, (1997)[64]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	Not clear	Yes	12
Garra G, (2005)[65]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	No	12
Gomez B, (2010)[9]	Yes	Yes	Yes	Not clear	No	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes	No	Yes	9
Herr SM, (2001)[10]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	13
Hoberman A, (1993)[47]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes	Not clear	Yes	11
Hsiao AL,(2006)[32]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	12
Jaskiewicz JA, (1994)[66]	Not clear	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	Yes	Yes	10
Jordan I, (2009)[71]	Yes	Yes	Yes	Not clear	Not clear	Yes	Yes	Not clear	No	Not clear	Not clear	Yes	No	Not clear	6
Kadish HA, (2000)[67]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Not clear	Yes	12
Kaplan RL, (2000)[68]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	13
King JC, Jr., (1987)[20]	Not clear	Yes	Not clear	Yes	Yes	Yes	No	Yes	No	Not clear	Not clear	Yes	Not clear	Not clear	6
Kuppermann N, (1997)[76]	Yes	Yes	Yes	Not clear	Yes	Not clear	Not clear	No	Yes	Not clear	Not clear	Yes	Not clear	Yes	7
Levine DA,	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	11

Study ID	Q1.Spectrum of patients	Q2. Selection criteria	Q3. Ref stand & index test length of time	Q4. Ref stand vs. index test period of time	Q5. Reference standard?	Q6. Same ref. standard?	Q7. Ref. stand independent of index test	Q8.Details of index test described	Q9. Replication	Q10.Index test interpreted without knowledge of RS	Q11.Ref. stand interpreted without knowledge of RS	Q12.Same Clinical Data Available	Q13. Uninterpretable	Q14. Withdrawals Explained	Total Score
(2004)[83]															
Lin DS, (2000)[48]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Not clear	Not clear	Yes	Not clear	Yes	10
Maniaci V, (2008)[49]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	No	Yes	11
Marom R, (2007)[11]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes	Not clear	Yes	10
McCarthy CA, (1990)[72]	no	Yes	Not clear	Not clear	Not clear	v	Yes	Yes	no	Not clear	Not clear	Yes	no	no	5
Meehan WP, (2008)[51]	Yes	Yes	Yes	Not clear	No	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes	No	Yes	9
Mintegi S, (2009)[21]	Not clear	Not clear	Not clear	Not clear	No	Not clear	Not clear	Yes	No	Not clear	Not clear	Yes	No	Yes	3
Olaciregui E, I, (2009)[52]	Yes	Yes	Yes	Not clear	No	Yes	Yes	Yes	Yes	Not clear	Yes	Yes	No	Yes	10
Pantell RH, (2004)[12]	Yes	Yes	Yes	Not clear	Yes	Not clear	Yes	Yes	Yes	Not clear	Not clear	Yes	Yes	Yes	10
Reardon JM, (2009)[53]	Not clear	No	Yes	Not clear	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Not clear	8
Rittichier KR, (2005)[77]	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Not clear	Not clear	Yes	Not clear	Not clear	8
Rosenberg N, (1985)[22]	Not clear	Yes	Yes	Yes	Yes	No	No	Yes	No	Not clear	Not clear	Yes	Not clear	Not clear	6
Rudinsky SL, (2009)[35]	Yes	Yes	Yes	Not clear	Not clear	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes	No	No	8
Schwartz S, (2009)[13]	Yes	Yes	Yes	Not clear	No	Yes	Yes	Yes	Yes	No	Not clear	Yes	No	Yes	9

Study ID	Q1.Spectrum of patients	Q2. Selection criteria	Q3. Ref stand & index test length of time	Q4. Ref stand vs. index test period of time	Q5. Reference standard?	Q6. Same ref. standard?	Q7. Ref. stand independent of index test	Q8.Details of index test described	Q9. Replication	Q10.Index test interpreted without knowledge of RS	Q11.Ref. stand interpreted without knowledge of RS	Q12.Same Clinical Data Available	Q13. Uninterpretable	Q14. Withdrawals Explained	Total Score
Shin SH, (2009)[84]	Yes	Yes	Yes	Not clear	Not clear	Yes	Yes	No	Yes	Not clear	Yes	Not clear	No	Not clear	7
Smitherman HF, (2005)[78]	No	Yes	Yes	Yes	Yes	Yes	Not clear	No	Yes	Not clear	Not clear	Yes	Not clear	Yes	8
Stanley R, (2005)[23]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	Yes	Yes	Yes	13
Titus MO, (2003)[79]	No	Yes	Yes	Yes	Yes	Yes	Not clear	No	Yes	Not clear	Not clear	Yes	Not clear	No	7
Wasserman GM, (1990)[14]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	14
Watt K, (2010)[73]	Yes	Yes	Yes	Not clear	Yes	Not clear	Yes	Yes	Yes	Not clear	Yes	Yes	No	No	9
Wolff M, (2009)[24]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Not clear	No	Yes	10

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