REVIEW ARTICLE

Occult Serious Bacterial Infection in Infants Younger Than 60 to 90 Days With Bronchiolitis

A Systematic Review

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Objective: To summarize the risk of occult serious bacterial infection in the youngest febrile infants presenting with either clinical bronchiolitis or respiratory syncytial virus infection.

Data Sources: We performed a systematic search of the Medline database for studies reporting rates of serious bacterial infection in infants younger than 90 days with clinical bronchiolitis and/or respiratory syncytial virus infection.

Study Selection: Studies reporting on cultures performed at the time of presentation to care and providing a denominator, ie, total number of each type of culture obtained, were analyzed.

Main Exposure: Admission for bronchiolitis.

Main Outcome Measures: Age-specific rates of urinary tract infection, bacteremia, and meningitis were extracted.

Results: The weighted rate of urinary tract infections in the youngest infants in the 11 studies analyzed was 3.3% (95% confidence interval, 1.9%-5.7%). No case of bacteremia was reported in 8 of 11 studies. No case of meningitis was reported in any of the studies. Summary statistics for meningitis and bacteremia are not provided because of an excess of zero events in these samples.

Conclusions: A screening approach to culturing for serious bacterial infections in febrile infants presenting with bronchiolitis or respiratory syncytial virus infection is very low yield. The rate of urine cultures positive for bacteria remains significant, though asymptomatic bacteriuria may confound these results.

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VIRAL BRONCHIOLITIS IS CURrently the most common reason for pediatric hospital admission in the United States, accounting for almost 20% of all-cause infant hospitalizations.[1,2] The concern for concomitant serious bacterial infection (SBI) can be a complicating factor for a significant proportion of these hospitalizations since many hospitalized infants are in high-risk age groups where regular screening for SBI is performed. When fever occurs in the setting of clinical bronchiolitis, clinicians may have difficulty determining if the fever is a consequence of the viral infection causing bronchiolitis or potentially indicative of occult SBI.

Significant decreases in the incidence of SBI in young children have been reported in the literature over the past 20 years, beginning with universal infant *Haemophilus influenzae* vaccination in the early 1990s and continuing with universal pediatric pneumococcal vaccination in the early 2000s.[3-5] In reference to bronchiolitis, the original literature on the topic suggested that SBI rarely occurred concomitantly and that overuse of broad-spectrum antibiotics actually increased the risk to the patient.[6] However, other researchers countered with reports of an association with pneumococcal disease.[7,8] To further complicate the picture, infants younger than 2 months are typically incompletely vaccinated as well as susceptible to a different set of pathogens acquired perinatally. Therefore, when these infants present with fever, clinicians remain uncertain about the ever-evolving risk of SBI. The available literature suggests that clinicians generally revert to universal screening for SBI in the youngest infants, despite the presence of other recognizable viral syndromes such as bronchiolitis.[9-25]

To better assess the risk of SBI in the setting of bronchiolitis in the youngest infants, we undertook a systematic review of the literature and meta-analysis of the available data. The primary question informing this study was what is the yield

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of screening for occult SBI in infants younger than 60 to 90 days with bronchiolitis and/or documented respiratory syncytial virus (RSV) infection?

METHODS

SEARCH STRATEGY AND STUDY SELECTION

The National Library of Medicine Medline database was systematically searched through December 31, 2010. Search terms included *serious bacterial infection*, *bacteremia*, *meningitis*, and *urinary tract infection* combined using *with bronchiolitis* as well as *respiratory syncytial virus* and used as medical subject headings where appropriate. The bibliographies of studies identified in this manner were then manually searched for studies not identified in the initial database search. Inclusion criteria were any study reporting the incidence of site-specific, concomitant SBI in the setting of fever and clinical bronchiolitis or documented RSV infection and that included in their reporting the total number of each type of culture collected (ie, reported a denominator). Studies were then screened for the ability to extract age-specific data for a population of infants younger than 60 to 90 days and the ability to determine presence or absence of fever in these infants. Finally, we excluded studies restricted to intensive care units and studies restricted to rates of pneumonia because of the significant diagnostic uncertainty associated with proving bacterial etiology, including controversies over diagnosis based specifically on serology results.

DATA COLLECTION

Primary outcomes for this study were rates of occult SBI, which were defined as meningitis, bacteremia, and urinary tract infection (UTI), in children younger than 60 to 90 days. Two investigators (S.R. and V.H.) reviewed and graded each study as to the level of evidence. All 3 investigators (S.R., V.H., and A.W.) extracted the age-specific rates of UTI, bacteremia, and meningitis separately, and discrepancies were resolved by consensus.

DATA SYNTHESIS AND ANALYSIS

The available studies were qualitatively evaluated and are described in the **Table**. Event rates for UTI, bacteremia, and meningitis were extracted and their 95% confidence intervals were calculated. For bacteremia and meningitis, meta-analysis was not done because of the excess number of zero events in the sample. A random-effects meta-analysis of UTI rates was performed. Subgroup analyses were conducted to assess the effects of study design (prospective vs retrospective), study setting (inpatient vs emergency department), and inclusion criteria (clinical bronchiolitis vs RSV positivity) on the proportion of UTIs in the included studies. A restricted maximum-likelihood random-effects meta-regression was used to test differences in the subgroups. Statistical analyses were performed using Stata version 11 (StataCorp, College Station, Texas) and Comprehensive Meta-analysis version 2 (Biostat, Englewood, NJ).

RESULTS

SEARCH RESULTS

The initial database search yielded 114 studies and 14 met the initial inclusion criteria. These studies were reviewed by all of us (S.R., V.H., and A.W.). A further 3 studies were identified from the bibliographies of the initial studies or interim searches for new literature, and a final article that was missed using our search criteria was included at the suggestion of an external reviewer for a total of 18 studies considered for inclusion.[6,9-25] Age-specific rates of SBI were calculable for a population of children younger than 60 to 90 days in 11 studies, which became the final study sample.[9-11,14-16,18,19,22-24] The 7 studies excluded were removed for the following reasons: did not include children younger than 90 days,[12] could not extract age- and/or site-specific rates of infection,[6,13,17,25] included overlapping data presented in a later, larger study,[20] and included only intensive care unit admissions.[21]

STUDY CHARACTERISTICS

The Table provides the details of study methods, setting, and inclusion and exclusion criteria. The majority of studies were retrospective (6 of 11) and the majority used clinical bronchiolitis as the primary inclusion criterion (6 of 11) while the remainder used RSV positivity. Seven studies provided data on children younger than 90 days or 3 months, and 4 studies used a 60-day or 4-weeks-of-age cut point. There was a degree of clinical heterogeneity in the studies, which can only be qualitatively expressed (Table); however, the overall intent of the studies appeared to be consistent, ie, they took a screening approach to febrile infants characterized by testing the majority of infants based on the single clinical criterion of fever.

STATISTICAL ANALYSIS

Figure 1 is the forest plot for UTI rates. The random-effects model was used for meta-analysis. The summary estimate for the prevalence of UTI was 3.3% (95% confidence interval, 1.9%-5.7%). Rates and 95% confidence intervals for bacteremia are presented in a forest plot in **Figure 2**, though the data were not considered appropriate for formal meta-analysis because of an excess of studies with zero events. There were no cases of meningitis reported in any of the studies reviewed and no further analysis was attempted because of the small sample sizes for this now rare event.

For rates of UTI, subgroup analysis was performed by study setting, study design, and inclusion criteria (bronchiolitis vs RSV positivity) to explore sources of heterogeneity. Study setting or study design did not explain heterogeneity; however, analysis by inclusion criteria did resolve a significant portion of the statistical heterogeneity. **Figure 3** presents a forest plot for this analysis. Rates of UTI were higher in the subgroup where study inclusion was based on RSV positivity (5.1%) compared with clinical bronchiolitis (2.0%) ($P < .05$).

COMMENT

Reported rates of SBI in febrile infants younger than 90 days with clinical bronchiolitis and/or RSV infection were generally low. No cases of meningitis were reported in the studies reviewed and very few cases of bacteremia were

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Table. Characteristics of Studies Included in the Analysis

Source	Type	Study Setting	Age	Inclusion Dx	Fever Confirmation	Exclusions
Kuppermann et al,[9] 1997	Prospective	ED, 30% admitted	≤2 mo	Clinical bronchiolitis	All: rectal temperature ≥38°C in ED	Lobar pneumonia on chest radiograph, antibiotics within 48 h, known chronic illness or receipt of immunosuppressive medication, identifiable viral infection other than bronchiolitis, focal bacterial infection other than otitis media
Antonow et al,[10] 1998	Retrospective	Inpatient	≤60 d	Clinical bronchiolitis	72.5% Documented febrile	PICU admission and chronic comorbidities such as congenital heart disease, bronchopulmonary dysplasia, and immunodeficiency
Liebelt et al,[11] 1999	Retrospective	ED	≤90 d	Clinical bronchiolitis	75% Documented febrile, depending on site cultured	Bronchopulmonary dysplasia, immunodeficiency, congenital heart disease, septic arthritis, cellulitis, osteomyelitis, and other identifiable viral infection
Melendez and Harper,[14] 2003	Retrospective	ED	<90 d	Clinical bronchiolitis	All: rectal temperature ≥38°C in ED	Lack of upper respiratory tract findings, focal or unilateral lung findings, bronchopulmonary dysplasia, immunodeficiency, congenital heart disease, other focal bacterial infection, or identifiable viral infection
Oray-Schrom et al,[15] 2003	Retrospective	ED, 80% admitted	≤90 d	RSV+	All: temperature ≥38°C (unspecified method)	None specified
Titus and Wright,[16] 2003	Retrospective	Inpatient	≤56 d	RSV+	All: temperature ≥38°C documented in medical record	Congenital heart disease, bronchopulmonary dysplasia, hydrocephalus or other neurologic disorder, metabolic disorders, hematologic abnormalities, or other significant medical history
Byington et al,[18] 2004	Prospective	Inpatient and outpatient	≤90 d	RSV+	All: temperature ≥38°C (unspecified method)	Receipt of antibiotics in the preceding 48 h or receipt of oral polio vaccination
Levine et al,[19] 2004	Prospective	ED (8 centers)	≤60 d	RSV and clinical bronchiolitis	All: rectal temperature ≥38°C in ED or by history	Antibiotics within 48 h of presentation, RSV testing not obtained, bacterial cultures not obtained
Purcell and Fergie,[22] 2007	Retrospective	Inpatient	<90 d	RSV bronchiolitis; RSV pneumonia; RSV NOS	All: temperature ≥38°C documented at or before admission	None specified
Bilavsky et al,[23] 2008	Prospective	Inpatient	≤3 mo	Clinical bronchiolitis	All: rectal temperature ≥38°C in hospital	Chronic diseases (heart failure, lung disease, renal failure); prematurity, GA <32 wk; antibiotics within 48 h of presentation; fever by history only
Luginbuhl et al,[24] 2008	Prospective	Outpatient, 50% admitted	<3 mo	Clinical bronchiolitis	All: temperature ≥38°C at home or in clinic	Presence of major comorbidities (congenital anomalies, extreme prematurity, organ system failure)

Abbreviations: Dx, diagnosis; ED, emergency department; GA, gestational age; NOS, not otherwise specified; PICU, pediatric intensive care unit; RSV, respiratory syncytial virus.

reported, most of which were associated with UTI. Urinary tract infection was the only SBI reported with significant frequency. Most of the studies were retrospective and subject to the biases inherent in that method. The major concern about retrospective reporting for this analysis would be selection bias resulting in underreporting of events. However, the available prospective studies reported lower rates of SBI than the retrospective studies, and we found no significant differences in rates in a subanalysis based on study design.

Most of the studies appear to be conducted under conditions of nonselective screening of febrile infants for culture, ie, regardless of clinical status or other factors, all febrile infants younger than 60 or 90 days had cultures collected. This assumption is not explicitly stated in all of the studies included; however, a selective approach to culturing would likely increase the rates of SBI, ie, if only sicker infants had cultures collected then the yield of the cultures should be higher, which is not consistent with the very low rates of SBI we encountered. Also, we in-

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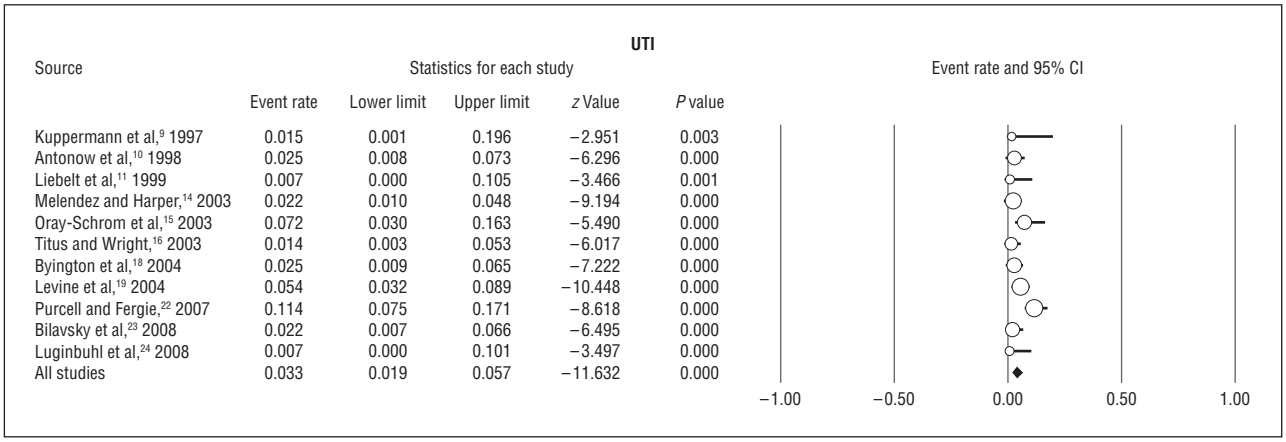

Figure 1. Urinary tract infection (UTI) rates in febrile infants with bronchiolitis or respiratory syncytial virus infection. CI indicates confidence interval.

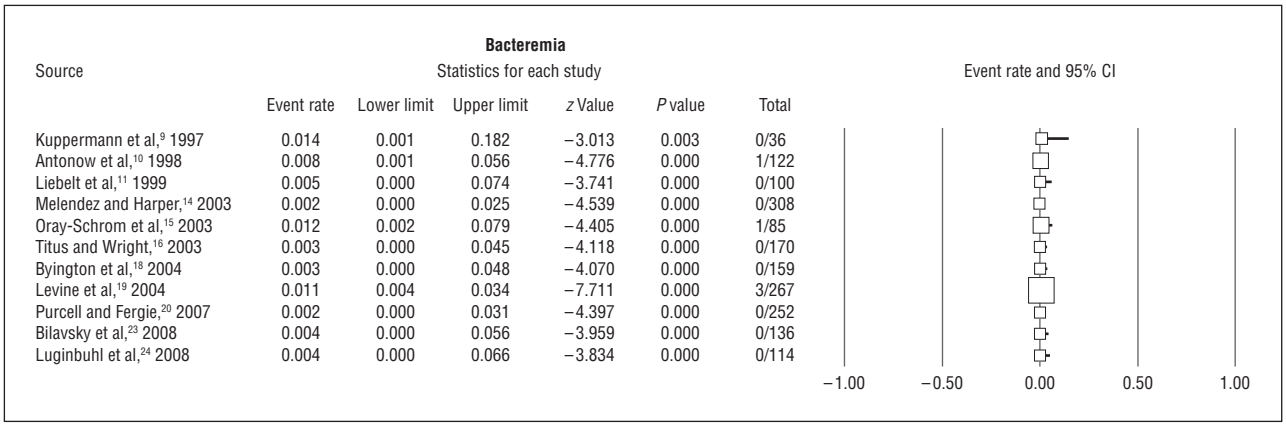

Figure 2. Bacteremia rates in infants with bronchiolitis or respiratory syncytial virus infection. CI indicates confidence interval.

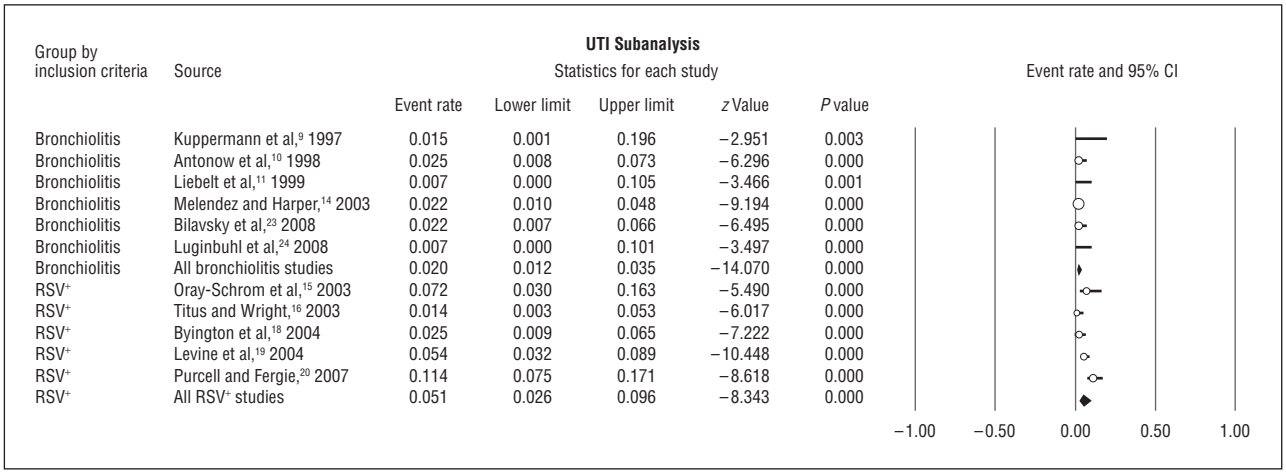

Figure 3. Urinary tract infection (UTI) rates subanalyzed by clinical bronchiolitis vs respiratory syncytial virus (RSV) positivity. CI indicates confidence interval.

cluded only rates of SBI where a denominator representing the total number of specific cultures obtained could be extracted, which should ameliorate any tendency toward underestimation of rates of SBI (a criticism of previous studies).

A particular weakness in our study is our inability to provide insight into the question of concomitant bacterial pneumonia in infants with bronchiolitis. Because of the high probability of abnormal radiographic findings in bronchiolitis and the difficulty in distinguishing bacterial from viral etiologies based on radiographs alone, the choice to avoid the question of pneumonia was somewhat inevitable. While there are important data linking invasive pneumococcal disease with preceding viral illnesses,[26,27] it is much less clear that there is any association between acute bronchiolitis and concomitant pneumonia. Many of the studies we analyzed chose to present rates of abnormal chest radiographs (unsurprisingly quite

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high) to complement their culture results and a few excluded lobar pneumonia as a focal finding. We present the exclusion criteria for each study in the Table primarily because we were unable to create a cohort with similar exclusions. For instance, 1 patient with pneumococcal bacteremia and *Escherichia coli* in the urine was excluded from the Kuppermann et al study[9] based on chest radiograph findings of lobar pneumonia. We analyzed our data both with and without this patient included as both a positive urine culture and blood culture. This patient alone did not impact the results significantly; however, the example makes it clear how selective exclusion of lobar pneumonia in the sample could skew our results toward underreporting of SBI. Nevertheless, given the large number of abnormal radiographs and the extremely low rates of bacteremia reported, it seems very unlikely that we have systematically missed a large population of concomitant bacterial pneumonia that is present on initial evaluation or admission for bronchiolitis.

The issue of infants younger than 30 days is not directly addressed in our study because there were not enough studies with extractable data for this age group. This is a significant weakness given that the younger than 30 days age group is at the highest risk of occult SBI. Differential application of screening strategies based on knowledge of risk may skew results in studies where screening was not universally mandated in the study protocol. However, no clear pattern emerges in the studies we examined; for example, age younger than 30 days was a strong predictor of receiving a sepsis workup in the outpatient setting, whereas it was not a significant predictor in the emergency department, with both studies using clinical bronchiolitis as the entry criterion.[11,24] Furthermore, and somewhat surprisingly, in the 2 studies with reporting of SBI rates by age younger than 30 days, there were no differences in rates of SBI in the younger vs the older infants.[19,22] Finally, 4 of the 10 studies we analyzed used a younger-than-60-days or 2 months' cut point rather than 90 days, further narrowing our sample to higher-risk infants.

Our study provides a synthesis that could be used to argue for a selective approach to screening febrile infants with clinical bronchiolitis or documented RSV infection for meningitis or bacteremia. A preponderance of evidence suggests that routine lumbar puncture and blood culture are very low yield in this clinical setting. Therefore, a policy of routine screening of all febrile infants younger than 90 days with these tests could be modified based on the presence of the recognizable viral syndrome of bronchiolitis. This is consistent with the literature on risk of SBI in other recognizable viral syndromes such as influenza. However, this recommendation should not apply to clinically unstable children or infants who have been hospitalized for more than a brief period prior to evaluation of the fever, ie, the included studies may not inform clinical decision making when an infant experiences an unexpected fever after several days of hospitalization; they more generally address the issue of fever at the time of presentation for acute care.

The question of UTI, the most common and least invasive SBI, remains more complicated. Given that most of the studies did not provide information from a urinalysis or imaging to complement the urine cultures positive for bacteria, it is hypothesized that some of these positives could represent asymptomatic bacteriuria. Given that the rate of asymptomatic bacteriuria (culture positive for bacteria in the absence of illness, inflammatory markers, or an active urine sediment) is reported to be at least 2%[28,29] and that there is an alternative cause of fever (clinical bronchiolitis or RSV infection) in the infants in these studies, this hypothesis must be considered seriously. We subanalyzed this group to further inform an approach to screening for UTI in the youngest infants. Our analysis suggests that clinical bronchiolitis performs better than RSV positivity in characterizing an infant as low risk for UTI. Given that universal screening for UTI in this population is relatively low risk and given its significant association with bacteremia in the youngest infants, our data do not strongly support any modification to this approach. However, this conclusion does not take into account any downside to misdiagnosing asymptomatic bacteriuria as UTI such as unnecessary antibiotic exposure and imaging.

Routine screening for SBI in febrile infants younger than 60 to 90 days with bronchiolitis or RSV infection appears very low yield and a more selective approach may be rational. Urinary tract infection is the only SBI reported with significant frequency, though the rates reported in this study may be confounded by asymptomatic bacteriuria. These conclusions generally apply to fever evaluated at the time of presentation to care and should not inform decisions about evaluating fever after prolonged illness or hospitalization.

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