Diagnosis and Testing in Bronchiolitis

A Systematic Review

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Background: The diagnosis of bronchiolitis is based on typical history and results of a physical examination. The indications for and utility of diagnostic and supportive laboratory testing (eg, chest x-ray films, complete blood cell counts, and respiratory syncytial virus testing) are unclear.

Objectives: To review systematically the data on diagnostic and supportive testing in the management of bronchiolitis and to assess the utility of such testing.

Design: In conjunction with an expert panel, we generated admissibility criteria and derived relevant terms to search the literature published from 1980 to November 2002 in MEDLINE and the Cochrane Collaboration Database of Controlled Clinical Trials. Trained abstractors completed detailed data collection forms for each article. We summarized the data in tables after performing data integrity checks.

Results: Of the 797 abstracts identified, we present evidence from 82 trials that met our inclusion criteria (17 are primary articles on diagnosis of bronchiolitis and 65 are reports of treatment or prevention trials). Numerous studies demonstrate that rapid respiratory syncytial virus tests have acceptable sensitivity and specificity, but no data show that respiratory syncytial virus testing affects clinical outcomes in typical cases of the disease. Seventeen studies presented chest x-ray film data. Abnormalities on chest x-ray films ranged from 20% to 96%. Insufficient data exist to show that chest x-ray films reliably distinguish between viral and bacterial disease or predict severity of disease. Ten studies included complete blood cell counts, but most did not present specific results. In one study, white blood cell counts correlated with radiologically defined disease categories of bronchiolitis.

Conclusions: A large number of studies include diagnostic and supportive testing data. However, these studies do not define clear indications for such testing or the impact of testing on relevant patient outcomes. Given the high prevalence of this disease, prospective studies of the utility of such testing are needed and feasible.

to change the clinical course, the management, or the prognosis. Supportive testing, nevertheless, is common and is associated with significant cost in the care of infants with this disease. Some institutions have developed evidence-based guidelines specifically to decrease the use of RSV enzyme-linked immunosorbent assays and supportive diagnostic testing.

In conjunction with an expert panel, we generated inclusion and exclusion criteria (Table 1) and derived relevant terms (Table 2) to search the literature in MEDLINE and the Cochrane Collaboration Database of Controlled Clinical Trials. For all studies, key inclusion criteria consisted of outcomes that were clinically relevant and could be abstracted. Meta-analyses were included in the search to examine their lists of included and excluded studies. We conducted hand searches of the reference lists of relevant included articles to ensure that we did not exclude important work. In addition, we consulted with the technical expert advisory group about any studies that were under way but not yet published. Our search was last updated in November 2002. Two additional studies published during this time were included.12,13

Trained abstractors completed detailed data collection forms for each included study. We summarized the information in tables after reviewing the data collection forms against the articles. Senior study personnel (W.C.B. and V.J.K.) performed data integrity checks by reviewing the articles a second time against the evidence tables.

We reviewed 797 abstracts identified using the search strategy. Of these, 17 are primary articles on diagnosis of bronchiolitis. None of these studies was designed specifically to measure the utility of diagnostic or supportive testing. However, considerable data on diagnosis and testing were found in the 65 treatment and prevention trials identified, so these are also included in our results.

The studies dealing with diagnosis fell into the following 5 categories: (1) case definitions and inclusion criteria used in the clinical trials; (2) viral causes of bronchiolitis when all subjects underwent testing; (3) comparison of various virus isolation techniques; (4) predictors of disease severity, complications, or both; and (5) studies in which standardized tests were performed on all patients as part of their evaluation (eg, chest x-rays and CBC counts).

### CASE DEFINITION AND INCLUSION CRITERIA

The challenge of this literature is the fact that bronchiolitis is a clinical diagnosis based on typical history and findings on physical examination. There is no specific diagnostic test or gold standard that confirms the diagnosis or excludes other diseases that may be clinically similar (eg, bacterial pneumonia). We reviewed the case definitions and inclusion criteria used in the clinical trials and found that most definitions were quite similar. Forty-three trials used tachypnea in the case definition or inclusion criteria; 42 used wheezing; 37 used oxygen saturation; and 32 used retractions. However, many studies simply stated that infants with signs and symptoms con-
The techniques for identifying RSV as the causative agent of bronchiolitis included viral cultures, rapid antigen detection tests (eg, direct immunofluorescence assay and enzyme immunoassays), polymerase chain reaction, and measurements of acute and convalescent antibody titers. Rapid antigen detection tests for RSV were used most frequently. In many studies, investigators performed viral cultures on cases with negative findings for RSV.

### Table 3. Studies Examining the Accuracy of Virological Tests

<table>
<thead>
<tr>
<th>Source</th>
<th>Gold Standard</th>
<th>Tests Compared</th>
<th>Results</th>
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<tbody>
<tr>
<td>Ahluwalia et al,17 1987</td>
<td>Viral culture of NPA and NPS</td>
<td>EIA, IFA on NPA and NPS specimens</td>
<td>EIA-NPA: Sn = 69%, Sp = 100%; EIA-NPS: Sn = 61%, Sp = 100%; IFA-NPA: Sn = 61%, Sp = 89%; and IFA-NPS: Sn = 52%, Sp = 78%</td>
</tr>
<tr>
<td>Chattopadhyya et al,22 1992</td>
<td>Viral culture</td>
<td>IFA, EIA by blocking test</td>
<td>IFA: Sn = 89%, Sp = 92%; EIA: Sn = 94%, Sp = 74%; and EIA by blocking test: Sn = 94%, Sp = 77%</td>
</tr>
<tr>
<td>Eugene-Ruellian et al,21</td>
<td>Viral culture and/or IFA</td>
<td>PCR</td>
<td>97% Concordance</td>
</tr>
<tr>
<td>Ahluwalia et al,21 1998</td>
<td>Viral culture</td>
<td>PCR</td>
<td>IFA detected 27 cases; PCR detected 28 cases</td>
</tr>
<tr>
<td>Warner et al,26 2001</td>
<td>Viral culture and/or IFA</td>
<td>EIA</td>
<td>Sn = 86%, Sp = 91%</td>
</tr>
</tbody>
</table>

Abbreviations: EIA, enzyme immunoassays; IFA, direct immunofluorescence assay; NPA, nasopharyngeal aspirate; NPS, nasopharyngeal suction; PCR, polymerase chain reaction; Sn, sensitivity; Sp, specificity.

### COMPARISON OF VIROLOGICAL TESTS

Five studies examined the accuracy of various virological tests for RSV and other causative viruses.21-25 Table 3 demonstrates that numerous tests for RSV exist and that their test characteristics vary. The 2000 Red Book from the American Academy of Pediatrics reports that the overall sensitivity of the rapid antigen detection tests ranges from 80% to 90%.26 Data presented in Table 3 are consistent with this estimate. Individual test manufacturers likely have additional, unpublished data on their own assays, as they generally report test characteristics in the package insert materials that accompany test kits. Our search strategy would not have identified this unpublished data. In addition to looking at test agreement, Ahluwalia et al21 compared 2 methods of specimen collection and demonstrated that viral culture, enzyme immunoassays, and direct immunofluorescence assays all yielded positive results more often when performed on nasopharyngeal aspirates than when performed on nasopharyngeal swabs.

We identified no trials that addressed the question of whether knowing RSV is the causative agent in bronchiolitis affects clinical outcomes.

### PREDICTORS OF DISEASE SEVERITY OR COMPLICATIONS

Four studies (Table 4) measured various predictors of disease severity.7,17-20 Shaw et al26 examined historical elements, physical examination findings, and laboratory results and identified the following 5 clinically important predictors of severe disease: ill or toxic appearance, oxygen saturation of less than 95%, gestational age of less than 34 weeks, respiratory rate of greater than 70 breaths per minute, and age younger than 3 months. Mulholland et al21 correlated clinical findings with disease severity defined by pulse oximetry findings and arterial blood gas measurements. Young age, cyanosis, crackles, and oxygen saturation of less than 90% all predicted more severe disease. Dawson et al27 studied the relationship between clinical severity based on clinical scales with the degree of radiological changes on chest x-rays. The authors found no correlation. Wright et al28 examined the relationship between demographic characteristics, viral shedding and antibody responses, and disease severity.
using data collected during the 2 RSV immunoglobulin clinical trials,20,29,30 Their report focused primarily on immunologic responses to RSV, but demonstrated that younger age, history of bronchopulmonary dysplasia, and history of congenital heart disease were independently associated with more severe disease.

Most textbooks cite young age, history of prematurity or other comorbidities, toxic appearance at presentation, and rapid progression of symptoms as risk factors for severe disease. The studies by Shaw et al,28 Mulholland et al,27 and Wright et al29 support these assertions.

**UTILITY OF CHEST X-RAYS IN BRONCHIOLITIS**

Seventeen studies obtained chest x-ray films on all patients (Table 5),7,12,19,20,28,30-41 but many clinical trials do not report chest x-ray film results. Two studies examined the relationship between x-ray film abnormalities and disease severity. In the trial by Shaw et al,28 the patients with atelectasis were 2.7 times more likely (95% confidence interval [CI], 1.97–3.70) to have severe disease than those without this x-ray film finding. This association persisted when it was included in a multivariable analysis. In contrast, the data from Dawson et al demonstrated no correlation between chest x-ray film findings and baseline disease severity as measured by a clinical severity scoring system.

Three studies compared chest x-ray films with cultures and management. In a prospective cohort of 128 infants younger than 7 years with clinical lower respiratory tract infections, Fries et al obtained viral and bacterial studies on nasopharyngeal secretions; they compared virus-infected children with or without bacteria in their secretions with data on the corresponding groups without virus infection. The x-ray film findings were normal significantly more often in the virus-positive–bacteria-negative group than in the other groups. Alveolar pneumonia appearing as lobar or segmental consolidations (“lobar” pneumonia) was observed with equal frequency and without relation to bacterial findings in the virus-positive and virus-negative groups. Roosevelt et al showed that the presence of chest x-ray film abnormalities was strongly correlated with the use of antibiotics, but did not examine the effectiveness of antibiotic treatment in these patients. Swin- gler et al examined the impact of chest x-ray films in acute lower respiratory tract infections on clinical outcomes by randomizing 522 infants aged 2 to 59 months to receive or not to receive a chest radiograph. Children in the chest radiograph group were more likely to be diagnosed as having pneumonia or upper respiratory tract infections and were more likely to be treated with antibiotics; children who did not receive a chest radiograph were more likely to be diagnosed as having bronchiolitis. Despite these differences, the median time to recovery was 7 days in both groups.

**UTILITY OF CBC COUNTS IN BRONCHIOLITIS**

Ten studies obtained CBC counts on all patients (Table 6),10,33,38,41-47 In most of these studies, however, the CBC results were not reported or used only to demonstrate that the treatment and control groups were similar at baseline. Saijo et al correlated white blood cell counts in 120 RSV-positive infants with radiologically de-

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<th>Outcome Predicted</th>
<th>Indicators Examined</th>
<th>Predictors</th>
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<tr>
<td>Dawson et al, 1990</td>
<td>Clinical score (mild, moderate, severe, or very severe)</td>
<td>CXR findings (ie, hyperinflation, atelectasis, and infiltrates)</td>
<td>There was no correlation between CXR findings and disease severity</td>
</tr>
<tr>
<td>Mulholland et al, 1990</td>
<td>Severity at the time of admission as assessed by means of oximetry and arterial blood gas results; O2 requirements during admission</td>
<td>Demographics, cyanosis, crackles, chest wall in drawing, RR &gt;50 breaths/min, Liver &gt;2 cm below costal margin, SaO2 &lt;90%, PaO2 &lt;80 mm Hg, Paco2 &gt;45 mm Hg, and RSV status</td>
<td>Indicators of severity at time of admission: young age, cyanosis, and crackles; predictors of oxygen requirement during admission: young age, cyanosis, crackles, high RR, chest wall indrawing, SaO2 &lt;90%, Paco2 &gt;45 mm Hg, Paco2 &gt;45 mm Hg, and PaO2 &lt;60 mm Hg</td>
</tr>
<tr>
<td>Shaw et al, 1991</td>
<td>Mild disease (defined as alert, active, and able to take fluids throughout their disease, no O2 therapy, etc) vs severe disease (defined as all others without mild disease)</td>
<td>Historical information: cyanosis or apnea, gestational age, age &lt;3 mo, decreased oral intake, perinatal complications, and URI symptoms &lt;3 d; physical examination and observations: ill or toxic appearance, Yale Observation Scale score ≥10, accessory muscle use, clinical asthma score ≥2, RR, and rales; and laboratory: pulse oximetry while quiet, pulse oximetry while sucking, CXR findings of atelectasis or hyperaeration, and isolation of RSV</td>
<td>The following 6 independent clinical and laboratory findings were strongly associated with more severe disease using multiple-factor analysis: ill or toxic appearance, oxygen saturation &lt;95%, gestational age &lt;34 wk, RR ≥70 breaths/min, and age &lt;3 mo</td>
</tr>
<tr>
<td>Wright et al, 2002</td>
<td>Illness severity in hospitalized infants with RSV bronchiolitis measured by (1) sum of respiratory illness scores, (2) duration of O2 therapy, (3) length of ventilatory support</td>
<td>Historical information: age; laboratory: serum neutralizing antibody titer; RSV shedding</td>
<td>History of BPD or congenital heart disease and younger age</td>
</tr>
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Abbreviations: BPD, bronchopulmonary disease; CXR, chest x-ray film; RR, respiratory rate; RSV, respiratory syncytial virus; SaO2, arterial oxygen saturation; URI, upper respiratory tract infection.
fined categories of lung disease (ie, lobar pneumonia vs bronchopneumonia vs bronchiolitis). They found that a white blood cell count of greater than 15,000/µL and a neutrophil count of greater than 10,000/µL were more likely in children with lobar pneumonia or bronchopneumonia than in children with bronchiolitis. The 3 disease categories were defined radiologically. None of the studies reporting CBC data demonstrated their utility in diagnosing bronchiolitis or guiding therapy.

Evaluating diagnostic tests for bronchiolitis is problematic because it is a disease that is diagnosed clinically. Thus,
there is no gold standard against which to compare testing strategies. Numerous tests for RSV, the leading cause of bronchiolitis, exist, but the clinical utility of RSV testing has not been demonstrated for any category of patients. The question of whether RSV testing is necessary in patients with bronchiolitis is of interest from the clinical and utilization points of view. Although such testing is commonly used to document the cause of bronchiolitis, knowing the cause rarely changes clinical management or outcomes.

Many institutions require RSV testing of all infants admitted to the hospital; the rationale is to allow cohorting of patients to decrease nosocomial infections. However, no direct evidence from randomized, controlled trials shows that this strategy prevents nosocomial transmission of RSV in children. A more logical strategy, followed by many infection control policies, is to isolate all infants with acute lower respiratory tract infection, regardless of the cause.

Data from clinical trials demonstrate that large numbers of infants with bronchiolitis have abnormalities on chest x-ray films. However, chest x-ray films do not discriminate well between bronchiolitis and other forms of lower respiratory tract infection. Although textbooks suggest that chest x-ray films be considered in the management of bronchiolitis, specific indications are lacking. The data in this review suggest that, in mild disease, chest x-ray films offer no information that is likely to affect treatment and should not be routinely performed. Data from the studies by Roosevelt et al and Swingler et al demonstrate that chest x-ray films may lead to the use of antibiotics, although this was not the focus of either of these studies. Given that most children with bronchiolitis or other forms of acute lower respiratory tract infection have viral infections, it could be argued that chest x-ray films are more likely to lead to inappropriate antibiotic use than to improved clinical outcomes.

Very few data exist on the utility of CBC counts. Although many of the treatment trials collected data on CBC counts, their results were either used to demonstrate that treatment and control groups were similar or not reported at all. Complete blood cell counts are commonly used to assist in determining whether a patient has bacterial disease. The large body of literature on febrile infants demonstrates that the test characteristics for CBC counts vary greatly on the basis of the cutoff used and that elevated white blood cell counts alone have low specificity and positive predictive value. Three studies have looked at bacteremia in febrile infants with bronchiolitis. Greenes and Harper found that the rate of bacteremia was 1 (0.2%) in 411 for subjects with bronchiolitis. Purcell and Fergie reviewed the medical records of 2396 infants admitted to a single hospital and found that 1.6% had positive findings in cultures of blood, urine, or spinal fluid. Both of these studies were retrospective, and CBC count results were not presented. Kupperman et al prospectively studied 163 infants with bronchiolitis and fever and found a 0% rate of bacteremia (95% CI, 0%-1.9%) and a 1.9% rate of urinary tract infections.

Our review has several limitations. First, all systematic reviews are at risk for publication bias. We searched the largest and most relevant databases for published studies but did not seek unpublished data or data maintained by pharmaceutical companies. Second, no search strategy is guaranteed to return all relevant studies. Additional studies may be indexed under terms not used in our search. To decrease the likelihood of missing important studies, we asked a technical advisory group of

<table>
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<th>Source</th>
<th>Purpose of Study</th>
<th>Use of CBC in Study</th>
<th>Results</th>
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<tbody>
<tr>
<td>Barry et al, 1986</td>
<td>RCT of ribavirin in acute bronchiolitis</td>
<td>Baseline assessment, completion of study</td>
<td>CBC results not reported</td>
</tr>
<tr>
<td>Can et al, 1998</td>
<td>RCT of salbutamol sulfate vs mist</td>
<td>Baseline assessment</td>
<td>Mean WBC, neutrophil, eosinophil, Hb, and Hct levels similar in 3 study groups</td>
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<tr>
<td>Chippa et al, 1993</td>
<td>RCT of interferon alfa-2a in hospitalized infants</td>
<td>Baseline assessment, day 5 of study</td>
<td>CBC results not reported</td>
</tr>
<tr>
<td>De Boeck et al, 1997</td>
<td>RCT of dexamethasone hospitalized infants</td>
<td>Baseline assessment</td>
<td>No difference in leukocyte count and eosinophilia between treatment groups</td>
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<tr>
<td>Friis et al, 1984</td>
<td>RCT of antibiotics in treatment of pneumonia and bronchiolitis</td>
<td>Baseline assessment</td>
<td>CBC results for bronchiolitis vs pneumonia not compared</td>
</tr>
<tr>
<td>Kjellhede et al, 1995</td>
<td>RCT of vitamin A in ALRI</td>
<td>Baseline assessment</td>
<td>CBC results not reported</td>
</tr>
<tr>
<td>Kong et al, 1993</td>
<td>RCT of Chinese herbs in hospitalized infants</td>
<td>Baseline assessment</td>
<td>CBC results not reported</td>
</tr>
<tr>
<td>Rodriguez et al, 1987</td>
<td>RCT of ribavirin in infants with RSV disease (included patients with bronchiolitis, pneumonia, and croup)</td>
<td>Baseline assessment</td>
<td>No differences between treatment groups</td>
</tr>
<tr>
<td>Saijo et al, 1996</td>
<td>Finding of lobar pneumonia vs bronchopneumonia vs bronchiolitis in hospitalized infants with RSV ALRI</td>
<td>WBC &gt; 15 × 10⁹/L; neutrophil count &gt; 10 × 10⁹/L; ESR &gt; 30 mm/h; and CRP level &gt; 3.0 mg/dL</td>
<td>The percentages of all 4 indicators were higher in patients with RSV lobar pneumonia vs bronchiolitis or bronchopneumonia</td>
</tr>
<tr>
<td>Taber et al, 1983</td>
<td>RCT of ribavirin in hospitalized infants</td>
<td>Baseline assessment, time of discharge, and follow-up</td>
<td>No differences between treatment groups; no differences from admission to discharge to follow-up</td>
</tr>
</tbody>
</table>

Abbreviations: ALRI, acute lower respiratory tract infection; CBC, complete blood cell; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; Hct, hematocrit; RCT, randomized controlled trial; RSV, respiratory syncytial virus; WBC, white blood cell.
Despite the large number of clinical trials and prospective cohort studies of bronchiolitis, evidence-based indications for RSV and other supportive testing do not exist. The data available suggest that such testing does not alter clinical outcome. This systematic review justifies a prospective clinical trial to address these questions that uses clinically relevant outcomes such as hospitalization rates, length of hospital stay, time to complete recovery, costs of care, and consequences of false-positive and false-negative test findings.

content experts to review our final list to identify missing studies. Third, our exclusion of non-English studies may have introduced bias as well, although most systematic reviews published in the United States use similar exclusions. Finally, we were not able to analyze quantitatively the data in this review because of the heterogeneity of the studies.

Despite the high prevalence of bronchiolitis, little consensus exists on optimal management.1,2,5,6,9 Diagnostic and supportive testing is common, but data demonstrating appropriate indications and efficacy of such testing do not exist. Wilson et al9 demonstrated wide institutional variations in the care of hospitalized infants with bronchiolitis that were not explained by disease severity. These variations correlated significantly with hospital costs and length of stay.

Perlstein et al,10 Adcock et al,35 and Kotagal et al36 have all demonstrated that evidence-based guidelines can be used to decrease the frequency of RSV testing, chest x-rays, and bronchodilator use in infants hospitalized with bronchiolitis. These studies demonstrated significant decreases in length of stay and no changes in readmission rates. These studies did not purport to test the utility of RSV testing, chest x-ray films, or CBC counts, but their findings suggest that the routine use of such testing is unnecessary. Additional prospective trials in emergency departments and other outpatient settings will help to validate these findings.

We recognize that, in some clinical situations, the cause of an infant’s illness can significantly affect the need for additional workup; examples include infants younger than 2 months with fever and signs of lower respiratory tract disease. Complete blood cell counts and chest x-rays can be useful in patients with unusual clinical courses or severe disease. However, in most infants with bronchiolitis, the limited evidence available does not support routine use of RSV testing, chest x-ray films, or CBC counts. Given the high prevalence of bronchiolitis, prospective trials of diagnostic and supportive testing are feasible and needed. Clinicians are understandably reluctant to change management practices without high-quality evidence to guide them.

Accepted for publication October 2, 2003.

This study was conducted by the RT International/University of North Carolina Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality, Rockville, Md (contract 290-97-0011). The full report is available at: http://www.ahrq.gov/clinic/evrptfiles.htm#bronch. The authors of this article are responsible for its content, including any clinical or treatment recommendations.

We thank Marian James, PhD, the Agency for Healthcare Research and Quality task order officer, for her assistance with this project. In addition, we thank the following members of our Technical Expert Advisory Group, who provided input and advice for the full evidence report on which this article is based: Henry L. Dorkin, MD, Cystic Fibrosis Center, Newton, Mass; Bernard Ewigman, MD, MSPH, School of Medicine, University of Missouri–Columbia; Glenn Flores, MD, Boston University School of Medicine, Boston, Mass; Anne Haddix, PhD, Rollins School of Public Health, Emory University, Atlanta, Ga; Allan S. Lieberthal, MD, Southern California–Permanente Medical Group, Panorama City, Calif; Jonathan L. Temte, MD, PhD, Department of Family Medicine, University of Wisconsin, Madison; and Steve Wegner, MD, NC Access, Inc, Morrisville, NC. We are indebted to our colleagues at RTI International and the University of North Carolina at Chapel Hill for their support in the development of this article. At RTI International, we thank Amanda Honeycutt, PhD, and John Wittenborn for their work on the cost-effectiveness analysis of the full report; Lorraine Monroe for superior secretarial assistance; Nash Herndon, MA, for editing expertise; and Linda Lux, MPA, and Philip Salib for technical assistance on the project. At the University of North Carolina, we acknowledge Sonya Harris-Hayward, MD, and Mary Maniscaldo, MD, for data abstraction; Cheryl Coon, PhD, for methods abstraction; and Joy Harris and Donna Curusi for superior research assistance.

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