Evidence Report/Technology Assessment
Number 69

Management of Bronchiolitis in Infants and Children

Agency for Healthcare Research and Quality

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Management of Bronchiolitis in Infants and Children

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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. 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 prior to their release.

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 written comments on this evidence report. They may be sent to: Acting Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 6010 Executive Blvd., Suite 300, Rockville, MD 20852.

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In addition, we extend our appreciation to the members of our Technical Expert Advisory Group (TEAG), who served as vital resources throughout our process. They are: Henry L. Dorkin, M.D., Massachusetts General Hospital and Harvard Medical School, Boston, Mass; Bernard Ewigman, M.D., M.S.P.H., School of Medicine, University of Missouri-Columbia, Columbia, Mo; Glenn Flores, M.D., Boston University School of Medicine, Boston, Mass; Anne Haddix, Ph.D., Rollins School of of Public Health, Emory University, Atlanta, Ga; Allan S. Liberthal, M.D., (representing the American Academy of Pediatrics) Southern CA-Permanente Medical Group, Panorama City, Calif; H. Cody Meissner, M.D., New England Medical Center, Boston, Mass; Jonathan L. Temte, M.D., Ph.D., (representing the American Academy of Family Physicians), Department of Family Medicine, University of Wisconsin, Madison Wis; and Steve Wegner, M.D., NC Access, Inc, Morrisville, NC.

We owe our thanks as well to our external peer reviewers, who provided constructive feedback and insightful suggestions for improvement of our report. Other peer reviewers were: Alan H.Cohen, M.D., Senior Director, Medical Affairs, MedImmune Inc. and Johns Hopkins Medical School, Gaithersburg, Md; Jeffrey M. Ewig, M.D., Pediatric Pulmonary Associates, PA, St. Petersburg, Fla; Anne Haddix, Ph.D., Rollins School of Public Health, Emory University, Atlanta, Ga; Elizabeth Susan Hodgson, M.D., Princeton, NJ; Allan S. Liberthal, M.D., Southern CA-Permanente Medical Group, Panorama City, Calif; Michael Light, M.D., University of Miami, North Miami Beach, Fla; H. Cody Meissner, M.D., New England Medical Center, Boston, Mass; Jeff Michael, D.O., University of Missouri-Columbia, Columia, Mo; and Tonse NK Raju, M.D., National Institute of Child Health and Human Development, Washington, DC.

Structured Abstract

Objectives. This systematic review seeks to clarify the existing knowledge base for the management of bronchiolitis and offers directions for future research. Specifically, the review addresses the effectiveness of appropriate diagnostic tools, the effectiveness of pharmaceutical therapies for treating bronchiolitis, the role of prophylactic therapy for prevention of bronchiolitis, and the cost-effectiveness of such prophylactic therapy.

Search strategy. The reviewers in conjunction with an expert panel generated admissibility criteria for each question and derived relevant terms to search the literature in three databases: MEDLINE®, Cochrane Collaboration Library, and Health Economic Evaluations Database (HEED).

Selection criteria. For the key question on diagnosis, the investigators included prospective cohort studies and randomized controlled trials (RCTs). To ensure greater strength of evidence for interventions, the investigators raised admissibility criteria to allow only RCTs for the key questions on treatment and prophylaxis. For the cost-effectiveness of prophylaxis, studies that employed economic analysis were reviewed. For all studies, key inclusion criteria included outcomes that were both clinically relevant and able to be abstracted. The investigators set a minimum sample size of 10; small case series and single case reports were excluded. Studies in languages other than English were not reviewed. The reviewers initially identified 744 abstracts for possible inclusion. Upon full review, a total of 83 articles for this systematic review were retained.

Data collection and analysis. A team of abstractors reviewed and abstracted information on study methodology and results into a data abstraction form. The Study Director entered data from studies on treatment and prophylaxis into evidence tables. The Scientific Directors performed quality control assessments of the evidence tables against the original article and independently assigned quality scores to each article. When they did not agree, the Scientific Directors reviewed the article together and arrived at a consensus.

Results and discussion. The diagnosis of bronchiolitis is primarily clinical; therefore, only limited literature is available on effectiveness of diagnostic tools for diagnosing bronchiolitis in infants and children. Only one study supported the clinical usefulness of diagnostic testing. Thus, the existing data do not support routine laboratory, radiologic, or other types of testing over purely clinical criteria to diagnose bronchiolitis.

The volume of literature is much greater for effectiveness of treatments. Trials included tested 15 classes of interventions (e.g., bronchodilators, steroids, antibiotics). However, the strength of evidence was limited by trials that were underpowered and outcomes that were not comparable across studies. At present, evidence is insufficient to recommend any of the treatments studied over good supportive care of affected infants and children. However, several interventions did show some potential for being efficacious and should be subjected to rigorously designed, adequately sized trials.

This review of the literature on respiratory syncytial virus immunoglobulin (RSVIG) suggests that it is effective for prophylaxis in high-risk infants and children who have underlying

bronchopulmonary dysplasia (BPD) or have been born prematurely and are less than 6 months of age. Use of prophylaxis in at-risk groups that were excluded from prior studies would need to be studied or reported before these agents can be recommended more broadly for other groups of infants and children at increased risk of more severe bronchiolitis.

When all costs of prophylaxis are adjusted to 2002 dollars, previous studies report incremental costs of prophylactic therapy for infants from 32 through 35 weeks' estimated gestational age (EGA) ranging from saving of $46,400 to costs of $535,400. Given these variations, evidence is insufficient at the present time to calculate the cost-effectiveness of administration of a prophylaxis for bronchiolitis in infants in this age group or who are premature with comorbidities.

Future research. Both specific and general recommendations for future research were identified.

Specific recommendations are:

1. Ancillary testing is common practice, but no data demonstrate the utility of such testing. Therefore, prospective trials of the utility of ancillary testing (chest x-rays, complete blood tests, respiratory syncytial virus [RSV] testing) should be considered. These should report clinical outcomes that are important to parents and clinicians, such as the change in physician management.

2. The following interventions should be studied in rigorously designed, adequately powered trials: nebulized epinephrine, nebulized salbutamol plus ipratropium bromide, nebulized ipratropium bromide, oral or parenteral corticosteroids, and inhaled corticosteroids. Despite the lack of evidence on the efficacy of these treatments, clinicians are likely to continue their use unless a large simple trial of the most common interventions is mounted.

3. Better estimates of the cost of palivizumab administration, hospitalization costs for infants who do do not receive palivizumab, and RSV hospitalization rates are needed to assess the cost-effectiveness of RSV prophylaxis. In particular, additional data are needed on the material and time costs of administration for parents and providers, the actual cost of palivizumab to providers and family, the consequences of palivizumab on long-term wheezing and chronic asthma, and the societal costs of morbidity.

General recommendations are:

1. Clinically relevant outcomes should be chosen for future studies. Examples of these types of outcomes for intervention studies are rates of hospitalization, need for more intensive services in the hospital, costs of care, parental satisfaction with treatment, and development of chronic asthma.

2. Studies should be powered to detect meaningful differences in clinically relevant outcomes. Power calculations must include sufficient numbers to account for multiple comparisons if multiple outcomes are to be measured.

3. Future investigations should carefully monitor and report adverse events associated with treatments; without this information determining whether the risks of particular treatments are low enough to support their clinical use is difficult.

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Management of Bronchiolitis in Infants and Children

Summary

Overview

Bronchiolitis is the most common lower respiratory tract infection in infants. Most infants and young children experience only a mild form of bronchiolitis, and they are managed on an outpatient basis. However, bronchiolitis-associated hospitalizations have increased considerably since 1980. Annual bronchiolitis hospitalization rates increased appreciably from 1988 to 1996, although hospitalization rates for lower respiratory tract diseases excluding bronchiolitis did not vary significantly during this time period.

The diagnosis of bronchiolitis is generally clinical. Whether diagnostic tests change the clinical course, management, or prognosis of the disease is unclear. Given the high incidence of disease among infants and children, different treatment modalities have been in practice for some years. Some of these therapies are specific to the virus (e.g., ribavirin); others are symptomatic (e.g., bronchodilators, corticosteroids). Evidence on their efficacy is conflicting. The relative severity of the disease among vulnerable subpopulations suggests that some infants and children may benefit from prophylactic therapy, although the cost-effectiveness of available interventions needs to be explored.

Given these issues of diagnosis, treatment, prophylaxis, and cost of prophylaxis, a systematic review of the evidence on the management of bronchiolitis is of interest to a wide audience. Interested parties include clinicians, health care providers, hospitals, and managed care organizations as well as patient and consumer organizations. The management of patients with this ailment is of particular concern to the American Academy of Pediatrics (AAP) and the American Academy of Family Physicians (AAFP), which nominated the topic for the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Program. The RTI-University of North Carolina Evidence-based Practice Center was chosen to undertake a systematic review of several aspects of this issue, including diagnosis, treatment, prophylaxis, and the cost-effectiveness of prophylaxis among significantly premature infants (32 to 35 weeks) and premature infants with comorbidities. To discharge this responsibility, the authors systematically reviewed and synthesized 83 articles on the management of bronchiolitis. In addition to summarizing the existing knowledge base, they identified limitations in the current literature and identified priorities for future research. As part of this effort, an eight-person Technical Expert Advisory Group (TEAG) provided assistance throughout the project.

Reporting the Evidence

This systematic review seeks to clarify the existing knowledge base for the management of bronchiolitis and offers directions for future research. Specifically, the review addresses four key questions:

1. *What is the effectiveness and relative effectiveness of appropriate diagnostic tools for diagnosing bronchiolitis in infants and children? Diagnostic tools might include chest x-ray and laboratory screening tests.*
2. *What is the efficacy or effectiveness of pharmaceutical therapies for treating bronchiolitis among infants and children? Therapies to be considered include corticosteroids, bronchodilators, antimicrobial*

agents, antiviral agents, and others. Does the evidence show that any single agent (or any single antimicrobial) is the most effective in improving outcomes?

3. *What is the role of prophylactic therapy for prevention of bronchiolitis among children? Are there any specific subpopulations within this group who would benefit from such prophylaxis?*
4. *What is the evidence concerning the cost-effectiveness of prophylactic therapy for prevention of bronchiolitis among infants born from 32 through 35 weeks of estimated gestational age (EGA) and premature infants with comorbidities?*

Methodology

This systematic review of the literature involved conducting a comprehensive literature identification and screening process, abstracting relevant information from the eligible articles, and generating summary evidence tables that present the key details and findings for the articles. In conjunction with the TEAG, the authors generated admissibility criteria for each question and derived relevant terms to search the literature in three databases: MEDLINE®, Cochrane Collaboration Library, and the Health Economics Evaluation Database (HEED).

For the key question on diagnosis, the investigators allowed both prospective studies and randomized controlled trials (RCTs). To ensure greater strength of evidence for interventions, the admissibility criteria were raised to allow only RCTs for the key questions on treatment and prophylaxis. For the cost-effectiveness of prophylaxis (Key Question 4), studies that employed economic analysis were reviewed. For all studies, key inclusion criteria included outcomes that were both clinically relevant and able to be abstracted. The investigators set a minimum sample size of 10; small case series and single case reports were excluded. Studies in languages other than English did not meet the admissibility criteria. Initially 744 abstracts were identified for possible inclusion in the analysis. Upon further review, the investigators retained a total of 83 articles for this systematic review.

A team of abstractors reviewed and abstracted information on study methodology and results into a data abstraction form. The Study Director entered studies on treatment and prophylaxis into evidence tables. The Scientific Directors reviewed the evidence tables and independently assigned quality scores to each article. When they did not agree, they reviewed the article together and arrived at a consensus. Of the 61 articles that were scored for quality for Key Questions 2 and 3, the Scientific Directors had an initial 98 percent rate of agreement within 1 point.

A trained abstractor completed a detailed data abstraction form. The Study Director used the forms and the original articles to generate summary evidence tables. The Scientific Directors performed quality control checks through review of the evidence tables against the original articles.

Findings

Diagnosis

Specific literature regarding diagnosis of bronchiolitis was not found. The disease is clinically defined using well-accepted criteria. A large amount of data exists on the use of a variety of supportive laboratory tests such as specific respiratory syncytial virus (RSV) assays, complete blood counts (CBCs), and chest x-rays. However, only 1 of 16 studies supported the clinical usefulness of such information. Thus, the existing data do not support the usefulness in testing to diagnose bronchiolitis.

The question of whether testing affects management and clinical outcome is more difficult to answer. Testing that can predict disease severity or worse clinical outcomes theoretically would be useful. One study suggests that testing may help identify patients likely to have more severe disease; however, five of the six predictors that emerged were based on history and physical examination (i.e., age, gestational age, general appearance, respiratory rate, and pulse oximetry).

Many clinicians are concerned that patients with more severe disease may have "bacterial superinfections." This may result in the addition of antibiotics to a patient's treatment. Such concerns are typically based on illness severity, chest x-ray appearance, and an elevated white blood count. No data were found to support these assumptions.

Treatment

The authors reviewed the efficacy or effectiveness of several major classes of pharmaceutical agents that have been studied in multiple RCTs as interventions for bronchiolitis. These classes of agents included epinephrine, beta-2 agonist bronchodilators such as albuterol or salbutamol, ipratropium bromide, oral and inhaled corticosteroids, ribavirin, and antibiotics. In addition, they located several interventions for which limited, single-trial evidence existed, such as surfactant and nebulized furosemide. Treatments for bronchiolitis for which there was strong and convincing evidence of effectiveness were not identified. However, the investigators did find several interventions that they believe show some potential for being efficacious and should be subjected to rigorously designed, adequately sized trials. These include nebulized epinephrine, nebulized salbutamol plus ipratropium bromide, nebulized ipratropium bromide, oral or parenteral corticosteroids (preferably dexamethasone), and inhaled corticosteroids (preferably budesonide). Two interventions in this category are applicable only to the most severely ill children: inhaled helium-oxygen and surfactant for ventilated children. Given that there is no current best treatment for bronchiolitis, the authors recommend that the above mentioned interventions should be studied in large, well-designed studies. In such studies, it is appropriate to use placebos in the comparison group when feasible; however, all subjects must be given standard supportive care.

This literature review also revealed several commonly used treatments for which the data are sufficient to reject, or at least doubt, their efficacy as treatments for bronchiolitis. These interventions are aerosolised ribavirin, antibiotics, nebulized furosemide, intravenous respiratory syncytial virus immunoglobulin (RSVIG IV) (as a treatment rather than as a prophylactic agent), inhaled alpha-interferon, and nebulized recombinant human deoxyribonuclease (rhDNase). Although the studies of these drugs were usually underpowered as well, because of lack of evidence of efficacy and a potential for increased harm with some, the investigators recommend that clinicians not use these treatments routinely. These drugs should be considered for treatment only as part of rigorously designed, controlled trials.

This literature review found two treatments for which occurrence of adverse events in studies warrants caution in their use until such time as trials with adequate power to detect adverse events are conducted. These treatments are inhaled budesonide and alpha-2-interferon. This is particularly important in the case of inhaled budesonide because this agent also appeared to confer at least modest benefit for some outcomes in some studies of its use.

No evidence that any single agent can be recommended for treatment of bronchiolitis was identified. At present, evidence is insufficient to recommend any of the treatments studied over good supportive care of affected infants and children.

Prophylaxis

Although most children who have bronchiolitis do well and have an uncomplicated disease with a self-limited course, for some children it is a serious and sometimes life-threatening illness. For the most part, these severely affected infants and children have coexisting conditions that put them at increased risk of complications. One of the objectives of this review was to assess whether prophylactic therapy has a role for prevention of severe RSV bronchiolitis and in particular whether any subpopulations might realize greater benefit from prophylaxis. The largest group of at-risk children are those born prematurely, who often have concurrent chronic lung disease (CLD). Palivizumab or RSVIG IV given on a monthly basis is effective for prophylaxis in high-risk infants and children who have underlying CLD or have been born prematurely and are less than 6 months of age. Clinically, palivizumab has largely supplanted RSVIG IV because of the former's ease of administration, lower incidence of adverse events, and increased efficacy.

None of the studies of immunization of at-risk infants with purified F protein (PFP) vaccines demonstrated benefit, although in some studies, older children with cystic fibrosis did seem to obtain some benefit from a similar vaccine. However, these types of vaccines are at early stages of development and the studies were small. An effective vaccine would be a preferable strategy for prevention of RSV bronchiolitis in at-risk children compared to the passive immunity created by monthly injections of RSVIG. Because of the early nature of the research and the potential benefits, RSV vaccine research should be encouraged.

Costs of Prophylaxis

Findings from the published literature vary widely, depending on the cost of prophylactic therapy assumed, the hospitalization and other health care costs assumed, the baseline rate of hospitalization for children with RSV bronchiolitis, and reductions in hospitalization rates associated with the use of palivizumab. When all costs are adjusted to 2002 dollars, results from the previous studies suggest that prophylactic therapy for infants from 32 through 35 weeks of estimated gestational age ranges from cost saving—meaning that the expected value of avoided health care utilization is greater than the costs of prophylactic therapy—to an upper bound of over $500,000. Given these variations, evidence is insufficient at the present time to calculate accurate expected incremental costs, or cost per hospitalization avoided, resulting from administration of a prophylaxis in infants who were born 32 through 35 weeks EGA or who are premature with comorbidities.

Future Research

Because the diagnosis of bronchiolitis is primarily clinical, little published literature exists on the relative effectiveness of diagnostic tools on the management of bronchiolitis. The volume of literature is much greater for questions regarding the effectiveness of treatments and prophylaxis; however, the strength of evidence was limited by trials that were underpowered and outcomes that were not comparable across studies. The cost-effectiveness of prophylaxis in vulnerable subpopulations cannot be fully addressed without additional data on hospitalization rates and social costs, which currently are widely variable. In addition, the evidence for cost-effectiveness will need review upon release of new trial data on palivizumab.

These significant gaps in the literature foster priorities for research. In addition, suggested guidelines for the choice of outcomes and study design that will improve the reporting of research findings and allow meaningful comparisons of study results are presented.

Priorities

Diagnosis. Prospective trials of the utility of ancillary testing (chest x-rays, complete blood tests, RSV testing) are feasible and should be performed. Studies of diagnostic tools used in the management of bronchiolitis should measure clinical outcomes that are important to both parents and clinicians. An important intermediate outcome for studies of diagnosis in the management of bronchiolitis is the change in physician management.

Treatment. The following interventions should be studied with well-designed, rigorously conducted RCTs, preferably with

placebo control: (a) nebulized epinephrine; (b) nebulized salbutamol plus ipratropium bromide; (c) nebulized ipratropium bromide; (d) oral corticosteroids, preferably dexamethasone; (e) inhaled budesonide; (f) inhaled helium-oxygen for severely ill children; (g) Chinese herbal therapy with Shuang Huang Lian (if its use can be practically accomplished in U.S. settings); and (h) surfactant for ventilated children. Studies of interventions should measure outcomes of primary interest to parents and clinicians, such as hospitalization, duration of hospitalization, need for more intensive care, and development of longer-term respiratory problems.

The treatment studies which were reviewed were almost universally underpowered and, as such, do not give clinicians adequate guidance for management of bronchiolitis. There is substantial evidence that clinicians commonly use several interventions for which, currently, evidence is insufficient. These treatment interventions include inhaled bronchodilators, inhaled corticosteroids, and inhaled epinephrine. These drugs are all available as generic products and, therefore, are relatively inexpensive; clinicians also consider them to be safe. The investigators believe that clinicians will continue to use these types of treatments unless a large simple trial of these most common interventions is mounted. Such a trial would need to be large enough to examine each of the interventions not only in the overall population, but also in subpopulations of interest (e.g. infants with and without a history of atopy). This type of trial is unlikely to be funded by industry and would therefore require governmental support.

Prophylaxis. Use of prophylaxis in at-risk groups that were excluded from prior studies would need to be studied or reported before these agents can be recommended more broadly for other groups of infants and children at increased risk of more severe bronchiolitis. (At the time this report was written, findings from a study of prophylaxis with palivizumab including 1,287 children less than 2 years of age with congenital heart disease were expected to be reported at the AAP meeting on October 18, 2002. This study should give definitive evidence regarding prophylaxis for children with both cyanotic and acyanotic congenital heart disease.)

Studies of palivizumab prophylaxis should examine the effect on long-term outcomes such as the development of symptoms such as wheezing, development of bronchiolitis, hospitalization, and severe disease. The question of the relationship between bronchiolitis and asthma remains unanswered and is beyond the scope of this report. However, if the question is answered through a basic science study, and there is evidence of a causative relationship, this would have significant impact on questions of prevention and the costs of prophylaxis.

RSV vaccine research should be encouraged as it would replace the need for prophylaxis.

Cost-effectiveness of prophylaxis. Current cost-effectiveness analyses of palivizumab prophylaxis do not provide accurate incremental cost or cost-effectiveness ratios. Wide variations in available parameter estimates have resulted in wide ranges in reported incremental costs and costs per hospitalization avoided. Data on important parameters such as long-term health consequences, social costs, and the efficacy and safety of palivizumab on infants with comorbidities other than CLD were not available for previous analyses, but they may be available in the near future. The cost-effectiveness of palivizumab prophylaxis should be reassessed as the new clinical trial data on palivizumab prophylaxis among infants in at-risk groups that were excluded from prior studies become available.

A new cost-effectiveness analysis should attempt to incorporate more social cost components and improved parameter values, and it should address as many subpopulations as possible by combining trial data on palivizumab safety and effectiveness from the IMpact-RSV and other new trials. Accurate social cost estimates for prophylaxis costs and hospitalization and outpatient utilization costs by cohort for each subgroup may influence cost-effectiveness ratios for each subpopulation. Prophylaxis cost estimates should reflect true costs to society, including identification of accurate palivizumab acquisition costs. As data become available, palivizumab's effects on long-term respiratory health should be addressed. Additional social costs would identify actual out-of-pocket expenses and productivity loss incurred by the family due to prophylaxis administration as well as RSV hospitalization and ambulatory care.

Accurate data on long-term consequences and family burden will help to integrate quality of life with costs in an economic evaluation. Current cost-effectiveness analyses report results in terms of incremental costs or cost per hospitalization avoided. Such measures do not fully quantify additional social burdens that RSV morbidity poses for infants and children and their families, and they do not provide guidance to policymakers when faced with the decision of determining acceptable limits on cost-effectiveness.

General Guidelines

Investigators should choose clinically relevant outcomes in future studies. Most of the outcomes studied in this literature are short-term and surrogate variables one measures, such as oxygen saturation or respiratory rate at 15-minute intervals after treatment. Investigators should concentrate on measuring outcomes that are of interest to parents, clinicians, and health systems. Examples of these types of outcomes for intervention studies are rates of hospitalization, need for more intensive services in the hospital, costs of care, parental satisfaction with treatment, and development of chronic asthma. An important intermediate outcome for studies of diagnosis in the management of bronchiolitis is the change in physician management.

Studies should be powered to detect meaningful differences in clinically relevant outcomes. Power calculations must

include sufficient numbers to account for multiple comparisons if multiple outcomes are to be measured.

Few studies reported adverse events associated with treatments. This gap hampers any determination of whether the risks of particular treatments are sufficient to exclude their clinical use. Future investigations should carefully monitor and report adverse events associated with treatments.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for AHRQ by the RTI International*–University of North Carolina at Chapel Hill Evidence-based Practice Center under Contract No. 290-97-0011. It is expected to be available in spring 2003. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 69, *Management of Bronchiolitis in Infants and Children*. Internet users will be able to access the report online through AHRQ's Web site at www.ahrq.gov.

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Evidence Report

1. Introduction

Background

Bronchiolitis is a viral infection of the lower respiratory tract.[1] This disease is characterized by acute inflammation, edema, and necrosis of epithelial cells lining small airways, increased mucus production, and bronchospasm. All these mechanisms obstruct the small airways. Clinically the disease is characterized by rhinitis, rapid breathing (tachypnea), wheezing, cough, crackles, use of accessory muscles, and/or nasal flaring. The disease can be classified as mild (managed as an outpatient), moderate (requiring hospitalization), or severe (resulting from respiratory failure requiring ventilatory support). Disease severity is directly related to an infant's age, size, the presence of other underlying diseases (e.g., prematurity, chronic lung disease [CLD] or bronchopulmonary dysplasia [BPD], congenital heart disease), multiple birth, siblings at home.[2,3]

Bronchiolitis is the most common lower respiratory tract infection in infants. Each year 21 percent of North American infants develop lower respiratory tract disease. Up to 3 percent of all children in their first year of life are hospitalized with bronchiolitis.[1] Respiratory syncytial virus (RSV) is responsible for 70 percent of all cases overall and 80 percent to 100 percent in winter months. Parainfluenza, adenovirus and influenza account for most of the remaining cases.[4]

Most infants and young children experience only a mild form of bronchiolitis, and they are managed on an outpatient basis. However, bronchiolitis-associated hospitalizations have increased significantly since 1980. Among children younger than one year, annual bronchiolitis hospitalization rates increased 2.4-fold, from 12.9 per 1000 in 1980 to 31.2 per 1000 in 1996. During 1988 to 1996, infant hospitalization rates for bronchiolitis increased significantly ($P < 0.001$), while hospitalization rates for lower respiratory tract diseases excluding bronchiolitis did not vary significantly ($P = 0.20$). The proportion of hospitalizations for lower respiratory tract illnesses among children younger than 1 year associated with bronchiolitis increased from 22.2 percent in 1980 to 47.4 percent in 1996.[5]

Clinical Issues

Diagnosis

Diagnosis of bronchiolitis is based primarily on history and physical examination alone. Infants with fever, rhinitis, tachypnea and wheezing between November and May can be presumed to have bronchiolitis. Most bronchiolitis occurs in winter months. Because some types of parainfluenza virus are present in other months, bronchiolitis can be seen year round.

Various laboratory studies can provide supportive data to the diagnosis, but none is highly sensitive or specific. Examples include chest x-ray and complete blood counts.

Specific testing can be done to determine the etiology of bronchiolitis (i.e., RSV vs. parainfluenza). Diagnostic methods include viral isolation, immunofluorescence, and enzyme-linked immunosorbent assays (ELISA) that detect antigen. Most clinicians use the RSV ELISA (e.g., a rapid test), which is performed on a specimen of nasal washing. These kits have sensitivities that range from 80 percent to 90 percent.[6]

The clinical utility of specific etiologic testing in cases of bronchiolitis is debatable. Such testing may be useful if other diagnoses are in the differential diagnosis (e.g., pneumonia or congestive heart failure) or if, in rare situations, treatment with ribavirin is being considered. In the vast majority of cases, however, determining that RSV is the cause of an individual case of bronchiolitis does little to change clinical course, management, or prognosis. In some institutions, evidence-based guidelines have been developed specifically to decrease the use of both RSV ELISA and supportive diagnostic testing.[7]

Treatment

Treatments for bronchiolitis can be categorized as specific and symptomatic. No specific therapy exists for parainfluenza virus. The only specific therapy for RSV is aerosolized ribavirin. Administration of ribavirin has been associated with improved oxygenation, improved clinical scores, and diminished levels of secretory mediators of inflammation associated with severe wheezing and disease. The use of ribavirin in certain infants at high risk of serious RSV disease was initially endorsed by the American Academy of Pediatrics (AAP) in 1993 based on initial carefully controlled clinical trials. However, the AAP modified the recommendation in 1996 from "should be used" to "may be considered" after several subsequent trials showed no significant effect on clinical outcomes. The use of ribavirin is further constrained by its high cost and possible risk to health care personnel who administer it.[8]

Among the popular symptomatic treatments are bronchodilators and corticosteroids. The widespread use of beta 2-agonist bronchodilators in bronchiolitis is likely explained by the similarity of symptoms and signs of bronchiolitis and asthma. However, the data to support their effectiveness in bronchiolitis are conflicting. Two systematic reviews have been published, the most recent one updated in 2001.[9,10] Kellner et al. examined 20 randomized controlled trials (RCTs) and found a statistically significant increase in the proportion of bronchodilator-treated infants demonstrating an improvement in their confidence interval [CI] 0.19 to 0.45).[10] Bronchodilator recipients did not show improvement in measures of oxygenation with a difference favoring the control population (pooled difference 0.7; 95% CI 0.36 to 1.35). The rate of hospitalization was not significantly reduced in bronchodilator recipients compared with controls (odds ratio [OR] 0.7; 95% CI 0.36 to 1.35). Hospitalization duration was also not reduced in bronchodilator recipients (pooled difference 0.19 days; 95% CI -0.3 to 0.5).

Flores and Horwitz found no evidence that beta 2-agonists either improved oxygen by a clinically significant amount or reduced admission rates from outpatient and emergency department settings.[9]

Infants with bronchiolitis have been treated with corticosteroids because they are well-known anti-inflammatory agents acting at a multitude of cellular levels.[11] Clinicians have considered them for use in infants with acute bronchiolitis, partly because of the clear benefits of steroids in

children with acute asthma. However, as with inhaled beta 2-agonists, data supporting the use of corticosteroids are conflicting. Clarification of potential benefit is of particular importance when the well-known adverse effects of corticosteroids are considered. Reported side effects from short-term administration include hypertension, hyperglycemia, hyponatremia, hypokalemic alkalosis, irritation and/or ulceration, and avascular necrosis in bones. However, serious side effects from short term administration over a few days such as might be used for bronchiolitis or an asthma exacerbation are rare.

Garrison et al. recently published a meta-analysis of six randomized trials performed with hospitalized infants.[11] Infants who received corticosteroids had a mean length of stay (LOS) or duration of symptoms (DOS) that was 0.43 days less than those who received the placebo treatment (95% CI: -0.81 to -0.05 days). The effect size for mean clinical score was -1.60 (95% CI: -1.92 to -1.28), favoring treatment. They concluded that the combined, published reports of the effect of systemic corticosteroids on the course of bronchiolitis suggest a statistically significant improvement in clinical symptoms, LOS, and DOS. Although the authors found a positive effect, they excluded several potentially relevant studies, and the clinical significance of an effect size of 1.6 is unclear. The *2000 Red Book* states: "In previously healthy infants with RSV bronchiolitis, corticosteroids are not effective and are not indicated."[6]

The AAP Committee on Infectious Diseases made recommendations about treatment for bronchiolitis in the *2000 Red Book*.[6] The group recommends supportive care as needed, including hydration, supplemental oxygen, and mechanical ventilation as the primary treatment modalities for bronchiolitis. Corticosteroids are judged to be ineffective and not indicated for previously healthy infants with RSV bronchiolitis. The committee states that antibiotics are rarely indicated as bacterial lung infection and bacteremia are uncommon in infants with bronchiolitis.

Prophylaxis for RSV infection with either RSVIG IV or palivizumab are recommended for infants and children younger than 2 years of age with chronic lung disease who have required treatment for chronic lung disease within 6 months prior to the anticipated RSV season. Palivizumab is the preferred agent for most children because of its ease of administration as an IM injection. Patients with more severe chronic lung disease may be considered for prophylaxis for two RSV seasons.

The recommendations also state that infants born at 32 weeks of gestation or earlier without chronic lung disease may benefit from prophylaxis with the primary considerations being gestational age and chronological age at the beginning of the RSV season. Infants born at 28 weeks of gestation or earlier may benefit from prophylaxis up to 12 months of chronological age while infants born at 29 to 32 weeks may benefit most up to 6 months of chronological age.

Until more data are available the AAP does not generally recommend these prophylactic agents for infants born between 32 and 35 weeks of gestation who do not have additional risk factors. Palivizumab and RSVIG IV are not currently licensed by the U.S. Food and Drug Administration (FDA) for patients with congenital heart disease. However, if the infant has chronic lung disease and/or was born prematurely and has asymptomatic acyanotic congenital heart disease then the Committee believes that such children may benefit from prophylaxis. The results of a large trial of prophylaxis in children with both cyanotic and acyanotic heart disease will be reported in mid-October 2002 and may change this recommendation. The AAP acknowledges that prophylaxis has not been evaluated in randomized trials in immunocompromised children, but notes that children with severe immunodeficiencies may

benefit. In children who are receiving standard IGIV on a monthly basis for immunodeficiency, RSVIG IV can be substituted during RSV season.

Prophylactic Therapy

Respiratory syncytial virus immune globulin intravenous (RSVIG IV) was first licensed in 1996 for prevention of severe RSV disease in children. The AAP recommended use for younger than 24 months with chronic lung disease or a history of premature birth, given the higher burden of disease in this age group.[12] The AAP quickly endorsed its use. This therapy requires monthly intravenous infusions throughout the RSV season. In 1997 compelling data supporting an alternative therapy, palivizumab (an RSV monoclonal antibody administered intramuscularly) were published. The AAP issued new recommendations for palivizumab. The therapy is currently recommended for children younger than 24 months with chronic lung disease and infants born at 32 weeks' gestation or earlier. It is not currently indicated in children with congenital heart disease, as evidence on its safety in this group of patients will only become available in late 2002. One systematic review of prophylactic immunoglobulin therapy concluded that it reduces admission to hospital and intensive care.

Cost of Prophylaxis

Although the effectiveness of prophylactic therapy is of critical importance in deciding whether it should be administered, cost is also an important factor.[13,14] The cost-effectiveness of RSV prophylaxis is very sensitive to the cost of the prophylaxis intervention and to the costs avoided as a result of the intervention. These costs are dominated by the acquisition cost of palivizumab and the cost of hospitalization, respectively.

Cost estimates used in published studies vary widely. Prophylaxis administration cost estimates used in previous analyses ranged from $2,754 to $4,957 per infant[14] (updated to August 2002). Estimates can vary because of differences in acquisition and administration costs, the number and size of doses, and the amount of wasted palivizumab. Hospitalization costs average about $14,000 per infant but can vary widely, with studies reporting costs ranging from $11,336 to $118,336[14] (updated to August 2002, adjusted to costs with cost/charge ratio of 0.6). Consequently, a summary of evidence from the literature on the cost-effectiveness of prophylactic therapy could prove valuable for deciding whether benefits are likely to outweigh costs.

Justification for this Evidence Report

Diagnosis of bronchiolitis is generally based on history and physical examination; it is unclear whether diagnostic tests change the clinical course, management, or prognosis of the disease. Given the high incidence of disease among infants and children, different treatment modalities have been in practice for some years. One of these therapies is specific to the virus

(e.g., ribavirin); others are symptomatic (e.g., bronchodilators, corticosteroids). Evidence on their efficacy is conflicting.

Systematic assessment of treatment efficacy is further complicated by the wide variety of outcome measures used by investigators. The majority of treatment studies focus on short-term changes in clinical findings (e.g., respiratory rate, heart rate wheezing, retractions) of composite clinical scores. A smaller number of studies use more globally relevant clinical outcomes such as need for hospitalization, duration of hospitalization, resource utilization and adverse effects. No single clinical score is used consistently across studies. Appendix A describes the various clinical scoring systems in detail.

The relative severity of the disease among the most vulnerable subpopulations suggests that they benefit from prophylactic therapy, although the cost-effectiveness of available interventions needs to be explored.

Given these issues of diagnosis, treatment, prophylaxis, and cost of prophylaxis, a systematic review of the evidence on the management of bronchiolitis is of interest to a wide audience. Interested parties include clinicians, health care providers, hospitals, and managed care organizations as well as patient and consumer organizations. The management of patients with this ailment is of particular concern to the AAP and the American Academy of Family Physicians (AAFP), which nominated the topic for the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Program. The RTI-University of North Carolina Evidence-based Practice Center (RTI-UNC EPC) was chosen to undertake a systematic review of several aspects of this issue, including diagnosis, treatment, prophylaxis, and the cost-effectiveness of prophylaxis among significantly premature infants (32 to 35 weeks) and premature infants with comorbidities.

Key Questions and Causal Pathways

The RTI-UNC EPC was originally presented with several key questions devised by AHRQ, the AAFP, and the AAP. As these key questions were not couched in terms of or in a format typically used in designing and conducting systematic reviews in the AHRQ program, the RTI-UNC staff proposed revised key questions that were acceptable to the professional societies and AHRQ.

Questions were further refined based on consultation with the project's Technical Expert Advisory Group (TEAG, a group of experts in the field who agreed to provide input during our research process; see Acknowledgements for a list of members) by conference call in late November 2001. The RTI-UNC EPC and the TEAG reviewed each question for overall clinical and theoretical significance as well as quantity and quality of evidence. TEAG members acknowledged that the evidence for some questions was less extensive than for others, but judged that all the questions would be of vital significance to a broad audience and, therefore, should be included in this evidence report. Revisions to the key questions based on these discussions were intended to increase the clarity of the questions and the specificity of the evidence for each question.

We developed causal pathways to reflect the changes in the key questions and the TEAG discussions. The final versions are presented in Figures 1 and 2. These figures depict the scope of our evidence report; they cover the four main areas of our review: diagnosis and treatment (Figure 1), prophylaxis and the costs of prophylaxis (Figure 2).

The final key questions are as follows:

1. What is the effectiveness and relative effectiveness of appropriate diagnostic tools for diagnosing bronchiolitis in infants and children? Diagnostic tools can include chest x-ray and laboratory screening tests.

2a. What is the efficacy or effectiveness of pharmaceutical therapies for treating bronchiolitis among infants and children? Therapies to be considered include corticosteroids, bronchodilators, antimicrobial agents, and antiviral agents.

2b. Does the evidence show that any single agent (or any single antimicrobial) is the most effective in improving outcomes?

3. What is the role of prophylactic therapy for prevention of bronchiolitis among children? Are there any specific subpopulations within this group who would benefit from such prophylaxis?

4. What is the evidence concerning the cost-effectiveness of prophylactic therapy for prevention of bronchiolitis among infants born from 32 through 35 weeks of estimated gestational age and premature infants with comorbidities?

Organization of this Report

Chapter 2 details our methods in undertaking this systematic review. We document the development and modification of our key questions and analytic framework, inclusion and exclusion criteria, and literature search. Chapter 3 presents the results of our literature search by key question. Chapter 4 discusses our findings further, and Chapter 5 offers suggestions for future research needs. Appendix A displays our clinical scales, Appendix B is the abstraction form; Appendix C contains our final abstraction form; and Appendix D displays our quality rating form.

2. Methodology

In this chapter, we outline our strategy for identifying and screening articles relevant to the management of bronchiolitis among infants and children. We describe the process of abstracting relevant information from the eligible articles and generating the summary evidence tables and cost analysis.

Literature Review Methods

Inclusion and Exclusion Criteria

Based on the final key questions specified in Chapter 1, we generated a list of inclusion and exclusion criteria for each key question (Table 1). We excluded studies that (1) did not pertain to infants and children; (2) were published in languages other than English; (3) did not report information pertinent to the key clinical questions; and (4) were not original studies.

Based on consultation with the TEAG, the RTI-UNC team revised the specification of the patient population of interest for Key Questions 1, 2 and 3 from "infants and children ages 0-5" to "infants and children." We made this revision because the age category 0 to 5 years did not reflect the fact that bronchiolitis is diagnosed primarily in children under 3 years of age. Also, the team wanted to be able to capture studies that looked at the long-term consequences of treatment of bronchiolitis in infancy or early childhood, even if those consequences were recorded at later ages. For Key Question 4 (cost-effectiveness of prophylaxis), the target populations for the cost-effectiveness question are (1) infants born 32 through 35 weeks' gestational age, and (2) infants born 32 through 40 weeks' gestational age with comorbid conditions.

The original geographic areas to which we intended to confine our literature searches and attention were North America, the United Kingdom, Australia, New Zealand, and Europe. Based on the recommendations of the TEAG, we removed this exclusion criterion for two reasons. First, some high-quality studies on this condition may well have been conducted elsewhere in the world, and we needed to be able to capture them. Second, including all areas may facilitate our examining information on different ethnicities and races in the report, as AHRQ and the professional societies had originally requested.

The criteria for study design were different for each key question based on the sufficiency and quality of evidence. Our diagnostic question (Key Question 1) was broad and required a lower admissibility standard. Therefore, we included both RCTs and prospective studies. The treatment and prophylaxis questions (Key Questions 2 and 3) were more specific and required greater strength of evidence; we thus elected to limit searches to RCTs. For the cost-effectiveness of prophylaxis (Key Question 4), we reviewed studies that employed economic analysis.

For all studies, key inclusion criteria included outcomes that were both clinically relevant and able to be abstracted. We set a minimum sample size of 10; small case series and single case

reports were excluded. For Key Question 4 alone, we also excluded article abstracts that did not mention using an analytical method such as cost, cost-effectiveness, cost-utility, or cost-benefit analysis.

To ensure that we were reviewing therapies relevant to current clinical practice, we excluded individual studies before 1980. Our search was last updated on April 1, 2002, and contains all abstracts entered into the MEDLINE® and other databases until that date.

Search Terms

Based on the inclusion/exclusion criteria above, we generated a list of Medical Subject Heading (MeSH) search terms (Table 2). The TEAG also reviewed these terms to ensure that we were not missing any critical areas. This list represents our collective decisions as to the MeSH terms to use for all searches.

Identification of Relevant Data Sources for Review

We used multi-faceted search strategies to include all the current valid research on the key questions. We searched standard electronic databases such as MEDLINE®, Cochrane Collaboration resources, and the Health Economic Evaluations Database (HEED) (Table 3). We conducted hand-searches of the reference lists of relevant articles to ensure that we did not miss any relevant studies. In addition, we consulted with the TEAG about any studies or trials that were under way but not yet published.

Literature Assessment

Using the inclusion/exclusion criteria (Table 1) and resulting search terms (Table 2), we identified a total of 744 abstracts for review; of these we retained 83 articles for all key questions.

For the clinical questions (Key Questions 1, 2 and 3), based on our initial search terms, we judged that 74 articles were possible inclusions, based upon full article review. The Scientific Directors independently evaluated each abstract for inclusion or exclusion, using the abstract review form (see Appendix B). When the Scientific Directors disagreed on an abstract, they reviewed it again together and came to a consensus. During the process of abstraction, we found that one article was a followup to a study not included by our search parameters. The original study was not classified under the MeSH term 'bronchiolitis'. In order to capture any RCTs on bronchiolitic children that we may have missed, we conducted a systematic search titles and abstracts in MEDLINE® of the term 'wheezing infants' and identified 81 studies. After reviewing the abstracts, we included 10 articles for full review. Upon full review of the articles, we retained 4 articles in which the recruitment was conducted specifically during winter months and had children presenting with viral symptoms including wheezing. This suggests that the majority of the subjects had a clinical diagnosis of bronchiolitis rather than asthma.

For the cost-effectiveness of prophylaxis (Key Question 4), we identified 82 unique articles that mention the economic analysis of prophylaxis for the prevention of bronchiolitis in infants.

Upon examination, we found that 21 article abstracts met our inclusion/exclusion criteria, and we obtained the full articles for review. We identified and ordered additional relevant articles based on a review of the reference lists from articles abstracted for any of the key questions. In all, we abstracted 41 articles for the cost-effectiveness questions.

In our review of the literature on prophylaxis and its costs for infants in the target populations, we identified published articles that describe two RCTs for RSVIG IV and one RCT for palivizumab; all met the inclusion criteria. We considered the possibility of pooling results from RCTs for RSVIG IV and palivizumab, but TEAG members discouraged this approach, citing that palivizumab exhibits higher efficacy, better safety, and ease of administration. TEAG members recommended that we consider only palivizumab in an evaluation of the cost-effectiveness of prophylaxis. However, because only one clinical trial has been conducted for palivizumab to date, data on outcomes for children in the intervention branch of the tree would necessarily be derived from this single study.[10]

Outcomes from the IMpact-RSV study are available for the following subpopulations of interest: (1) >32 weeks and = 35 weeks' gestational age and = 6 months at the time of randomization and (2) infants with a diagnosis of BPD and = 24 months upon randomization. The primary study outcome is rate of hospitalization. Although secondary endpoints included hospital length of stay, frequency and length of stay for intensive care unit (ICU), and mechanical ventilation, these results were not reported separately for the subpopulations of interest.

Our primary analysis focuses on the six articles that review the cost-effectiveness of palivizumab.

Data Collection

The data collection process involved abstracting relevant information from the eligible articles and generating summary evidence tables that present the key details and findings for the articles. A trained abstractor completed a detailed data abstraction form. The Study Director used the forms and the original articles to generate summary evidence tables. The Scientific Directors performed quality control assessments by reviewing each of the evidence tables against the original articles.

Abstractors and Trainers

The RTI-UNC EPC used both clinical and methods abstractors. All abstractors attended three training sessions. At the first session, we explained the process and goals of data abstraction, and then sent the abstractors home with an article to review. We then reconvened the group and, through a review of the test article, ensured that the abstractors understood what was expected of them. The reviewers abstracted an additional two test articles, reconvened, and reviewed their work. At this time the Scientific Directors determined that the abstractors were able to abstract the data as required, and we began the data abstraction process. The Research Coordinator monitored progress and routed the data abstractors' questions or issues to the Scientific Directors.

Data Abstraction Forms

For Key Questions 1, 2 and 3, the Study Director and the Scientific Directors created a single data abstraction form (Appendix C). This form was developed through multiple rounds of pretesting on different articles spanning the entire range of interventions to ensure that it would adequately capture all relevant issues. We solicited feedback from the data abstractors during training to refine further the data abstraction form.

For Key Question 4, we used a systematic approach to review and abstract economic data.[15] We first developed and used a standardized abstraction form to identify information from each article about the study design, analytic perspective used, cost components included in the analysis, and value of the economic summary measure (e.g., cost, cost-effectiveness ratio, or cost-utility ratio). This form is an adaptation of the Economic Evaluation Abstraction Form (version 3.0) developed and used to evaluate economic studies for the *Guide to Community Preventive Services.*[16]

We made adjustments to summary measures from the abstracted articles to facilitate comparisons across study findings. For example, to account for cost differences across studies attributable solely to price inflation, we used the medical care price index (MCPI) to adjust all estimated costs to constant 2001 dollars. The MCPI is a subset of the Consumer Price Index compiled by the Bureau of Labor Statistics; it includes medical care items such as prescription drugs and medical supplies, physicians' services, eyeglasses/eye care, and hospital services.

We also focused our comparisons on specific components of cost, such as treatment or hospital costs, rather than on total cost measures, because different studies may have included different resources in their total cost estimates. In some cases, we could not adjust study results because of differences in methods. For example, if costs were not presented separately for each component included in the study, we could not make adjustments to total cost estimates for comparability.

For articles that did not indicate the year for which costs were reported, we assumed that the costs were valued in constant dollars for the year prior to publication.

Development of Evidence Tables

After abstracting the included articles, we developed evidence tables to present the essential information to address Key Questions 2 and 3 relating to treatment and prophylaxis. These tables appear in at the end of this report and cover the following pieces of information:

- Setting of the intervention: country, patient setting;
- Followup: acute (48 hours after intervention), short-term (2-14 days after intervention) and long-term (14 days and more);
- Research design: randomized trials, including placebo-controlled, nonplacebo-controlled (both those comparing active treatment and control groups to nonplacebo), and crossover trials;
- Length of enrollment;
- Masking;
- Objective of the study;
- Inclusion/exclusion criteria;

- Number enrolled in and completed study;
- Sex;
- Mean age at enrollment and mean gestational age;
- Comorbidities;
- Interventions;
- Results and significance tests for primary and secondary outcomes and subgroup analysis;
- Adverse events;
- Quality; and
- Significant differences at baseline and other comments.

Given the wide range of reported outcomes, we assigned results in evidence tables as primary or secondary outcomes based on their clinical relevance to the key questions. In studies with multiple outcomes, we generally listed the more clinically important outcomes such as length of hospitalization or development of long-term sequellae as primary outcomes and the more physiologic measurements such as heart rate or respiratory rate as secondary outcomes. Applying this rule, however, depended on the nature of results presented in the study. When the authors presented pulmonary function tests as their primary outcomes and did not present data on length of hospitalization or development of long-term sequellae, the Scientific Directors may have chosen physiologic measurements as the more clinically relevant outcome from that study and placed them as the primary outcome for the purposes of the evidence table.

For primary outcomes, individual results for each study arm and *P* values were always recorded where possible. For secondary outcomes, *P* values were generally reported when results were positive.

Grading the Strength of Evidence

For Key Question 1 on diagnosis, we initially intended to assign quality scores to the diagnostic studies using standard criteria.[17] However, several factors prevented this. First, no articles specifically assessed diagnostic tests or criteria for bronchiolitis. The literature, the TEAG, and our study team all agreed that bronchiolitis is a clinical diagnosis for which no true or "gold standard" test exists.

Second, the majority of diagnostic information extracted for review came from the 61 treatment studies. As such, the data had not been collected for the purposes of assessing their diagnostic utility. In most studies, viral studies, clinical scores, complete blood counts (CBCs), and chest x-rays were all used as baseline independent variables.

We did use selection criteria that ensured a minimal study validity. We took diagnostic data only from the RCTs in which all patients were tested (i.e., rather than at the discretion of the investigators or treating physicians). Of the non-RCT articles identified that included diagnostic data, all were prospective cohort studies.

For Key Questions 2 and 3, the Scientific Directors developed a quality assessment form for RCTs of treatment or prophylaxis (Appendix D). In prior work for AHRQ, the RTI-UNC EPC had developed an exhaustively peer-reviewed evidence report on systems to rate the strength of scientific evidence.[18] We based our quality assessment tool on this work, with appropriate modifications for the literature on the management of bronchiolitis in infants and children. The

quality assessment tool comprised four individual elements: randomization; masking, statistical analysis, and funding/sponsorship.

We rated each element as excellent, adequate, inadequate, or unable to determine. In addition to these four elements, we considered the appropriateness of the population studied, the clarity and relevance of outcome used, and the appropriateness of the statistical analysis used. Based on the composite of the assigned scores and their individual comments on each study, the Scientific Directors assigned an overall quality score on a four point scale, ranging from 1 (poor) to 4 (excellent). The subjectivity involved in this method of scoring the quality of evidence was reduced by the independent assessment of each article by both Scientific Directors. When they did not agree, they reviewed the article together and arrived at a consensus. Of the 61 articles that were scored for quality for Key Questions 2 and 3, the Scientific Directors had a 98 percent rate of agreement within one point.

For Key Question 4 on the cost-effectiveness of prophylaxis, we adopted the *Guide to Community Preventive Services* convention for the Centers for Disease Control and Prevention (CDC) of not scoring economic studies on quality. As Carande-Kulis et al. explain, differences in economic methods may be attributable to differences in study objectives; even when differences result from variations in quality, they may not have a large impact on study findings.[15] Further, the number of economic studies available for review is quite limited, so we adopted the CDC approach of reviewing all available studies but adjusting results to account for differences in methods.

Analysis Strategy

In developing an approach for synthesizing the literature for the evidence on the management of bronchiolitis in infants and children, our review of the literature and conversations with the TEAG made apparent that each key question would require a different analysis strategy. These are briefly described below.

Key Question 1: Diagnosis

The TEAG agreed that we should retain this question because of its theoretical importance. TEAG members generally agreed that patients with bronchiolitis undergo many tests but that few influence clinical management or outcome; they do affect the costs of care. We identified 16 studies dealing with diagnosis. We also reviewed 61 clinical trials for additional data on diagnostic testing. The data available fell into several natural categories:

- Case definitions and inclusion criteria used in the clinical trials;
- Etiology of cases of bronchiolitis when all subjects were tested;
- Comparison of various virus isolation techniques;
- Predictors of disease severity or complications; and
- Studies in which standardized tests were performed on all patients as part of their evaluation (e.g., chest x-rays, complete blood counts).

Key Questions 2 and 3: Treatment and Prophylactic Therapy

Our assessment of the literature for Key Questions 2 and 3 suggested a range of interventions, with studies choosing to report a widely varying set of outcomes measured at different time intervals. Given the disparity in outcomes, we grouped studies by type of intervention rather than by outcomes for Chapter 3 (Results). This grouping resulted in 15 sets of interventions and evidence tables:

- Nebulized epinephrine versus nebulized saline placebo;
- Subcutaneous epinephrine versus saline placebo;
- Nebulized epinephrine versus nebulized bronchodilators (salbutamol or albuterol);
- Nebulized bronchodilators (salbutamol or albuterol) versus placebo or other treatments;
- Nebulized bronchodilators (salbutamol or albuterol) plus ipratropium bromide versus either nebulized salbutamol or nebulized albuterol alone and/or placebo;
- Oral corticosteroids versus placebo, with or without bronchodilators;
- Parenteral dexamethasone versus placebo;
- Nebulized corticosteroids versus placebo or usual care;
- Ribavirin versus placebo;
- Antibiotics versus no treatment or other antibiotics;
- RSVIG IV as treatment for bronchiolitis
- Other miscellaneous treatments for bronchiolitis;
- RSVIG IV versus placebo or standard care to prevent RSV bronchiolitis;
- Monoclonal antibody for prophylaxis of RSV bronchiolitis; and
- Vaccines to prevent RSV bronchiolitis.

Key Question 4: Cost-Effectiveness of Prophylactic Therapy

To determine whether we could assess the cost-effectiveness of prophylactic therapy using existing data, we used a decision analysis framework to describe the treatment options and the possible costs and outcomes that could result. Based on our initial findings from the literature and on input from the TEAG, we developed a decision tree to show treatment alternatives—administer prophylactic therapy versus no treatment intervention—and the possible outcomes associated with each alternative.

The resulting decision tree is shown in Figure 3. By convention, open squares represent decision nodes, circles represent chance nodes, and each line emanating from a chance node denotes an uncertain outcome associated with the preceding action. Solid black squares represent terminal nodes. This decision tree in Figure 3 depicts only one decision node—the decision to administer prophylactic therapy or not. The possible outcomes associated with either choice are identical—an infant may or may not develop bronchiolitis, may or may not need ambulatory care, may or may not require hospitalization, and so on—but the likelihood of experiencing each outcome and the associated costs may differ depending on whether this infant received prophylactic therapy. Although administering prophylactic therapy will have higher initial costs than not intervening, the potential cost savings associated with prophylaxis, perhaps

through reduced ambulatory care or hospitalization costs, could outweigh the initial cost of intervention.

As shown in Figure 3, an analysis of the cost-effectiveness of prophylactic therapy from the societal perspective would require an extensive amount of data on costs and outcome probabilities. For example, some of the information needed for a cost-effectiveness analysis includes the rates of bronchiolitis infection, ambulatory care for bronchiolitis, hospitalization, and admission to ICU — both for children who receive prophylactic therapy and for those who do not.

In Chapter 3 we summarize results from existing economic analyses of prophylactic therapy for the prevention of bronchiolitis. However, as we discuss in some detail in Chapter 5, the existing literature contains many gaps, and much of the data required for a cost-effectiveness analysis from the societal perspective are not available. Our discussion section in Chapter 4 summarizes these data gaps and offers recommendations about additional data needed to answer the question of whether prophylactic therapy is cost-effective when used in the target population.

Peer Review Process

We requested review of this report from several individual experts in the field and from relevant professional societies and public organizations. They are acknowledged at the beginning of this report. We revised the report in response to suggestions from these outside agents.

3. Results

We included a total of 83 articles in our analysis. Of these, 16 are primary articles on diagnosis of bronchiolitis, 52 pertain to the treatment of bronchiolitis, and nine are on prophylactic therapies. Finally, although we found several articles that are relevant to the cost-effectiveness of prophylaxis, our primary analysis is limited to six articles that reviewed cost-effectiveness for palivizumab. Our results are organized by key questions, with tables at the end of the chapter and Evidence Tables.

Key Question 1: Effectiveness of Diagnostic Tools for Diagnosing Bronchiolitis in Infants and Children

Our retrieval and review of abstracts based on the inclusion/exclusion criteria in Table 1 resulted in the final inclusion of 16 articles that addressed some aspects of Key Question 1. In addition, we examined the case definitions and inclusion criteria used in 61 clinical trials to see how bronchiolitis had been defined or diagnosed.

The studies reviewed that dealt with diagnosis, in the most general sense, fell into the following categories:

- Case definitions and inclusion criteria used in the clinical trials;
- Etiology of cases of bronchiolitis when all subjects were tested;
- Comparison of various virus isolation techniques;
- Predictors of disease severity, complications, or both; and
- Studies in which standardized tests were performed on all patients as part of their evaluation (e.g., chest x-rays, complete blood counts).

The challenge with this literature is the fact that bronchiolitis is a clinical diagnosis based on a typical history and findings on physical examination. Specifically, it is a disease of infants and young children characterized by initial signs and symptoms of upper respiratory infection followed by cough, tachypnea, and wheezing. Additional signs can include fever, hypoxia, and retractions. No diagnostic test or "gold standard" confirms the disease. Various tests exist that are used to diagnosis the specific etiology of bronchiolitis.

The TEAG twice reviewed this issue. All TEAG members agreed that bronchiolitis is a clinical diagnosis. However, the TEAG advised U.S. to examine the effectiveness of numerous ancillary studies that are commonly performed on infants with bronchiolitis, such as chest x-rays and CBCs.

Case Definition and Inclusion Criteria

We reviewed the case definition and inclusion criteria from the clinical trials. Case definitions were quite similar: (a) 38 used tachypnea in either the case definition or inclusion criteria; (b) 39 used wheezing; (c) 30 used oxygen saturation; and (d) 28 used retractions.

However, many studies simply stated that infants with signs and symptoms consistent with bronchiolitis were cases eligible for inclusion. Many authors referred to the historical definition of bronchiolitis published by Court.[19]

Eligibility criteria in the clinical trials varied to a greater extent, especially with respect to variables such as age, duration of symptoms, comorbidities (e.g., prematurity, chronic lung disease), history of previous wheezing, and severity of disease. This variation was determined by the specific objectives of the studies (e.g., numerous studies included only infants who were positive for RSV disease).

Most trials measured disease severity both as a baseline independent variable and as a dependent outcome (i.e., change in disease severity resulting from treatment). Disease severity was most commonly measured using clinical scales (43 of the 52 treatment trials). The variety of scales used made comparisons between studies difficult. Appendix A describes the numerous clinical scales used.

Some studies used clinical scales that had been validated in previous studies such as the Respiratory Distress Assessment Instrument (RDAI).[20-23] Others were created or modified by authors for their particular trial.[24,25] Despite this variation, the clinical scales all incorporated measures of respiratory rate, respiratory effort, severity of wheezing, and oxygenation.

Identification of Etiology of Bronchiolitis

Many, but not all, of the included studies attempted to identify the etiology of the enrolled cases. As mentioned above, a subset of the treatment trials enrolled only infants who were RSV positive.

Of the 52 treatment studies, 42 performed RSV testing on all subjects. In the studies that tested all and included all regardless of RSV status, the range in the prevalence of cases caused by RSV was 26 percent to 95 percent. Twelve studies tested patients for other viral etiologies (e.g., parainfluenza viruses) in addition to RSV. It is recognized that RSV testing of patients with bronchiolitis is justified in several situations. First, isolation of RSV as the etiology of fever in an infant under 3 months may support a clinician's decision to forego additional testing in the traditional "rule out sepsis" work-up. Second, RSV testing may be helpful in clinical situations where the diagnosis of bronchiolitis is not clear. Third, RSV testing will be essential in research settings where RSV-specific therapies are being evaluated for effectiveness. Finally, RSV testing is an important tool to epidemiologists and public health officials responsible for surveillance of lower respiratory tract infections in infants. However, most reported results as percentage positive for RSV versus "other viruses."

Various techniques for identifying RSV as the causative agent of bronchiolitis were used, including viral cultures, rapid antigen detection tests (e.g., direct immunofluorescence assay [IFA], enzyme immuno-assays [EIA]), polymerase chain reaction (PCR), and measurements of acute and convalescent antibody titers. Rapid antigen detection tests for RSV were used most frequently. In many of these, viral cultures were performed on cases that were negative for RSV.

Comparison of Virologic Tests

Five studies examined the accuracy of various virologic tests for RSV and other causative viruses (Table 4).[26-30] Table 4 demonstrates (1) that numerous tests for RSV exist and (2) that their test characteristics vary. The *AAP Red Book* reports the overall sensitivity of the rapid antigen detection tests to be in the 80 percent to 90 percent range.[6] The data in Table 4 are consistent with this estimate. It is likely that individual test manufacturers have additional, unpublished data on their own assays, as they generally report test characteristics in the package insert materials that come with these test kits. Our search strategy would not have identified this unpublished data. In addition to looking at test agreement, Ahluwalia et al. compared two methods of specimen collection and demonstrated that viral culture, EIA, and IFA all yielded positive results more often when performed on nasopharyngeal aspirates than when performed on nasopharyngeal swabs.[26]

Of interest from both the clinical and utilization points of view is the question of whether RSV testing is necessary in all patients with bronchiolitis. Although such testing is commonly used to document the etiology of bronchiolitis, the etiology rarely changes clinical management. Many institutions require testing all infants being admitted to the hospital; the rational involves assisting with identifying cohorts (i.e., to decrease nosocomial RSV infections). However, no good quality RCTs examine the effects of cohort segregation in preventing nosocomial transmission of bronchiolitis.[31] As a result, many infection control policies recommend that all infants with acute lower respiratory infection (ALRI) be isolated, regardless of etiology. No study we reviewed addressed the issue of utility of RSV testing.

Predictors of Severe Disease or Complications

Several studies measured various predictors of disease severity; these are summarized in Table 5. Our search strategy did not specifically set out to capture all studies that examine disease severity. Shaw et al. directly use five types of clinically important data to predict clinically important outcomes denoted "mild" or "severe" disease.[32] The Mulholland study, focused on oximetry and arterial blood gases, is useful as well, although most clinicians check arterial blood gases only on patients who appear to be in respiratory failure.[33]

In contrast, Cherian et al. focused on determining the reliability of easily observed physical findings in diagnosing ALRI in developing countries, as used in current World Health Organization (WHO) algorithms.[34] The Saijo et al. study focused on using laboratory studies to predict three categories of RSV disease defined radiographically rather than clinically.[35] As such, these findings have limited usefulness to clinicians.

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. Two studies support these assertions.[32,33] Additional prospective studies of disease severity or clinical prediction models are lacking.

Utility of Chest Radiographs in Bronchiolitis

In 14 studies of bronchiolitis investigators performed chest x-rays on all patients (Table 6).[24,25,32,36-45] Large numbers of infants with bronchiolitis have abnormalities on chest x-rays. However, data are insufficient to demonstrate that these chest x-rays correlate well with disease severity.

Two studies set out to examine the relationship between x-ray abnormalities and disease severity. Shaw et al.'s data show that the patients with atelectasis were 2.7 times more likely (95% CI: 1.97-3.70) to have severe disease than those without this x-ray finding.[32] This association persisted when it was included in a multivariable analysis. In contrast, Dawson's data demonstrated no correlation between chest x-ray findings and baseline disease severity as measured by a clinical severity scoring system.[36]

The Roosevelt et al. study showed that the presence of chest x-rays abnormalities was strongly correlated with the use of antibiotics.[43] The effectiveness of antibiotic treatment in these patients was not examined. The fact that bronchiolitis is usually a viral illness calls in to question this course of disease management.

These data suggest that in mild disease, chest x-rays offer no information that is likely to affect treatment and that, therefore, they should not be routinely performed. In fact, the Roosevelt et al. data suggest that such x-rays may lead to inappropriate use of antibiotics, although this was not the focus of their study.[43] Chest x-rays may be useful in predicting which patients are likely to have more severe disease in cases in which this assessment is not otherwise clear.

Utility of Complete Blood Counts in Bronchiolitis

The research teams in 10 studies did CBCs on all patients (Table 7).[24,35,42,45-51] Although investigators in many of the clinical trials included CBCs, results were often not reported or were used only to demonstrate that the treatment and control groups were similar at baseline. Only the Saijo et al. study attempted to correlate white blood counts with category of lung disease defined radiographically (i.e., lobar pneumonia vs. bronchopneumonia vs. bronchiolitis).[35] None of these studies demonstrated that CBCs were useful in either diagnosing bronchiolitis or guiding therapy.

Key Question 2: Efficacy and Effectiveness of Pharmaceutical Therapies for Treatment of Bronchiolitis

Overall, we found 52 studies meeting our inclusion criteria that dealt with treatment of bronchiolitis in infants and young children. Treatments studied included nebulized epinephrine, nebulized bronchodilators, nebulized ipratropium bromide, oral inhaled or parenteral corticosteroids, aerosolized ribavirin, oral antibiotics, and a variety of other treatments. These interventions were studied against either placebo or each other. These studies are summarized in

Evidence Tables 1 through 12 at the end of this report. Key features of selected studies are presented below.

In addition, we reviewed nine articles on prophylactic interventions for bronchiolitis among high-risk infants and children. These studies are summarized in Evidence Tables 13, 14 and 15 and are discussed at the end of this section.

Nebulized Epinephrine versus Nebulized Saline Placebo

Detailed Results

We found one small double-blind, placebo-controlled RCT of nebulized racemic adrenaline for bronchiolitis in infants and toddlers without comorbidities, presented in Evidence Table 1.[52] The dose of racemic adrenaline varied by weight of the subject and ranged from 2.0 mg for infants under 5 kg to 5.0 mg for those greater than 10 kg. This was a small trial (29 children completing the study). The primary outcomes were mean symptom score and mean change in oxygen saturation recorded at 15-minute intervals after treatment for 1 hour. Immediately post-treatment, the adrenaline group improved significantly in mean change in oxygen saturation. Clinical scores were significantly improved in the adrenaline group at all time intervals. Outcomes were tracked out to only 1 hour after treatment.

The group randomized to racemic adrenaline had significantly lower baseline oxygen saturation. A subgroup analysis indicated that, compared with less severely affected infants, more severely affected infants (those with baseline oxygen saturation levels of <93 percent) had significantly elevated oxygen saturation in the hour post-treatment. This raises some concern that baseline maldistribution of subjects could, in part, account for the positive finding of improved oxygen saturation in the adrenaline group. However, the concurrent findings of improved overall clinical scores may argue for a true positive effect of the treatment.

Conclusions

The Kristjansson et al. study is one of the few to demonstrate a statistically significant outcome, i.e., increased oxygen saturation, after the administration of nebulized epinephrine and improvement in clinical scores.[52] However, outcomes were evaluated for only the first hour after treatment and may not translate into longer term benefits. Moreover, this study is too small to make conclusions regarding the efficacy of nebulized epinephrine as a treatment for bronchiolitis, particularly for longer term outcomes and outcomes that are more clinically relevant such as length of hospitalization.

Finally, definitive evidence about the effects of nebulized epinephrine should be subjected to investigation using an appropriately designed and sized RCT. A primary outcome should be meaningful to parents and clinicians, such as the need for hospitalization after emergency room treatment or the development of persistent wheezing. Secondary outcomes might include a standardized respiratory symptom score or total costs of the episode of care.

Subcutaneous Epinephrine versus Saline Placebo

Detailed Results

We located one study that employed subcutaneous epinephrine for the treatment of wheezing in infants under 24 months of age presented in Evidence Table 2. Infants with previous bronchodilator therapy were excluded in an attempt to limit the population to non-asthmatic infants. However, 47% of the epinephrine group and 43% of the placebo group had a prior history of wheezing, but had never been on bronchodilators. Thirty infants were randomized to either two does of 0.1mg/kg of subcutaneous epinephrine administered 15 minutes apart versus subcutaneous saline placebo. The primary outcomes studied were absolute change in the RACS clinical score and a four or more point improvement in the RACS score. Both primary outcomes significantly favored the subcutaneous epinephrine group. Fifty-six percent of the epinephrine group had four or greater point improvement on the RACS compared with 7% of the placebo group. Ten children had laboratory proven RSV infections and seven of these 10 responded to epinephrine with a four or more point improvement on the RACS scale. However, the paper is not clear about whether RSV testing was done in the placebo group. There were no significant differences noted when subgroup analysis of the infants by 6 month age groups was done. Adverse events were not reported by the authors.

Conclusions

This is the only study we located on the use of subcutaneous use of epinephrine to treat acutely wheezing infants. Prior to the availability of newer treatments subcutaneous epinephrine was a standard treatment for asthma in children. Although the results of this study certainly favor the epinephrine group, it is small and important outcomes such as need for hospitalization or length of hospitalization are not reported. We also had concerns that the patients in this study represented a mixed population. This was one of the four papers identified using the search terms for "wheezing infant." A substantial proportion of the population had a prior history of wheezing despite the fact that none had been on bronchodilators and over 70% had a family history of atopy. A subsequent bout of wheezing, even in the context of a virally mediated illness, may indicate that these children have a reactive airway disease that may respond better to agents like epinephrine than would children without such a disease component. The heterogeneous population in this small study raises concerns about generalizing from this study and we do not believe that this single study provides any evidence of effectiveness for this intervention. If investigators are interested in studying this drug as a treatment modality for bronchiolitis then a carefully designed trial would be needed.

Nebulized Epinephrine versus Nebulized Bronchodilators (Salbutamol or Albuterol)

Detailed Results

Evidence Table 3 presents a group of four studies that compared nebulized epinephrine to nebulized salbutamol (three studies) or albuterol (one study).[22,53-55] All four studies were double blinded. Three of the four studies were conducted in children ages 4 years or younger;[22,53,55] one study admitted those under 2 years of age.[54] None of the studies included children with serious comorbidities, but one study did include a small percentage of children who had had previous episodes of wheezing.[54] The studies were small, ranging from 33 to 100 subjects (the latter divided among four study arms). The doses of epinephrine and bronchodilators were not uniform and were not always dosed on a per-kilogram (kg) basis. Epinephrine doses varied from 0.5 mg to 3 mg as standing doses and 0.1 mg/kg to 0.9 mg/kg by weight. Salbutamol and albuterol doses ranged from 1.5 mg to 2.5 mg standing doses and 0.15 mg/kg to 0.30 mg/kg on a weight basis. Primary outcomes included duration of hospitalization, changes in various clinical scores, respiratory rates, heart rates, need for oxygen therapy, and oxygen saturation.

Virtually no outcome measure differed significantly between study groups. The Menon et al. study was a notable exception; at 60 minutes post-treatment, oxygen saturation was statistically significantly higher in the epinephrine group than in the salbutamol group.[22] This team also found statistically significant differences in several secondary outcomes including fewer infants requiring hospitalization in the epinephrine group (33 percent vs. 81 percent in the salbutamol group). Children in this study were defined as admitted to hospital if they were formally admitted or if they received care in the emergency department for more than 6 hours. No post-epinephrine symptom rebound was reported

In terms of adverse events, the Bertrand et al. study found statistically significantly increased heart rates in the epinephrine group compared to the salbutamol group on the second day.[53] Another study found a higher incidence of pallor in the epinephrine group at 30 and 60 minutes post-treatment; however, the 90-minute post-treatment heart rate in the epinephrine group was actually lower than in the salbutamol group.[22]

Of note, the Sanchez et al. study in Canada in the early 1990s sedated infants with chloral hydrate before administration of each drug in a cross-over design trial; the aim was to facilitate gathering clinical measurements, including pulmonary mechanical parameters.[55] The sedation may not only have influenced the physiologic measures for the infants but also masked any adverse effects. Whether this type of trial (requiring sedating infants) would be approved today is open to question.

Conclusions

Overall, these studies were likely too small to detect a clinically meaningful difference in their primary outcomes. The primary outcomes in these studies were, for the most part, not of substantial relevance to parents or clinicians. None of these studies, with the exceptions noted in the Menon et al. study,[22] demonstrated important differences among the outcomes that were examined. We did not conduct a formal meta-analysis of these four small studies because of the lack of uniformity in both the drug doses and outcomes studied. Finally, the results of the

Menon et al. study[22] combined with the findings of the Kristjansson et al. study[52] (Evidence Table 1) may argue for further investigation of nebulized epinephrine as a treatment for bronchiolitis.

Nebulized Bronchodilators (Salbutamol or Albuterol) versus Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment

Detailed Results

Evidence Table 4 shows the 11 studies comparing nebulized bronchodilators to placebo (e.g., nebulized saline), no treatment, or another intervention that met our inclusion criteria.[21,24,37,44,56-62] As to the last, the active arms in Goh et al.'s study compared nebulized salbutamol to nebulized ipratropium bromide.[61] The studies were of moderate size for this literature; the largest had 158 participants.[24] Nearly all the studies included children up to 24 months of age; three included infants of up to 6,[62] 15,[59] and 18 months[60] of age.

Five of the 11 studies compared more than two treatment groups against each other.[24,58-61] The doses of drugs varied substantially. For example, the lowest dose of salbutamol employed was 0.1 mg/kg and the highest standing dose was 2.5 mg/dose, which would be appropriate for only a 25-kg (55-lb.) child. Although the primary route of delivery was via nebulizer, Cengizlier et al. studied the use of salbutamol administered with a metered dose inhaler (MDI) to the oral preparation,[58] and and Hickey et al. examined the use of albuterol via an MDI compared to placebo.[57] Gadomski et al. compared nebulized albuterol to oral albuterol to placebo groups for each of the active arms of the study.[59] The primary outcomes studied included hospitalization, respiratory rate, heart rates, oxygen saturation, and various clinical scores. Virtually all the outcomes studied were short-term surrogate measures. All statistically significant outcomes occurred within the first hour after treatment was given.

Can and colleagues compared nebulized salbutamol to nebulized saline to mist in a tent.[24] They found that the Respiratory Distress Score (RDS) was significantly better for the salbutamol group against both other arms at both 30 and 60 minutes post treatment. The Klassen et al. study of nebulized salbutamol versus saline placebo found that the Respiratory Distress Assessment Instrument (RDAI) score was significantly better in the salbutamol group at 30 minutes post treatment.[21] There was a trend toward improved RDAI scores at 60 minutes as well ($P = 0.12$). Schweich and colleagues found that there was a significant improvement in the mean clinical score in the nebulized albuterol group compared with the saline placebo group at one hour after the start of the intervention.[56] Infants in this study received two doses of nebulized albuterol 30 minutes apart. There was a trend toward improved RDAI scores at 60 minutes as well ($P = 0.12$). The only other significant difference among primary outcomes was found in Gadomski et al.'s US-based study comparing nebulized albuterol to saline placebo to oral albuterol to oral placebo; the heart rates of infants who had been randomly assigned to the oral albuterol group were higher at 60 minutes after treatment was begun.[59]

Cengizlier et al. found that both the oral and inhaled salbutamol groups had improved clinical scores compared to the baseline at admission, but both groups' scores were virtually identical to those for the control group who received no bronchodilator therapy.[58] However, the time frame

for obtaining these clinical scores in this hospitalized population is not clear. Bronchiolitis is largely a self-limited illness; if sufficient time in hospital had passed, the groups might well have had similar scores at discharge as an alternate explanation to the no-treatment-effect explanation. This was also a small study (31 patients randomized into three groups).

Dobson et al. reported that all three patients withdrawn from the study by their physicians for worsening hypoxia and respiratory distress were in the albuterol group.[37] This finding was of borderline statistical significance ($P = 0.10$) and raises concern that repetitive doses of albuterol may be of harm to some infants. Ho and colleagues also noted that nearly all infants given salbutamol experienced oxygen desaturation from baseline values.[62]

The study by Klassen and colleagues (described above) was one of the better studies in our review of this literature.[21] The report is clearly written and the methods are transparent. It is one of the few studies to include a sample size calculation in the paper.

Conclusions

Like the studies in Evidence Table 1, the studies in this group are largely underpowered to detect meaningful differences among study groups. The Schweich and Hickey studies both included infants with wheezing who may have had asthma given that a substantial proportion of the enrollees had a prior history of wheezing in both studies.[56,57] The Schweich study even defined bronchiolitis as "wheezing in infants." In addition, the differences in agents, doses, delivery systems, settings and outcomes chosen limit comparisons and may make meta-analytic pooling of results from these nine studies of dubious validity.

The Can et al. and Klassen et al. research teams both demonstrated short-term benefit in clinical scores in the 30- to 60-minute time frame after treatment. However, these studies do not provide evidence to suggest that these interventions are effective in improving longer-term and more clinically relevant outcomes.[21,24] If future investigators are interested in refining studies of bronchodilators, then they should select appropriate long-term outcomes such as need for and duration of hospitalization and strive to reach some consensus on specific drugs and doses to be studied. Moreover, ensuring that future investigations of these agents have adequate power (sample sizes) is especially critical.

Not all studies reported adverse effects of treatment. However, several studies did report events that would warrant observation in any future investigations. Gadomski et al.[59] found elevated heart rates among children who received oral albuterol; both the Klassen et al. and Schuh et al. studies demonstrated significantly higher heart rates among those randomized to nebulized salbutamol and albuterol, respectively.[21,44] Ho et al. found that the majority of children who received salbutamol had oxygen desaturation compared with their baseline measurements, although mean maximum falls in oxygen saturation were not significantly different.[62] Schweich found "a small decrease" (magnitude not specified and statistical comparison not provided) in oxygen saturation after the first of two nebulized albuterol treatments that resolved after the second treatment.[56]

Nebulized Salbutamol or Albuterol plus Nebulized Ipratropium Bromide versus Bronchodilators or Ipratropium Bromide Alone and/or Saline Placebo

Three studies that compared nebulized bronchodilators in combination with ipratropium bromide to other treatments met our inclusion criteria (Evidence Table 5).[63-65] Two of these studies randomized patients into four groups: salbutamol plus ipratropium bromide, each agent individually, and a placebo group. Salbutamol doses were identical at 0.15 mg/kg in all three; the Chowdhury et al. study used a standing dose of ipratropium bromide for all infants,[63] and the Wang et al. study used a choice of two dose levels depending on age.[65] The third study in this group compared albuterol plus ipratropium bromide to albuterol plus a saline placebo.[64]

These studies included between 62 and 102 participants, but two studies divided subjects among four groups, resulting in small group sizes.[63,65] Chowdhury et al.'s study excluded significant numbers of children after randomization (13 of 102) primarily for subsequent findings of lung consolidation. All three studies included children up to 2 years of age.

Primary outcomes included duration of hospitalization, respiratory rate, and clinical score. Primary outcomes did not differ significantly for any of the treatment groups. Wang et al. demonstrated a statistically significant improvement in the mean change in oxygen saturation. A secondary outcome, considering salbutamol plus ipratropium bromide versus salbutamol alone and ipratropium bromide alone, showed no difference when compared to the placebo group.[65] Schuh et al. did not report any benefit of nebulized ipratropium bromide in addition to nebulized albuterol for vital signs, oxygen saturation, or clinical scores.[64]

Chowdhury et al. did not report any adverse events;[63] Wang et al. noted that one infant in the salbutamol group was withdrawn for tremulousness.[65] As expected with use of these agents, Schuh et al. found a heart rate increase with use of albuterol.[64]

Conclusions

This group of studies suffered from lack of sufficient power to demonstrate meaningful differences in outcomes. The differences seen in oxygen saturation in the Wang et al. study may warrant further investigation of salbutamol plus ipratropium bromide and ipratropium bromide alone.[65] However, the largest arm of the Wang et al. study included only 17 children, so clinically meaningful differences would not likely be able to be detected. There was also a trend toward decreased length of hospitalization in the treatment groups that included ipratropium bromide. Including clinically relevant outcomes such as the need for and duration of hospitalization and duration of symptoms, in future research is a reasonable lesson to draw from these studies.

Oral Corticosteriods versus Placebo, With or Without Bronchodilators

The five studies in Evidence Table 6 met our inclusion criteria.[66] We found two articles on one study; the second reported 5-year outcomes.[23,67-69]

All studies compared oral corticosteroids (i.e., prednisolone, prednisone, or dexamethasone) to placebo. Except for Van Woensel et al., all employed bronchodilators as a cointervention in

all arms of the study.[23,66,69,70] Val Woensel et al. allowed the use of bronchodilators as needed and reported no difference in use between study groups.[67,68] The studies by Goebel et al., Berger et al. and Schuh et al. used albuterol (Berger et al. allowed the use of either oral or nebulized albuterol); the Klassen et al. study used salbutamol as the bronchodilator of choice. The studies were small (51 and 72 subjects). Most of the studies enrolled children up to 2 years of age, although Berger et al. admitted infants up to 18 months and Klassen et al. included infants up to 15 months of age. Van Woensel et al. admitted infants with severe disease and comorbidities, including those on ventilators and with BPD. All studies used some type of symptom score as an outcome. Other primary outcomes included hospitalization, readmission, persistent symptoms, and need for other treatments. Adverse events, largely unreported, were limited to the expected side effects of bronchodilator use.

These research teams found few differences between study groups overall. Goebel et al. reported a statistically significant difference in clinical scores between days 0 and 2; the group that received both prednisolone and albuterol improved more than the placebo and albuterol groups.[66] Berger et al. demonstrated no difference in clinical scores, respiratory rate, or oxygen saturation between the prednisone and placebo groups.[70] They also were able to contact approximately three-quarters of the parents at 2 years after the initial study; for this group, they determined that infants who had received oral prednisone experienced more respiratory symptoms (35.7 percent in the prednisone group versus 28.6 percent in the control group, *P*-value not reported). Overall, about one-third of the followup population had persistent respiratory symptoms at 2 years. Schuh et al. found significantly lower rates of hospitalization (19 percent vs 44 percent), improved clinical scores at 240 minutes post-treatment, and less need for corticosteriods after discharge in the dexamethasone plus nebulized albuterol group compared with the placebo plus albuterol group.[23]

The initial Van Woensel et al. study found a significantly greater mean decline in symptom score among the 39 nonventilated patients and a shorter duration of hospitalization among the 14 ventilated patients.[68] Five-year followup did not demonstrate any significant differences in long-term outcomes such as wheezing in the first year of life or persistent or late-onset wheezing.[67]

Conclusions

As noted for other clinical issues, these studies were likely underpowered to detect many outcomes. Primary outcomes included many surrogate outcomes such as clinical scores, but this group of studies also measured several outcomes of interest to parents and clinicians such as hospitalization and development of asthma. Differences in agents, doses, duration of treatment, and outcomes measured limit comparison and pooling of results in this group of studies. The majority of these studies did not report adverse events; no outcomes specific to the side effects of corticosteroids were reported.

Three studies measured hospitalization or hospital duration as a primary outcome.[23,66,68] Only Schuh et al. found a statistically significant difference between groups.[23] Two studies, those by Berger et al. and Van Woensel et al., examined longer-term respiratory symptoms; both found that the group assigned to oral corticosteroids had increased symptoms on followup.[67,68,70] Two other studies, Schuh et al. and Klassen et al., used dexamethasone, although the Schuh et al. team used a substantially higher dose.[23,69] Because Schuh et al. was the only one to demonstrate a difference in hospitalization of nonventilated patients, a future study may want to compare dexamethasone to placebo and higher versus lower doses of dexamethasone. Finally, several other significant differences appeared between treatment groups. Although many of these

outcomes were of less clinical significance than measures such as hospitalization, the results of this group of studies warrant at least one adequately powered study with clinically relevant outcomes to determine whether corticosteroids are a helpful adjunct to or a primary treatment for bronchiolitis.

Parenteral Dexamethasone versus Placebo

Detailed Results

Two studies in Evidence Table 7 employed parenteral dexamethasone to treat patients with bronchiolitis.[43,48] Roosevelt et al. used 1 mg/kg of dexamethasone administered intramuscularly (IM) each day for 3 days in 122 hospitalized infants under 1 year of age.[43] De Boeck et al. studied 32 hospitalized children younger than 24 months of age.[48] The active treatment group was given a loading dose of 1.2 mg/kg of dexamethasone administered IV with the dose divided and given twice per day on day one. Infants were given "0.015 mg/kg on days 2 and 3", but it is unclear whether this dose was given every day or twice per day. If it is a total dose, then clinically it appears low for maintenance therapy, we would then question whether there might be a typographical error in the article. Children in this study by DeBoeck and colleagues also received salbutamol plus ipratropium bromide aerosolized every 6 hours while hospitalized.

Primary outcomes measured were duration of oxygen therapy and time to normalization of clinical score for the Roosevelt et al. study and duration of hospitalization for the DeBoeck et al. study. Neither study demonstrated significant differences between study groups for either these primary outcomes or their particular secondary outcomes. However, the Roosevelt et al. study may have had an allocation imbalance; significantly more infants with low oxygen saturation had been allocated to the dexamethasone group.

The Roosevelt group reported two episodes of occult stool blood in the dexamethasone group and one in the placebo group. The DeBoeck et al. team did not report adverse events. Neither study examined longer term outcomes such as persistent or recurrent wheezing.

Conclusions

We found no evidence that parenteral corticosteroids represent an effective treatment for bronchiolitis. Although neither of these studies reported sample size calculations, together they included a total of 154 subjects. This is likely a large enough group to safely conclude that the negative results of these studies cannot be attributed simply to low power. Both studies were conducted among hospitalized patients, although only the DeBoeck et al. study measured duration of hospitalization as an outcome (finding no significant differences). Baseline oxygen saturation imbalance in the Roosevelt et al. study may have created a situation in which detecting a significant difference in the primary outcomes would have been impossible. Finally, given that oral corticosteroids achieve blood levels equivalent to those for parenteral dosing, we advise that subsequent studies of corticosteroids for bronchiolitis concentrate on oral preparations.

Nebulized Corticosteroids versus Placebo or Usual Care

Detailed Results

We included seven studies of inhaled corticosteroid (Evidence Table 8).[71-77] Six of the studies used budesonide;[71-76] while Wong et al. used fluticasone.[77] Fox et al. and Wong et al. used a metered dose inhaler (MDI) for medication administration; the remaining studies employed nebulized budesonide.[73,77] Four studies compared inhaled corticosteroids to placebo;[71,73,73,75,76,76,77,77] one used a usual-treatment control group. Usual treatment in this case could include bronchodilators, oxygen, and/or racemic epinephrine. Reijonen et al. compared inhaled budesonide to usual treatment and included a group randomized to inhaled cromolyn sodium in a 3-arm study. Daugbjerg and colleagues compared combinations of nebulized budesonide, nebulized terbutaline, oral prednisolone, and placebo controls in a four arm study.

For the most part, this set of studies enrolled a population younger than those described in earlier evidence tables. Of these six studies, four enrolled infants up to a year of age; the Kajosaari et al. study enrolled children up to 9 months of age and the Reijonen et al. study accepted children up through 23 months of age. These studies measured a diverse range of primary outcomes, including duration of hospitalization, rehospitalization, oxygen requirement, clinical scores, need for other treatments, withdrawal from study because of clinical deterioration and asthma symptoms at time periods up to 2 years after treatment.

Fox et al. found a statistically significant increase in symptoms scores and the median number of symptomatic episodes at 12 months in the group treated with budesonide for 8 weeks after the acute episode of bronchiolitis compared to the placebo group.[73] A subgroup analysis was performed to control for differences by sex among the followup group at 12 months. Although the trial entry groups did not differ significantly by sex, more males had persistent symptoms and had been enrolled in the budesonide group. The authors concluded that there were no differences after controlling for sex, but the *P*-value on this analysis was 0.051, raising concerns that budesonide might unexpectedly have contributed to the increased symptoms in the group that received it. This study violated principles of an intention-to-treat analysis, 11 of 60 subjects were excluded from the final analysis because of loss to followup, partial followup, or noncompliance with treatment. This loss of nearly 20 percent of the original group may have contributed to these findings.

In the Kajosaari et al. study, one budesonide arm received 0.5 mg three times a day for 7 days and the other arm received 0.5 mg twice a day for 2 months. Both arms were compared to infants receiving symptomatic treatment alone. Fewer budesonide infants required asthma inhalation therapy at 2 years after study entry.[74] The Reijonen et al. study found statistically significant decreases in the number of infants who had greater than or equal to one episode of wheezing at the 9 to 16 week followup interval for both the cromolyn sodium and the budesonide groups compared with a group that received no treatment.[75] They also found fewer infants who had at least two episodes of wheezing at the 1-16 week follow up period, but in the budesonide group alone compared with both the cromolyn sodium and no treatment groups. In the Richter et al. work, of 21 infants who received budesonide, 10 were readmitted for respiratory problems. By contrast, of the 19 infants who received placebo, two were readmitted. This group reported no other significant differences in any other outcomes.[76]

Daugbjerg et al. studied 114 children from 6 weeks to 18 months of age who had acute wheezing.[72] This study made no attempt to distinguish between bronchiolitis and asthma and infants with recurrent wheezing were admitted to the study. Infants were randomized into four groups. Group A received a three day oral prednisolone course, nebulized terbutaline every four hours for up to five days and a second nebulized placebo. Group B received the nebulized terbutaline along with nebulized budesonide every four hours for up to five days, and an oral placebo for three days. Group C was given nebulized terbutaline with a placebo nebulized agent and an oral placebo while Group D received all three agents as placebo. All groups who received active treatment versus placebo showed significant improvement as measured by fewer withdrawals for treatment failure, but differences between active treatment groups were not found. There were statistically significant differences between the groups for mean days of hospitalization with Groups A and B having the shortest duration of hospitalization. No adverse events were observed.

Although most of the outcomes measured by this series of studies were intermediate in nature, several significant differences were found. That worsened outcomes in the budesonide group occurred in two of the six studies is of concern, but these differences may be simply a matter of chance.

Wong et al. found no significant differences in audio-recorded episodes of night cough or lung function tests except for a small but statistically significant decrease in these measures at the 36-week followup period in the fluticasone group.[77] Symptom scores were low in both the fluticasone and the placebo groups and showed no statistical differences after correction for multiple comparisons. Two infants on fluticasone developed oral candidiasis.

Of interest, all these studies examined longer-term respiratory symptoms such as persistent wheezing, at 4 to 24 months after study entry. Only the Fox et al. and Kajosaari et al. studies demonstrated improvements in these outcomes in the more clinically relevant followup period of 12 to 24 months.[73,74] Duration of inhaled corticosteroid use was relatively brief in all these studies; both the Fox et al. and Kajosaari et al. studies continued corticosteroids for 8 weeks; only the Wong et al. continued treatment for a longer time (3 months).

Conclusions

Six of these seven studies of inhaled corticosteroids employed budesonide, but at total initial daily doses that ranged from 0.4 mg to 2 mg per day. Duration of treatment with budesonide ranged from 1 to 8 weeks. The variety of dosing regimens and the wide array of outcomes makes comparison across these studies problematic.

Although the number of outcome events in these studies are small, three studies demonstrated longer-term symptom improvement such as fewer episodes of wheezing and less need for asthma therapy. An adequately powered definitive study of inhaled budesonide is needed to determine whether inhaled budesonide is an effective treatment for bronchiolitis or results in improved long-term outcomes such as less development of persistent wheezing and cough. It appears from this review that studies that continued inhaled corticosteroids for longer periods of time after the episode of bronchiolitis (e.g., 8 weeks) were more likely to show this effect. Studies examining the effectiveness of both the dose and duration of inhaled corticosteroid therapy are needed.

Two of the five studies using inhaled budesonide for 6 and 8 weeks after an episode of bronchiolitis compared to placebo found worse outcomes in the budesonide group.[73,76] These adverse outcomes warrant clinical caution in use of inhaled budesonide for bronchiolitis at this

time; a trial with adequate power to detect adverse events will help to clarify these issues in the future.

Ribavirin versus Placebo

Detailed Results

Ribavirin is an antiviral medication that is administered as a continuous aerosol for a number of hours per day. It has been studied as a specific treatment for bronchiolitis caused by respiratory syncytial virus. We located seven articles that met our inclusion criteria (Evidence Table 9).[42,45,46,78-81] Details of the randomization protocol in the Barry study were confusing, although the abstract of the article did state that it was a "randomized double blind placebo controlled trial" (p. 593).[46] However, the article states (p. 593) that "Infants were allocated to active treatment or placebo by a process of minimization of the differences in the pretreatment distribution of age, arterialised capillary carbon dioxide tension, respiratory rate and interval since onset of chest symptoms, and in the incidence of a random factor". In addition, the abstract of the Taber et al. study calls it a "double-blind study," and the paper states (p. 613) that "assignment to treatment or control groups was prepared from a table of random numbers".[45]

As a group these were small studies; the largest enrolled 42 patients.[79] Most of the enrolled infants were younger than 6 months of age; only one study enrolled infants with serious comorbidities. All six studies compared aerosolised ribavirin to saline placebo. Three of the studies used a 20 mg/ml concentration of ribavirin administered 18 hours per day.[46,79,80] Primary outcomes assessed included various symptoms, clinical scores, duration of hospitalization or ventilation, time to clinical improvement, respiratory rate, pulmonary function tests, need for other treatments, readmission to hospital, and development of persistent symptoms such as wheezing.

Barry et al. found that the mean time to sustained improvement in both cough and crepitations was significantly better in the ribavirin group.[46] However, they detected no significant differences in nasal discharge or flaring, feeding, wheezing, rhonchi, and chest retractions. They also reported significant differences in changes in respiratory rate at 24 and 30 hours after enrollment. Heart rate tended to fall more rapidly in the ribavirin group, but the decrease was not significantly different in the treatment compared to the control group at any point during treatment.

Rodriguez and colleagues conducted two studies.[42,81] The initial study involved 30 children randomized in a 2 to 1 ratio to ribavirin or distilled water.[42] The rate of change in the symptom severity score was significantly higher in the ribavirin group at days 2 and 3 compared with day zero. However, the symptom scores in the ribavirin group were nonsignificantly greater at day zero as well. The second concerned longer-term followup of the infants who had been enrolled in their 1987 study and information on an additional 10 infants who had been enrolled in the later study.[81] They state that the same study protocol was used. Over these two seasons 42 patients were randomized (25 to ribavirin and 17 to placebo) and 35 (24 from the ribavirin group and 11 from the placebo group) participated in the followup study. Followup data were collected for up to 6 years of age. Fewer children (four of 24 in the ribavirin group versus six of 11 in the placebo group) had two or more episodes of wheezing at ages 1 to 6 years. Of the 35 patients enrolled in the followup study, 19 completed pulmonary function testing. Significantly more

children in the placebo group had moderate to severe scores (6 of 13 versus 6 of 6, $P = 0.04$). However, the followup participation rate for the ribavirin group was higher (96 percent vs. 65 percent, $P < 0.02$) than in the placebo group. Children with more severe disease might be more likely to followup in both groups; that is, the differentially higher losses to followup in the placebo group raises concern that the less affected individuals did not participate in the followup study.

In the Taber et al. trial, the mean symptom score was lower on day 3 in the ribavirin group than in the placebo group ($P = 0.044$).[45] However, they reported no significant differences in mean symptom scores on Days 1 and 2. Infants in the control group were more likely to experience a four-fold rise in RSV-neutralizing antibody than were infants in the ribavirin group ($P = 0.045$), but no other significant differences occurred in more clinically relevant secondary outcomes such as length of treatment or time to discharge.

Three articles reported adverse events.[46,78,79] These included one episode of transient eyelid erythema thought secondary to ribavirin exposure and one episode of acute respiratory distress leading to discontinuation of ribavirin.

Conclusions

The studies of ribavirin are all very small and likely underpowered to detect significant differences in outcomes. Studies did not account for multiple comparisons in design. Most reported a myriad of outcomes, and most of these were intermediate or surrogate in nature. No significant differences in clinical meaningful outcomes were found in this set of studies. A previously published meta-analysis of ribavirin studies supports this conclusion.[20]

Antibiotics versus No Treatment or Other Antibiotics

Detailed Results

Although our literature search did not locate any primary studies of the effect of antibiotics for treatment of bronchiolitis, we did find two RCTs evaluating the effectiveness of antibiotics for lower respiratory infection in which subsets of enrolled patients had bronchiolitis.[49,82] Evidence Table 10 summarizes the bronchiolitis subgroup analyses of these studies.

Friis et al. studied 61 children with an average age at enrollment of approximately one and a half years who were RSV positive.[49] The active treatment group received oral ampicillin if under 2 years of age and oral penicillin if over 2 years of age. Penicillin-allergic children were treated with erythromycin. The control group did not receive antibiotic therapy on a routine basis, although seven of 27 children ultimately did receive antibiotics for other reasons such as cyanosis or persistent fever. Primary outcomes included duration of hospitalization and whether the child was considered "pulmonarily healthy" on day 3, at discharge, and at 3 weeks after treatment. The study groups did not differ significantly on any of these outcomes.

A large open-label study by Klein enrolled 348 children with acute community-acquired lower respiratory tract infections of whom 19 had bronchiolitis.[82] Children in this study were randomized in a 2:1 ratio to oral cefpodoxime proxetil or oral amoxicillin/clavanulate. In the overall study the group randomized to amoxicillin/clavanulate was significantly older than the cefpodoxime porxetil group (3.1 vs. 1.8 years), but data are not presented individually for the

bronchiolitis subgroup. The primary outcome was clinical cure or improvement. Significance testing was not performed, but Klein reports that nine of 10 children in the cefpodoxime proxetil group versus four of four children in the amoxicillin/clavanulate group experienced a clinical cure or improvement. The time frame for this outcome is not stated. Four patients in each group in the overall study discontinued their treatment medication because of side effects such as vomiting, diarrhea, and rash. Adverse events for the bronchiolitis subgroup are not presented separately.

Conclusions

These two studies were not primarily designed to answer the question of whether antibiotic therapy is useful in the treatment of bronchiolitis. Rather, they had subgroups of children with bronchiolitis who had been randomized into larger studies of the effect of antibiotic therapy on lower respiratory illnesses. These subgroup analyses likely lacked power to detect potentially important outcome differences. Subgroup allocation imbalances and treatment cross-overs may have imposed substantial biases into the bronchiolitis-specific analyses.

No evidence suggests that antibacterial antibiotic therapy is an effective treatment for bronchiolitis. Bronchiolitis in infants and children is caused by viruses, primarily RSV. Therefore, no a priori reason exists to assume that antimicrobial agents effective against bacteria would be appropriate treatment for a viral illness. Antibiotic treatment should be reserved for children who develop complications related to subsequent bacterial infection.

It should be noted, however, that a substantial proportion of infants with bronchiolitis may have acute otitis media (AOM) and thus may have a primary indication for antibiotic therapy. Andrade and colleagues enrolled 42 children with bronchiolitis, age 2 months to 2 years, in a prospective study.[83] They found that 62 percent had or developed AOM within 10 days. While automatic treatment of AOM with antibiotics is controversial, at least some of these infants will likely have a warranted indication for treatment.

RSVIG IV as Treatment for Bronchiolitis

Detailed Results

Rodriguez and colleagues studied the use of RSVIG administered intravenously for treatment of RSV bronchiolitis in two studies (Evidence Table 11). The first study was done with a group of previously healthy infants and the second was conducted among infants at high risk for complications from RSV bronchiolitis. The first studied a group of 101 previously healthy infants under 2 years of age who were hospitalized with moderate to severe RSV-positive bronchiolitis and/or pneumonia and followed them for 1 year after the intervention.[25] This medication is generally used for prophylaxis against RSV bronchiolitis among high-risk infants during RSV season. (The studies detailing its use in this manner appear in the results section for Key Question 3.) However, in these studies by Rodriguez and colleagues the drug was used as a treatment for infants who already had bronchiolitis rather than as a prophylactic agent. The intervention group in the first Rodriguez study received a single dose of 1500 mg/kg IV RSVIG or 0.5 percent albumin placebo. Mean days of hospitalization (4.58 vs. 5.52, $P = 0.24$) and mean days of mechanical ventilation (4.31 vs. 5.54, $P = 0.45$) were not statistically different between

the treatment and placebo groups. However, there was a trend toward a decrease in the mean number of days of ICU admission (3.92 vs. 6.60, $P = 0.06$). There were no adverse events related to RSVIG therapy. The study was designed with 90 percent power to detect a 20 percent decrease in duration of hospitalization assuming that the control group had a mean stay of 3.5 days. Although the study achieved its target enrollment, hospital stays among the control group averaged 5.52 days. Thus, the study was underpowered to detect less than a 35 percent difference in duration of hospitalization.

Rodriguez et al. also studied 107 high-risk infants under 2 years of age who had severe BPD, other serious chronic lung disease, or congenital heart disease or who had been premature at under 32 weeks' gestation with a chronological age of less than 6 months.[41] Infants were randomized to 1500 mg/kg IV RSVIG or albumin placebo and were followed into the next RSV season to assess possible harms, including whether there was any increased risk of enhanced RSV disease in children who did develop the disease in the second season. No meaningful difference was noted between the groups in the primary outcome of duration of hospitalization (8.41 days vs, 8.89 days, $P = 0.73$). No significant differences were reported for secondary outcomes such as duration of ICU admission, duration of mechanical ventilation, need for supplemental oxygen, change in respiratory scores after infusions, need for additional medications (bronchodilators, ribavirin, or steroids), development of RSV in the subsequent season, or readmission during the subsequent season. Some differences between the study groups could have contributed to the negative findings of this study. The RSVIG group had higher entry respiratory scores and more severe disease episodes than did the placebo group. Forty-seven percent and 28 percent, respectively required ICU admission, and 31 percent and 18 percent needed mechanical ventilation.

Conclusions

The Rodriguez et al. studies of the use of RSVIG IV as a treatment modality among normal infants with more severe disease did show a trend toward lowered duration of ICU hospitalization, but it was underpowered to detect a difference in total length of hospitalization.[25] Similarly, the study conducted among high-risk infants failed to demonstrate the effectiveness of RSVIG IV as a treatment modality although this study was relatively small and baseline differences between groups could have accounted, at least in part, for the negative results. In either case, a larger study would be required to detect meaningful clinical differences.

Other Miscellaneous Treatments for Bronchiolitis

Detailed Results

Evidence Table 12 groups six heterogeneous studies that each examined a novel treatment for bronchiolitis: Alpha-2 interferon,[47] helium-oxygen therapy,[84] Chinese herbs,[51] porcine-derived surfactant,[39] aerosolized furosemide,[85] and recombinant human deoxyribonuclease.[40] We consider the results of these studies individually although for convenience we grouped them in this single evidence table.

Chipps et al. enrolled 22 infants with acute bronchiolitis under 2 years of age to receive intramuscular injections of alpha-2 interferon or placebo for five days.[47] Six of these infants

were on ventilators: four in the interferon group and two in the placebo group. The primary outcomes were a clinical symptom score and the number of days on oxygen therapy. The researchers found no significant differences between study groups for either these outcomes or for any secondary outcomes. They also noted no adverse events. However, the study was halted after other reports of interferon (IFN) cardiotoxicity were published.

Hollman and colleagues studied 13 infants with RSV-positive bronchiolitis in a randomized cross-over trial of inhaled helium-oxygen versus inhaled air-oxygen mixtures.[84] Virtually all the patients also received nebulized albuterol, and most had some comorbidity such as cardiac disease and clinical asthma. The primary outcome was change in clinical asthma scores. The authors reported a significant improvement in clinical score for infants on the helium-oxygen mixture compared to baseline ($P < 0.05$). Analysis of trial results is difficult not only because of the small numbers involved, but also because five nonrandomized patients were included in the report of many outcomes.

Kong et al. studied 96 previously well children up to 4 years of age admitted to hospital with lower respiratory tract disease and serologic evidence of RSV. Subjects were randomized to three groups.[51] The first group received a traditional Chinese herbal treatment, Shuang Huang Lian, intravenously for 7 days. The second group received the herbal preparation plus either lincomycin or cephazolin, also for 7 days. The third group received only the antibiotics as for group two. The authors provided no rationale for the seemingly interchangeable use of these two antibiotics. Primary outcomes studies included mean days of wheezing, mean days of any sign or symptom, and mean duration of hospital stay. The analyses tested the first two groups, those that received Shuang Huang Lian with or without antibiotics, against the third group that received only antibiotics. The authors report statistically significant improvements in the mean days with any sign or symptom and mean duration of hospital stay for groups one and two compared to group three. The fact that these patients were hospitalized for extended periods makes generalizability to other populations questionable.

The Luchetti et al. study was designed to assess the effect of porcine-derived surfactant therapy for children with severe bronchiolitis requiring continuous positive pressure ventilation for at least 24 hours without clinical improvement prior to study entry.[39] One group received two to three doses of surfactant instilled into the trachea via an endotracheal tube along with continuous positive pressure ventilation; the other group had continuous positive pressure ventilation. Children were sedated and paralyzed prior to administration of surfactant. A careful reading of the paper does not find any indication that the control group was sedated or paralyzed or received any placebo. Both groups received other standard care as needed. The primary outcome measures were mean duration of ICU stay and of continuous positive pressure ventilation. The authors reported that the surfactant group showed statistically significant improvements in both outcome measures. Mean duration of ventilation was 4.4 days in the surfactant group versus 8.9 days in the control group ($P < 0.05$). Similarly, mean ICU stay duration was 10.1 days in the surfactant group versus 15.7 days in the control group ($P < 0.05$). The authors do not address the question of whether differential use of sedation and paralytic agents in the surfactant group might have influenced any of the outcome variables considered, but the effects of these types of medications are generally transient.

Van Bever et al. studied the effect of inhaled aerosolized furosemide versus saline placebo on 28 infants having a first episode of acute bronchiolitis with wheezing.[85] The primary outcome was the mean clinical score at baseline, and 15 and 30 minutes after treatment. Although clinical

scores improved for both groups, they did not differ significantly between groups. The study reported power of 79 percent to detect a clinical score difference at 30 minutes post treatment.

Nasr et al. conducted a randomized placebo-controlled study of nebulized recombinant human deoxyribonuclease (rhDNase) in 86 previously healthy hospitalized children under 2 years of age with proven RSV infection.[40] The treatment group received 2.5 mg of nebulized rhDNase in an excipient vehicle daily for up to 5 days and the placebo group received the excipient alone. The primary outcome was mean duration of hospitalization, which was nearly identical between the two groups (3.34 days in the placebo group vs. 3.33 days in the rhDNase group, $P = 0.97$). The treatment and control groups did not differ significantly in terms of secondary outcomes of mean change in respiratory, wheezing, and retraction scores; they did differ significantly in the chest x-ray change score, but the clinical meaningfulness of this measure is dubious in view of the other outcomes. There was a trend toward more severe disease in the rhDNase group compared with the placebo group, but these differences did not reach statistical significance. No adverse events were reported.

Conclusions

The one trial of alpha-2-interferon was small and underpowered to detect meaningful clinical outcomes.[47] It was stopped early because of concerns about cardiotoxicity, although the researchers reported no such adverse events. On this basis alpha-2-interferon does not appear to offer promise as a treatment for bronchiolitis.

The Hollman et al. study of inhaled helium-oxygen for severely ill children with RSV bronchiolitis was very small; it is statistically significant difference in asthma scores may be due to chance or to the specific choice of outcome.[84] However, helium-oxygen may be worth studying in a well-designed and adequately powered RCT to determine whether positive outcomes can be replicated. This intervention is clearly not applicable to the majority of infants and children with bronchiolitis, who rarely have severe disease.

Although the results of the Kong et al. study are intriguing, we do not believe this intervention to be practical in the United States because of the paucity of clinical locations able to administer this type of traditional Chinese herbal therapy and because the sheer length of hospitalization required does not match current U.S. practice patterns.[51] Length of hospital stay differed significantly, but the range among study groups was 7 to nearly 10 days.

The Luchetti et al. study was also small, but its positive results in both primary outcomes (both of which would be of clinical relevance to both clinicians and parents) argue for a well-designed and adequately powered RCT to determine whether the use of surfactant as an adjuctive treatment for severely ill, ventilated infants with bronchiolitis is efficacious.[39]

The Van Bever et al. study was small; the longest time frame for outcome measurement was 30 minutes.[85] If an adequately powered study is mounted, then it will need to measure patient-oriented outcomes at appropriate time intervals.

The study from the Nasr team did not demonstrate that nebulized rhDNase provides a clinical benefit in the treatment of bronchiolitis.[40] Any use of this agent should be restricted to properly designed trials.

Key Question 3: The Role of Prophylaxis in Prevention of Bronchiolitis

RSVIG IV versus Placebo or Standard Care to Prevent RSV Bronchiolitis

We located four studies of intravenous RSVIG to prevent bronchiolitis among both high-risk and standard-risk infants (Evidence Table 13).[86-89] This medication is administered monthly during the RSV season and may be administered in the hospital or a clinic. In some locations, the infusion may also be administered by a home intravenous therapy team. In clinical practice its use has largely been superceded by palivizumab, which will be addressed in the next section.

Groothuis and colleagues studied 249 children less than 48 months of age with BPD due to prematurity, congenital heart disease or cardiomyopathy, or a history of prematurity along with a chronological age of less than 6 months.[87] These children, who were all at high risk for RSV infections, were randomized to either high-dose (750 mg/kg IV every month) or low-dose (150 mg/kg IV every month) RSVIG or a standard care and control group. Primary outcomes included total and moderate-to-severe episodes of RSV and non-RSV respiratory illness. They found both significantly fewer total cases RSV-related lower respiratory infections and fewer severe cases in the higher-dose RSVIG IV group compared to the standard-care group. The low-dose group and the control group did not differ significantly on primary outcomes. Differences between the high- and low-dose groups were not reported. In secondary outcomes they also reported significantly fewer hospitalizations, hospital days, and ICU days for the high-dose group compared to the standard-care group. Eight-five percent of the 249 enrollees were followed into the subsequent RSV season and there was no suggestion of enhanced disease in either the high or low dose groups who were hospitalized for RSV infections. Enhanced disease had been a concern in early RSV vaccine trials such that these investigators were asked to specifically look for this adverse effect.

Groothuis et al. also published a subgroup analysis of the 162 premature infant from this study, excluding the children with congenital heart disease.[86] There were 102 preterm children with BPD and the remaining 60 had no evidence of lung disease. The analysis was further restricted to a comparison of the high-dose (n = 58) and control groups (n = 58) as the original analysis had not demonstrated efficacy of the low-dose therapy. Subjects were followed monthly during the 5 months of the intervention and then into the subsequent RSV season. Primary outcomes for this analysis included total incidence of RSV illnesses, incidence of severe RSV illness, hospitalizations for RSV infections, mean duration of ICU admission, and mean worst respiratory score. There were statistically significant differences favoring the high-dose group over the control group with the exception of the mean difference in duration of hospitalization which achieved borderline significance ($P = 0.06$). This study had potential problems with the masking of study personnel because an unblinded team was responsible for enrollment, examinations at the time of infusion, and well-infant examinations. A masked team was responsible for weekly followup and evaluation of all respiratory illnesses. Follow up of all of the preterm children into their second RSV season did not demonstrate any enhanced RSV illness upon infection with RSV.

Simoes et al. studied a group of 425 children under 48 months of age with congenital heart disease or cardiomyopathy; they randomized subjects to 750 mg/kg IV RSVIG every month during RSV season or to a control group that received no intervention.[88] As with the Groothuis et al. studies, the Simoes et al. team responsible for enrollment, treatment, and clinical assessment was not masked, whereas the team responsible for weekly surveillance and clinical evaluation of respiratory illnesses was masked. The primary outcomes were total acute respiratory illnesses, total upper and lower RSV-associated respiratory illnesses, and both RSV-associated and nonassociated lower respiratory tract illness hospitalizations.

The investigators reported significantly fewer acute respiratory illnesses (73 percent vs. 82 percent, $P = 0.02$) and total hospitalizations for lower respiratory tract illnesses (17 percent vs. 27 percent, $P = 0.02$) in the RSVIG group compared to the no-treatment group. In subgroup analysis they found fewer RSV hospitalizations in the treatment group under 6 months of age. They found no significant overall differences for RSV hospitalization by cardiac subgroup, but when they removed the group of children with biventricular heart disease with right-to-left shunt from the analysis, they detected a trend toward a decrease among infants with all other types of heart disease (biventricular without shunts, biventricular with left-to-right shunt, and single ventricle or hypoplastic left heart) included in the study (11 percent vs. 27 percent, $P = 0.06$.) A randomization imbalance resulted in more children with left-to-right cardiac shunt in the control group and more with right-to-left shunt in the treatment group. A significantly increased rate of serious adverse events related to cardiac surgery and increased rate of cyanotic spells was observed in children with cyanotic congenital heart disease receiving RSVIG IV and were thought due to receipt of the RSVIG IV treatment

The PREVENT Study Group conducted a multicenter trial involving 510 high-risk infants less than 2 years of age with BPD or who were premature (= 35 weeks) and under 6 months of age at the time of enrollment.[89] The intervention group received 750 mg/kg IV RSVIG monthly during RSV season; the control group received albumin placebo. Several significant positive differences between groups occurred, including fewer RSV-related hospitalizations (8 percent vs. 13.5 percent, $P = 0.047$), fewer total number of RSV-related hospital days (60 vs. 129, $P = 0.045$) and days in hospital requiring oxygen therapy per 100 children (34 vs. 85, $P = 0.007$). The RSVIG IV treatment group also experienced fewer hospital days with severe clinical scores per 100 children (49 vs. 106, $P = 0.049$), incidence of total respiratory hospitalizations (16 percent vs. 27 percent, $P = 0.005$) and total number of respiratory hospital days per 100 children (170 vs. 317, $P = 0.005$). In a set of subgroup analyses for prematurity, presence of BPD, age less than 6 months at trial entry, and weight under 4.3 kg, trends emerged toward fewer hospitalizations in all subgroups receiving RSVIG IV, but statistical testing was not performed for these exploratory secondary analyses. The paper does not mention statistical correction for multiple comparisons. When infusions were incomplete or prolonged because of an adverse event judged potentially related to the study drug, the problem occurred more often in the group receiving RSVIG IV (3.2 percent vs. 1 percent).

Conclusions

RSVIG IV administered at a dose of 750 mg/kg IV on a monthly basis during RSV season appears to be an effective prophylactic treatment for children at high risk of RSV disease and its complications. The adverse effects of this therapy included fluid overload and respiratory distress, but all deaths in studies were judged to have been caused by underlying disease rather than receipt of the drug.

Monoclonal Antibody for Prophylaxis of RSV Bronchiolitis

We located one large randomized placebo-controlled study of palivizumab as a prophylactic intervention (Evidence Table 14).[90] This agent is a humanized monoclonal IgG antibody that binds to the RSV fusion protein providing passive immunity against RSV. Like RSVIG IV it must be administered monthly during RSV season. Palivizumab was approved by the U.S. Food and Drug Administration in June 1998. Further trials of this intervention are in process and data are expected to be released later in 2002, including results of a study among children with congenital heart disease. We also located one preliminary trial of another monoclonal antibody, (SB 209763), which has not been subject to further study and is not available for use.

The IMpact-RSV Study Group studied 1,502 high-risk infants who were premature (= 35 weeks) and under 6 months of age or were 24 months of age and younger with symptomatic BPD.[91] Children were randomized in a two-to-one ratio to either palivizumab 15 mg/kg IM or placebo every 30 days for up to 5 month. The primary outcome was incidence of RSV hospitalizations. In the placebo group, 53 of 500 children (10.6 percent) were hospitalized for RSV infection, compared to 48 of 1,002 children (4.8 percent) in the palivizumab group ($P <$ 0.001.) The majority of secondary outcomes showed statistically significant benefits of the treatment as well. Among these secondary outcomes were total numbers of hospitalizations and hospital days per 100 children (62.6 vs. 36.4 days, $P < 0.001$), total days of RSV hospitalizations requiring oxygen therapy per 100 children (50.6 vs. 30.3 days, $P < 0.001$), hospital days with a severe clinical score per 100 children (47.4 vs. 29.6 days, $P < 0.001$), and incidence of ICU care (3 percent vs. 1.3 percent, $P = 0.026$). The differences observed in secondary outcomes are attributable to decreased RSV incidence and severity in the palivizumab group as the incidence of respiratory hospitalization unrelated to RSV was similar between the groups (14 percent vs. 13 percent, $P = 0.505$). Subgroup analyses examined the incidence of RSV hospitalization by weight, prematurity without BPD and BPD alone. All of these subgroup analyses showed a significant benefit of palivizumab. Adverse events, including development of fever, nervousness/irritability, injection site reaction, and diarrhea were not significantly different between the treatment and control groups. The overall rate of reported adverse events judged to be related to the study drug was 10 percent in the placebo group and 11 percent in the palivizumab group.

Meissner and colleagues conducted a trial to evaluate the safety, pharmokinetics and immungenicity of SB 209763, a humanized monoclonal antibody against RSV fusion protein.[92] The study population consisted of 43 infants with BPD or without BPD who had been born prematurely at less than or equal to 35 weeks of gestation. Infants were randomized to receive two doses of the antibody 8 weeks apart, at one of four dosage levels ranging from 0.25 to 10.0 mg/kg per dose at each administration. The so-called "placebo" group was actually a group of infants who received placebo at the first administration and then were crossed over to receive a dose of SB 209763 at the dosage level that had been assigned in their randomization scheme 8 weeks later. The 5.0 and 10.0 mg/kg doses of both SB 209763 and placebo were split into two syringes and administered one into each thigh. However, there was no attempt made to completely blind the administration of lower dose levels by giving two injections as well. There was a trend toward fewer episodes of proven RSV infection in the group that received the 10.0 mg/kg dose of SB 209763 vaccine compared to placebo (1 of 22 vs. 2 of 10, $P = 0.20$) this difference did not reach statistical significance. There was a lower rate of proven RSV infection at the three other dose levels as well, but the *P*-values ranged from 0.72 at the 0.25 mg/kg dose to

0.49 at the 5.0 mg/kg dose level. Four adverse events judged related to the study drug were identified and included three episodes of mild/moderate purpura and one episode of thrombocytosis. The authors suggested that the doses used might have been too low to confer adequate clinical immunity and that future trials test higher doses of monoclonal antibody.

Conclusions

Palivizumab administered monthly during RSV season is an effective and safe intervention to prevent severe disease and decrease hospitalizations among infants and children at high risk for developing severe RSV infections. This prophylactic agent is more convenient for children and parents than RSVIG IV as it does not require intravenous access or other associated care. There is insufficient evidence on SB 209763 to recommend its further study, particularly when another monoclonal antibody, palivizumab, is available as the standard of care.

Additional information on palivizumab comes from a single-arm, unblinded cohort study by Groothuis and colleagues. They studied 565 high-risk infants with BPD or who were less than 6 months of age at the time of enrollment and born prematurely at less than or equal to 35 weeks gestation.[90] The purpose of the study was to gather additional safety data from areas in the Northern Hemisphere where palivizumab was not yet licensed. The treatment consisted of 15mg/kg of RSVIG administered intramuscularly once every 30 days during RSV season for a maximum of five doses. There were 78 hospital admissions during the 150 days after enrollment; 65 percent of these admissions (51 cases) were attributed to respiratory causes. Of these 51 children, 29 were tested for RSV; seven tested positive, for an RSV positivity rate of 24 percent. Forty-five percent of subjects experienced some sort of adverse event, with 2 percent of subjects (11 of 564) discontinuing treatment because of the adverse event. However, the investigators believed that only three of these 11 adverse events were directly attributable to the treatment. Adverse events reported in this single-arm study were equal to or fewer than those reported in the more restricted IMpact trial described above. There were two deaths, neither thought related to the drug.

Vaccines to Prevent RSV Bronchiolitis

Our literature search revealed three studies of purified fusion protein (PFP) vaccination to prevent RSV disease (Evidence Table 15).[92-95] These are all small studies with enrollment ranging from 21 to 43. The first two studies were in high risk young children with a history of BPD and/or prematurity while the Piedra studies were conducted in older children with cystic fibrosis.

Groothuis and colleagues randomized 21 infants under 12 months of age with BPD. All infants had a proven RSV infection in the previous RSV season. These infants had previously had influenza vaccination in the previous year and were then randomized to vaccination with PFP-2 vaccine or trivalent influenza vaccine in the subsequent year.[93] Their primary outcome was RSV infection in the subsequent season. One of 10 in the treatment group and six of 11 in the control group had subsequent season RSV infections. This result was borderline statistical significance with a *P* value of 0.06. Some of the immunological secondary outcomes, including such items as mean neutralizing antibody 1 and 6 months after vaccination, were found to be statistically higher in the group that received PFP-2 compared to the placebo group. This is obviously a small study lacking sufficient power to detect even large differences between groups.

Piedra and colleagues reported the results of two studies using PFP-2 vaccine in children at high risk from RSV infection because of underlying cystic fibrosis. The first study of 34 children randomized groups to PFP-2 or saline placebo.[94] There were baseline group imbalances with the PFP group being taller, older and with lower body fat composition. There were no differences demonstrated in the development of RSV or total days of RSV illness between groups. However, there were significantly more children with one or more than one acute lower respiratory tract infection (15 of 17 vs. 9 of 17, $P = 0.024$) and with more ill days per subject (67 vs.30.5, $P < 0.001$) in the control group compared with the vaccine group. The vaccine group had fewer antibiotic courses (4.5 vs.2.2, $P < 0.001$) and fewer acute lower respiratory tract infections per subject (2.1 vs.0.8, $P = 0.005$) than did the control group. There were no significant differences in adverse events between the groups, although the vaccine group did report more cases of tenderness at the vaccine site ($P = 0.09$).

A second study by Piedra was conducted to evaluate the effectiveness of sequential yearly administration of PFP-2 versus a single administration in children with underlying cystic fibrosis.[95] A group of 29 or the 34 children who had participated in the previous study of PFP-2 vaccine discussed above were recruited into this study of sequential annual administration of vaccine. They were enrolled in this open label study to PFP-2 vaccine and all enrollees received a 50 microgram dose of the vaccine in the second season. Thus there were two groups, one which received vaccine each autumn for two seasons or saline placebo in the first year followed by PFP-2 vaccine in the second season. The sequential vaccine group which received active vaccine in both seasons had fewer children with more than one acute lower respiratory tract infection during the second season (9 of 13 vs.15 of 15, $P = 0.035$.) The sequential vaccine group was also found to have fewer acute lower respiratory tract infections per subject (1.2 vs. 2.1, $P = 0.004$) and ill days per subject (36 vs. 64.8, $P = 0.001$) compared with the group that only received the active vaccine in the second season. There were no significant differences in total number of illnesses per subject or mean number of courses of antibiotics per subject. Although only a total of 11 children had confirmed RSV infections in the second season, the sequential vaccine group of RSV infected children did have significantly fewer episodes of acute lower respiratory tract infections, days of illness and courses of antibiotics per subject. There were baseline differences between the two groups with the control group being taller, older and more likely to attend day care. Given the nature of cystic fibrosis disease and day care exposures, these baseline differences could have accounted for the outcome differences seen between the two groups. Adverse events and their distribution was comparable to those which were seen in the first Piedra study.

Conclusions

PFP-2 vaccines appear to be a promising prophylactic intervention for high risk children with BPD and/or prematurity. The available studies are small such that well-designed and properly powered studies are needed to make a definitive conclusion regarding this intervention. Administration of PFP-2 vaccine to children with cystic fibrosis may be effective at preventing acute lower respiratory tract infections and lessening the need for antibiotic use in these subjects as well. If future studies are done they may want to explore initiating the vaccine at earlier ages and further examining the effectiveness of single versus multiple vaccinations to confer immunity.

Key Question 4: Cost-effectiveness of Prophylaxis for Management of Bronchiolitis

Although palivizumab has demonstrated that it reduces RSV hospitalization in infants 32-35 weeks estimated gestational age (EGA), indication of its use in this population is reserved for infants with additional risk factors due to questions over its cost-effectiveness in the wider population. To gather and synthesize findings on the cost-effectiveness of prophylactic therapy in two particularly vulnerable subgroups of infants, we conducted a review of the published literature on the cost-effectiveness of prophylactic therapy. We sought to address the following specific questions:

- What is the evidence concerning the cost-effectiveness of prophylactic therapy for prevention of bronchiolitis among infants born from 32 through 35 weeks EGA?
- What is the evidence concerning the cost-effectiveness of prophylactic therapy for prevention of bronchiolitis among infants born from 32 through 40 weeks EGA with comorbid conditions?
- Can the cost-effectiveness of prophylactic therapy for children in the target populations be assessed from a societal perspective using information from secondary sources or the literature?

Cost-effectiveness denotes an economic evaluation producing either an incremental cost or a ratio intended to provide guidance to policy-makers tasked with health-care resource allocation. Cost-effectiveness ratios indicate the cost incurred per measure of disease avoided, such as cost per life-year saved or cost per hospitalization. Palivizumab prophylaxis has been demonstrated to reduce hospitalizations, so we adopt a standard measure of effectiveness of cost per hospitalization avoided when comparing results. Thus, policy-makers must consider quality of life and ethical issues when interpreting the value society should place on avoiding RSV hospitalization.

We identified a total of 10 studies in the literature that considered the economic consequences of prophylactic therapy for the prevention of RSV bronchiolitis. Evidence from these studies is mixed with regards to the cost-effectiveness of prophylaxis for infants born from 32 through 35 weeks EGA and infants with comorbidities, such as BPD. Some of the analyses were for RSVG-IV, an intravenous form of prophylaxis that has largely been replaced by palivizumab. Because palivizumab is less invasive and less costly than RSVIG IV, and because the TEAG members indicated that the question of cost-effectiveness should focus on the use of palivizumab versus no intervention, the economic findings described in this section are taken only from analyses of palivizumab. Four studies concentrated exclusively on palivizumab, one addressed palivizumab and RSVIG IV separately, and one analyzed a population in which approximately 75 percent of infants were given palivizumab and the other 25 percent were given RSVIG IV.

The IMpact RSV trial is the only study to date that has assessed the effectiveness of palivizumab for preventing healthcare utilization related to RSV infection among preterm infants.[91] IMpact RSV was a randomized, placebo controlled trial conducted during the 1996-1997 RSV season. The trial included 1502 children (500 in the placebo group and 1002 in the palivizumab group) born 35 weeks EGA or less, including children diagnosed with BPD. The trial did not include infants with other comorbidities, such as congenital heart disease or immune

deficiencies. Study infants were administered five monthly doses of palivizumab during the course of the RSV season, and 92 percent received all five doses.

The trial tracked hospitalization outcomes among study infants, and upon hospitalization, infants were given an RSV antigen test and a Lower Respiratory Tract Illness/Infection (LRI) score. Other outcomes measured included days of hospitalization for RSV, days with increased oxygen, total days with a moderate or severe respiratory illness (based on LRI), days of stay in ICU, and the use of mechanical ventilation. All subjects were included in the safety and efficacy analyses, but no statistically significant differences in adverse event rates were reported between treatment and control groups. Among the adverse events where the palivizumab group reported statistically insignificant, although higher, rates (such as rash at injection site) none were serious and no measurable costs were associated with these events. Key findings from the IMpact RSV trial are shown in Table 8.

The IMpact RSV trial demonstrated the effectiveness of palivizumab in preventing episodes of hospitalization and other healthcare resource utilization associated with RSV bronchiolitis. However, questions over the cost-effectiveness of palivizumab among infants 32-35 weeks EGA did not lead to un-reserved indication of palivizumab prophylaxis for this population. Consequently, evidence on the cost-effectiveness of palivizumab could prove valuable for deciding whether to administer palivizumab to the large group of infants born from 32 through 35 weeks EGA and infants with comorbid conditions. In the next subsection, we summarize findings from economic analyses of palivizumab.

Summary of Findings from the Literature on the Cost-effectiveness of Palivizumab Prophylaxis

As mentioned previously, six studies have assessed the cost or cost-effectiveness of palivizumab in preventing RSV bronchiolitis. For each of these studies, we provide a brief description, present key findings, and discuss limitations.

Summary of Findings from Marchetti et al.

Marchetti et al. assessed the cost-effectiveness of palivizumab using providers' charges.[96] Their analysis used baseline hospitalization rates from the Impact RSV trial, two trials of RSVIG IV (PREVENT and the National Institute of Allergy and Infectious Diseases [NIAID]-Respiratory Syncytial Virus Immune Globulin), and the literature (rates ranging from 10.6 to 42.6 percent). Costs were estimated as hospital charges drawn from the literature, and ranged from $10,000 to $166,000 per RSV episode requiring hospitalization. Charges do not reflect costs to society, and are usually converted to costs using a cost/charge ratio. The impact of palivizumab on hospitalization rates and severity of infection (based on LRI scores) was taken from the IMpact RSV trial.

Assuming a 55 percent reduction in hospitalization rates for children who received prophylactic therapy, the authors estimated incremental charges (charges above the costs for infants who did not receive prophylaxis) ranging from saving of $36,040 to costs of $3,424 per infant. They found that prophylaxis was most cost-effective in infants born at 32 through 35 weeks EGA with no diagnosis of CLD and least cost-effective in infants with CLD.

The authors did not provide the sources of information for the cost of prophylaxis or for their baseline hospital charges, and the cost of prophylactic therapy was not provided. The year in which costs were valued was not provided and authors did not explain how LRI scores were used in the calculation of expected costs. Additionally, the authors used charges, which overstate costs, and this biases results to appear more cost-effective.

Summary of Findings from Joffe et al.

Joffe et al. analyzed the cost-effectiveness of both palivizumab and RSVIG IV in the prevention of bronchiolitis.[13] Theirs is the only study reviewed in this report which adopted a societal perspective. In addition to medical costs, the authors attempted to value parents' lost time from work, travel costs, and future productivity losses associated with premature mortality. Hospitalization rates and costs were obtained from a cohort of 1721 premature infants discharged from six Kaiser Permanente NICUs in Northern California (KPMCP-NC). The infants in this cohort were divided into eight subgroups based on gestational age at birth, length of oxygen therapy, and month of NICU discharge. For each subgroup, Joffe et al., calculated the baseline, or no intervention, hospitalization rate for subsequent RSV-related inpatient stays. These rates ranged from 1.2 to 24.6 percent. The impact of prophylaxis on hospitalization rates was taken from the IMpact RSV trial for palivizumab (55 percent reduction in hospitalization). The authors pooled data from the IMpact RSV trial and two previous studies on RSVIG IV, PREVENT and NIAD, to estimate the mortality rate for RSV bronchiolitis among hospitalized infants (1.2 percent of all hospitalizations). Cost data were compiled from internal KPMCP-NC records as well as from published sources. Prophylaxis costs were estimated for four doses per infant, and were $2,800 for palivizumab (drug and administration costs).

Parents' lost time from work was estimated to be $44 for treatment with palivizumab and $358 for an average hospitalization (regardless of whether prophylactic therapy was given). The estimated medical cost of outpatient services for RSV bronchiolitis was $198; the estimated cost for hospitalization was $8,502. The authors found that results varied greatly by subgroup. For the highest risk subgroup (23-32 weeks EGA, = 28 days on oxygen, and discharged from September through November), estimated costs were $12,000 per hospitalization avoided (not including productivity losses resulting from premature mortality). For infants born from 33 through 36 weeks EGA, the most cost-effective group was those requiring = 28 days of oxygen and released from the neonatal intensive care unit (NICU) from September through November. The estimated cost-effectiveness ratio for this subgroup was $38,000 per hospitalization avoided.

Although Joffe et al. attempted to include important nonmedical costs, such as parents' lost time from work and travel expenses to obtain treatments, these cost estimates were based on assumptions about parents' behavior rather than actual data.[13] The authors also use data on hospitalization rates for each of eight subgroups of vulnerable children, but these rates vary widely, possibly in part because of the small number of observations in some subgroups. In analyses of the productivity losses resulting from premature mortality, Joffe et al. used a mortality rate of 1.2 percent among hospitalized infants, but there is no evidence that palivizumab prevents death.

Summary of Findings from Numa

Numa performed an economic analysis of palivizumab from the Australian providers' perspective.[97] The analysis was based on record review from the Sydney Children's Hospital

(SCH) to identify children younger than 2 years of age with an admission for RSV infection. For this cohort, Numa calculated average hospitalization costs for both the general ward and the ICU. The impact of prophylaxis was based on results from the IMpact RSV trial for palivizumab and from the PREVENT trial for RSVIG IV.

Numa compared the estimated cost of administering prophylactic therapy to the estimated cost savings of prophylaxis (through reduced hospitalization and ICU lengths of stay) for the SCH cohort and concluded that the cost of administering either palivizumab or RSVIG IV outweighed the potential cost savings.

Cost differences for children who received prophylactic therapy versus those who did not were assumed to be entirely due to differences in lengths of stay in the hospital and ICU. Because of data limitations in the SCH records, Numa's analysis did not account for differences in the incidence of hospitalization that may be associated with prophylactic therapy receipt.

Summary of Findings from Lofland et al.

Lofland et al. assessed the cost-effectiveness of palivizumab from the providers' perspective.[14] The authors used healthcare resource utilization and effectiveness data from the literature and from the IMpact RSV trial. Data on hospitalization costs were obtained from a university-affiliated hospital cost-accounting system. A range of values was used for baseline hospitalization rates (10 to 38 percent) and for palivizumab costs ($2,500 to $4,500 per child per season). The authors estimated a mean cost of $10,486 per RSV hospitalization, but this value was also varied.

Results indicated that the cost per episode of RSV infection avoided—where an episode included outpatient care, home healthcare, and hospitalization—ranged from cost saving (i.e., the cost of palivizumab therapy was more than offset by the cost savings associated with reduced healthcare resource use for the intervention group) to $79,706. Results were sensitive to changes in hospitalization cost, cost of palivizumab therapy, and the baseline incidence of hospitalization.

Because results were not provided separately for the 32 through 35 week EGA subgroup of infants or those with comorbidities, the Lofland et al. results may not be applicable to these subgroups. Lofland's analysis assumed a 5 percent hospitalization rate for infants who received palivizumab, which is significantly higher than the 1.9 percent hospitalization rate from the IMpact RSV trial for infants born 32 through 35 weeks EGA.

Summary of Findings from Schrand et al.

Schrand et al. conducted an economic analysis from the providers' perspective.[98] They used data on costs and effectiveness from the University of Iowa Hospitals and Clinics (UIHC). The UIHC introduced RSVIG IV to the formulary in 1996, and by the 1998-99 RSV season, all infants meeting the healthcare organization's criteria for receiving prophylaxis were being given palivizumab, and in some cases, RSVIG IV. Baseline hospitalization rates were generated by searching UIHC hospital records for relevant diagnosis codes for infants meeting the criteria for prophylaxis during the 1994-95 RSV season (the period prior to the implementation of the prophylaxis policy). Hospitalization rates for infants receiving prophylactic therapy were generated using the same approach for the 1998-99 RSV season (the post-implementation period). Estimated rates were based on 10 hospitalizations among 40 infants (25 percent) in the baseline group and one hospitalization among 61 infants (1.6 percent) in the prophylaxis group.

Hospitalization costs were estimated for infants in the 1994-95 RSV cohort and adjusted to 1999 dollars.

Estimated cost for hospitalization with RSV infection was $17,031 (in 1999 dollars) and for prophylactic therapy (drug and administration costs) was $3,461. Because the authors' estimates of hospitalization incidence suggested a much larger impact of prophylaxis than was found in the IMpact RSV trial (i.e., a relative rate of hospitalization of approximately 0.06), rates from the IMpact RSV trial and from a study that focused on chronic lung disease[99] were used in sensitivity analyses. When using data on hospitalization rates from the IMpact RSV trial, findings suggested that the cost savings of prophylactic therapy (i.e., reduced hospitalization costs) approximately offset the costs of administration. Prophylaxis was cost saving when assessed using data from the UIHC system and Groothuis et al.

Schrand's analysis did not focus on the subgroups of interest for our review (infants born 32-35 weeks EGA or with comorbidities), which may limit the applicability of these results. Additionally, hospitalization rate estimates were based on extremely small sample sizes, and estimates for the baseline group were for a period 4 years prior to the time period for which rates were estimated for the prophylaxis group, which may affect the comparability of findings.

Summary of Findings from Fariña et al.

Fariña et al. conducted a regional analysis of the cost-effectiveness of palivizumab therapy among high-risk infants in Argentina.[100] They identified patients enrolled in a publicly supported hospital, which serves a population of primarily low income households within 62 miles of the facility. Forty-two child patients were tracked for two years, and over the two-year period, the rate of hospitalization for RSV infection was 23.8 percent. Average cost was $18,477 for hospitalization and $1,100 per patient per dose for palivizumab therapy.

By applying the 55 percent relative reduction in hospitalization rates from the IMpact RSV trial, the authors estimated a cost to prevent one hospitalization of $15,358. These findings are very sensitive to the baseline hospitalization rate used in the analysis, and the high rate among this study population was largely due to poor living conditions, such as overcrowding, poverty, and a lack of education among family members.

The number of observations used to estimate the hospitalization rate among this population is very small. Moreover, because the socioeconomic characteristics of the study population are so different from the population studied in the IMpact RSV trial, it is not clear whether the IMpact RSV results are applicable.

General Findings Across Economic Analyses

The CEAs summarized in the previous subsection varied greatly in the approaches used, estimates of key parameters, and findings. Although the Panel on Cost-Effectiveness in Health and Medicine has recommended that a societal perspective be used for economic evaluations of clinical interventions, only Joffe et al. attempted to incorporate a societal perspective; the other studies adopted a payers' or providers' perspective.[13] Three factors had a large impact on cost-effectiveness results from all of the studies: hospitalization incidence, healthcare costs, and the costs of palvizumab therapy. In this subsection, we discuss differences identified in these factors across studies and how these differences are likely to affect the cost-effectiveness of palivizumab.

Incidence of Hospitalization

Estimates of the incidence of hospitalization for RSV bronchiolitis vary widely, and these differences can have a considerable impact on the estimated cost and cost-effectiveness of prophylactic therapy. Table 9 shows some of the RSV hospitalization rates found in the literature. Note that baseline hospitalization rates for infants from about 32 through 35 weeks EGA vary from 1.2 to 25 percent.

One possible reason for the limited evidence on hospitalization rates is because of the difficulty of obtaining consistent diagnoses of RSV bronchiolitis across hospital settings. Bronchiolitis is generally a clinical diagnosis, and therefore hospitalization incidence rates based on a diagnosis of bronchiolitis may under- or over-attribute RSV as the infectious agent. For studies that used universal antigen testing to determine the presence of RSV, variations in the epidemiology and prevalence of RSV by geographic or socioeconomic group as well as variations in virulence and subspecies, can greatly affect findings.

Cost of Health Care Resource Utilization

Hospital and other medical resource costs can vary by severity of illness, geographical area, and institution. The source of cost information can also change the value of the estimate. Charges overstate costs to society, as most payers pay significantly less. Cost to charge ratios to convert charges can be calculated from Medicare data and indicate that costs are typically less than 60 percent as high as charges, but use of cost to charge ratios for non-Medicare hospitalizations introduces even more uncertainty into the actual costs. The values obtained from hospital cost accounting systems are likely to be the most accurate measures of cost available, although they best reflect medical costs for a particular geographical region and may not reflect any profit. In the economic analyses of palivizumab described in the previous subsection, hospitalization and other medical care cost estimates varied widely. These estimates, adjusted to 2001 dollars using the MCPI, are shown in Table 10. Diagnosis codes designating RSV hospitalization are now available, and may facilitate estimation of more accurate cost values.

Cost of Palivizumab Therapy

The single largest barrier to wide-scale use of palivizumab is its cost. Palivizumab cost estimates from the literature are shown in Table 11. Most of the analyses used the average wholesale price (AWP), or a catalog price, as an estimate of the cost of palivizumab. However, AWPs are not calculated from actual sales; they are essentially suggested wholesale prices and may not accurately reflect actual costs. Wholesalers sometimes use the AWP as a list price in catalogs and then negotiate discounts with customers. Physician practices and insurance companies, especially those that use group purchasing organizations and pharmacy benefits managers, may be able to obtain palivizumab at a much lower unit cost than the published AWP. Indeed, certain Federal agencies (Department of Defense [DoD], Veterans Affairs [VA], and Health and Human Services [HHS], and the Coast Guard) are able to purchase palivizumab for 48 percent less than the published AWP.

Another component of the cost of palivizumab that varies across economic analyses is the number of doses required for a successful prophylaxis program. Palivizumab is recommended to be taken monthly during the 5 months of RSV season, but infants born during RSV season may

take less than the full five doses. Schrand et al. reported that all infants in their treatment group received all required doses, but that the average number of doses per infant was 3.28.[98] Analyses that used an estimate of five, or nearly five, doses may overstate the costs for full administration.

Cost to Avoid Hospitalization

Table 11 lists results from the four palivizumab cost-effectiveness analyses conducted in the U.S and indicates cost-effectiveness ratios when average parameter values from Tables 9 and 10 (Marchetti's hospital charges were converted to costs with a cost to charge ratio of 0.6) were used in the analysis. The costs are expressed in terms of cost per hospitalization avoided. The costs listed for Marchetti were derived by using the incremental cost per infant for the general population, and then multiplying this by the number needed to treat to avoid a hospitalization based on incidence rates from the IMpact-RSV trial.[96] Marchetti did not indicate incremental costs for the subpopulations, but provided a break-even analysis which indicated that infants born 32-35 weeks EGA were the most cost-effective, and those with a diagnosis of CLD were the least cost-effective. Had incremental costs for the appropriate subpopulations been used instead of the cost for the general population, one could expect that the cost to prevent a hospitalization for the 32-35 week EGA group would be lower, and the corresponding cost for infants with CLD would be higher.

Schrand et al. reported results as incremental costs, based on the hospitalization rates seen in their institution, as well as based on rates from the IMpact-RSV trial as part of the sensitivity analysis.[98] It was not possible to derive the incremental costs or hospitalization rates specific for the sub-populations of interest, but since this CEA reported all of their parameter values, we were able to derive an incremental cost for each subpopulation for the IMpact-RSV rate results. Lofland et al. and Joffe et al. reported cost per hospitalization avoided for certain subpopulations. Joffe reported based on sub-populations grouped by EGA, as well as oxygen usage and month of discharge from NICU, which were found to have significant correlation with hospitalization rates.[13] Lofland reported results for the $4,500 prophylaxis cost provided by MedImmune, Inc.[14] Given that this estimate is higher than the others, Lofland also provided results based on a $2,500 prophylaxis cost, which is lower than other estimates. The final row in Table 11 presents the cost to prevent a hospitalization if the average parameter values from Tables 9 and 10 were used. The costs represent the average hospitalization cost reported for the four U.S.-based CEAs, as well as the societal costs used by Joffe. The prophylaxis cost is also based on the average cost (using the $2,500 estimate from Lofland et al.), and includes the relevant social costs of palivizumab prophylaxis from Joffe et al. Hospitalization rates for those taking and not taking palivizumab, as compiled from the literature, are used to predict the effect of palivizumab prophylaxis. These rates should be treated with caution, since they are compiled from rates from disparate sources and the baseline characteristics, study design, and horizon will differ between the prophylaxis and no prophylaxis groups. These costs per hospitalization avoided should not be used for interpreting the cost-effectiveness of prophylaxis; they are intended only to facilitate comparison of the published literature.

Cost to Avoid a Hospitalization by Administering Palivizumab to Infants Born 32-35 Weeks EGA

The cost to avoid a hospitalization for infants born from 32 through 35 weeks EGA range from savings to costs of $328,000 for infants discharged from the NICU during low-risk months

and with less than 28 days of supplemental oxygen use in Joffe et al. The results based on averages for parameter values in the literature suggest a $54,500 cost to avoid a hospitalization. The average cost to avoid one RSV hospitalization among the four U.S.-based CEAs was $54,214, but this dropped to $33,595 when the two lowest risk cohorts from Joffe et al. were excluded. The average cost of RSV hospitalization was $14,485, in addition to intrinsic morbidity costs associated with hospitalization.

Cost to Avoid a Hospitalization by Administering Palivizumab to Infants with CLD

The evidence on the cost-effectiveness of palivizumab prophylaxis on infants based on a diagnosis of CLD is less conclusive. The IMpact-RSV trial indicated that palivizumab was least effective on this group but Table 9 indicates that this population may have higher RSV-hospitalization incidence rates.[91] Based on this effectiveness data, the four analyses indicated that infants with CLD would require higher expenditures to avoid a hospitalization. If the use of supplemental oxygen for 28 days or more is used as an approximation for a diagnosis of CLD to allow the inclusion of data from Joffe et al., then the average cost to prevent a hospitalization reported by the CEAs would be $40,168. This contrasts greatly with the cost obtained when using the average parameters from Tables 9 and 10, which was $19,540 to prevent a hospitalization. This result is so low because the incidence data for this group in Table 9 would yield a lower number of infants need to treat to avoid a hospitalization. If Groothuis et al. 1988 was eliminated from consideration, the cost to prevent a hospitalization would be $24,176. If Sorrentino and Powers was eliminated, the cost to prevent a hospitalization would be $38,015. If both were eliminated, the result would be $49,935, which is similar to the average of the results for infants born 32-35 weeks EGA. If the result of $19,540 were included in the average of the results of the CEAs, the cost to prevent a hospitalization by administering palivizumab to infants with CLD would be $36,713, with one RSV hospitalization costing $14,485 in addition to morbidity costs.

4. Conclusions

Diagnosis

Specific literature regarding diagnosis of bronchiolitis was not found. The disease is clinically defined using well-accepted criteria described by Engle and Newns,[105] Court,[19] Denny and Clyde,[106] and others.

A large amount of data exists on the use of a variety of supportive laboratory tests such as specific RSV assays, CBCs, and chest x-rays. However, only the Shaw and Bell study supported the clinical usefulness of such information.[32] Thus, looking at the original causal pathway in Figure 1, the existing data do not support the usefulness in testing to diagnose bronchiolitis.

Ancillary laboratory testing may be useful in determining if an infant with respiratory distress has bronchiolitis versus another disease (e.g., congestive heart failure, pneumonia). However, this question is not covered by the key questions. Fortunately, in most instances, the diagnosis of bronchiolitis is clear from a carefully conducted history and physical.

The question of whether testing affects management and clinical outcome in patients with bronchiolitis is more difficult. Testing that can predict disease severity or worse clinical outcomes theoretically would be useful. Shaw and Bell's study suggests that testing may help sort out patients likely to have more severe disease.[32] However, five of the six predictors that emerged from their modeling were based on history and physical examination (i.e., age, gestational age, general appearance, respiratory rate, and pulse oximetry).

Many clinicians are concerned that patients with more severe disease may have "bacterial superinfections." This may result in the addition of antibiotics to a patient's treatment. Such concerns are typically based on illness severity, chest x-ray appearance, and an elevated WBC. No data support these assumptions. Saijo et al. demonstrated that elevated WBC findings correlated with radiographically determined RSV lobar pneumonia vs. bronchiolitis or bronchopneumonia.[35] Roosevelt et al. showed that 90 percent of patients with visible infiltrates compared to 44 percent of patients without infiltrates were treated with antibiotics.[43] Dobson et al. showed poor correlation between chest x-ray findings and baseline disease severity.[37] However, none of these studies examined whether these associations and treatments affected outcomes.

Complicating this question is the poor ability to document bacterial pathogens in infants with lower respiratory tract infections. Nasal and tracheal suction methods do not accurately predict lower respiratory tract pathogens. Bronchoalveolar lavage (BAL) or tissue cultures are considered the gold standard, but these techniques are generally not indicated in infants with uncomplicated disease.

No studies directly addressed questions of the utility of supportive testing on clinical outcomes or costs. In some studies, use of such tests was reduced through evidence-based quality improvement intervention, but these studies were not prospective RCTs designed to demonstrate changes in clinical outcomes.[107]

Treatment

Key Question 2 concerned the efficacy or effectiveness of pharmaceutical therapies for treating bronchiolitis among infants and children. Therapies to be considered include corticosteroids, bronchodilators, antimicrobial agents, antiviral agents, and others.

This review located several major classes of pharmaceutical agents that have been studied in multiple RCTs as treatments for bronchiolitis. These classes of agents included epinephrine, beta-2 agonist bronchodilators (i.e., albuterol or salbutamol), ipratropium bromide, oral and inhaled corticosteroids, ribavirin, and antibiotics. In addition, we located several interventions, such as surfactant and nebulized furosemide, for which there was limited single-trial evidence. Our results are summarized in Table 12.

Unfortunately, we did not identify any treatments for bronchiolitis for which there was strong and convincing evidence of effectiveness (see Table 12). We did, however, find several interventions that we believe show some potential for being efficacious and should therefore be subjected to rigorously designed, adequately sized trials. We found enough evidence to suggest that the following interventions, in particular, should be studied: nebulized epinephrine; nebulized salbutamol plus ipratropium bromide, nebulized ipratropium bromide; oral or parenteral corticosteroids (preferably dexamethasone); and inhaled corticosteroids (preferably budesonide).

We also identified two interventions in this category that are applicable only to the most severely ill children: inhaled helium-oxygen and surfactant for ventilated children.
Given that there is no current best treatment for bronchiolitis, we would recommend that the above-mentioned interventions be studied in large, well-designed studies. In such studies, it is appropriate to use placebos in the comparison group when feasible; however, all subjects must be given standard supportive care. Additional information in these studies on days since onset of disease and duration of therapy would aid in the evaluation of these interventions.

This literature review also revealed several commonly used treatments for which data are sufficient to doubt their efficacy as treatments for bronchiolitis. These interventions are aerosolised ribavirin, antibiotics, nebulized furosemide, RSVIG IV (as a treatment), and inhaled alpha-interferon and nebulized recombinant human deoxyribonuclease (rhDNase). Although the studies of these drugs were usually underpowered as well, because of lack of evidence of efficacy and a potential for increased harm with some, we recommend that clinicians not use these treatments routinely. These drugs should be considered for treatment only as part of rigorously designed, controlled trials.

This literature review found two treatments – inhaled budesonide and alpha-2-interferon – where occurrence of adverse events in studies warrant caution in their use until such time as trials with adequate power to detect adverse events are conducted. This is particularly important in the case of inhaled budesonide, as this agent also appeared to confer at least modest benefit for some outcomes in some studies of its use.

Key Question 2b focused specifically on the question of whether any single agent or antimicrobial is the most effective in improving symptoms of bronchiolitis. We did not find any evidence that such a single agent can be recommended for treatment of bronchiolitis. At present, evidence is insufficient to recommend any of the treatments studied over good supportive care of affected infants and children.

Most of the outcomes studied in this literature are short term and reflect surrogate measures such as oxygen saturation or respiratory rate at 15-minute intervals after treatment. Looking across interventions we found that fewer than half of the treatment studies asked the most clinically relevant question of whether the intervention lessened the need for hospitalization or decreased the length of hospitalization for admitted patients. Fewer than 10 of the studies addressed the effect on long-term outcomes such as asthma.

Prophylactic Therapy

Although most children who have bronchiolitis do well and have an uncomplicated and self-limited disease, it is a serious and sometimes life-threatening illness for some children. For the most part, these severely affected infants and children have coexisting comorbidities that put them at increased risk of complications. Key Question 3 asked whether prophylactic therapy has a role in prevention of bronchiolitis and, in particular, whether any subpopulations might realize greater benefit from prophylaxis. Table 13 summarizes our results.

The largest group of at-risk children are those who are born prematurely, who often have concurrent BPD or chronic lung disease. Palivizumab or RSVIG IV on a monthly basis is effective for prophylaxis in high-risk infants and children who have underlying BPD or have been born prematurely and are under 6 months of age. Palivizumab has supplanted RSVIG IV because of the ease of administration of palivizumab. Studies of the use of prophylaxis in other at-risk groups who were excluded from the IMpact-RSV trial, such as those with congenital heart disease, will need to be released before this agent can be recommended more broadly for all infants and children at increased risk of more severe bronchiolitis. Studies of palivizumab prophylaxis should also examine the effect on long-term outcomes such as the development of symptoms such as wheezing, development of bronchiolitis, hospitalization, and severe disease. The question of the relationship between bronchiolitis and asthma remains unanswered and is beyond the scope of this report. However, if the question is answered through a basic science study, and there is evidence of a causative relationship, this would have significant impacts on questions of prevention and the costs of prophylaxis.

Neither of the studies of immunization of at-risk infants with purified F protein (PFP) vaccines demonstrated benefit. The older children with cystic fibrosis in the Piedra et al. studies did seem to obtain some benefit from a similar vaccine.[94,95] However, these types of vaccines are at early stages of development and the studies were small. An effective vaccine would be a preferable strategy for prevention of RSV bronchiolitis in at-risk children compared to the passive immunity created by monthly injections of RSVIG. Because of the early nature of the research and the potential benefits, RSV vaccine research should be encouraged.

Cost of Prophylaxis

Six articles have considered the cost-effectiveness of prophylactic therapy for preterm or other high-risk infants.[13,14,96-98,100] Findings from these studies suggest that the cost per hospitalization avoided varies widely, depending on the cost of prophylactic therapy assumed, the hospitalization and other health care costs assumed, the baseline rate of hospitalization for

children with RSV bronchiolitis, and reductions in hospitalization rates associated with the use of palivizumab. When all costs are adjusted to 2002 dollars, results from the previous studies suggest that prophylactic therapy for infants from 32 through 35 weeks of EGA ranges from cost saving (e.g., Marchetti et al.[96])—meaning that the expected costs associated with the outcomes along the treatment intervention branch of the decision tree are lower than the costs of no prophylactic therapy— to an upper bound of $328,000 (e.g., Joffe et al.).[14] Typical results indicated costs per hospitalization avoided of about $40,000 to $50,000, but given the wide variation in results, current analyses do not provide a reliable estimate of the cost-effectiveness of RSV prophylaxis.

Previous analyses were limited in several respects. First, all but one of these studies used effectiveness data from the only large RCT to date for palivizumab—the IMpact-RSV study.[91] This trial did not report statistically significant, secondary end-points for subpopulations. The IMpact trial did not include any comorbidities other than BPD. The results from a trial on infants with cardiac disease are not yet available. The study that used alternative data on the impact of prophylactic therapy on hospitalization rates for RSV bronchiolitis had only 40 infants in the control group and 61 infants in the treatment group; hence, the quality of their results is seriously limited by the small number of study observations.[98]

Second, most economic analyses of palivizumab have focused on estimating costs from the payer or provider perspective, rather than from the societal perspective, which is the approach recommended by the Panel on Cost-Effectiveness in Health and Medicine.[108] Consequently, most of these studies have excluded important costs that may result from a child's infection with bronchiolitis, such as parents' lost time from work, the family's nonreimbursable travel or parking expenses, and the productivity losses associated with the premature death or chronic morbidity of the affected infant (if, for example, bronchiolitis has long-term negative outcomes, such as asthma). Although Joffe et al. included parents' productivity losses associated with a provider visit for obtaining palivizumab and a child's hospitalization for RSV bronchiolitis infection, estimated losses were based on ad hoc assumptions about the amount of parental time required for outpatient visits to obtain palivizumab therapy and parental time spent with a hospitalized infant.[13]

Third, the baseline (no prophylactic therapy) rate of hospitalization in infants with bronchiolitis is unknown and may vary depending on the characteristics of the patient population, region of residence and method of measurement. Estimates used in the literature on the cost-effectiveness of prophylactic therapy range from 1.2 percent to 25 percent for infants born prior to 36 weeks EGA. Such widely varying estimates of baseline hospitalization rates have the most significant impact on the results of cost-effective analyses.

Finally, the literature contained a broad range of estimated costs for palivizumab and hospitalization for RSV bronchiolitis. Differences in acquisition costs for palivizumab, administration costs, and the number of doses lead to differences across studies in the estimated cost of prophylaxis. The estimated costs of hospitalization found in the literature also varied widely. Some studies have used hospital charges rather than cost estimates, which explains part of the difference in hospitalization costs observed across studies. However, estimated hospital costs also vary because of differences in the course of treatment, the inclusion of expenses that are unrelated to a child's diagnosis with bronchiolitis (such as surgery), and differences in the allocation of hospital overhead expenses.

One possibility that we considered for assessing the cost-effectiveness of palivizumab was to conduct an analysis from the societal perspective that uses data from the literature and from

secondary data sources. However, such an analysis would suffer from many of the same limitations identified in existing studies. In particular, estimates of the impact of palivizumab would need to be drawn from the IMpact-RSV trial; as mentioned already, the only outcomes readily available in the literature for the subgroups of interest are hospitalization rates. The impact of palivizumab on length of hospital stay and on incidence of ICU admission is provided only for the full study sample. Although a RCT of palivizumab that focuses on children with congenital heart disease is currently under way, study results will not be available until late fall 2002. Data on baseline hospitalization rates would also need to be drawn from the literature, and these vary widely because of differences in methods and differences in the underlying risk factors for RSV bronchiolitis infection in the population.

Estimating hospital charges for children with bronchiolitis is possible from national data sets, such as the Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project at AHRQ. However, although diagnosis codes are now available indicating RSV, the presence of these codes may not accurately indicate the true burden of this disease as RSV-antigen testing is often not routinely done, and gestational age at birth is not indicated.

Another challenge to conducting an analysis of the cost-effectiveness of palivizumab from the societal perspective is that additional data would need to be collected to estimate the impact of a child's bronchiolitis on the family and to assess whether palivizumab therapy affects long-term outcomes, such as chronic asthma. Without these data, only analyses from the provider perspective are possible.

Given the gaps in the literature, high variation in parameters, and the wide ranges in results, the true cost-effectiveness of RSV prophylaxis among infants in the target population has not been demonstrated. Questions over cost-effectiveness and cost-benefit of palivizumab among infants 32 to 35 weeks EGA have been cited as reasons for reserving indication of prophylaxis, except for instances where there are specific risk-factors. Although infants born 32-35 weeks EGA may be expected to encounter lower RSV hospitalization rates than infants born less than 32 weeks EGA, the IMpact-RSV trial indicated that this difference may not be very significant, while also demonstrating that palivizumab had better efficacy in these more premature infants. Thus, although cost-effectiveness has not been quantified for this population, prophylaxis in this population cannot be assumed to be less cost-effective than among infants already indicated for palivizumab. Cost-effectiveness is one factor for use when deciding whether or not to use a health-care intervention. At this time, usable measures of cost-effectiveness of palivizumab prophylaxis for each of the target populations are not available.

Racial and Ethnic Subpopulations

One of the objectives of this evidence report was to include racial and ethnic subgroups in our analysis. The literature suggests that severity of disease or rate of hospitalization differ by race, with particularly high rates in native American, native Canadian and native New Zealand and Pacific Island children and populations.[5,109] However, to what extent socioeconomic status explains this association is not clear. Complicating the association between race and disease severity are differential rates of comorbidities among races, with premature white male infants being more likely to develop BPD and black infants being more likely to be premature.

We were not able to assess differences in outcomes by race or ethnicity for intervention studies. Without exception, none of the treatment studies attempted subgroup analysis by race.

The majority did not present information on race and ethnicity. Of the 60 treatment studies in which setting was specified, 36 were conducted entirely in settings outside the United States. These countries included Australia, Belgium, Canada, Chile, China, Denmark, Egypt, Finland, France, Germany, Israel, Italy, Netherlands, Saudi Arabia, Singapore, South Africa, Sweden, Turkey, and the United Kingdom. In our examination of racial characteristics of the study populations, we assumed that any racial subgroup analysis in these 36 studies was specific to the country in which they were performed. Of the remaining 24 studies that were at least partly conducted in the United States, 11 provided racial characteristics of their study populations.[23,24,37,41,57,66,87-89,91,94,95] In eight of 11 studies, whites constituted more than 50 percent of the patient population. Of the three exceptions, one study[37] had an almost entirely Hispanic population; the other two had black study populations between 71 and 81 percent.[57,66]

5. Future Research

Because the diagnosis of bronchiolitis is primarily clinical, we could find little evidence in the literature to answer fully our Key Question 1. By contrast, the volume of literature available to answer Key Questions 2 and 3 was much greater. However, the strength of evidence was limited by trials that were underpowered and outcomes that were not comparable across studies (Table 12). Key Question 4 cannot be fully addressed without additional data on hospitalization rates and social costs, which are currently widely variable. Also, the evidence for Key Question 4 will need review upon release of new trial data on palivizumab. Given these significant gaps in the literature, we propose some priorities for further research. We also suggest some guidelines for the choice of outcomes and study design that will improve the reporting of research findings and allow meaningful comparisons of study results.

Priorities for Further Research

Diagnosis

Prospective trials of the utility of ancillary testing (chest x-rays, complete blood tests, RSV testing) are feasible and should be performed. Studies of diagnostic tools used in the management of bronchiolitis should measure clinical outcomes that are meaningful to both parents and clinicians. An important intermediate outcome for studies of diagnosis in the management of bronchiolitis is the change in physician practices (i.e., whether results of diagnostic steps alter the ways that physicians elect to manage their patients with this condition).

Treatment

Our review revealed that for several interventions for bronchiolitis, data are simply insufficient to exclude them as possible effective treatments. Until these interventions are shown to be efficacious, our conclusion is that their clinical use ought to be limited to study situations. The following interventions, in particular, should be studied with well-designed, rigorously conducted RCT, preferably with placebo control: (a) nebulized epinephrine; (b) nebulized salbutamol plus ipratropium bromide; (c) nebulized ipratropium bromide; (d) oral corticosteroids, preferably dexamethasone; (e) inhaled budesonide; (f) inhaled helium-oxygen for severely ill children; (g) Chinese herbal therapy with Shuang Huang Lian (if its use can be practically accomplished in U.S. settings); and (h) surfactant for ventilated children.

The treatment studies we reviewed were almost universally underpowered and as such do not give clinicians adequate guidance for management of bronchiolitis. There is substantial evidence that clinicians commonly use several interventions such as inhaled bronchodilators, inhaled corticosteroids, and inhaled epinephrine for which, currently, evidence is insufficient. These drugs are all available as generic products and, therefore, relatively inexpensive; clinicians also

consider them to be safe. We believe that clinicians will continue to use these types of treatments unless a large simple trial of these most common interventions is mounted. Such a trial would need to be large enough to examine each of the interventions not only in the overall population, but also in subpopulations of interest (e.g. infants with and without a history of atopy). This type of trial is unlikely to be funded by industry and would therefore require governmental support.

Prophylactic Therapy

Studies of the use of prophylaxis in at-risk groups that had been excluded from earlier studies will need to be released before this agent can be recommended more broadly for infants and children who are at increased risk of more severe bronchiolitis. Studies of prophylaxis should examine the effect on long-term outcomes such as the development of asthma.

Evidence is insufficient about the use of PFP-2 vaccine among high-risk infants with chronic lung disease or among children with cystic fibrosis. Our conclusion is that this vaccine ought not to be used except in the context of well-designed, properly powered RCTs to determine its effectiveness, safety, and cost-effectiveness.

Costs of Prophylaxis

Better estimates of the cost of palivizumab are needed to assess whether the drug is cost-effective. In particular, additional data are needed on the cost of administration. Key issues include typical dosage amount and number of doses, time required for parents and providers to administer it, and the actual cost of palivizumab to providers, which may be less than the average wholesale or catalog prices used in most previous analyses.

Estimates of baseline hospitalization rates for RSV bronchiolitis in the specific subgroups of interest (infants 32 through 35 weeks' EGA or with comorbidities) are needed to assess better whether prophylactic therapy is cost-effective for these populations. These analyses should also consider how hospitalization rates differ depending on socioeconomic characteristics of the population and region of residence.

To assess the cost-effectiveness of palivizumab from the societal perspective, data are needed on family costs. Family costs may be incurred for the receipt of prophylactic treatment (e.g., productivity losses and out-of-pocket expenditures) or for a child's infection with RSV bronchiolitis and subsequent treatment. Other data needed to estimate the societal costs of bronchiolitis are information on excess chronic morbidity for infants in the palivizumab treatment group (e.g., asthma) and premature death.

Data are needed to assess whether outpatient service utilization and costs and length of acute episodes differ between the prophylaxis and no-prophylaxis groups of infants for the populations of interest. Although the cost of outpatient services is largely dwarfed by hospitalization costs, if children who receive prophylactic therapy require much less ambulatory care and their families incur significantly less expenses and productivity loss, these differences may be significant.

Although many studies have attempted to measure the impact of EGA and the presence of comorbidities on RSV infection rates, the importance of other risk factors should also be considered. For example, the impact of day care attendance, multiple birth, exposure to

secondhand smoke, room-sharing with siblings, socioeconomic status, and general hygiene should also be considered when assessing the impact of palivizumab on RSV infection and subsequent illness.

General Guidelines for Further Research

Outcomes

In the future, investigators should choose clinically relevant outcomes. Most of the outcomes studied in this literature are short term; often they are only surrogate outcomes such as oxygen saturation or respiratory rate at 15-minute intervals after treatment. Investigators should concentrate on measuring outcomes that matter to parents, clinicians, and health systems. Examples include rates of hospitalization or rehospitalization, duration of hospitalization, need for more intensive services in hospital, costs of care, parental satisfaction with treatment, and development of chronic asthma.

Design

Studies should be powered to detect meaningful differences in clinically relevant outcomes. Power calculations must include sufficient numbers to account for multiple comparisons if multiple outcomes are to be measured.

Reporting of Adverse Events

Few studies reported adverse events associated with treatments. Determining whether the risks of particular treatments are sufficient to exclude their clinical use is difficult. Future investigations should carefully monitor and report adverse events associated with treatments.

References

1. Glezen WP, Taber LH, Frank AL, Kasel JA. Risk of primary infection and reinfection with respiratory syncytial virus. *Am J Dis Child.* 1986;140:543-546.

2. Eriksson M, Bennet R, Rotzen-Ostlund M, von Sydow M, Wirgart BZ. Population-based rates of severe respiratory syncytial virus infection in children with and without risk factors, and outcome in a tertiary care setting. *Acta Paediatr.* 2002;91:593-598.

3. Wang EE, Law BJ, Stephens D. Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) prospective study of risk factors and outcomes in patients hospitalized with respiratory syncytial viral lower respiratory tract infection. *J Pediatr.* 1995;126:212-9.

4. Hall CB. Respiratory syncytial virus and parainfluenza virus. *N Engl J Med.* 2001;344:1917-1928.

5. Shay DK, Holman RC, Newman RD, Liu LL, Stout JW, Anderson LJ. Bronchiolitis-associated hospitalizations among US children, 1980-1996. *JAMA.* 1999;282:1440-1446.

6. American Academy of Pediatrics. Respiratory Syncytial Virus. In: Pickering LK, ed. *2000 Red Book: Report of the Committee on Infectious Diseases*. 25th ed. Elk Grove Village, Il: American Academy of Pediatrics; 2000:484.

7. Perlstein PH, Kotagal UR, Bolling C, et al. Evaluation of an evidence-based guideline for bronchiolitis. *Pediatrics.* 1999;104:1334-1341.

8. Committee on Infectious Diseases. Reassessment of the indications for ribavirin therapy in respiratory syncytial virus infections. *Pediatrics.* 1996;97:37-140.

9. Flores G, Horwitz RI. Efficacy of beta2-agonists in bronchiolitis: a reappraisal and meta-analysis. *Pediatrics.* 1997;100:233-239.

10. Kellner JD, Ohlsson A, Gadomski AM, Wang EE. Bronchodilators for bronchiolitis. *Cochrane Database Syst Rev.* 2000;CD001266.

11. Garrison MM, Christakis DA, Harvey E, Cummings P, Davis RL. Systemic corticosteroids in infant bronchiolitis: A meta-analysis. *Pediatrics.* 2000;105:E44.

12. American Academy of Pediatrics Committee on Infectious Diseases and Committee of Fetus and Newborn. Prevention of respiratory syncytial virus infections: indications for the use of palivizumab and update on the use of RSV-IGIV. *Pediatrics.* 1998;102:1211-1216.

13. Joffe S, Ray GT, Escobar GJ, Black SB, Lieu TA. Cost-effectiveness of respiratory syncytial virus prophylaxis among preterm infants. *Pediatrics.* 1999;104:419-427.

14. Lofland JH, O'Connor JP, Chatterton ML, et al. Palivizumab for respiratory syncytial virus prophylaxis in high-risk infants: a cost-effectiveness analysis. *Clin Ther.* 2000;22:1357-1369.

15. Carande-Kulis VG, Maciosek MV, Briss PA, et al. Methods for systematic reviews of economic evaluations for the Guide to Community Preventive Services. Task Force on Community Preventive Services. *Am J Prev Med.* 2000;18:75-91.

16. Centers for Disease Control. The Community Guide: Guide to Community Preventive Services. 1996. Web Page. Available at: http://www.thecommunityguide.org/PDFS/ECONEVAL_version 3.pdf. Last accessed October 14, 2002

17. Richardson WS, Wilson M, Moyer V, Naylor CD. Diagnosis - Clinical Manifestations of Disease . In: Guyatt G, Rennie D, eds. *User's Guide to the Medical Literature: A Manual for Evidence-Based Clinical Practice*. Chicago, Ill: American Medical Association; 2002:449-516.

18. West SL, King V, Carey TS, et al. *Systems to Rate the Strength of Scientific Evidence*. Evidence Report, Technology Assessment No. 47. Rockville, Md.: Agency for Healthcare Research and Quality. AHRQ Publication No. 02-E016; 2002.

19. Court SD. The definition of acute respiratory illnesses in children. *Postgrad Med J.* 1973;49:771-776.

20. Randolph AG, Wang EE. Ribavirin for respiratory syncytial virus lower respiratory tract infection. A systematic overview. *Arch Pediatr Adolesc Med.* 1996;150:942-947.

21. Klassen TP, Rowe PC, Sutcliffe T, Ropp LJ, McDowell IW, Li MM. Randomized trial of salbutamol in acute bronchiolitis. *J Pediatr.* 1991;118:807-811.

22. Menon K, Sutcliffe T, Klassen TP. A randomized trial comparing the efficacy of epinephrine with salbutamol in the treatment of acute bronchiolitis. *J Pediatr.* 1995;126:1004-1007.

23. Schuh S, Coates AL, Binnie R, et al. Efficacy of oral dexamethasone in outpatients with acute bronchiolitis. *J Pediatr.* 2002;140:27-32.

24. Can D, Inan G, Yendur G, Oral R, Gunay I. Salbutamol or mist in acute bronchiolitis. *Acta Paediatr Jpn.* 1998;40:252-255.

25. Rodriguez WJ , Gruber WC, Groothuis JR, et al. Respiratory syncytial virus immune globulin treatment of RSV lower respiratory tract infection in previously healthy children. *Pediatrics.* 1997;100:937-942.

26. Ahluwalia G, Embree J, McNicol P, Law B, Hammond GW. Comparison of nasopharyngeal aspirate and nasopharyngeal swab specimens for respiratory syncytial virus diagnosis by cell culture, indirect immunofluorescence assay, and enzyme-linked immunosorbent assay. *J Clin Microbiol.* 1987;25:763-767.

27. Chattopadhya D, Chatterjee R, Anand VK, Kumari S, Patwari AK. Lower respiratory tract infection in hospitalized children due to respiratory syncytial (RS) virus during a suspected epidemic period of RS virus in Delhi. *J Trop Pediatr.* 1992;38:68-73.

28. Eugene-Ruellan G, Freymuth F, Bahloul C, Badrane H, Vabret A, Tordo N. Detection of respiratory syncytial virus A and B and parainfluenzavirus 3 sequences in respiratory tracts of infants by a single PCR with primers targeted to the L-polymerase gene and differential hybridization. *J Clin Microbiol.* 1998;36:796-801.

29. Ong GM, Wyatt DE, O'Neill HJ, McCaughey C, Coyle PV. A comparison of nested polymerase chain reaction and immunofluorescence for the diagnosis of respiratory infections in children with bronchiolitis, and the implications for a cohorting strategy. *J Hosp Infect.* 2001;49:122-128.

30. Waner JL, Whitehurst NJ, Todd SJ, Shalaby H, Wall LV. Comparison of directigen RSV with viral isolation and direct immunofluorescence for the identification of respiratory syncytial virus. *J Clin Microbiol.* 1990;28:480-483.

31. Lozano J.M., Wang E. Bronchiolitis. *Clin Evid* . 2002;272-282.

32. Shaw KN, Bell LM, Sherman NH. Outpatient assessment of infants with bronchiolitis. *Am J Dis Child.* 1991;145:151-155.

33. Mulholland EK, Olinsky A, Shann FA. Clinical findings and severity of acute bronchiolitis. *Lancet.* 1990;335:1259-1261.

34. Cherian T, Steinhoff MC, Simoes EA, John TJ. Clinical signs of acute lower respiratory tract infections in malnourished infants and children. *Pediatr Infect Dis J.* 1997;16:490-494.

35. Saijo M, Ishii T, Kokubo M, Murono K, Takimoto M, Fujita K. White blood cell count, C-reactive protein and erythrocyte sedimentation rate in respiratory syncytial virus infection of the lower respiratory tract. *Acta Paediatr Jpn.* 1996;38:596-600.

36. Dawson KP, Long A, Kennedy J, Mogridge N. The chest radiograph in acute bronchiolitis. *J Paediatr Child Health.* 1990;26:209-211.

37. Dobson JV, Stephens-Groff SM, McMahon SR, Stemmler MM, Brallier SL, Bay C. The use of albuterol in hospitalized infants with bronchiolitis. *Pediatrics.* 1998;101:361-368.

38. Friis B, Eiken M, Hornsleth A, Jensen A. Chest X-ray appearances in pneumonia and bronchiolitis. Correlation to virological diagnosis and secretory bacterial findings. *Acta Paediatr Scand.* 1990;79:219-225.

39. Luchetti M, Casiraghi G, Valsecchi R, Galassini E, Marraro G. Porcine-derived surfactant treatment of severe bronchiolitis. *Acta Anaesthesiol Scand.* 1998;42:805-810.

40. Nasr SZ, Strouse PJ, Soskolne E, et al. Efficacy of recombinant human deoxyribonuclease I in the hospital management of respiratory syncytial virus bronchiolitis. *Chest.* 2001;120:203-208.

41. Rodriguez WJ , Gruber WC, Welliver RC, et al. Respiratory syncytial virus (RSV) immune globulin intravenous therapy for RSV lower respiratory tract infection in infants and young children at high risk for severe RSV infections: Respiratory Syncytial Virus Immune Globulin Study Group. *Pediatrics.* 1997;99:454-461.

42. Rodriguez WJ , Kim HW, Brandt CD, et al. Aerosolized ribavirin in the treatment of patients with respiratory syncytial virus disease. *Pediatr Infect Dis J.* 1987;6:159-163.

43. Roosevelt G, Sheehan K, Grupp-Phelan J, Tanz RR, Listernick R. Dexamethasone in bronchiolitis: a randomised controlled trial. *Lancet.* 1996;348:292-295.

44. Schuh S, Canny G, Reisman JJ, et al. Nebulized albuterol in acute bronchiolitis. *J Pediatr.* 1990;117:633-637.

45. Taber LH, Knight V, Gilbert BE, et al. Ribavirin aerosol treatment of bronchiolitis associated with respiratory syncytial virus infection in infants. *Pediatrics.* 1983;72:613-618.

46. Barry W, Cockburn F, Cornall R, Price JF, Sutherland G, Vardag A. Ribavirin aerosol for acute bronchiolitis. *Arch Dis Child.* 1986;61:593-597.

47. Chipps BE, Sullivan WF, Portnoy JM. Alpha-2A-interferon for treatment of bronchiolitis caused by respiratory syncytial virus. *Pediatr Infect Dis J.* 1993;12:653-658.

48. De Boeck K, Van der Aa N, Van Lierde S, Corbeel L, Eeckels R. Respiratory syncytial virus bronchiolitis: a double-blind dexamethasone efficacy study. *J Pediatr.* 1997;131:919-921.

49. Friis B, Andersen P, Brenoe E, et al. Antibiotic treatment of pneumonia and bronchiolitis. A prospective randomised study. *Arch Dis Child.* 1984;59:1038-1045.

50. Kjolhede CL, Chew FJ, Gadomski AM, Marroquin DP. Clinical trial of vitamin A as adjuvant treatment for lower respiratory tract infections. *J Pediatr.* 1995;126:807-812.

51. Kong XT, Fang HT, Jiang GQ, Zhai SZ, O'Connell DL, Brewster DR. Treatment of acute bronchiolitis with Chinese herbs. *Arch Dis Child.* 1993;68:468-471.

52. Kristjansson S, Lodrup Carlsen KC, Wennergren G, Strannegard IL, Carlsen KH. Nebulised racemic adrenaline in the treatment of acute bronchiolitis in infants and toddlers. *Arch Dis Child.* 1993;69:650-654.

53. Bertrand P, Aranibar H, Castro E, Sanchez I. Efficacy of nebulized epinephrine versus salbutamol in hospitalized infants with bronchiolitis. *Pediatr Pulmonol.* 2001;31:284-288.

54. Reijonen T, Korppi M, Pitkakangas S, Tenhola S, Remes K. The clinical efficacy of nebulized racemic epinephrine and albuterol in acute bronchiolitis. *Arch Pediatr Adolesc Med.* 1995;149:686-692.

55. Sanchez I, De Koster J, Powell RE, Wolstein R, Chernick V. Effect of racemic epinephrine and salbutamol on clinical score and pulmonary mechanics in infants with bronchiolitis. *J Pediatr.* 1993;122:145-151.

56. Schweich PJ, Hurt TL, Walkley EI, Mullen N, Archibald LF. The use of nebulized albuterol in wheezing infants. *Pediatr Emerg Care.* 1992;8:184-188.

57. Hickey RW, Gochman RF, Chande V, Davis HW. Albuterol delivered via metered-dose inhaler with spacer for outpatient treatment of young children with wheezing. *Arch Pediatr Adolesc Med.* 1994;148:189-194.

58. Cengizlier R , Saraclar Y, Adalioglu G, Tuncer A. Effect of oral and inhaled salbutamol in infants with bronchiolitis. *Acta Paediatr Jpn.* 1997;39:61-63.

59. Gadomski AM, Lichenstein R, Horton L, King J, Keane V, Permutt T. Efficacy of albuterol in the management of bronchiolitis. *Pediatrics.* 1994;93:907-912.

60. Gadomski AM, Aref GH, el Din OB, el Sawy IH, Khallaf N, Black RE. Oral versus nebulized albuterol in the management of bronchiolitis in Egypt. *J Pediatr.* 1994;124:131-138.

61. Goh A, Chay OM, Foo AL, Ong EK. Efficacy of bronchodilators in the treatment of bronchiolitis. *Singapore Med J.* 1997;38:326-328.

62. Ho L, Collis G, Landau LI, Le Souef PN. Effect of salbutamol on oxygen saturation in bronchiolitis. *Arch Dis Child.* 1991;66:1061-1064.

63. Chowdhury D, al Howasi M, Khalil M, al-Frayh AS, Chowdhury S, Ramia S. The role of bronchodilators in the management of bronchiolitis: a clinical trial. *Ann Trop Paediatr.* 1995;15:77-84.

64. Schuh S, Johnson D, Canny G, et al. Efficacy of adding nebulized ipratropium bromide to nebulized albuterol therapy in acute bronchiolitis. *Pediatrics.* 1992;90:920-923.

65. Wang EE, Milner R, Allen U, Maj H. Bronchodilators for treatment of mild bronchiolitis: a factorial randomised trial. *Arch Dis Child.* 1992;67:289-293.

66. Goebel J, Estrada B, Quinonez J, Nagji N, Sanford D, Boerth RC. Prednisolone plus albuterol versus albuterol alone in mild to moderate bronchiolitis. *Clin Pediatr.* 2000;39:213-220.

67. van Woensel JB, Kimpen JL, Sprikkelman AB, Ouwehand A, van Aalderen WM. Long-term effects of prednisolone in the acute phase of bronchiolitis caused by respiratory syncytial virus. *Pediatr Pulmonol.* 2000;30:92-96.

68. van Woensel JB, Wolfs TF, van Aalderen WM, Brand PL, Kimpen JL. Randomised double blind placebo controlled trial of prednisolone in children admitted to hospital with respiratory syncytial virus bronchiolitis. *Thorax.* 1997;52:634-637.

69. Klassen TP, Sutcliffe T, Watters LK, Wells GA, Allen UD, Li MM. Dexamethasone in salbutamol-treated inpatients with acute bronchiolitis: a randomized, controlled trial. *J Pediatr.* 1997;130:191-196.

70. Berger I, Argaman Z, Schwartz SB, et al. Efficacy of corticosteroids in acute bronchiolitis: short-term and long-term follow-up. *Pediatr Pulmonol.* 1998;26:162-166.

71. Cade A, Brownlee KG, Conway SP, et al. Randomised placebo controlled trial of nebulised corticosteroids in acute respiratory syncytial viral bronchiolitis. *Arch Dis Child.* 2000;82:126-130.

72. Daugbjerg P, Brenoe E, Forchhammer H, et al. A comparison between nebulized terbutaline, nebulized corticosteroid and systemic corticosteroid for acute wheezing in children up to 18 months of age. *Acta Paediatr.* 1993; 82:547-51.

73. Fox GF, Everard ML, Marsh MJ, Milner AD. Randomised controlled trial of budesonide for the prevention of post-bronchiolitis wheezing. *Arch Dis Child.* 1999;80:343-347.

74. Kajosaari M, Syvanen P, Forars M, Juntunen-Backman K. Inhaled corticosteroids during and after respiratory syncytial virus-bronchiolitis may decrease subsequent asthma. *Pediatr Allergy Immunol.* 2000;11:198-202.

75. Reijonen T, Korppi M, Kuikka L, Remes K. Anti-inflammatory therapy reduces wheezing after bronchiolitis. *Arch Pediatr Adolesc Med.* 1996;150:512-517.

76. Richter H, Seddon P. Early nebulized budesonide in the treatment of bronchiolitis and the prevention of postbronchiolitic wheezing. *J Pediatr.* 1998;132:849-853.

77. Wong JY, Moon S, Beardsmore C, O'Callaghan C, Simpson H. No objective benefit from steroids inhaled via a spacer in infants recovering from bronchiolitis. *Eur Respir J.* 2000;15:388-394.

78. Everard ML, Swarbrick A, Rigby AS, Milner AD. The effect of ribavirin to treat previously healthy infants admitted with acute bronchiolitis on acute and chronic respiratory morbidity. *Respir Med.* 2001;95:275-280.

79. Guerguerian AM, Gauthier M, Lebel MH, Farrell CA, Lacroix J. Ribavirin in ventilated respiratory syncytial virus bronchiolitis. A randomized, placebo-controlled trial. *Am J Respir Crit Care Med.* 1999;160:829-834.

80. Janai HK, Stutman HR, Zaleska M, et al. Ribavirin effect on pulmonary function in young infants with respiratory syncytial virus bronchiolitis. *Pediatr Infect Dis J.* 1993;12:214-218.

81. Rodriguez WJ , Arrobio J, Fink R, Kim HW, Milburn C. Prospective follow-up and pulmonary functions from a placebo-controlled randomized trial of ribavirin therapy in respiratory syncytial virus bronchiolitis. Ribavirin Study Group. *Arch Pediatr Adolesc Med.* 1999;153:469-474.

82. Klein M. Multicenter trial of cefpodoxime proxetil vs. amoxicillin-clavulanate in acute lower respiratory tract infections in childhood. International Study Group. *Pediatr Infect Dis J.* 1995;14:S19-S22.

83. Andrade MA, Hoberman A, Glustein J, Paradise JL, Wald ER. Acute otitis media in children with bronchiolitis. *Pediatrics.* 1998;101:617-619.

84. Hollman G, Shen G, Zeng L, et al. Helium-oxygen improves Clinical Asthma Scores in children with acute bronchiolitis. *Crit Care Med.* 1998;26:1731-1736.

85. Van Bever HP , Desager KN, Pauwels JH, Wojciechowski M, Vermeire PA. Aerosolized furosemide in wheezy infants: a negative report. *Pediatr Pulmonol.* 1995;20:16-20.

86. Groothuis JR , Simoes EA, Hemming VG. Respiratory syncytial virus (RSV) infection in preterm infants and the protective effects of RSV immune globulin (RSVIG). Respiratory Syncytial Virus Immune Globulin Study Group. *Pediatrics.* 1995;95:463-467.

87. Groothuis JR , Simoes EA, Levin MJ, et al. Prophylactic administration of respiratory syncytial virus immune globulin to high-risk infants and young children. The Respiratory Syncytial Virus Immune Globulin Study Group. *N Engl J Med.* 1993;329:1524-1530.

88. Simoes EA, Sondheimer HM, Top FHJ, et al. Respiratory syncytial virus immune globulin for prophylaxis against respiratory syncytial virus disease in infants and children with congenital heart disease. The Cardiac Study Group. *J Ped.* 1998;133:492-499.

89. The PREVENT Study Group. Reduction of respiratory syncytial virus hospitalization among premature infants and infants with bronchopulmonary dysplasia using respiratory syncytial virus immune globulin prophylaxis. *Pediatrics.* 1997;99:93-99.

90. Groothuis JR . Safety and tolerance of palivizumab administration in a large Northern Hemisphere trial. Northern Hemisphere Expanded Access Study Group. *Pediatr Infect Dis J .* 2001;20:628-630.

91. The IMpact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics.* 1998;102:531-537.

92. Meissner HC, Groothuis JR, Rodriguez WJ, et al. Safety and pharmacokinetics of an intramuscular monoclonal antibody (SB 209763) against respiratory syncytial virus (RSV) in infants and young children at risk for severe RSV disease. *Antimicrob Agents Chemother.* 1999;43:1183-1188.

93. Groothuis JR , King SJ, Hogerman DA, Paradiso PR, Simoes EA. Safety and immunogenicity of a purified F protein respiratory syncytial virus (PFP-2) vaccine in seropositive children with bronchopulmonary dysplasia. *J Infect Dis.* 1998;177:467-469.

94. Piedra PA, Grace S, Jewell A, et al. Purified fusion protein vaccine protects against lower respiratory tract illness during respiratory syncytial virus season in children with cystic fibrosis. *Pediatr Infect Dis J.* 1996;15:23-31.

95. Piedra PA, Grace S, Jewell A, et al. Sequential annual administration of purified fusion protein vaccine against respiratory syncytial virus in children with cystic fibrosis. *Pediatr Infect Dis J.* 1998;17:217-224.

96. Marchetti A, Lau H, Magar R, Wang L, Devercelli G. Impact of palivizumab on expected costs of respiratory syncytial virus infection in preterm infants: potential for savings. *Clin Ther.* 1999;21:752-766.

97. Numa A. Outcome of respiratory syncytial virus infection and a cost-benefit analysis of prophylaxis. *J Paediatr Child Health.* 2000;36:422-427.

98. Schrand LM, Elliott JM, Ross MB, Bell EF, Mutnick AH. Cost-benefit analysis of RSV prophylaxis in high-risk infants. *Ann Pharmacother.* 2001;35:1186-1193.

99. Groothuis JR, Gutierrez KM, Lauer BA. Respiratory syncytial virus infection in children with bronchopulmonary dysplasia. *Pediatrics.* 1988;82:199-203.

100. Farina D, Rodriguez SP, Bauer G, et al. Respiratory syncytial virus prophylaxis: cost-effective analysis in Argentina. *Pediatr Infect Dis J.* 2002;21:287-291.

101. Sorrentino M, Powers T. Effectiveness of palivizumab: evaluation of outcomes from the 1998 to 1999 respiratory syncytial virus season. The Palivizumab Outcomes Study Group. *Pediatr Infect Dis J.* 2000;19:1068-1071.

102. Cunningham CK, McMillan JA, Gross SJ. Rehospitalization for respiratory illness in infants of less than 32 weeks' gestation. *Pediatrics.* 1991;88:527-532.

103. Paul DA, Leef KH, Chidekel A, Tran K, Eppes S, Stefano JL . Home delivery of palivizumab: outcomes and compliance in regional preterm infants. *Del Med J.* 2002;74:11-15.

104. Joffe S, Lieu T. Pallivizumab (Synagis): Counting "costs" and values. *Pediatrics.* 1999;106:1168.

105. Engle S, Newns GH. Proliferative mural bronchiolitis. *Arch Dis Child.* 1940;15:219.

106. Denny FW, Clyde WA. Acute lower respiratory tract infections in nonhospitalized children. *J Pediatr.* 1986;108:635-646.

107. Perlstein PH, Kotagal UR, Schoettker PJ, et al. Sustaining the implementation of an evidence-based guideline for bronchiolitis. *Arc Pediatr Adolesc Med.* 2000;154:1001-1007.

108. Gold M. Panel on cost-effectiveness in health and medicine. *Med Care.* 1996;34:DS197-DS199.

109. Wohl ME. Bronchiolitis. *Pediatr Ann.* 1986;15:307-309, 312-313.

110. Lowell DI, Lister G, Von Koss H, McCarthy P. Wheezing in infants: the response to epinephrine. *Pediatrics.* 1987;79:939-945.

111. Wang EE, Milner RA, Navas L, Maj H. Observer agreement for respiratory signs and oximetry in infants hospitalized with lower respiratory infections. *Am Rev Respir Dis.* 1992;145:106-109.

112. Tal A, Bavilski C, Yohai D, Bearman JE, Gorodischer R, Moses SW. Dexamethasone and salbutamol in the treatment of acute wheezing in infants. *Pediatrics.* 1983;71:13-8.

113. Tal A, Sanchez I, Pasterkamp H. Respirosonography in infants with acute bronchiolitis. *Am J Dis Child.* 1991;145:1405-1410.

114. Westley CR, Cotton EK, Brooks JG. Nebulized racemic epinephrine by IPPB for the treatment of croup: a double-blind study. *Am J Dis Child.* 1978;132:484-487.

115. Wood DW, Downes JJ, Lecks HI. A clinical scoring system for the diagnosis of respiratory failure. Preliminary report on childhood status asthmaticus. *Am J Dis Child.* 1972;123:227-228.

116. Bruhn FW, Yeager AS. Respiratory syncytial virus in early infancy. Circulating antibody and the severity of infection. *Am J Dis Child* . 1977;131:145-148.

Glossary for Evidence Tables

Glossary for Evidence Tables

ALRTI	acute lower respiratory tract infection
AMS	accessory muscle score
ARDS	acute respiratory distress syndrom
AURTI	acute upper respiratory tract infection
BID	twice daily
BPD	bronchopulmonary dysplasia
C	Celsius
C_{DYN}	dynamic compliance
CF	cystic fibrosis
CHD	congenital heart disease
CI	confidence interval
CPPV	continuous positive pressure ventilation
CXR	chest radiograph
d	days
Diff(s)	difference(s)
ED	emergency department
ELISA	Enzyme - Linked Immunosorbent Assay
ER	emergency room
GI	gastrointestinal
Grp	group
Hr(s)	hour(s)
ICU	intensive care unit
IFA	immunofluorescent assay
IFN	Interferon
IGIV	immunoglobulin intravenous
IM	intramuscular
IV	intravenous
Kg	kilogram
L/min	liters per minute
LRI	lower respiratory infection
LRTI	lower respiratory tract infection
MDI	metered dose inhaler
meq/L	milliequivalents per liter
Mg	milligram
Min(s)	Minute(s)
Ml	millileter
mmHg	millimeters of mercury
Mo(s)	month(s)
N	number of patients
NR	not reported
O_2	oxygen
PEEP	positive end expiratory pressure
PFP	purified F protein
PIP	peak inspiratory pressure
PO	oral
Pt(s)	patient(s)
Q	every
QID	four times daily
RCT	randomized controlled trials
RCT-C	randomized controlled trials – Crossover
RCT-P	randomized controlled trials – Placebo
RDAI	Respiratory Distress Assessment Instrument

Glossary for Evidence Tables (continued)

RDS	respiratory distress score
rhDNASE	recombinant human deoxyribonuclease
RR	respiratory rate
RSV	respiratory syncytial virus
RSVIG	respiratory syncytial virus immunoglobulin
SaO_2	transcutaneous hemoglobin oxygen saturation
SD	standard deviation
SE	standard error
Sig	significant
$TcPo_2$(kPa)	transcutaneous oxygen tension (measure of blood gases)
TID	three times daily
Ti/Ttot	duration of inspiration as fraction of total breath duration
URI	upper respiratory infection
URTI	upper respiratory tract infection
vs.	versus
V_T	tdal volume
Wk(s)	weeks
Yr(s)	year(s)

Evidence Tables

Evidence Table 1. Nebulized Epinephrine vs. Nebulized Saline Placebo

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Comorbidities
Author Kristjansson et al., 1993[52] **Setting:** Sweden, Norway, multi-center, inpatient **Followup:** Acute **Study design** RCT-P **Length of enrollment** NR **Masking** Double-blind	To examine the effect of nebulized racemic adrenaline in infants and toddlers with acute bronchiolitis	**Inclusion criteria** • < 18 mos • No atopic eczema • Symptom score of 4 or more (0 - 10 scale) • Diagnosis of bronchiolitis according to the criteria of Court:[19] – rapid respiration, dyspnea, wheezing, chest recession, cough, rales, ronchi very frequent (present in 50% or more of children in age group) – visible chest distension, increased pulmonary translucency on chest radiograph, nasal discharge, red pharynx frequent (present in 25% - 50% of children in age group) – Fever very frequent, high fever uncommon • Symptom score of 4 or more (0 - 10 scale) **Exclusion criteria** None listed	**Number** 34 eligible, 29 completed study **Sex** Racemic adrenaline: 67% male (10/15) Placebo: 64% male (9/14) **Mean age at enrollment** NR **Mean gestational age** NR **Comorbidities** None

Evidence Table 1. Nebulized Epinephrine vs. Nebulized Saline Placebo (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 15)** Nebulized racemic adrenaline (20 mg/µl) 0.1 ml if < 5 kg 0.15 ml if 5 - 6.9 kg 0.2 ml if 7 - 9.9 kg 0.25 ml if >10 kg Mixed in 3 ml 0.9% saline, nebulized with air flow of 8 L/min via spacer and close fitting facemask **Group B (n = 14)** Nebulized placebo Identically appearing solution and schedule **Other treatment** NR	**Outcomes** Primary outcome • Mean symptom score at 0, 15, 30, 45, 60 mins after inhalation • Mean change in SaO_2 at 0, 15, 30, 45, 60 mins after inhalation **Secondary outcomes** • Mean change in $TcPo_2$ (kPa) at 0, 15, 30, 45, 60 mins after inhalation • Mean respiratory rate (breaths/min) at 0, 15, 30, 45, 60 mins after inhalation • Mean heart rate (beats/min) at 0, 15, 30, 45, 60 mins after inhalation • Mean diastolic and systolic pressure (mm Hg) at 0, 15, 30, 45, 60 mins after inhalation **Subgroup analysis** Severely affected infants with baseline SaO_2 < 93% (n = 11) **Adverse events** None other than circumoral paleness	**Significant differences between study groups** • Clinical score significantly lower in adrenaline group at all time intervals (P < 0.05) • SaO_2 improvement in adrenaline group significant (P < 0.05) immediately post-treatment but not thereafter • Significantly different at all time internals (P < 0.05) • No significant differences at 1 hr • No significant differences at 1 hr • No significant differences at 1 hr • SaO_2 significantly elevated throughout one hr period post-treatment (P < 0.05)	**Quality** Fair **Significant differences at baseline** SaO_2 and $TcPo_2$ lower in racemic adrenaline group, difference significant for $TcPo_2$ only (P < 0.05) **Other comments** • Adrenaline group had lower $TcPo_2$ but CIs have significant overlap • No statistical correction for multiple comparisons

Evidence Table 2. Subcutaneous Epinephrine vs. Saline Placebo

Study characteristics	Stated objective of study	Inclusion/exclusion criteria	Demographic Characteristics and Cormorbidities
Author Lowell et al., 1987[110] **Setting:** United States, ED **Followup:** Acute **Study design** RCT-P **Length of enrollment** October 1982-May 1983 **Masking** Double-blind	To evaluate the efficacy of subcutaneous epinephrine in improving respiratory distress in children under the age of 24 months with acute episodes of wheezing	**Inclusion criteria** • < 24 months of age • Wheezing on physical exam (high pitched, continuous, musical, respiratory sound on 2 examinations at least 5 mins. apart) **Exclusion criteria** • Prior bronchodilator therapy • Chronic cardorespiratory problem (cystic fibrosis or congenital heart disease) • Heart rate = 200 beats/min. • Respiratory rate = 100 breaths/min • Lethargy judged to be in incipient respiratory failure	**Number** 45 eligible, 30 randomized, 12 entered in observational cohort **Sex** Epinephrine: 63 % male (10/16) Placebo: 71% male (10/14) **Mean age at enrollment in mo. ± SD** Epinephrine: 8.9 ± 5.8 Placebo: 9.9 ± 5.6 **Mean gestational age** NR **Comorbidities** None

Evidence Table 2. Subcutaneous Epinephrine vs. Saline Placebo (continued)

Intervention	Outcome		Quality
Intervention **Group A (n=16)** Epinephrine 0.1 ml/kg (1 mg/ml) x 2 15 mins. apart **Group B (n=14)** Placebo Saline 0.01 ml/kg x 2 15 mins. apart **Other treatment** NR	**Outcomes** **Primary outcome** • Absolute change in clinical score (respiratory assessment change score or RACS) - Graphical presentation, figures cannot be extracted • Improvement, defined as RACS = 4 or RACS<4 (epinephrine vs. placebo) - 56% vs. 7% **Subgroup analysis** • Age - < 6 mo. - = 6 mo. to < 12 mo. - = 12 mo. to < 18 mo. - = 18 mo. to < 24 mo. **Adverse events** NR	**Significant differences between study groups** • *P* < 0.05 • *P* = 0.0067 • *P* values NR	**Quality** Good **Significant differences at baseline** None **Other comments** Observational cohort included to account for selection bias, observational cohort more likely to be moderately or severely ill (58%) compared to experimental cohort (30%)

Evidence Table 3. Nebulized Epinephrine vs. Nebulized Bronchodilators (Salbutamol or Albuterol)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Bertrand et al., 2001[53] **Setting** Chile, inpatient **Followup** Short term **Study design** RCT non-placebo **Length of enrollment** May to Sept 1994 **Masking** Double-blind	To compare the efficacy of multiple doses of epinephrine versus salbutamol in infants hospitalized with acute bronchiolitis	**Inclusion criteria** • < 1 yr of age • First wheezing episode • Acute onset of respiratory distress • X-ray of chest compatible with bronchiolitis **Exclusion criteria** • Prematurity • Chronic lung or cardiac disease • Lower respiratory tract infection within previous 3 mos • Bronchodilator or steroid therapy within the month	**Number** 33 enrolled, 30 completed study **Sex** Salbutamol: 50% male (7/14) Epinephrine: 56% male (9/16) **Mean age at enrollment (mo.± SE)** Salbutamol: 3.7 ± 0.6 Epinephrine: 3.9 ± 0.4 **Mean gestational age** NR **Comorbidities** None

Evidence Table 3. Nebulized Epinephrine vs. Nebulized Bronchodilators (Salbutamol or Albuterol) (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 14)** Salbutamol 0.5 ml (2.5 mg) plus 0.9% saline to total volume of 4 ml q 2 to 4 hrs **Group B (n = 53)** Epinephrine (1:1000) 0.5 ml (0.5 mg) plus 0.9% saline to total volume of 4 ml q 2 to 4 hrs Both salbutamol and epinephrine nebulized with continuous oxygen flow at 6 to 8 L/min via facemask **Other treatment** NR	**Outcomes**	**Significant differences between study groups**	**Quality** Good **Significant differences at baseline** None **Other comments** • The scores of 3 enrolled patients who were transferred to receive mechanical ventilation were excluded from the final analysis • Two of the significant outcomes (hospital - ization on Days 4 and 5) may be influenced by the larger number of adverse events in salbutamol group • Did not use intent to treat analysis
	Primary outcome • Mean duration of hospitalization in days ± SE (salbutamol vs. epinephrine): - 5.2 ± 1.0 vs. 4.1 ± 1.1 • Change in clinical scores pre and post treatment (at baseline, 24 and 36 hrs)	• No (P = 0.11) • Significant only for epinephrine at baseline (P = 0.025)	
	Secondary outcomes • Hospitalization on Day 4 (salbutamol vs. epinephrine) • Hospitalization on Day 5 (salbutamol vs. epinephrine) • Readmission within 2 wks • Mean length of O_2 treatment in days • Average % of O_2 required to maintain O_2 saturation > 94%	• Yes (P = 0.03) • Yes (P = 0.025) • No • No • No	
	Subgroup analysis None		
	Adverse events • Increase in heart rate on second day (mean heart rate ± SE),: - Salbutamol: 146 ± 4 - Epinephrine: 153 ± 2.9 • Development of atelectasis - Salbutamol: 3/14 - Epinephrine: 0/16 • Bacterial super - infection - Salbutamol: 2/14 - Epinephrine: 0/13	• P = 0.02	

Evidence Table 3. Nebulized Epinephrine vs. Nebulized Bronchodilators (Salbutamol or Albuterol) (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Menon et al., 1995[22] **Setting** Canada, Emergency department **Followup** • Acute • Short term **Study Design** RCT non-placebo **Length of enrollment** Jan 1994 - March 1994 **Masking** Double-blind	To compare the efficacy of epinephrine with that of salbutamol in outpatients with acute bronchiolitis	**Inclusion criteria** • 6 wks to 1 yr • O_2 saturation $\geq$ 85% and $\leq$ 96% • RDAI score $\geq$ 4 • First episode of wheezing • Clinical symptoms of viral respiratory infection (temperature $\geq$ 38°C or coryza) **Exclusion criteria** • Chronic cardiac or pulmonary disease • Diagnosis of asthma by a physician • Any previous use of bronchodilators • Severe disease requiring resuscitation or heart rate < 200 beats/min • Received glucocorticoids within the previous 24 hrs	**Number** 41 completed study **Sex** NR **Mean age (yrs ± SD)** Salbutamol: 0.4 ± 0.2 Epinephrine: 0.5 ± 0.2 **Mean gestational age** NR **Comorbidities** None

Evidence Table 3. Nebulized Epinephrine vs. Nebulized Bronchodilators (Salbutamol or Albuterol) (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 21)** Salbutamol 0.3 ml of a 5 mg/ml solution (1.5 mg) combined with 2.7 ml of 0.9 % saline at 0 and 30 mins **Group B (n = 20)** Epinephrine 3 ml of 1:1000 solution at 0 and 30 mins nebulized with continuous flow of O_2 at 5 to 6 L/min **Other interventions** Higher concentration of O_2 or extra doses of salbutamol as needed	**Outcomes**	**Significant difference between groups**	**Quality** Good **Significant differences at baseline** None reported **Other comments** None
	Primary Outcomes		
	• O_2 saturation at 30, 60 and 90 mins (salbutamol vs. epinephrine) - 60 mins: 94% vs. 96%	• Yes, at 60 mins (P = 0.02)	
	Secondary Outcomes		
	• Clinical scores at 30, 60 and 90 mins	• No (P values NR)	
	• Respiratory rate (breaths/min) at 30, 60, 90 mins	• No (P values NR)	
	• Heart rate (beats/min ± SD) at 30, 60 and 90 mins (salbutamol vs. epinephrine) - 90 mins: 165 ± 13 vs. 151 ± 16	• Yes, at 90 mins (P = 0.003)	
	• Hospitalization (salbutamol vs. epinephrine) - 81% (17/21) vs. 33% (7/20)	• Yes (P = 0.003)	
	• Mean duration of admission	• No (P = 0.4)	
	• Rate of discharge from ED in first 4 hrs	• Yes, faster for epinephrine group (P = 0.02 for survival analysis)	
	• Return visits to hospital within 24 hrs of hospital discharge	• No (P = 0.94),	
	Other analysis Effect of time, group, and interaction between time and group on outcomes based on repeated measures analysis		
	Adverse events Higher incidence of pallor in epinephrine group at 30 and 60 mins, diminished by 90 mins	• P = 0.01 at 30 mins P = 0.06 at 60 mins P = 0.13 at 90 mins	

Evidence Table 3. Nebulized Epinephrine vs. Nebulized Bronchodilators (Salbutamol or Albuterol) (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Reijonen et al., 1995[54] **Setting** Finland, Emergency room **Followup** Acute **Study design** RCT-P **Length of enrollment** Jan 1992 to Nov 1993 **Masking** Double-blind	To determine whether early treatment with nebulized racemic epinephrine improves RDAI score in infants with acute bronchiolitis	**Inclusion criteria** • Hospitalized patients age 1 - 23 mons • Clinical criteria of acute bronchiolitis: wheezing and respiratory distress in patient with acute URTI **Exclusion criteria** • Chronic cardiorespiratory disease (asthma, BPD, CHD) • Use of oral, nebulized or parenteral bronchodilator in preceding 6 hrs • Impending respiratory failure • If admitted at night (10 pm to 7 am)	**Number** 100 enrolled **Sex** REP[1]: 58% male (14/24) AP: 59% male (16/27) PRE: 79% male (19/24) PA: 84% male (21/25) **Mean age at enrollment (mo).± SD)** REP: 10.6 ± 5.6 AP: 9.9 ± 5.5 PRE: 10.1 ± 5.7 PA: 10.3 ± 7.5 **Mean gestational age** NR **Comorbidities** • 13% with previous history of wheezing (no sig diffs among groups) • 31% with atopy (no sig diffs among groups)

[1] REP: Racemic epinephrine followed by placebo
AP: Nebulized albuterol followed by placebo
PRE: Placebo followed by nebulized racemic epinephrine
PA: Placebo followed by nebulized albuterol

Evidence Table 3. Nebulized Epinephrine vs. Nebulized Bronchodilators (Salbutamol or Albuterol) (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 24)** REP Racemic epinephrine: 0.9 mg/kg in 2 ml saline Placebo: 0.9% saline **Group B (n = 27)** AP Albuterol: 0.15 mg/kg in 2 ml saline solution Placebo: 0.9% saline **Group C (n = 24)** PRE Same as REP **Group D (n = 24)** PA Same as AP All groups received 2 nebs 30 mins apart via nebulizer with continuous oxygen flow of 5 L/min **Other treatment** • O_2 as needed • IM epinephrine for all patients 60 mins after first inhalation	**Outcomes** **Primary outcomes** • Change in RDAI score - all groups showed improvement • Respiratory rates at 0, 15, 30, 45, 60, 75, 90 mins • SaO_2 at 0, 15, 30, 45, 60, 75, 90 mins • O_2 treatment • Heart rate at 0, 15, 30, 45, 60, 75, 90 mins **Subgroup analyses** • Age - <1 yr - >1 yr • Severity of disease - RDAI > 8 - RDAI = 8 **Adverse events** None observed	**Significant differences between study groups** • No • No • No • NR • No • No • No	**Quality** Good **Significant differences at baseline** None **Other comments** • Percentage of children with history of atopy high • All children admitted to ER care (and enrolled in subsequent study)[75]

Evidence Table 3. Nebulized Epinephrine vs. Nebulized Bronchodilators (Salbutamol or Albuterol) (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Sanchez et al., 1993[55] **Setting** Canada, Inpatient **Followup** Acute **Study design** RCT-C **Length of enrollment** Dec 1991 to Apr 1992 **Masking** Double-blind	To compare inhaled racemic epinephrine vs. salbutamol to test the efficacy of a combined a - and ß - receptor agonist in acute bronchiolitis	**Inclusion criteria** • <1 yr of age • acute bronchiolitis **Exclusion criteria** • Previous bronchodilator treatment prior to admit • History of: - wheezing - chronic cardiorespiratory disease (asthma, CF, BPD, CHD) - parental history of asthma	**Number** 32 enrolled, 24 completed study **Sex** 50% male (12/24) **Mean age at enrollment (mo ± SD)** 4.6 ± 0.5 **Mean gestational age** Not reported **Comorbidities** None

Evidence Table 3. Nebulized Epinephrine vs. Nebulized Bronchodilators (Salbutamol or Albuterol) (continued)

Intervention	Outcome		Quality
Interventions (n = 24) Infants sedated with oral chloral hydrate (80 mg/kg first dose) After 1 hr, infants received either salbutamol (0.03 ml/kg in 2 ml in 0.9% saline) or racemic epinephrine (0.1 ml/kg in 2 ml in 0.9% saline) 2.5 hrs later, a second dose of chloral hydrate (40 mg/kg) followed in 30 mins by the drug not previously given **Other treatment** Supplemental oxygen as needed	**Outcomes** **Primary Outcomes** • Respiratory rate (mean values before vs. after ± SD) - Salbutamol 47.0 ± 1.5 vs. 40.8 ± 0.8 - Racemic epinephrine 46.5 ± 1.4 vs. 35.5 ± 0.4 • SaO_2 (mean values before vs. after ± SD) - Salbutamol 91.5 ± 0.7 vs. 92.1 ± 0.7 - Racemic epinephrine 91.8 ± 0.8 vs. 93.0 ± 0.7 **Secondary Outcomes** Pulmonary function tests: • V_T • Heart rate • Minute ventilation • C_{DYN} - total • Resistance - inspiratory • Resistance - expiratory • Ti/Ttot **Adverse events** None observed	**Significant differences between study groups** • Not significant before treatment (*P* value NR), significant after treatment ($P < 0.001$) • Not significant before or after treatment (*P* value NR) • Not significant before or after treatment • Not significant before or after treatment • Not significant before treatment, significantly lower after epinephrine than after salbutamol • Not significant before or after treatment • Not significant before treatment, significantly lower after epinephrine than after salbutamol • Not significant before treatment, significantly lower after epinephrine than after salbutamol • Not significant before or after treatment	**Quality** Fair **Significant differences at baseline** None reported **Comments** • Limited generaliz-ability due to selection of infants with mild to moderate bronchiolitis, sedation of infants with chloral hydrate • Did not examine role of rebound after racemic epinephrine

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Can et al., 1998[24] **Setting** Turkey, emergency department **Followup** Acute **Study Design** RCT-P **Length of enrollment** Jan 1994 - Jan 1996 **Masking** Double-blind	To evaluate the efficacy and safety of salbutamol in infants with acute bronchiolitis	**Inclusion criteria** Derived from study by Wohl et al. 1990,[109] details not provided **Exclusion criteria** • < 24 mons • Prematurity and mechanical ventilation after birth • Chronic cardiopulmonary disease • Previous bronchodilator and steroid administration during the admission • Symptoms > 1 wk • Heart rate > 200 beats/min and/or respiratory rate > 80 breaths/min • Lethargy or stupor • History of previous attack • Respiratory Distress Score < 5	**Number** 158 enrolled, 156 completed study **Sex** Salbutamol: 48% male Saline: 76% male Mist: 51% male **Mean age at enrollment (mo ± SD)** Salbutamol: 7.2 ± 4.2 Saline: 6.8 ± 2.1 Mist: 7.4 ± 5.3 **Mean gestational age** NR **Comorbidities** None

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 52)** Nebulized salbutamol 0.15 mg/kg in 2 ml saline **Group B (n = 52)** Nebulized saline **Group C (n = 52)** Mist in a tent In all groups, second dose given at 30 mins if RDS > 5 **Other treatment** Humidified O_2 at 5 L/min given to all groups	**Outcomes** **Primary Outcomes** • Mean RDS ± SD (salbutamol vs. saline vs. mist) - Initial: 11.0 ± 3.2 vs. 11.3 ± 3.6 vs. 10.8 ± 33 (33 quoted from text) - 30 mins.: 7.0 ± 3.1 vs. 9.7 ± 3.7 vs. 10.8 ± 3.6 - 60 mins.: 5.2 ± 1.8 vs. 10.2 ± 3.5 vs. 9.6 ± 3.4 • Percent with RDS> 5 at 30 mins (salbutamol vs. saline vs. mist) - 28% vs. 3% vs. 11% **Secondary Outcomes** • SaO_2 changes • Heart rate **Subgroup analysis** • Age - < 6 mo. vs. > 6 mo. **Adverse events** Frequency of tachycardia and hypoxia did not reach statistical significance, no details provided	**Significant differences between study groups** - No ($P > 0.05$) - $P < 0.0001$ for both salbutamol vs. saline and salbutamol vs. mist. Saline vs. mist not significant - $P < 0.0001$ for both salbutamol vs. saline and salbutamol vs. mist. Saline vs. mist not significant • P - value NR • Salbutamol lower, but not statistically significant • No • No	**Quality** Fair **Significant differences at baseline** • Group A had CXR findings consistent with acute bronchiolitis significantly more often ($P < 0.05$) than groups B and C **Other comments** • Followup limited to 60 mins • "Mist" not defined

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Cengizlier et al., 1997[58] **Setting** Turkey, Inpatient **Followup** • Acute • Short term **Study design** RCT non-placebo **Length of enrollment** NR **Masking** Cannot be determined	To evaluate the efficacy of oral or MDI salbutamol using a coffee cup as a spacer device in bronchiolitis	**Inclusion criteria** • First episode of bronchiolitis • 6 to 24 mons • Bronchiolitis diagnosed by ward pediatrician as expiratory wheezing of acute onset with signs of viral illness **Exclusion criteria** • Asthma • Cystic fibrosis • Congenital heart disease	**Number** 31 completed study **Sex** Oral salbutamol: 55% male (6/11) Inhaled salbutamol: 58% male (7/12) Control: 38% male (3/8) **Mean age at enrollment in mo. ± SD** Oral salbutamol: 9.6 ± 6.4 Inhaled salbutamol: 11.6 ± 1.2 Control: 9.2 ± 3.6 **Mean gestational age** NR **Comorbidities** None

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 11)** Oral salbutamol 0.1 mg/kg/dose QID **Group B (n = 12)** Inhaled salbutamol 200 µg/dose every 3° using an inhaler with a coffee cup as a spacer device **Group C (n = 8)** Control No therapy **Other treatment** Routine supportive care	**Outcomes** **Primary outcome** • Mean duration of hospitalization in days - oral salbutamol: 5 - inhaled salbutamol: 6 - control: 5 • Mean change in clinical scores between admission and discharge ± SD - oral salbutamol: 1.9 ± 0.4 - inhaled salbutamol: 2.0 ± 0.2 - control: 1.8 ± 0.3 **Secondary outcomes** • Increase in heart rate 1 hr after first dose of bronchodilator **Subgroup analysis** None **Adverse events** NR	**Significant differences between study groups** • No ($P > 0.05$ for both oral salbutamol vs. control and inhaled salbutamol vs. control) • No ($P > 0.05$ for both oral salbutamol vs. control and inhaled salbutamol vs. control) • No	**Quality** Fair **Significant differences at baseline** None: *P* values not provided, but groups do not appear to be significantly different **Other comments** None

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Dobson et al., 1998[37] **Setting** United States, inpatient **Followup** Short term **Study design** RCT-P **Length of enrollment** Dec 1995 - March 1996 **Masking** Double-blind	To determine whether albuterol enhances clinical and physiological recovery in hospitalized infants with moderately severe bronchiolitis	**Inclusion criteria** • < 24 months of age • First episode of wheezing during bronchiolitis season • Moderately severe bronchiolitis defined by the presence of one of the following - SaO_2 < 94% - moderate to severe accessory muscle use (= 2) or moderate to severe wheezing (= 2) **Exclusion criteria** • Underlying chronic cardiac or pulmonary disease • Significant concurrent illness (sepsis, meningitis, pneumonia, urinary tract infections, gastroenteritis) • Current gestational age <38 wks • History of wheezing requiring hospitalization or bronchodilator therapy before current illness • Concurrent steroid treatment • Severe bronchiolitis requiring intensive care (mechanical ventilation, documented apnea, heart rate > 200 beats/min, hypercarbia)	**Number** 58 enrolled, 52 completed study **Sex** Albuterol: 61% male (14/23) Placebo: 45% male (13/29) **Mean age at enrollment (mo.± SD)** Albuterol: 5.1 ± 3.7 Placebo: 6.1 ± 5.4 **Mean gestational age (wks. ± SD)** Albuterol: 39.2 ± 1.6 Placebo: 38.8 ± 2.4 **Comorbidities** None reported

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 23)** Nebulized albuterol Dose: 1.25 mg if <10 kg, 2.5 mg if >10 mg q. 2 hr x 24 hos then q. 4 hr x 48 hrs **Group B (n = 29)** Placebo 3ml normal saline by nebulized aerosol following same dosing schedule **Other treatment** Routine supportive care as needed	**Outcomes** **Primary Outcomes** • Improvement in % SaO_2 on room air over time for albuterol vs. placebo (95% CI) - 0 - 24 hrs: 1.8% (0.1% - 3.6%) vs. 1.6% (0.2% - 3.0%) - 24 hrs to max SaO_2: 2.2% (1.3% - 3.1%) vs. 1.8% (0.9% - 2.8%) - Time 0 to max SaO_2: 4.0% (2.6% - 5.4%) vs. 3.4% (2.4% - 4.5%) **Secondary Outcomes** • Percent patients discharged from hospital at 24, 48, 72 hrs • Length of hospital stay **Subgroup analysis** • Age - <12 mons of age **Adverse events** "Comparison of adverse events for albuterol vs. control groups approaches, but does not reach, statistical significance" (no details provided)	**Significant differences between study groups** • No • No • No	**Quality** Good **Significant differences at baseline** None **Other comments** Had 90% power to detect change in SaO_2 of = 2%

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Gadomski et al., 1994[60] **Setting** Egypt, outpatient and emergency room **Followup** Acute **Study Design** RCT-P, Group E not randomized **Length of enrollment** NR **Masking** Double-blind	• To determine the efficacy of albuterol in reducing respiratory distress in infants with bronchiolitis • To assess effectiveness of route of delivery (nebulization vs. oral) • To determine the incidence of positive blood culture among first-time wheezing infants	**Inclusion criteria** • <18 mons • First episode of wheezing • Recurrent wheezers/asthmatics recruited as open-label control subjects **Exclusion criteria** • Chronic diseases of the cardiorespiratory system • Heart rate > 200 beats/min • Cyanosis • Apathy, lethargy, or an otherwise depressed sensorium suggestive of incipient respiratory failure or sepsis • Persistent vomiting • Refused feedings	**Number** Number enrolled not stated, 128 randomized and 41 enrolled in study of recurrent wheezing, 169 completed study **Sex** Nebulized albuterol: 75% male Nebulized saline: 72% male Oral albuterol: 69% male Oral saline: 75% male Recurrent wheezers: 63% male **Median age at enrollment** Nebulized albuterol: 4.0 mos Nebulized saline: 5.0 mos Oral albuterol: 5.5 mos Oral saline: 4.0 mos Recurrent wheezers: 12.0 mos **Mean gestational age** NR **Comorbidities** None reported

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Intervention	Outcome		Quality
Intervention	**Outcomes**	**Significant differences between study groups**	**Quality**
Group A (n = 32) Nebulized albuterol 0.15 mg/kg x 2 doses 30 mins. apart **Group B (n = 32)** Nebulized saline 0.9% solution x 2 doses 30 mins apart All doses delivered via nebulizer with pediatric face mask with room air at flow rate of 4 - 6 L/min **Group C (n = 32)** Oral albuterol 0.15 mg/kg PO **Group D (n = 32)** Oral rehydration solution (with similar color and odor as Group C) **Group E (n = 41)** Recurrent wheezers treated with nebulized albuterol 0.15 mg/kg x 2 or 3 doses **Other treatment** After 60 mins, open-label albuterol nebulization treatment given to infants whose clinical condition had worsened or not improved prior to breaking randomization code	**Primary Outcomes** • Clinical scores at baseline, 30 and 60 mins • Respiratory rates at baseline, 30 and 60 mins • Heart rates at baseline, 30 and 60 mins • Oxygen saturation at baseline, 30 and 60 mins **Secondary Outcomes** • Leukocyte counts • Antimicrobial activity in urine • Blood culture • Chest x-rays **Subgroup analysis** Change in state (i.e., falling asleep, waking up) **Adverse events** NR	• No • No • No • No • No • No • No • No • No	**Significant differences at baseline** Recurrent wheezers older, heavier, more likely to have received meds before visit **Other comments** Group E not randomized

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Gadomski et al., 1994[59] **Setting** United States, Emergency department and outpatient clinic **Followup** Acute **Study design** RCT-P **Length of enrollment** Feb 1990 – Dec 1992 **Masking** Double-blind	To examine the efficacy of albuterol (oral and nebulized) in the management of bronchiolitis	**Inclusion criteria** • 15 months of age • First episode of wheezing • Clinical definition of bronchiolitis: - acute infection of lower respiratory tract - fever - rhinitis - tachypnea - expiratory wheezing - increased respiratory effort **Exclusion criteria** • Previous use of bronchodilator • History of intubation and mechanical ventilation • Chronic cardiorespiratory diseases (congenital heart disease, CF, BPD) • Severely ill infants: - heart rate > 200 beats - respiratory rate > 100 breaths/min - apathy/lethargy - depressed sensorium suggestive of incipient respiratory failure or sepsis	**Number** 93 randomized, 5 withdrawn, 13 in pilot study and did not complete protocol, 76 completed both assessments **Sex** Nebulized albuterol: 45% male (10/22) Nebulized saline: 57% male (13/23) Oral albuterol: 58% male (11/19) Oral placebo: 63% male (15/24) **Mean age at enrollment (mo)** Nebulized albuterol: 5.6 Nebulized saline: 5.8 Oral albuterol: 4.8 Oral placebo: 5.3 **Mean gestational age** NR **Comorbidities** None

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 22)** Nebulized albuterol If = 7 kg, 1 mg/dose nebulized albuterol in 3 mL saline x 2 doses, 30 mins apart If > 7 kg, 0.15 mg/kg/dose nebulized albuterol in 3 mL x 2, 30 mins apart Nebulized with compressed air at 6 L/min with pediatric face mask **Group B (n = 23)** Nebulized saline 3 mL saline x 2, 30 mins apart **Group C (n = 19)** Oral albuterol If = 7 kg, 2.5 mL (1 mg) If > 7 kg, 0.15 mg/kg/dose **Group D (n = 24)** Oral placebo Oral rehydration solution, same color as oral bronchodilator	**Outcomes** **Primary outcome** • Respiratory rate at baseline, 30 and 60 mins • Change in respiratory rate between baseline and 30 mins and baseline and 60 mins **Secondary outcomes** • Clinical score at baseline, 30 and 60 mins • Change in clinical score between baseline and 30 mins and baseline and 60 mins • Oxygen saturation at baseline, 30 and 60 mins • Change in oxygen saturation between baseline and 30 mins and baseline and 60 mins • Heart rate at baseline, 30 and 60 mins • Change in heart rate between baseline and 30 mins and baseline and 60 mins • Need for additional treatment • Number hospitalized **Subgroup analysis** • Age - < 6 mo vs. = 6 mo. • Change in state	**Significant differences between study groups** • No • No • No • No • No • No • Yes (heart rate significantly higher for oral albuterol group at 60 mins, *P* = 0.006) • Yes (change in heart rate significantly higher for oral albuterol group at 60 mins, *P* = 0.008) • No • No • No • Yes (*P* = 0.01 for change in RR and change in clinical score)	**Quality** Good **Significant differences at baseline** None **Other comments** Oral placebo same color as active drug, but no attempt made to mask flavor of albuterol itself

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Gadomski et al., 1994[59] (continued)			

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Intervention	Outcome	Quality
Other treatment After 60 mins, open-label albuterol nebulization treatment given to infants whose clinical condition had worsened or not improved prior to breaking randomization code	**Adverse events** • Increased heart rate among oral albuterol group • Facial flushing at 60 mins (3 nebulized albuterol subjects, 1 oral albuterol subject) • Hyperactivity (2 nebulized albuterol subjects, 1 oral albuterol subject) • Coughing (1 nebulized saline subject, 1 oral placebo subject) • Tremor at 60 mins (1 oral albuterol subject)	

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Goh et al., 1997[61] **Setting** Singapore, Inpatient **Followup** Acute **Study design** Placebo, salbutamol and ipratropium bromide: RCT-P Humidified oxygen: open label **Length of enrollment** Placebo, salbutamol and ipratropium bromide: Aug 1992 to Jul 1993 Humidified oxygen: Nov 1993 to Apr 1994 **Masking** Attending physician blinded, not clear if caretakers were blinded	To determine the efficacy of bronchodilators in the treatment of bronchiolitis	**Inclusion criteria** • < 2 yrs old • Admitted for signs and symptoms of bronchiolitis **Exclusion criteria** • Congenital heart disease • Immunocompromised patients • Recurring mechanical ventilation • History of previous wheeze	**Number** Between Aug 1992 and Jul 1993, 99 patients randomized, 89 completed study Between Nov 1993 and Apr 1994, 21 patients included **Sex** Placebo: 69% male (20/29) Salbutamol: 80% male (24/30) Ipratropium bromide: 67% male (20/30) Humidified oxygen 73% male (22/30) **Mean age at enrollment (mo ± SD)** Placebo: 7.4 ± 0.89 Salbutamol: 5.7 ± 0.77 Ipratropium bromide: 5.2 ± 0.67 Humidified oxygen: 5.9 ± 0.71 **Mean gestational age** NR **Comorbidities** None

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 29)** Nebulized normal saline 2 ml **Group B (n = 30)** Nebulized salbutamol 2.5 mg/mL If = 6 mo., 0.3 mL made up to 2 mL with normal saline If > 6 mo., 0.6 mL made up to 2 mL with normal saline **Group C (n = 30)** Nebulized ipratropium bromide 250 µg/mL made up to to 2 ml saline by age as above All nebulizations over 10 to 15 mins by face mask driven by oxygen flow at flow rate of 6 to 8 L/min **Group D (n = 31)** Humidified oxygen **Other treatment** As indicated	**Outcomes** **Primary outcome** • Mean duration of hospitalization in days for all groups: - 4 (no other details provided) **Secondary outcomes** • Severity scores at baseline, Day 1, Day 2 and Day 3 **Subgroup analysis** • Duration of hospitalization by age • Age > 6 mo vs. age < 6 mo - Hospitalization days - Number of nebulizations **Adverse events** NR	**Significant differences between study groups** • No ($P > 0.05$) • No ($P > 0.05$) • No ($P > 0.05$) • No ($P > 0.05$)	**Quality** Fair **Significant differences at baseline** None **Other comments** Humidified oxygen group was enrolled 1 yr after the RCT portion of the study, not randomized

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide or Saline Placebo or No Treatment

Study characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Hickey et al., 1994[57] **Setting:** United States, Emergency Department **Followup:** Acute **Study design** RCT-C **Length of enrollment** Dec 1989 to Feb 1990, Nov 1990 to March 1991 **Masking** Double-blind	To determine the efficacy of albuterol delivered via metered-dose inhaler with spacer for the treatment of wheezing infants	**Inclusion criteria** • 1-18 months • Wheezing **Exclusion criteria** • Cardiac or musculoskeletal disease • History of treatment with supplemental oxygen • Bronchodilator use in the previous 24 hrs • Severe respiratory distress (very poor air entry, cynanosis or fatigue)	**Number** 47 eligible, 42 enrolled **Sex** Group 1: 74% male (14/19) Group 2: 61% male (14/23) **Median age at enrollment in mo (range)** Group 1: 6.2 (1.2-18.3) Group 2: 7.0 (2.3-18) **Mean gestational age** NR **Comorbidities** None

Evidence Table 4: Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide or Saline Placebo or No Treatment (continued)

Intervention	Outcome		Quality
Intervention **Group A (n=19)** 2 treatments of albuterol followed by 2 treatments of placebo **Group B (n=23)** 2 treatments of placebo followed by 2 treatments of albuterol 2 puffs per treatment, either 90 µg of albuterol per puff or only the oleic acide dispersant. 20 mins. interval between treatments, delivered via metered-dose inhaler and "home-made" spacer device crafted at the Children's Hospital of Pittsburgh **Other treatment** NR	**Outcomes** **Primary outcome** • Improvement in wheezing scores – Graphical presentation, figures cannot be extracted • Improvement in retraction scores – Graphical presentation, figures cannot be extracted • Mean respiratory rate at baseline, 40 mins and 80 mins • Mean heart rate at baseline, 40 mins and 80 mins • Mean oxygen saturation at baseline, 40 mins and 80 mins	**Significant differences between study groups** • No sig. diffs. between groups, however Group A scores improved significantly from baseline by 2nd treatment ($P < 0.05$), Group B scores improved significantly only by 4th treatment ($P < 0.05$) • No sig. diffs. between groups, however Group A scores did not improved significantly from baseline, Group B scores improved significantly by 4th treatment ($P < 0.05$) • No diffs between groups at any time, no significant improvement within group over time • No diffs between groups at any time, no significant improvement within group over time • No diffs between groups at any time, no significant improvement within group over time	**Quality** Good **Significant differences at baseline** None **Other comments** None

Evidence Table 4: Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide or Saline Placebo or No Treatment (continued)

Study characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Hickey et al., 1994[57] (continued)			

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide or Saline Placebo or No Treatment (continued)

Intervention	Outcome		Quality
	Subgroup analysis • First episode of wheezing • RSV status	• Retraction scores lower for albuterol for first wheezers and RSV positive ($P < 0.05$), no other significant outcomes	
	Adverse events NR		

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Ho et al., 1991[62] **Setting** Australia, Inpatient **Followup** Acute **Study Design** RCT-C **Length of enrollment** NR **Masking** Double-blind	To determine the effect of inhaled salbutamol on SaO_2 among infants with bronchiolitis	**Inclusion criteria** • Children admitted with cough and wheeze due to acute bronchiolitis within 5 days of admission • Clinical findings of hyperinflation with wheeze and crackles on auscultation • Respiratory syncytial virus isolated by immunoflorescence of a postnasal aspirate **Exclusion criteria** • Severely ill children and those with associated chronic disabilities • Prior history of respiratory problems	**Number** 21 completed study **Sex** NR **Mean age at enrollment (range)** 3 mos (3 wks to 6 mo) **Mean gestational age** NR **Comorbidities** None

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 13)** Nebulized salbutamol 2.5 mg/2 mL Nebulized placebo 2 mL normal saline All nebulizations with compressed air at flow rate of 6 L/min for 10 mins, followed by other treatment 30 mins later **Group B (n = 8)** Identical interventions in reverse order **Other treatment** Supplemental oxygen for 3 subjects	**Outcomes** **Primary outcome** • O_2 saturation at 5, 10, 15, 20, and 25 mins of first neb., during 10 mins. to next neb., 5, 10, 15, 20, and 25 mins of second nebulizstion – 11 of 13 given salbutamol first had a desaturation from baseline. – 8 of 8 given salbutamol second had desaturation from baseline **Subgroup analysis** None **Adverse events** NR, see primary outcome	**Significant differences between study groups** • No significant difference between groups for median maximum falls in SaO_2	**Quality** Fair **Significant differences at baseline** NR **Other comments** None

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Klassen et al., 1991[21] **Setting** Canada, Emergency department **Followup** Acute **Study design** RCT-P **Masking** Double-blind **Length of enrollment** Nov 1988 - Apr 1990	To test the hypothesis that nebulized salbutamol would provide greater short term improvement in respiratory status than a placebo in young children with bronchiolitis	**Inclusion criteria** • <24 months old • Wheezing present on auscultation at initial presentation and at least 5 mins later on examination by one of the investigators • RDAI > 3 **Exclusion criteria** • History of bronchodilator therapy • History of chronic disease (including asthma) • Severe respiratory disease as evidenced by a pulse rate > 200 beats/min, a respiratory rate > 80 breaths/min an RDAI score > 15, or profound lethargy	**Number** 85 eligible, 83 completed study **Sex** Salbutamol: 52% male (22/42) Placebo: 61% male (25/41) **Mean age at enrollment (mo ± SE)** Salbutamol: 7.3 ± 4.2 Placebo: 7.0 ± 3.9 **Mean gestational age (wk ± SE)** NR **Comorbidities** None

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 42)** Nebulized salbutamol 0.1 mg/kg added to 2 ml of 0.9% saline solution administered through updraft nebulizer for 5 to 8 mins with continuous flow of oxygen for 5 to 6 L/min Treatment repeated 30 mins after study entry **Group B (n = 41)** Nebulized saline 0.02 ml/kg of 0.9% saline, administered as above **Other treatment** If after 60 mins, improvement in RDAI score < 3, 0.1 mg/kg salbutamol with 2 ml of 0.9% saline	**Outcomes** **Primary outcome** • RDAI score at baseline, 30 mins and 60 mins (salbutamol vs. placebo) **Secondary outcomes** • Heart rate at baseline, 30 mins and 60 mins (salbutamol vs. placebo) • Respiratory rate at baseline, 30 mins and 60 mins (salbutamol vs. placebo) • Oxygen saturation at baseline, 30 mins and 60 mins (salbutamol vs. placebo) **Subgroup analysis** • Age < 1 yr – RDAI score significantly different at 30 mins, but not at 60 mins • Positive RSV status – RDAI score significantly different at 30 mins in RSV+ infants, but not at 60 mins **Adverse events** • Heart rate among salbutamol group significantly higher than placebo group (159 ± 16 vs. 151 ± 16)	**Significant differences between study groups** • Yes (P = 0.04 at 30 mins alone) • No • No • No • P = 0.01 at 30 mins, P = 0.08 at 60 mins • P = 0.04 at 30 mins, P = 0.1 at 60 mins • Yes (P = 0.03)	**Quality** Excellent **Significant differences at baseline** None **Other comments** None

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Schuh et al., 1990[44] **Setting** Canada, emergency department **Followup** Acute **Study design** RCT-P **Masking** Double-blind **Length of enrollment** Dec 1988 to Apr 1989	To evaluate the clinical response to nebulized albuterol in infants and young children with acute bronchiolitis	**Inclusion criteria** • 6 wks to 24 mon • History and clinical findings compatible with bronchiolitis **Exclusion criteria** • History of prematurity or mechanical ventilation • History of LRTI, wheezing or bronchodilatory therapy • History suggestive of chronic aspiration or cardiac disease • Current episode that started more than 2 wks prior to ED evaluation • Presentation between 12 midnight and 8 am	**Number** 40 randomized **Sex** Overall: 85% male (34/40) **Mean age at enrollment (mo ±SE)** Albuterol: 6.1 ± 1.3 Placebo: 5.3 ± 1.2 **Mean gestational age** NR **Comorbidities** None

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 21)** Nebulized albuterol 0.15 mg/kg/dose in 3 mL of 0.9% normal saline x 3 doses at 1 hr intervals **Group B (n = 19)** Nebulized saline 2 doses of saline 1 hr apart, followed by third dose of nebulized albuterol, as above All doses delivered by face mask and nebulizer, driven by oxygen at flow rate of 6 to 7 L/min over 15 mins **Other treatment** As indicated	**Outcomes** **Primary outcome** • Hospitalization (albuterol vs. placebo): – 19% (4/21) vs. 10.5% (2/19) • Mean percentage decrease in respiratory rate ± SD (albuterol vs. placebo) - After dose 1: 16.2 ± 3.3 vs. 15.5 ± 3.5 - After dose 2: 19.6 ± 3.4 vs. 8.0 ± 3.0 **Secondary outcomes** • Mean decrease in AMS ± SD (albuterol vs. placebo) - After dose 1: 0.7 ± 0.1 vs. 0.3 ± 0.1 - After dose 2: 0.86 ± 0.1 vs. 0.37± 0.1 • Mean decrease in wheeze score ± SD (albuterol vs. placebo) - After dose 1: 0.43 ± 0.1 vs. 0.32 ± 0.1 - After dose 2: 0.67 ± 0.1 vs. 0.47± 0.2 • Mean change in oxygen saturation ± SD (albuterol vs. placebo) - After dose 1: +0.71 ± 0.3 vs. -0.47 ± 0.3 - After dose 2: +0.76 ± 0.04 vs. -0.79 ± 0.5 • Mean change in heart rate ± SD (albuterol vs. placebo) - After dose 1: +4.3 ± 3.2 vs. -1.5 ± 3.0 - After dose 2: +7.8 ± 2.7 vs. -6.8 ± 3.8	**Significant differences between study groups** • NR • Not significant after dose 1, significant after dose 2 ($P = 0.01$) • Yes ($P = 0.01$ after dose 1, $P < 0.01$ after dose 2) • No significant differences • Yes ($P = 0.01$ after dose 1, $P = 0.01$ after dose 2) • Not significant after dose 1, significant after dose 2 ($P = 0.003$)	**Quality** Good **Significant differences at baseline** None **Other comments** Study powered to detect difference of 1 SD in respiratory rate

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Schuh et al., 1990[44] (continued)			

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment (continued)

Intervention	Outcome	Quality
	Subgroup analysis • History of eczema - 19.4% decrease in respiratory rate for 13 patients with a family history of eczema vs. 19.7% for 8 patients without family history of eczema - 0.92 drop in accessory muscle score for 13 patients with a family history of eczema vs. 0.75 for 8 patients without family history of eczema	• NR
	Adverse events Increase in heart rate in albuterol group from mean of 153.2 to 160.9 beats/min	• NR

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide or Saline Placebo or no Treatment (continued)

Study characteristics	Stated objective of study	Inclusion/Exclusion criteria	Demographic Characteristics and Comorbidities
Author Schweich et al., 1992[56] **Setting:** United States, ED **Followup:** Acute **Study design** RCT-P **Length of enrollment** November 1989-March 1990 **Masking** Double-blind	To evaluate the efficacy of nebulized albuterol in the treatment of wheezing infants	**Inclusion criteria** • < 2 yrs old • Wheezing **Exclusion criteria** • Current sympathomimetic medicine • Chronic cardiac or pulmonary disease • Other major chronic diseases • Impending respiratory failure	**Number** 25 patients enrolled and randomized **Sex** Placebo: 50% male (6/12) Albuterol: 46% male (7/13) **Mean age at enrollment in mo.** Placebo: 8.7 Albuterol: 6.0 **Mean gestational age** NR **Comorbidities** None

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide or Saline Placebo or no Treatment (continued)

Intervention	Outcome		Quality
Intervention **Group A (n=12)** Albuterol 0.15 mg/kg in 3 ml of normal saline **Group B (n=13)** Placebo 0.03 ml/kg normal saline in 3 ml of normal saline 2 blinded treatments 30 mins. apart administered with continuous flow oxygen at 6 L/min Code broken 30 mins. after 2nd treatment, placebo patients given albuterol **Other treatment** Supplemental oxygen as needed	**Outcomes** **Primary outcomes** • Mean change in retraction score after first treatment ± SD (albuterol vs. placebo) – -0.54 ± 1.05 vs. -0.58 ± 0.79 • Mean change in retraction score after second treatment ± SD (albuterol vs. placebo) – -1.25 ± 1.35 vs -0.41 ± 0.90 • Mean change in total score after first treatment ± SD (albuterol vs. placebo) – -1.54 ± 2.36 vs. -1.58 ± 2.46 • Mean change in total score after second treatment ± SD (albuterol vs. placebo) – -4.08 ± 2.91 vs -1.33 ± 2.38 **Secondary outcomes** • Mean change in wheeze score after first treatment ± SD (albuterol vs. placebo) – -1.00 ± 2.00 vs. -1.00 ± 2.04 • Mean change in wheeze score after second treatment ± SD (albuterol vs. placebo) – -2.83 ± 2.55 vs. -0.92 ± 1.62 • Mean change in respiratory rate after first treatment (albuterol vs. placebo) – -1.8 vs. 2.9 • Mean change in respiratory rate after second treatment (albuterol vs. placebo) – -1.4 vs. -0.5 • Mean change in retraction rate after first treatment (albuterol vs. placebo) – -3.5 vs. 0.7 • Mean change in retraction rate after second treatment (albuterol vs. placebo) – 2.4 vs. -0.4	**Significant differences between study groups** • No, *P* value NR • No, *P* value NR • No, *P* value NR • Yes (*P* = 0.019) • No, *P* value NR • Yes (*P* = 0.039) • No, *P* value NR • No, *P* value NR • Yes (*P* = 0.018) • No, *P* value NR	**Quality** Good **Significant differences at baseline** None **Other comments** None

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide or Saline Placebo or no Treatment (continued)

Study characteristics	Stated objective of study	Inclusion/Exclusion criteria	Demographic Characteristics and Comorbidities
Author Schweich et al., 1992 (continued)			

Evidence Table 4. Nebulized Bronchodilators (Salbutamol or Albuterol) vs. Oral Bronchodilators, Nebulized Ipratropium Bromide or Saline Placebo or no Treatment (continued)

Intervention	Outcome		Quality
	• Mean change in heart rate after first treatment (albuterol vs. placebo)	• No, *P* value NR	
	• -14 vs. -9	• No, *P* value NR	
	• Mean change in heart rate after second treatment (albuterol vs. placebo)		
	– -13 vs. -15		
	Subgroup analysis		
	RSV status	• *P* value NR (n too low for statistical testing)	
	Adverse events		
	Small decrease in oxygen saturation in albuterol group		

Evidence Table 5. Nebulized Salbutamol or Albuterol plus Nebulized Ipratropium Bromide vs. Bronchodilators or Ipratropium Bromide Alone and/or Saline Placebo

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Chowdhury et al., 1995[63] **Setting:** Saudi Arabia, inpatient **Followup:** • Acute • Short term **Study design** RCT-P **Length of enrollment** Oct 1992 to Jan 1993 **Masking** Double-blind until 36 hrs, investigator unblended thereafter	To compare the efficacy of salbutamol, ipratropium bromide, and a combination of both vs. saline placebo in treating children hospitalized for bronchiolitis	**Inclusion criteria** • Admission for bronchiolitis defined as history of cough and/or wheeze, tachypnea, intercostals retractions, and on auscultation, rhonchi and rales • < 2 yrs • Presence of wheezing – audible or auscultation **Exclusion criteria** • Previous history of wheezing or use of bronchodilators • Chronic pulmonary disease • Congenital heart disease • CXR evidence of consolidation • Patients judged by admitting resident to be not sufficiently sick or to require intensive monitoring or therapy	**Number** 102 eligible, 89 completed study **Sex** Salbutamol[2]: 70% male (14/20) Ipratropium bromide: 70% male (16/23) Salbutamol + Ipratropium bromide: 70% male (16/23) Placebo: 77% male (17/22) **Mean age at enrollment (mo.± SE)** Salbutamol: 3.9 ± 2.3 Ipratropium bromide: 4.2 ± 2.4 Salbutamol + Ipratropium bromide: 3.6 ± 1.8 Placebo: 3.7 ± 2.3 **Mean gestational age** NR **Comorbidities** None

[2] S: Salbutamol
I: Ipratropium bromide
S+ I: Salbutamol and Ipratropium bromide
P: Placebo

Evidence Table 5. Nebulized Salbutamol or Albuterol plus Nebulized Ipratropium Bromide vs. Bronchodilators or Ipratropium Bromide Alone and/or Saline Placebo (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 20)** Salbutamol 0.15 mg/kg nebulized q. 6 hrs x 36 hrs **Group B (n = 23)** Ipratropium bromide 12.5 µg/kg nebulized q. 6 hrs x 36 hrs **Group C (n = 24)** Salbutamol + Ipratropium bromide nebulized Same dosing and schedule as Groups A and B **Group D (n = 22)** Placebo 0.3 mg/kg All doses with 100% oxygen at 6 to 7 L/min with pediatric nebulizers **Other treatment** NR	**Outcomes** **Primary outcome** • Mean duration of hospitalization in days ± SD - S: 4.5 ± 1.3 - I: 4.4 ± 1.4 - S+I: 4.6 ± 1.4 - P: 4.3 ± 1.1 • Clinical score at 30 mins, 60 mins, 6 hrs, 12 hrs, 24 hrs, 36 hrs **Subgroup analysis** • Age - < 3 mo. - > 3 mo. • RSV status **Adverse events** NR	**Significant differences between study groups** • No (P = 0.79) • No (P values ranged from 0.23 at 30 mins to 0.93 at 60 mins • No • No	**Quality** Fair **Significant differences at baseline** None **Other comments** Investigators unblinded at 36 hrs

Evidence Table 5. Nebulized Salbutamol or Albuterol plus Nebulized Ipratropium Bromide vs. Bronchodilators or Ipratropium Bromide Alone and/or Saline Placebo (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Schuh et al., 1992[64] **Setting** Canada, emergency department **Followup** Acute **Study Design** RCT-P **Length of enrollment** Dec 1989 - March 1991 **Masking** Double-blind	To determine whether infants with bronchiolitis would show a greater clinical response to nebulized albuterol-ipratropium combination compared with albuterol alone	**Inclusion criteria** • 6 wks to 24 months of age • Acute bronchiolitis, including upper respiratory tract infection with wheezing and respiratory distress (defined as respiratory rate ≥ 40 minute and/or chest retractions) • Presentation in ER between 8 am and midnight • First episode of wheezing **Exclusion criteria** • Very severe bronchiolitis, defined as either cyanosis at initial examination or initial respiratory rate ≥ 90 per minute with severe restrictions • History of mechanical ventilation after birth • Past history of wheezing or bronchodilator therapy • Concurrent cardiopulmonary disease • Recurrent aspiration • Respiratory distress started more than 2 wks prior to hospital visit	**Number** 72 enrolled, 69 completed study **Sex** NR **Mean age at enrollment (mos ± SD)** I+A[3]: 9.4 ± 6.1 P+A: 8.7 ± 5.2 **Mean gestational age** NR **Comorbidities** None

[3] I+A: Ipratropium bromide plus Albuterol
P+ A: Placebo plus Albuterol

Evidence Table 5. Nebulized Salbutamol or Albuterol plus Nebulized Ipratropium Bromide vs. Bronchodilators or Ipratropium Bromide Alone and/or Saline Placebo (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 36)** Nebulized albuterol 0.15 mg/kg and Nebulized ipatropium bromide 250 µg/kg; 2 doses 1 hr apart **Group B (n = 33)** Nebulized albuterol 0.15 mg/kg and saline placebo; 2 doses 1 hr apart All doses delivered via nebulizer with a tight - fitting small face mask, driven by oxygen at flow rate of 6-7 L/min **Other treatment** None reported	**Outcomes** **Primary Outcomes** • Mean change in respiratory rate from baseline to 120 mins ± SD (I+A vs. P+A) - 10.6 ± 10.0 vs. 8.6 ± 10.2 **Secondary Outcomes** Mean change from baseline to 120 mins in • Accessory muscle score • Wheeze score • SaO_2 increase • Heart rate increase • Overall responsiveness **Subgroup analysis** • Atopic history • Age - < 9 mo. vs. = 9 mo. **Adverse events** • Decline in oxygen saturation of 3% or more in both groups (2/36 vs. 3/33)	**Significant differences between study groups** • No ($P > 0.42$) • No • No • No • No • No • No • NR	**Quality** Good **Significant differences at baseline** None **Other comments** None

Evidence Table 5. Nebulized Salbutamol or Albuterol plus Nebulized Ipratropium Bromide vs. Bronchodilators or Ipratropium Bromide Alone and/or Saline Placebo (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Wang et al., 1992[65] **Setting** Canada, inpatient **Followup:** • Acute • Short term **Study design** RCT-P **Length of enrollment** NR **Masking** Double-blind	To examine the efficacy of inhaled bronchodilators in hospitalized patients using pulse oximetry and clinical score	**Inclusion criteria** • 2 mos - 2 yrs of age • First hospitalization for bronchiolitis • Did not have adequate improvement with emergency department management which always included salbutamol • Bronchiolitis diagnosed in the presence of expiratory wheezing of acute onset accompanied by signs of viral illness such as coryza **Exclusion criteria** • Known underlying cardiac or pulmonary disease • Transferred from another hospital • Condition rapidly deteriorating • Parental refusal or attending physician refusal	**Number** 150 eligible, 62 randomized **Sex** S + I:[4] 53% male (9/17) S: 57% male (8/14) I: 73% male (11/15) P: 38% male (6/16) **Mean age at enrollment** NR **Mean gestational age** NR **Comorbidities** None

[4] S+ I : Salbutamol and Ipratropium bromide
S: Salbutamol
I: Ipratropium bromide
P: Placebo

Evidence Table 5. Nebulized Salbutamol or Albuterol plus Nebulized Ipratropium Bromide vs. Bronchodilators or Ipratropium Bromide Alone and/or Saline Placebo (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 17)** Salbutamol + Ipratropium Salbutamol: 0.15 mg/kg in 2ml saline Ipratropium bromide: 125 µg if < 6mo., 250 µg if > 6mo. **Group B (n = 14)** Salbutamol 0.15 mg/kg in 2ml saline, then 0.5 ml or 1 ml saline I hr later **Group C (n = 15)** Ipratropium 0.03 ml/kg of saline in 2ml saline followed by ipratropium bromide 125 µg if < 6mo., 250 µg if > 6mo. **Group D (n = 16)** Placebo Saline, same volumes as indicated above All treatments administered through face mask and nebulizer driven by oxygen at flow rate of 6 - 7 L/min every 4 hrs of hospitalization or 3 days whichever came first **Other treatment** Routine care as needed, Ribavirin(1 patient), systematic steroids and theophylline(1 patient)	**Outcomes** **Primary outcome** • Mean duration of hospitalization in days ± SE - S+I: 2.5 ± 0.3 - S: 3.2 ± 0.4 - I: 2.4 ± 0.3 - P: 2.9 ± 0.4 **Secondary outcomes** • Mean change in clinical score • Mean change in oxygen saturation **Subgroup analysis** None **Adverse events** 1 child in salbutamol group had tremulousness, leading to withdrawal from study	**Significant differences between study groups** • No (*P* values NR) • No • Significantly greater for S+I vs. S (*P* = 0.002) and S+I vs. I (*P* = 0.04), but not S+I vs. P (*P* > 0.1). Significantly worse for S vs. P (*P* = 0.03)	**Quality** Good **Significant differences at baseline** Fewer boys in placebo group than other groups **Other comments** None

Evidence Table 6. Oral Corticosteroids vs. Placebo, With or Without Bronchodilators

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author: Berger 1998[70] **Setting** Israel, Emergency department at baseline **Followup** • Acute • Short term - 1 wk followup • Long-term - 2 yr telephone followup **Study design** RCT-P **Length of enrollment** Winter months 1993 - 1994 **Masking** Double-blind	To assess the Short term and Long-term effects of prednisone in infants suffering from mild to moderate bronchiolitis	**Inclusion criteria:** • 1 - 18 months of age (Bronchiolitis defined as first episode of wheezing associated with low - grade fever, rhinitis, tachypnea, and increased respiratory effort in a previously healthy infant during the winter months) **Exclusion criteria:** • Chronic cardiopulmonary disease, including asthma • Proven or suspected acute bacterial infection • Previous treatment with corticosteroids by any route • The presence of symptoms more than 7 days • Fever >38.5 C • Respiratory distress or total clinical score >7 • Infant requiring immediate medical care including oxygen	**Number** 42 enrolled, 38 completed 1 - wk followup, 28 contacted for 2 yr followup **Sex** NR **Mean age at enrollment (mos ± SD)** Prednisone: 5.2 ± 0.7 Placebo: 4.8 ± 0.9 **Mean gestational age** NR **Comorbidities** None

Evidence Table 6. Oral Corticosteroids vs. Placebo, With or Without Bronchodilators (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 20)** Prednisone Dose: 1 mg/kg PO BID x 3 d **Group B (n = 53)** Placebo Dose: Identically appearing solution and schedule **Other treatment** Inhaled albuterol solution Dose: 0.15mg/kg/dose q. 4 - 6 hrs via aerosol micromist nebulizer as indicated	**Outcomes** **Primary Outcomes** • Mean total score ± SD (prednisone vs. placebo) - Before treatment: 4.4 ± 2 vs. 1.95 ± 1.9 - After treatment: 1.95 ± 1.9 vs. 2.05 ± 3 - Mean change: 2.45 ± 0.12 vs. 2.45 ± 0.3 **Secondary Outcomes** • Accessory muscle score • Wheezing score • Respiratory rate • SaO_2 • Hospitalization rate – 25% vs. 11% • Parent's report of clinical status at 1 wk followup • Need for repeat evaluation in ER or outpatient clinic by 1 wk followup • Need for continued therapy at 1 wk followup • Recurrent respiratory symptoms at 2 yr followup – 35.7% vs. 28.6% **Adverse events** NR	**Significant differences between study groups** • No - *P* = 0.82 - *P* = 0.59 • No • No • No • No • NR • No • No • No • NR	**Quality** Good **Significant differences at baseline** None **Comments** Intent-to-treat analysis not used

Evidence Table 6. Oral Corticosteroids vs. Placebo, With or Without Bronchodilators (continued)

Study characteristics	Stated objective of study	Inclusion/Exclusion Criteria	Demographic Characteristics and Comorbidities
Author Daugbjerg et al., 1993[72] **Setting:** Denmark, inpatient **Followup:** Acute Short term **Study design** RCT-P **Length of enrollment** Winter seasons 1989-1990, 1990-1991 **Masking** Double-blind	To evaluate the effect of nebulized corticosteroids in combination with bronchodilators in the treatment of acute wheezing in children up to 18 months of age	**Inclusion criteria** • = 18 months • 5-15 kg • Symptom score of 3 or more • First or recurrent attack of wheezing **Exclusion criteria** • Pretreatment with steroids • Chronic lung disease or heart disease • Requiring assisted ventilation • Allergy to the test medication	**Number** 124 enrolled, 114 remaining for evaluation **Sex** P + T[5]: 71% male (22/31) B + T: 69% male (20/29) T: 70% male (19/27) P: 59% male (16/27) **Mean age at enrollment in mo. ± SD** P + T: 10.2 ± 4.5 B + T: 9.1 ± 4.4 T: 8.6 ± 3.6 P: 9.3 ± 3.9 **Mean gestational age** NR **Comorbidities** None

[5] P + T: Prednisolone + terbutaline
B + T: Budesonide + terbutaline
T: Terbutaline
P: Placebo

Evidence Table 6. Oral Corticosteroids vs. Placebo, With or Without Bronchodilators (continued)

Intervention	Outcome		Quality
Intervention **Group A (n=31)** Soluble prednisolone + placebo inhalation + terbutaline inhalation **Group B (n=29)** Soluble placebo + budesonide inhalation + terbutaline inhalation **Group C (n=27)** Soluble placebo + placebo inhalation + terbutaline inhalation **Group D (n=27)** Soluble placebo + placebo inhalation + normal saline inhalation Prednisolone: Day 1: 4-6 mg/kg Days 2,3: 1.6-2.6 mg/kg Budesonide: 0.5 mg q. 4 hrs until discharge or for five days Terbutaline: 0.12-0.2 mg/kg q. 4 hrs until discharge or for five days Both budesonide and terbutaline dissolved in normal saline, administered with oxygen at flow of 8 L/min via facemask. Night inhalation omitted if child was asleep, **Other treatment** NR	**Outcomes** **Primary outcomes** • Treatment failures (withdrawal from study because of deterioration of condition) – P + T: 16% (5/31) – B + T: 3% (1/29) – T: 11% (3/27) – P: 2% (14/27) • Mean days of hospitalization ± SD – P + T: 3.5± 1.4 – B + T: 3.5 ± 1.1 – T: 4.3 ± 1.4 – P: 4.1 ± 1.0 **Secondary outcomes** • Mean temperature ± SD – P + T: 37.4 ± 0.5 – B + T: 37.3 ± 0.6 – T: 37.5 ± 03 – P: 37.2 ± 0.5 • Mean respiratory rate ± SD – P + T: 39 ± 10 – B + T: 42 ± 8 – T: 41 ± 10 – P: 42 ± 5 • Mean respiratory rate ± SD – P + T: 39 ± 10 – B + T: 42 ± 8 – T: 41 ± 10 – P: 42 ± 5 **Subgroup analysis** • Age (Treatment failures for steroids groups vs. terbutaline + placebo) • Under 12 mos • Over 12 mos **Adverse events** None observed	**Significant differences between study groups** • Differences between all treatments vs. placebo are significant ($P < 0.01$), differences among treatment group not significant ($P = 0.1$) • Yes ($P = 0.04$) • Yes ($P = 0.02$) • Yes ($P = 0.08$) • Yes ($P = 0.009$)	**Quality** Good **Significant differences at baseline** None **Other comments**

Evidence Table 6. Oral Corticosteroids vs. Placebo, With or Without Bronchodilators (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Goebel et al., 2000[66] **Setting** United States, Emergency department **Followup** • Acute • Short term **Study design** RCT-P and open label albuterol **Length of enrollment** NR **Masking** Double-blind	To compare albuterol plus prednisolone versus albuterol plus placebo in young children with mild to moderate bronchiolitis	**Inclusion criteria** • = 23 mos of age • Symptoms of viral respiratory tract infection (rhinorrhea, cough, rectal temp to 38.5°C) during fall and winter months • First time wheezing not completely cleared by 1 dose of albuterol **Exclusion criteria** • History of - immune defect - neurologic disease with possible aspiration - gastroesophageal reflux - congenital or acquired heart or lung disease - mechanical ventilation - birth before 36 wks gestation • Fever > 38.5°C rectally, antibiotic therapy within 1 wk or antipyretics within 8 hrs • Evidence of bacterial infection • Emesis precluding administration of oral meds • Initial bronchiolitis score < 2 or > 9	**Number** 51 randomized, 48 at conclusion of study, 32 with complete data **Sex** Prednisolone plus albuterol: 75% male (18/24) Placebo plus albuterol: 67% male (16/24) **Median age at enrollment in months (range)** Prednisolone plus albuterol: 4.0 (0 - 13) Placebo plus albuterol: 4.5 (0 - 16) **Mean gestational age** NR **Comorbidities** None

Evidence Table 6. Oral Corticosteroids vs. Placebo, With or Without Bronchodilators (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 24)** Prednisolone plus albuterol Prednisolone: PO 2mg/kg/d PO divided BID x 5 days Albuterol: PO 0.3 mg/kg/day PO, divided TID or 0.15 mg/kg/dose QID by nebulizer **Group B (n = 24)** Placebo plus albuterol Placebo: Identically appearing solution, given at same dose and schedule Albuterol: Same as Group A **Other treatment** NR	**Outcomes** **Primary outcome** • Clinical scores (Prednisolone plus albuterol vs. placebo plus albuterol) - Day 0: 4.5 ± 1.7 vs. 4.9 ± 1.4 - Day 2: 2.7 ± 1.4 vs. 4.0 ± 1.5 • Clinical scores on Day 3 (values NR) • Clinical scores on Day 6 (values NR) **Subgroup analysis** • RSV status, culture positive vs. culture negative **Adverse events** • 1 subject in Grp A jittery, resolved after reduction of albuterol dose	**Significant differences between study groups** • Significant change for prednisolone plus albuterol between days 0 and 2 ($P < 0.05$), no significant change for placebo plus albuterol between days 0 and 2 ($P > 0.05$) • No (P value NR) • No (P value NR) • Trend toward improvement in Grp A regardless of RSV status but not statistically significant (P value NR)	**Quality** Good **Significant differences at baseline** None **Other comments** • Possible confounding effects from different methods of dosing albuterol • Incomplete followup • Post-hoc exclusion of 3 subjects

Evidence Table 6. Oral Corticosteroids vs. Placebo, With or Without Bronchodilators (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Klassen et al., 1997[69] **Setting** Canada, Inpatient **Followup** • Acute • Short term - 1 wk after discharge **Study design** RCT-P **Length of enrollment** Nov 1993 - Apr 1995 **Masking** Double-blind	To determine the clinical benefit of oral dexamethasone in children admitted to the hospital with bronchiolitis treated with nebulized salbutamol	**Inclusion criteria** • First episode of wheezing (lasting < 7days) • Clinical evidence of viral infection: - rhinorrhea - temp > 37.5°C • > 6 wks. to < 15 mo of age • O_2 < 95% at admission • RDAI > 6 **Exclusion criteria** • Underlying disease which affects cardiopulmonary status: - cystic fibrosis - bronchopulmonary dysplasia - congenital heart disease - immunodeficiency • Physician diagnosed asthma • Wheezing or cough treated by bronchodilators • Steroid treatment within 2 wks of admission	**Number** 72 eligible, 72 randomized, 67 completed study **Sex** Placebo: 47% male (15/32) Dexamethasone: 63% (22/35) **Mean age at enrollment in years** Placebo: 0.39 Dexamethasone: 0.39 **Mean gestational age** NR **Comorbidities** None

Evidence Table 6. Oral Corticosteroids vs. Placebo, With or Without Bronchodilators (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 32)** Placebo 70% sucrose solution **Group B (n = 53)** Dexamethasone 70% sucrose solution and dexamethasone, 0.5 mg/kg initial, 0.3 mg/kg q. morning until discharge **Other treatment** • Nebulized salbutamol (0.15mg/kg) q 4 hrs x first 24 hrs • 35% O_2 via plastic tent	**Outcomes** **Primary outcome** • Change in RDAI from baseline to 12, 24, 36, 48 and 60 hrs (placebo vs. dexamethasone) **Secondary outcomes** • Mean duration of hospitalization in hrs (range) (placebo vs. dexamethasone) - 48 (42, 54) vs. 57 (38, 76) • Readmission (placebo vs. dexamethasone) - 1 (3%) vs. 4 (11%) • Change in oxygen saturation from baseline to 12, 24, 36, 48 and 60 hrs (placebo vs. dexamethasone) • Change in respiratory rate at same intervals (placebo vs. dexamethasone) • Visits to MD/other health professionals (placebo vs. dexamethasone) - 24 (75%) vs. 29 (83%) • Salbutamol at discharge (placebo vs. dexamethasone) - 6 (19%) vs. 6 (17%) • Orciprenaline at discharge (placebo vs. dexamethasone) - 2 (6%) vs. 7 (20%) • Antibiotic use (placebo vs. dexamethasone) - 13 (41%) vs. 10 (29%) • IV hydration (placebo vs. dexamethasone) - 5 (16%) vs. 3 (8%) • Number of salbutamol inhalations after first 24 hrs - Details NR **Subgroup analysis** None **Adverse events** NR	**Significant differences between study groups** • No (*P* values range from 0.23 to 0.74) • No (*P* = 0.19) • No (*P* = 0.36) • No (*P* values range from 0.28 to 0.47) • No (*P* values range from 0.09 to 0.78) • No (*P* = 0.77) • No (*P* = 0.82) • No (*P* = 0.16) • No (*P* = 0.3) • No (*P* = 0.46) • No	**Quality** Excellent **Significant differences at baseline** None **Other comments** None

Evidence Table 6. Oral Corticosteroids vs. Placebo, With or Without Bronchodilators (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Schuh et al., 2002[23] **Setting** Canada, emergency department **Followup** • Acute • Short term – Day 7 at patient's home – Day 28 by telephone **Study design** RCT-P **Masking** Double-blind **Length of enrollment** Nov 1997 to Apr 2000	To investigate in outpatients younger than 2 yrs with acute bronchiolitis the clinical benefits of oral dexamethasone within 4 hrs of administration in the emergency department and after 5 d of continued therapy after discharge	**Inclusion criteria** • 8 wks - 23 mo • First wheezing episode associated with respiratory distress • RDAI rating of ≥ 6 at baseline • Presentation between 8 am to 9 pm **Exclusion criteria** • Previous history of wheezing or bronchodilator therapy • Prematurity • Neonatal ventilation • Chronic lung/cardiac disease • Aspiration • Neurologic/neuromus - cular problems • Immunodeficiency • Critically ill infants requiring immediate airway stabilization • Previous use of oral or inhaled corticosteroids • Exposure to varicella within 21 days before arrival	**Number** 71 eligible, 70 randomized, 67 evaluated at Day 7, 65 contacted on Day 28 **Sex** Dexamethasone: 56% male (20/36) Placebo: 68% male (23/34) **Mean age at enrollment (mo ± SE)** Dexamethasone: 6.1 ± 3.5 Placebo: 6.9 ± 3.9 **Mean gestational age (wk ± SE)** NR **Comorbidities** None

Evidence Table 6. Oral Corticosteroids vs. Placebo, With or Without Bronchodilators (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 36)** Oral dexamethasone 1 mg/kg in wild cherry syrup **Group B (n = 34)** Placebo syrup Identical color, texture, taste and smell **Other treatment** • Nebulized albuterol for all patients via vented nebulizer 2.5 mg per dose in 3 mL of normal saline with oxygen flow of 6 - 7 L/min with a tight - fitting face mask at 0, 30, 60 and 120 mins • Acetaminophen for fever as indicated • Discharged infants received dexamethasone in 0.6mg/kg/dose PO qd x 5 days or placebo as randomized, and albuterol 1.5 mg (0.3 µL) QID with same nebulizer	**Outcomes** **Primary outcome** • Rate of hospitalization (dexamethasone vs. placebo) – 44% (15/34) vs. 19% (7/36) **Secondary Outcomes** • Mean RACS from baseline to 240 mins ± SD (dexamethasone vs. placebo) – - 5.0 ± 3.1 vs. - 3.2 ± 3.7 • Mean RDAI from baseline to 240 mins ± SD (dexamethasone vs. placebo) – 5.4 ± 2.1 vs. 7.2 ± 2.8 • Mean RACS from baseline to Day 7 ± SD (dexamethasone vs. placebo) – - 8.9 ± 5.2 vs. - 9.3 ± 4.9 • Mean RDAI from baseline to Day 7 ± SD (dexamethasone vs. placebo) – 2.4 ± 3.1 vs. 2.6 ± 3.0 • Use of additional corticosteroids after discharge (dexamethasone vs. placebo) – 0/35 vs. 7/32 **Subgroup analysis** None **Adverse events** NR	**Significant differences between study groups** • Yes (P = 0.039) • Yes (P = 0.029) • No (P = 0.064) • No (P = 0.75) • No (P = 0.754) • Yes (P = 0.004)	**Quality** Excellent **Significant differences at baseline** Dexamethasone group more likely to have family history of atopy (P = 0.013) **Other comments** None

Evidence Table 6. Oral Corticosteroids vs. Placebo, With or Without Bronchodilators (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Van Woensel et al., 2000[67] **Setting** Telephone followup of original Inpatient sample **Followup** 5 yrs after original study (Aug 1998 to April 1999) **Study design** RCT-P **Length of enrollment of original study** Dec 1992 - April 1995 **Masking** Double-blind	A followup study of van Woensel[68] to investigate the effect of oral prednisolone vs. placebo during the acute phase of RSV bronchiolitis on the prevalence of wheezing during the first yr of life and asthma at age 5 yrs	**Inclusion criteria of original study** • < 2 yrs of age • Microbiologically proven RSV bronchiolitis • Bronchiolitis defined as first attack of acute tachypnea, wheezing and/or decreased breath sounds, cyanosis, and the use of accessory respiratory muscles in the presence of an apparent viral infection **Exclusion criteria of original study** • Use of corticosteroids (systemic or by inhalation) during the 2 mos before admission	**Number** 54 randomized in original study, 47 completed 5 yr followup **Sex** Prednisolone: 63% male (15/24) Placebo: 61% male (14/23) **Mean age at enrollment in yrs ± SE** Prednisolone: 4.9 ± 0.13 Placebo: 5.1± 0.16 **Mean gestational age** NR **Comorbidities** Prematurity, chronic lung disease, heart disease - Prednisolone: 5/24 (21%) - Placebo: 8/23 (35%)

Evidence Table 6. Oral Corticosteroids vs. Placebo, With or Without Bronchodilators (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 24 at followup)** Oral prednisolone 1 mg/kg/day in 2 divided doses x 7 days **Group B (n = 23 at followup)** Placebo Identical capsules, broken and dissolved in water **Other treatment** Supplemental oxygen, bronchodilators or antibiotics as indicated (NR in this study, details in original study)	**Outcomes** **Primary outcome** Wheezing outcomes in past 3 months (prednisolone vs. placebo) • No wheezing - 8/24 (33%) vs. 9/23 (39%) • Transient wheezing (wheezing during first[t] yr of life, stopped before age 5) - 2/24 (8%) vs. 4/23 (17%) • Persistent wheezing (wheezing during first yr of life, asthma or asthma attacks at age 5) - 10/24 (42%) vs. 7/23 (31%) • Late onset wheezing (no wheezing during first yr of life, asthma or asthma attacks at age 5) - 4/24 (17%) vs. 3/23 (13%) **Subgroup analysis** • Severe bronchiolitis - pretreatment severity score = 6 (range: 0 - 12) and those needing mechanical ventilation **Adverse events** None	**Significant differences between study groups** • No (*P* value NR) • No (*P* value NR) • No (*P* value NR) • No (*P* value NR) • No (*P* value NR)	**Quality** Fair **Significant differences at baseline** None **Other comments** None

Evidence Table 6. Oral Corticosteroids vs. Placebo, With or Without Bronchodilators (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author van Woensel et al., 1997[68] **Setting** Netherlands, Inpatient **Followup** Acute **Study design** RCT-P **Length of enrollment** Dec 1993 - April 1995 **Masking** Double-blind	To determine the effect of prednisolone on the clinical course of children admitted to hospital with RSV bronchiolitis, including patients with severe disease	**Inclusion criteria** • < 2 yrs of age • Microbiologically confirmed RSV bronchiolitis • Bronchiolitis defined as acute tachypnea, wheezing, and/or decreased breath sounds, cyanosis and use of accessory respiratory muscles, in the presence of an apparent viral infection **Exclusion criteria** • Corticosteroids (systemic or by inhalation) during the two mos before admission	**Number** 54 randomized, 53 included in efficacy analysis **Sex** Prednisolone: 67% male (18/27) Placebo: 41% male (11/27) **Median age at enrollment in mo. (inter - quartile range)** Prednisolone: 3.3 (1.4 - 5.9) Placebo: 3.9 (1.9 - 6.1) **Mean gestational age** NR **Comorbidities** Patients on ventilators at entry: 14, 7 in each group Bronchopulmonary dysplasia: 6/27 for prednisolone vs. 9/27 for placebo

Evidence Table 6. Oral Corticosteroids vs. Placebo, With or Without Bronchodilators (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 27)** Oral prednisolone 1mg/kg/day in two divided doses x 7 days **Group B (n = 27)** Placebo Identical capsules, broken and dissolved in water **Other treatment** Supplemental oxygen, bronchodilators or antibiotics as indicated	**Outcomes** **Primary outcome** • Mean decline in symptom score among non-ventilated patients ± SE (prednisolone vs. placebo, N = 39) – - 1.2 ± 0.2 vs. 0.6 ± 0.2 • Mean duration of hospitalization in days among non-ventilated patients ± SE (prednisolone vs. placebo) – 7.3 ± 1.2 vs. 8.3 ± 0.9 • Mean duration of hospitalization in days among ventilated patients ± SE (prednisolone vs. placebo) – 11.0 ± 0.7 vs. 17.0 ± 2.0 • Mean duration of mechanical ventilation in days ± SE (prednisolone vs. placebo) – 4.7 ± 1.1 vs. 6.3 ± 1.6 **Secondary outcomes** • Duration of supplemental oxygen • Bronchodilator use • Antibiotic use **Subgroup analysis** • Baseline severity score • Family history of atopic disease • IgE level at entry **Adverse events** 1 death unrelated to intervention	**Significant differences between study groups** • Yes ($P = 0.02$) • No ($P < 0.54$) • Yes ($P < 0.01$) • No ($P < 0.556$) • No • No • No • No • No • No	**Quality** Good **Significant differences at baseline** NR **Other comments** Ill study group with high degree of comorbidity

Evidence Table 7. Parenteral Dexamethasone vs. Placebo

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author De Boeck et al., 1997[48] **Setting:** Belgium, Inpatient **Followup** Acute **Study design** RCT-P **Length of enrollment** Epidemic of 1991 to 1992 **Masking** Double-blind	To reevaluate the efficacy of intravenous corticosteroids in previously healthy infants without underlying disease hospitalized with proven RSV primary infection	**Inclusion criteria** • < 24 months admitted to hospital • Signs of bronchiolitis: prodromal rhinorrhea, cough, or low-grade fever followed by at least 2 of the following signs: chest retractions, tachypnea, wheezing, or rales • Detection of RSV in nasal wash taken on admission by ELISA • First episode of wheezing or shortness of breath • Onset of illness within previous 5 days **Exclusion criteria** • Underlying heart, lung, or immune disorder • Premature (< 34 wks gestational age)	**Number** 32 enrolled, 29 completed study **Sex** NR **Median age at enrollment in days (range)** Dexamethasone: 186 (111 - 224) Placebo: 213 (133 - 267) **Mean gestational age (wks ± SE)** NR **Comorbidities** None

Evidence Table 7. Parenteral Dexamethasone vs. Placebo (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 51)** Dexamethasone 0.6 mg/kg IV x 2 on Day 1, 0.015mg/kg on Days 2 and 3 **Group B (n = 53)** Placebo Details NR **Other treatment** • Salbutamol (0.5%), 0.25 ml and ipratropium bromide (0.025%), 0.5 ml aerosolized every 6 hrs • Oxygen to maintain oxygen saturation > 90% • Antibiotics as indicated • Standardized concomitant therapy	**Outcomes** **Primary outcome** • Mean duration of hospitalization in days ± SE (dexamethasone vs. placebo) - 6.0 ± 0.3 vs. 6.6 ± 0.7 **Secondary outcomes** • Improvement in clinical scores after aerosol • Respiratory rate • Oxygen saturation • Pulmonary function tests • Treatment with antibiotics **Subgroup analysis** None **Adverse events** NR	**Significant differences between study groups** • No (*P* value NR) • No • No • No • No	**Quality** Fair **Significant differences at baseline** None **Other comments** None

Evidence Table 7. Parenteral Dexamethasone vs. Placebo (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author: Roosevelt et al., 1996[43] **Setting** United States, Inpatient **Followup** • Acute • Short term - telephone followup 10 - 14 days after discharge **Study design** RCT-P **Length of enrollment** Dec 1993 to March 1994, Dec 1994 to March 1995 **Masking** Double-blind	To assess the efficacy and safety of dexamethasone in infants with bronchiolitis who require hospital management	**Inclusion criteria** • < 12 mos of age • first episode of wheezing **Exclusion criteria** • infants < 4 wks old • admitted to ICU • known history of congenital heart disease • history of intubation, ventilation, supplemental oxygen	**Number** 122 enrolled, 118 completed study **Sex** Dexamethasone: 63% male (41/65), Placebo: 62% male (33/53) **Mean age at enrollment (mo.± SD)** Dexamethasone: 5.3 ± 3.7 Placebo: 5.0 ± 2.5 **Mean gestational age** NR **Comorbidities** None

Evidence Table 7. Parenteral Dexamethasone vs. Placebo (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 65)** Dexamethasone Dose: 1 mg/kg IM q day x 3 days **Group B (n = 53)** Placebo Dose: Identically appearing solution and schedule **Other treatment** Antibiotics and nebulized bronchodilators used as needed	**Outcomes** **Primary outcome** • Time to resolution (number of 12 hr periods needed for SaO_2 >95% while receiving no supplemental oxygen, accessory muscle score of 0, wheeze of 0 or 1, and resumption of normal feeding) - Hazard ratio (95% C.I.): 1.3 (0.9 - 1.3) • Duration of oxygen therapy - Hazard ratio (95% C.I.): 0.9 (0.6 - 1.4) **Secondary outcomes** • Use of antibiotics, nebulized beta-agonist and other bronchodilators • Visits to health professionals for respiratory symptoms • Steroid use started in hospital after study completed • Symptoms reported by parents at 14 day followup **Subgroup analyses** • RSV status • Hypoxia (<95% SaO_2) • Family history of atopy • RSV and family history of atopy **Adverse events** Positive stool for occult blood in 2/65 for dexamethasone vs. 1/53 for placebo	**Significant differences between study groups** • No (P = 0.22) • No (P = 0.74) • No • No • No • No • No • No • No • No	**Quality** Good **Significant differences at baseline** Dexamethasone group had significantly more patients with SaO_2 <95% (79% vs. 59%, P = 0.02) **Other comments** None

Evidence Table 8. Nebulized Corticosteroids vs. Placebo or Usual Care

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Cade et al., 2000[71] **Setting** United Kingdom, Inpatient **Followup** United Kingdom **Study Design** RCT-P **Length of enrollment** NR **Masking** Double-blind	To evaluate the short and long term effects of giving a short course of nebulized budesonide to hospitalized infants with RSV positive bronchiolitis	**Inclusion criteria** • < 12 months of age • Confirmed RSV infection • Randomization within 12 hrs of admission **Exclusion criteria** • Previous hospital admissions with respiratory tract illness • Chronic respiratory illness • Congenital heart disease • Prematurity • Pre-existing immunodeficiencies • Recent exposure to varicella or tuberculosis • Prolonged exposure to systemic steroids	**Number** 165 enrolled, 161 completed study **Sex** 56% male (45/82) for budesonide 60% male (47/79) for placebo **Mean age (days ± SD)** Budesonide: 130 ± 85 Placebo: 120 ± 84 **Mean gestational age** NR **Comorbidities** NR

Evidence Table 8. Nebulized Corticosteroids vs. Placebo or Usual Care (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 82)** Budesonide 1mg nebulized twice daily until 14 days after discharge, up to a maximum of 21 days **Group B (n = 79)** Placebo Nebulized vehicle given in place of budesonide, using same schedule as Group A **Other interventions** Ipratropium bromide, beta agonists, antibiotics, oral or intravenous steroids as indicated	**Outcomes** **Primary outcomes** • Coughing and wheezing episodes in 12 mo followup period (budesonide vs. placebo) - 99% vs. 99% **Secondary outcomes** • Days from first nebulization until fit for hospital discharge - Hazard ratio (95% C.I.): 1.1 (0.80 - 1.51) • Time to become asymptomatic for 48 hrs - Hazard ratio (95% C.I.): 1.41 (0.98 - 2.04) • Mean number of coughing/ wheezing episodes from discharge to day 28 ± SD (budesonide vs. placebo) - 17.0 ± 7.6 vs. 17.1 ± 8.5 • Readmission for respiratory morbidity over 12 months (budesonide vs. placebo) - 16% vs. 17% • Mean visits for respiratory morbidity(budesonide vs. placebo) - 4 vs. 4.5 • Prescription for bronchodilator (budesonide vs. placebo) - 60% vs. 67% • Prescription for steroids(budesonide vs. placebo) - 50% vs. 60% **Subgroup analysis** • Outcomes (1) Respiratory related readmissions (2) GP respiratory visits by - Initial severity score - Duration of symptoms at presentation - Atopic history - Exposure to cigarette smoke or damp in household **Adverse events** NR	**Significant differences between study groups** • No (*P* =0.98) • No (*P* = 0.51) • No (*P* = 0.07) • No (*P* = 0.91) • No (*P* = 0.78) • No (*P* = 0.29) • No (*P* = 0.42) • No (*P* = 0.23) • No significant differences between budesonide and placebo for both outcomes by all subgroups	**Quality** Good **Significant differences at baseline** More furry pets in placebo households (36% vs. 21%) **Other comments** None

Evidence Table 8. Nebulized Corticosteroids vs. Placebo or Usual Care (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Fox et al., 1999[73] **Setting:** United Kingdom, inpatient at baseline, diary records and Outpatient followup **Followup** • Long term - 12 months **Study design** RCT-P **Length of enrollment** NR **Masking** Double blind	To assess the efficacy of inhaled budesonide in reducing the incidence of coughing and wheezing episodes during the first yr after acute viral bronchiolitis	**Inclusion criteria** • = 12 mo of age • Clinical diagnosis of acute viral bronchiolitis requiring hospital admission • Clinical diagnosis based on tachypnea (respiratory rate > 40/mins), chest hyperinflation, soft tissue recession, and bilateral crackles, with or without wheezes **Exclusion criteria** • Underlying cardiopulmonary disease • Congenital heart disease • Bronchopulmonary dysplasia • Cystic fibrosis • History of respiratory problems in the neonatal period • Requiring mechanical ventilation during present illness	**Number** 60 enrolled, 49 patients with full followup **Sex** Budesonide: 77% male (20/26) Placebo: 50% male (14/28) **Median age at enrollment in weeks (range)** Budesonide: 11 (1-38) Placebo: 10 (3-42) **Mean gestational age** NR **Comorbidities** None

Evidence Table 8. Nebulized Corticosteroids vs. Placebo or Usual Care (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 26)** Budesonide 200 µg 1 puff BID x 8 wks by metered dose inhaler and modified spacer and face mask system **Group B (n = 28)** Placebo Similar schedule and route as intervention **Other treatment** Routine supportive care as needed	**Outcomes** **Primary outcome** • Number with wheezing/cough at (budesonide vs. placebo) - 1 mo: 4/26 vs. 5/28 - 2 mo: 11/26 vs. 11/28 - 6 mo: 15/26 vs. 12/27 - 12 mo: 21/25 vs. 12/24 • Hospital admissions by 12 mo followup (budesonide vs. placebo): - 5/25 vs. 6/24 • Number with =3 symptom episodes at 12 mo followup (budesonide vs. placebo): - 11/25 vs. 6/24 • Median (range) symptom episodes at 12 mo followup (budesonide vs. placebo): - 2 (0-13) vs. 1(0-11) • Median (range) symptom days at 12 mo. followup (budesonide vs. placebo): - 18(0-106) vs. 9(0-90) **Subgroup analysis** • Logistic regression of symptoms at 12 mo. followup, controlling for differences in sex (no significant differences for sex at baseline, but 24/30 males vs. 9/19 females had symptoms at followup and more males got budesonide) **Adverse events** • Admission to hospital with viral gastroenteritis (1/24 in placebo group) • Mild coughing and wheezing (1/25 in budesonide group)	**Significant differences between study groups** • Significant only at 12 mo - (*P* = 1.0) - (*P* = 0.82) - (*P* = 0.49) - (*P* = 0.03) • No (*P* = 0.94) • No (*P* = 0.27) • Yes (*P* = 0.02) • No (*P* = 0.08) • No (*P* = 0.051)	**Quality** Fair **Significant differences at baseline** None **Other comments** • When possible confounding effect of sex is controlled, diff between study groups in symptoms at 12 mo reduces in significance • 11 patients concluded from final data analysis for loss to followup, partial loss to followup or poor compliance

Evidence Table 8. Nebulized Corticosteroids vs. Placebo or Usual Care (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Kajosaari et al., 2000[74] **Setting** Finland, needing hospital treatment at baseline, Outpatient at 2 and 6 mo, telephone interview at 2 yrs **Followup** • Acute • Long-term – 2 mo – 6 mo – 2 yrs **Study design** RCT - nonplacebo **Length of enrollment** NR **Masking** None	To determine whether inhaled corticosteroids in infants during and after the acute phase of RSV infections influences their subsequent respiratory status	**Inclusion criteria** • 0 - 9 months of age • Needing hospital treatment because of RSV bronchiolitis • Healthy, full-term babies **Exclusion criteria** • Mechanical ventilation • Pre-term babies	**Number** 117 randomized and initial study size, 109 completed followup study at 2 yrs **Sex** NR **Mean age range at enrollment in months** Group A: 0.5 - 5.2 Group B: 0.3 - 6.4 Group C: 0.5 - 5.9 **Mean gestational age** NR **Comorbidities** None

Evidence Table 8. Nebulized Corticosteroids vs. Placebo or Usual Care (continued)

Intervention	Outcome		Quality
Intervention	**Outcomes**	**Significant differences between study groups**	**Quality**
Group A (n = 41 at baseline, 38 at 2 yr followup)			Poor
Symptomatic treatment: oxygen, bronchodilators and/or racemic epinephrine	**Primary outcome**		**Significant differences at baseline**
	• Asthma inhalation therapy at 2 yrs (Grp A vs. Grp B vs. Grp C)	• Yes	Grp A had lower proportion of atopic heredity
Group B (n = 40 at baseline, 39 at 2 yr followup)	- 37% (14/38) vs. 18% (7/39) vs. 12% (4/32)		
Symptomatic treatment + inhaled budesonide	- Odds ratio (95% C.I.) of Grp A vs. Grp C: 4.08 (1.39 - 11.98)	- Grp A vs. Grp B: *P* = 0.006	**Other comments**
	- Odds ratio (95% C.I.) of Grp A vs. Grp B: 2.67 (0.98 - 7.27)	- Grp A vs. Grp C: *P* = 0.01	8 children concluded from final analysis: 3 due to loss to followup, 1 for RSV infection, 1 for prematurity, 3 for non-compliance
500 µg TID x 7 days	- Odds ratio (95% C.I.) of Grp A vs. (Grp B + Grp C): 3.18 (1.25 - 8.12)	- NR	
Group C (n = 36 at baseline, 32 at 2 yr followup)	• Atopic status at 6 mo	• NR	
Symptomatic treatment + inhaled budesonide	- Grp 1: 13% (5/38)		
	- Grp 2: 28% (11/39)		
500 µg BID x 2 mos	- Grp 3: 25% (8/32)		
Other treatment	**Secondary outcomes**		
Routine care as indicated	NR		
	Subgroup analysis		
	None		
	Adverse events		
	NR		

Evidence Table 8. Nebulized Corticosteroids vs. Placebo or Usual Care (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Reijonen 1996[75] **Setting** Finland, inpatient **Followup** • Acute • Long-term - Outpatient followup at 6 and 16 wks **Study design** RCT non-placebo **Masking** Investigators not blinded, unclear for others	To determine whether early treatment with nebulized cromolyn sodium or budesonide reduces the frequency of wheezing episodes among infants with acute bronchiolitis	**Inclusion criteria** • Hospitalized patients age 1 - 23 mos • Clinical criteria of acute bronchiolitis: wheezing and respiratory distress in patient with acute URTI **Exclusion criteria** • Chronic cardiorespiratory disease (asthma, BPD, CHD) • Received medication for any pulmonary disease	**Number** 100 enrolled, 98 at 6 wk followup, 92 at 16 wk followup **Sex** Cromolyn sodium: 65% male (22/34) Budesonide: 65% male (22/34) Control: 81% male (26/32) **Mean age at enrollment (mo± SD)** Cromolyn sodium: 9.6 ± 6.2 Budesonide: 10.1 ± 5.0 Control: 11.1 ± 6.9 **Mean gestational age** NR **Comorbidities** • 13% with previous history of wheezing (no sig. diffs. among groups) • 29% with atopy (no sig. diffs. among groups)

Evidence Table 8. Nebulized Corticosteroids vs. Placebo or Usual Care (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 34)** Cromolyn sodium Dose: 20mg QID x 8 wks then 20mg TID x 8 wks **Group B (n = 34)** Budesonide Dose: 500µg BID x 8 wks then 250µg BID x 8 wks **Group C (n = 32)** No treatment All meds given with face mask using a foot pump and pumping rate at 60/minute **Other treatment** • Oral bronchodilating drugs advised for 1 wk after acute bronchiolitis, as needed thereafter • Oral slow - release theophylline as needed	**Outcomes** **Primary outcome** • Mean days with symptomatic wheezing (cromolyn sodium vs. budesonide vs. no treatment) at - 1 to 4 wks: 5.1 vs. 4.9 vs. 5.3 - 5 to 8 wks: 4.5 vs. 3.5 vs. 3.9 - 9 to 16 wks: 9.1 vs. 7.5 vs. 2.3 - 13 to 16 wks: 2.4 vs. 2.2 vs. 3.0 • At least one Physician-diagnosed wheezing episode at 1 - 8, 9 - 16 and 1 - 16 wks - Cromolyn sodium vs. control at 9 - 16 wks: 6/31 vs. 14/31 - Budesonide vs. control at 9 to 16 wks: 5/31 vs. 14/31 • Repeated (2 or more) Physician-diagnosed wheezing episodes at 1 to 16 wks - Cromolyn sodium vs. control: 6/31 vs. 12/31 - Budesonide vs. control 3/31 vs. 12/31 • Hospital care for repeat wheezers (detail NR) **Subgroup analysis** • Age (> 1 yr vs. < 1 yr) • Atopic patients (n = 36) - Physician-diagnosed wheezing: Cromolyn sodium: 4/13 Budesonide:2/11 Control: 8/12 - Hospitalized for treatment of wheezing: Cromolyn sodium: 1/13 Budesonide:1/11 Control: 7/12 **Adverse events** NR	**Significant differences between study groups** • No – $P = 0.97$ – – $P = 0.87$ – – $P = 0.55$ – $P = 0.87$ • Significantly diff. from control group only at 9 - 16 wks: Cromolyn sodium vs. control ($P = 0.01$), Budesonide vs. control ($P = 0.01$) • Significantly diff. only for budesonide vs. control group ($P = 0.01$) • No (P values NR) • No • Not significant for Physician-diagnosed wheezing, ($P > 0.05$), significant for hospitalization ($P < 0.05$)	**Quality** Fair **Significant differences at baseline** None **Other comments** • No placebo group • Investigators not blinded • Percentage of children with history of atopy high • All enrollees had participated in a Racemic epinephrine vs. Albuterol trial prior to enrollment in this study[54]

Evidence Table 8. Nebulized Corticosteroids vs. Placebo or Usual Care (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Richter et al., 1998[76] **Setting** United Kingdom, Inpatient at baseline, Outpatient at followup **Followup** • Acute • Short term - 6 wks • Long-term - 6 mo **Study design** RCT-P **Length of enrollment** NR **Masking** Double-blind	To determine the effectiveness of nebulized budesonide in reducing the severity and duration of lower respiratory symptoms in acute bronchiolitis and in preventing postbronchiolitic cough and wheezing	**Inclusion criteria** • < 12 months of age • No previous wheezing episodes • Hospitalized with clinical features of bronchiolitis, (tachypnea, recession, wheezing, and crepitations) **Exclusion criteria** • Congenital abnormality • Preexisting pulmonary disease • Immune deficiency • Need for assisted ventilation	**Number** 40 randomized, 40 completed study **Sex** Budesonide: 57% male (12/21) Placebo: 53% male (10/19) **Median age at enrollment in wks (range)** Budesonide: 16.3 (4.4 to 40.6) Placebo: 10.8 (3.6 to 29.1) **Median gestational age in wks (range)** Budesonide: 38 (34 to 41) Placebo: 39 (36 to 42) **Comorbidities** None

Evidence Table 8. Nebulized Corticosteroids vs. Placebo or Usual Care (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 21)** Nebulized budesonide 1 mg in 2 mL BID x 5 days, then 500 µg/mL BID for remainder of 6 wk period **Group B (n = 19)** Placebo 2 mL q. 12 hrs x 6 wks **Method of delivery** Side Stream nebulizer with face masks with oxygen flow of 6 L/mins, and Portaneb compressors after discharge **Other treatment** Other treatment as needed, including terbutaline	**Outcomes** **Primary outcome** *Acute* • Days in oxygen after trial entry (budesonide vs. placebo) - 1.0 (0 to 7) vs. 1.0 (0 to 6) • Maximum oxygen requirement after trial entry (budesonide vs. placebo) - 30% (21% to 60%) vs. 30% (21% to 50%) • Median (range) duration of hospitalization in days from trial entry to discharge (budesonide vs. placebo) - 2.0 (1 - 11) vs. 3.0 (1 - 7) • Change in clinical scores 48 hrs after trial entry (range) (budesonide vs. placebo) - - 2.0 (-6 - +6) vs. - 1.0 (-9 - +2) *Chronic - 6 wks* • Infants not given bronchodilators during 6 wk treatment (budesonide vs. placebo) - 9 (45%) vs. 8 (42%) • Infants not given bronchodilators on 5+ occasions during 6 wk treatment (budesonide vs. placebo) - 10 (50%) vs. 4 (21%) • Mean daily symptom scores (budesonide vs. placebo) - 2.7 vs. 1.5 • Median no. of symptom - free days (budesonide vs. placebo) - 8.5 vs. 12.0 *Chronic - 6 mos* • Prevalence of wheeze during 6 mo followup (budesonide vs. placebo) - 15 (75%) vs. 15 (79%) • Infants given bronchodilators during 6 mo followup (budesonide vs. placebo) - 13 (65%) vs. 10 (53%)	**Significant differences between study groups** • No (*P* = 0.29) • No (*P* = 0.33) • No (*P* = 0.65) • No (*P* = 0.92) • No (*P* = 1.0) • No (*P* = 0.1) • No (*P* = 0.94) • No (*P* = 0.57) • No (*P* = 1.0) • No (*P* = 0.52)	**Quality** Good **Significant differences at baseline** None **Other comments** None

Evidence Table 8. Nebulized Corticosteroids vs. Placebo or Usual Care (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Richter et al., 1998[76] (continued)			

Evidence Table 8. Nebulized Corticosteroids vs. Placebo or Usual Care (continued)

Intervention	Outcome	Quality
	• Infants given inhaled + oral steroids during 6 mo followup (budesonide vs. placebo) - 3 (15%) vs. 3 (16%)	• No (*P* = 1.0)
	• Infants readmitted for respiratory problems (budesonide vs. placebo) - 10 (50%) vs. 2 (10.5%)	• Yes (*P* = 0.01)
	• Median scores for cough and wheeze (budesonide vs. placebo) - 10.0 vs. 10.0	• No (*P* = 1.0)
	• Median scores for wheeze only (budesonide vs. placebo) - 4.5 vs. 5.0	• No (*P* = 0.97)
	Subgroup analysis • Family history of atopy - prevalence of wheeze - median score for cough and wheeze - median score for wheeze alone	• No significant differences for any outcome
	Adverse events • Median growth in cm/wk (budesonide vs. placebo) - 0.43 vs. 0.47	• No (*P* = 0.16)

Evidence Table 8. Nebulized Corticosteroids vs. Placebo or Usual Care (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Wong et al., 2000[77] **Setting** United Kingdom, inpatient **Followup** • Acute • Long term at 3, 6, 9, and 12 mo after entry **Study design** RCT-P **Masking** Double-blind **Length of enrollment** Mar 1994 - Apr 1996	To assess the efficacy and safety of inhaled fluticasone propionate during the trial period, and the following 9 mos	**Inclusion criteria** • Age 2 wks to 12 mo • First episode of lower respiratory tract infection **Exclusion criteria** • Birth before 36 wks of gestation • CHD or syndromic abnormalities • Established systemic or chronic illnesses • Treatment with corticosteroids before entering study • Mechanical ventilation before entering study • Parents unable to use inhaler/babyhaler	**Number** 48 randomized, 43 completed trial, 41 in long-term study **Sex** Fluticasone propionate: 54% (13/24) Placebo: 58% (14/24) **Mean age at enrollment in mo. (range)** Fluticasone propionate: 3.8 (0.9 - 4.7) Placebo: 3.9 (1.0 - 10.9) **Mean gestational age in wks. (range)** Fluticasone propionate: 39.4 (36.8 - 43.0) Placebo: 39.7 (36.0 - 42.0) **Comorbidities** None

Evidence Table 8. Nebulized Corticosteroids vs. Placebo or Usual Care (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 21)** Fluticasone propionate (FP) 3 puffs of 50 µg BID x 3 mo. from MDI administered via the babyhaler (spacer) with a face mask attachment **Group B (n = 23)** Placebo Type of placebo not reported, same delivery as above **Other treatment** Bronchodilators, steroids and/or antibiotics as indicated	**Outcomes** **Primary outcome** • Overnight oxygen saturation (details NR) • Night cough events (single cough) during treatment and followup at 3, 6, 12, 24 and 36 wks from baseline • Night cough episodes (period of coughing with = 10 seconds before and after) during treatment and followup at 3, 6, 12, 24 and 36 wks from baseline • Symptom frequency as recognized by parent (FP vs. Placebo) – Cough: 95.8 vs. 89.6 – Wheeze: 99.7 vs. 94.5 **Secondary outcomes** • Lung function tests 6 mo. after discharge • Use of rescue respiratory medications ($ß_2$ - agonists, corticosteroids, antibiotics) • Increase in respiratory symptoms leading caregivers to seek medical advice • Hospital admissions at 9 mos after treatment • Received treatment at 9 mos after treatment **Subgroup analysis** None **Adverse events** Oral candidiasis (2 FP patients)	**Significant differences between study groups** • No (*P* values NR) • No (*P* values range from 0.20 - 0.64) • Significant only at 36 wks (*P* = 0.05), not significant at other time periods • No (*P* values NR) • No • No, however more placebo subjects received bronchodilators /steroids, diff not significant (*P* = 0.07) • No • No • No	**Quality** Good **Significant differences at baseline** None **Other comments** • Missing data value extrapolated from previous visit • 3 FP patients withdrawn, 2 placebo patients withdrawn

Evidence Table 9. Ribavirin vs. Placebo

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Barry et al., 1986[46] **Setting** United Kingdom, multi-center inpatient **Followup** • Acute • Short term – length of hospitali-zation **Study design** RCT-P **Length of enrollment** NR **Masking** Double-blind	To test the efficacy of ribavirin in infants with acute bronchiolitis	**Inclusion criteria** • Diagnosis of bronchiolitis defined as history of URTI followed by cough, breathlessness and wheezing and clinical signs of chest overinflation, tachypnea, rhonchi or crepitations. **Exclusion criteria** • < 2 wks old • < 41 wks since mother's last menstrual period • Underlying chest or heart disease • Previous bronchiolitis • Immune defect • > 72 hrs of chest symptoms	**Number** 26 enrolled, 26 completed study **Sex** Ribavirin: 64% male (9/14) Placebo: 83% male (10/12) **Age at enrollment** NR **Mean gestational age** NR **Comorbidities** None

Evidence Table 9. Ribavirin vs. Placebo (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 14)** Aerosolized ribavirin 20 mg/ml **Group B (n = 12)** Saline placebo Both administered for 18 out of 24 hrs for at least 3 days **Other treatment** Oxygen and antibiotics as indicated	**Outcomes** **Primary outcome** • Median hrs to sustained improvement (ribavirin vs. Placebo) in – cough (24 vs. 66) – nasal discharge – feeding – nasal flare – wheeze – chest recession – rhonchi – crepitations (23 vs. 44) • Change in respiratory rate – Graphical data presented with text, specific values not detailed • Change in heart rate – Graphical data presented with text, specific values not detailed **Subgroup analysis** RSV status **Adverse events** Transient redness of eyelids possibly from deposition of the drug on the skin (1 ribavirin patient)	**Significant differences between study groups** • Not significant except for median hrs to sustained improvement in cough and crepitations ($P < 0.05$) • Yes ($P < 0.05$) • No • Significant difference only for decrease in chest recession ($P < 0.05$)	**Quality** Fair **Significant differences at baseline** None **Other comments** Details of randomization protocol not provided; however, assignment to treatment or control was specifically to minimize differences in age, arterialized capillary CO_2, respiratory rate, and interval since onset of chest symptoms

Evidence Table 9. Ribavirin vs. Placebo (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Everard et al., 2001[78] **Setting** United Kingdom, Inpatient at baseline, Outpatient at followup **Followup** • Acute • Short term 6 wks • Long-term 6 mos **Study design** RCT-P **Length of enrollment** 3 RSV seasons **Masking** Double-blind	To determine the effect of ribavirin therapy on (a) the course of the acute illness (b) bronchial responsiveness at 6 mos and (c) the frequency of lower respiratory tract symptoms in the yr following admission	**Inclusion criteria** • Previously fit infants • Moderately severe bronchiolitis • No high risk factors for severe disease • Bronchiolitis defined as: evidence of URI followed by development of lower respiratory tract involvement characterized by airways obstruction and widespread crepitations on auscultation **Exclusion criteria** None listed	**Number** 40 randomized, 35 completed study **Sex** Ribavirin: 43% male (9/21) Placebo: 47% male (9/19) **Mean age at enrollment in days (range)** Ribavirin: 93.7 (15 - 188) Placebo: 89.4 (16 - 266) **Mean gestational age** NR **Comorbidities** NR

Evidence Table 9. Ribavirin vs. Placebo (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 16)** Ribavirin 6 g in 180 ml H_20 by SPAG (Small Particle Aerosol Generator) over 18 hrs per day **Group B (n = 19)** Normal saline placebo Same protocol as Ribavirin group **Other treatment** Other treatments as needed	**Outcomes** **Primary outcomes** • Mean days in oxygen (ribavirin vs. placebo) – 3.36 vs. 2.52 • Change in clinical score between day 1 and day 0 (ribavirin vs. placebo) – - 0.83 vs. -1.05 • Change in oxygen saturation measured in air between day 1 and day 0 (ribavirin vs. placebo) – 2.05 vs. 0.57 • Days to discharge (ribavirin vs. placebo) – 5.58 vs. 3.95 • Days fit for discharge – 4.77 vs. 3.86 **Secondary outcomes** • Bronchial hyper - responsiveness • Admitted with lower respiratory tract (LRT) symptoms during first yr (ribavirin vs. placebo) – 2 (12.5%) vs. 3 (15.8%) • Bronchodilators during first yr (ribavirin vs. placebo) – 5 (31.3) vs. 8 (42.1%) • Inhaled steroids during first yr (ribavirin vs. placebo) – 2 (12.5%) vs. 1 (5.3%) • No LRT symptoms during first yr (ribavirin vs. placebo) – 4 (25%) vs. 5 (26.3%) • Readmission in first yr (ribavirin vs. placebo) – 2 (12.5%) vs. 3 (15.8%) **Subgroup analysis** None **Adverse events** • 1 patient died some months after discharge, death unrelated to ribavirin therapy	**Significant differences between study groups** • No (P = 0.41) • No (P = 0.83) • No (P = 0.15) • No (P = 0.11) • No (P = 0.37) • No • P values NR • P values NR • P values NR • P values NR • No (P = 0.46)	**Quality** Fair **Significant differences at baseline** None **Other comments** None

Evidence Table 9. Ribavirin vs. Placebo (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Guerguerian et al., 1999[79] **Setting** Canada, ICU **Followup** • Acute • Short term – length of hospitali-zation **Study design** RCT-P **Length of enrollment** March 94 to April 97 **Masking** Double-blind	To test the clinical effectiveness of ribavirin in previously well infants without underlying illnesses who require ventilatory support secondary to a first episode of RSV bronchiolitis	**Inclusion criteria** • First episode of bronchiolitis diagnosed with presence of tachypnea, chest retraction, prolonged expiratory time, pulmonary rales, or wheezing and hyperinflation on chest radiograph • Mechanical ventilation instituted for respiratory distress manifested by one or more of the following: – extreme fatigue, or impending respiratory arrest, or severe apnea if preceded by significant respiratory distress – uncompensated respiratory acidosis (pH < 7.30 and PCO_2 > 60 mm Hg – hypoxia (PaO_2 < 60 mm Hg or pulse oximetry saturation [SpO_2] < 93% with fraction of inspired oxygen [FIO_2] = 0.6) • Proven RSV etiology	**Number** 51 eligible, 42 enrolled, 41 used for intent-to-treat analysis **Sex** Placebo: 52% male (11/21) Ribavirin: 65% male (13/20) **Mean age at enrollment in days ± SD** Placebo: 62.5 ± 35.9 Ribavirin: 62.7 ± 30.9 **Mean gestational age** NR **Comorbidities** None

Evidence Table 9. Ribavirin vs. Placebo (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 20)** Aerosolized ribavirin 6 grams diluted w/ sterile water to a volume of 300 ml (20 mg/ml) **Group B (n = 21)** Saline placebo 300 ml saline (0.9%) Both administered by aerosol generator, over 18 hrs every 24 hrs for a maximum of 7 days or extubation **Other treatment** Sedation, paralysis, inhaled albuterol, steroids, antibiotics, chest physiotherapy as indicated	**Outcomes** **Primary outcome** • Mean length of mechanical ventilation in hrs ± SD (ribavirin vs. Placebo) – 102.16 ± 65.26 vs. 126.28 ± 78.72 **Secondary outcomes** • Length of aerosol therapy • Length of ICU stay • Length of oxygen therapy • Length of hospitalization **Subgroup analysis** No **Adverse events** • Acute respiratory distress syndrome leading to withdrawal from study (1 ribavirin pt.) • Right lobar pneumonia (1 placebo patient)	**Significant differences between study groups** • No (P = 0.29) • No (P = 0.31) • No (P = 0.42) • No (P = 0.44) • No (P = 0.32)	**Quality** Excellent **Significant differences at baseline** More preterm infants (< 37 wks gestation) in control group (P < 0.1) **Other comments** Length of ventilation among ribavirin pts reduces to 90.9 hrs when 1 patient. with ARDS is dropped from the analysis (P = 0.09)

Evidence Table 9. Ribavirin vs. Placebo (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Guerguerian et al., 1999[79] (continued)		**Exclusion criteria:** • Cyanotic congenital heart disease, congenital heart disease under medication or associated with pulmonary hypertension • Chronic respiratory disease e.g., BPD, CF, chronic aspiration, pulmonary hypoplasia, or neuromuscular disease • Central hypoventilation syndrome or altered airway protection • Primary or secondary immune deficiency • Chronic liver disease or renal failure • Previous treatment with ribavirin • Mechanical ventilation for > 24 hrs prior to the start of the aerosol treatment • Nosocomial acquired RSV infection (after 7 d of hospitalization) • Ribavarin administered for less than 18 hrs	

Evidence Table 9. Ribavirin vs. Placebo (continued)

Intervention	Outcome	Quality

Evidence Table 9. Ribavirin vs. Placebo (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Janai et al., 1993[80] **Setting** United States, inpatient **Followup** • Acute • Short term – 7 days after aerosol treatment **Study design** RCT-P **Masking** Double-blind **Length of enrollment** Winter of 1988 to 1989	To assess the effect of ribavirin on pulmonary function in infants with RSV bronchiolitis	**Inclusion criteria** • Clinical diagnosis of bronchiolitis • Presumptive rapid laboratory identification of RSV • Previously healthy • No ongoing cardiac, pulmonary, or immunologic disease • Products of normal gestation and delivery Bronchiolitis defined by presence of cough, dyspnea, expiratory wheezing, and hyperinflation on chest x-ray **Exclusion criteria** None listed	**Number** 26 randomized, 19 completed study **Sex** Placebo: 56% male (5/9) Ribavirin: 50% male (5/10) **Age at enrollment in weeks (interquartile range)** Placebo: 12 (6 to 16) Ribavirin: 14 (6 to 20) **Mean gestational age** NR **Comorbidities** None

Evidence Table 9. Ribavirin vs. Placebo (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 9)** Placebo 0.9% saline **Group B (n = 10)** Ribavirin 20mg/ml Both delivered by small particle aerosol generator (SPA6) for 18 hrs/day x 3 days (5 days for 1 infant) **Other treatment** Albuterol given prn to 8/9 placebo and 8/10 ribavirin patients 0.1 mg/kg/dose x 3 days Antibiotics and oxygen when indicated	**Outcomes** **Primary outcome** • Respiratory rate (numbers not reported) • Pulmonary function tests (compliance and resistance measured by sedating infant with 50 - 100 mg chloral hydrate on days 1, 2 and 7) **Subgroup analysis** None **Adverse events** None	**Significant differences between study groups** • No • Not significant except for change in compliance from day 1 to 7 (P = 0.05)	**Quality** Fair **Significant differences at baseline** None **Other comments** No clinically relevant outcomes

Evidence Table 9. Ribavirin vs. Placebo (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Rodriguez 1987[42] **Setting** United States, Inpatient **Followup** • Acute • Short term – 4 days after treatment **Study design** RCT-P **Length of enrollment** Dec 1983 - Mar 1984 **Masking** Double-blind	To assess the clinical and microbiologic effectiveness of ribavirin in the treatment of RSV disease	**Inclusion criteria** Admitted with acute ALRTI Proven RSV infection **Exclusion criteria** • Congenital heart disease	**Number** 30 patients enrolled **Sex** Placebo: 20% male (2/10) Ribavirin: 55% male (11/20) **Mean age at enrollment (mo.±SD)** Placebo: 3.2 ± 2.30 Ribavirin: 6.1 ± 7.1 **Mean gestational age (wks)** Placebo: 37.2 Ribavirin: 37.8 **Comorbidities** • Prematurity (20% in placebo grp, 15% in ribavirin grp) • Intraventricular hemorrhage (1 ribavirin pt) • BPD: (20% in placebo grp, 10% in ribavirin grp)

Evidence Table 9. Ribavirin vs. Placebo (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 10)** Placebo Distilled water **Group B (n = 20)** **Ribavirin** 6 mg in 300 ml sterile water Aerosols administered at the rate of 12.5 l/mins continuously (except for 1 - 3 period before daily nasal specimen collection or during nursing or medical procedures which required removing the infant from the tent) until considerable clinical improvement until 1+ on the analogue severity scale **Other treatment** O_2 as indicated	**Outcomes** **Primary outcome** • Mean severity of symptoms on analogue scale for Days 0, 1, 2, 3, and 4 after treatment (placebo vs. ribavirin) – day 0: 2.4 vs. 2.9 – day 1: 2.0 vs. 2.0 – day 2: 1.7 vs. 1.4 – day 3: 1.2 vs. 0.7 – day 4: 1.2 vs. 0.6 • Rate of change of symptom severity – day 0 to day 2 – day 0 to day 3 • Mean length of treatment in hrs (placebo vs. ribavirin) – 58.6 vs. 55.7 **Secondary outcomes** • Number of days treated • Number. of followup days in the hospital • Rectal temperatures • Days of fever from onset of illness • Days of fever from start of therapy • Rate of improvement in oxygen saturation from first day to last **Subgroup analysis** None **Adverse events** 2 deaths after treatment period (unrelated to intervention), 1 in placebo group (BPD and respiratory failure) and 1 in ribavirin grp (BPD, chronic hypoxemia, bronchiolitis, respiratory failure)	**Significant differences between study groups** • *P* values not reported • Yes – *P* = 0.007 – *P* = 0.001 • No (*P* = 0.63) • No (*P* = 0.46) • No (*P* = 0.09) • Ribavirin patients had significantly higher rectal temperatures on Day 1 (*P* = 0.02) and Day 2 (*P* = 0.01) but not thereafter • No (*P* = 0.54) • No (*P*=0.61) • Significant only for ribavirin grp (*P* = 0.02)	**Quality** Good **Significant differences at baseline** None **Other comments** None

Evidence Table 9. Ribavirin vs. Placebo (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Rodriguez et al., 1999[81] **Setting** Followup after hospital discharge of prior study[42] (Initial study Dec 1983 to February 1985) **Followup** Up to 6 yrs after RSV bronchiolitis **Study design** RCT-P (initial protocol) **Length of enrollment** Dec 1983 to Feb 1985 **Masking** Double-blind for initial study; not clear if masking maintained for followup	To determine any long-term differences in adverse effects and pulmonary function between infants with respiratory syncytial virus and lower respiratory tract infection who were treated with ribavirin and a control group	**Inclusion criteria** This study consists of the longitudinal evaluation of patients prospectively randomized to a ribavirin or a placebo control group. Initial therapeutic study • Infants = 1 month old • Admitted to the hospital with ALRTI • Proven RSV infection confirmed with indirect immunoflorescent antibody methods • Infants who were expected to stay 3 days or longer in the hospital **Exclusion criteria** • Congenital heart disease	**Number** 42 enrolled, 35 completed study (N varies by outcome) Initial study had N = 30 for this study. N for this study includes enrollees from next season **Sex** Ribavirin: 63% male (15/24) Placebo: 73% male (8/11) **Mean age at enrollment (mo)** Ribavirin: 4 Placebo: 3.3 **Mean gestational age (wks ± SE)** NR **Comorbidities** Patients with chronic pulmonary disease and prematurity included

Evidence Table 9. Ribavirin vs. Placebo (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 24)** Ribavirin **Group B (n = 11)** Placebo **Other treatment** NR	**Outcomes**	**Significant differences between study groups**	**Quality** Good **Significant differences at baseline** NR **Other comments**
	Primary outcome		
	• Mean score for presence of Pneumonia, RAD and wheezing during yrs 1 - 3 after RSV Bronchiolitis ± SD (ribavirin vs. placebo)	• No (P = 0.10)	
	– 16.02 ± 27.69 vs. 22.31 ± 27.69		
	• Mean score for presence of Pneumonia, RAD and wheezing during yrs 1 - 6 after RSV Bronchiolitis ± SD (ribavirin vs. placebo)	• No (P = 0.10)	
	– 16.08 ± 27.78 vs. 22.18 ± 27.78		
	–		
	• Number. with 2 or more wheezing episodes during yrs 1 - 6 (ribavirin vs. placebo)	• Yes (P = 0.04)	
	– 17% (4/24) vs. 55% (6/11)		
	Secondary outcomes		
	• PFTs measured on 6 placebo and 13 Ribavirin patients	• Placebo patients more likely to have moderate to severe findings compared to ribavirin group (P = 0.043)	
	• Methacholine challenge on 5 placebo and 7 ribavirin patients	• Results in favor of less severity in ribavirin group, significant only when weighted for disease severity without correction for small sample size	
	Subgroup analysis RSV status		
	Adverse events NR		

Evidence Table 9. Ribavirin vs. Placebo (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Taber et al., 1983[45] **Setting** United States, 2 hospitals Inpatient at baseline, not specified at followup **Followup** • Acute • Short term – 2 wks **Study Design** RCT-P **Length of enrollment** Dec 1981 to Feb 1982 **Masking** Partial blinding of observers	To examine the efficacy of ribavirin in the treatment of bronchiolitis associated with RSV infection in infants	**Inclusion criteria** • Hospitalization • Recent onset of acute lower respiratory infection consistent with bronchiolitis • RSV in nasal secretions **Exclusion criteria** All infants were full term and without cardiac and pulmonary disease. Unclear whether exclusion criteria or chance	**Number** 26 eligible and initiated study **Sex** Ribavirin: 33% male (4/12) Control: 71% male (10/14) **Mean age at enrollment in mo. ± SE** Ribavirin: 3.9 ± 3.3 Control: 3.7± 2.9 **Mean gestational age** NR **Comorbidities** None

Evidence Table 9. Ribavirin vs. Placebo (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 12)** Ribavirin by aerosol 0.8 mg/kg/hr for ~ 12 hrs/day up to 4 days **Group B (n = 14)** Control (saline aerosol) no additional details provided **Other treatment** Standard care, details not reported	**Outcomes** **Primary outcome** • Mean symptom score from 0 - 3+ on Day 0, 1, 2, and 3 (ribavirin vs. control) – Day 0 (Grp A= 14, Grp B=16): 2.0 vs. 2.0 – Day 1 (Grp A= 11, Grp B=12): 1.5 vs. 1.7 – Day 2 (Grp A= 9, Grp B=11): 1.0 vs. 1.3 – Day 3 (Grp A= 7, Grp B=10): 0.6 vs. 1.3 **Secondary outcomes** • Length of treatment • End of treatment to discharge • Total time, onset to discharge • RSV Titers in nasal secretions • RSV Neutralizing antibody response • Hematologic indices **Subgroup analysis** None **Adverse events** None	**Significant differences between study groups** • Significantly diff on day 3 alone (P = 0.044) • No • No • No • No • Yes (P = 0.045) • No	**Quality** Fair **Significant differences at baseline** Patients in control group had symptoms longer before beginning treatment, diff not statistically significant **Other comments** • No Intent-to-treat analysis • Only 17 of 26 patients remained for the one outcome that was significant • Results do not support conclusion

Evidence Table 10. Antibiotics vs. No Treatment or Other Antibiotics

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Friis et al., 1984[49] **Setting** Denmark, Inpatient **Followup** • Acute • Short term - 3 wks **Study design** RCT - No placebo **Length of enrollment** Dec 1979 to Nov 1982 **Masking** Open label	To assess the effect of routine administration of antibiotics in the treatment of viral pneumonia and bronchiolitis	**Inclusion criteria** • Children with pneumonia admitted to pediatric wards • Ill for less than one wk • No antibiotics before hospital admission **Exclusion criteria** • Chronic pulmonary or cardiac disease • Mental retardation • Oncologic diseases • Severe breathing difficulties or cyanosis • Oxygen treatment or artificial ventilation • Suspected septicemia	**Number** 136 eligible of which 61 had RSV (evidence table limited to RSV Subgroup) **Sex** Antibiotics: 65% male (47/72) Control: 67% male (44/66) **Median age at enrollment in mos** Antibiotics: 18 Control: 17.5 **Mean gestational age** NR **Comorbidities** None

Evidence Table 10. Antibiotics vs. No Treatment or Other Antibiotics (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 34)** Antibiotics If < 2 yrs, Ampicillin PO 100mg/kg/day TID x 6 days If > 2 yrs, V Penicillin 300000 IU TID x 6 days If > 2 yrs with penicillin allergy, erythromycin 30 - 50mg/kg/day TID x 6 days Treatment changed if strains were resistant (No details reported) **Group B (n = 27)** Control No therapy, 7 patients given antibiotics when they developed cyanosis, or bacterial complications, or fever lasting more than 4 days without viral infection diagnosed by IFA antibody test **Other treatment** NR	**Outcomes** **Primary outcome** • Mean duration of hospitalization in days ± SE (antibiotics vs. control for RSV subgroup) - 5.2 ± 0.3 vs. 5.4 ± 0.4 • 'Pulmonarily healthy' on day 3 (antibiotics vs. control for RSV subgroup) - 11 (32.4%) vs. 9 (33.3%) • 'Pulmonarily healthy' at discharge (antibiotics vs. control for RSV subgroup) - 25 (73.5%) vs. 24 (88.9%) • 'Pulmonarily healthy' after 3 wks (antibiotics vs. control for RSV subgroup) - 27 (79.4%) vs. 20 (74.1%) **Secondary outcomes** • Respiratory rate per mins measured at days 1, 2, 3 and discharge • Radiological findings on admission and after 3 wks **Adverse events** Fever, respiratory distress, coughing, otalgia, skin eruptions, GI symptoms, medical attention, antibiotics after day 10 for all patients, details NR for bronchiolitis group	**Significant differences between study groups** • No, *P* value NR • No, *P* value NR • No, *P* value NR • No, *P* value NR • No, *P* value NR	**Quality** Fair **Significant differences at baseline** NR **Other comments** • Neither patients nor investigators were blinded

Evidence Table 10. Antibiotics vs. No Treatment or Other Antibiotics (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Klein 1995[82] **Setting:** France, Belgium, Germany, South Africa; setting for enrollment NR **Followup** • Short term - end of treatment at Day 12 - 13 • Long term - days 20 - 30 **Study design** RCT non-placebo **Masking** Open label	To compare cefpodoxime proxetil with amoxicillin/clavanulate in the treatment of community - acquired acute febrile lower respiratory tract infections (14 patients with bronchiolitis were included)	**Inclusion criteria** • Age 3 mos to 10 yrs • Weight = 7 kg • Fever = 38°C • Suspected bacterial infection • Abnormal chest x-ray • Signs and symptoms of acute lower respiratory tract infection such as cough, tachypnea, wheezes (rhonchi) and crackles (rales) **Exclusion criteria** • Allergy to beta-lactams • Tuberculosis present or suspected • Bronchiectasis or congenital respiratory anomalies • Nosocomial pneumonia • Need for parenteral antibiotics • Antibiotic therapy within previous 48 hrs	**Number** 348 enrolled, 278 at Day 12 - 13, 233 at followup 19 with bronchiolitis **Sex** NR **Mean age at enrollment (yrs)** Grp A: 1.8 Grp B: 3.1 **Mean gestational age** NR **Comorbidities** NR

Evidence Table 10. Antibiotics vs. No Treatment or Other Antibiotics (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 234, n for bronchiolitis subgroup NR)** Cefpodoxime proxetil Scheduled dose: 40 mg BID if >7 to <15 kg 80 mg BID if =15 kg Actual dose: 5 to 12 mg/kg/day BID **Group B (n = 114, n for bronchiolitis subgroup NR)** Amoxicillin/clavanulate Scheduled dose: 125/31.25 mg TID if >7 to <15 kg 250/62.5 mg TID if =15 kg Actual dose: 25 to 53/6 to 13 mg/kg/day TID **Other treatment** Analgesics, antipyretics, bronchodilators, physiotherapy as needed	**Outcomes** **Primary outcome** • Clinical cure or improvement for bronchiolitis subgroup (%: Grp A vs. Grp B) - 90 (9/10) vs. 100 (4/4) **Adverse events** • Vomiting, viral disease, bronchospasm, diarrhea and rash for all patients (not reported for bronchiolitis subgroup) • 4 patients in 0 overall study group discontinued due to side effects	**Significant differences between study groups** • NR	**Quality** Poor **Significant differences at baseline** Grp A younger than Grp B, *P* = 0.03 **Other comments** • Patients with Bronchiolitis made up only 4% of patients in study • Loss to followup 20% without accounting for reasons • Outcomes for 14 out of 19 bronchiolitis patients, loss not explained

Evidence Table 11. RSVIG IV as Treatment for Bronchiolitis

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Rodriguez et al., 1997[25] **Setting** United States, Inpatient at baseline, telephone followup **Followup** • Acute • Short term - Monthly telephone calls • Long-term at 1 yr after intervention **Study design** RCT-P **Length of enrollment** 4 RSV seasons (yrs not stated) **Masking** Double-blind	To determine the safety and efficacy of RSVIG in the treatment of previously healthy children hospitalized with RSV infection	**Inclusion criteria** • Previously healthy • = 2 yrs of age • Hospitalized with bronchiolitis and/or pneumonia with nasal wash specimens positive for RSV • Acute lower respiratory symptoms of less than 4 days duration • Respiratory score of = 2.5 **Exclusion criteria** • Known or suspected cardiopulmonary disease • Premature birth with a gestational age < 32 wks • Immunodeficiency disease (including human immunodeficiency virus infection) • Known serum IgA deficiency • Renal failure • Previous reaction to blood products • Receipt of blood or blood products in the preceding 60 days • Established diagnosis of reactive airway disease • Apnea without evidence of LRI on presentation • Inability to establish an intravenous line after 4 attempts • Admitted for Ribavarin therapy	**Number** 101 eligible, 98 completed study **Sex** RSVIG: 48% male (22/46) Placebo 50% male (26/52) **Mean age at enrollment (yr.± SD)** RSVIG: 0.20 ± 0.03 Placebo: 0.19 ± 0.03 **Mean gestational age (wk.± SD)** RSVIG: 38.0 ± 0.4 Placebo: 38.2 ± 0.4 **Comorbidities** Patients on ventilators: RSVIG: 12/46 (26%) Placebo: 19/52 (37%)

Evidence Table 11. RSVIG IV as Treatment for Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 46)** RSVIG 30ml/kg (1500 mg/kg) IV infusion x 1 dose **Group B (n = 52)** Placebo IV Albumin 0.5%, same volume as intervention **Other treatment** Ribavirin therapy, IV fluids, nebulization treatments, steroids or antibiotics, supplemental oxygen, mechanical ventilation	**Outcomes**	**Significant differences between study groups**	**Quality** Good **Significant differences at baseline** • RSVIG grp more likely to have = 85% study entry O_2 saturation level (46% vs. 29%, *P* = 0.07) • Placebo grp more likely to need ICU care and mechanical ventilation (*P* value NR) **Other comments** • If pt received 25% of infusion, was eligible for adverse outcomes reporting and if 75% of infusion then also for all other outcomes
	Primary outcome • Mean duration of hospitalization in days ± SE (RSVIG vs. Placebo) - 4.58 ± 0.4 vs. 5.52 ± 0.69 • Mean duration of stay in ICU in days ± SE (RSVIG vs. placebo) - 3.92 ± 0.58 (n = 25) vs. 6.60 ± 1.31 (n = 33)	• No (*P* = 0.24) • No (*P* = 0.06)	
	Secondary outcomes • Duration of mechanical ventilation • Duration of oxygen therapy • Use of ribavirin • Supplemental oxygen • RSV neutralizing antibody • Proportion of cultures for RSV • Hospitalization of LRI in subsequent season • Hospitalization of RSV LRI in subsequent season	• No (*P* = 0.45) • No • No • No • No • No • NR • NR	
	Subgroup analysis • Severity of illness - Among subgroup with more severe disease (respiratory scores = 3.0), lower duration of hospitalization in RSVIG grp than placebo • ICU stay at entry - Lower duration of hospitalization in RSVIG grp than placebo	• *P* values not provided, n too small • *P* values not provided, n too small	
	Adverse events • Benign nocturnal myoclonus not related to RSVIG (1 RSVIG pt.) • Cardiopulmonary findings (6 RSVIG pts, 8 placebo pts)		

Evidence Table 11. RSVIG IV as Treatment for Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Rodriguez et al., 1997[41] **Year** 1997 **Setting:** United States, Multi-center, Inpatient **Followup** • Acute • Short term - Monthly telephone calls • Long-term at 1 yr after intervention **Study design** RCT-P **Masking** Double-blind	To evaluate the efficacy of intravenous RSVIG to treat severe RSV in high risk infants	**Inclusion criteria** • High risk infants and children 2 yrs and younger • Hospitalized for RSV, bronchiolitis and/or pneumonia • Positive for RSV antigens High-risk criteria definitions: - severe BPD - other serious chronic lung disease - congenital heart disease - preterm infants <6 months old and <32 wks gestation **Exclusion criteria** • Poorly controlled congestive heart failure before RSV illness • Renal failure • Ventilator dependency before RSV illness • Life expectancy< 6 months from study onset • Treatment with ribavirin before enrollment • Previous adverse reaction to blood products • Known IgA or other immunodeficiency • Enrollment in concurrent RSVIG study • Cystic fibrosis • Asthma • Reactive airway disease w/o BPD • Apnea w/o LRI • Admission for ribavirin therapy	**Number** 107 enrolled, 102 received adequate dose, 96 at 8 wk followup, 98 at 1 yr followup **Sex** RSVIG: 45% male (23/51) Placebo: 57% male (29/51) **Mean age at enrollment (yr.± SE)** RSVIG: 0.55 ± 0.07 Placebo: 0.58 ± 0.06 **Mean gestational age (wk.± SE)** RSVIG: 31.0 ± 0.8 Placebo: 30.7 ± 0.7 **Comorbidities** • Groups balanced at entry for BPD, congenital heart disease and prematurity. • History of LRI significantly more frequent in placebo group (37% for placebo vs. 18% for RSVIG)

Evidence Table 11. RSVIG IV as Treatment for Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 51)** RSVIG 30 mL/kg (1.5 mg/kg) IV x 1 dose over 12 hrs **Group B (n = 53)** Placebo 0.15 mg/kg albumin (identically appearing solution and schedule) **Other treatment** Supplemental oxygen, mechanical ventilation, ribavirin therapy	**Outcomes**	**Significant differences between study groups**	**Quality** Excellent **Significant differences at baseline** RSVIG group had more severe disease than placebo group: - ICU admission: 47% vs. 28% (*P* = 0.03) - Mechanical ventilation: 31% vs. 18% (*P* = 0.01) - Mean respiratory scores of 4 - 5: 45% vs. 29% (*P* = 0.38) **Other comments**
	Primary outcome		
	• Mean duration of hospitalization in days ± SE (RSVIG vs. placebo)	• No (*P* = 0.73)	
	- 8.41± 0.97 vs. 8.89 ± 0.99		
	• Mean duration of ICU stay in days ± SE (RSVIG vs. placebo)	• No (*P* = 0.90)	
	- 9.77± 1.66 (n = 31) vs. 10.27 ± 1.81 (n = 18)		
	• Development of RSV in hospitalized patients during subsequent respiratory season	• No (*P* value NR)	
	- 3/48 (6%) vs. 3/50 (6%)		
	• Readmission during subsequent respiratory season(RSVIG vs. placebo)	• No (*P* value NR)	
	- 5/48 (10%) vs. 6/50 (12%)		
	Secondary outcomes		
	• Duration of mechanical ventilation	• No	
	• Requirement for supplemental oxygen during hospitalization	• No	
	• Change in respiratory scores 24, 48, 72 and 96 hrs after infusion	• No	
	• Bronchodilator use	• No	
	• Ribavirin use	• No	
	• Steroid use	• No	
	Subgroup analysis		
	• Underlying diagnosis	• No	
	• Gestational age, year, center	• No	
	• Respiratory score	• No	
	• ICU stay at entry	• No	
	Adverse events		
	• RSVIG		
	- 22 events in 16 patients		
	- 16/22 possibly drug - related		
	• Placebo		
	- 11 events in 10 patients		
	- 8/11 events possibly drug - related		

Evidence Table 12. Other Miscellaneous Treatments for Bronchiolitis

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Chipps et al., 1993[47] **Setting** United States, Multi-center, Inpatient **Followup** None **Study design** RCT-P **Length of enrollment** Winters of 1989 to 1990 and 1990 to 1991 **Masking** Double-blind	To test whether the treatment of RSV bronchiolitis with alpha-2A-interferon (IFN) results in decreased symptoms and duration of illness	**Inclusion criteria** • < 24 mos of age • Lower respiratory disease caused by RSV (increased work of breathing, elevated respiratory rate, rales and/or wheezing) • Supplemental oxygen needed to maintain O_2 saturation > 92% **Exclusion criteria** • Cyanotic congenital heart disease • Underlying chronic disease	**Number** 22 completed study **Sex** NR **Age at enrollment** NR **Mean gestational age** NR **Comorbidities** Patients on ventilators: 6

Evidence Table 12. Other Miscellaneous Treatments for Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 11)** IFN 70,000 units/kg/day IM q x 5 days **Group B (n = 11)** Placebo 0.9% saline in similar volume IM **Other treatment** Inhaled beta-agonists, oxygen, antibiotics when indicated and fluids for hydration	**Outcomes** **Primary outcomes** • Total symptom score - wheezing - muscle retractions - accessory muscle use • Number of day of O_2 therapy to maintain O_2 > 92% **Secondary outcomes** • Respiratory rate • Pulse rate • ELISA assays for RSV antigens • RSV shedding in nasal secretions **Subgroup analysis** None **Adverse events** None	**Significant differences between study groups** • No (P > 0.05) • No (P values NR) • No (P > 0.05) • No (P > 0.05) • No (P values NR) • No (P values NR)	**Quality** Good **Significant differences at baseline** • Significant differences in baseline symptom scores suggesting failure of randomi - zation • Mechanical ventilation for 4 IFN patients vs. 2 placebo patients **Other comments** • Power is too low to detect differences in scores between study groups (study was halted because of concerns about cardiotoxicity in other studies, although none noted in this study) • Dose possibly too low to produce therapeutic effect

Evidence Table 12. Other Miscellaneous Treatments for Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Hollman et al., 1998[84] **Setting** United States, Intensive care unit **Followup** Acute **Study design** RCT-C (not all patients randomized) **Length of enrollment** NR **Masking** Double-blind	To determine the efficacy of a helium-oxygen mixture in children admitted to the pediatric intensive care unit with acute respiratory syncytial virus (RSV) bronchiolitis	**Inclusion criteria** • Positive for RSV • Signs of lower respiratory tract disease **Exclusion criteria** • FIO_2 > 0.50 requirement • Helium concentrations < 50% • Intubated • Signs of upper airway obstruction	**Number** 21 eligible, 3 excluded for technical reasons, 18 studied, 13 randomized **Sex** NR **Median age** 2.5 mos (3 wks - 24 mos) **Mean gestational age** NR **Comorbidities** Clinical asthma: 12 Underlying cardiac disease: 5 History of laryngomalacia: 1 Treacher Collins syndrome: 1

Evidence Table 12. Other Miscellaneous Treatments for Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention For randomized patients (n = 13): **Group A (n = 6)** Helium-oxygen mixture, followed by air-oxygen mixture, each for 20 mins **Group B (n = 7)** Air-oxygen mixture, followed by helium-oxygen mixture, each for 20 mins For non - randomized patients (Clinical Asthma score ≥ 6) (n = 5): Helium-oxygen mixture **Other treatment** Nebulized albuterol (17/18)	**Outcomes** **Primary outcome** • Mean change in Clinical Asthma scores ± SE, compared with baseline - Helium-oxygen mixture: 0.46 ± 0.18 - Air-oxygen mixture: 0.04 (SE not provided) **Secondary outcomes** • Mean heart rate • Respiratory rate **Adverse events** Mechanical ventilation, intubation and balloon angioplasty in 1 patient with coarctation of the aorta	**Significant differences between study groups** • Significant only for helium-oxygen mixture - $P < 0.05$ - Not significant, *P* value NR • No • No	**Quality** Fair **Significant differences at baseline** NR **Other comments** None

Evidence Table 12. Other Miscellaneous Treatments for Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author: Kong et al., 1993[51] **Setting:** China, Inpatient **Followup** • Acute • Short term **Study design** RCT-AT **Length of enrollment** 1988 - 1989 **Masking** Single-blind trial (investigator blind to treatment)	To test the hypothesis that Shuang Huang Lian is a safe and effective treatment of acute bronchiolitis	**Inclusion criteria:** Children admitted with lower respiratory tract disease and serological evidence of RSV **Exclusion criteria:** Underlying illness such as congenital heart disease	**Number** 96 enrolled, 96 completed study **Sex** Grp A: 68.8% male (22/32) Grp B: 67.6% male (23/34) Grp C: 63.3% male (19/30) **Median age at enrollment in months (range)** Grp A: 12 (3 - 48) Grp B: 12 (2 - 36) Grp C: 10 (2 - 48) **Mean gestational age** NR **Comorbidities** None, previous history of LRI not reported

Evidence Table 12. Other Miscellaneous Treatments for Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 32)** Shuang Huang Lian <6 mo.: 20 ml IV 7 - 36 mo.:40 ml IV 36+ mo.: 60 ml IV qd x 7 d. **Group B (n = 34)** Shuang Huang Lian plus antibiotics Shuang Huang Lian: same dose and schedule as Group A, qd x 7 d. Antibiotics: Lincomycin IV 30 mg/kg/day or Cephazolin IV 100mg/kg/day, qd x 7 d. **Group C (n = 30)** Antibiotics, same dose and schedule as Group B **Other treatment** Aspirin as indicated	**Outcomes** **Primary outcomes** • Mean days of wheezing (95% C.I.) (n = 87) - Grp A: 4.2 (3.7 - 4.9) - Grp B: 4.0 (3.4 - 4.6) - Grp C: 6.1 (5.2 - 7.3) • Mean days of any sign or symptom (C.I.) (n = 96) - Grp A: 6.4 (5.6 - 7.3) - Grp B: 6.0 (5.0 - 7.1) - Grp C: 8.6 (7.5 - 9.8) • Hospital stay (C.I.) (n = 96) - Grp A: 7.8 (7.0 - 8.6) - Grp B: 7.0 (6.3 - 7.8) - Grp C: 9.8 (8.8 - 11.0) **Secondary outcomes** • Cough • Fever • Chest wheezes • Chest crackles **Subgroup analysis** None **Adverse events** None observed	**Significant differences between study groups** • Yes for groups AB combined vs. C ($P < 0.01$) • Yes for groups AB combined vs. C ($P < 0.01$) • Yes for groups AB combined vs. C ($P < 0.01$) • Yes for groups AB combined vs. C ($P < 0.01$) • No • Yes for groups AB combined vs. C ($P < 0.01$) • Yes for groups AB combined vs. C ($P < 0.01$)	**Quality** Fair **Significant differences at baseline** None **Other comments:** • No rationale provided for the use of two different antibiotics • 7 day stay in hospital impractical in Western context • Statistical tests compared grp A and B compared with grp C

Evidence Table 12. Other Miscellaneous Treatments for Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Luchetti et al., 1998[39] **Setting** Italy, intensive care unit **Followup** Acute **Study Design** RCT non-placebo **Length of enrollment** Winters of 1995 - 1996 and 1996 - 1997 **Masking** Cannot determine	To assess the effect of surfactant treatment on gas exchange, PIP, duration of mechanical ventilation and ICU stay in children with severe bronchiolitis	**Inclusion criteria** • 20 days - 2.5 yrs • Severe bronchiolitis requiring mechanical ventilation • On CPPV for 24 hrs without significant improvement • PIP > 35 cm H_2O after 24 hrs of CPPV **Exclusion criteria** None listed	**Number** 20 completed study **Sex** Surfactant: 60% male (6/10) Control: 50% male (5/10) **Mean age at enrollment (mo ± SE)** Surfactant: 10.4 ± 1.8 Control: 11.2 ± 2.0 **Mean gestational age (wk ± SE)** NR **Comorbidities** None reported

Evidence Table 12. Other Miscellaneous Treatments for Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 10)** **CPPV + porcine-derived surfactant** Surfactant 50 mg/kg instilled into trachea in 2 to 3 doses (details NR) CPPV • Postural drainage and chest clapping performed between doses • Ventilatory management same for 2 groups • Respiratory rate 20 - 40 breaths/min based on age of child • Tidal vol. 10 ml/kg. • PEEP always used increasing from 5 - 10 cm H_2O over 12 - 24 hrs • FiO_2 as low as possible. • Children sedated and paralyzed during surfactant administration. • CPPV discontinued when clinical and x-ray signs of disease disappeared and blood gas values as follows: • PaO_2 = 12.6 KPa with FiO_2 =0.3 • $PaCO_2$ = 5.6 KPa **Group B (n = 10)** CPPV **Other treatment** • All patients received O_2, ß2 - agonists and antibiotics. • Aminophylline and systematic corticosteroids for some patients, no significant differences across study groups	**Outcomes** **Primary outcome** • Mean duration of ICU stay in days ± SD (CPPV + surfactant vs. CPPV): - 10.1 ± 1.2 vs. 15.7 ± 1.5 • Mean duration of CPPV in days ± SD (CPPV + surfactant vs. CPPV): - 4.4 ± 0.4 vs. 8.9 ± 1.0 **Secondary outcomes** • Mean PaO_2/FiO_2 ratio ± SD (CPPV + surfactant vs. CPPV) at: - 1 hr: 25.7 ± 2.2 vs. 19.0 ± 1.8 - 3 hr: 23.7 ± 1.9 vs. 18.3 ± 1.9 - 12 hr: 30.0 ± 2.5 vs. 19.7 ± 1.9 - 24 hr: 30.8 ± 2.7 vs. 19.4 ± 1.6 • $PaCO_2$ at 12 and 24 hrs • Peak inspiratory rate at 3, 12 and 24 hrs **Subgroup analysis** None **Adverse events** None	**Significant differences between study groups** • Yes ($P < 0.05$) • Yes ($P < 0.05$) • Significant for all time periods - ($P < 0.05$) - ($P < 0.05$) - ($P < 0.01$) - ($P < 0.01$) • Yes (all $P < 0.05$) • Yes (all $P < 0.05$)	**Quality** Fair **Significant differences at baseline** None **Other comments** Masking of investigators not reported

Evidence Table 12. Other Miscellaneous Treatments for Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Van Bever et al., 1995[85] **Setting** Belgium, emergency department **Followup** None **Study design** RCT-P **Length of enrollment** NR **Masking** Double-blind	To study the effects of aerosolized furosemide on: • acutely wheezing babies and • intermittently wheezing babies Study also enrolled a second population of "intermittently wheezing babies" using PFTs as primary outcome. These data were excluded from this evidence table	**Inclusion criteria** • Initial attack of acute bronchiolitis for Part A inclusion **Exclusion criteria** • Previous bronchodilator therapy • Severe dyspnea • Lethargy • Underlying cardiorespiratory disease • Underlying metabolic disease • Underlying liver disease • Underlying renal disease • Premature babies with bronchopulmonary disease	**Number** 48 total enrolled, 28 in Part A (acute wheezing), 20 in Part B (intermittent wheezing) **Sex** Part A: 61% male **Mean age at enrollment (mo ± SE)** Part A: 6.1± 3.2 mos **Mean gestational age** NR **Comorbidities** None for Part A

Evidence Table 12. Other Miscellaneous Treatments for Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention **Part A (n = 28)** Nebulized furosemide (N not reported) 10 mg over 10 mins, with nebulizer flow at 6 to 8 L/min Placebo (N not reported) 4 ml saline over 10 mins **Other treatment** NR	**Outcomes** **Primary outcome** • Log of total clinical score ± SD at baseline, 15 mins and 30 mins after therapy for Part A (mean ± SD for Furosemide vs. placebo) - Baseline: 0.72 ± 0.16 vs. 0.71 ± 0.19 - 15 mins: 0.67 ± 0.19 vs. 0.62 ± 0.27 - 30 mins: 0.59 ± 0.28 vs. 0.56 ± 0.24 **Subgroup analysis** None **Adverse events** NR	**Significant differences between study groups** • No (*P* values NR)	**Quality** Good **Significant differences at baseline** None **Other comments** None

Evidence Table 12. Other Miscellaneous Treatments for Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Nasr et al., 2001[40] **Setting** United States, two-center study, inpatient **Followup** Acute **Study design** RCT-P **Length of enrollment** Feb 1996 - Mar 1998 **Masking** Double-blind	To test whether therapy with recombinant human deoxyribonuclease (rhDNase) may result in shorter length of hospitalization, improved clinical scores, and improved CXR's in hospitalized infants with RSV infection as a result of its mucolytic properties	**Inclusion criteria** • = 2 yrs of age • Previously healthy full-term neonates • Proven RSV infection **Exclusion criteria** None listed	**Number** 86 enrolled, 75 completed study **Sex** Placebo: 63% male (22/35) rhDNase: 63% male (25/40) **Mean age at enrollment (mo.± SD)** Placebo: 4.53 (4.56) rhDNase: 5.43 (6.26) **Mean gestational age** NR **Comorbidities** Patients on ventilators: 6

Evidence Table 12. Other Miscellaneous Treatments for Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 35)** Placebo 2.5 mL excipient once daily up to 5 days **Group B (n = 40)** rhDNase 2.5 mg (1mg/mL) in 2.5 mL of excipient once daily up to 5 days, nebulized using tight - fitting face mask **Other treatment** Nebulized albuterol as per institutional RSV protocol	**Outcomes** **Primary outcome** • Mean duration of hospitalization in days ± SD (Placebo vs. rhDNase): - 3.34 ± 2.3 vs. 3.33 ± 2.00 **Secondary outcomes** • Mean change between hospital admission and discharge ± SD (Placebo vs. rhDNase) for - Respiratory score - Wheezing score - Retraction score - CXR score: - 0.60 ± 1.38 vs. 0.46 ± 1.06 **Adverse events** None	**Significant differences between study groups** • No (P = 0.97) • No significant differences for any outcome other than CXR score (P < 0.001)	**Quality** Good **Significant differences at baseline** Trends suggest rhDNase grp more ill than placebo grp, no significant differences **Other comments** None

Evidence Table 13. RSVIG IV vs. Placebo or Standard Care to Prevent RSV Bronchiolitis

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Groothuis et al., 1993[87] **Setting:** United States, multi-center, outpatient at baseline, telephone survey at followup **Followup** • Long-term - monthly for 5 months during initial RSV season - subsequent RSV season **Study design** RCT non-placebo **Masking** Non-blinded team responsible for enrollment and well-baby exams and exams at the time of infusion; blinded team responsible for weekly followup and evaluation of all respiratory illnesses	To test whether RSV infection could be attenuated or prevented in high-risk children by monthly infusions of RSVIG during the RSV season	**Inclusion criteria** • Less than 48 mos old at beginning of study • Had congenital heart disease or cardiomyopathy, bronchopulmonary dysplasia, or premature delivery (= 35 wks) and a chronological age of less than 6 mos **Exclusion criteria** • Immunodeficiency • Poorly controlled heart or renal failure • Dependence on a ventilator • Expected survival of less than 6 mos	**Number** 249 enrolled, data on 249 in first season study, 210 contacted for followup in subsequent season **Sex** High-dose RSVIG: 57% male (46/81) Low - dose RSVIG 49% male (39/79) Control: 63% (56/89) **Mean age at enrollment (mo.± SE)** High-dose RSVIG: 8.4 ± 6.1 Low - dose RSVIG: 7.6 ± 6.1 Control: 8.4 ± 7.2 **Mean gestational age (wk.± SE)** NR **Comorbidities** See inclusion criteria

Evidence Table 13. RSVIG IV vs. Placebo or Standard Care to Prevent RSV Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 81)** High-dose RSVIG 750 mg/kg IV per month **Group B (n = 79)** Low - dose RSVIG 150 mg/kg IV per month **Group C (n = 89)** Control Standard care, no RSVIG **Other treatment** Routine care as needed, including ribavirin, hospitalization or ICU admission, mechanical ventilation	**Outcomes** **Primary outcome** • RSV-related acute respiratory disease - Grp A: 19 - Grp B: 16 - Grp C: 29 • Non-RSV acute respiratory disease - Grp A: 65 - Grp B: 77 - Grp C: 72 • RSV-related lower respiratory tract infections (respiratory score of 2+) - Grp A: 7 - Grp B: 13 - Grp C: 20 • Non-RSV lower respiratory tract infections (respiratory score of 2+) - Grp A: 14 - Grp B: 22 - Grp C: 24 • Moderate to severe RSV-related lower respiratory tract infections (respiratory score of 3+) - Grp A: 3 - Grp B: 5 - Grp C: 12 • Moderate to severe Non-RSV lower respiratory tract infections (respiratory score of 3+) - Grp A: 2 - Grp B: 4 - Grp C: 5	**Significant differences between study groups** • No - Grp A vs. Grp C: *P* = 0.19 - Grp B vs. Grp C: *P* = 0.08 • No - Grp A vs. Grp C: *P* = 0.99 - Grp B vs. Grp C: *P* = 0.49 • Significant for some comparisons - Grp A vs. Grp C: *P* = 0.01 - Grp B vs. Grp C: *P* = 0.35 • No - Grp A vs. Grp C: *P* = 0.20 - Grp B vs. Grp C: *P* = 0.79 • Significant for some comparisons - Grp A vs. Grp C: *P* = 0.03 - Grp B vs. Grp C: *P* = 0.13 • No - Grp A vs. Grp C: *P* = 0.45 - Grp B vs. Grp C: *P* = 0.99	**Quality** Good **Significant differences at baseline** History of hospitalization for proven RSV illness more common among high-dose RSVIG group (*P* = 0.05) **Other comments** Benefit statistics tend to be greatest for preterm infants and infants with BPD but supporting data were not reported

Evidence Table 13. RSVIG IV vs. Placebo or Standard Care to Prevent RSV Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Groothuis et al., 1993[87] (continued)			

Evidence Table 13. RSVIG IV vs. Placebo or Standard Care to Prevent RSV Bronchiolitis (continued)

Intervention	Outcome		Quality
	Secondary Outcomes		
	• Hospitalizations - Grp A: 6 - Grp B: 10 - Grp C:18	• Significant for some comparisons - Grp A vs. Grp C: *P* = 0.02 - Grp B vs. Grp C: *P* = 0.19	
	• Hospital days - Grp A: 43 - Grp B: 63 - Grp C: 128	• Significant for some comparisons - Grp A vs. Grp C: *P* = 0.02 - Grp B vs. Grp C: *P* = 0.12	
	• Admission to ICU - Grp A: 1 - Grp B: 0 - Grp C: 6	• Significant for some comparisons - Grp A vs. Grp C: *P* = 0.12 - Grp B vs. Grp C: *P* = 0.03	
	• Days in ICU - Grp A: 1 - Grp B: 0 - Grp C: 34	• Yes - Grp A vs. Grp C: *P* = 0.05 - Grp B vs. Grp C: *P* = 0.03	
	Adverse events 19 in 580 infusions (3%) • Fluid overload (5 pts) • Oxygen desaturation (8 pts) • Fever • Death (unrelated to intervention) • At least 1 problem with IV success in 60% of children		

Evidence Table 13. RSVIG IV vs. Placebo or Standard Care to Prevent RSV Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Groothuis et al., 1995[86] **Setting** United States, multicenter, outpatient at baseline, telephone survey at followup **Followup** • (From Groothuis 1993,[87] details NR in this study) • Long-term - monthly for 5 months during initial RSV season - subsequent RSV season **Study design** **Study design** • (From Groothuis 1993,[87] details NR in this study) RCT non-placebo **Length of enrollment** 3 RSV seasons	Subgroup analysis study of original trial to evaluate the safety and efficacy of RSVIG in the prevention of severe RSV lower respiratory tract infection in infants born prematurely, with or without BPD	**Inclusion criteria** • Infants enrolled in prophylaxis trial by Groothuis and colleagues • = 35 wks gestational age • With or without BPD **Exclusion criteria** • Congenital heart disease	**Number** 249 enrolled, data on 249 in first season study, 210 contacted for followup in subsequent season in original study, 116 (58 high-dose RSVIG and 58 control) in this analysis out of a total 162 preterm children **Sex** NR **Mean age at enrollment** NR **Mean gestational age** NR **Comorbidities** All preterm with BPD: 102 All preterm without BPD: 60 Details NR for subset in this analysis of high-dose RSVIG vs. control (n = 116)

Evidence Table 13. RSVIG IV vs. Placebo or Standard Care to Prevent RSV Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 58)** RSVIG High-dose RSVIG 750 mg/kg IV per month for a total of 3 to 5 doses during RSV season **Group B (n = 58)** Control Standard care, no RSVIG **Other treatment** (From Groothuis 1993, details NR in this study) Routine care as needed, including ribavirin, hospitalization or ICU admission, mechanical ventilation **Masking** • (From Groothuis 1993,[87] details NR in this study) Unblinded team responsible for enrollment and well-baby exams and exams at the time of infusion • Blinded team responsible for weekly followup and evaluation of all respiratory illnesses	**Outcomes** **Primary outcome** • Incidence of RSV LRTI (score = 2) (RSVIG vs. control) - 4 (6.9%) vs. 14 (24.1%) • Incidence of moderate to severe RSV LRTI (respiratory score = 3) (RSVIG vs. control) - 1 (1.7%) vs. 10 (17.2%) • Hospitalization for RSV infection (RSVIG vs. control) - 4 (6.9%) vs. 13 (22.4%) • Mean duration of hospitalization in days (RSVIG vs. control) - 31 vs. 83 • Mean duration in ICU in days (RSVIG vs. control) - 1 vs. 30 • Mean worst respiratory score with RSV ± SD - 1.5 ± 0.26 vs. 2.63 ± 0.31 **Subgroup analysis** None **Adverse events** 5% of all RSVIG infusions resulted in acute reactions, details NR in this study	**Significant differences between study groups** • Yes (*P* = 001) • Yes (*P* = 0.006) • Yes (*P* = 0.02) • No (*P* = 0.06) • Yes (*P* = 0.05) • Yes (*P* = 0.02)	**Quality** Good **Significant differences at baseline** History of hospitalization for proven RSV illness more common among high-dose RSVIG group (*P* = 0.05) **Other comments** None

Evidence Table 13. RSVIG IV vs. Placebo or Standard Care to Prevent RSV Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Simoes et al., 1998[88] **Setting** United States, multi-center **Followup** Short term **Study Design** RCT non-placebo **Length of enrollment** 3 RSV seasons from 1992 to 1995 **Masking** Enrollment and treatment team non-blinded, weekly surveillance and clinical evaluation team blinded	To examine the effectiveness of Respiratory syncytial virus immune globulin administered intravenously in reducing hospitalization for treatment of RSV in children with congenital heart disease	**Inclusion criteria** • < 48 mos of age • Congenital heart disease or cardiomyopathy **Exclusion criteria** • Immunodeficiency disease • RSV infection immediately before study entry • Previous reaction to blood products • Poor venous access • Renal failure • Ventilator dependency • Heart transplant candidates • Life expectancy < 6 mos	**Number** 425 enrolled, 416 completed study, no explanation provided for dropouts **Sex** RSVIG: 53% male (108/202) Control: 53% male (114/214) **Mean age in mo ± SD** RSVIG: 9.3 ± 9.4 Control:10.7 ± 10.1 **Mean gestational age in wks ± SD** RSVIG: 38.6 ± 2.2 Control:38.3 ± 2.9 **Comorbidities** See inclusion criteria

Evidence Table 13. RSVIG IV vs. Placebo or Standard Care to Prevent RSV Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention	**Outcomes**	**Significant differences between groups**	**Quality**
	Primary outcomes		Good
Group A (n = 202)			
RSVIG IV	• Acute respiratory illness (RSVIG IV vs. control)	• Yes (*P* = 0.02)	**Significant differences at baseline**
750 mg/kg (15ml/kg) IV of q month during RSV season	- 73% vs. 82%		• More children with tetralogy of Fallot or tricuspid atresia in RSVIG IV group
Group B (n = 214)	• RSV URI (RSVIG IV vs. control)	• No (*P* = 0.97)	• More children with left-to-right shunt in control group)
Control	- 6% vs. 7%		
	• RSV LRI (RSVIG IV vs. control)	• No (*P* = 0.26)	
Other interventions	- 19% vs. 24%		
Not reported	• All LRI associated hospitalizations (RSVIG IV vs. control)	• Yes (*P* = 0.02)	
	- 17% vs. 27%		
	• RSV LRI associated hospitalizations (RSVIG IV vs. control)	• No (*P* = 0.16)	
	- 10% vs. 15%		
	• Non-RSV LRI associated hospitalizations (RSVIG IV vs. control)	• No (*P* = 0.06)	
	- 6% vs. 12%		
	• RSV-LRI score = 3 (RSVIG IV vs. control)	• No (*P* = 0.36)	**Other comments**
	- 5% vs. 7%		None
	Secondary outcomes		
	• Admission to ICU for RSV LRI	• No	
	• Mechanical ventilator for RSV LRI	• No	
	• RSV hospital days/100 children	• No	
	• RSV hospital days with a score = 3/100 children	• No	
	• RSV ICU days/100 children	• No	
	• RSV mechanical ventilation/100 children	• No	

Evidence Table 13. RSVIG IV vs. Placebo or Standard Care to Prevent RSV Bronchiolitis (continued)

Study Characteristics	Stated objective	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Simoes et al., 1998[88] (continued)			

Evidence Table 13. RSVIG IV vs. Placebo or Standard Care to Prevent RSV Bronchiolitis (continued)

Intervention	Outcome		Quality
(continued)	**Subgroup analysis** RSV hospitalization by age and cardiac subgroup • Age: - < 6 months vs. = 6 months • Cardiac subgroup - Subgroup 1: biventricular heart without shunts - Subgroup 2: biventricular heart with right-to-left shunt - Subgroup 3: biventricular heart with left-to-right shunt - Subgroup 4: single ventricle or hypoplastic left heart	• Significant for all cardiac subgroups for age < 6 mos (P = 0.02), not significant for age = 6 mos (P = 0.74)	
	Adverse events Several listed	• Significantly greater for treatment groups for cardiac surgery associated adverse events other than death	

Evidence Table 13. RSVIG IV vs. Placebo or Standard Care to Prevent RSV Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author The PREVENT Study Group 1997[89] **Setting** United States, multi-center, outpatient **Followup** Long-term **Study design** RCT-P **Length of enrollment** 1994 - 1995 RSV season **Masking** Double-blinding	To determine the safety and efficacy of RSVIG IV prophylaxis for reducing the rate of RSV hospitalization among children with BPD and/or a history of prematurity	**Inclusion criteria** • ≤ 24 months old with BPD (diagnosed by a neonatologist or pulmonologist) and a requirement for supplemental oxygen within the past 6 months or • <6 mos old and premature at birth (35 wks gestation or less) **Exclusion criteria** • Required hospitalization at time of randomization (unless discharge was anticipated within 30 days) • Mechanically ventilated • Life expectancy < 6 mos • Active or recent RSV infection • Known immunoglobulin A deficiency • Known immunodeficiency • Previous reaction to blood products, albumin, or immune globulin (intravenous) [IGIV] • Treated with IGIV or any other immunoglobulin product within the previous 2 mos • Known renal impairment (creatinine > 2.5 mg/dL)	**Number** 510 randomized, 510 completed study **Sex** Placebo: 57.7% male (150/260) RSVIG IV: 57.2% male (143/250) **Mean age at enrollment (mos ± SE)** Placebo: 5.9 ± 0.27 RSVIG IV: 5.6 ± 0.29 **Mean gestational age (wks ± SE)** Placebo: 28.6 ± 0.21 RSVIG IV: 28.5 ± 0.20 **Comorbidities** BPD and prematurity, no other Comorbidities

Evidence Table 13. RSVIG IV vs. Placebo or Standard Care to Prevent RSV Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 260)** Placebo 1% albumin, administered by IV infusion **Group B (n = 250)** RSVIG IV 750 mL/kg, administered by IV infusion at a rate of 1.5 mL/kg/hr for the first 15 mins, then 3 mL/kg/hr from 15 - 30 mins, then 6 mL/kg/hr until the end of infusion Both placebo and RSVIG IV administered every 30 days from Nov Dec 1994 through April 1995 **Other treatment** Hospitalization, supplemental oxygen, ICU care, mechanical ventilation as indicated	**Outcomes** **Primary outcome** • Incidence of RSV hospitalizations (placebo vs. RSVIG IV) - 35/260 (13.5%) vs. 20/250 (8.0%) • Total number of RSV hospitalization days/100 children (placebo vs. RSVIG IV) - 129 vs. 60 • Total days of RSV hospitalization requiring supplemental oxygen/100 children (placebo vs. RSVIG IV) - 85 days vs. 34 days • Hospital days/100 children on which LRI score ≥ 3 (placebo vs. RSVIG IV) - 106 vs. 49 • ICU care for RSV (placebo vs. RSVIG IV) - 12/260 (4.6%) vs. 8/250 (3.2%) • Mechanical ventilation (placebo vs. RSVIG IV) - 5/260 vs. 5/250 • Incidence of overall respiratory hospitalizations (placebo vs. RSVIG IV) - 69 (27%) vs. 41 (16%) • Total number of respiratory hospital days/100 children (placebo vs. RSVIG IV) - 317 vs. 170 **Secondary outcomes** • Ribavirin use (placebo vs. RSVIG IV) - 10/35 (29%) vs. 7/20 (35%)	**Significant differences between study groups** • Yes (P = 0.047) • Yes (P = 0.045) • Yes (P = 0.007) • Yes (P = 0.049) • No (P value NR) • No (P value NR) • Yes (P = 0.005) • Yes (P = 0.005) • No (P = 0.62)	**Quality** Excellent **Significant differences at baseline** None **Other comments** 94% in placebo and 95% in RSVIG IV group completed protocol

Evidence Table 13. RSVIG IV vs. Placebo or Standard Care to Prevent RSV Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author The PREVENT Study Group, 1997[89] (continued)			

Evidence Table 13. RSVIG IV vs. Placebo or Standard Care to Prevent RSV Bronchiolitis (continued)

Intervention	Outcome		Quality
(continued)	**Subgroup analysis** • Prematurity - ≤ 6 mo at entry - ≤ 3 mo at entry • BPD • Age - ≤ 6 mo at entry • Weight ≥ or < 4.3 kg	• Trend toward fewer hospitalizations in all subgroup analyses for patients receiving RSVIG IV with reductions in hospitalizations ranging from 17% to 58%	
	Adverse events • Fever (1 in placebo, 2 in RSVIG IV) • Rash (1 in placebo) • Erythema multiforme (1 in placebo) • Respiratory distress (2 in RSVIG IV) • Acrocyanosis (2 in RSVIG IV) • Agitation and tachypnea (1 in RSVIG IV) • Decreased O_2 saturation (1 in RSVIG IV) • Death due to complications of prematurity and/or underlying chronic illness unrelated to study assignment • Adverse events judged potentially related to study drug as a reason for incomplete or prolonged infusion (1% in placebo vs. 3.2% in RSVIG IV)		

Evidence Table 14. Monoclonal Antibody for Prophylaxis of RSV Bronchiolitis

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author The IMpact – RSV Study Group 1998[91] **Setting** United States, United Kingdom, Canada, Inpatient and Outpatient **Followup** • Long-term – 150 days **Study design** RCT-P (2:1 randomization) **Length of enrollment** 1996 - 1997 RSV seasons **Masking** Double-blind	To evaluate the safety and effectiveness of monthly administration of palivizumab as prophylaxis for serious RSV illness in high-risk children	**Inclusion criteria** • ≤ 35 wks gestation and ≤ 6 mos old *or* • ≤ 24 mos old and had a clinical diagnosis of BPD requiring ongoing medical treatment (i.e. supplemental oxygen, steroids, bronchodilators, or diuretics within the past 6 mos **Exclusion criteria** • Hospitalization at the time of entry that was anticipated to last more than 30 days • Mechanical ventilation at the time of entry • Life expectancy less than 6 months • Active or recent RSV infection • Known hepatic or renal dysfunction, seizure disorder, immunodeficiency, allergy to 1gG products • Receipt of RSV immune globulin within past 3 months • Previous receipt of palivizumab, other monoclonal antibodies, RSV vaccines, or other investigational agents • Congenital heart disease, except children with patent ductus arteriosus or a septal defect that was uncomplicated and homodynamically insignificant	**Number** 1502 randomized, 1486 completed followup **Sex** Placebo: 56.8% male (284/500) Palivizumab: 56.9% male (570/1002) **Mean age at enrollment in mos ± SE** Placebo: 6.0 ± 0.21 Palivizumab: 5.7 ± 0.15 **Mean gestational age in wks ± SE** Placebo: 29 ± 0.14 Palivizumab: 29 ± 0.10 **Comorbidities** None other than prematurity and BPD

Evidence Table 14. Monoclonal Antibody for Prophylaxis of RSV Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 500)** Placebo 0.02 % Tween - 80 added to sterile water, IM every 30 days for a total 5 days, identical in appearance to palivizumab **Group B (n = 1002)** Palivizumab 15 mg/kg IM every 30 days for a total of 5 doses (final concentration of palivizumab = 100 mg/mL) **Other treatment** Hospitalization, oxygen supplementation, ICU care and mechanical ventilation as needed	**Outcomes** **Primary outcome** • Incidence of RSV hospitalizations (placebo vs. palivizumab) – 53/500 (10.6%) vs. 48/1002 (4.8%) **Secondary outcomes** • Total number of RSV hospitalization days/100 children (placebo vs. palivizumab) – 62.6 days vs. 36.4 days • Total days of RSV hospitalization requiring supplemental oxygen/100 children (placebo vs. palivizumab) – 50.6 days vs. 30.3 days • Hospital days/100 children on which LRI score ≥ 3 (placebo vs. palivizumab) – 47.4 vs. 29.6 • Incidence of ICU care for RSV (placebo vs. palivizumab) – 3% vs. 1.3% • Total days ICU care (placebo vs. palivizumab) – 12.7 vs. 13.3 • Incidence of mechanical ventilation (placebo vs. palivizumab) – 0.2% vs. 0.7% • Total days of mechanical ventilation (placebo vs. palivizumab) – 1.7 vs. 8.4 • Incidence of respiratory hospitalizations unrelated to RSV (placebo vs. palivizumab) – 14% vs. 13% • % children with at least 1 episode of otitis media – 40% vs. 42%	**Significant differences between study groups** • Yes ($P < 0.001$) • Yes ($P < 0.001$) • Yes ($P < 0.001$) • Yes ($P < 0.001$) • Yes ($P = 0.026$) • Yes ($P = 0.023$) • No ($P = 0.28$) • No ($P = 0.21$) • No ($P = 0.470$) • No ($P = 0.505$)	**Quality** Excellent **Significant differences at baseline** None **Other comments** None

Evidence Table 14. Monoclonal Antibody for Prophylaxis of RSV Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author The IMpact – RSV Study Group 1998[91] (continued)			

Evidence Table 14. Monoclonal Antibody for Prophylaxis of RSV Bronchiolitis (continued)

Intervention	Outcome		Quality
	Subgroup analysis		
	• Incidence of RSV hospitalizations by weight	• Yes	
	– > 5 kg	– (*P* 0.014)	
	– ≤ 5 kg	– (*P* = 0.001)	
	• Incidence of RSV hospitalizations by primary inclusion populations	• Yes	
	– Prematurity (no BPD)	– (*P* 0.001)	
	– BPD	– (*P* = 0.038)	
	• Incidence of RSV hospitalizations by length of gestation	• Yes	
	– <32 wks	– (*P* 0.003)	
	– 32 - 35 wks	– (*P* = 0.002)	
	Adverse events		
	• Fever	• No	
	• Nervousness	• No	
	• Injection site reaction	• No	
	• Diarrhea	• No	
	• Rash	• No	
	• Upper respiratory infection	• No	
	• Liver function abnormalities	• No	
	• Vomiting	• No	
	• Cough	• No	
	• Rhinitis	• No	
	• Death unrelated to study drug (5 in placebo group, 4 in palivizumab group)	• NR	

Evidence Table 14. Monoclonal Antibody for Prophylaxis of RSV Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Meissner et al., 1999[92] **Setting** Unspecified, Multi-center **Followup** • Acute • Short term - 8 wk followup **Study design** RCT-C **Length of enrollment** 1995 - 1996 RSV season **Masking** Double-blind	To evaluate the safety and pharmacokinetics of single and repeat in specified intramuscular doses of a humanized monoclonal antibody against RSV in a pediatric population at risk for severe RSV disease	**Inclusion criteria** • Born prematurely (= 35 wks), chronological age = 6 months *or* • Less than 37 months of age and history of BPD • Life expectancy of at least 6 mos **Exclusion criteria** • Known preexisting heart, liver, or renal disease • Recognized immune system abnormality • Severe respiratory illness requiring assisted ventilation • Previous gamma globulin infusion	**Number** 43 randomized, 42 completed study **Sex** 0.25 mg/kg SB209763: 38% male (3/8) 1.25 mg/kg SB209763: 45% male (5/11) 5.0 mg/kg SB209763: 27% male (3/11) 10.0 mg/kg SB209763: 77% male (10/13) **Mean age at enrollment in months (range)** 0.25 mg/kg SB209763: 6.0 (4 - 11) 1.25 mg/kg SB209763: 9.8 (0.75 - 30) 5.0 mg/kg SB209763: 9.8 (0.25 - 33) 10.0 mg/kg SB209763: 5.4 (0.75 - 13) **Mean gestational age** NR **Comorbidities** Prematurity:11 BPD plus prematurity:15 BPD alone:17

Evidence Table 14. Monoclonal Antibody for Prophylaxis of RSV Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention	**Outcomes**	**Significant differences between study groups**	**Quality**
Group A (n = 8) 0.25 mg/kg SB209763 (n = 6) IM into single thigh muscle, reconstituted with sterile water to a concentration of 45 mg/ml Placebo (n = 2) Similar volume as intervention After 8 wks, placebo group crossed over to SB209763 and both groups received 2nd IM dose	**Primary clinical outcome** • RSV infection episodes/dosage (10 mg/kg SB209763 vs. placebo) - 1/22 vs. 2/10 • RSV infection episodes/dosage (5 mg/kg SB209763 vs. placebo) - 2/19 vs. 2/10 • RSV infection episodes/dosage (1.25 mg/kg SB209763 vs. placebo) - 2/20 vs. 2/10 • RSV infection episodes/dosage (0.25 mg/kg SB209763 vs. placebo) - 2/14 vs. 2/10 **Adverse events** • Safety (SB209763 vs. placebo) - 37 events in 10 patients receiving placebo - 192 events in 35 patients receiving SB209763 • 4 events considered related to study - 3 episodes of mild to moderate purpura - 1 episode of thrombocytosis	• No (P = 0.20) • No (P = 0.49) • No (P = 0.46) • No (P = 0.72)	Good **Significant differences at baseline** None **Other comments** • High dose group mostly male • Primary purpose of study was safety and pharmaco - dynamics, not efficacy
Group B (n = 11) 1.25 mg/kg SB209763 (n = 9) IM into single thigh muscle Placebo (n = 2) Similar volume as intervention Dosing schedule: Similar crossover as Group A (placebo to intervention at 8 wks, second dose IM)			
Group C (n = 12) 5.0 mg/kg SB209763 (n = 8) Divided into 2 doses, IM into each thigh muscle Placebo (n = 3) Similar volume as intervention			

Evidence Table 14. Monoclonal Antibody for Prophylaxis of RSV Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Meissner et al., 1999[92] (continued)			

Evidence Table 14. Monoclonal Antibody for Prophylaxis of RSV Bronchiolitis (continued)

Intervention	Outcome	Quality
Dosing schedule: Similar crossover as Group A (placebo to intervention at 8 wks, second dose IM) **Group D (n = 13)** 10.0 mg/kg SB209763 (n = 10) Divided into 2 doses, IM into each thigh muscle Placebo (n = 3) Similar volume as intervention Dosing schedule: Similar crossover as Group A (placebo to intervention at 8 wks, second dose IM) Max volume at highest dose 0.22ml/kg **Other treatment** NR		

Evidence Table 15. Vaccines to Prevent RSV Bronchiolitis

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Groothuis et al., 1998[93] **Setting** United States, Outpatient at baseline, weekly telephone followup, Outpatient at 1 mo. and 6 mo. after intervention **Followup** • Short term: 1 mo. after intervention • Long-term: 6 mo. after intervention and the subsequent RSV season **Study design** RCT non-placebo **Length of enrollment** Oct and Nov 1991 **Masking** Double-blind	To assess the safety, immunogenicity, and efficacy of an improved purified F protein vaccine (PFP-2) in a high-risk population of young seropositive children with BPD	**Inclusion criteria** • < 12 months of age with bronchopulmonary dysplasia • Proven RSV infections in a previous respiratory season • Influenza vaccination in previous year • Outpatients in Neonatal High Risk Follow Up Program at Children's Hospital, Denver **Exclusion criteria** None listed	**Number** 21 randomized, 21 completed study **Sex** NR **Age at enrollment in months** PFP-2: 32.2 Placebo: 30.0 **Mean gestational age** NR **Comorbidities** NR

Evidence Table 15. Vaccines to Prevent RSV Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 10)** PFP-2 vaccine 0.5 ml IM **Group B (n = 11)** Trivalent influenza vaccine 0.5 ml IM **Other treatment** All patients received unblinded dose of trivalent influenza vaccine 4-6 wks after study vaccine	**Outcomes** **Primary outcome** • RSV infections in subsequent season (PFP-2 vs. Influenza vaccine) - 1/10 vs. 6/11 **Secondary outcomes** • Mean F protein antibody before vaccination PFP-2 vs. Influenza vaccine) • Mean F protein antibody 1 month after vaccination (PFP-2 vs. Influenza vaccine) • Mean F protein antibody 6 month after vaccination (PFP-2 vs. Influenza vaccine) • Mean neutralizing antibody before vaccination (PFP-2 vs. Influenza vaccine) • Mean neutralizing antibody 1 month after vaccination (PFP-2 vs. Influenza vaccine) • Mean neutralizing antibody 6 month after vaccination (PFP-2 vs. Influenza vaccine) **Subgroup analysis** None **Adverse events** • Irritability (2 PFP - 2 patients, 2 influenza vaccine) • Drowsiness (1 PFP - 2 patient) • PIain and tenderness (1 PFP - 2 patients, 1 influenza vaccine) • Redness (1 PFP - 2 patient)	**Significant differences between study groups** • No (P = 0.06) • No (P = 0.22) • Yes (P 0.0001) • Yes (P = 0.002) • No (P = 0.78) • Yes (P = 0.006) • Yes (P = 0.009)	**Quality** Good **Significant differences at baseline** None **Other comments**

Evidence Table 15. Vaccines to Prevent RSV Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Piedra et al., 1996[94] **Setting** United States, Outpatient at baseline, telephone interview at followup **Followup** • Short term - length of the RSV season **Study design** RCT-P **Length of enrollment** 1993 to 1994 RSV season **Masking** Double-blind	To determine the safety and immunogenicity of the PFP-2 vaccine in children with CF who are at high risk of LRTI with RSV infection	**Inclusion criteria** • Diagnosis of CF based on two of following criteria: - sweat chloride > 60 meq/L - genetic testing demonstrating homozygosity for the delta F508 allele - clinical features consistent with cystic fibrosis **Exclusion criteria** • Pre-vaccine RSV serum neutralizing antibody filter of < 1:4 • History of epilepsy • Recent history of febrile seizure	**Number** 34 completed study **Sex** PFP-2: 59% male Saline: 65% male **Mean age at enrollment (yr ± SD)** PFP-2: 4.5 ± 1.6 Saline: 5.8 ± 1.6 **Mean gestational age** NR **Comorbidities** All enrollees had CF

Evidence Table 15. Vaccines to Prevent RSV Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 17)** PFP-2 IM 50 µg of PFP-2 composed of F glycoprotein of the A2 strain of RSV compounded with alum, 1 dose **Group B (n = 17)** IM Saline 0.5 ml **Other treatment** Antibiotics	**Outcomes**	**Significant differences between study groups**	**Quality** Good **Significant differences at baseline** PFP-2 group significantly taller, older, and had lower triceps fat fold thickness **Other comments** None
	Primary outcomes		
	• Development of RSV ± SD (PFP-2 vs. Saline)	• No (P = 0.73)	
	- 7/17 (41%) vs. 9/17 (53%)		
	• Total days of illness of RSV infection ± SD (PFP-2 vs. Saline)	• NR	
	- 45 vs. 119		
	• Hospitalization	• No (P = 0.087)	
	- 1/17 vs. 5/17		
	• No. with = 1 ALRTI (acute lower respiratory tract infection)	• Yes (P = 0.024)	
	- 9/17 vs. 15/17		
	• Mean no. of AURTI/subject (acute upper respiratory tract infection) ± SD (PFP-2 vs. Saline)	• No (P = 0.35)	
	- 2.0 ± 1.5 vs. 2.5 ± 1.6		
	• Mean no. of ALRTI/subject ± SD (PFP-2 vs. Saline)	• Yes (P = 0.005)	
	- 0.8 ± 0.9 vs. 2.1 ± 1.4		
	• Mean no. of antibiotic courses/subject ± SD (PFP-2 vs. Saline)	• Yes (P < 0.001)	
	- 2.2 ± 1.3 vs. 4.5 ± 1.5		
	• Mean no. of days ill/subject	• Yes (P < 0.001)	
	- 30.5 ± 16.1 vs. 67 ± 25.8		
	Subgroup analysis		
	• RSV exposure status	• No significant differences	
	Adverse events		
	• Weakness/ache/nausea	• No significant differences	
	• Any systematic symptoms (PFP-2 vs. saline)	• No significant differences	
	– 5 vs. 6		
	• Any local reaction (PFP2 vs. saline)	• No significant differences	
	– 8 vs. 4		

Evidence Table 15. Vaccines to Prevent RSV Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Piedra et al., 1998[95] **Setting** United States, Outpatient **Followup** • Acute • Short term - weekly • Long-term - 1 yr after initial vaccine **Length of enrollment** 1993 - 1995 **Study design** Open - label followup of original study that was RCT-P, all patients received followup vaccine **Masking** Not clear if parents/ caregivers were unblinded in this study	To determine the safety and immunogenicity of yearly sequential administration of the PFP-2 vaccine in children with cystic fibrosis Note: This is a followup of Piedra et al. 1996.	**Inclusion criteria** Diagnosis of CF as previously described in Piedra et al.[94] on two of following criteria: - sweat chloride > 60 meq/l - genetic testing demonstrating homozygosity for the delta F508 allele - clinical features consistent with cystic fibrosis **Exclusion criteria** Details NR in this study. Piedra et al. 1996[94] states • Pre - vaccine RSV serum neutralizing antibody filter of < 1:4 • History of epilepsy • Recent history of febrile seizure	**Number** 34 in initial study, 29 completed this 2nd study **Sex** PFP/PFP: 57% male (8/14) Saline/PFP: 60% male (9/15) **Mean age at enrollment in years ± SD** PFP/PFP: 5.6 ± 1.8 Saline/PFP: 6.8 ± 1.5 **Mean gestational age** NR **Comorbidities** CF, mild lung disease

Evidence Table 15. Vaccines to Prevent RSV Bronchiolitis (continued)

Intervention	Outcome		Quality
Intervention **Group A (n = 14)** PFP/PFP IM 50 µg of PFP-2 in 0.5 ml in Fall 1993 and Fall 1994 **Group B (n = 15)** Saline/PFP Saline placebo in Fall 1993 (details not reported) PFP/PFP: IM 50 µg of PFP-2 in 0.5 ml in Fall 1994 **Other treatment** Antibiotics	**Outcomes** **Primary outcome** • No. with = 1 ALRTI - 9/13 vs. 15/15 • Mean no. of illnesses/subject ± SD (PFP/PFP vs. Saline/PFP) - 3.2 ± 1.5 vs. 4.1 ± 1.2 • Mean no. of AURTI/subject ± SD (PFP/PFP vs. Saline/PFP) - 2.1 ± 1.3 vs. 2.1 ± 1.2 • Mean no. of ALRTI/subject ± SD (PFP/PFP vs. Saline/PFP) - 1.2 ± 1.0 vs. 2.1 ± 0.5 • Mean no. of antibiotic courses/subject ± SD (PFP/PFP vs. Saline/PFP) - 2.8 ± 2.5 vs. 4.4 ±. 2.0 • Mean no. of days ill/subject - 36. ± 19.4 vs. 64.8 ± 27.0 **Subgroup analysis** • Confirmed RSV infection - No. with = 1 ALRTI - Mean no. of illnesses/subject ± SD (PFP/PFP vs. Saline/PFP) - Mean no. of AURTI/subject ± SD (PFP/PFP vs. Saline/PFP) - Mean no. of ALRTI/subject ± SD (PFP/PFP vs. Saline/PFP) - Mean no. of antibiotic courses/subject ± SD (PFP/PFP vs. Saline/PFP) - Mean no. of days ill/subject	**Significant differences between study groups** • Yes (P = 0.035) • No (P = 0.098) • No (P = 0.98) • Yes (P = 0.004) • No (P = 0.077) • Yes (P = 0.001) • Some outcomes significantly different between groups	**Quality** Fair **Significant differences at baseline** • Saline/PFP taller (P value NR) and older (P = .06) • Saline/PFP children more likely to attend daycare/ school (P = 0.08) **Other comments** • Significant effects may be explained by lower incidence of RSV exposure in PFP/PFP group due to lower daycare attendance • N for subgroup analysis very low

Evidence Table 15. Vaccines to Prevent RSV Bronchiolitis (continued)

Study Characteristics	Stated Objective of Study	Inclusion/Exclusion Criteria	Demographic Characteristics and Cormorbidities
Author Piedra et al.1998[95] (continued)			

Evidence Table 15. Vaccines to Prevent RSV Bronchiolitis (continued)

Intervention	Outcome		Quality
	Adverse events • 1 death unrelated to vaccination or RSV infection (1 PFP/PFP pt.) • Weakness/ache/nausea • Fever • Headache • Any systemic reaction – 7/14 vs. 7/15 • Tenderness at vaccine site • Edema at vaccine site • Red at vaccine site • Any local reaction – 4/14 vs. 5/15	• No significant differences between groups	

Appendix A

Appendix A. Clinical Scales

This appendix briefly describes the various scales used in the articles reviewed in this evidence report. The materials are presented by evidence table in alphabetical order by author.

Evidence Table 1:

Kristjansson et al., 1993[52]

A **clinical scoring system** was used to evaluate infants and toddlers on admission and a score of 4 or more on a scale of 0 to 10 was required for eligibility as a study participant. A score of 0 was given for respiratory rate < 40 breaths/min; no respiratory chest recessions; vesicular auscultatory breath sounds; normal skin color; and general condition not affected. A score of 1 was given for respiratory rate of 40 to 60 breaths/min; moderate costodiaphragmatic respiratory chest recessions; wheeze+rales/ronchi auscultatory breath sounds; pallor of skin color; and general condition moderately affected. A score of 2 was given for respiratory rate > 60 breaths/min; moderate costodiaphragmatic respiratory chest recessions with rib and jugular retractions; faint with or without severe wheeze with or without pronounced rales and ronchi auscultatory breath sounds; cyanosis; and general condition severely affected. The **symptom score** consisted of the sum of each of the scores for respiratory rate, respiratory chest recessions, auscultatory breath sounds, skin color, and general condition.

Evidence Table 2:

Lowell et al, 1987[110]

A **clinical scoring system** consisted of scores for wheezing and retractions using the Respiratory Distress Assessment Instrument developed specifically for the study. Wheezing and retractions were each scored on a scale of 0 to 3. The maximum total points for wheezing are 8 and for retractions are 9. A wheezing score of 0 was given for no wheezing at expiration, no wheezing at inspiration and no wheezing in specific location. A wheezing score of 1 was given for wheezing at end expiration, at part of inspiration, and segmental (= 2 of 4 lung fields) in location. A wheezing score of 2 was given for wheezing at one-half expiration, at all of inspiration, and diffuse (> 3 of 4 lung fields) in location. A wheezing score of 3 was given for wheezing during three-quarters of expiration, and a wheezing score of 4 was given for wheezing during all of expiration. A retraction score of 0 was given for no supraclavicular, intercostal, or subcostal retractions. A retraction score of 1 was given for mild supraclavicular, intercostal, or subcostal retractions. A retraction score of 2 was given for moderate supraclavicular, intercostal, or subcostal retractions. A retraction score of 3 was given for marked supraclavicular, intercostal, or subcostal retractions. A total score combined the wheezing and retraction scores. The **respiratory score** was obtained by summing the wheezing and retraction subscores. The **overall respiratory assessment change score (RACS)** was calculated as the sum of change scores in each of the variables. Improvement was defined as an RACS of = 4 units in the positive direction, while a RACS < 4 was defined as no improvement.

Evidence Table 3:

Bertrand et al., 2001[53]

The **clinical scoring system** includes respiratory rate modified for age, wheezing, use of accessory muscles, and presence of cyanosis modified by measuring oxygen concentration needed to keep oxygen saturation at 94 percent to 97 percent. This scoring system was adapted from Bierman and Pierson as modified by Tal et al. A score of 0 was given for respiratory rate (breaths/min) < 40 if < 6 months or < 30 if > 6 months; no wheezing; no retractions; and no oxygen requirement. A score of 1 was given for respiratory rate (breaths/min) of 40 to 55 if < 6 months or of 30 to 45 if > 6 months; end expiratory wheezing; + retractions; and 21 percent to 28 percent oxygen supply. A score of 2 was given for respiratory rate (breaths/min) of 56 to 70 if < 6 months or of 46 to 60 if > 6 months; inspiratory and expiratory wheezing with stethoscope; ++ retractions; and of 29 to 35 percent oxygen supply. A score of 3 was given for respiratory rate (breaths/min) > 70 if < 6 months or > 60 if > 6 months; audible inspiratory and expiratory wheezing; +++ retractions; and > 35 percent oxygen supply.

Menon et al., 1995[22]

A **Respiratory Distress Assessment Instrument score** = 4 was an eligibility requirement for entry into this study. The RDAI uses an ordinal scale from 0 to 17 and measures expiratory wheezing (0 to 4 points), inspiratory wheezing (0 to 2 points), location of wheeze (0 to 2 points), supraclavicular indrawing (0 to 3 points), and subcostal indrawing (0 to 3 points.) No further details are given regarding scoring criteria.

Reijonen, 1995[54]

The **RDAI score** is based on wheezing and retractions. This scoring system comes from Lowell, et al.[110] Wheezing and retractions were each scored on a scale of 0 to 3. The maximum total points for wheezing are 8 and for retractions are 9. A wheezing score of 0 was given for no wheezing at expiration, no wheezing at inspiration, and no wheezing in specific location. A wheezing score of 1 was given for wheezing at end expiration, at part of inspiration, and segmental (= 2 of 4 lung fields) in location. A wheezing score of 2 was given for wheezing at one-half expiration, at all of inspiration, and diffuse (>3 of 4 lung fields) in location. A wheezing score of 3 was given for wheezing during three-quarters of expiration, and a wheezing score of 4 was given for wheezing during all of expiration. A retraction score of 0 was given for no supraclavicular, intercostal, or subcostal retractions. A retraction score of 1 was given for mild supraclavicular, intercostal, or subcostal retractions. A retraction score of 2 was given for moderate supraclavicular, intercostal, or subcostal retractions. A retraction score of 3 was given for marked supraclavicular, intercostal, or subcostal retractions. A total score combined the wheezing and retraction scores. The RDAI score was obtained by summing the wheezing and retraction subscores. The **overall respiratory assessment change score (RACS)** was calculated by subtracting the RDAI scores assessed before and after treatment and by summing the change unit with respiratory rate.

Sanchez et al., 1993[55]

A **clinical score** assessed respiratory rate, wheezing, cyanosis, and accessory muscle use. The maximum possible score was 12, which indicated severe disease. No further details were provided about the scoring system.

Evidence Table 4:

Can et al., 1998[24]

A **respiratory distress score (RDS)** incorporates respiratory rate, cyanosis, wheezing, and retractions. A score of 0 was given for respiratory rate < 30; no cyanosis; no expiratory, inspiratory, or localized wheezing; and no subcostal, intercostal, or supraclavicular retractions. A score of 1 was given for respiratory rate 31 to 45; circumoral cyanosis on crying only; end expiratory, part inspiratory, localized wheezing; and mild/moderate subcostal, intercostal, or supraclavicular retractions. A score of 2 was given for respiratory rate 46 to 60; circumoral cyanosis at rest; entire expiratory, all inspiratory, or diffuse wheezing; and marked subcostal, intercostal, or supraclavicular retractions. A score of 3 was given for respiratory rate > 60; generalized cyanosis at rest; and audible wheezing without stethoscope. If nasal flaring exists, add 1 to the score.

Cengizlier et al., 1997[58]

A **clinical score** assessed respiratory rate, wheezing, retraction, and general condition on admission and discharge or day 3 if still hospitalized. The difference between the initial and discharge scores were determined as score change for each patient. A score of 0 was given for respiratory rate (breaths/min) = 30; no wheezing; no retraction; and normal general condition. A score of 1 was given for respiratory rate (breaths/min) of 30 to 45; wheezing on terminal expiration or only with stethoscope; and intercostal retraction only. A score of 2 was given for respiratory rate (breaths/min) 46 to 60; wheezing during entire expiration or audible on expiration without stethoscope; and tracheosternal retraction. A score of 3 was given for respiratory rate (breaths/min) > 60; wheezing during inspiration and expiration without stethoscope; severe retraction with nasal flow; and general condition irritable/lethargic, poor feeding.

Dobson et al., 1998[37]

The **clinical score** was adapted from Schuh et al.[44] and assessed general appearance, accessory muscle use, and wheezing. To be eligible for the study, infants had to have an accessory muscle use score = 2 or wheezing score = 2. A score of 0 was given for asleep; no retraction; and no wheezing or crackles. A score of 1 was given for calm, content, happy, and/or interactive; mild retractions; and scattered, end-expiratory wheezes or crackles only. A score of 2 was given for mildly irritable when touched, occasional crying, but able to be consoled; moderate retractions; and moderate wheezing including diffuse expiratory wheezes with or without scattered early inspiratory wheezes. A score of 3 was given for moderately irritable, difficult to console, less interactive; severe retractions; and severe wheezing including diffuse inspiratory and expiratory wheezing. A score of 4 was given for extremely irritable, cannot be comforted, crying throughout examination, or not interactive.

Gadomski et al., 1994[60]

Clinical scoring was performed before and after bronchodilator treatment. Infants were scored on a scale from 0 to 3 on the degree of grunting, nasal flaring, supraclavicular retractions, intercostal retractions, chest indrawing, air entry, air hunger, wheezing, and general appearance. The scoring system used pictoral aids for each category. The final scoring system was modified and included some collapsed categories and some unreliable observations were deleted. No further information is provided.

Gadomski, 1994[59]

The **severity of illness** was graded using a **scoring system** developed specifically for this trial. The following parameters were scored on a scale of 0 to 3: grunting, flaring, supraclavicular and intercostal retractions, air entry, air hunger, respiratory cycle and location of wheeze, and general appearance. The scoring form included pictoral representations of each category to increase reliability. Scores were assigned as follows: grunting (0 = none, 1 = intermittent, 3 = audible and persistent); nasal flaring (0 = none, 1 = minimal or intermittent, 3 = marked persistent); supraclavicular retractions (0 = none, 1 = just visible, 2 = evident, 3 = marked or obvious); intercostal retractions (0 = none, 1 = just visible, 2 = evident, 3 = marked or obvious); air entry (0 = normal, 3 = reduced); air hunger (0 = none, 1 = not anxious, comfortable, 2 = anxious, ill at ease, 3 = apathetic, lethargic); duration of wheeze in respiratory cycle (0 = none, 1 = terminal only, 2 = entire expiratory, 3 = inspiratory and expiratory or minimal air entry); location of wheezes (0 = none, 1 = segmental, < 2 of 4 lung fields, 2 = diffuse, > 3 of 4 lung fields, 3 = audible without stethoscope); and general appearance (0 = content, happy, interactive, 1 = mildly irritable when touched, occasional crying, can be comforted, is interactive, 2 = moderately irritable, intermittently crying, resists comforting, less interactive, 3 = extremely irritable, cannot be comforted, crying throughout examination or not interactive).

Goh et al., 1997[61]

A **severity score** assessed respiratory rate, subcostal retractions, presence of crepitations, presence of wheeze, oxygen requirement, nebulisation, and intravenous infusion. The severity score is equal to the sum of each of the scores for the categories listed above. A score of 0 was given for respiratory rate/min = 30; no subcostal retractions; no crepitations; no wheeze; no oxygen requirement; no nebulisation; and no intravenous infusion. A score of 1 was given for respiratory rate/min of 31 to 40; mild subcostal retractions; presence of crepitations; wheeze with stethoscope; oxygen requirement; nebulisation; and intravenous infusion. A score of 2 was given for respiratory rate/min of 41 to 50; moderate subcostal retractions; and presence of wheeze with quiet breathing. A score of 3 was given for respiratory rate/min of 51 to 60; severe subcostal retractions; and presence of wheeze with use of accessory muscle. A score of 4 was given for respiratory rate/min of > 60; and presence of wheeze with obvious distress.

Hickey et al., 1994[57]

A **clinical scoring system** consisted of scores for wheezing and retractions with each scored on a scale of 0 to 3 with increasing score reflecting increasing distress. The wheezing score was assigned as follows: 0 = absent, 1 = end-expiratory, 2 = pan-expiratory, 3 = audible to naked ear or too tight to wheeze. The retraction score was assigned as follows: 0 = absent, 1 = intercostal only, 2 = supraclavicular, 3 = heaving shoulders or sternocleidomastoid. Mean wheezing and mean retraction scores were reported.

Ho et al., 1991[62]

No scales.

Klassen et al., 1991[21]

The **RDAI** assessed wheezing and retractions. If two different observers assessed the same patient, the mean score was used. The RDAI came from Lowell et al.[110] Wheezing and retractions were each scored on a scale of 0 to 3. The maximum total points for wheezing are 8 and for retractions are 9. A wheezing score of 0 was given for no wheezing at expiration, no wheezing at inspiration and no wheezing in specific location. A wheezing score of 1 was given for wheezing at end expiration, at part of inspiration, and segmental (= 2 of 4 lung fields) in location. A wheezing score of 2 was given for wheezing at one-half expiration, at all of inspiration, and diffuse (> 3 of 4 lung fields) in location. A wheezing score of 3 was given for wheezing during three-quarters of expiration, and a wheezing score of 4 was given for wheezing during all of expiration. A retraction score of 0 was given for no supraclavicular, intercostal, or subcostal retractions. A retraction score of 1 was given for mild supraclavicular, intercostal, or subcostal retractions. A retraction score of 2 was given for moderate supraclavicular, intercostal, or subcostal retractions. A retraction score of 3 was given for marked supraclavicular, intercostal, or subcostal retractions. A total score combined the wheezing and retraction scores.

Schuh et al., 1990[44]

Each child was assessed with an **accessory muscle score** and a **wheeze score.** The accessory muscle score was assigned as follows: 0 = no indrawing, 1 = mild intercostal indrawing, 2 = moderate indrawing with tracheosternal retractions, and 3 = severe retractions with nasal flaring. The wheeze score was assigned as follows: 0 = no wheezing, 1 = end-expiratory wheeze only, 2 = wheeze during entire expiratory with or without inspiratory phase, audible with stethoscope only, 3 = inspiratory and expiratory wheezing audible without stethoscope.

Schweich et al., 1992[56]

A **respiratory score** referenced to Lowell et al.,[110] consisted of two additional scores, the **wheezing score** and the **retraction score.** A wheezing score of 0 was given for no wheezing at expiration, no wheezing at inspiration and no wheezing in specific location. A wheezing score of 1 was given for wheezing at end expiration, at part of inspiration, and segmental (= 2 of 4 lung fields) in location. A wheezing score of 2 was given for wheezing at one-half expiration, at all of inspiration, and diffuse (> 3 of 4 lung fields) in location. A wheezing score of 3 was given for wheezing during three-quarters of expiration, and a wheezing score of 4 was given for wheezing during all of expiration. A retraction score of 0 was given for no supraclavicular, intercostal, or subcostal retractions. A retraction score of 1 was given for mild supraclavicular, intercostal, or subcostal retractions. A retraction score of 2 was given for moderate supraclavicular, intercostal, or subcostal retractions. A retraction score of 3 was given for marked supraclavicular, intercostal, or subcostal retractions. A total score combined the wheezing and retraction scores.

Evidence Table 5:

Chowdhury et al., 1995[63]

The **modified RDAI** was used. The modified RDAI assesses intercostal retractions, wheezing, and respiratory rate. A score of 0 was given for no expiratory, inspiratory, or localized wheezing; no supraclavicular, intercostal, or subcostal retraction; and a respiratory rate of 20 to 25. A score of 1 was given for end expiratory, partial inspiratory, or localized wheezing in < 2 of 4 lung fields; mild supraclavicular, intercostal, or subcostal retraction; and a respiratory rate of 26 to 35. A score of 2 was given for one-half expiratory, all inspiratory, or localized wheezing in < 3 of 4 lung fields; moderate supraclavicular, intercostal, or subcostal retraction; and a respiratory rate of 36 to 45. A score of 3 was given for three-quarters expiratory wheezing; marked supraclavicular, intercostal, or subcostal retraction; and a respiratory rate > 45. A score of 4 was given for all expiratory, inspiratory, or localized wheezing. The maximum total score equals 20 points.

Schuh et al., 1992[64]

Accessory muscle score and **wheezing score** were used. The accessory muscle score was assigned as follows: 0 = no indrawing, 1 = minimal intercostal indrawing, 2 = moderate indrawing with tracheosternal retractions, 3 = severe retractions with nasal flaring. The wheezing score was assigned as follows: 0 = no wheezing and well, 1 = end-expiratory wheeze only, 2 = wheezing during entire expiratory with or without inspiratory phase, 3 = inspiratory and expiratory wheezing audible without stethoscope.

Wang et al., 1992[65]

A **clinical score** assessed four signs, including respiratory rate, wheezing, retractions, and general condition. A score of 0 was given for respiratory rate < 30; no wheezing; no retractions; and normal general condition. A score of 1 was given for respiratory rate of 31 to 45; wheezing at terminal expiration or only with stethoscope; and intercostal retractions only. A score of 2 was given for respiratory rate of 46 to 60; wheezing at entire expiration or audible on expiration without stethoscope; and tracheosternal retractions. A score of 3 was given for respiratory rate > 60; wheezing at inspiration and expiration without stethoscope; severe retractions with nasal flaring; and general condition irritable, lethargic, and with poor feeding.

Evidence Table 6:

Berger, 1998[70]

The clinical scoring system included a **total score, accessory muscle score,** and **wheezing score.** The total score was on a scale of 0 to 9, while both the accessory muscle score and the wheezing score were on a scale of 0 to 3. A score of 0 was given for no retractions; no wheezing; and a respiratory rate/min < 40. A score of 1 was given for mild retractions; end expiratory wheezing; and a respiratory rate of 40 to 50. A score of 2 was given for moderate retractions; expiratory and inspiratory wheezing including tracheo-sternal; and a respiratory rate of 50 to 60. A score of 3 was given for severe retractions including nasal flaring; expiratory and inspiratory wheezing heard without a stethoscope or "silent chest"; and a respiratory rate/min > 60.

Daugbjerg et al., 1993[72]

Wheezing, use of accessory respiratory muscles, prolonged expiration and general condition were scored on a scale of 0 to 3. No further details are given regarding scoring system. A sum of **symptom score** is reported which represents the mean sum of scoring for wheezing, accessory respiratory muscle use, prolonged expiration and general condition from day 1 until discharge or day 5, whichever came first.

Goebel et al., 2000[66]

A **bronchiolitis score** was determined using a modification of the scoring system described by Tal et al.[112] A score was assigned for each of the following categories: respiratory rate/min, flaring or retractions, oxygen saturation (percentage in room air), and wheezing. The subscores for each of the categories were summed to create the bronchiolitis score. A subscore of 0 was given for respiratory rate/min of = 30; no flaring or retractions; oxygen saturation = 95 percent; and no wheezing. A subscore of 1 was given for respiratory rate/min 31-45; mild flaring or retractions; oxygen saturation 90 to 94 percent; and end-expiratory wheezing audible only by stethoscope. A subscore of 2 was given for respiratory rate/min 46 to 60; moderate flaring or retractions; oxygen saturation 85 to 89 percent; and full expiratory wheezing audible only by stethoscope. A subscore of 3 was given for respiratory rate/min > 60; severe flaring or retractions; oxygen saturation < 85 percent; and wheezing audible without stethoscope or markedly decreased air exchange on auscultation.

Klassen et al., 1997[69]

The **Respiratory Distress Assessment Instrument (RDAI)** is an ordinal scale from 0 to 17 that measures expiratory wheezing, inspiratory wheezing, location of wheeze, and supraclavicular, intercostal, and subcostal indrawing. Points were assigned as follows: expiratory wheezing(0 = none, 1 = end of expiratory phase, 2 = half of expiratory phase, 3 = three fourths of expiratory phase, 4 = all of expiratory phase); inspiratory wheezing (0 = none, 1 = part of inspiratory phase, 2 = all of inspiratory phase); location of wheeze (0 = none, 1 = fewer than two of four lung fields, 2 = fewer than three of four lung fields); and supraclavicular, intercostal, and subcostal indrawing (0 = none, 1 = mild, 2 = moderate, 3 = marked).

Schuh et al., 2002[23]

The **Respiratory Assessment Change Score (RACS)** assesses changes in the retractions and wheezing as measured by changes in the **Respiratory Disease Assessment Instrument (RDAI)** and change in respiratory rate. The RDAI assigns a maximum of 8 points for wheezing and 9 points for retractions and the scores vary depending on the location and severity of the wheezing and retractions. Changes in RDAI were determined by subtracting scores from later readings from scores of earlier reading. The overall RACS was calculated as the arithmetic sum of the RDAI change and of the standardized respiratory rate change. A decrease in RACS shows improvement; an increase shows deterioration.

Van Woensel et al., 1997[68]

A **symptom score** evaluated the following symptoms: respiratory rate, presence of wheezing, presence of cyanosis, and the use of accessory respiratory muscles. Each symptom was scored on an ordinal scale from 0 (normal or none) to 3 (severe). The symptom score ranged from 0 (no symptoms) to 12 (severe bronchiolitis). No other details were provided.

Van Woensel et al., 2000[67]

A **severity score** of acute infection of = 6 defined severe bronchiolitis. Other than defining the range of 0 to 12 for the severity score, no other details were provided.

Evidence Table 7:

De Boeck et al., 1997[48]

The **clinical score** devised by Tal et al.[113] was modified by substituting the assessment of cyanosis by the oxygen saturation measurement as follows: 0 = = 95 percent, 1 = 90 to 95 percent, 2 = < 90 percent, and 3 = < 85 percent. No further details were provided in this article.

Roosevelt et al., 1996[43]

A **clinical score** consists of individual scores for accessory muscle use and wheezing. For the **accessory muscle score** 0 = no intercostal indrawing, 1 = mild intercostal indrawing, 2 = moderate indrawing with tracheosternal retractions, and 3 = severe retractions with nasal flaring. For the **wheezing score**, 0 = no wheezing, 1 = end-expiratory wheezing only, 2 = wheezing during entire expiratory phase or inspiratory phase audible with stethoscope only, and 3 = inspiratory and expiratory wheezing audible without a stethoscope.

Evidence Table 8:

Cade et al., 2000[71]

The **clinical symptom score** assessed clinical severity from 0 to 11 based on heart rate, respiratory rate, supplemental oxygen requirements, and the presence or absence of chest wall retractions. No further details were provided.

Fox et al., 1999[73]

No scales.

Kajosaari et al., 2000[74]

No scales.

Reijonen, 1996[75]

No scales.

Richter et al., 1998[76]

Baseline clinical scores were assigned for respiratory rate, oxygen concentration required to keep the oxygen saturation above 92 percent, presence of wheeze, degree of recession, and the need for intravenous fluid or nasogastric tube feeding. The scoring system was adapted from Westley et al.[114] No additional details were provided.

Daytime and nighttime cough and wheeze were each scored on a scale of 0 to 3 based on severity. No additional details were provided.

Wong et al., 2000[77]

Cough, wheeze and **general well-being** were scored from 0 to 3 (0 = none, 1 = mild, 2 = troublesome, 3 = severe.) No additional details were provided.

Evidence Table 9:

Barry et al., 1986[46]

Eight clinical variables were recorded, including **cough, nasal discharge, feeding, nasal flare, wheeze, chest recession, rhonchi,** and **crepitations**. All variables were scored on a 3-point scale according to severity, except for feeding (which was recorded as normal, slow, tube fed, or parenteral). No further details were provided.

Everard et al., 2001[78]

A **daily severity score** was assessed. The score ranged from 1 to 10 with 1 representing no symptoms and 10 being a ventilated patient. No further details were provided.

Guerguerian et al., 1999[79]

No scales.

Janai et al., 1993[80]

No scales.

Rodriguez, 1987[42]

A **severity of illness score** was determined daily for each patient. The scale ranged from 0 (normal) to 4+ (most severe) and was assigned by a single investigator for all patients. The specific values were determined using an analogue scale similar to one developed by Hall et al.

Rodriguez et al., 1999[81]

A blinded observer assigned a **severity rating value** ranging from 0 (normal) to 4+ (most severe). No additional details were given.

Taber et al., 1983[45]

A **severity of illness score** was made daily for each patient based on written responses to questionnaires. The scale ranged from 0 (normal) to 3+ (most severe illness). No further details were provided.

Evidence Table 10:

Friis et al., 1984[49]

No scales.

Klein M Max 1995[82]

No scales.

Evidence Table 11:

Rodriguez et al., 1997[25]

A **respiratory score** was used as inclusion criteria and for stratified analyses in this study; it is defined as the sum of the component scores for respiratory rate, oxygen saturation, and physical findings divided by 3. A respiratory component score of 0 was given for well or baseline clinical condition; respiratory rate/min no value stated; oxygen saturation-none; adventitial (wheezing, rales)-none; and retractions-none. A respiratory component score of 1 was given for upper respiratory infection (URI) mild clinical condition; respiratory rate/min < 45; oxygen saturation = 95 percent; adventitial (wheezing, rales)-none; and retractions-none. A respiratory component score of 2 was given for lower respiratory infection (LRI) clinical condition; respiratory rate/min of 45 to 59; oxygen saturation 91 to 94 percent; adventitial (wheezing, rales)-mild; and retractions-intercostal. A respiratory component score of 3 was given for moderate LRI clinical condition; respiratory rate/min of 60 to 74; oxygen saturation of 86 to 90 percent; adventitial (wheezing, rales)-moderate; and retractions-intercostal and subcostal. A respiratory component score of 4 was given for severe LRI clinical condition; respiratory rate/min of 75+; oxygen saturation = 85 percent; adventitial (wheezing, rales)-severe; and retractions-intercostal and subcostal with seesaw chest motion. A respiratory component score of 5 was given for respiratory failure clinical condition; respiratory rate/min-mechanical ventilation; oxygen saturation-mechanical ventilation; adventitial (wheezing, rales)-mechanical ventilation; and retractions-mechanical ventilation.

The **physical finding LRI component score** consists of the wheezing, rales, and retractions score divided by 2. For wheezing: 0 = no wheezing and an inhalation to exhalation (I:E) ratio normal, 1 = intermittent wheezing with I:E ratio normal, 2 = wheezing present throughout and I:E ratio 1:1, 3 = wheezing throughout with I:E ratio 1:2, 4 = wheezing audible without stethoscope. For rales: 0 = clear, 1 = inspiratory only and disappears with coughing, 2 = inspiratory not cleared with coughing, 3 = inspiratory and expiratory and don't clear with coughing.

The **LRI score** was based on an experienced clinician's assessment of patients. For LRI score 0 = no respiratory disease, 1 = upper respiratory tract infection/disease, 2 = mild LRI/disease, 3 = moderate LRI/disease, 4 = severe LRI/disease, and 5 = respiratory failure.

The **analog scale** is a visual disease severity scoring system measuring incremental clinical improvement based on a continuous line representing the total spectrum of illness severity. The left-most position of the line represented normal or baseline, while the right-most position represented the most severe. A blind assignment of numbers from 0 to 15 was done by a statistician at the end of the study.

Rodriguez et al., 1997[41]

A **respiratory score** was used as inclusion criteria and for stratified analyses in this study. The respiratory score consists of relevant measures of RSV severity, and is defined as the sum of the component scores for respiratory rate, oxygen saturation, and physical findings (adventitial sounds and retractions) divided by 3. The respiratory score ranged from 0 to 5. A clinically significant change was defined as a reduction of illness from moderate or more severe LRI (= 2.5) to mild or no LRI (= 1.6). A respiratory component score of 0 was given for well or baseline clinical condition; respiratory rate/min no value stated; oxygen saturation-none; adventitial (wheezing, rales)-none; and retractions-none. A respiratory component score of 1 was given for URI mild clinical condition; respiratory rate/min < 45; oxygen saturation = 95 percent;

adventitial (wheezing, rales)-none; and retractions-none. A respiratory component score of 2 was given for LRI clinical condition; respiratory rate/min of 45 to 59; oxygen saturation 91 to 94 percent; adventitial (wheezing, rales)-mild; and retractions-intercostal. A respiratory component score of 3 was given for moderate LRI clinical condition; respiratory rate/min of 60 to 74; oxygen saturation 86 to 90 percent; adventitial (wheezing, rales)-moderate; and retractions-intercostal and subcostal. A respiratory component score of 4 was given for severe LRI clinical condition; respiratory rate/min 75+; oxygen saturation = 85 percent; adventitial (wheezing, rales)-severe; and retractions-intercostal and subcostal with seesaw chest motion. A respiratory component score of 5 was given for respiratory failure clinical condition; respiratory rate/min-mechanical ventilation; oxygen saturation-mechanical ventilation; adventitial (wheezing, rales)-mechanical ventilation; and retractions-mechanical ventilation.

The **physical finding LRI component score** consists of the wheezing, rales, and retractions score divided by 2. For wheezing: 0 = no wheezing and an I:E ratio normal, 1 = intermittent wheezing with I:E ratio normal, 2 = wheezing present throughout and I:E ratio 1:1, 3 = wheezing throughout with I:E ratio 1:2, 4 = wheezing audible without stethoscope. For rales: 0 = clear, 1 = inspiratory only and disappears with coughing, 2 = inspiratory not cleared with coughing, 3 = inspiratory and expiratory and don't clear with coughing.

The **LRI score** was based on an experienced clinician's assessment of patients. For LRI score 0 = no respiratory disease, 1 = upper respiratory tract infection/disease, 2 = mild LRI/disease, 3 = moderate LRI/disease, 4 = severe LRI/disease, and 5 = respiratory failure.

The **analog scale** is a visual disease severity scoring system measuring incremental clinical improvement based on a continuous line representing the total spectrum of illness severity. The left-most position of the line represented no illness, while the right-most position represented the most severe life-threatening illness.

Evidence Table 12:

Chipps et al., 1993[47]

The daily evaluation included a **total symptom score,** a **wheezing score,** a **muscle retraction score,** and an **accessory muscle use score.** Each of the scores for wheezing, muscle retractions, and accessory muscle use were assigned from 0 (absent) to three (severe). The same investigator did scoring for each patient. The total symptom score represents the sum of the wheezing, muscle retractions, and accessory muscle use scores.

Hollman et al., 1998[84]

A **clinical asthma score** was used to assess level of respiratory distress. This scoring system was originally developed by Wood et al.,[115] and was modified slightly for this study. Four scores ranging from 0 to 2 were assigned for each of the following categories: cyanosis (SpO_2), inspiratory breath sounds, accessory muscles used, expiratory wheezing, and cerebral function. The scores were assigned as follows: cyanosis (SpO_2) 0 = none, 1 = in room air (<94% SpO_2),
2 = in 0.40 FI O_2 (<94% SpO_2); inspiratory breath sounds 0 = normal, 1 = unequal, 2 = decreased/absent; accessory muscles used 0 = none, 0.5 = mild, 1 = moderate, 2 = maximal; expiratory wheezing 0 = none, 0.5 = mild, 1 = moderate, 2 = marked; cerebral function 0 = normal, 1 = depressed/agitated, 2 = coma.

Kong et al., 1993[51]

Used a **modified severity score** referenced to Bruhn, et al.[116] No further details were given in the article except to say that the categories included mild, moderate, and severe disease.

Luchetti et al., 1998[39]

No scales.

Van Bever et al., 1995[85]

Used **clinical scoring system** of Tal, et al.[112] The clinical scoring system assesses the infant's respiratory rate, wheezing, cyanosis, and accessory muscle use. Each of these four components is rated on a scale of 0 to 3. A value of 0 was assigned for respiratory rate < 30; no wheezing; no cyanosis; and no accessory muscle use. A value of 1 was assigned for respiratory rate of 31 to 45; wheezing at terminal expiration with stethoscope only; circumoral cyanosis on crying only; and with or without accessory muscle use. A value of 2 was assigned for respiratory rate of 46 to 60; wheezing during entire expiration and inspiration with stethoscope only; circumoral cyanosis at rest; and ++ accessory muscle use. A value of 3 was assigned for respiratory rate > 60; wheezing during entire expiration and inspiration without stethoscope; generalized cyanosis at rest; and ++++ accessory muscle use.

Nasr et al., 2001[40]

The **clinical assessment scoring** in this study was described by Wang et al.[111] One point was given for respiratory rate of 31 to 45/minute; wheezing at terminal expiration or only with stethoscope; intercostal retraction; and normal general condition. Two points were given for respiratory rate of 45 to 60/minute; wheezing during the entire expiration or audible on expiration without stethoscope; tracheosternal retractions; and stable general condition. Three points were given for respiratory rate > 60/minute; inspiratory and expiratory wheezing without stethoscope; severe retraction with nasal flaring; and general condition including irritability, lethargy, and poor feedings. No further information was given regarding this scoring system, but the summary of results table showed respiratory rate score, wheezing score, and retraction score.

The **Chest X-Ray scoring system** in this study was developed based on review of the literature and the experience of radiologists. Each chest x-ray was graded for perihilar markings, hyperinflation, atelectasis or focal opacities, and general opacities, and each of these categories was graded on a 0 to 3 point scale with 0 being normal and 3 being markedly abnormal. A score of 0 was given for normal perihilar markings; normal hyperinflation on lateral view; hyperinflation = 15 on anteroposterior view; normal atelectasis/focal opacities; and no generalized opacity. A score of 1 was given for subtle increase in perihilar markings; hyperinflation characterized by mild flattening of diaphragm on lateral view; hyperinflation 16 on anteroposterior view; atelectasis/focal opacities characterized by a single area of segmental/subsegmental opacity; and generalized opacity characterized by mild parahilar haze. A score of 2 was given for definite increase in perihilar markings; hyperinflation characterized by completely flat diaphragm on lateral view; hyperinflation 17 on anteroposterior view; atelectasis/focal opacities characterized by two segments/subsegments; and generalized opacity characterized by bilateral symmetric ground-glass opacity. A score of 3 was given for perihilar markings characterized by course, irregular peripheral marking; hyperinflation characterized by

inverted diaphragm on lateral view; hyperinflation = 18 on anteroposterior view; atelectasis/focal opacities characterized by three segments/subsegments; and generalized opacity characterized by bilateral diffuse airspace disease. Hyperinflation was scored separately on the anteroposterior chest x-ray and on the lateral chest x-ray and the two scores were averaged. Only the anteroposterior chest x-ray score was used if the lateral chest x-ray was not available. Each of the other three findings was given a single score and the scores for each exam finding were summed to give an overall examination score. The final score ranged from 0 if all findings were normal to 12 if all findings were markedly abnormal.

Evidence Table 13:

Groothuis et al., 1993[87]

The **respiratory scoring system** was used to describe disease severity and was based on changes from baseline in respiratory rate, oxygen saturation, and pulmonary findings including retractions, wheezing, and crackles. For each of these three variables, a score from 0 to 5 was determined by the degree of difference between the observed measurement and the baseline measurement for the child. An **overall respiratory score** ranging from 0 to 5 was determined to be the mode of the three component scores or the mean, if there was no mode. For oxygen saturation: 0 = baseline value (no upper respiratory tract infection [URTI]), 1 = baseline value (URTI), 2 = decrease < 5 percent, 3 = decrease 5 to 10 percent, 4 = decrease > 10 percent, and 5 = assisted ventilation. For respiratory rate: 0 = baseline value (no URTI), 1 = baseline value (URTI), 2 = increase 1 to 14/min, 3 = increase 15 to 30/min, 4 = increase > 30/min, and 5 = assisted ventilation. For retractions, wheezing, crackles: 0 = no change (no URTI), 1 = minimal, 2 = mild, 3 = moderate, 4 = severe, and 5 = assisted ventilation. For respiratory score: 0 = baseline value (well), 1 = URTI, 2 = mild LRTI, 3 = moderate LRTI, 4 = severe LRTI, and 5 = assisted ventilation.

Groothuis et al., 1995[86]

The **respiratory scoring system** was used to describe disease severity and was based on changes from baseline in respiratory rate, oxygen saturation, and pulmonary findings including retractions, wheezing, and crackles. The score for each of the three components was determined by the difference between the observed measurement and a baseline measurement taken at the most recent monthly clinic visit. The **overall respiratory score** was the mode (or mean if no mode) of the three scores and ranged from 0 being well or baseline to 5 representing respiratory failure. A respiratory score of 1 defined an upper respiratory tract infection, = 2 defined a lower respiratory tract infection, and = 3 defined a moderate to severe lower respiratory tract infection (LRTI).

Simoes et al., 1998[88]

Cardiac disease severity score based on a scale from 0-6 on the basis of cyanosis (room air saturation, 0 = > 85 percent, 1 = = 85 percent), left-to-right shunt (0 = absent, 1 = present), pulmonary hypertension (0 = none, 1 = ½ -2/3 systemic pressures, 2 = >2/3 systemic pressure), and congestive heart failure (0 = none, 1 = controlled with medications, 2 = uncontrolled.)

Respiratory scores mentioned but no details provided about determination of score.

LRI scores mentioned but no details provided about determination of score.

The PREVENT Study Group, 1997[89]

The **LRI score** was based on an experienced clinician's assessment of patients' respiratory status. For LRI score 0 = no respiratory illness/infection, 1 = upper respiratory tract illness/infection, 2 = mild LRI, 3 = moderate LRI, 4 = severe LRI, and 5 = mechanical ventilation.

Groothuis, 2001[90]

No scales.

Evidence Table 14:

The Impact-RSV Study Group, 1998[91]

The **Lower Respiratory Tract Illness/Infection (LRI) Score** was used as follows: 0 = no respiratory illness/infection, 1 = upper respiratory tract illness/infection, 2 = mild LRI, 3 = moderate LRI, 4 = severe LRI, 5 = mechanical ventilation.

Meissner et al., 1999[92]

No scales.

Evidence Table 15:

Groothuis et al., 1998[93]

A **respiratory score** was used to rate the severity of RSV respiratory disease using a scale of 1 to 5 as follows: 1 = upper respiratory tract infection, 2 = mild lower respiratory tract infection, 3 = moderate lower respiratory infection, 4 = serious lower respiratory infection, and 5 = lower respiratory infection requiring assisted ventilation.

Piedra et al., 1996[94]

A **modified Shwachman clinical score** representing a respiratory/nutritional score developed for CF children was performed to assess the severity of clinical disease and ranged from 75 = best to 4 = worst. No further details given.

The **Brasfield scoring system** was utilized to quantitate radiographic disease and ranged from 25 = best to 4 = worst. No further details given.

A **respiratory assessment score** was used to distinguish between an acute upper respiratory tract illness (AURTI) and an acute lower respiratory tract illness (ALRTI). An AURTI was assigned if the child had one or more of the following signs: sneeze, coryza (rhinorrhea, nasal congestion, or nasal crusting) and/or pharyngitis (hyperemic pharynx or exudative pharynx). An ALRTI was assigned if one of more of the following signs was present: wheeze or rales on auscultation of the lungs, shortness of breath on exam, respiratory rate > 15 breaths/min above the child's baseline at enrollment, increase in sputum production or a change in the quality of the sputum (from clear to turbid yellow or green), or increase in coughing episodes.

Piedra et al., 1998[95]

A **modified Shwachman clinical score** representing a respiratory/nutritional score developed for CF children was performed to assess the severity of clinical disease and ranged from 75 = best to 4 = worst. No further details given.

The **Brasfield scoring system** was utilized to quantitate radiographic disease and ranged from 25 = best to 4 = worst. No further details given.

A **respiratory assessment score** was used to distinguish between an acute upper respiratory tract illness (AURTI) and an acute lower respiratory tract illness (ALRTI). An AURTI was assigned if the child had one or more of the following signs: sneeze, coryza (rhinorrhea, nasal congestion, or nasal crusting) and/or pharyngitis (hyperemic pharynx or exudative pharynx). An ALRTI was assigned if one of more of the following signs was present: wheeze or rales on auscultation of the lungs, shortness of breath on exam, respiratory rate > 15 breaths/min above the child's baseline at enrollment, increase in sputum production or a change in the quality of the sputum (from clear to turbid yellow or green), or increase in coughing episodes. (Referenced to previous article Piedra, et al., 1996 in text).

Appendix B

Appendix B. Abstract Review Form

Bronchiolitis in Infants and Children

Article Author: _____
Journal: _____
Year of Article: _____
Abstractor Initials: ___ ___ ___

1. Includes children birth to 5.	Yes	No	Cannot Determine
2. Addresses one or more of the following. (Check all that apply.) ____ Diagnosis (KQ1) ____ Treatment (KQ2) ____ Prophylaxis (KQ3) ____ Cost Effectiveness Analysis (KQ4) If any KQ is checked, check "Yes" in box.	Yes	No	Cannot Determine
3. Original research design. (Exclude editorials, commentaries, letters to editor, reviews, etc.)	Yes	No	Cannot Determine
4. Study N is greater than or equal to 10 subjects.	Yes	No	Cannot Determine
5. Study conducted in North America, United Kingdom, Australia/New Zealand and/or Europe.	Yes	No	Cannot Determine
6. Study published between 1980 and 2001.	Yes	No	Cannot Determine
7. If KQ1 (diagnosis): ____ RCT study design used ____ Prospective cohort If either is checked, check "Yes" in box.	Yes	No	Cannot Determine
8. If KQ2 or KQ3 (treatment and/or prophylaxis): RCT study design used.	Yes	No	Cannot Determine
9. Published in English. If non-English specify language: _____ Applies to key question # _____	Yes	No	Cannot Determine

_____ CHECK HERE IF ARTICLE TO BE PULLED FOR BACKGROUND.

IF ANY ITEM IS IN GRAY BOX THE ARTICLE IS EXCLUDED.

IF ITEMS 7, 8 OR 9 MARKED "NO," ARTICLE MAY BE EXCLUDED IN FUTURE.

IF CANNOT DETERMINE, ARTICLE WILL BE PULLED FOR REVIEW.

Appendix C

Appendix C. Final Abstraction Forms

SECTION 1: ABSTRACTION IDENTIFIERS

1. Abstractor name:
2. Date of abstraction:
3. Name of second abtractor/reviewer:
4. Date of review:

SECTION 2: ARTICLE IDENTIFIERS

5. Year published:
6. Surname of first author:
7. Title:
8. Journal:

SECTION 3a: SCREENING FOR INCLUSION

If any response to Questions 9–13 below is "No", STOP, and forward this article to the Research Coordinator

	Yes	No
9. Patients are infants and children (< 5 years)	?	?
10. N=10 or more (i.e., sum of treatment and control=10)	?	?
11. Original data (not a systematic review or meta-analysis)	?	?
12. Treatment of bronchiolitis **or** prophylaxis for bronchiolitis in infants and children	?	?
13. Is the study an RCT?	?	?

SECTION 3b: SCREENING FOR COSTS

14. Are the costs of managing bronchiolitis explicitly discussed?	?	?

SECTION 4: HEALTH AND GEOGRAPHIC SETTINGS

	Yes	No
15. Multi-center study	?	?
16. If "yes", list the centers in which study was conducted		

17. Setting at recruitment:	Yes
Inpatient	?
Outpatient	?
Emergency Department	?
ICU	?
Other (specify)	?
Not reported	?

18. If additional followups were conducted **outside the original setting** please specify:
    (a) the interval at which followup was conducted (i.e., 5 days, 6 months, etc)
    (b) the setting at followup(s)

19. Where was study conducted? (List all countries)

SECTION 5: FUNDING SOURCE

	Yes
20. Industry	?
21. Government	?
22. Professional society	?
23. Hospital/Managed Care Organization	?
24. Foundation/Charity	?
25. Consumer/Patient Organization	?
26. Not specified	?
27. Other (specify)	?

SECTION 6: OBJECTIVE OF THE ARTICLE

28. Page no.:
29. Paragraph no.:
30. Quote:

SECTION 7a: MASKING

31. Masking as defined by authors:	***Yes***
Single blinding	?
Double blinding	?
Triple blinding	?
Other (please specify)	?
Cannot determine	?

SECTION 7b: DESIGN

	Yes	**No**
32. Is it placebo-controlled?	?	?
33. Is it a cross-over design?	?	?

SECTION 8: STUDY SIZE

	Number	**Cannot determine**
34. Number screened:		?
35. Number eligible:		?
36. Number randomized:		?
37. Study size and number of dropouts for primary outcome. List number of and reasons for withdrawals and/or losses to followup		?

SECTION 9: INCLUSION/EXCLUSION CRITERIA

38. List all inclusion criteria for the study
39. List all exclusion criteria for the study

SECTION 10: CLINICAL SCALES/COMPOSITE SCORES

	Yes	No
40. Were any diagnostic clinical scales or composite scores used **as criteria for entry into the study?**	?	?
41. If “yes”, name of scale(s) and briefly describe:		
42. If “yes”, is the scale referenced?	?	?
43. Please provide full reference for scale(s):		
44. Any scales used otherwise in the study?	?	?
45. If "yes", note name of scale(s), reference, and briefly describe:		

SECTION 11: DEMOGRAPHIC CHARACTERISTICS OF PATIENT

Record numbers as presented in article, in the order of treatment presented in the tables in the article. If data are not recorded in the article, write NR. If reporting measure of precision/variation, then write in left-hand column.

Demographic characteristics	NR	Report sig. tests as written (note if NR)	Group 1	Group 2	Group 3	Group 4	Overall
46. Defining characteristic of each group (Placebo/name(s) of intervention)							
47. Number of patients at randomization	?						
48. Age at enrollment (specify days/weeks/months/years):							
Minimum age	?						
Maximum age	?						
Mean/median (specify)	?						
49. Estimated gestational age (specify days/weeks/months):							
Minimum age	?						
Maximum age	?						
Mean/median (specify)	?						

SECTION 11: DEMOGRAPHIC CHARACTERISTICS OF PATIENT (continued)

Record numbers as presented in article, in the order of treatment presented in the tables in the article. If data are not recorded in the article, write NR. If reporting measure of precision/variation, then write in left-hand column.

Demographic characteristics	NR	Report sig. tests as written (note if NR)	Group 1	Group 2	Group 3	Group 4	Overall
50. Number of male patients	?						
51. Number of female patients	?						
52. Birthweight (specify unit of measurement)	?						
53. Exposure to maternal smoking during pregnancy	?						
54. Exposure to smoking at home at the time of recruitment	?						

SECTION 11: DEMOGRAPHIC CHARACTERISTICS OF PATIENT (continued)

Record numbers as presented in article, in the order of treatment presented in the tables in the article. If data are not recorded in the article, write NR. If reporting measure of precision/variation, then write in left-hand column.

Demographic characteristics	NR	Report sig. tests as written (note if NR)	Group 1	Group 2	Group 3	Group 4	Overall
55. Race:	?						
White	?						
Hispanic	?						
African-American	?						
Asian	?						
Native American	?						
Other (please specify)	?						
56. Breastfeeding (as defined in study)	?						
Definition of breastfeeding used in study							

SECTION 12: BASELINE AND DIAGNOSTIC CHARACTERISTICS

Record numbers as presented in article, in the order of treatment presented in the tables in the article. If data are not recorded in the article, check NR. If Exclusion Criteria or Not Applicable, write it across the row. If reporting measure of precision/variation, then write in left-hand column.

Diagnostic criteria	NR	Check if used for diag-nosis	Report sig. tests as written (note if NR)	Group 1	Group 2	Group 3	Group 4	Overall
57. General appearance (e.g. toxic, moderately ill, well)	?	?						
58. Behavior/ alertness/ cerebral function	?	?						
59. Fever/temperature	?	?						

SECTION 12: BASELINE AND DIAGNOSTIC CHARACTERISTICS (continued)

Record numbers as presented in article, in the order of treatment presented in the tables in the article. If data are not recorded in the article, check NR. If Exclusion Criteria or Not Applicable, write it across the row. If reporting measure of precision/variation, then write in left-hand column.

Diagnostic criteria	NR	Check if used for diag-nosis	Report sig. tests as written (note if NR)	Group 1	Group 2	Group 3	Group 4	Overall
60. Respiratory rate/ Tachypnea/ hyperventilation	?	?						
61. Intercostal retractions/ recessions/ grunting/ nasal flaring/ accessory muscle use/ increased respiratory effort	?	?						
62. Nasal discharge/ rhinorrhea/ rhinitis	?	?						

SECTION 12: BASELINE AND DIAGNOSTIC CHARACTERISTICS (continued)

Record numbers as presented in article, in the order of treatment presented in the tables in the article. If data are not recorded in the article, check NR. If Exclusion Criteria or Not Applicable, write it across the row. If reporting measure of precision/variation, then write in left-hand column.

Diagnostic criteria	NR	Check if used for diagnosis	Report sig. tests as written (note if NR)	Group 1	Group 2	Group 3	Group 4	Overall
63. Wheezing	?	?						
64. Pulse oximetry/ O_2 saturation	?	?						
65. Arterial blood gas	?	?						
66. Cyanosis	?	?						

SECTION 12: BASELINE AND DIAGNOSTIC CHARACTERISTICS (continued)

Record numbers as presented in article, in the order of treatment presented in the tables in the article. If data are not recorded in the article, check NR. If Exclusion Criteria or Not Applicable, write it across the row. If reporting measure of precision/variation, then write in left-hand column.

Diagnostic criteria	NR	Check if used for diag-nosis	Report sig. tests as written (note if NR)	Group 1	Group 2	Group 3	Group 4	Overall
67. Rhonchi	?	?						
68. Rales/ Crackles/ Adventitial breathing/ Crepitations	?	?						
69. Oxygen requirement	?	?						

SECTION 12: BASELINE AND DIAGNOSTIC CHARACTERISTICS (continued)

Record numbers as presented in article, in the order of treatment presented in the tables in the article. If data are not recorded in the article, check NR. If Exclusion Criteria or Not Applicable, write it across the row. If reporting measure of precision/variation, then write in left-hand column.

Diagnostic criteria	NR	Check if used for diag-nosis	Report sig. tests as written (note if NR)	Group 1	Group 2	Group 3	Group 4	Overall
70. Clinical Scales	?	?						
71. Other (please describe below, e.g., poor feeding)								

SECTION 12: BASELINE AND DIAGNOSTIC CHARACTERISTICS (continued)

Record numbers as presented in article, in the order of treatment presented in the tables in the article. Provide denominator where available. If data are not recorded in the article, check NR. If Exclusion Criteria or Not Applicable, write it across the row. If there are no patients in the category for reasons other than exclusion, write 0. If reporting measure of precision/variation, then write in left-hand column.

TREATMENT GROUP	NR	Report sig. tests as written (note if NR)	Group 1	Group 2	Group 3	Group 4	Overall
72. Presence of comorbidities:							
Chronic lung disease	?						
Congenital heart disease	?						
Previous history of wheezing/ Lower Respiratory Infection	?						
Asthma	?						
Atopy/ allergies of the subject	?						
Oncologic/ leukemia/ cancer/ brain tumor	?						
Other (please describe)	?						

SECTION 12: BASELINE AND DIAGNOSTIC CHARACTERISTICS (continued)

Record numbers as presented in article, in the order of treatment presented in the tables in the article. Provide denominator where available. If data are not recorded in the article, check NR. If Exclusion Criteria or Not Applicable, write it across the row. If there are no patients in the category for reasons other than exclusion, write 0. If reporting measure of precision/variation, then write in left-hand column.

TREATMENT GROUP	NR	Report sig. tests as written (note if NR)	Group 1	Group 2	Group 3	Group 4	Overall
73. Presence of RSV	?						
74. Family history of wheezing/ atopy	?						
75. Patients on ventilators	?						
76. Other ventilatory support (please describe below):	?						

SECTION 12: BASELINE AND DIAGNOSTIC CHARACTERISTICS (continued)

Record numbers as presented in article, in the order of treatment presented in the tables in the article. Provide denominator where available. If data are not recorded in the article, check NR. If Exclusion Criteria or Not Applicable, write it across the row. If there are no patients in the category for reasons other than exclusion, write 0. If reporting measure of precision/variation, then write in left-hand column.

TREATMENT GROUP	NR	Report sig. tests as written (note if NR)	Group 1	Group 2	Group 3	Group 4	Overall
77. Other clinical differences (please specify)	?						

SECTION 13: FURTHER TESTS

Record numbers as presented in article, in the order of treatment presented in the tables in the article. If data are not recorded in the article, check NR. If reporting measure of precision/variation, then write in left-hand column.

Tests	NR	Report sig. tests as written (note if NR)	Group 1	Group 2	Group 3	Group 4	Overall
78. CXR	?						
79. If "yes" for CXR, were any specific criteria used? (e.g., hyperinflation / peribronchial thickening / infiltrates / atelectasis)							
80. Complete Blood Counts (CBCs)	?						
81. Blood cultures	?						

SECTION 13: FURTHER TESTS (continued)

Record numbers as presented in article, in the order of treatment presented in the tables in the article. If data are not recorded in the article, check NR. If reporting measure of precision/variation, then write in left-hand column.

							Yes	No
82. Viral studies:							?	?
Type of viral study	**NR**	**Report sig. tests as written (note if NR)**	**Group 1**	**Group 2**	**Group 3**	**Group 4**	**Overall**	
RSV detection (e.g., IFA, DFA, ELISA)	?							
RSV cultures	?							
Other virus detection, specify below (e.g., parainfluenza, influenza, adenovirus, etc)	?							

SECTION 13: FURTHER TESTS (continued)

Record numbers as presented in article, in the order of treatment presented in the tables in the article. If data are not recorded in the article, check NR. If reporting measure of precision/variation, then write in left-hand column.

Tests	NR	Report sig. tests as written (note if NR)	Group 1	Group 2	Group 3	Group 4	Overall
83. Pulmonary function tests (PFTs, Lung Volumes, e.g., FEV, FVC)	?						

SECTION 13: FURTHER TESTS (continued)

Record numbers as presented in article, in the order of treatment presented in the tables in the article. If data are not recorded in the article, check NR. If reporting measure of precision/variation, then write in left-hand column.

Tests	NR	Report sig. tests as written (note if NR)	Group 1	Group 2	Group 3	Group 4	Overall
84. Immunologic studies:							
Eosinophilis	?						
Immunoglobulin levels	?						
Erythrocyte sedimentation rate	?						
C-reactive protein	?						
Other immunologic studies	?						

SECTION 13: FURTHER TESTS (continued)

Record numbers as presented in article, in the order of treatment presented in the tables in the article. If data are not recorded in the article, check NR. If reporting measure of precision/variation, then write in left-hand column.

Tests	NR	Report sig. Tests as written (note if NR)	Group 1	Group 2	Group 3	Group 4	Overall
85. Other tests (please specify below)	?						

SECTION 14: TREATMENT

TREATMENT GROUP	Group 1	Group 2	Group 3	Group 4
86. Frequency, dose, route, duration and other notes on treatment				

SECTION 14: TREATMENT (continued)

	Yes	No
87. Were other standard treatments given as needed?	?	?
88. Specify type of treatment below		
89. Were all other treatments the same for each treatment group? If not, please specify below. (If patients received usual care at discretion of physician do not report).	?	?

SECTION 15: OUTCOMES OF TREATMENT/PROPHYLAXIS

Where possible, please fill out table below. Be sure to specify: (1) whether change or absolute value (2) unit of measurement (3) Table no. in the article. NR = not reported. N = sample size. If you are not able to fill out the table, you MUST provide reference to the Table numbers in the article.

Outcomes	NR	Time period	Report sig. tests as written (note if NR)	Group 1 N=	Group 2 N=	Group 3 N=	Group 4 N=
90. Clinical scores Specify Score: Specify measure, e.g., change in score	?						

SECTION 15: OUTCOMES OF TREATMENT/PROPHYLAXIS (continued)

Where possible, please fill out table below. Be sure to specify: (1) whether change or absolute value (2) unit of measurement (3) Table no. in the article. NR = not reported. N = sample size. If you are not able to fill out the table, you MUST provide reference to the Table numbers in the article.

Outcomes	NR	Time period	Report sig. tests as written (note if NR)	Group 1 N=	Group 2 N=	Group 3 N=	Group 4 N=
91. Respiratory rate/ Tachypnea/ hyper-ventilation	?						
92. Intercostal retractions/ recessions/ grunting/ nasal flaring/ accessory muscle use/ increased respiratory effort	?						

SECTION 15: OUTCOMES OF TREATMENT/PROPHYLAXIS (continued)

Where possible, please fill out table below. Be sure to specify: (1) whether change or absolute value (2) unit of measurement (3) Table no. in the article. NR = not reported. N = sample size. If you are not able to fill out the table, you MUST provide reference to the Table numbers in the article.

Outcomes	NR	Time period	Report sig. tests as written (note if NR)	Group 1 N=	Group 2 N=	Group 3 N=	Group 4 N=
93. Wheezing	?						
94. Pulse oximetry/ O_2 saturation	?						
95. Pulmonary Function Tests	?						

SECTION 15: OUTCOMES OF TREATMENT/PROPHYLAXIS (continued)

Where possible, please fill out table below. Be sure to specify: (1) whether change or absolute value (2) unit of measurement (3) Table no. in the article. NR = not reported. N = sample size. If you are not able to fill out the table, you MUST provide reference to the Table numbers in the article.

Outcomes	NR	Time period	Report sig. tests as written (note if NR)	Group 1 N=	Group 2 N=	Group 3 N=	Group 4 N=
96. Oxygen treatment? Length of treatment Mean O_2 concentration Other	?						

SECTION 15: OUTCOMES OF TREATMENT/PROPHYLAXIS (continued)

Where possible, please fill out table below. Be sure to specify: (1) whether change or absolute value (2) unit of measurement (3) Table no. in the article. NR = not reported. N = sample size. If you are not able to fill out the table, you MUST provide reference to the Table numbers in the article.

Outcomes	NR	Time period	Report sig. tests as written (note if NR)	Group 1 N=	Group 2 N=	Group 3 N=	Group 4 N=
97. Bronchodilator use? Type of bronchodilator Length of treatment Other	?						

SECTION 15: OUTCOMES OF TREATMENT/PROPHYLAXIS (continued)

Where possible, please fill out table below. Be sure to specify: (1) whether change or absolute value (2) unit of measurement (3) Table no. in the article. NR = not reported. N = sample size. If you are not able to fill out the table, you MUST provide reference to the Table numbers in the article.

Outcomes	NR	Time period	Report sig. tests as written (note if NR)	Group 1 N=	Group 2 N=	Group 3 N=	Group 4 N=
98. Ribavirin use	?						
99. Steroid use? Type of steroid Length of treatment Other	?						

SECTION 15: OUTCOMES OF TREATMENT/PROPHYLAXIS (continued)

Where possible, please fill out table below. Be sure to specify: (1) whether change or absolute value (2) unit of measurement (3) Table no. in the article. NR = not reported. N = sample size. If you are not able to fill out the table, you MUST provide reference to the Table numbers in the article.

Outcomes	NR	Time period	Report sig. tests as written (note if NR)	Group 1 N=	Group 2 N=	Group 3 N=	Group 4 N=
100. Antibiotic use? Type of antibiotic Length of treatment Other	?						

SECTION 15: OUTCOMES OF TREATMENT/PROPHYLAXIS (continued)

Where possible, please fill out table below. Be sure to specify: (1) whether change or absolute value (2) unit of measurement (3) Table no. in the article. NR = not reported. N = sample size. If you are not able to fill out the table, you MUST provide reference to the Table numbers in the article.

Outcomes	NR	Time period	Report sig. tests as written (note if NR)	Group 1 N=	Group 2 N=	Group 3 N=	Group 4 N=
101. Hospitalization Decision to admit Duration of stay (specify hrs, days, etc) Readmission	?						

SECTION 15: OUTCOMES OF TREATMENT/PROPHYLAXIS (continued)

Where possible, please fill out table below. Be sure to specify: (1) whether change or absolute value (2) unit of measurement (3) Table no. in the article. NR = not reported. N = sample size. If you are not able to fill out the table, you MUST provide reference to the Table numbers in the article.

Outcomes	NR	Time period	Report sig. tests as written (note if NR)	Group 1 N=	Group 2 N=	Group 3 N=	Group 4 N=
102. Visits to MD/other health professional	?						
103. Repeat wheezing illness/ asthma	?						
104. If "yes" for repeat wheezing, length of wheezing	?						

SECTION 15: OUTCOMES OF TREATMENT/PROPHYLAXIS (continued)

Where possible, please fill out table below. Be sure to specify: (1) whether change or absolute value (2) unit of measurement (3) Table no. in the article. NR = not reported. N = sample size. If you are not able to fill out the table, you MUST provide reference to the Table numbers in the article.

Outcomes	NR	Time period	Report sig. tests as written (note if NR)	Group 1 N=	Group 2 N=	Group 3 N=	Group 4 N=
105. Other outcomes (Please describe below)	?						

IF NOT APPLICABLE/NOT ABOUT PREVENTION, SKIP TO SECTION 17

SECTION 16: PREVENTION OF BRONCHIOLITIS

Where possible, please fill out table below. NR = not reported. N = sample size. If you are not able to fill out the table, you MUST provide reference to the Table numbers in the article.

Outcomes	NR	Time period	Report sig. tests as written (note if NR)	Group 1 N=	Group 2 N=	Group 3 N=	Group 4 N=
106. Symptom-free days	?						
107. Development of RSV	?						
108. Decision to admit (y/n)	?						
109. If "yes", length of stay	?						

SECTION 16: PREVENTION OF BRONCHIOLITIS (continued)

Where possible, please fill out table below. NR = not reported. N = sample size. If you are not able to fill out the table, you MUST provide reference to the Table numbers in the article.

Outcomes	NR	Time period	Report sig. tests as written (note if NR)	Group 1 N=	Group 2 N=	Group 3 N=	Group 4 N=
110. Readmission	?						
111. ICU care (y/n)	?						
112. If "yes" to ICU care, length of stay	?						
113. Ventilator use (respiratory failure) (y/n)	?						
114. If "yes" to ventilator use, length of treatment	?						

SECTION 16: PREVENTION OF BRONCHIOLITIS (continued)

Where possible, please fill out table below. NR = not reported. N = sample size. If you are not able to fill out the table, you MUST provide reference to the Table numbers in the article.

Outcomes	NR	Time period	Report sig. tests as written (note if NR)	Group 1 N=	Group 2 N=	Group 3 N=	Group 4 N=
115. Death	?						
116. Other	?						

SECTION 17: SUB-GROUP ANALYSIS

	Yes	*No*
117. Any sub-group analysis?	?	?
118. If “yes", provide details below		

SECTION 18: ADVERSE EFFECTS/HARMS

For all adverse effects below, present figures as reported in the article. Follow percent with %. If adverse effects were measured, but figures are not reported, write NR. If adverse effects were not measured, write NA.

TREATMENT GROUP	NR	N	Report sig. tests as written (note if NR)	Time period	Group 1	Group 2	Group 3	Group 4	Overall
119. Provide information on all adverse effects; e.g., vomiting, rash, GI bleeding, growth retardation, secondary infections, etc	?								

SECTION 19: LIMITATIONS

120. Please describe limitations of the study:

SECTION 20: COST OF MANAGING BRONCHIOLITIS

	Yes	No
121. Costs of treatment provided in article?	?	?
122. If "yes" please provide page number(s) for references to costs of treatment		
123. Costs of prophylaxis provided in article?	?	?
124. If "yes" please provide page number(s) for references to costs of prophylaxis		
125. Other monetary costs provided?	?	?
126. If "yes" please specify below:		
127. If "yes" please provide page number(s) for references to other costs		
128. Other non-monetary costs provided?	?	?
129. If "yes" please specify below		
130. If "yes" please provide page number(s) for references to other costs		

ECONOMIC EVALUATION ABSTRACTION FORM FOR 06919.009.001

I. CLASSIFICATION INFORMATION

1. Reviewer's Name		
2. First Author, Title, Date		
3. Tracking Number		
4. Study Type	❑ Published article ❑ Technical report ❑ Unpublished dissertation/thesis ❑ Abstract/presentation ❑ Book/book chapter	
5. Study Design	**Analytic Method** ❑ Cost Effectiveness Analysis (CEA) ❑ Average CEA ❑ Incremental CEA ❑ CE Ratio (specify): ❑ Cost-Utility Analysis (CUA) ❑ Average CUA ❑ Incremental CUA ❑ CU Ratio (specify): ❑ Cost-Benefit Analysis (CBA) ❑ Average CBA ❑ Incremental CBA ❑ CB Ratio (specify): ❑ Cost Analysis ❑ Total Cost (specify): ❑ Average Cost (specify):	**Summary Measure** ❑ Dollars per case or injury averted ❑ Dollars per person reached by intervention ❑ Dollars per life saved ❑ Dollars per life-year saved ❑ Dollars per year of healthy life saved ❑ Other (specify): ❑ Dollars per Quality-Adjusted Life Year (QALY) ❑ Dollars per Disability-ALY (DALY) ❑ Other (specify): ❑ Dollars ❑ Dollar per dollar ❑ Other (specify): ❑ Dollars ❑ Dollars per unit of service rendered ❑ Dollars per add'l. unit of service rendered ❑ Other (specify):

II. INTERVENTION DESCRIPTION	
6. Describe Study Population	
7. Age Range of Study Pop.	
8. Other Characteristics of Study Pop.	
9. Comparator	❑ Status quo (specify) : ❑ Other (specify): ❑ No Comparator ❑ Cannot Determine ❑ Does Not Apply
10. Intervention Description	
11. Other Interventions Included in the Analysis	A. B.
12. Community Intervention Included	❑ All Links--Community Interventions with Health Outcomes Analyzed ❑ Initial Links Only--Community Interventions with an Intermediate Outcome Analyzed ❑ Final Links Only--Clinical Intervention or Behavior Change with Health Outcomes Analyzed
13. Effect Size	❑ Specify:
14. Sources of Data for Effect Size	❑ Single Original Study ❑ Single Reported Study ❑ Compilation of Studies ❑ Expert Opinion ❑ Meta-Analysis ❑ Other (specify): ❑ Cannot Determine ❑

III. Study Information		
15. Location		
16. Audience	❑ MCO ❑ Providers ❑ Other Clinical ❑ Academic Org. ❑ CBO ❑ Congress ❑ State Legislature	❑ Public Health Agency: *Federal State Local* ❑ Other Govt. Dept./Org. *Federal State Local* ❑ Other Non-Govt. (specify): ❑ Other Audience (specify): ❑ Cannot Determine ❑ Does Not Apply
17. Setting	❑ Hospital ❑ Clinic or Provider Office ❑ Nursing Home ❑ Child Care Center ❑ Drug Treatment Facility ❑ Mental Health setting ❑ CBO ❑ School ❑ Workplace	❑ Religious Institution ❑ Home ❑ Prison ❑ Street ❑ Shelter ❑ Community wide (specify): ❑ Other Setting (specify): ❑ Cannot Determine ❑ Does Not Apply
18.Perspective	❑ Societal ❑ Patient and Patient Family ❑ Healthcare Provider **HMO Non-HMO** ❑ Public Health Agency Program **Federal State Local**	❑ Other Govt. Dept./Org. **Federal State Local** ❑ Self-Insured Employer ❑ Private Insurer ❑ Other Perspective(s) (specify): ❑ Cannot Determine ❑ Does Not Apply
19. Time Frame and Analytic Horizon	**Time Frame** ❑ Yes (specify): ❑ No ❑ Cannot Determine ❑ Does Not Apply	**Analytic Horizon** ❑ Yes (specify): ❑ No ❑ Cannot Determine ❑ Does Not Apply

20. Cost Data	❑ Estimated Directly in Study ❑ Medstat data ❑ Published related Article ❑ Unpublished related work ❑ Expert opinion ❑ Physicians fee and coding guide ❑ DRG ❑ Medicare Data ❑ Medicaid data ❑ *Statistical Abstract of the U.S. (*US Dept. of Commerce, Economics, and Statistics) ❑ *Health United States* (US DHHS) ❑ National Hospital Discharge Data ❑ Natl. Medical Care Utilization and Expenditures Survey (MEPS) ❑ Natl. Ambulatory Medical Care Survey (NAMCS)	❑ Natl. Mortality Followback Survey ❑ National Health Interview Survey ❑ American Hospital Association Survey ❑ AHRQ Statistics ❑ HIAA Data ❑ BC/BS ❑ Natl. Health and Nutrition Examination Survey ❑ HCFA/CMS RVUs ❑ HCFA/CMS Fee Schedule ❑ Natl. Testing Center ❑ HRSA ❑ Managed Care Data (specify): ❑ Other (specify): ❑ Cannot Determine ❑ Does Not Apply
21.Intervention or Program Costs	**Financial Costs** ❑ Vaccines ❑ Drugs ❑ Tests ❑ Lab/Diagnostic Procedures ❑ Personnel ❑ Communications ❑ Transportation ❑ Advertising ❑ Overhead ❑ Capital Equipment ❑ Real Estate ❑ Miscellaneous ❑ Followup ❑ Other (specify):	**Economic Costs** ❑ Volunteer Time ❑ In Kind ❑ Other (specify):

22. Participants' Cost-of-Illness	**Medical Costs** ❑ Drugs ❑ Tests ❑ Lab/Diag. Procedures ❑ Personnel ❑ Communication ❑ Transportation **Capital Equipment** ❑ Hospital Stay ❑ Real Estate ❑ Overhead ❑ Miscellaneous ❑ Followup ❑ Disease Sequels ❑ Other (specify):	**Nonmedical Costs** ❑ Travel Time ❑ Child Care ❑ Miscellaneous ❑ Other (specify):	**Productivity Losses** ❑ Travel ❑ Waiting ❑ Service ❑ Income Forgone Because of Illness ❑ Income Forgone by Accompanying Parent or Guardian ❑ Income Forgone Because of Death ❑ Other (specify):
23. Value of Summary Measure	❑ Selected from Study ❑ Recalculated ❑ Ratio, Cost-Savings or NPV:		
24. Location of Selected Ratio, Costs, Cost-Savings or NPV in article	❑ Page No.: ❑ Table No.:		
25. Comments			

Appendix D

Appendix D. Quality Rating Form

Quality Assessment for Randomized Controlled Trials of Treatment or Prophylaxis – EPC Bronchiolitis Project

Author: _____

Journal: _____ Year: _____

Quality Abstractor: _____ _____

	Inadequate	Unable to Determine	Adequate	Excellent
1. Randomization				
Adequate approach to sequence generation				
Adequate allocation concealment				
Similarity of groups at baseline				
2. Masking/ Blinding				
Double-blinding of treatment allocation				
3. Statistical Analysis				
Appropriate handling of withdrawals, losses to followup, and missing data with use of an intent to treat analysis				
4. Funding/ Sponsorship				
Type and/ or level of support detailed				
Overall Assessment of Study Quality (circle one)	Poor	Fair	Good	Excellent

Comments on study Quality- Please consider the following in addition to other factors that you think are important to consider in your final overall quality assessment:

Was the population selected appropriate to answer the question?
Was the outcome clearly defined?
Was the outcome clinically relevant?
Was the statistical analysis appropriate?