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.