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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.

*RTI International is a trade name of Research Triangle Institute.

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