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]