Early Ribavirin Treatment of Bronchiolitis*
Effect on Long-term Respiratory Morbidity

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Background: The mortality rate from respiratory syncytial virus (RSV) bronchiolitis has significantly reduced over the last decade. A major concern now is the long-term respiratory morbidity following RSV bronchiolitis.

Methods: In this prospective study, we randomly assigned 49 previously healthy infants with severe RSV bronchiolitis, early in the course of illness (<5 days duration), to receive either conservative treatment (n = 21) or additional ribavirin treatment (n = 24). Both groups were closely matched for age and clinical characteristics.

Results: During a prospective, closely monitored, 1-year follow-up period, the group treated with ribavirin had significantly fewer episodes (2.7 ± 2.3 episodes vs 6.4 ± 4.2 episodes per patient per year) and reduced severity of reactive airway disease (0.08 episodes vs 1.09 episodes of moderate-to-severe illness per patient per year) and respiratory illness-related hospitalization (25 hospital days vs 90 hospital days per 100 patients per year).

Conclusions: Early ribavirin treatment of RSV bronchiolitis in previously healthy infants resulted in reduction of incidence and severity of reactive airway disease as well as respiratory illness-related hospitalization. (CHEST 2002; 122:935–939)

Key words: bronchiolitis; reactive airway disease; respiratory syncytial virus; ribavirin

Abbreviation: RSV = respiratory syncytial virus

Respiratory syncytial virus (RSV) bronchiolitis is a major cause of respiratory illness in infants worldwide. Over the past decade, the mortality rate from acute RSV bronchiolitis has been significantly reduced, mainly due to improved case management and intensive care support. Long-term respiratory morbidity remains very high. Up to 70% of infants will have increased reactivity and/or impaired pulmonary function for up to 10 years following initial RSV bronchiolitis. Presently, ribavirin is considered for treatment of RSV bronchiolitis only in some high-risk infants and immunocompromised hosts. The effect of ribavirin treatment on long-term morbidity is somewhat unclear. Several studies have examined this issue with variable results; these studies have been inconsistent in the control of different confounding variables that could influence the outcome of the ribavirin intervention specially duration of illness prior to intervention. This may be important since ribavirin is virustatic and the viral burden and resultant chemokine release may be extremely variable at different stages of evolution of the acute illness. It is quite likely that in the later phase of the illness, once the viral load has peaked and maximal chemokine release has occurred, that any intervention with an antiviral or anti-inflammatory agent is less likely to alter the extent and nature of lung injury attributed directly or indirectly to the viral infection. Based on our understanding of the shortcomings of previous studies as well as our own retrospective study, we conducted the present study in a prospective manner, with random allocation of interventions to a homogenous group of infants very early in the course of RSV bronchiolitis and a very closely monitored follow-up period.

Materials and Methods

The study was conducted at West Jefferson Medical Center after obtaining approval from the Institutional Review Board and

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written parental consent for all patients. West Jefferson Medical Center is located in a geographically distinct community on the west bank of the Mississippi River in the New Orleans area. It is the only pediatric subspecialty service in the area. All children deemed to require pediatric pulmonary subspecialty care, such as those with severe RSV bronchiolitis, are referred to the only pediatric pulmonologist in this community, who is the principal investigator of this study. For the purpose of this prospective study, all previously healthy infants <180 days old with a clinical diagnosis of severe bronchiolitis and referred to the pediatric pulmonologist for further management were screened for inclusion in this study over an 18-month period covering two RSV seasons (1997–99). Only those infants with a confirmed diagnosis of RSV bronchiolitis and requiring hospitalization were considered for inclusion in the study. Further, those infants with duration of any upper or lower respiratory tract symptoms >5 days were excluded. Also, infants who were born prematurely (<38 weeks gestation) or had any underlying cardiopulmonary disease, neurologic impairment, immunocompromised status, or history of RSV bronchiolitis were excluded. Infants with either parent having asthma or atopic disease were also excluded. A positive enzyme-linked immunosorbent assay finding and subsequent positive viral culture finding from the nasopharyngeal aspirate confirmed the diagnosis of RSV. The predetermined criteria for hospitalization were the presence of signs or symptoms of severity, such as respiratory distress, acidosis (blood pH <7.33), hypercarbia (Paco₂ >45 mm Hg), and hypoxemia (transcutaneous oxygen saturation of <93% on room air). Using a printed checklist of inclusion and exclusion criteria, all patients were fully screened by the same physician who made the final decision about inclusion in the study. Patients fulfilling all entry criteria were assigned to receive either conservative treatment or additional treatment with ribavirin using simple randomization using a predetermined table of 100 odd and even random numbers corresponding to the two treatment groups respectively.

Once admitted to the study, the next consecutive treatment option as per the table was automatically assigned. Both treatment protocols were predetermined and standardized. Conservative treatment involved the use of oxygen to maintain transcutaneous oxygen saturation >92%, IV fluids to maintain optimal hydration, 2.5 mg of albuterol administered via nebulizer every 3 to 4 h, IV corticosteroids (methylprednisolone at 1 mg/kg per dose administered q12h for 3 days), and ranitidine administered orally (3 mg/kg per dose q12h). Ribavirin was administered as the “high-dose, short-duration” regimen (60 mg/mL over three 2-h periods for a total of 6 g) in a nebulized form via a small particle aerosol generator for 3 days. For the first 24 h, the infants were fed nothing by mouth, and then if in stable clinical condition they were fed their regular formula thickened with rice cereal in a concentration of one heaping tablespoonful (approximately 4 g) per 30 mL of formula. Thickened feeds were provided during the course of hospitalization and advised to be continued for 2 to 4 weeks after discharge from the hospital. All patients were managed by the same pediatric pulmonologist. All of the nurses working in the pediatric ward and pediatric ICU underwent an in-service detailing of the treatment protocols and entry and exclusion criteria of the study. They were involved in the screening process and in ensuring meticulous following of the treatment protocols.

On discharge from the hospital, the parents were instructed to maintain a daily respiratory and nonrespiratory symptom and medication diary. They were set up on a schedule of follow-up evaluation every 2 weeks for a period of 54 weeks by the nurse clinician, who was unaware of the initial treatment rendered. Each follow-up evaluation involved either a telephone interview by the nurse clinician or an outpatient evaluation by the pediatric pulmonologist if the patient had respiratory symptoms. During the telephone interview, the parents were asked to refer to their diary for providing the previous 2-week data. Interim evaluation was performed by the pulmonologist if there were any new respiratory symptoms or if a change in treatment was required. All follow-up data were recorded by the nurse clinician on preformed data sheets.

Uniform treatment was provided during follow-up. All respiratory illnesses were treated by the same pulmonologist on an intent to treat at an outpatient basis and according to a predetermined management protocol. Upper respiratory illnesses (“runny” nose, nasal congestion without respiratory distress, or wheezing) were treated with oral decongestants such as pseudoephedrine. Otitis media was diagnosed by an otoscopic examination and treated with oral antibiotics. Lower respiratory illness with radiologic evidence of pneumonia was treated with antibiotics. Nasopharyngeal aspirates were obtained for RSV from every patient presenting with lower respiratory tract symptoms. As in our previously published study, wheezing illness was classified as mild, moderate, or severe depending on the treatment required to alleviate the symptomatology specifically wheezing and respiratory distress. These criteria were developed after a consensus of six pediatric pulmonologists. Mild wheezing illness was defined as an episode that required frequent use (up to every 6 h) of albuterol via a nebulizer for alleviation of symptoms and an intent to treat as an outpatient basis. Moderate illness was one that required the additional use of short-term (<7 days) oral corticosteroids with or without an initial parenteral dose to alleviate symptomatology and an intent to treat on an outpatient basis. Episodes were labeled severe if symptoms could not be alleviated with the above treatment, and hospitalization for inpatient management was required especially for more frequent albuterol use and supplemental oxygen to maintain oxygen saturation >92%. Episodes of respiratory illness separated by a ≥48-h symptom-free interval were regarded as new episodes. Patients were excluded from the study if they missed two consecutive appointments or a total of three appointments at any time during follow-up. The total duration of follow-up was for 54 weeks following discharge from the hospital. The above-mentioned treatment protocol was described in detail in our previous study.

For data analysis, all discrete variables were compared using the χ² test and the Fisher exact test with Yates modification. The group means were compared by Student t test. Incidence of wheezing was compared using Mann-Whitney U test and analysis of variance.

RESULTS

Table 1 provides the patient enrollment details. Over a period of two RSV seasons, a total of 49 patients fulfilled all the entry criteria and were enrolled in the study. They were randomly assigned to receive either conservative treatment (control group) or additional treatment with ribavirin (study group). A total of 45 patients completed the study. The dropout rate was comparable in both groups (p >0.05). The dropouts were seen very early in the follow-up period, all occurring within the first 3 months. The control and study populations were comparable for mean age, sex distribution, and all hospital admission criteria (ie, respiratory rate, blood pH, Paco₂, oxygen saturation, and duration of illness;
Table 1—Patient Characteristics on Hospital Admission*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control Group</th>
<th>Study Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients enrolled in the study, No.</td>
<td>23</td>
<td>26</td>
</tr>
<tr>
<td>Patients completing the study, No. (%)</td>
<td>21 (91.3)</td>
<td>24 (92.3)</td>
</tr>
<tr>
<td>Age, mo</td>
<td>3.1 ± 1.2</td>
<td>3.2 ± 1.4</td>
</tr>
<tr>
<td>Duration of illness, d</td>
<td>3.7 ± 0.68</td>
<td>3.6 ± 0.62</td>
</tr>
<tr>
<td>Oxygen saturation on room air, %</td>
<td>90.2 ± 1.6</td>
<td>89.7 ± 1.4</td>
</tr>
</tbody>
</table>

*pData are presented as mean ± SD unless otherwise indicated. p > 0.1 for all corresponding comparisons between control and study groups.

The duration of illness prior to hospitalization was < 5 days in all patients.

The data on incidence of wheezing and nonwheezing respiratory illnesses are provided in Table 2. Reactive airway disease was defined as three or more episodes of wheezing illness and reversibility with nebulized albuterol. Patients with only one or two wheezing episodes during the 1-year follow-up were not regarded as having reactive airway disease. In the control group, a significantly higher percentage of patients (80.9%) had recurrent wheezing illness, classified as reactive airway disease, as compared to 62.5% in the study group (p < 0.05). The incidence of reactive airway disease was significantly higher in the control group as compared to the treated group (p < 0.01). There was a significant reduction in the severity of reactive airway disease in the study group (ie, in patients treated with ribavirin; p < 0.01). The control group had 1.09 episodes of moderate-to-severe reactive airway disease per patient per year as compared to 0.09 episodes in the ribavirin-treated group. In the study group, there were no severe episodes of reactive airway disease (ie, none of the 24 infants were hospitalized for reactive airway disease during the 1-year follow-up period). In the study group, almost all the episodes (97%) were mild and easily managed with nebulized albuterol. In the control group, 83% episodes were mild. The incidence of otitis media was higher in the study group, but there were fewer episodes of nonwheezing lower and upper respiratory tract illness and repeat RSV bronchiolitis in the ribavirin-treated group as compared to the control group (p < 0.05).

There was a significant reduction in respiratory illness-related hospitalizations in the ribavirin-treated group as compared to the conservatively treated group (p < 0.05). Over the 1-year follow-up period, 6 of 21 patients in the control group were hospitalized for respiratory illnesses as compared to 2 of 24 patients in the study group. The total number of days of hospitalization for respiratory illnesses in the control group of 21 patients was 19 days (corrected to 90 days per 100 patients per year). This was significantly higher than the 6 days of hospitalization for the 24 patients in the study group (corrected to 25 days per 100 patients per year; p < 0.05). In the control group, the reasons for the six hospitalizations were severe reactive airway disease (n = 3), repeat RSV bronchiolitis (n = 2), and pneumonia (n = 1). The reasons for the two hospitalizations in the study group were pneumonia and repeat RSV bronchiolitis, respectively.

**DISCUSSION**

Our study shows that in previously healthy infants with RSV bronchiolitis, treatment with ribavirin early in the course of the disease leads to a significant reduction in the incidence and severity of reactive airway disease and respiratory illness-related hospitalization over a 1-year period following the initial RSV illness. Several features of our study need to be highlighted. All infants were treated with ribavirin very early in the course of the disease. Early treatment may be the key in influencing a favorable response of reduced reactivity of airways. Viral-induced lung injury is recognized as the most likely event predisposing to subsequent development of reactivity. This concept is supported by well-gathered data from a large prospective study. An important previously published prospective study...
with ribavirin intervention did not control duration of illness prior to intervention as a confounding variable, and it is no surprise that no difference was observed in the long-term respiratory morbidity in the treated vs untreated groups. There is an enormous release of a variety of chemokines early in RSV bronchiolitis.\textsuperscript{13} In \textit{vitro} data have shown that an early, one-time introduction of ribavirin in the tracheal cell cultures infected with RSV leads to a dramatic drop in these chemokine concentrations,\textsuperscript{14} which could possibly lead to decrease in the degree of inflammation. This supports the contention that early treatment with ribavirin may play a potential role in reducing the risk of viral-mediated inflammation and resulting lung injury that is a major factor influencing subsequent development of pulmonary morbidity.

Another interesting feature of our study is the attention to the oral feeding process during RSV bronchiolitis. We have shown that infants during RSV bronchiolitis are at a high risk of aspiration,\textsuperscript{15} a long-suspected but only recently documented fact. Aspiration can cause lower respiratory tract symptoms indistinguishable from bronchiolitis, thus giving an incorrect impression of the severity and natural history of RSV bronchiolitis. Further, aspiration \textit{per se} can lead to food protein sensitization and airway dysfunction.\textsuperscript{16,17} None of the previously published intervention studies have controlled for feeding as a confounding variable. We have also shown that the risk of swallowing dysfunction during RSV bronchiolitis is significantly reduced with thickened feeds.\textsuperscript{18} In the present study, feeding was controlled; hence, unlike the other studies, the data are less likely to be contaminated with the immediate and long-term consequences of aspiration.

Corticosteroids \textit{per se} also seem to have a variable effect on the short-term course or outcome of RSV bronchiolitis.\textsuperscript{19,20} Their impact on long-term respiratory morbidity is questionable.\textsuperscript{21} In our study, all infants in the study as well as the control group received corticosteroids; therefore, the reduced long-term morbidity in the study group is unlikely to be an outcome of corticosteroids \textit{per se}. The favorable effect of treatment in the study group is most likely related to ribavirin alone or to the potentially synergistic combination of ribavirin and corticosteroids. This hypothesis maybe supported by the results of a recent study by Prince et al.\textsuperscript{22} They used three interventions in a cotton rat model of RSV: corticosteroids alone; RSV monoclonal antibody alone, and a combination of corticosteroids and RSV monoclonal antibody. They monitored viral clearance and improvement in lung pathology. Treatment with corticosteroids alone showed improved lung pathology but delayed clearance of virus. Treatment with RSV monoclonal antibody resulted in no change in lung pathology but rapid clearance of virus. In the combination group, there was improved lung pathology as well as clearance of virus. This suggests that combining an antiviral modality with a corticosteroid would result in a better outcome than either agent administered alone.

The prospective nature of our study was somewhat different than previous studies. All infants were followed up, evaluated, and treated by the same pediatric pulmonologist on an intent to treat at an outpatient level and along a predetermined protocol throughout the course of the study. This eliminated the bias introduced by variable skills and practice patterns of multiple physicians. This was also important for uniform assignment of severity of reactive airway disease during follow-up. Further, even though our protocol called for a two-weekly telephone follow-up by the nurse clinician, the physician evaluated several infants, especially the ones who had respiratory symptoms develop, more frequently. This resulted in the observations being better monitored. Most previously published studies\textsuperscript{4,6,7} have been retrospective with recalls of up to 10 years. Other prospective studies,\textsuperscript{5,9,10} even though planned and executed prospectively, have used recalls of up to 6 months. Long recalls will not affect data on pulmonary functions but certainly taint the data on symptoms. Our method of follow-up with two-weekly interviews and recalls based on daily diaries is likely to provide a higher degree of accuracy.

Another set of important confounding variables that can affect the outcome is the patient’s clinical characters on admission. We ensured homogeneity in the patient groups by limiting the entry criteria to previously healthy infants only. This helped avoid the problems encountered by including variable numbers of patients with different kinds and severities of underlying conditions such as cardiopulmonary disease, immunodeficiency syndromes, and levels of prematurity. Also, all the parameters of severity of bronchiolitis were matched in both the groups. In addition, the duration of illness prior to intervention was matched in both groups and was <5 days in all infants. Patients with family history of asthma or atopic disease were also excluded as potential factors affecting incidence of airway reactivity. Under these conditions, the study and control groups were better matched, thus making the comparisons in the outcome more meaningful. Such meticulous matching has not been performed in any of the previously published studies.

Ribavirin treatment resulted in not only a reduced incidence and severity of reactive airway disease but also a significant reduction in the overall respiratory illness-related hospitalization that could result in
some economic benefit. We also observed a significant reduction in the occurrence of nonwheezing upper respiratory tract illness. The mechanism and implication of this finding are speculative and beyond the scope of this discussion.

In conclusion, the infants in the study group experienced a significant reduction in the incidence of reactive airway disease. While it may seem that all the benefit is attributable to ribavirin treatment alone, in a true sense it may be difficult to dissect out the true credit due to ribavirin. It is likely that the beneficial effects seen in the study group may be secondary to the ribavirin alone or to the synergistic effect of early use of ribavirin plus the additional interventions that may have the potential of reducing airway reactivity in previously healthy infants following RSV bronchiolitis. Our data should provide the rationale of evaluating early interventions in RSV bronchiolitis with a view to prevent long-term morbidity. Such interventions should utilize the potential synergy of early use of an optimal antiviral along with an anti-inflammatory/immunomodulator and prevention of aspiration.

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