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Editorial

RSV, Recurrent Wheezing, and Ribavirin

In this issue of *Pediatric Pulmonology,* Edell et al.[1] report their observations of subsequent episodes of ''reactive airway disease'' in a group of infants who had been hospitalized for respiratory syncytial virus bronchiolitis. They noticed a higher incidence of lower respiratory symptoms suggesting reactive airways in children who had been treated conservatively (bronchodilators, intravenous fluids, etc.) compared to children who had been treated with ribavirin in addition to conservative measures. If valid, this observation has two potentially important implications. First, as the authors speculate, the prevention of subsequent wheezing might be an indication for the use of ribavirin in infants with RSV bronchiolitis. A second, less direct (but no less important) potential implication is that a severe RSV infection itself contributes to subsequent respiratory morbidity in such children.

Indications for the use of ribavirin for hospitalized infants with RSV bronchiolitis are, to say the least, controversial. Although it is likely that ribavirin would be used by most clinicians in the United States for infants with RSV lower respiratory infection who are immunocompromised, many clinicians have taken issue with the use of ribavirin in immunocompetent, previously well infants.[2] Our own use of ribavirin is closer to that outlined by the ''Red Book'' committee,[3] but we agree whole-heartedly with nearly everyone involved in this controversy that consensus on a rational approach to the use of ribavirin will continue to await well-designed randomized clinical trials.

The increasing prevalence and severity of asthma over the last decades have led to considerable interest in whether or not RSV infection in infancy contributes to wheezing and/or the development of asthma later in childhood. There is general agreement that even infants with mild bronchiolitis are more likely than children without this history to experience repeated episodes of wheezing during the first two or three years of life.[4] However, a variety of factors cloud the issue of whether or not RSV ''causes'' recurrent wheezing. Over 50% of infants are infected with RSV in the first year of life, so that the majority of children who do not wheeze thereafter have also been infected with RSV. There is also compelling evidence that children who wheeze subsequently are those with lower levels of lung function prior to the RSV infection, raising the possibility that both the severe initial RSV infection and subsequent wheezing are both simply signs of an underlying susceptibility to lower airway dysfunction.[5] Children who wheeze after an RSV infection may have been destined to wheeze even without the initial infection.

The roots of recurrent wheezing in infancy may involve more than one factor, however. The fact that subsequent wheezing is predicted by initial levels of pulmonary function does not eliminate a severe RSV infection as an important contributing factor. It could be that infants with subnormal lung function develop recurrent wheezing *only* if they initially have a severe RSV infection. Long et al.[6] have suggested that a definitive answer is most likely to come from controlled intervention trials in which RSV infection is prevented (? a vaccine) or effectively modified/treated (an antiviral agent) in one group of infants. In either case, a difference (or lack of difference) in the prevalence or severity of subsequent wheezing or airway hyperreactivity between treated and control infants would be powerful evidence that RSV does or does not contribute to asthma or lower respiratory problems later in life.

For a number of reasons, the data of Edell et al. are less likely to clarify the indications for ribavirin and the role of RSV in subsequent wheezing than to engender additional controversy. As the authors point out, the study has several methodologic weaknesses. The most important is the fact that subjects were not randomized with regard to ribavirin treatment. It is not clear why infants were selected for ribavirin treatment. In the absence of randomization, it is impossible to be sure that the two groups are comparable in their predisposition to wheeze. Another potential source of bias is the low rate of follow up of infants who had been initially hospitalized for RSV (41 of 77 hospitalized infants). The reader is also left with the problem of reconciling the findings of Edell, et al, with those of other investigators who have addressed this issue recently. Long et al.[7] reported follow-up pulmonary function measurements and clinical symptom monitoring in children initially involved over 10 years ago in a double-blind, randomized trial of ribavirin. There were no important differences in these measures of airway function between ribavirin and placebo-treated subjects. Krilov et al.[8] have published follow-up data on patients treated in a number of institutions during the 1986-1987 RSV season, and could find no difference in the diagno-

sis of reactive airway disease between ribavirin and conservatively treated subjects.

The possibility that ribavirin might decrease the airway dysfunction and susceptibility to wheezing lower respiratory illnesses that often follow a severe RSV infection in infancy might well enter into the decision of whether or not to use this agent. An effect of ribavirin on the prevalence of subsequent wheezing would also strongly suggest that modifying or preventing this ubiquitous disease of the first year of life might have important implications for subsequent airway disease. The methodologic weaknesses of the study of Edell et al. and the lack of consensus in the literature on this point will prevent many thoughtful clinicians from altering their present approaches to the use of ribavirin. This paper makes even more attractive, a large, carefully-controlled trial of the effectiveness of ribavirin in the acute treatment of acute RSV lower respiratory infection and in the prevention of subsequent lower airway dysfunction.

REFERENCES

1. Edell E, Bruce E, Hale K, Edell E, Khoshoo V. Reduced long-term respiratory morbidity after treatment of RSV bronchiolitis with ribavirin in previously healthy infants. Pediatr. Pulmonol. 1998;154–158.
2. Moler FW, Ohmit SE, Stedham GL. Effectiveness of rib avirin in otherwise well infants with respiratory syncytial virus-associated respiratory failure. Pediatric Critical Study Group. J Pediatr. 1996; 128:422–428.
3. American Academy of Pediatrics Committee on Infection Disease. Reassessment of indications for ribavirin therapy. Pediatrics. 1996;97:137–140.
4. McConnochie KM, Roghmann KJ. Predicting clinically significant lower respiratory illness in childhod following mild bronchiolitis. Am J Dis Child. 1985; 139:625–631.
5. Martinez FD, Morgan WJ, Wright AL, Holberg CJ, Taussig LM. The Group Health Medical Associates' Personnel. Diminished lung function as a predisposing factor for wheezing respiratory illness in infants. N Engl J Med. 1988;319:1112–1117.
6. Long CE, McBride JT, Hall CB. Sequelae of RSV infection: a role for intervention studies. Am J Resp Crit Care Med. 1995;151: 1678–1680.
7. Long CE, Voter KZ, Barker WH, Hall CB. Longterm follow up of children hospitalized with Respiratory Syncytial Viral lower respiratory tract infection and randomly treated with ribavirin or placebo. Pediatr Inf Dis J. 1997;16:1023–1028.
8. Krilov LR, Mandel FS, Barone SR, Fagin JC. Followup of children with respiratory syncytial virus bronchiolitis in 1986 and 1987: potential effect of ribavirin on long-term pulmonary function. Pediatr Infect Dis J. 1997;16:273–276.

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