

Respiratory syncytial virus: Back to basics

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Respiratory syncytial virus (RSV) is the most important cause of acute lower respiratory tract illness in infants and young children.¹ The virus produces annual epidemics throughout the world and is estimated to cause 1 million deaths per year.² RSV preferentially infects the epithelium of the smallest airways: the bronchioles. As a result, the caliber of the airway is compromised, causing reduced air exchange. Because the airways tend to collapse at the time of expiration, increased effort is required, and expiratory wheezing is clinically evident. Partial airway collapse may result in air trapping, whereas complete collapse results in atelectasis. Reduced gas exchange often leads to hypoxia, which in young infants may produce an aberrant response, apnea; death may ensue if the infant is unattended. Most of the hospitalizations in the United States occur during the first 6 months of life.³ The peak time of admission to hospital is the second month of life. In recent years, RSV epidemics have become more severe and prolonged, resulting in a doubling of the annual rate of hospitalizations. Epidemiologic studies from 1977 to 1980 estimated hospitalization rates of about 1 per 100 infants during RSV epidemics. By 1992 to 1996, the annual rate of RSV-related hospitalizations had doubled, and the period of epidemics had lengthened from 8 to 10 weeks to 16 to 18 weeks each year. This increase was confirmed by national surveys showing that rates of hospitalization of infants for bronchiolitis had a similar increase from 1980 to 1996.

Despite the fact that the virus was identified 50 years ago, little progress has been made in development of a practical approach to prevention. One of the reasons is that a formalin-inactivated whole virus vaccine tested in the early 1960s resulted in a paradoxical outcome, with vaccinated subjects developing more severe disease at the time of natural challenge than unvaccinated controls.¹ As a consequence, inactivated vaccines cannot be tested in naive subjects younger than 1 year. Most of the current research involves the testing of live attenuated virus vaccines that are safe for infants beginning in the neonatal period. The candidate strains that are benign for this age group do not stimulate a

serum neutralizing antibody response, the best correlate of immunity.⁴ This is not unexpected, because infants less than 6 months of age do not consistently produce an immune response to natural infection, and natural reinfection in the second year of life is common.⁵ Longitudinal studies have shown that about two thirds of infants are infected during the first year of life, and all are infected before the second birthday. Furthermore, about one half are reinfectd during the second year, resulting in an infection rate of 82 per 100. The risk of infection decreases only after the second natural infection and the second year of life. Both the previous RSV infections (2) and the maturity of the immune system may be important for developing protection. All of these facts diminish the likelihood that effective active immunization can be accomplished in infants less than 6 months of age, recognizing that multiple doses of vaccine will probably be necessary at intervals of about 4 weeks.

Passive immunization may be a reasonable alternative. Studies have shown that infants endowed with high levels of RSV neutralizing antibody from their mothers are protected from severe RSV disease during the first months of life, as recently confirmed by a large Danish study by Stensballe et al⁶ recorded in this issue of the Journal. Infants with high levels of RSV neutralizing antibody in cord sera are significantly less likely to be hospitalized with laboratory-confirmed RSV bronchiolitis. The authors reach other conclusions that are not completely supported by the data. Wheezing illness is very common in infants less than 2 years of age, but relying on mothers to determine the number of wheezing episodes over a 12-month period is problematic. Infants have at least 6 acute respiratory illnesses during the first year, and examination with a stethoscope by a trained clinician is necessary to determine whether the noisy breathing originates in the upper or lower airways. Relating the frequency of these episodes to the level of RSV antibody in the cord blood is difficult without laboratory studies to determine the etiology of the acute respiratory episodes. With new laboratory techniques (PCR), virtually all wheezing episodes in young children are associated with a viral infection—usually RSV, rhinovirus, parainfluenza type 3, or human metapneumovirus.⁷ In our longitudinal study of infants followed from birth, we found that those who wheezed with the first RSV infection were unlikely to wheeze with the second and, conversely, those who wheezed with the second RSV infection had not wheezed with the first.⁵ Some infants were likely to wheeze with any virus infection, and those infants were diagnosed with asthma at a later age. Specific etiologic diagnoses could clarify some of the observations by Stensballe et al⁶ and edify the conclusions. Although the infants with recurrent wheeze in this study had physician confirmation of wheezing at least once, most of episodes before and after RSV hospitalization were not clinically confirmed, making the conclusions tentative.

The underlying theme of Stensballe et al⁶ is that the pathogenesis of RSV disease is immune-mediated. The recent study by Welliver et al⁸ has discounted the theories of immunopathological mechanisms by showing in fatal cases the destruction of the

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respiratory epithelium and the absence of immune T cells and high levels of cytokines. Infants with mild bronchiolitis have higher levels of proinflammatory cytokines than infants who require admission to the hospital.⁹ Infants who survive RSV bronchiolitis do have impaired pulmonary function that persists for some months and results in recurrent wheezing episodes.¹ The focus should be on prevention of the RSV damage to lungs that have not fully developed. The longitudinal studies by Martinez et al¹⁰ have shown that children who eventually develop asthma have worse outcomes (diminished pulmonary function at 6 years of age) if they have a history of hospitalization for acute lower respiratory illness in the first year of life. At this juncture, the safest approach to protecting infants in the first months of life would be to boost the levels of neutralizing antibodies transmitted from mother to infant by immunization during pregnancy with a potent RSV subunit vaccine. Recent studies have demonstrated the effectiveness of maternal immunization with influenza vaccine for protection of infants less than 6 months of age against febrile respiratory illness.¹¹ Passive immunity that protects for the first months should be reinforced by active immunization at a later age, when the child is better able to mount a good immune response. Immunization of older children with an effective live attenuated vaccine should provide indirect protection of infants by reducing exposure to RSV infection.¹² The same factors (increased population density and urbanization) that have increased the severity of RSV epidemics in recent years also impinge on children with the genetic propensity for atopy. These include increased exposure to many respiratory virus infections that render them more vulnerable to environmental allergens and irritants

(air pollution). These factors provide challenges for the future that will be difficult to remedy.

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