EDITORIAL COMMENTARY

A New Direction in Understanding the Pathogenesis of Respiratory Syncytial Virus Bronchiolitis: How Real Infants Suffer

John P. DeVincenzo
Departments of Pediatrics and Molecular Sciences, University of Tennessee School of Medicine, LeBonheur Children’s Medical Center, and The Children’s Foundation Research Center, Memphis

(See the article by Welliver et al., on pages 1126–36.)

An understanding of the mechanism of human disease should be led by a thorough study of pathology. This statement seems an obvious central tenet of medicine, but a failure to adhere to it may have led to fundamental misunderstandings of the pathogenesis of infant viral lower respiratory tract infections. Viral lower respiratory tract disease, particularly that caused by respiratory syncytial virus (RSV), has long been thought to be the result of an exuberant and aberrant pathogenic immune response. However, a logistically elegant and detailed study of the pathology of fatal infant RSV and influenza infections by Welliver et al. [1] in this issue of the Journal, along with other studies, may be changing this assumption.

RSV infects >68% of the birth cohort annually [2] and is the most common cause of lower respiratory tract infections in children <1 year of age, resulting in significant morbidity [3, 4]. RSV also causes significant mortality [5], with rates ∼10 times those for influenza in infants [6]. Although infants with prematurity, chronic lung disease, congenital heart disease, or immunodeficiencies are at increased risk for severe RSV disease, most infants with RSV infection requiring hospitalization are previously healthy [7, 8]. Worldwide, as many as 1 million children may die from RSV infection annually [9, 10]. An understanding of this disease is clearly important.

Prevailing concepts of the immunopathogenic nature of RSV infection have been influenced heavily by previous experiences with vaccine-enhanced RSV disease [11–13], which revealed a prominent eosinophilic pulmonary infiltration after natural RSV infection in the unfortunate vaccine recipients in this fatal experiment. This prevailing immunopathogenic concept has since been perpetuated by findings in rodent models [14–16]. Thus, RSV disease has been thought to result from exaggerated Th2 cellular responses [17] and the bystander killing effects of activated cytotoxic T cells [18]. As pointed out in this issue of the Journal, this dominant focus on the putative role played by the immune response in causing RSV disease may be inaccurate, at least in infants. This controversy has major implications for the development of prophylactic and therapeutic strategies for RSV.

Despite the importance of the virus to the health of infants and children, to date there has been little study of RSV pathology in human infants. The most important reason that the pathology of RSV infection has not been studied directly in infants is logistical in nature. Lung specimens are simply not available in the United States or Europe because of the availability of emergency triage and mechanical ventilation systems, which keep infants with RSV infection alive long enough for them either to recover or, in infants with fatal cases, to generally clear the virus while overlaying and confusing the RSV-induced pathology with that of severe and late barotrauma-induced processes. Welliver et al. have overcome this barrier by collecting autopsy specimens from Chilean infants who had unfortunately suffered fatal RSV infection without the availability of mechanical ventilation, by evaluating their immune responses in situ, and by comparing these tissue responses with those in similar fatal cases of influenza.

Surprisingly, evidence for the predicted pathogenic cytotoxic immune response was not found. The authors’ iconoclastic findings instead describe a disease process associated with overwhelming RSV anti-
gen in the lungs accompanying massive apoptotic sloughing of respiratory cells and a distinct relative absence of cytotoxic T cells. Furthermore, the infant deaths were reported as occurring at a mean of 4 days after onset of disease, a time when RSV and influenza pulmonary disease is nearing its zenith. This timing essentially eliminates the possibility that an exuberant pathogenic immune response contributing substantially to the severe disease might have occurred later. Welliver et al. go on to describe the cytokine profiles of a series of infants who survived lower respiratory tract disease caused by RSV and compare them with profiles for surviving infants infected with influenza virus. In keeping with the lack of a robust adaptive cytotoxic immune response suggested by the in situ studies, the cytokine concentrations in RSV-infected surviving infants were indicative of a blunted adaptive cell-mediated immune response. Namely, concentrations of cytokines were generally lower in RSV infections than in influenza virus infections, despite the RSV-infected infants being more ill than their influenza virus–infected comparators. This included significantly lower concentrations of certain lymphocyte-derived cytokines (interferon-γ, interleukin [IL]–17, and IL-4) in RSV infections as compared with influenza virus infections. Furthermore, the putative release of lymphocyte-derived cytokines (either Th1 or Th2) were not related to disease severity in RSV infections, because the concentrations of these cytokines were shown to be similar in surviving infants with mild (upper respiratory tract) disease and in those with more severe (lower respiratory tract) disease. Finally, Welliver et al. demonstrate that the T lymphocyte cytokine concentrations do not appear to be increasing over time but are actually decreasing, suggesting that a late pathogenic T cell–mediated immune response is not developing.

A great deal of the lung functional deficit commonly witnessed during RSV infection can be explained simply by the physical sloughing of RSV-infected cells and RSV-positive staining debris into the infants’ airways and alveoli. Welliver et al. also demonstrate evidence of massive quantities of RSV-infected respiratory epithelial cells in situ. This finding has also been recently noted in detail in an independent report studying archival tissue from infants with similar fatal RSV cases [19]. This epithelial cell sloughing appears to be the result of RSV-induced apoptosis. The massive quantity of apoptotic sloughing into the airways is not seen in fatal influenza cases and helps to explain the higher mortality of RSV infection as compared with influenza virus infection in this age group [6]. Alongside the sloughing of infected respiratory epithelial cells is a significant influx of neutrophils and macrophages, which has long been noted as a hallmark of infant RSV infection but is a feature not seen in rodent models of the disease.

These findings combine to suggest a picture of infant RSV pathogenesis in which rapid and profound RSV replication induces direct lung injury and in which an effective adaptive cell-mediated immune response fails to curb the infection and indeed does not even develop. Several other lines of evidence support this direct pathologic evidence. First, it is well known that corticosteroids are ineffectual in altering the RSV disease process in infants [20]. Second, the dynamics of RSV replication in infants matches the findings of Welliver et al. There is a correlation between the quantity of RSV in infants’ respiratory tract secretions and their RSV disease severity [21, 22]. Infants with greater viral quantities in respiratory tract secretions are at greater risk for prolonged hospitalization, for intensive care unit stay, and at greater risk for mechanical ventilation [21]. Furthermore, a detailed study of RSV dynamics has shown that infants with less-rapid clearance of RSV have greater disease severity [23]. Disease that is more directly a consequence of uncontrolled viral replication as opposed to a pathogenic immune response clearly supports the idea that controlling viral replication could lead to reduced clinical disease. Taken together, these independent lines of evidence have clear and profound implications for the development of RSV antivirals, especially in infants.

Although this line of evidence is becoming increasingly convincing, it is important not to overinterpret these findings. A central tenet of pediatrics, and one that applies here, is that children are not little adults. These findings are being demonstrated in, and apply to, primary RSV infections, the types of infections that RSV epidemiology would dictate are occurring in the studied patients. The extent to which this pathophysiology also applies to subsequent RSV infections or to RSV infections of adults or immunocompromised populations [24] remains to be elucidated.

Despite the growing knowledge of RSV pathogenesis, intriguing questions remain unanswered. RSV-infected infants continue to cough and wheeze for weeks after an acute infection, long after virus is no longer able to be cultured from their upper respiratory tract secretions. What accounts for the persistence of this disease? Could it be related to viral persistence [25, 26]? Why are children, and even adults, susceptible to repeated RSV infections throughout life despite few demonstrable changes in the viral antigens of the infecting strains? These and other questions will likely be answered by using a wide range of investigative approaches. However, as is so aptly demonstrated by Welliver et al.’s article, studying disease and pathology directly in infected humans should always focus and lead our investigative efforts. Meanwhile, children infected with RSV continue to suffer. Taken literally, the word “pathology” can be translated as the study of suffering (pathos), and only through the study of suffering can we hope to achieve its relief.

References

1. Welliver TP, Garofalo RP, Hosakote Y, et al. Severe human lower respiratory tract illness caused by respiratory syncytial virus and influenza virus is characterized by the absence...