Introduction

Respiratory Syncytial Virus and Reactive Airway Disease

New Developments Prompt a New Review

JAN L. L. KIMPEN and ERIC A. F. SIMOES

Department of Pediatrics, Wilhelmina Children's Hospital, Utrecht, The Netherlands; and Section of Infectious Diseases, Department of Pediatrics, University of Colorado School of Medicine and The Children's Hospital, Denver, Colorado

Respiratory syncytial virus (RSV) is the most common viral cause of lower respiratory tract infection (LRTI) in infants and young children worldwide and is the most important cause of bronchiolitis in the first 2 yr of life. The disease burden of severe RSV infection is very high in terms of both morbidity and economic costs. No vaccine is available currently, but prophylactic interventions have been shown to be safe and effective in clinical trials.

Extensive research, which began some four decades ago, has expanded our knowledge regarding the specific mechanisms involved in the pathogenesis of RSV bronchiolitis. Follow-up studies have demonstrated that bronchiolitis caused by RSV is strongly associated with postbronchiolitic wheezing in the ensuing years. During the acute infection, both immunologic and nonimmunologic responses may induce this long-lasting detrimental effect. Studies of RSV and its association with subsequent chronic obstructive airways disease have been performed in humans, cell culture models, and animal models, each with its own specific limitations. What is perhaps most confounding is the fact that not all children infected with this virus, even with the same RSV subtype, go on to develop recurrent wheezing; therefore, the mechanism must be multifactorial. A better understanding of the pathogenesis of RSV-induced reactive airway disease (RAD) or asthma will be of considerable help in developing specific therapeutic and preventive strategies.

On September 10, 2000, we conducted an international roundtable meeting, "RSV and RAD—Possibilities for Prevention?" in Paris, France, at which the association between RSV and RAD was discussed and the most recent data regarding this link were reviewed. Dr. Nele Sigurs reviewed the epidemiologic evidence for and against this link. She presented new 7-yr follow-up data from a cohort of 47 children recruited during infancy who had been hospitalized with RSV LRTI and 93 control subjects that showed that RSV bronchiolitis in infancy is associated with an increased risk of future bronchial obstructive symptoms. The symptoms may persist for up to 7 yr and cannot be explained by a family history of atopy and/or asthma. Dr. Peter Openshaw discussed recent developments in the immunopathogenesis of RSV and suggested several possible mechanisms for the association. He noted that the different patterns of lung pathology observed in animal models of RSV infection appear to depend, at least in part, on the genetic predisposition of the host and may determine the delayed effects of infection. Dr. Jan Kimpen discussed the role of the monocyte/macrophage in the pathogenesis of RSV disease and presented evidence showing that the interaction between RSV and antigen-presenting cells may play a role in RSV severity and subsequent recurrent wheezing. Dr. Giovanni Piedimonte presented results of studies in rats that examined the neural control of airway inflammation. He reported that the upregulation of substance P during RSV infection may establish important neuroimmune interactions, which undergo long-term dysregulation after RSV infection and predispose to airway inflammation and hyperreactivity. Dr. Eric Simoes reviewed the effects of antiviral and antiinflammatory therapy (during and after an RSV LRTI) on subsequent obstructive airway disease. He then noted that RSV immune globulin and palivizumab are effective prophylactic agents for preventing RSV lower respiratory illness in high-risk infants. He presented data that suggested that immunoprophylaxis with these agents might have a long-term impact on the development of recurrent wheezing and associated health outcomes. These talks are presented in this supplement to the *American Journal of Respiratory and Critical Care Medicine*.

During the course of these presentations, several key issues were identified. First, a better understanding of the epidemiologic studies linking atopy or allergy/asthma with RSV disease is needed. Second, we need to elucidate the relationship between the physiologic phenomena that occur in the airways and the immunopathologic phenomena at other sites. Third, we need to understand the interplay of the various immunologic models. Fourth, it will be important to determine whether the findings derived from animal models hold true in humans. Finally, preventive studies—perhaps using palivizumab, alone or in combination with investigational preventive measures such as tumor necrosis factor antagonists—should be conducted to see whether it is possible to minimize or completely avoid severe RSV disease and the recurrent wheezing it causes. We believe these are the major areas on which future research should focus.

Correspondence should be addressed to Eric A. F. Simoes, M.D., DCH, Department of Pediatrics, Children's Hospital, Box B070, 1056 E. 19th Avenue, Denver, CO 80218. E-mail: eric.simoes@uchsc.edu.

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