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Introduction: Emerging Importance of the Rhinovirus

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Acute viral respiratory infections (VRIs) encompass a range of illnesses that together constitute the most frequent infections of humans. The most prevalent syndrome is that characterized by signs and symptoms of the common cold, or acute viral rhinosinusitis. These illnesses are typically acute, self-limiting events associated primarily with upper respiratory symptoms, but they also cause symptoms that are indicative of lower respiratory involvement, particularly in the very young, the elderly, and those with preexisting airways disease.[1-3] Rhinoviruses are the most common pathogen causing VRIs and account for approximately 50% of colds on an annual basis. Not surprisingly, the recent development of antiviral compounds with activity targeted against rhinoviruses has intensified interest in these infections. This supplement contains a series of articles based on presentations by internationally regarded experts who met on April 3 and 4, 2001 in Philadelphia, Pennsylvania, to discuss current knowledge and recent advances regarding the epidemiology, clinical impact, pathogenesis, and management of rhinoviral VRIs.

Children get an average of 3 to 8 colds annually.[4] Preschool children get an average of 5 to 7 per year, but 10% to 15% may get up to 12 per year.[5] The incidence decreases with age to an average of about 2 to 4 colds per year by adulthood.[5,6] Data from a survey conducted in 1996 by the National Center for Health Statistics reported that 62 million cases of colds required some form of treatment.[7] This survey also showed that colds were associated with 148 million days of restricted activity, approximately 20 million days of missed work, 22 million days of missed school, and 45 million days during which individuals were bedridden.[7] Gonzales et al[8] reported that in 1998 there were 25 million office visits to primary care providers for upper respiratory tract infections. Furthermore, costs associated with the common cold have been estimated to exceed $3.5 billion per year in the United States.[9]

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Another important factor contributing to the cost of VRIs is the use of antibiotics. Common colds and related VRI syndromes are among the most frequent reasons for inappropriate antibiotic use in the United States, which increases the costs of illness unnecessarily and contributes to the increasing prevalence of antibiotic-resistant bacteria.[10] The Centers for Disease Control and Prevention estimates that about 50% of the approximately 100 million courses of antibiotics prescribed by office-based physicians each year are unnecessary.[11] In 1994, it was estimated that more than 12 million antibiotic prescriptions were written annually for upper respiratory infections, at a cost of $37.5 million.[12] In this regard, some of the common attributes of rhinovirus infection, discolored nasal discharge and postnasal drainage, are significantly associated with antibiotic prescribing.[13] Furthermore, even though physicians are aware of the lack of benefit of antibiotics for these infections, surveys have shown that physicians were much more likely to prescribe antibiotics when they believed that their patients expected to receive them.[11] However, physicians also overestimate the desire of their patients for an antibiotic.[14]

Given the substantial personal and societal impact of VRIs, the development of a safe and effective antiviral compound specifically targeted to the most common pathogen involved would represent a major advance in the field of respiratory infections. The picornavirus family includes important respiratory pathogens. The major groups causing VRIs are the rhinoviruses, which consist of more than 100 serotypes, and the enteroviruses, which comprise approximately 70 antigenic types. Rhinoviruses are the cause of about 50% of colds, and enteroviruses cause 5% to 15% of VRIs.[1]

Rhinoviruses are not only the primary etiologic agent in common colds; they also cause complications involving the upper and lower respiratory tract. These include otitis media, particularly in children; sinusitis; and exacerbations of asthma and other forms of airways disease, such as chronic obstructive pulmonary disease (COPD) and cystic fibrosis.[1,16-18] In addition, rhinoviruses can cause serious lower respiratory disease in certain populations, including infants and young children,[13,15,19] elderly persons,[20] and immunocompromised patients.[21] Unfortunately, many clinical microbiology laboratories do not use optimal techniques to detect rhinovirus infections, so they remain underappreciated pathogens. These techniques, such as culture, are not available in a clinically useful timeframe. Also, recently developed polymerase chain reaction (PCR) techniques, which are the most sensitive for rhinovirus identification, are available only at research facilities.

In this supplement, Dr. Arnold S. Monto begins with a review of

epidemiologic studies that have assessed the age-related rates of respiratory illness, the pathogens involved, and their seasonality, as well as the modes of transmission of rhinovirus infections. These studies have confirmed rhinoviruses as the cause of a majority of common colds, particularly when advanced techniques have been applied, such as viral RNA detection by reverse-transcription PCR testing. They also have reported the year-round occurrence of rhinovirus illness, with peaks in the fall and spring in temperate climates, and have highlighted the importance of children in introducing infections into the household. This information will be important in targeting specific antiviral therapy for VRIs resulting from picornaviruses and other viral respiratory pathogens.

In the second article, Dr. Jack M. Gwaltney, Jr. discusses emerging information about the pathogenesis of infections with rhinoviruses. Rhinovirus infection is efficient, and the infectious dose is quite small in the immunologically susceptible host. Furthermore, symptoms develop rapidly, within 16 hours of infection under experimental conditions, and are related to virally induced host responses, including the release of inflammatory mediators and neurogenic reflexes. Knowledge of the pathogenesis is important in the timing of any therapeutic approach. These findings highlight the importance of antiviral therapy to address the primary cause of illness and of early intervention, within the first day of symptom onset, in order to reduce viral replication promptly.

The third article, by Dr. James E. Gern, is an overview of the pathogenesis and clinical implications of rhinovirus VRIs in asthma. Viral infections, especially those caused by rhinovirus, are the most common cause of asthma exacerbations. Dr. Gern reviews several studies demonstrating the contribution of the host immune response to rhinovirus illness and the association between rhinovirus infection and exacerbations in individuals with established asthma. In the experimental setting, increased colds severity is associated with increased airway reactivity as measured by objective tests. The mechanisms by which a mucosal viral infection elicits systemic immune responses and contributes to exacerbations are areas of active investigation. This complex interaction is incompletely understood at present; important questions must be answered regarding the frequency and extent of viral replication in the lower respiratory tract, and the host inflammatory responses to infection need to be more completely characterized.

Patients with COPD and the elderly are also at risk for the development of serious lower respiratory tract illness caused by rhinoviruses. Dr. Stephen B. Greenberg reviews this topic in the fourth article and discusses the findings of a prospective observational study in older ambulatory

adults with or without COPD who were monitored over several years. The impact of rhinovirus infection in these populations was substantial. Dr. Greenberg's study found that picornaviruses, 75% of which were identified as rhinoviruses, were the most common pathogen found, followed by parainfluenza viruses and coronaviruses. Influenza was less common because of the high immunization rate in the populations studied. VRIs in the patients with COPD were associated with 2-fold higher health-care utilization rates including hospitalizations. Furthermore, as the population of the United States ages, the burden of disease will increase with respect to medical care resource utilization. One approach to decreasing the disease burden is development of a vaccine. Because more than 100 rhinovirus serotypes exist, however, this task is impractical. Given the low likelihood of an effective vaccine for rhinovirus infections, effective antiviral medications might prove beneficial in reducing this burden. Intervention studies targeting these populations are needed.

In the fifth article, Dr. Gwaltney discusses both historical perspectives and recent therapeutic trials in the treatment of rhinovirus VRIs. He reminds us of the importance of rigorous tests of common cold treatments under appropriately controlled and blinded conditions because of the variable but relatively short natural history of illness, the paucity of objective measures, and the large potential placebo effect, which earlier investigators commented on more than 60 years ago.[22] Because the pathogenesis of symptoms is related to the host immune response to the virus, combining early treatment with an antiviral agent and an anti-inflammatory compound may be the most effective therapeutic approach for VRIs resulting from rhinovirus and other viral respiratory pathogens. Although all of the candidate antirhinoviral agents are currently investigational, the studies to date have established the potential for prevention and early treatment of rhinovirus infections by selective antiviral agents.[23]

The supplement concludes with a review by Dr. Joseph S. Bertino of the burden of disease of VRIs and its association with excess antibiotic use, particularly in young children, and with the growing problem of antibiotic resistance in pathogenic respiratory bacteria. Dr. Bertino discusses recent surveys of patient and physician attitudes and practices that confirm the significant impact of VRIs. This article also summarizes the controlled studies that indicate that antibiotic therapy generally has shown no clinical benefits or reductions in complications in those with colds or purulent rhinitis. He then outlines the steps that can be taken to facilitate the introduction of antivirals into clinical practice and reminds us of the

limitations and possible side effects of the over-the-counter medications commonly used for VRIs.

In summary, the articles in this supplement underscore the significant burden of VRIs resulting from rhinovirus for the individual sufferer, for health care practitioners, and for society as a whole. They illustrate that for certain patient populations, the clinical consequences of VRIs can be serious. The purpose of this supplement is to discuss the increasingly recognized importance of rhinovirus infections in persons with or without comorbidities and to review current understanding of rhinovirus infection pathophysiology in light of newly developed agents targeted to this pathogen.

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