Editorial Response: Rhinovirus Pneumonia—A Clinical Entity?

Human rhinoviruses account for about one-half of common colds and 80%–90% of such illnesses during the early autumn in temperate northern areas [1]. The initial site of replication of rhinoviruses is the respiratory epithelium of the nasal passages, particularly the posterior nasopharynx (an area rich in ICAM-1, the cellular receptor for most rhinovirus serotypes). With use of biopsy specimens of nasal and nasopharyngeal epithelium collected during experimental rhinovirus infection, it has been shown by in situ hybridization that rhinovirus replication occurs mostly in ciliated epithelial cells but also in nonciliated cells [2]. Remarkable features of this infectious process are that the structure of the epithelium is preserved, only a small proportion of the epithelial cells are infected, and there is modest histological evidence of inflammatory cell invasion. Nevertheless, rhinovirus infection induces neurogenic reflexes and release of host inflammatory mediators leading to the symptoms of the common cold. Recently, viral RNA has been identified in maxillary sinus and middle-ear secretions from patients with acute sinusitis or otitis media [3, 4]. These findings suggest that rhinoviruses could also replicate in the epithelium of the paranasal cavities, although it is not rigorously established whether active rhinovirus replication is occurring at these sites.

See article by Ghosh et al. on pages 528–32.

In this issue of Clinical Infectious Diseases, Ghosh et al. [5] suggest that rhinovirus infections are also responsible for severe pneumonia in immunocompromised hosts, specifically pancycopenic blood and marrow transplant recipients receiving high doses of chemotherapy. During a 5-year observational study of acute respiratory illnesses in such patients, they identified 22 rhinovirus infections, seven of which were associated with progression to pneumonia and fatal respiratory failure. These cases were notable for a high frequency of fever, which is uncommon in uncomplicated rhinovirus infection; a prolonged interval between development of upper respiratory symptoms and development of pneumonia (median, 12 days), which appeared to exceed the duration of viral shedding (median, 8 days); a high rate of nosocomial acquisition (64% of cases); and a high frequency of busulfan exposure among those whose infections progressed to pneumonia (six of seven) compared with those whose infections did not (one of 15).

In six of the seven cases of fatal pneumonia, rhinovirus was isolated before death from a bronchoalveolar lavage fluid specimen and/or endotracheal aspirate. In five cases, autopsy was performed, and in four, no other infectious process was identified. Histopathologic examination of lung tissue specimens revealed interstitial pneumonitis and/or acute respiratory distress syndrome (ARDS). These observations suggest that rhinovirus could replicate in the lower respiratory tract and possibly cause viral pneumonia. An alternative explanation is that the histological changes were due to another cause and that the presence of rhinovirus was due to the patient’s cold. Of note, at the Fred Hutchinson Cancer Research Center (Seattle, WA) only one (3%) of 29 rhinovirus-infected marrow transplant recipients had recovery of rhinovirus from bronchoalveolar lavage specimens [5a].

What evidence is available to support or refute the hypothesis that rhinovirus can replicate in the lower respiratory tract and cause lung parenchymal damage? Under in vitro conditions, rhinoviruses grow well on human bronchial respiratory epithelial cells. The optimal temperature for rhinovirus replication in vitro is 33°C, which occurs in the nasal passages and large portions of the trachea and bronchi [6]. The warmer core temperature of the pulmonary parenchyma, particularly in a febrile patient, is an obstacle for optimal rhinovirus replication. Consequently, it is important to distinguish between recovery of virus from bronchi and that from lung tissue.

Despite the difficulty in definitely ruling out contamination from the upper respiratory tract, there is increasing direct and indirect evidence indicating that rhinoviruses can replicate in the tracheobronchial tree. Identification by culture of rhinovirus in bronchoalveolar lavage fluid, although infrequent, has been documented during natural infection [7] as well as during experimental infection [6]. Viral RNA was identified in bronchoalveolar lavage fluid specimens from healthy adults or asthmatic subjects experimentally infected with rhinovirus several days after inoculation [8]. Rhinovirus RNA was largely associated with cells from bronchial specimens and was less frequently identified in the fluids of these specimens, a finding arguing against contamination by upper respiratory secretions. More recently, a preliminary report described the identification of rhinovirus RNA in bronchial epithelia of four of 10 experimentally infected healthy or asthmatic adults by in situ hybridization [9]. Bronchial biopsies showed epithelial cells containing rhinovirus RNA 4 days after initial inoculation in the nasal cavity, whereas no rhinovirus RNA was detected during baseline biopsies. All these findings are direct arguments in favor of the ability of rhinoviruses to replicate in the lower respiratory tract.

Indirect evidence is provided by clinical and epidemiological studies. In the elderly, particularly in nursing homes, rhinovirus is responsible for 20% of respiratory tract infections, and more
than one-half of these patients have lower respiratory symptoms [10, 11]. In asthmatic children, as well as in adults, a high proportion of asthma exacerbations are associated with rhinovirus infections [12, 13], and following experimental infection, infiltration of the bronchial mucosa by inflammatory cells has been documented [14]. Rhinovirus infection is also associated with pulmonary dysfunction in patients with cystic fibrosis and exacerbations of chronic bronchitis. It has also been claimed to cause pneumonia in premature infants [15] and serious respiratory illness causing hospitalization in children [15a]. Moreover, one report described a case of fatal pneumonia in an asthmatic child in which rhinovirus was recovered from lung tissue at autopsy [16]. Taken together, these observations suggest that rhinovirus can replicate in the lower respiratory tract.

The observation of Ghosh et al. is of interest for clinicians but must be interpreted cautiously in part because of the retrospective observational nature of the study. The report raises many unanswered questions relevant to understanding how important rhinovirus replication was in the pathogenesis of the disease in these patients. It would be important to know how many patients with interstitial pneumonia and/or ARDS had cultures negative for rhinovirus, how often rhinovirus was recovered from lung tissue at autopsy and in what quantities relative to other sites in the respiratory tract, how often did myelosuppressed patients (unlike normal hosts) have rhinovirus-induced cytopathology in the upper airway or bronchial biopsy specimens, how well did the isolates from these patients replicate under different temperature-restricted conditions in vitro, and particularly whether rhinovirus RNA was demonstrable in lung parenchyma by in situ hybridization? The relatively long shedding of rhinovirus observed in two patients (>9 days after the onset of symptoms) is not uncommon in rhinovirus colds and, therefore, is not a strong argument in favor of replication in the lower respiratory tract.

In addition, the presence of other infections could have been associated with the lung injury found in some patients. Moreover, ARDS described in some of these patients could be associated with other causes (e.g., drug toxicity related to chemotherapy, particularly busulfan). It is not clear also whether the high mortality rate observed among patients with pneumonia was attributable to pneumonia itself or associated with other organ failure or other reasons. However, all these uncertainties are for the most part inherent to blood and marrow transplant patients themselves and their ability to develop multiple infections and unusual complications. The clinical observation reported in this issue of Clinical Infectious Diseases is original and raises the possibility that an innocent common cold could be associated with serious pulmonary complications.

A surprising finding of this study is that most of the rhinovirus infections were acquired during hospitalization. Nosocomial transmission of respiratory viruses is a well-documented threat; influenza viruses, respiratory syncytial virus, and parainfluenza viruses have all been associated with nosocomial outbreaks. The present report and a previous observation among institutionalized elderly persons [17] suggest that rhinovirus should also be included in this list of viruses. This observation reminds us that under experimental conditions the transmission of rhinoviruses by aerosols is not very efficient but that transmission following skin or finger contact with an infected donor is highly efficient [18]. Under natural conditions, hand contamination leading to self-inoculation also appears to be an important route of transmission, thus emphasizing the importance of hand washing, restriction of hospital staff with respiratory illnesses from contact with high-risk patients, and adherence to infection control measures.

It should be noted that chemoprophylaxis with intranasal IFN-α has been shown to be effective in preventing infection and symptoms in healthy persons [19, 20] but remains unstudied in immunocompromised hosts. Several new antiviral drugs active against rhinoviruses are under development, and clinical studies using Pleconaril (ViroPharma, Exton, PA), a capsid-binding agent, are well under way. In addition, studies of a 5C protease inhibitor are just being initiated. The possible value of these agents in treating immunocompromised hosts with rhinovirus infection should be defined in the next few years.

Is rhinovirus pneumonia a clinical entity? The available evidence does not allow a positive conclusion. Experimental and clinical data suggest that rhinovirus probably can spread from the initial site of replication in the nasopharynx to the tracheobronchial tree. Under certain circumstances, such as severe immunosuppression and neutropenia, this process might result in lung injury by an as yet undefined mechanism. However, the report in this issue of Clinical Infectious Diseases does not establish this sequence of events or prove that these patients died of rhinovirus pneumonia. Until more information becomes available, the recommendation that the identification of rhinovirus infection should postpone transplantation seems prudent. This recommendation extends to other respiratory viruses and, therefore, to all patients with acute upper respiratory tract symptoms. Further clinical observations from studies with larger populations are needed to determine the impact of rhinovirus infections in immunocompromised persons.

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References


