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Respiratory Illness Caused by Picornavirus Infection: A Review of Clinical Outcomes

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ABSTRACT

Background: Respiratory infections result from invasion of the respiratory tract, mainly by viruses, and are the leading cause of acute morbidity in individuals of all ages worldwide. During peak season, picornaviruses cause 82% of all episodes of acute nasopharyngitis (the common cold), the most frequent manifestation of acute respiratory infection, and produce more restriction of activity and physician consultations annually than any other viral or bacterial source of respiratory illness.

Objective: This article reviews the clinical impact and outcomes of picornavirus-induced respiratory infections in specific populations at risk for complications. It also discusses the potential economic impact of the morbidity associated with picornavirus-induced respiratory infection.

Methods: Relevant literature was identified through searches of MEDLINE, OVID, International Pharmaceutical Abstracts, and Lexis-Nexis. The search terms used were *picornavirus*, *rhinovirus*, *enterovirus*, *viral respiratory infection*, *upper respiratory infection*, *disease burden*, *economic*, *cost*, *complications*, *asthma*, *COPD*, *immunocompromised*, *elderly*, *otitis media*, and *sinusitis*. Additional publications were identified from the reference lists of the retrieved articles.

Conclusions: Based on the clinical literature, picornavirus infections are associated with severe morbidity as well as considerable economic and societal costs. Future research should focus on identifying patterns of illness and the costs associated with management of these infections. New treatments should be assessed not only in terms of their ability to produce the desired clinical outcome, but also in terms of their ability to reduce the burden of disease, decrease health care costs, and improve productivity.

Key words: picornavirus, rhinovirus, cold, cost, clinical outcomes. (*Clin Ther.* 2001; 23:1615–1627)

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INTRODUCTION

Respiratory infections are recognized as the leading cause of acute morbidity in individuals of all ages worldwide. In developing countries, the morbidity associated with respiratory infections may be at least as severe as that in industrialized countries, and these infections are the leading cause of death in children under 5 years of age.^{1,2} The Health Interview Survey quantifies illnesses that result in disability and/or physician consultation in the US population. Based on this survey, the annual incidence of acute respiratory infections in the United States in 1996 was 79%, exceeding the rates of digestive conditions, injuries, and infective/parasitic conditions combined.³ These infections may result from invasion of the respiratory tract by bacteria, viruses, or, in rare cases, other infectious agents; however, viruses are the most frequently identified pathogens. The viral pathogens primarily associated with acute respiratory infections include picornaviruses, coronaviruses, adenoviruses, parainfluenza viruses, influenza viruses, and respiratory syncytial viruses¹ (Figure 1⁴).

Picornaviruses are a large group of RNA viruses. In terms of causing acute respiratory infection in humans, the most important picornaviruses are the rhinoviruses and enteroviruses. Picornaviruses contribute significantly to the incidence of acute respiratory infections. In a study conducted during the autumn,⁵ picornaviruses were found to cause 82% of all episodes of acute nasopharyngitis, which is the most common manifestation of acute respiratory infection. Individually, the incidence of acute nasopharyngitis in adults ranges from 2 to 4 cases per year

and in children from 6 to 8 cases per year.^{6,7} Although picornavirus-induced nasopharyngitis is often referred to as the common cold, the morbidity associated with these infections should not be trivialized. In fact, because rhinovirus-induced illnesses are so common, they produce more restriction of activity and physician consultations annually than respiratory illnesses caused by other viruses or bacteria.⁸

This article reviews the clinical impact and outcomes associated with picornavirus-induced respiratory infection in specific populations at risk for complications secondary to these infections. It also discusses the potential economic impact of the morbidity associated with picornavirus-induced respiratory infections. Relevant literature was identified through searches of MEDLINE, OVID, International Pharmaceutical Abstracts, and Lexis-Nexis. The search terms used were *picornavirus*, *rhinovirus*, *enterovirus*, *viral respiratory infection*, *upper respiratory infection*, *disease burden*, *economic*, *cost*, *complications*, *asthma*, *COPD*, *immunocompromised*, *elderly*, *otitis media*, and *sinusitis*. Additional publications were identified from the reference lists of the retrieved articles.

CLINICAL MANIFESTATIONS AND OCCURRENCE

Rhinovirus infections are associated with more pronounced clinical manifestations than respiratory infections of other viral etiologies. As many as 70% to 88% of human rhinovirus infections result in symptomatic respiratory episodes characterized by rhinorrhea, nasal obstruction, cough, and hoarseness.⁹ The median duration of illness in young adults is 7 days; however,

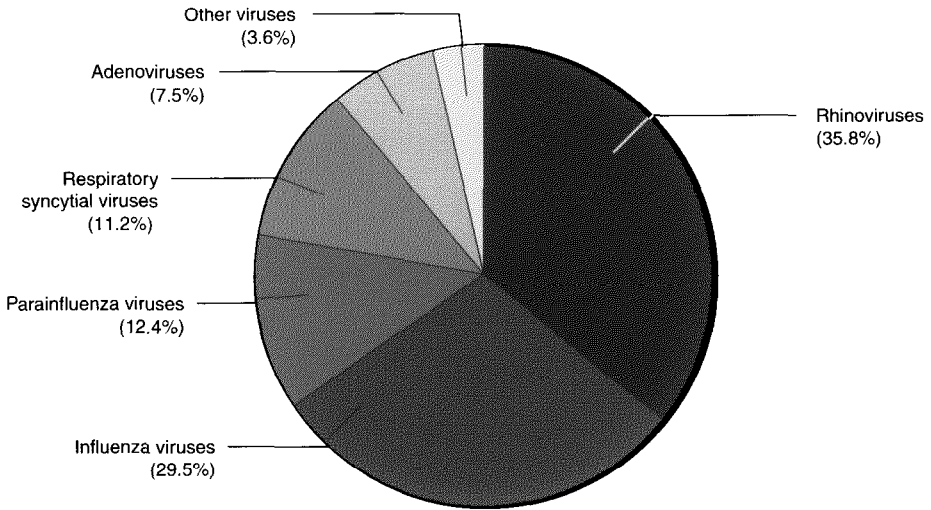


Figure 1. Distribution of viral isolates in a study of rhinovirus-associated illnesses in Tecumseh, Michigan, from 1976 to 1981. Reprinted with permission from Monto et al, *Journal of Infectious Diseases*, University of Chicago Press.

symptoms may last up to 2 weeks in one quarter of cases, and the duration of illness may be even longer in children and the elderly.⁹ There is a peak in the incidence of rhinovirus infection in early fall and again in mid- to late spring¹⁰ (Figure 2⁴). Younger children appear to be more susceptible to viral respiratory infections, as demonstrated by the fact that preschool children can have 5 to 9 respiratory infections per year.¹¹ In fact, during an outbreak of a new virus strain, over three fourths of the children in a nursery school were infected.¹² Also, secondary attack rates in family members have been observed to range from 25% to 70%, depending on the immune status of the exposed individual.¹²

The high incidence of viral respiratory infections is most likely due to the large number of rhinovirus types and the fact

that immunity is type specific and of short duration. For these reasons among others, the role of rhinoviruses has overshadowed that of enteroviruses, which also contribute to the morbidity of viral respiratory infections. It is estimated that enteroviruses infect between 10 and 15 million people annually. Episodes of enterovirus-induced respiratory infection are seen throughout the year; however, the most prominent respiratory syndrome caused by these pathogens occurs in children during the summer months.¹³ These enteroviral infections typically result in a nonspecific febrile illness complicated by respiratory symptoms.¹⁴

Although viral respiratory infections due to picornaviruses appear to be self-limiting in most healthy adults, they are increasingly implicated in acute infectious exacerbations of illnesses in high-risk

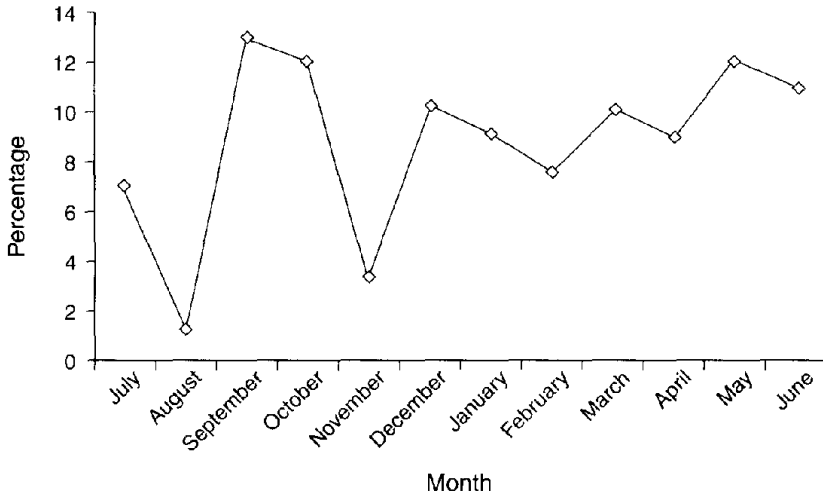


Figure 2. Distribution of rhinoviruses isolated by month in a study of rhinovirus-associated illnesses in Tecumseh, Michigan, from 1976 to 1981. Reprinted with permission from Monto et al, *Journal of Infectious Diseases*, University of Chicago Press.

populations. Technological advances such as polymerase chain-reaction testing have made virus identification more sensitive and readily available. This, in turn, has made it possible to identify specific patient populations (eg, the elderly, infants, and immunocompromised persons), who are particularly susceptible to picornavirus infection and in whom infectious episodes typically significantly increase the use of health care resources.¹⁵ In addition, these advances in technology have confirmed the results of earlier studies, further demonstrating the significance of rhinoviruses in causing or predisposing patients to otitis media and sinusitis and exacerbating other chronic respiratory diseases such as asthma, cystic fibrosis, and chronic obstructive pulmonary disease (COPD).

ROLE OF PICORNAVIRUSES IN ASTHMA

Asthma is estimated to affect >17 million people (6% of the population) in the United States, resulting in over 100 million days of restricted activity and 470,000 hospitalizations annually.^{16,17} In 1990, the estimated cost of treating asthma was \$6.2 billion; 43% of those costs were associated with emergency department visits, hospitalizations, and death.¹⁸ Respiratory infections caused by picornaviruses are believed to be a major contributor to asthma exacerbations, particularly in children. Asthmatic children appear to experience a significantly greater number of viral respiratory infections compared with nonasthmatic children.¹⁹ Up to 45% of acute asthma exacerbations in children are

thought to be related to viral respiratory infections.²⁰ The most common cause of these infections are the rhinoviruses, which have been recovered from the respiratory tract at the onset of an asthma attack, suggesting that the virus may have been an initiating factor in the attack.²¹

Several studies have identified rhinovirus as the pathogen most commonly associated with asthma in those >2 years of age.¹⁵ Rakes et al²² conducted a cross-sectional study examining the prevalence of respiratory viruses in children presenting to the emergency department because of wheezing episodes. They found that respiratory viruses were present in 82% of children <2 years of age and in 83% of children between 2 and 16 years of age. Rhinovirus was the predominant pathogen isolated in children >2 years of age (71%), indicating that the majority of wheezing episodes in this age group may be associated with rhinoviruses.

The prevalence of rhinoviruses in asthmatic children was further investigated by Johnston et al.²³ In a 13-month trial, these authors evaluated 108 children between the ages of 9 and 11 years with the respiratory symptoms of wheezing and/or cough and a decrease in peak expiratory flow rate (PEFR). Respiratory viruses, two thirds of which were rhinoviruses, were detected in 77% of patients. Viral respiratory infections were implicated in 85% of episodes with upper respiratory symptoms and 80% of episodes with reductions in PEFR. The median reduction in PEFR was 81 L/min, and the median duration of decline in PEFR was 14 days. Based on their results, the authors reported that 80% to 85% of asthma exacerbations in school-aged children appear to be associated with viral respiratory infections, primarily with rhinoviruses.

The association between viral respiratory infections and asthma exacerbations is less clear in adults. Previous studies have reported the presence of viral respiratory infections in only 10% to 21% of adult asthmatic patients.²⁰ However, Beasley et al²⁴ found the prevalence of viral respiratory infections to be 36% in adults with severe asthma and 10% in those with mild exacerbation of asthma. Nicholson et al²⁵ conducted a longitudinal trial in asthmatic adults between the ages of 19 and 46 years, evaluating 315 episodes of respiratory illness over 2 years. The average duration of asthma in the patient population was ~20 years. Thirty-eight percent of the patients had previously been hospitalized for asthma. The investigators found that 80% of subjective asthma exacerbations occurred with symptomatic colds and 89% of symptomatic colds were associated with symptoms of asthma. These findings suggest that acute respiratory infections may be as commonly linked to exacerbations of asthma in adults as they are in children. In this study, 84 clinical episodes of respiratory illness were associated with objective evidence of an asthma exacerbation (decrease in PEFR \geq 50 L/min). Sixty-three percent of laboratory-confirmed acute respiratory infections were found to be caused by rhinoviruses. Of the 84 clinical episodes of respiratory illness associated with an objective asthma exacerbation, patients consulted a general practitioner in 49% of episodes, required oral steroids in 38%, required a nebulizer in 21%, and were prescribed antibiotics in 33%.

In addition to the clinical impact of rhinoviruses in asthma, their impact on medical resource use has also been demonstrated. Teichtahl et al²⁰ compared the incidence of respiratory infection in 79

patients admitted to the respiratory medical unit for acute asthma with that in 54 control subjects admitted to the surgical unit for elective surgery. Twenty-nine (37%) of the patients who were admitted for asthma exacerbation had evidence of a respiratory infection, compared with 5 (9%) of the control group ($P < 0.001$). Of the 23 asthma patients with confirmed evidence of a viral infection, 9 (39%) had rhinovirus infections.

ROLE OF PICORNAVIRUSES IN THE ELDERLY

Significant mortality resulting from viral respiratory infections is routinely observed in the elderly. Although mortality resulting specifically from rhinoviral respiratory infections has not been demonstrated, considerable morbidity is associated with these infections. In a study by Nicholson et al,²⁶ 533 adults aged between 60 and 90 years were monitored for episodes of viral upper respiratory tract infections. The annual incidence of viral respiratory infections was found to be 1.2 per patient. A total of 231 pathogens were identified in 211 (42%) of the 497 episodes for which specimens were available. Of the pathogens identified, 121 (52%) were rhinoviruses. Of the 96 (45%) patients in whom rhinovirus was the sole pathogen isolated, 60 (63%) patients had lower respiratory tract involvement. The median duration of illness in these patients was 16 days. Of the 60 patients with lower respiratory tract involvement, 25 (42%) had to restrict their normal activities (eg, cleaning, grocery shopping), and 16 (27%) were bedridden. A total of 41 (68%) patients sought medical attention, and antibiotics were prescribed for 76%.²⁷ Altogether, 3 patients were hospitalized, 1 of

whom died from exacerbation of COPD by rhinovirus infection. The authors reported that the overall burden of rhinovirus infection was greater than that of the viruses typically associated with significant morbidity and mortality, such as influenza.²⁶

A second study assessing the impact of rhinovirus infection on the elderly focused on an outbreak of respiratory illness among patients in a long-term care facility.²⁸ Specimens from the throat and nasopharynx of 67 patients were obtained and cultured. Of the 67 cultures, 33 (49%) were positive for rhinovirus. Each of the patients with rhinovirus-positive cultures had upper respiratory tract symptoms, 23 (70%) had systemic symptoms, 22 (67%) had gastrointestinal symptoms, and 11 (33%) had lower respiratory tract symptoms. More severe disease progression was found in 17 (52%) rhinovirus-infected patients with concomitant COPD. Five of 17 (29%) patients with COPD required pharmacologic bronchodilation, 2 (12%) had to be transferred out of the facility because of declining respiratory function, and 1 (6%) died of respiratory failure. These findings indicate that outbreaks of rhinovirus infections in nursing homes should be considered potentially serious.

ASSOCIATION OF VIRAL RESPIRATORY INFECTIONS WITH OTITIS MEDIA AND SINUSITIS

A study from the 1960s indicated that 2.0% of community respiratory diseases were complicated by otitis media and 0.5% by sinusitis.⁷ Although such percentages may seem insignificant, the high frequency of respiratory infections means that large numbers of patients are affected. A conservative estimate places the inci-

dence of viral respiratory infections in the United States at 0.7 infection per person per year.⁹ Based on these data, an estimated 196 million people in the United States experience a viral respiratory infection each year, with ~4 million of these infections complicated by otitis media and almost 1 million complicated by sinusitis. New technologies that permit more accurate identification of viral pathogens will probably reveal that the frequency of virally induced infections is even higher and that viral pathogens are a precursor in more cases of otitis media and sinusitis than originally estimated; however, further research is necessary.

It has been estimated that >90% of patients with otitis media also have symptoms of upper respiratory tract infections that are probably the result of a primary viral infection.²⁹ This correlation is supported by the fact that 40% to 50% of patients with otitis media have detectable virus in the nasopharynx, and 17% have detectable virus in the middle ear.²⁹ Viruses can also complicate the course of recovery for patients with otitis media. In 2 recent studies,^{30,31} viruses in the middle ear have been implicated in the apparent failure of antibiotic treatment by complicating the response to treatment. In a study in 71 patients with combined viral and bacterial otitis media,³¹ the presence of rhinovirus was associated with a higher failure rate of antibiotic therapy than was respiratory syncytial virus, parainfluenza virus, or influenza virus.

Rhinovirus has been identified as a potential pathogen in ~40% of cases of community-acquired sinusitis.³² Although there is evidence that these viruses contribute to the development of sinusitis, their exact role remains undefined. In a study by Turner et al,³³ 34 healthy adults

were experimentally infected with rhinovirus. On magnetic resonance imaging, changes were observed in the paranasal sinuses of 33% of subjects. The relationship between viral infections and sinusitis was further investigated in a study evaluating naturally acquired acute nasopharyngitis.³⁴ In this study, sinus abnormalities were detected by computed tomography in over 85% (29) of adult patients. After 2 weeks of observation, spontaneous resolution of these abnormalities occurred in almost 80% (27) of untreated patients, indicating that the cause of a significant proportion of sinusitis cases may be solely viral.

RHINOVIRAL RESPIRATORY INFECTIONS AND LOWER RESPIRATORY TRACT INVOLVEMENT IN HIGH-RISK POPULATIONS

Data from several trials suggest that viral or secondary bacterial pneumonia may develop in the wake of viral upper respiratory tract infections in some patient populations.¹⁵ Although the role of picornaviruses in these more serious diseases of the lower respiratory tract cannot be determined definitively without more extensive sampling of the lower respiratory tract, recent studies have pointed to the importance of picornavirus infection in these disease processes in particular patient populations.¹⁵

Infants with bronchopulmonary dysplasia are at a significantly increased risk for acute episodes of severe viral respiratory infection. In a study by Daily,³⁵ 27 of 41 (66%) preterm infants with bronchopulmonary dysplasia required rehospitalization, the most common cause being upper respiratory tract infection. Whereas some

studies^{10,15} have indicated that respiratory syncytial virus is the pathogen most commonly isolated in these patients, others^{36,37} have demonstrated that rhinovirus makes a substantial contribution. In fact, because none of these studies used assays suitable for identifying rhinoviruses, the role of these agents may have been underestimated. Chidekel et al³⁷ studied 40 patients (44 cases) with a history of bronchopulmonary dysplasia for an average of 16 months and identified 8 (18%) cases of severe lower respiratory tract infection that were associated with rhinoviruses. Of the 7 patients in these 8 cases, 5 (71%) required hospitalization for a mean duration of 11 days, and 4 (57%) were admitted to the intensive care unit. Patients with rhinoviral respiratory infections required additional long-term medical therapy, suggesting that rhinoviruses can have lasting clinical implications.

Patients with cystic fibrosis are also at increased risk for complications of viral respiratory infections. In fact, 18% to 38% of pulmonary exacerbations are preceded by viral respiratory infections. Collinson et al³⁸ recorded 147 episodes of acute nasopharyngitis over 17 months in 37 children with cystic fibrosis aged between 2 months and 18 years, translating into an annual incidence of 2.7%. Cultures were available for 119 of the 147 episodes, and the causative pathogen was identified as rhinovirus in 21 (18%) episodes. These viral respiratory infections were associated with acute decreases in pulmonary function, increased rates of disease progression, and a predisposition to bacterial pulmonary infection.

Lower respiratory tract infections are the most common complication of viral respiratory infection in immunocompromised patients.³⁹ In one study,⁴⁰ the com-

monly identified causes of viral respiratory infection in immunocompromised patients included cytomegalovirus, herpes simplex virus, and varicella-zoster virus; however, viruses such as the picornaviruses were also implicated. In this and other studies, it is not certain that the techniques used were capable of detecting rhinovirus and whether these viruses were accurately represented in the study findings. Immunocompromised patients are at risk for developing serious or life-threatening disease as a result of a viral infection of the respiratory tract. In the study by Rabella et al,⁴⁰ both rhinoviruses and enteroviruses were identified as viral pathogens in 785 immunosuppressed patients (ie, patients infected with HIV, bone marrow transplant recipients, organ transplant recipients, patients with hematologic malignancies) with a suspected respiratory infection between January 1991 and December 1995. Picornavirus infections were associated with respiratory failure in 2 patients, 1 of them requiring mechanical ventilation and the other having a clinical course resulting in pneumonia.

In a study conducted at the University of Texas M.D. Anderson Cancer Center (MDACC),⁴¹ 130 cases of picornavirus infection were identified in adult patients with leukemia and bone marrow transplant recipients. More than 90% of the picornavirus infections tested were found to be caused by rhinoviruses. In several patients, the infection progressed to pneumonia that appeared to be bacterial or fungal in origin. However, some patients had a clinical course consistent with viral pneumonia and died of unexplained interstitial pneumonia.

In a 5-year retrospective follow-up study of 23 blood and bone marrow transplant recipients who had symptoms of up-

per respiratory tract infection,⁴² rhinovirus was identified as the causative pathogen in all patients. Eight (35%) patients developed progressive pneumonia that resulted in death. Autopsies on 5 of 6 patients demonstrated interstitial pneumonitis and/or changes of acute respiratory distress syndrome. The deaths were attributed to progressive viral pneumonia on the basis of histologic features and ante mortem isolation of rhinovirus from lower respiratory tract sites.

In a prospective study conducted at MDACC,⁴³ an evaluation of adult bone marrow transplant recipients hospitalized for an acute viral respiratory infection demonstrated that 18% of the 217 identified infections were due to picornaviruses. Of 12 patients in whom rhinovirus had been implicated as the causative pathogen, 7 (58%) developed complicating pneumonia, and 3 (25%) died as a result. Findings from autopsies performed on 2 of the patients were consistent with progressive viral pneumonia. A third trial at MDACC investigating acute respiratory illnesses in hospitalized patients with leukemia found that 18% of viral infections were caused by picornaviruses.⁴¹ Together, the results of these studies demonstrate that immunocompromised hosts are at increased risk from serious picornavirus infections, which have the potential to result in death.

ECONOMIC IMPLICATIONS

Although the economic impact of picornavirus infections is most pronounced in the at-risk populations described, these infections have a significant economic impact on the general population as well. Picornavirus infection is manifested primarily as acute nasopharyngitis. According to estimates from the National Center for

Health Statistics,³ >62 million cases of the common cold required medical attention and resulted in 148 million days of restricted activity in 1996. Even more significant from the economic and productivity perspectives, acute nasopharyngitis caused ~20 million lost workdays in adults aged ≥ 18 years and 21 million lost school days in children aged < 18 years.

Also important from an employer's perspective is the fact that employees miss days of work not only when they themselves are ill but when they stay home to care for sick children. Productivity is also diminished when employees come to work with a picornavirus-induced respiratory infection. The compromised quality of life associated with these infections in turn has a negative effect on productivity. Furthermore, many of the medications currently used for the palliative treatment of respiratory symptoms cause drowsiness, which may further diminish efficiency and productivity in the workplace. Finally, because respiratory picornavirus infections are easily transmitted to persons in proximity to infected individuals, other employees are likely to become infected, resulting in additional losses in productivity. Because factors affecting productivity and quality of life are increasingly important in today's health care environment, further analyses are needed to better quantify the impact of respiratory picornavirus infections on the overall health care population.

To date, the direct use of health care resources associated with viral respiratory illness in the general population has not been investigated comprehensively. The current literature focuses primarily on at-risk populations. These data indicate that use of emergency department and hospital services for exacerbations or compli-

cations caused by picornavirus infections is the major factor in the economic impact of respiratory infections within such at-risk subpopulations as asthma patients, the elderly, high-risk patients with diseases of the lower respiratory tract, cystic fibrosis patients, and immunocompromised patients. Patients with sinusitis or otitis media are an exception, with physician office visits and antibiotic use accounting for the majority of the economic impact.

The economic impact of picornavirus infections is illustrated by findings that asthma exacerbations are linked to rhinovirus infections in 57% of children and 15% of adults hospitalized for asthma exacerbations.^{20,23} If these statistics are applied to the average 463,500 asthma-related hospitalizations per year (34.6% of which involve children),¹⁸ rhinovirus infections are responsible for an estimated 136,800 hospitalizations annually. Based on these figures and an average cost of \$3000 per hospitalization for an asthma exacerbation, the cost of hospitalizations due to rhinovirus-induced asthma exacerbations would be >\$410 million annually. A prospective economic analysis of hospitalizations due to respiratory infections in the asthmatic population remains to be conducted. Other markers of the economic impact of rhinoviral respiratory infections in the asthmatic population are not as well defined as the costs associated with hospitalization. Factors such as the use of other health care resources (medications and physician office visits), productivity, quality of life, and work and school absenteeism have not been measured to a significant extent, and further evaluation of these variables will be crucial to establishing the true economic burden of viral respiratory infections in the asthmatic population.

Patients with picornavirus infections who are at high risk for complications because of age (infants, the elderly), lower respiratory tract involvement (patients with COPD), or immune status (cystic fibrosis patients, immunocompromised patients) constitute additional populations in which hospital and emergency department use are the greatest contributors to overall costs. Again, the literature described in this review illustrates a definite link between picornavirus infections and increased health care use in these populations; however, the overall patterns of resource use and costs of illness have not been defined.

CONCLUSIONS

In addition to the significant morbidity associated with picornavirus infections in the clinical literature, these infections also have substantial economic and societal implications. Because the magnitude of these implications is not yet well defined, future research should focus on identifying the patterns of illness and costs associated with the management of these infections. The ability to determine the costs associated with viral respiratory infections will be particularly important when evaluating new treatments, which should be viewed not only in terms of their ability to produce the desired clinical outcome, but also in terms of their ability to reduce the burden of disease, decrease health care costs, and improve productivity.

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