The Laryngoscope
Issue: Volume 106(10), October 1996, pp 1298-1305

Publication Type: [Independent Papers]
ISSN: 0023-852X
Accession: 00005537-199610000-00025

[Independent Papers]

Prechallenge Antibodies: Moderators of Infection Rate, Signs, and Symptoms in Adults Experimentally Challenged With Rhinovirus Type 39

Alper, Cuneyt M. MD; Doyle, William J. PhD; Skoner, David P. MD; Buchman, Craig A. MD; Seroky, James T. MA; Gwaltney, Jack M. MD; Cohen, Sheldon A. PhD

Author Information

From the Department of Pediatric Otolaryngology (C.M.A., W.J.D., C.A.B. J.T.S.) andthe Department of Allergy and Immunology (D.P.S.), Children's Hospital of Pittsburgh and the University of Pittsburgh School of Medicine; from the Center for Prevention of Disease and Injury (J.M.G.), University of Virginia School of Medicine, Charlottesville; and from the Department of Psychiatry (S.A.C.), Carnegie Mellon University, Pittsburgh.

Presented at the 18th Midwinter Research Meeting of the Association for Research in Otolaryngology, St. Petersburg Beach, Fla., February 1995.

This work was supported in part by National Institutes of Health grant DC 01260 and grant MH 50429.

Editor's Note: This Manuscript was accepted for publication May 17, 1996.

Send Reprint Requests to Cuneyt M. Alper, MD, Department of Pediatric Otolaryngology, Children's Hospital of Pittsburgh, 3705 5th Ave. at DeSoto St., Pittsburgh, PA 15213.

Abstract

This study determined the influence of serum neutralizing antibody titers on infection rate, symptom manifestations, and provoked signs and pathophysiologies in adults experimentally exposed to rhinovirus type 39(RV-39). Antibody status was determined for 151 healthy volunteers who were then cloistered in a hotel for 6 days. At the end of the first cloister day, the volunteers were challenged with RV-39 in a median tissue culture infective dose of 100. On each of the 6 days, a nasal examination was performed, symptoms were scored, and objective tests of nasal mucociliary function, nasal airway patency, secretion production, and middle ear pressures were completed. Both subjects and investigators were blinded to the prechallenge serum homotypic antibody titers of the subjects.

Four subjects presented with a wild virus and were excluded from the analysis. Of the 147 included subjects, prechallenge serum antibody titers to RV-39 were low (under 2) in 56 subjects, intermediate (2 to 8) in 51 subjects, and high (above 16) in 40 subjects. The high-titer group was significantly different from the low-titer group with respect to viral shedding, symptom load, subjective extent of illness, and secretion production, as well as in the frequency of subjects with abnormal nasal mucociliary clearance and positive middle ear pressures. The study results document that for experimental RV-39 exposure, high levels of homotypic serum neutralizing antibody titers are associated with protection from infection and a lessened degree of disease expression, but not with a reduction of otologic complications.

Laryngoscope, 106:1298-1305, 1996

INTRODUCTION

Upper respiratory tract infections (URIs) are the most common illnesses in people of all ages. These infections are associated with localized regional inflammation expressed as nasal and throat signs and symptoms, as well as more general systemic expressions, including fever, malaise, muscle aches, and other indicators of ill health.

Because of their high incidence, URIs contribute greatly to morbidity in the human population, and they impose a significant economic burden as a result of work and school absenteeism and monetary expenditures on symptomatic treatments. Moreover, URIs often precede the development of pathology in anatomically contiguous structures, such as the eustachian tube, the middle ear, the paranasal sinuses, and the lower airways. These complications, which include sinusitis, otitis media, asthma exacerbation, and pneumonia, contribute further to the morbidity and economic burden of acute respiratory disease.[1-7]

Epidemiologic studies document that the majority of URIs have a viral etiology, with the rhinoviruses contributing to as many as 30% to 40% of infections.[8,9] Because of virus specificity, acquired resistance, and the potential toxicity of available antiviral compounds, effective treatment for most viral URIs is not feasible at present. For certain viruses, such as the influenza A virus, prevention of infection by vaccination has been shown to be effective in limiting the frequency of both primary virus expression and its complications.[10] However, this strategy is not applicable to other viruses, including the rhinoviruses.

Human rhinoviruses exhibit a high degree of antigenic variation, and over 100 serotypes have been identified.[11] Past studies have shown that anti-rhinovirus antibodies are highly serotype-specific, demonstrating little or no cross-neutralization of heterologous serotypes. Moreover, the mechanism of antibody-mediated neutralization of rhinoviruses is not completely understood. Antibodies have been postulated to neutralize infectivity by inducing structural changes in the capsid, by interfering with attachment, or, possibly, by preventing uncoating by intracapsid cross-linking.[12,13]

We recently completed a large adult study that was designed to define the factors that influence the rate of infection and the symptoms, signs, pathophysiologies, and complications of common colds resulting from experimental rhinovirus exposure. The data presented in this article focus on the role of preexisting homotypic serum antibodies in moderating those aspects of disease expression.

MATERIALS AND METHODS

Study Population

The subjects for this study were recruited by newspaper advertisement from the communities surrounding the University of Pittsburgh. Potential subjects were screened by history for previous nasal or otologic disease, and they were given a general physical examination. Urinalysis was performed, and standard methods were used to conduct blood assays for markers of hepatic and renal function and serum antibodies to human immunodeficiency virus (HIV), hepatitis viruses and rhinovirus type 39 (RV-39). Subjects were excluded if they presented with findings or a history suggestive of systemic illness or recent URI, if they had marked elevations in the assayed parameters indicative of hepatic or renal impairment, if they required prescription medication for any condition other than birth control, or if they had antibodies to HIV.

The study population included 151 healthy adult volunteers with a mean age of 28 years (range: 18 to 55 years). The 85 female and 66 male subjects were divided into three cohorts, which were studied in May 1993 (n=46), October 1993(n=48), and May 1994 (n=57). Of the 151 subjects, 21 subjects (14%) were African American, 2 subjects were (1.4%) Hispanic, 2 subjects (1.4%) were Asian, and the remainder (83%) were Caucasian.

Protocols, monitoring procedures, the viral challenge strain, the cloister site, and the study personnel were identical for the three cohorts. All subjects and investigators were blinded to the prechallenge antibody levels. The study was approved by the Human Rights Committee at the University of Pittsburgh, and all subjects provided written informed consents for HIV screening and study participation.

Study Protocol

The subjects were cloistered in separate rooms of a local hotel for a 6-day period (study days 0 to 5). On each day of cloister, symptoms were scored by the subjects, signs were evaluated by a physician, temperatures and vitals signs were recorded, and objective measurements of nasal mucociliary transport rate, airway patency, secretion production, and middle ear pressures were obtained. Nasal lavage was also performed, and samples were submitted for quantitative rhinovirus culture.

Twenty-four hours after admission to cloister (i.e., the end of study day 0), all subjects were intranasally inoculated with a safety-tested clinical isolate of RV-39 in a median tissue culture infective dose of approximately 100(100 $TCID_{50}$), using a method previously described.[1,2] At the end of study day 5, the subjects were dismissed from the cloister, but they returned to the laboratory on day 19, 20, or 21 for phlebotomy to assess convalescent antibody titers.

Methods of Assessment

On arriving at the cloister site, the subjects were provided with preweighed tissues. They were instructed to expel their nasal secretions into the tissues before they performed the rhinomanometric tests and at other times as needed. Expended tissues were sealed in a plastic bag of known weight. At the completion of each day, the bags were weighed, and the total secretion weight expelled during the day was determined by subtraction.

In the morning of each day, the subjects were given a general physical examination. Vital signs were recorded, pulmonary function was evaluated by spirometry, and nasal lavage was performed for virus culture using standard methods for isolation and quantification of rhinovirus.[8,14] At that time, and again in the afternoon and early evening hours, temperatures were recorded.

In the morning and evening of each day, nasal airway patency was evaluated by active anterior rhinomanometry using a microcomputer-assisted rhinomanometer developed in our laboratories. Inspiratory nasal conductance (the airflow at a given pressure, in liters per second per centimeter of water) was determined from the data collected over a period of 20 seconds while the subject was breathing in a relaxed manner.2 In the morning, afternoon and evening hours, middle ear status was assessed by tympanometry using a commercially available clinical instrument (Teledyne Impedance Screener). At each testing, middle ear pressures and acoustic emittance were recorded bilaterally.

In the afternoon hours, eight specific symptoms previously identified as characterizing a cold were scored by the subject on a five-point scale corresponding to none, mild, moderate, moderate to severe, and severe.2 These symptoms included sneezing, headache, malaise, chilliness, nasal discharge, nasal congestion, cough, and sore throat. The subjects were also asked whether or not they believed that they had a cold on that day.

In the afternoon hours, the subjects also underwent a nasal examination with headlight and nasal speculum. Nasal patency was scored from 0 to 4, corresponding to wide open, open, slightly obstructed, moderately obstructed, and severely obstructed. Mucosal edema was scored from 0 to 3, corresponding to none, mild, moderate, and severe. The color of the mucosa was coded as normal, pale, pink, or red. The observed quantity of rhinorrhea was scored from 0 to 4, corresponding to none, scanty, some, moderate, and profuse, and the quality of rhinorrhea was coded as none, serous, seromucoid, mucoid, or purulent. The color of the rhinorrhea was coded as none, colorless, white, or yellow. Any observation of middle meatus drainage suggestive of sinus disease was recorded. Other relevant findings, such as mucosal erosion and epistaxis, were also recorded.

Nasal mucociliary transport times were measured using a modification of the dyed saccharin technique.15 The time from the introduction of the dyed saccharin solution into the nose to the time when the subject reported a sweet taste, confirmed by the visual observation of dye in the nasopharynx, was defined as the clearance time. For these test, each subject was followed for a maximum of 30 minutes.

Statistical Methods

For the analysis, the subjects were assigned to one of three groups according to their prechallenge RV-39 neutralizing antibody titers. The subjects with titers of less than 2 were assigned to the low-titer (LT) group, those with titers of 2, 4, and 8 were assigned to the intermediate-titer (IT) group, and those with titers of 16 or more were assigned to the high-titer (HT) group.

Subjects were defined as being infected if RV-39 was recovered from their nasal lavage fluids on any of study days 0 to 5 or if a fourfold rise in homotypic antibody was documented for the convalescent (vs. the prechallenge) serum. Subjects were classified as having had a symptomatic cold on the basis of a modification of the criteria described by Jackson, et al.16: that is, a total baseline-adjusted symptom score of at least 6 during the period of cloister and either symptoms of rhinorrhea for 3 days or the subjects' belief that they had had a cold.

In a preliminary analysis, the data for the frequency of infected subjects and the frequency of subjects with colds were compared among groups using a chi-squared test. Because the infection rates differed significantly between the groups, the remaining comparisons were performed using the data available for the infected subjects in each group. For each recorded variable, the average values for each of the three groups were plotted as a function of time to gain a visual appreciation of the temporal pattern for expression (Fig. 1). To avoid problems associated with multiple comparisons at different time points, all statistical analyses of the differences among groups for the measured variables were based on comparisons of the summary response variables defined below and presented in Table I.

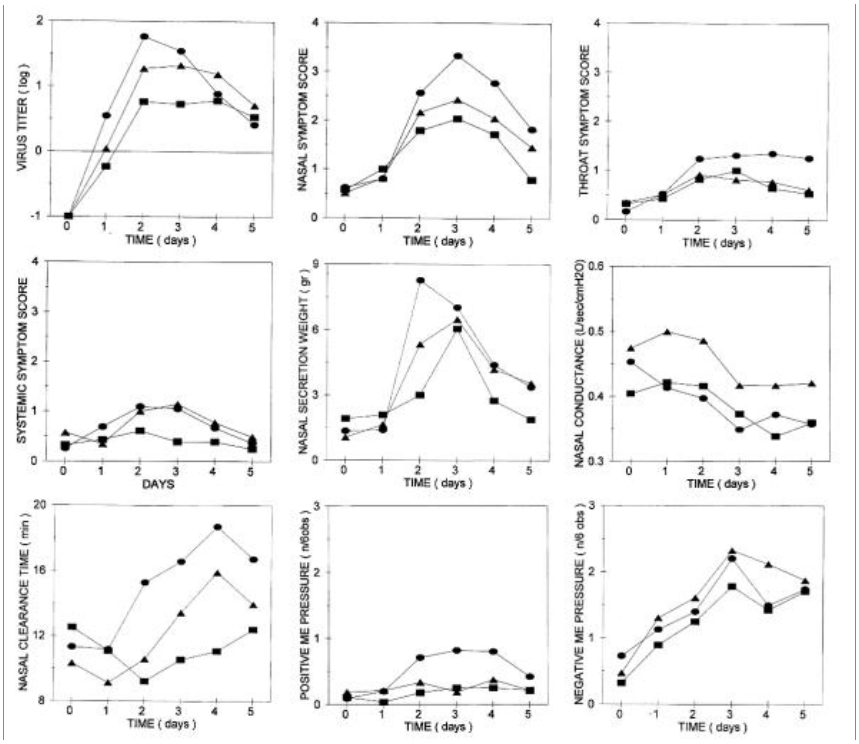

Fig. 1. Average daily values for the high-titer([black small square]), intermediate-titer ([black up pointing small triangle]), and low-titer (•) groups, as defined by the preexisting serum RV-39 antibody titer.

Response Variable	LT	IT	HT	LT vs. HT	LT vs. IT	IT vs. HT
Congestion	3.67±3.60	2.57±3.27	1.79±3.24	*		
Rhinorrhea	2.80±3.85	2.34±3.15	1.18±3.33	*		
Sneezing	1.71±3.33	1.43±2.21	1.50±2.30			
Cough	2.29±3.38	0.61±1.66	0.82±3.42	*	*	
Sore throat	2.56±2.97	1.29±2.91	1.00±2.61	*	*	
Malaise	1.62±2.71	1.16±2.54	0.43±1.89	*		
Headache	0.47±2.87	−0.53±3.97	0.29±3.02			
Chill	0.51±1.32	0.27±0.79	−0.25±1.24	*		
Nasal patency	1.93±3.73	2.57±3.36	3.36±3.28			
Mucosal edema	2.42±2.45	1.94 ±2.00	2.36±2.28			
Quantity of rhinorrhea	3.96±4.62	3.76±3.77	4.14±4.24			
Nasal conductance	−0.38±1.05	−0.13±1.1	−0.11±0.71			
Secretion weight	17.72±31.2	15.93±39.82	6.18± 28.95			
Nasal clearance time	21.8±37.18	11.37±32.74	−9.21± 33.03	*		*
Abnormal positive middle ear pressure	2.49±4.36	0.37± 2.73	0.39±2.82	*	*	
Abnormal negative middle ear pressure	4.27±7.17	6.90±7.10	5.46±8.09			

*P<.05.

TABLE I. Average and Standard Deviations of the Response Variables for Infected Subjects in the High-Titer (HT), Intermediate-Titer(IT), and Low-Titer (LT) Groups.

For each recorded measure, a summary response variable was defined from the data available for each subject.[17] The magnitude of the summary variables for symptoms, scaled nasal signs, mucociliary clearance time, nasal conductance, and nasal secretion weight was determined by summing the differences between the recorded value of the variable at each observation point and the baseline value of the respective variable (i.e., the baseline-adjusted area under the curve). For middle ear pressure, the response variable was defined as the number of observations considered to be abnormal according to previously published criteria (-50<normal<+20 mm H_2O).[1,2]

The significance of the differences among groups for parametric measures was determined using analysis of variance, with variance partitioned by group and subject. If significance was established with alpha equal to .05, pairwise between-group testing was done using a least significant difference test. For nonparametric variables, the significance of difference among groups was analyzed using a chisquared test with Yates correction or, where appropriate, Fisher's exact test. All analyses were performed on a microcomputer using the program CSS:STATISTICA (StatSoft). Statistical significance was evaluated at the P<.05 level using two-tailed significance tests.

RESULTS

Infection and Colds

Virus culture identified a wild virus (non-RV-39) in the nasal lavage fluids of 4 (2.5%) of the 151 subjects, and these individuals were excluded from the analysis. Of the remaining 147 subjects, 56 (38.1%) were in the LT group, 51(34.7%) were in the IT group, and 40 (27.2%) were in the HT group based on their prechallenge serum RV-39 antibody

titers. Viral shedding was documented in 26 (65%) of the subjects in the HT group, 46 (90.2%) of the subjects in the IT group, and 54 (96.4%) of the subjects in the LT group (*P*<.05, HT vs. LT and IT) A fourfold rise in convalescent RV-39 antibody titer was documented in 14 (35%) of the subjects in the HT group, 39 (76.5%) of the subjects in the IT group, and 28 (50%) of the subjects in the LT group (*P*<.05, IT vs. HT and LT).

Based on the predefined criterion for infection, 28 (70%) of the subjects in the HT group, 49 (96%) of the subjects in the IT group, and 55 (98.2%) of the subjects in the LT group were infected with RV-39 (*P*<.05, HT vs. IT and LT). According to the modified Jackson criteria,16 5 (12.5%) of the subjects in the HT group were considered to have a symptomatic cold, compared with 22 (43.1%) of the subjects in the IT group and 32 (57.1%) of the subjects in the LT group (*P*<.05, HT vs. IT and LT).

Symptoms, Signs, and Pathophysiologies

To avoid bias associated with the differences among groups in the rates of infection, summary data for the variables associated with signs, symptoms, and pathophysiologies were compared using the data for infected subjects only. For the three comparison groups defined by preexisting serum RV-39 antibody titer, the average daily values for virus titer, nasal symptoms, throat symptoms, systemic symptoms, secretion weights, nasal conductance, nasal clearance times, positive middle ear pressures, and negative middle ear pressures are shown, in Figure 1. The averages, standard deviations, and significance of between-group differences for summary variables related to symptoms, signs, and pathophysiologies are presented in Table I.

The average log titer of virus increased in all groups to a peak on day 2 and then decreased by day 5. While similar in temporal pattern, the function for the HT group had a much lesser peak magnitude when compared with that of the other two groups. The average summary score for this variable was significantly less for the HT group (7.6±3.3) than for either the LT group (10.2±2.2) or the IT group (9.6±4.9).

Daily rhinoscopic examination was performed by an otolaryngologist using a nasal speculum and head lamp. The temporal pattern for the rhinoscopic signs in all groups showed a progressive decrease in the area of the nasal airway, an increase in mucosal swelling, and an increase in the quantity of rhinorrhea to a plateau for the remainder of the study. Among the groups, no obvious differences were found in the temporal pattern or the magnitudes of these physicianrated signs. No significant differences among groups were found in the summary response variables for the physician-rated signs of nasal congestion, mucosal swelling, or quantity of rhinorrhea.

For the three groups, total nasal symptoms (the sum of congestion, rhinorrhea, and sneezing) showed a similar temporal profile that was characterized by an early increase to a peak on day 3 and a noted decrease that approached baseline by day 5. The magnitude of the response was greatest for the LT group and least for the HT group. Total throat symptoms (the sum of cough and sore throat) increased in all groups to a plateau from days 2 through 5. The magnitude of the increase was greater for the LT group and less, but similar, for the IT and HT groups. In contrast, systemic symptoms (the sum of chills, headache, and malaise) showed little patterned increase with time in the HT group, but a clear rise and fall of similar magnitudes for the LT and IT groups.

For the eight individual-subject-rated symptoms, the average summary symptom score was lower in the HT group than in the LT group, with the between-group differences in congestion, rhinorrhea, cough, sore throat, malaise, and chills achieving statistical significance. In general, the average summary scores for the IT group were intermediate between those of the HT and LT groups, with a few between-group differences achieving statistical significance (Table I).

The average daily secretion weights showed an initial increase on day 2, with peaks on day 2 or 3 and a return to baseline levels by day 5. The response magnitude was greatest for the LT group, intermediate for the IT group, and lowest for the HT group. However, the differences among groups in the average summary response scores for this variable were not statistically significant.

For all groups, the daily average nasal conductance showed a shallow decrease to a minimum on day 3 or 4, with no evidence of recovery during the period of follow-up. There were no significant between-group differences for the summary variable related to nasal conductance. In contrast, nasal clearance times were unchanged over time in the HT group but showed a progressive increase to a peak on day 4 in the IT and LT groups. The relative magnitude of the increase was greater in the LT group than in the IT group. Pairwise between-group differences were statistically significant for the HT vs. LT and HT vs. IT comparisons but not for the IT vs. LT comparison.

The percentage of abnormal middle ear pressure observations on each day showed a parallel increase in all groups from 5.5% (HT group) and 13.7% (LT group) on day 0 to a maximum of between 34% (HT group) and 50.3% (LT group) on day 3. When considering the abnormal positive pressures and abnormal negative pressures separately, the observed differences between groups were appreciable only for the frequency of abnormal positive pressure observations. The

summary response variable, the number of observations with positive middle ear pressure, was significantly different between the HT and LT groups and between the IT and LT groups, while the between-group differences in the number of observations of negative middle ear pressure were not significant.

DISCUSSION

Common colds resulting from rhinovirus infection cause considerable morbidity. Even though the infection is usually self-limited in otherwise healthy persons, it may predispose individuals to complications involving other pathogens and/or anatomic structures, such as the paranasal sinuses, the middle ears, and the lungs.[1-7] The primary mechanism for limiting the spread of rhinovirus infections is the avoidance of contact with infected persons.[9] However, many infected persons do not have apparent symptoms or signs of infection, or they have such minimal signs and symptoms that they do not feel ill and, thus, do not absent themselves from their social environment.

A number of factors have been implicated in moderating disease expression during viral URIs (e.g., stress levels and allergic status), with specific serum antibody levels recognized as a primary moderating factor.[18-23] These serum antibodies most likely result from systemic immune responses to RV-39.[18] In this study, the effect of preexisting specific antibodies on the rate of virus infection and disease expression was evaluated in a large population of adults experimentally exposed to RV-39.

Before the RV-39 challenge, 27% of the subjects in this randomly chosen adult population had high (16 or greater) RV-39 serum antibody titers, and 35% had intermediate (greater than or equal to 2, 4, or 8) RV-39 serum antibody titers. These antibody titer levels are most likely evidence of previous RV-39 infection, since seroconversion has been reported for about 50% of infected cases and serum antibodies to rhinovirus are extremely type-specific.[8,9,14,19,20] In the present study, 50% of the infected subjects in the LT group had at least a fourfold increase in RV-39 specific serum antibody titer. A higher percentage of subjects (77%) in the IT group had a fourfold increase in RV-39 titer, perhaps evidencing an amnesic response of the immune system to the previously encountered RV-39 virus. While only 35% of the subjects in the HT group showed an antibody response, this is most probably an artifact of the assay methods, where the highest titer reported was 64, thereby limiting the potential for a fourfold increase to the subset of subjects with preexisting titers of 16.

Past studies suggested that high specific serum antibody titers are associated with resistance to both natural and experimental homologous-type rhinovirus infections.[19-23] The present study supports this possibility in that 30% of the subjects with high antibody titers were protected from infection, as opposed to only 4% of the subjects with intermediate serum RV-39 antibody titers and 2% of those with low RV-39 antibody titers. High serum antibody titers were also associated with a significantly reduced viral load but not with an abbreviated time course for viral shedding in those subjects with documented infection.

The preexisting serum RV-39 antibody titers also affected disease expression. While a clinical cold, on the basis of the modified Jackson criteria,[16] developed in 57% and 43% of subjects with, respectively, low and intermediate RV-39 antibody titers, only 13% of the subjects with high RV-39 antibody titers developed a cold. This effect was not entirely attributable to the higher frequency of uninfected and presumably asymptomatic subjects in the HT groups, since lesser symptoms and pathophysiologies were also documented for the infected subset of that group when compared with the infected subsets of the other groups.

Of particular interest was the low magnitude of nasal and throat symptoms and the apparent lack of systemic symptoms reported by infected persons with preexisting high RV-39 antibody titers. If these symptoms contribute greatly to a person's assessment of his or her degree of illness, infected individuals with high specific antibodies may be less likely to absent themselves from social interactions and thereby may provide a source of virus for disseminating infection to other members of the population.

The responses of the subjects in this study to RV-39 infection were similar in magnitude and extent to those previously described for experimental and natural rhinovirus infections.[24] Specifically, the subjects reported a number of symptoms consistent with those of a common cold, they had physician-documented nasal signs of inflammation, and they developed increased amounts of nasal secretions, decreased nasal patency, and decreased nasal mucociliary clearance rates, as well as abnormal middle ear pressures.

Interestingly, while subject-reported symptoms were clearly related to preexisting antibody titer levels, physician-assessed signs of nasal inflammation were not. This is consistent with the results of earlier studies that reported physician-assessed signs to be poor indicators of the degree of illness perceived by the subjects.16 Also, three objective measures of nasal pathophysiology were made during the study, including measurements of nasal secretion production, nasal patency, and nasal mucociliary clearance. While all measures showed a rank ordering of response magnitude consistent with a protective effect of preexisting serum antibodies, only the results for between-group comparisons of nasal mucociliary clearance were statistically significant.

For secretion production, the failure to detect between-group differences was most likely associated with its large inter-individual variability in all groups. The previously reported high variability in secretion production had already limited the use of this measure as an outcome for efficacy trials of a variety of interventions.17 Since this is not explained by preexisting antibody status, other factors may have a more profound influence on secretion production in rhinovirusinfected individuals.

In contrast, the failure to detect between-group differences in nasal patency most probably reflects the low magnitude of the measured congestive response in individuals infected with RV-39. In this study, the conductance of the nasal airway was decreased by approximately 22% in the infected LT group and by approximately 15% in the HT group. The low magnitude of response for this variable severely limits the power of any statistical test by decreasing the maximum difference achievable, an effect noted in an earlier study of decongestant-antihistamine treatment of rhinovirus colds.17

Curiously, while the objective measure of nasal congestion showed relatively minor changes following RV-39 infection, the change in average nasal congestion symptom score reported by the subjects was relatively large. Indeed, congestion was the most frequently reported symptom and exhibited the highest magnitude of change after RV-39 infection. These results suggest that the individual subject's perception of congestion is not an accurate assessment of the magnitude of change in the resistance of the nasal airway as measured by rhinomanometry. Other contributors to the symptom of nasal congestion may include an exaggerated amplitude of the nasal cycle, the generation of turbulent flows due to the presence of secretions in the nasal airway, or as yet unidentified factors.

Previous studies documented a depressed nasal mucociliary clearance rate in subjects with both natural and experimental viral URIs.2,17,25-27 In this study, the mucociliary transit time, an inverse measure of clearance rate, was demonstrated to increase significantly following RV-39 infection in the LT and IT groups. In contrast, no increase in average clearance time was documented for subjects in the HT group. As mucociliary clearance has been ascribed a protective role with respect to nasal infections with bacteria and viruses, the maintenance of a well-functioning system in individuals with high antibody titers may prevent dissemination of the primary infection to adjacent anatomical spaces and/or the development of local or disseminated secondary bacterial infections.

Otitis media with effusion, a frequent complication of viral URIs, has been documented in adults with experimental virus infections and in children with natural infections.28,29 In those studies, the presence of abnormal middle ear pressures was shown to herald the development of otitis media during a URI and was considered to be a precipitating factor. In adults experimentally infected with rhinovirus, both abnormal positive and negative middle ear pressures have been documented, and the results of the present study confirm those observations.1,2,17

In the present study, the frequency of abnormal positive, but not abnormal negative, middle ear pressures was indirectly related to the prechallenge RV-39 serum antibody titers. Of note is the fact that for all infected subjects, there was a significant positive correlation between secretion production and the number of observations of positive (r=.34), but not negative, middle ear pressures. This provides indirect support for the previously posited hypothesis that positive middle ear pressures are generated during nose blowing and other activities, resulting in high positive nasopharyngeal pressures.

The pathogenesis of otitis media during a viral URI has been related to virus-associated effects, such as altered local and systemic immune responses and/or impaired eustachian tube function. These effects may precipitate conditions favoring changes in the nasopharyngeal bacterial flora, followed by dissemination of viral or bacterial infection to the middle ear via the eustachian tube, or conditions causing middle ear pressure dysregulation with the subsequent development of otitis media by hydrops ex vacuo.

The failure to demonstrate an effect of antibody titer on negative middle ear pressure generation shows that high prechallenge antibody levels do not provide protection against this middle ear complication. When combined with the data for symptoms, these results suggest that a significant proportion of patients may be unaware that they have a subclinical viral URI that has progressed to negative middle ear pressures. This may result in an underestimation of the degree of relatedness of the two disease conditions in epidemiologic studies of otitis media and an under-appreciation of the percentage of otitis media episodes that are potentially preventable by intervening in the course of a URI.

CONCLUSION

This study shows that the presence of specific serum antibodies is associated with reduced rates of infection and lesser symptomatic expression of a cold in volunteers exposed to a homologous rhinovirus type. A causal relationship between the two cannot be demonstrated using these data, since previous work supports both a protective role for secretory antibodies and a high correlation between specific secretory and serum antibody titers.[22,23] Because secretory antibody levels were not measured, they could represent a confounding variable with respect to data interpretation.

Regardless of the specific mechanism, the protection afforded by preexisting homologous antibodies is not complete with respect to either infection or the development of symptomatic colds and their complications. Indeed, the existence in the population of high-titer individuals may encourage viral transmission via the continued social interactions of persons who have subclinical viral infections.

BIBLIOGRAPHY

1. Doyle WJ, McBride TP, Swarts JD, et al. The response of the nasal airway, middle ear, and eustachian tube to experimental rhinovirus infection. Am J Rhinol. 1988;2:149-154. [Context Link]

2. McBride TP, Doyle WJ, Hayden FG, et al. Alterations of the eustachian tube, middle ear, and nose in rhinovirus infection. Arch Otolaryngol Head Neck Surg. 1989;115:1054-1059. **HSLS Link Resolver** | **Search Pubmed for Abstract** | [Context Link]

3. Lemanske RF, Dick EC, Swenson CA, et al. Rhinovirus upper respiratory infection increases airway hyperreactivity and late asthmatic reactions. J Clin Invest. 1989;83:1-10. **HSLS Link Resolver** | **Search Pubmed for Abstract** | [Context Link]

4. Hamory BH, Sande MA, Snydor A Jr, et al. Etiology and antimicrobial therapy of acute maxillary sinusitis. J Infect Dis. 1979;139:197-202. **HSLS Link Resolver** | **Search Pubmed for Abstract** | [Context Link]

5. Gregg I. Respiratory viruses and host factors: doubts and certainties concerning their roles in acute respiratory illness. In: Nicholson K, ed. HIV and Other Highly Pathogenic Viruses. London: Royal Society of Medicine Services Limited, 1988:43-68. [Context Link]

6. Henderson FW, Collier AM, Sanyal MA, et al. A longitudinal study of respiratory viruses and bacteria in the etiology of acute otitis media with effusion. N Engl J Med. 1982;306:1377-1383. **HSLS Link Resolver** | **Search Pubmed for Abstract** | [Context Link]

7. Casselbrant ML, Brostoff LM, Cantekin EI, et al. Otitis media with effusion in preschool children. Laryngoscope. 1985;95:428-436. **Ovid Full Text** | **HSLS Link Resolver** | **Search Pubmed for Abstract** | [Context Link]

8. Gwaltney JM Jr, Jordan WS Jr. Rhinovirus and respiratory illness in university students. Am Rev Respir Dis. 1966;93:362-371. **HSLS Link Resolver** | [Context Link]

9. Hendley JO, Gwaltney JM Jr, Jordan WS Jr. Rhinovirus infections in an industrial population. IV. Infections within families of employees during two fall peaks of respiratory illness. Am J Epidemiol. 1969;89:184-1969. **HSLS Link Resolver** | **Search Pubmed for Abstract** | [Context Link]

10. Heikkinen T, Ruuskanen O, Waris M, et al. Influenza vaccination in the prevention of acute otitis media in children. Am J Dis Child. 1991;145:445-448. **HSLS Link Resolver** | **Search Pubmed for Abstract** | [Context Link]

11. Hamparian VV, Colonno RJ, Cooney MK, et al. A collaborative report: rhinoviruses-extension of the numbering system from 89 to 100. Virology. 1987;159:191-192. **HSLS Link Resolver** | **Search Pubmed for Abstract** | [Context Link]

12. Hamre D. Rhinoviruses. Monogr Virol. 1967;1:1-85. **HSLS Link Resolver** | **Search Pubmed for Abstract** | [Context Link]

13. Smith TJ, Olson NH, Cheng RH, et al. Structure of a human rhinovirus-bivalently bound antibody complex: implications for viral neutralization and antibody flexibility. Immunology. 1993;90:7015-7018. **HSLS Link Resolver** | [Context Link]

14. Gwaltney JM Jr. Micro-neutralization test for identification of rhinovirus serotypes. Proc Soc Exp Biol Med. 1986;122:1137-1141. [Context Link]

15. Duchateau GS, Graamans K, Zuidema J, et al. Correlation between nasal ciliary beat frequency and mucus transport rate in volunteers. Laryngoscope. 1985;95:854-859. **Ovid Full Text** | **HSLS Link Resolver** | **Search Pubmed for Abstract** | [Context Link]

16. Jackson GG, Dowling HF, Spiesman IG, et al. Transmission of the common cold to volunteers under controlled conditions. I. The common cold as a chemical entity. Arch Intern Med. 1958;101:267-278. **HSLS Link Resolver** | [Context Link]

17. Doyle WJ, McBride TP, Skoner DP, et al. A double-blind, placebo-controlled clinical trial of the effect of chlorpheniramine on the response of the nasal airway, middle ear and eustachian tube to provocative rhinovirus challenge. Pediatr Infect Dis J. 1988;7:229-238. **Ovid Full Text** | **HSLS Link Resolver** | **Search Pubmed for Abstract** | [Context Link]

18. Skoner DP, Whiteside TL, Wilson JW, et al. Effect of rhinovirus 39 infection on cellular immune parameters in allergic and nonallergic subjects. J Allergy Clin Immunol. 1995;92:732-743. **HSLS Link Resolver** | **Search Pubmed for Abstract** | [Context Link]

19. Hendley JO, Edmondson WP, Gwaltney JM Jr. Relation between naturally acquired immunity and infectivity of two rhinoviruses in volunteers. J Infect Dis. 1972;125:243-248. **HSLS Link Resolver** | **Search Pubmed for Abstract** | [Context Link]

20. Kellner G, Popow-Kraupp T, Binder C, et al. Respiratory tract infections due to different rhinovirus serotypes and the influence of maternal antibodies on the clinical expression of the disease in infants. J Med Virol. 1991;35:267-272. **HSLS Link Resolver** | **Search Pubmed for Abstract** | [Context Link]

21. Cate TR, Couch RB, Johnson KM. Studies with rhinoviruses in volunteers: production of illness, effect of naturally acquired antibody, and demonstration of a protective effect not associated with serum antibody. J Clin Invest. 1964;43:56-67. **HSLS Link Resolver** | **Search Pubmed for Abstract** | [Context Link]

22. Cate TR, Rossen R, Douglas RG, et al. The role of nasal secretion and serum antibody in the rhinovirus common cold. Am J Epidemiol. 1966;84:352-363. **HSLS Link Resolver** | **Search Pubmed for Abstract** | [Context Link]

23. Mufson MA, Ludwig WM, James HD, et al. Effect of neutralizing antibody on experimental rhinovirus infection. JAMA. 1963;186:578-584. **HSLS Link Resolver** | **Search Pubmed for Abstract** | [Context Link]

24. Rao SS, Hendley JO, Hayden FG, et al. Symptom expression in natural and experimental rhinovirus colds. Am J Rhinol. 1995;9:49-52. **HSLS Link Resolver** | [Context Link]

25. Sasaki Y, Togo Y, Wagner HN Jr, et al. Mucociliary function during experimentally induced rhinovirus infection in man. Ann Otol Rhinol Laryngol. 1973;82:203-211. [Context Link]

26. Sakakura Y. Changes of mucociliary function during colds. Eur J Respir Dis. 1983;(suppl 128):348-354. **HSLS Link Resolver** | [Context Link]

27. Pedersen M, Sakakura Y, Winther B, et al. Nasal mucociliary transport, number of ciliated cells and beating pattern in naturally acquired common colds. Eur J Respir Dis. 1983;(suppl 128):355-364. **HSLS Link Resolver** | [Context Link]

28. Buchman CA, Doyle WJ, Skoner D, et al. Otologic manifestations of experimental rhinovirus infection. Laryngoscope. 1994;104:1295-1299. **Ovid Full Text** | **HSLS Link Resolver** | **Search Pubmed for Abstract** | [Context Link]

29. Tos M, Poulsen G, Borch J. Etiologic factors in secretory otitis. Arch Otolaryngol. 1979;105:582-588. [Context Link]

Fourth Annual Golf Seminar Scheduled

The Fourth Annual Golf Seminar-Advances in Otolaryngology-Head and Neck Surgery, sponsored by the University of Washington School of Medicine Virginia Merrill Bloedel Hearing Research Center, will be held at Pinehurst Resort & Country Club in North Carolina, on March 11-16, 1997. It will feature presentations on new techniques in facial plastic surgery, endoscopic surgery, otology/neurotology, head and neck surgery, and general otolaryngology.

To receive a brochure please contact: Leslie Sullivan, Coordinator, University of Washington, Box 357923, Seattle, WA 98195-7923; Tel: 206-685-2962 Fax: 206-616-1828 E-mail: sullivan@u.washington.edu

---

IMAGE GALLERY

Select All **Export Selected to PowerPoint**

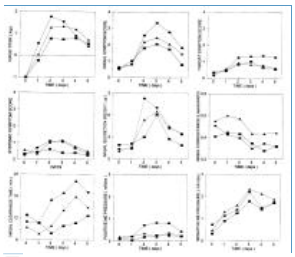

Fig. 1

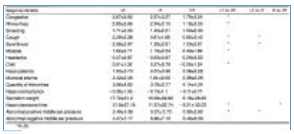

Table I

Back to Top