Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Epidemiology, Pathogenesis, and Treatment of the Common Cold

J. Owen Hendley, MD

The common cold is an acute illness of the upper respiratory tract caused by a virus acquired from another person. Some viruses that produce colds are capable of infecting an individual repeatedly (eg, respiratory syncytial virus); others, with many serotypes (eg, rhinovirus), infect only once. The sustained epidemic of colds that occurs annually during September through April is explained by successive waves of different viruses moving through a community. The peak incidence of colds occurs in preschool children, who typically sustain at least one illness per month during the epidemic period. Clinical manifestations of colds are largely subjective in adults. Colds in preschoolers differ from those in adults as follows: (1) fever is common in children during the first 3 days; (2) colored nasal secretions may be the only indication of nasal involvement in children; and (3) colds in children last 10 to 14 days, as compared with a duration of less than a week in adults. The paranasal sinuses and the middle ear cavities are commonly involved during viral colds in adults (and presumably in children) in the absence of bacterial superinfection. Cold symptoms are due to the host's response to the virus rather than to destruction of the nasal mucosa. Viral infection of a very limited portion of the nasal epithelium results in an influx of polymorphonuclear leukocytes, cytokine release, and a vascular leak. Colds are self-limited illnesses. Therefore, in the absence of adequate blinding of controls, ineffective treatments erroneously may be considered efficacious. None of the medicines used for symptom relief in colds is curative.

By definition, the common cold is an acute self-limited illness involving the upper respiratory tract that is caused by a virus. Because viruses are not part of the normal flora of the upper respiratory tract (human herpesvirus 6 in saliva and adenovirus in adenoid tissue of healthy children being possible exceptions), the virus must be acquired from other people to cause a cold. Colds occur frequently throughout childhood and adulthood for two reasons (Table 1): (1) some of the viruses are capable of infecting an individual repeatedly (ie, immunity to reinfection is not provided by an infection) and (2) other viruses can infect an individual only once (ie, immunity follows infection), but there are numerous serotypes, each of which can infect once. Infection with respiratory syncytial virus (RSV) (one type with two subgroups), parainfluenza viruses (four types), or coronavirus (two dominant antigenic variants) does not produce lasting immunity; therefore, symptomatic infection with each of these viruses may occur year after year. The primary infection with RSV during the first 2 years of life frequently causes lower respiratory tract disease which can be severe, but subsequent infections in children and adults produce a common cold. Infections with rhinoviruses, adenoviruses, influenza viruses, and the enteroviruses usually produce lasting immunity, which is serotype-specific. However, because there are approximately 200 different serotypes, conceivably a person could sustain four colds a year for 50 years without experiencing reinfection by a serotype responsible for a preceding infection.

From the Department of Pediatrics, University of Virginia Health Sciences Center, Charlottesville, VA.

Address correspondence to J. Owen Hendley, MD, University of Virginia Health Sciences Center, Department of Pediatrics, Box 386, 1051 Cobb Hall, Hospital Dr, Charlottesville, VA 22908.

1045-1870/98/0901-0010$8.00/0

Epidemiology and Transmission

Colds have always been most common in preschool-age children, presumably because of both global susceptibility to infection with respiratory viruses due to a lack of prior experience and to poor personal hygienic practice that results in frequent exposure of the respiratory tract mucosa to infectious secretions of other humans. A 10-year (1948-57) study of families with children provided an accurate picture of the age-specific attack rates of respiratory illnesses in children.[1] In these children (who did not attend a daycare facility), the peak frequency of respiratory infections (7.4 to 8.3 colds per person per year) occurred among preschoolers 1 through 5 years old (Table 2). This illness rate is almost certainly higher in preschool children who attend a daycare facility. With an expected yearly frequency of at least eight colds, a typical preschooler will have one

Table 1. Immunity to Common Cold Viruses

Virus	Serotypes
Long-lasting immunity not produced by infection (repeated infection with same serotype usual)	
Respiratory synctial virus	1
Parainfluenza virus	4
Coronavirus	2
Immunity produced by infection (reinfection with same serotype uncommon)	
Rhinovirus	>100
Adenovirus	≥33
Influenza	3 (type A subtypes change)
Echovirus	31
Coxsackie virus group A	23
Coxsackie virus group B	6

Reprinted with permission from Hendley JO: Immunology of viral colds; in Veldman JE, McCabe BF, Huizing EH, et al (eds): Immunobiology, Autoimmunity, Transplantation in Otorhinolaryngology. Amsterdam, The Netherlands, Kugler Publications, 1985, pp 257-260.

upper respiratory tract infection monthly from September through April each year (discussed later). Children experiencing this expected pattern often are labelled as having "recurrent infections" and mistakenly suspected of having undue susceptibility to infection. In fact, this is the usual pattern for children who have an appropriate amount of social contact with other humans.

Colds occur in yearly "epidemics" in temperate climates. The annual epidemics begin from late September through early October, after children have returned to school, and last through the colder months until April (Fig 1). In view of the variety of viruses that cause colds, the sustained epidemic curve is explained by successive waves of different viruses moving through the community.[2] Rhinovirus infections occur year-round, but a sharp rise in the attack rate occurs every September to initiate the epidemic. Parainfluenza viruses appear in October and November, and coronaviruses and RSV follow in the colder months. Influenza A virus often produces a sharp peak of activity in mid- to late-winter. A low rate of adenovirus infection may be present over the course of many months. Finally, the end of the epidemic often is marked by a small peak of rhinovirus disease. Determinants of this yearly epidemic must include both human behavior and attributes of the causative viruses. Certainly, the increased close interpersonal contact that occurs when people spend more time indoors during cold months is an important factor. Viral attributes of importance may include prolonged survival of enveloped viruses (parainfluenza and influenza viruses, coronavirus, and respiratory syncytial virus) in the low relative humidity encountered inside heated homes during the winter.

Table 2. Incidence of Common Respiratory Diseases in Members of Cleveland Families With Children (1948-1957)

Age (years)	*Illnesses per person per year*
<1	6.7
1-5	7.4-8.3
6-12	5.0-6.2
12-16+	4.6-4.8
Fathers	3.5
Mothers	4.8

Adapted and reprinted with permission.[1]

Transmission of the viruses causing colds occurs by one (or more) of three routes.[3] Small particle aerosols (<5 μ in diameter), usually generated by coughing, may remain suspended in the air for an hour and may result in infection when inhaled. Large particle aerosols (>10 μ diameter) travel less than a meter and infect by landing on conjunctival or nasal mucosa. Spread of secretions containing virus may occur by direct contact between contaminated hands and conjunctival or nasal mucosa. Inoculation of virus into the mouth is not an efficient way to transmit infection. Neither RSV[4] nor rhinovirus[5] causes infection when inoculated by the oral route, presumably because the stratified squamous epithelium of the mouth and oropharynx is not susceptible. Influenza virus[6] and coronavirus[7] can spread readily by small particle aerosol; RSV cannot.[8] Whether rhinovirus spreads by small particle aerosol is controversial.[9,10] The route(s) of viral transmission under natural conditions has not been definitely established. Experimental interventions designed to interrupt spread under natural conditions of RSV in the hospital[11] and rhinovirus in the home[3] indicated that direct contact and/or large particle transmission were the most likely routes, consistent with the conclusion concerning the importance of the home (or a daycare facility) environment for viral spread.

Natural History of Uncomplicated Colds

The clinical manifestations of colds are largely subjective, often with little in the way of objective findings in older children and adults. Sore/scratchy throat, nasal obstruction, moderate rhinorrhea, and malaise may be experienced by the person with the cold but may not be apparent to others. When present, cough, sneezing, or hoarseness will be notable. Moderate anterior cervical adenopathy is common in children with colds. With few exceptions, the clinical manifestations of the cold are similar regardless of the specific virus causing the illness.

The natural history of a cold in infants or preschool age children is different from that in adults (Table 3). First, fever (≥38°C) is very uncommon in an adult with a cold but is common during the first 3 days of a cold in preschoolers. Second, nasal congestion and sore throat associated with colds are readily appreciated by an adult, but similar symptoms in the preschool child typically go unreported. Instead, the parent and/or physician may notice nasal involvement only when colored nasal secretions appear. Finally, a cold in an adult usually lasts for less than a week, whereas an uncomplicated cold in a young child usually persists for 10 to 14 days.

There is recent evidence that the paranasal sinuses are commonly involved during uncomplicated viral colds. This observation differs from the traditional belief that any involvement of the sinuses during a viral cold represents secondary bacterial infection. The evidence for frequent involvement of the sinuses in viral colds was provided by Gwaltney et al,[12] who used coronal computed tomography (CT) scans to image the

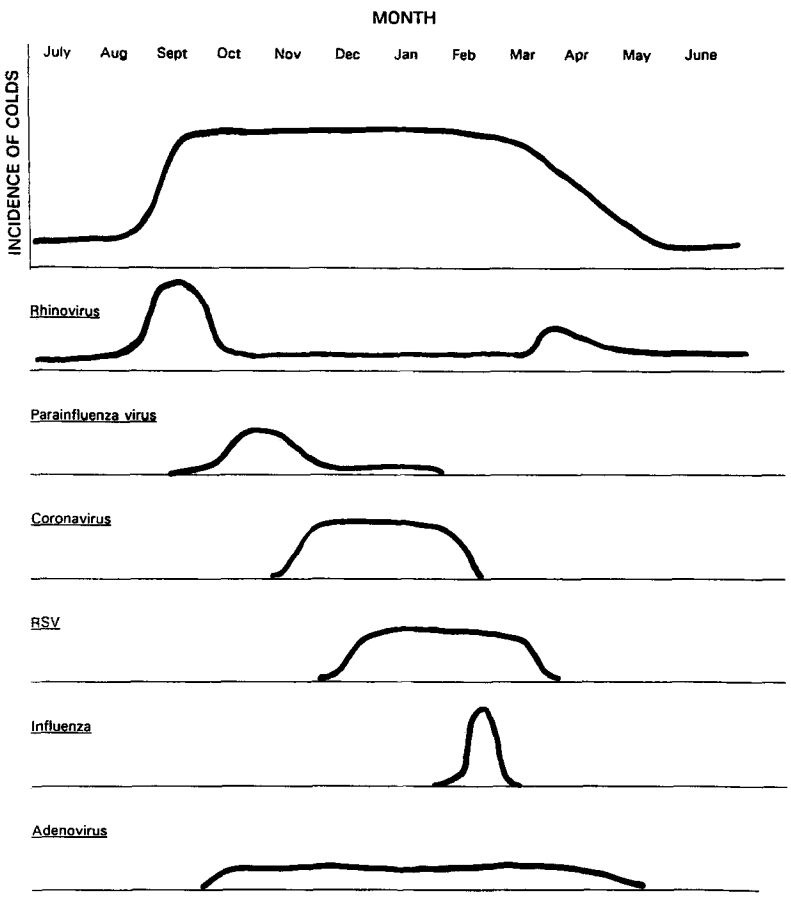

Figure 1. Schematic diagram of the incidence of colds and frequency of causative viruses. Reprinted with permission.[35]

sinuses of 31 young adults with "fresh" colds of average severity. Eighty-seven percent of those studied by CT scan had abnormalities (mucosal thickening or air-fluid levels) in one or more sinuses. One half of the subjects who had an abnormal scan during their colds had a follow-up CT scan 2 to 3 weeks later; 11 of 14 reimaged after clinical recovery showed resolution or marked improvement of the previously documented sinus abnormalities (Fig 2). As none of the subjects had received antibacterial therapy, it is reasonable to conclude that fluid in the sinus(es) occurs commonly during uncomplicated viral colds. Whether the abnormalities of the paranasal sinuses were caused by a virus infecting the sinus mucosa or simply to altered drainage of the sinuses because the viral rhinitis impairs mucus clearance from the nasal ostiomeatal complex is not known.

Table 3. Characteristics of Viral Colds

	Adults	*Children Less Than 6 Years Old*
Frequency	2-4 per year	One per month, September-April
Fever	Never	Common during first 3 days
Nasal manifestations	Congestion	Colored nasal discharge
Duration of illness	5-7 days	14 days

The middle ear has also been shown to be involved in uncomplicated colds in adults. Using tympanometry, Elkhatieb et al[13] serially measured middle ear pressures through the course of colds caused by rhinovirus. They reported abnormalities in 74% of 91 patients; the frequency of abnormal middle ear pressures peaked on days 2 through 5 of the illness. The abnormalities resolved within 2 to 3 weeks. Otitis media was not diagnosed clinically during the study, but after the study, 1 of the subjects was treated by his physician with an oral antibiotic for suspected otitis media. The middle ear pressure abnormalities were presumably caused by altered function of the Eustachian tube. Like the sinus abnormalities associated with a cold, it is unclear if the dysfunction of the Eustachian tube resulted from viral infection of the middle ear mucosa itself, or was secondary to viral nasopharyngitis. As with adults, involvement of the middle ear almost certainly occurs during uncomplicated colds in children.

Pathogenesis of Symptoms

Cold symptoms have long been thought to result from viral disruption of nasal epithelium. However, Winther et al examined nasal biopsies during and after illness and showed in both natural and experimentally induced colds in young adults that the epithelium was undamaged during symptomatic illness.[14,15]

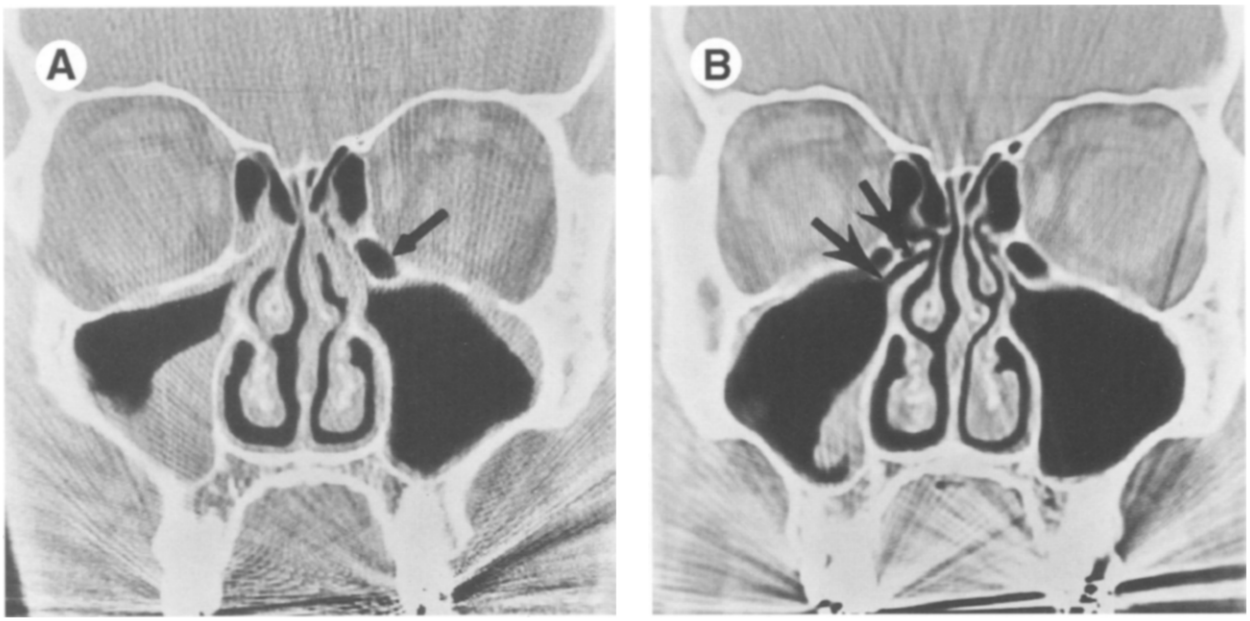

Figure 2. Sinus CT scan of adult during symptomatic cold (left panel) and 2 weeks later (right panel). Arrow in the left panel denotes an infraorbital air cell (Haller cell). Bilateral abnormalities were observed in the ethmoid and maxillary sinuses during the cold, with an air-fluid interface in the right maxillary sinus. Two weeks later, all abnormalities had cleared except for a residual density in the right maxillary sinus. The infundibulum (two arrows) draining the maxillary antrum was now open. (Courtesy of Dr Jack M. Gwaltney, Jr, Department of Internal Medicine, University of Virginia School of Medicine, Charlottesville, Virginia. Reprinted with permission.[35])

The only histological change detected in the biopsy specimens taken early in the course of uncomplicated colds was an influx of polymorphonuclear leukocytes (PMNs) into submucosa and epithelium. An increase in PMNs in the nose during the early stages of viral infection was confirmed by Naclerio et al,[16] who showed a 100-fold increase in PMN concentration in nasal washings obtained from volunteers 1 to 2 days after inoculation with rhinovirus. This notable influx of PMNs occurred simultaneously with the onset of symptoms. A clinical correlate of this influx of PMNs into nasal secretions during viral infection of the nose may be the presence of colored nasal discharge, a result that is often mistakenly attributed to secondary bacterial infection. Winther et al[17] reported that fully one half of medical students reported colored nasal discharge by day 3 to 5 of uncomplicated colds; colored discharge was not associated with bacterial overgrowth in either the nasal cavity or the nasopharynx. An increase in PMNs in nasal secretions[16] may produce a yellow or white color; myeloperoxidase and other enzymatic activity associated with PMNs may cause green discoloration.

The lack of detectable damage to the nasal mucosa reported by Winther et al[14,15] was confirmed by Turner et al,[18] who reported that only a small number of infected ciliated cells were sloughed into nasal secretions during experimental rhinovirus colds. More recently, Bardin et al[19] and Arruda et al,[20] using in situ hybridization techniques, provided an explanation for the lack of damage to nasal epithelium. In nasal epithelial biopsies obtained from infected volunteers, they showed that rhinovirus replication was present only in epithelial cells and that the number of infected cells at the time of sampling was extremely small. Finally, Winther et al showed in vitro that rhinovirus and coronavirus replicating in cultured nasal epithelial cells produced no discernible cytopathic effect, whereas influenza A virus and adenovirus produced obvious damage to the monolayer of epithelial cells.[21]

Having established that neither mucosal damage nor bacterial overgrowth is responsible for either the symptoms or the influx of PMNs associated with a cold, the best current hypothesis is that virus infection of a few nasal and nasopharyngeal epithelial cells results in an outpouring of cytokines and other mediators that are the effectors of the symptomatic and cellular responses. Turner[22] provided evidence consistent with this hypothesis by demonstrating that cells in culture produced a chemoattractant for PMNs in response to infection with rhinovirus. The chemoattractant was subsequently reported to be interleukin (IL)-8, a chemokine.[23] The concept that epithelial cells can produce a variety of cytokines in response to infection with respiratory viruses has been supported by the work of several investigators.[24-26] In addition, elevated levels of several cytokines (IL-1β, IL-6, IL-8) have been shown in nasal secretions of children[27] and adults[28] with colds. It seems that proinflammatory cytokines may play a role in the pathophysiology of both symptom production and the early influx of PMNs associated with viral infection of the nasal mucosa.

In experimental rhinovirus infections, Naclerio et al[16] showed that the concentration of albumin and kinins (predominantly bradykinin) in nasal secretions increased coincident with the onset of symptoms. The concentration of histamine did not rise. The increased concentration of serum albumin in nasal secretions of symptomatic volunteers signified increased submucosal vascular permeability, allowing leakage of plasma proteins. The

simultaneous appearance of kinins probably represented leakage of kininogen from blood vessels, with conversion to bradykinin by kinin generating enzymatic activity in the submucosa. Although it may contribute to the volume of nasal secretions produced, the albumin would be expected to have no effect on the nasal mucosa. On the other hand, the presence of kinins in secretions may augment the symptoms of the cold as occurred when rhinitis and sore throat resulted after bradykinin alone was sprayed into the noses of uninfected volunteers.[29] The means by which vascular leak is initiated by viral infection has not been established, but the leak may be perpetuated by the presence of kinins in the secretions.

In summary, it seems the symptoms of a cold are caused by the host's response to the viral infection rather than to a direct destructive effect of the virus on the nasal mucosa. One implication may be that killing the virus is not a requisite for effective amelioration of cold symptoms. It would be of interest to determine if kinin blockade and/or interruption of the proinflammatory cytokine cascade would ablate symptoms while the viral infection in the nose continued unabated.

Treatment

Viral colds are self-limited infections. Consequently, virtually any treatment regimen that is not deleterious to health may superficially appear to result in a cure within 7 days in an adult and 14 days in a child. Antibiotics directed against the bacterial flora of the nasopharynx frequently are used to treat children with colds. Antibacterial agents do not hasten resolution of the viral infection nor do they reduce the risk of secondary bacterial infection.[30] No antiviral agents effective in treating viral colds are currently available.

Because the clinical manifestations of colds are largely subjective, there is a potentially large placebo effect associated with the use of virtually any treatment; hence, adequate blinding of patients and physicians is a critical requirement for clinical trials designed to evaluate therapies for colds. A variety of ineffective treatments seemed to be effective in studies in which placebo-recipient/control subjects realized that they were not receiving active drugs.[31] Studies of zinc-containing lozenges for cold treatment provide a noteworthy illustration of this potential pitfall. To blind subjects adequately in trials of zinc gluconate lozenges, Farr et al[32] developed a taste-matched placebo lozenge containing denatonium benzoate (which is so bitter that it has been painted on thumbs of children to discourage thumbsucking). In their double-blind trial with effective blinding, Farr et al did not find that zinc showed a therapeutic benefit.

A wide array of medicines is available for symptomatic relief of the common cold, including antipyretics/analgesics, topical and systemic decongestants, antihistamines, cough suppressants, and mucoevacuants. Many of these agents are partially effective in reducing symptoms; none is curative. Topical interferon-α treatment used in established infection reduces viral titer but does not improve symptoms. Recently, steroid therapy has been shown[33] to reduce kinin levels but not symptoms, possibly because of simultaneous increase in intranasal viral titer. A novel approach, combining an antiviral compound with antimediator treatment,[34] may be required to reduce the burden of illness caused by the common cold.

References

1. Dingle JH, Badger GF, Jordan WS: Illness in the home. Cleveland, OH, Press of Case Western Reserve University, 1964
2. Glezen WP, Denny FW: Epidemiology of acute lower respiratory disease in children. N Engl J Med 288:498-505, 1973
3. Hendley JO, Gwaltney JM Jr: Mechanisms of transmission of rhinovirus infections. Epidemiol Rev 10:242-258, 1988
4. Hall CB, Douglas RG, Schnabel KC, et al: Infectivity of respiratory syncytial virus by various routes of inoculation. Infect Immun 33:779-783, 1981
5. Hendley JO, Wenzel RP, Gwaltney JM Jr: Transmission of rhinovirus colds by self-inoculation. N Engl J Med 288:1361-1364, 1973
6. Moser MR, Bender TR, Margolis HS, et al: An outbreak of influenza aboard a commercial airliner. Am J Epidemiol 110:1-6, 1979
7. Turner RB, Meschievitz CK, Streisand AC, et al: Mechanism of transmission of coronavirus 229E in human volunteers. Clin Res 35:145a, 1987
8. Hall CB, Douglas RG: Modes of transmission of respiratory syncytial virus. J Pediatr 99:100-103, 1981
9. Dick EC, Jennings LC, Mink KA, et al: Aerosol transmission of rhinovirus colds. J Infect Dis 156:442-448, 1987
10. Gwaltney JM Jr, Moskalski PB, Hendley JO: Hand-to-hand transmission of rhinovirus colds. Ann Intern Med 88:463-467, 1978
11. Gala CL, Hall CB, Schnabel KC, et al: The use of eye-nose goggles to control nosocomial respiratory syncytial virus infection. JAMA 256:2706-2708, 1986
12. Gwaltney JM Jr, Phillips CD, Miller RD, et al: Computed tomographic study of the common cold. N Engl J Med 330:25-30, 1994
13. Elkhatieb A, Hipskind G, Woerner D, et al: Middle ear abnormalities during natural rhinovirus colds in adults. J Infect Dis 168:618-621, 1993
14. Winther B, Brofeldt S, Christensen B, et al: Light and scanning electron microscopy of nasal biopsy material from patients with naturally acquired common colds. Acta Otolaryngol (Stockh) 97:309-318, 1984
15. Winther B, Farr B, Turner RB, et al: Histopathologic examination and enumeration of polymorphonuclear leukocytes in the nasal mucosa during experimental rhinovirus colds. Acta Otolaryngol (Stockh) 413:19-24, 1984 (suppl)
16. Naclerio RM, Proud D, Lichtenstein LM, et al: Kinins are generated during experimental rhinovirus colds. J Infect Dis 157:133-142, 1988
17. Winther B, Brofeldt S, Gronborg H, et al: Study of bacteria in the nasal cavity and nasopharynx during naturally acquired common colds. Acta Otolaryngol (Stockh) 98:315-320, 1984
18. Turner RB, Hendley JO, Gwaltney JM Jr: Shedding of infected ciliated epithelial cells in rhinovirus colds. J Infect Dis 145:849-853, 1982
19. Bardin PG, Johnston SL, Sanderson G, et al: Detection of rhinovirus infection of the nasal mucosa by oligonucleotide in situ hybridization. Am J Respir Cell Mol Biol 10:207-213, 1994
20. Arruda E, Boyle TR, Winther B, et al: Localization of human rhinovirus replication in the upper respiratory tract by in situ hybridization. J Infect Dis 171:1329-1333, 1995
21. Winther B, Gwaltney JM Jr, Hendley JO: Respiratory virus infection of monolayer cultures of human nasal epithelial cells. Am Rev Respir Dis 141:839-845, 1990
22. Turner RB: Rhinovirus infection of human embryonic lung fibroblasts induces the production of a chemoattractant for polymorphonuclear leukocytes. J Infect Dis 157:346-350, 1988
23. Turner RB: Elaboration of interleukin 8 (IL-8) from fibroblast

(MRC-5) cells and human nasal epithelium in response to rhinovirus (RV) challenge, 1994. Abstracts of the 34th Interscience Conference on Antimicrobial Agents and Chemotherapy. Orlando, FL, American Society for Microbiology, 1994 (abstr B43)

24. Proud D: Epithelial derived cytokines and the modulation by virus infection, 1995. Proceedings I. Madrid, Spain, XVI European Congress of Allergology and Clinical Immunology (ECACI), 1995, pp 357-362
25. Choi AMK, Jacoby DB: Influenza A infection induces interleukin-8 gene expression in human airway epithelial cells. FEBS Lett 309:327-329, 1992
26. Noah TL, Becker S: Respiratory syncytial virus-induced cytokine production by a human bronchial epithelial cell line. Am J Physiol 265:L472-478, 1993
27. Noah TL, Henderson FW, Wortman IA, et al: Nasal cytokine production in viral acute upper respiratory infection of childhood. J Infect Dis 171:584-592, 1995
28. Roseler S, Holtappels G, Wagenmann M, et al: Elevated levels of interleukins IL-1β, IL-6 and IL-8 in naturally acquired viral rhinitis. Eur Arch Otolarhinolaryngol 252:S61-S63, 1995 (suppl 1)
29. Proud D, Reynolds CJ, Lacapra S, et al: Nasal provocation with bradykinin induces symptoms of rhinitis and a sore throat. Am Rev Respir Dis 137:613-616, 1988
30. Heikkinen T, Ruuskanen O, Ziegler T, et al: Short-term use of amoxicillin-clavulanate during upper respiratory tract infection for prevention of acute otitis media. J Pediatr 126:313-316, 1995
31. Sperber SJ, Hayden FG: Chemotherapy of rhinovirus colds. Antimicrob Agents Chemother 32:409-419, 1988
32. Farr BM, Conner EM, Betts RF, et al: Two randomized controlled trials of zinc gluconate lozenge therapy of experimentally induced rhinovirus colds. Antimicrob Agents Chemother 31:1183-1187, 1987
33. Gustafson LM, Proud D, Hendley JO, et al: Oral prednisone therapy in experimental rhinovirus infections. J Allergy Clin Immunol 97:1009-1014, 1996
34. Gwaltney JM Jr: Combined antiviral and antimediator treatment of rhinovirus colds. J Infect Dis 166:776-782, 1992
35. Hendley JO: The common cold, in Bennet JC, Plum F (eds): Cecil Textbook of Medicine, (ed 20). Philadelphia, PA, Saunders, 1996, pp 1747-1749