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Epidemiology, Pathogenesis, and Treatment of the Common Cold

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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.

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. 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 3 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...
The Common Cold

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Table 1. Immunity to Common Cold Viruses

| Virus                        | Serotypes |
|------------------------------|-----------|
| Respiratory syncytial virus  | 1         |
| Parainfluenza virus          | 4         |
| Coronavirus                  | 2         |
| Rhinovirus                   | >100      |
| Adenovirus                   | 33        |
| Influenza                    | 3 (type A)|
| Echovirus                    | 31        |
| Coxsackie virus group A      | 23        |
| Coxsackie virus group B      | 6         |

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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                           |

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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.

Transmission of the viruses causing colds occurs by one (or more) of three routes. Small particle aerosols (<3 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 nor rhinovirus causes infection when inoculated by the oral route, presumably because the stratified squamous epithelium of the mouth and oropharynx is not susceptible. Influenza virus and coronavirus can spread readily by small particle aerosol; RSV cannot.

Whether rhinovirus spreads by small particle aerosol is controversial. 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 and rhinovirus in the home 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 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, who used coronal computed tomography (CT) scans to image the
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 antibiotic therapy, it is reasonable to conclude that fluid in the sinuses 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 al13 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
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., 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. 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 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. was confirmed by Turner et al., 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. and Arruda et al., 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.

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 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. 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. In addition, elevated levels of several cytokines (IL-1, IL-6, IL-8) have been shown in nasal secretions of children and adults 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. 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. 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. 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 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 receiving active drugs. 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 developed a taste-matched placebo lozenge containing denatonium benzoate (which is so bitter that it has been painted on thumbs of children to discourage thumb sucking). 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 to reduce kinin levels but not symptoms, possibly because of simultaneous increase in intranasal viral titer. A novel approach, combining an antiviral compound with antimeriator treatment, may be required to reduce the burden of illness caused by the common cold.

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