CHAPTER 9

THE COMMON COLD

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I. INTRODUCTION

The common cold, also known as acute catarrh, coryza, and rhinitis, is the most frequent infectious-contagious disease suffered by human beings. It is characterized by nasal symptoms (rhinorrhea, nasal obstruction, sneezing) and occasionally by amygdalopharyngeal symptoms (pain and inflammation) accompanied by general malaise and sometimes fever. Because the symptoms are related to infection of the upper respiratory tract, the common cold is often also described as an "acute upper respiratory infection," a term which is too broad, or as "nasopharyngitis," which is not entirely accurate because the common cold does not always involve the pharynx (*1, 2*).

The common cold is a self-limiting disease, which may affect persons of any age, sex, or socioeconomic status. Although it is not fatal, the general malaise it produces sometimes causes children to miss school and adults to miss work (*3, 4*).

II. ETIOLOGY

In popular literature, colds are often attributed to exposure to low temperatures, because they occur most frequently during winter. It is interesting to note, however, that long before viruses were discovered, the 18th-century American physicist, inventor, and statesman Benjamin Franklin observed that colds were the result of contact with someone who had the illness, not exposure to cold or dampness. In other words, he identified the contagious nature of the disease (*1*).

This relationship was clarified in a study conducted by Douglas and associates, who experimentally reproduced an infection with type 15 rhinovirus in human volunteers. When these volunteers were exposed to cold temperatures (4° C) during the periods of incubation, illness, and convalescence, no differences were found with respect to the control group (which was not exposed to cold) in terms of factors such as susceptibility to infection, severity of symptoms, virus shedding, antibody response, and changes in bacterial flora in the upper respiratory tract. The investigators therefore concluded that exposure to cold had no influence on the response of the host to rhinovirus infection (*5*).

Many years before viruses were shown to be the causal agents of the common cold, the disease had been reproduced through intranasal inoculation of the filtrate of nasal secretions from patients (*1*). Later it was determined that those infective particles were the virus.

It is now known that the most important etiologic agents are two main groups of viruses: rhinoviruses and coronaviruses. Less frequently, colds may be caused by other respiratory viruses such as parainfluenza virus, respiratory syncytial virus (RSV), influenza virus, and adenovirus, which cause a more serious respiratory illness in children. In some cases, colds are caused by viruses that have not yet been identified (*6*).

Rhinoviruses are members of the group of picornaviruses and are biologically related to poliovirus and other enteroviruses. They are RNA viruses measuring approximately 25 nm in diameter. There are more than 100 recognized serotypes and some not yet typed. Rhinoviruses can be easily grown in culture media. They show a clear propensity for the respiratory epithelium, and in particular the nasal epithelium, which is probably related to their optimal growth temperature of 33°-37° C. The identification of serotypes is difficult because they are so numerous and for many serotypes no serologic test is available. A particular serotype can be recognized serologically in a specimen through neutralizing antibodies, if the serotype that produced the infection is known (*7, 8*).

It is difficult to isolate the coronaviruses, which belong to a different group from the rhinoviruses, although under natural conditions they infect the same cells. The coronaviruses are also RNA viruses, but they are larger than rhinoviruses, measuring 100-120 nm. To date, three serotypes have been recognized. Because of the technical difficulties, under natural conditions, often no etiologic diagnosis is established. However, serologic testing, utilizing complement fixation, hemagglutination inhibition, and ELISA, has permitted the identification of some of these coronaviruses (*7*).

III. Epidemiological aspects

The common cold is a universal disease, and a large part of the knowledge that exists about it is based on observations of the illness produced by the rhinoviruses and on studies of the effects of experimental infection of adult volunteers with these viruses (*4*).

Longitudinal studies, as well as cumulative information from clinical consultations, have revealed that children generally suffer three to eight colds a year, and the disease occurs more frequently among preschool children than among school-age children (*1, 9-11*).

Common colds, like most acute respiratory infections (ARI), are more common in winter or, in the tropics, during the rainy season. This frequency has been found to vary, depending on the etiology of the infection; rhinovirus infection is more frequent in fall and spring (*10*), while coronavirus infection tends to occur more frequently in winter (*7*).

A sero-epidemiologic study of rhinovirus infections at different ages found that newborns had antibodies to approximately 20% of 56 serotypes. This percentage decreased during the first year of life but then increased between the second year and adolescence as a result of repeated exposure to infection during this period of life (*12*).

During the course of the disease, virus shedding varies over a period of five days. An infected individual is probably most contagious between the third and fifth days, which is the period during which the symptoms are most severe and the greatest virus shedding takes place (*8*).

The mechanism of contagion for rhinovirus under natural conditions has not been established. In experiments with volunteers, both infection and illness occur when the virus is inoculated into the nose or conjunctiva (*8, 13*).

Children serve as the principal reservoirs of rhinoviruses through infections acquired at school and brought into their homes, where mothers become the most frequent secondary cases (*7, 13*). Infection with the same serotype has been found among people living in the same household and children in the same school classroom.

Most infections produce illness. There is no evidence of an asymptomatic carrier state (*13*). Rhinoviruses replicate in the upper respiratory tract, apparently mainly in the nose, since large quantities of virus have been recovered from nasal secretions but very few from pharyngeal secretions (*8, 13*). Rhinovirus has also been detected on the skin of the face and hands as a result of contamination with respiratory secretions. The virus has not been found in stool or blood (*8, 13*).

Under conditions of natural infection, rhinovirus has been found on the hands of 39% of 43 infected persons (*14, 15*) and also on 6% of 114 objects in the homes of the infected persons (*15*). Under experimental conditions, rhinovirus has been isolated from the hands of between 42% and 58% of infected volunteers (*16, 17*). Hence, it appears that rhinoviruses can be easily passed from the nose to the hands.

Under experimental conditions, in contacts between infected persons and susceptibles, more susceptibles were infected (11 of 15) when there was only hand contact than when the subjects were separated by a table (1 of 12). No infections occurred (0 of 10) when they were separated by a barrier that allowed the passage of small aerosol particles (*15*).

Given that people generally touch their noses and/or their eyes with their hands twice an hour, an ill or infected person can contaminate his hands by rubbing his nose and then can contaminate other objects or the hands of other people by touching them. Once the hands of a susceptible person have been contaminated, if he touches his nasal passages he becomes infected. It should also be noted that the skin and the environment can be contaminated by airborne droplets, mainly from sneezes (*13*).

In a study of married couples, transmission of the virus was associated with a large concentration of virus in nasopharyngeal secretions, detection of the virus on the hands of infected individuals, and spending 122 hours or more in the house together during the observation week (*17*). This indicates that, for infection to occur, not only is the mode of transmission important (contaminated hands and presumably airborne droplets from respiratory secretions), but so is the virus content of the inoculum (heavy concentration of virus in secretions) and the duration of exposure (*18-21*).

Mothers are able to easily recognize the common cold because the disease occurs so frequently and because they, their children, and other family members have all had it, and they tend to seek professional attention only when the symptoms are very severe or fever is present (*2*). Medical care is generally sought to rule out some more serious disease (*22*) or to obtain a prescription that will "cure" the cold or alleviate the symptoms (*22, 23*).

IV. Pathogenesis

Previously it was thought that viral invasion of the respiratory epithelium, especially in the nostrils, led to destruction of the cells of the mucous membranes (*24*). However, biopsies of exfoliated cells from the nasal mucous membranes of infected volunteers have not revealed any cellular changes when compared to biopsies performed prior to infection (*25*). In addition, studies of the nasal mucous cells of infected volunteers have shown that, in 16 of 17 infected individuals, the mucus contained exfoliated ciliated epithelial cells that contained viral antigens. The proportion of these cells averaged from 1% to 2% and was never more than 10%, and this percentage was not related to the severity of the symptoms. It was also observed that polymorphonuclear leukocytes increased from around 65% prior to infection to levels of between 80% and 95% during the infection (*26*). Some investigators therefore maintain that no destruction of mucous membranes occurs during a rhinovirus infection and that the symptoms are due mainly to two factors, namely:

a) the presence of chemical mediators of the inflammation, which are assumed to produce an increase in capillary permeability, leading to edema of the nasal mucosa, which would explain the nasal obstruction; at the same time, these mediators are assumed to produce an increase of serum in the mucus, which would explain the rhinorrhea;
b) the viruses presumably stimulate or irritate certain receptors in the mucous membranes, which in turn produces a cholinergic stimulus, increasing the production of mucus; this would contribute to the rhinorrhea and, in addition, would lead to bronchoconstriction, which would explain the cough and changes in pulmonary function observed in patients (*24*).

Tyrell observed that the infection has a marked effect on the cilia, affecting mucociliary movement and causing loss of cilia, although it is not clear if this is due to a significant destruction of the mucous membranes (*6*). It would be useful to determine if the effects mentioned by

Turner (*26*) are due only to rhinovirus or are also present with other viruses that cause the common cold.

In recent studies of adults, it has been observed that the situation of stress and an introverted personality are factors that increase susceptibility to colds (*6, 27*). In addition, a relationship between visual pattern and higher susceptibility to illness with a particular type of virus has been encountered (*28*). Thus, there seems to be evidence of an interaction between the brain (pattern sensitivity, introversion, stress) and the immune response (susceptibility to infection or illness).

V. Clinical findings

After a one- to two-day incubation period, the predominant symptoms of the common cold are rhinorrhea, nasal obstruction, and sneezing. Other frequent symptoms are cough, sore throat, headache, and general malaise. The frequency and intensity of fever are quite variable. Although the symptoms mentioned relate to the upper respiratory tract, symptomatology may be observed in other systems, as a result of which the patient may experience conditions such as chest pain, eye irritation, vomiting, diarrhea, muscle pain, and abdominal pain.

The clinical picture may depend on both etiology and host response. From an etiologic standpoint, the adenoviruses seem to produce symptomatology that is more generalized, rather than being confined to the upper respiratory system. The symptoms of influenza virus infection frequently include myalgia, while the respiratory syncytial virus tends to produce symptoms in the lower respiratory tract.

Symptoms are more pronounced in infants, who generally have fever (*1*). With regard to respiratory symptoms, the smaller the child, the more intense the nasal obstruction. Since infants have difficulty breathing through their mouths, the obstruction caused by nasal congestion and secretions impedes respiration, especially while nursing or sleeping, a fact that should be borne in mind in treating the symptoms of this ailment. Most children with a common cold have a cough, which might be explained by the fact that cough reflex receptors exist in the nostrils. Nevertheless, because the greatest number of cough receptors are found in the larynx, trachea, and bronchial passages, the cough is believed to be a manifestation of simultaneous involvement of the lower respiratory tract. The presence of cough has also been explained as a reflex due to postnasal drip. Additionally, it has been noted that upper respiratory infection is one of the factors that triggers the phenomenon of bronchial hyperreactivity. Asthmatic children have been found to suffer more frequent common colds than non-asthmatic children (*1, 29, 30*).

The common cold lasts for an average of seven days, with the symptoms becoming most intense between the third and fifth days. However, some symptoms, especially cough, may last for up to two weeks (*4, 31*).

Some children with common cold experience earache, but it must be determined whether the pain is transient or persistent. If the pain is transient, it is probably a result of changes in pressure inside the ear due to congestion of the Eustachian tube, which is lined with the same kind of mucous membrane as the rest of the upper respiratory system and may also be involved.

If the pain is persistent, there is greater probability that the ear itself is affected, and the tympanic membrane should be examined for signs of ear infection. To detect this painful condition, it is important for the child to be able to describe it, which may be possible only for older children; very young children (infants) will express their discomfort indirectly through irritability or by touching the ear or refusing to eat (*2*).

VI. Complications

The common cold is a self-limiting disease and only a small percentage of children suffer complications such as otitis media or sinusitis. It may be difficult to determine whether these complications are due to a secondary bacterial infection or are an extension of the primary viral infection. This is important because some children with these complications recover quickly without the use of antibiotics, in cases in which rhinovirus has been isolated in secretions from the middle ear or the paranasal sinuses (*1, 32*).

The presence of complaints characteristic of these complications, the exacerbation of these complaints, or a deviation from the usual course of the common cold will probably suggest that the child is suffering from a true complication. The presence of intense and/or persistent ear pain, the persistence of nasal discharge, or a purulent change in the discharge, combined with the appearance, persistence, and/or intensification of fever, are some of the signs that facilitate the clinical diagnosis of otitis media and/or sinusitis.

The purulence of the nasal secretions is the result of the presence of exfoliated epithelial cells and polymorphonuclear leukocytes produced in response to the infection. This occurs frequently in the course of the common cold and may not necessarily be indicative of bacterial superinfection, unless it is accompanied by exacerbation or reappearance of fever, or if this change occurs after the time within which the common cold would normally resolve (after 7-10 days).

VII. Diagnosis and differential diagnosis

The clinical picture of the common cold is characteristic and self-limiting, making auxiliary examinations unnecessary. It is useful, however, to seek the immediate epidemiological antecedent—i.e., a similar clinical picture in another member of the family or in someone with whom the child has been in contact, or the appearance in a family member of similar symptoms within the following two to four days, which would confirm the diagnosis of the common cold (*2*).

When a child suffers frequent colds—more than the normal three to five episodes per year—or if the child has persistent nasal symptoms, the possibility of a family history of respiratory allergies should be investigated or the nasal secretions should be analyzed for the presence of eosinophils, to rule out the possibility of allergic rhinitis.

A child who has a foreign body lodged in a nostril may also exhibit rhinorrhea, but it will generally be unilateral, frequently accompanied by a foul odor and sometimes bleeding.

With regard to differential diagnosis, it should be noted that several diseases may initially mimic the common cold. These include measles, whooping cough, and others. However, although the initial course of such diseases may be indistinguishable from that of the common cold, the early symptoms will be rapidly followed by symptoms specific to each illness.

VIII. Treatment

At present there is no specific treatment that is effective against the common cold, and treatment therefore consists essentially of alleviating the symptoms (*4, 33*).

The difficulty of developing a good antiviral drug for clinical use is understandable, since the drug would have to be a broad-spectrum agent, effective not just against the rhinoviruses but also against the coronaviruses and other viruses that cause the common cold.

Several antirhinovirus drugs are currently being tested and have shown the capacity to inhibit growth of the virus *in vitro*. These include zinc gluconate, enviroxime, interferon, flavonoids, and pirodavir.

After it was observed that zinc alleviated the symptoms in an immunocompromised child who suffered frequent and severe colds, it was demonstrated that some of the viruses that cause the common cold are sensitive to zinc *in vitro*, and zinc was therefore used in the treatment of cases of the common cold. A double-blind study found that zinc gluconate shortened the duration of the cold (*34*), but in two other controlled trials using volunteers in whom rhinovirus colds had been experimentally induced, no therapeutic effect from the zinc gluconate was observed (*35*). The effectiveness of this treatment should therefore be considered questionable.

Enviroxime is a benzimidazole derivative that is extremely effective *in vitro* against rhinovirus. It has been shown to reduce symptoms and lessen the amount of virus in nasal secretions, especially when applied topically to the nasal passages rather than taken orally (*36, 37*). Nevertheless, further clinical testing in a larger number of patients is required to demonstrate its clinical effectiveness.

Interferons are a heterogenous group of proteins of low molecular weight that are produced by infected host cells and protect uninfected neighboring cells from viral infection. They have been used experimentally as nasal sprays, but have proved effective only for prophylaxis, not for treatment of an established cold (*38, 39*).

Flavonoids are considered to be among the most powerful inhibitors of human rhinovirus replication. New molecules of this type are being synthesized with slight variations in their formula, which results, *in vitro*, in an increase in their spectrum of action (*40*).

There are various synthetic antiviral agents that inhibit the replication of human rhinovirus. One of the most recent is pirodavir (R77975), which is 500 times more powerful than its predecessor (R61837) and inhibits replication of 80% of the rhinovirus serotypes. In a clinical trial, pirodavir applied as a nasal spray six times a day, with a total of 25 applications, was effective in preventing both infection and illness, as well as in reducing the severity of illness, pro-

viding it was administered before the infection. The drug was well tolerated when applied intranasally, unlike other intranasal drugs, which can cause local irritation (*41*).

A specific antiviral treatment (antirhinovirus) is still being sought and there is hope of finding one, although some of the drugs used cause local (intranasal) irritation and must be administered frequently to be effective.

To treat the symptoms of the common cold, numerous drugs are available. Most are a combination of antihistamines, decongestants, and cough suppressants, but they have not been proven to be effective, whether used singly or in combination.

It is known that it is not histamine but kinins that are involved in the nasal symptoms of the common cold, and consequently there is no reason to use antihistamines (*42, 43*). Decongestants, generally derived from ephedrine, have not been shown to shorten the duration of the disease. As far as cough suppressants are concerned, it should be remembered that coughing is a defense mechanism by which the body clears the airways, and it is therefore counterproductive to use these medications (*44*).

Several observations, however, indicate that these drugs do work to some extent, and people therefore tend to justify their use, for two principal reasons. The first is of a pharmacological nature: antihistamines have an anticholinergic effect and they do therefore reduce mucus secretion; decongestants are effective vasoconstrictors and they reduce nasal congestion; and cough suppressants do effectively suppress the cough reflex when this is necessary to relieve the patient. The second reason is that medical attention is sought for most children when the symptoms are at their worst; it is possible that they would improve on their own over the next 24-48 hours simply as a result of the normal course of the disease, but this natural improvement may coincide with the use of one of these medications (*2*).

The main reason not to recommend these types of drugs is that their side effects may be so harmful that they cancel out any beneficial effect that the drug might have. For example, the anticholinergic effect of antihistamines will dry up nasal secretions, but this in turn may make it more difficult to eliminate them. Suppressing the cough reflex may also impede the elimination of secretions. With regard to decongestants, the greatest risk is their rebound effect, especially in infants, whose nasal congestion may actually worsen once the initial effect of the drug passes. Another possible side effect of decongestants that should not be overlooked is arterial hypertension, especially if the recommended dose is exceeded, which may occur because most of these products, for children, take the form of syrups. Other effects of antihistamines, in addition to their atropinic action, may include irritability and somnolence, which may or may not be dose-related (*44*). From the foregoing discussion, it is apparent that the side effects of the medications frequently used to treat the common cold are far from insignificant.

Current recommendations for treating the common cold in children consist of simple measures to relieve nasal congestion and control fever, maintaining a normal diet, offering the child liquids frequently, and observing the child to detect complications.

Relieving nasal symptoms through adequate removal of secretions and the use of normal saline solution—applied directly in the nostrils three or four drops each time as necessary–to

alleviate nasal congestion are simple measures that carry no risk whatsoever and will help the child to feel better (*45*).

If the child has a fever that is high (39° C or more) or causes him discomfort, the normal dose of an antipyretic (acetaminophen or aspirin for older children, 10-15 mg/kg/dose) should be given. The child should be given his normal, accustomed diet and should also be offered liquids frequently in order to facilitate elimination of the secretions by coughing.

It is important to remember that the common cold is a self-limiting disease for which the prognosis is good. Hence, rather than prescribing some cold medication, the health practitioner should be sure that the child's family members understand the usual course of the disease, so that they will be alert to any change in the normal pattern—either in the duration or in the intensity of the symptoms—that might signal possible complications.

With regard to symptomatic relief, the use of some analgesics, antipyretics, and anti-inflammatories yields contradictory clinical results. With the use of drugs such as acetaminophen and aspirin, several adverse effects have been noted, including suppression of the neutralizing antibody response and increase in the nasal signs and symptoms during the cold (*46*). However, these effects have not been observed with certain anti-inflammatories such as ibuprofen and naproxen (*46, 47*). It is therefore recommended that they be used only when fever or general malaise are relatively intense, but that they not be taken regularly or on an hourly schedule over several days.

Several clinical studies have shown that the administration of antibiotics during a common cold does not shorten the course of the illness or prevent complications, and there is therefore no justification for prescribing them on a routine basis (*49-51*).

Although physicians continue to prescribe antibiotics frequently, their use is not appropriate for the treatment of acute upper respiratory infections, most of which are viral infections. Several factors that influence the decision to use antibiotics have been identified (*52*):

- Anxiety on the physician's part with respect to his own performance, especially fear of making a mistake, as a result of which doctors will frequently opt to treat an ARI episode with antibiotics when they are unable to differentiate a viral infection from a bacterial infection.
- The physician's response to social pressure, which occurs mainly when the physician is unsure and yields to the anxiety of the family.
- Family anxiety, which often prompts consultations for the same symptoms of the same episode or a similar set of symptoms. If the physician does not bear in mind that episodes of ARI are quite common and that the majority are of viral origin, he is apt to give in to the pressure and quickly prescribe antibiotics to "control" the infection.
- The physician's fear of possible complications of presumed streptococcal infections, especially when the clinical picture of the cold includes pharyngeal symptoms, although most viral infections can cause the same symptoms.

Linus Pauling, winner of the Nobel prize for chemistry, maintained that vitamin C is effective in fighting the common cold (*53*), but its effectiveness continues to be debated. Some authors affirm that it is useful for prophylaxis and treatment of the common cold, but others deny its usefulness, asserting that the reported benefits are the result of statistical artifacts and a placebo effect, and do not represent any real benefit from ascorbic acid or vitamin C (*54, 55*).

Clinical studies of the use of measures such as breathing steam or drinking hot beverages, as well as the use of popular medications such as menthol, have yielded similarly contradictory results (*56-60*).

In the search for an effective treatment, tests of the simultaneous use of an antiviral agent (interferon, applied intranasally), an anti-inflammatory (naproxen, taken orally), and an anticholinergic (ipratropium, applied intranasally) to treat experimentally induced colds in adults have produced satisfactory results, including a shortened period of virus shedding, lower virus titers, and an improvement in symptoms, compared with a group that received a placebo (*61*). Nevertheless, the value of this treatment must be weighed against its high cost and the fact that the disease has a self-limiting course. Its use should therefore perhaps be reserved for severe cases or patients with immunodeficiency disorders, who are more likely to have severe cases.

IX. Prevention

Specific prevention through rhinovirus vaccines is not possible, owing mainly to the large number of rhinovirus serotypes that exist and to the fact that the antigenic content of these viruses changes constantly and new serotypes are continually appearing.

The use of interferon for prophylaxis is promising because this mediator is believed to play an important role in recovery from rhinovirus infection. Experiments suggest that interferon must be administered intranasally and in large doses to obtain good results (*39*).

Nonspecific prophylaxis to prevent transmission may also give satisfactory results. Since it is known that rhinoviruses can also be transmitted by hands contaminated with nasal secretions, ways are being sought to avoid this type of contagion through the use of virucides for hand-washing, although it should be remembered that ordinary hand-washing in itself is effective to some extent (*31*). Elimination of nasal secretions is also important. Disposable tissues should be used for this purpose to avoid greater contamination of the hands (*62*). Nevertheless, some of these measures are not applicable to children, especially very young children, and it is therefore necessary to seek other preventive measures to avoid contagion by this means.

X. Conclusion

The common cold is a frequent infectious disease in children and adults which is highly contagious and of viral origin. Because it is self-limiting, treatment—at least for the present—is limited to symptomatic measures, mainly for the nasal symptoms. Antiviral drugs and effective control measures will no doubt become available in the relatively near future and will spare

both children and adults the misery of this illness. In the meantime, it is important for parents or those who care for children to recognize when a common cold ceases to be a simple cold, whether due to its duration or to the appearance of warning signs, which depend on the age of the child (e.g., chest indrawing or tachypnea). In these cases, a physician should be consulted to determine the most appropriate treatment.

XI. References

1. Cherry JD. *The common cold.* In: Feigin RD, Cherry JE, eds. Textbook of pediatric infectious diseases. 2nd. Ed. Philadelphia PA: Saunders; 1987:155-160.
2. Hernández H. *Resfrío común.* In: Meneghello J, ed. Diálogos en pediatría. Santiago, Chile: Publicaciones Técnicas Mediterráneo; 1990:113-120.
3. Smillie WG. *The common cold*. New York, NY: Funk and Wagnalls; 1937:7-12.
4. Stickler GB, Smith TF, Broughton, DD. *The common cold.* Eur J Pediatr 1985;144:4-8.
5. Douglas Jr. RG, Lingren KM, Couch RB. *Exposure to cold environment and rhinovirus common cold. Failure to demonstrate effect.* N Engl J Med 1968;279:742-747.
6. Tyrrell D. *What's new on the common cold.* Practitioner 1990;234:391-395.
7. Reed SE. *The aetiology and epidemiology of common cold, and the possibilities of prevention.* Clin Otolaryngol 1981;6:379-387.
8. Gwaltney Jr. JM. *Rhinovirus.* In: Evan AS, ed. Viral infections of humans: Epidemiology and control. New York, NY: Plenum Medical; 1982:491-517.
9. Pan American Health Organization. *Acute respiratory infections in children.* Washington, DC; 1983.
10. Fox JP, Cooney MK, Hall CE, et al. *Rhinoviruses in Seattle families.* 1975-1979. Am J Epidemiol 1985;122:830-846.
11. Dong-lu Z, Zi-jing Z, Zhi-liang W, et al. *Surveillance of acute respiratory infections in three kindergartens in Beijing.* Chinese Med J 1988;101:787-792.
12. Hamparian VV, Conant RM, Thomas DC. *Rhinovirus Reference Laboratory, Annual Contract Progress Report to the National Institute of Allergy and Infectious Disease.* Bethesda, MD, National Institutes of Health. Contract No. 69-2062. December 1, 1969-November 30, 1970.
13. Hendley JD, Gwaltney Jr. JM. *Mechanisms of transmission of rhinovirus infections.* Epidemiol Rev 1988;10:242-258.
14. Hendley JO, Wenzel RP, Gwaltney Jr. JM. *Transmission of rhinovirus colds by self-inoculation.* N Engl J Med. 1973;288:1361-1364.
15. Gwaltney Jr. JM, Moskalski PB, Hendley JO. *Hand-to-hand transmission of rhinovirus colds.* Ann Inter Med 1988;88:463-467.
16. Reed SE. *An investigation of the possible transmission of rhinovirus colds through indirect contact.* J Hyg (Comb) 1975;75:249-258.

17. D'Alessio DJ, Peterson JA, Dick CR, et al. *Transmission of experimental rhinovirus colds in volunteer married couples.* J Infect Dis 1976;133:28-36.

18. Gwaltney Jr. JM, Moskalski PB, Hendley JO. *Interruption of experimental rhinovirus transmission.* J Infect Dis 1980;142:811-815.

19. Meschievitz CK, Schultz SB, Dick EC. *A model for obtaining predictable natural transmission of rhinovirus in human volunteers.* J Infect Dis 1984;150:195-201.

20. D'Alessio DJ, Meschievitz CK, Paterson JA, et al. *Short-duration exposure and the transmission of rhinovirus colds.* J Infect Dis 1984;150:189-194.

21. Dick EC, Jennings LC, Mink KA, et al. *Aerosol transmission of rhinovirus common cold.* J Infect Dis 1987;156:442-448.

22. Cowan PF. *Patient satisfaction with an office visit for the common cold.* J Fam Pract 1987;24:412-413.

23. Mayefsky JH, El-Shinaway Y, Kelleher P. *Families who seek care for the common cold in a pediatric emergency department.* J Pediatr 1991;119:933-934.

24. Hendley JO. *Rhinovirus colds: Immunology and pathogenesis*. Eur J Respir Dis 1983;64(Suppl 128):340-343.

25. Douglas Jr. RG, Alford BR, Couch RB. *Atraumatic nasal biopsy for studies of respiratory virus infection in volunteers.* Antimicrob Agents Chemother 1968;8:340-343.

26. Turner RB, Hendley JO, Gwaltney JM. *Shedding of infected ciliated epithelial cells in rhinovirus colds.* J Infect Dis 182;145:849-853.

27. Cohen S, Tyrrell DAJ, Smith AP. *Psychological stress and susceptibility to the common cold.* N Engl J Med 1991;325:606-612.

28. Smith AP, Tyrrell DA, Barrow W, et al. *The common cold, pattern sensitivity and contrast sensitivity.* Psychol Med 1992;22:487-494.

29. Lambert HP, Stern H. *Infective factors in exacerbations of bronchitis and asthma.* Br Med J 1972;3:323.

30. Horn MEC, Reed SE, Tayor P. *Role of viruses and bacteria in acute wheezy bronchitis in childhood: A study of sputum.* Arch Dis Child 1979;54:587-592.

31. Gwaltney Jr. JM. *Rhinovirus colds: Epidemiology, clinical characteristics and transmission.* Eur J Respir Dis 1983; 64(Suppl 128):336-339.

32. Gwaltney Jr. JM, Sydnor Jr. A, Sande MA. *Etiology and antimicrobial treatment of acute sinusitis.* Ann Otol Rhinol Laryngol 1981;84:68.

33. Del Mar C. *Managing viral upper respiratory infections*. Aust Fam Phy 1991;20:557-561.

34. Eby GA, Davis DR, Halcomb WW. *Reduction in duration of common colds by zinc gluconate lozenges in a double-blind study.* Antimicrob Agents Chemother 1984;25:20-24.

35. Farr BM, Conner EM, Betts FF, et al. *Two randomized controlled trials of zinc gluconate lozenge therapy of experimentally induced rhinovirus colds.* Antimicrob Agents Chemother 1987;31:1183-1187.

36. Philpotts RJ, Jones RW, Delohg DC, et al. *The activity of enviroxime against rhinovirus in man.* Lancet 1981;i:1342-1344.

37. Phillpots RJ, Wallace J, Tyrrell DA, et al. *Therapeutic activity of enviroxime against rhinovirus infection in volunteers.* Antimicrob Agents Chemother 1983;23:671-675.

38. Douglas RM, Moore BW, Miles HB, et al. *Prophylactic efficacy of intranasal alpha 2 interferon against rhinovirus infections in the family setting.* N Engl J Med 1986;314:65-70.

39. Monto AS, Shope JC, Schwartz SA, et al. *Intranasal interferon-2b for seasonal prophylaxis of respiratory infection.* J Infect Dis 1986;154:128-133.

40. Conti C, Tomao P, Genovese G, et al. *Mechanism of action of the antirhinovirus flavonoid 4',6-dicyanoflavan.* Antimicrob Agents Chemother 1992;36:95-99.

41. Hayden FG, Andries K, Janssen PA. *Safety and efficacy of intranasal pirodavir (R77975) in experimental rhinovirus infection.* Antimicrob Agents Chemother 1992;36:727-732.

42. Bluestone CD, Connel JT, Doyle WJ, et al. *Symposium: Questioning the efficacy and safety of antihistamines in the treatment of upper respiratory infection.* Pediatr Infect Dis J 1988;7:215-242.

43. Proud D, Naclerio RM, Gwaltney Jr. JM, Hendley JO. *Kinins are generated in nasal secretions during natural rhinovirus colds.* J Infect Dis 1990;161:120-123.

44. Pruitt AW. *Rational use of cold and cough preparation.* Pediatric Ann 1985;14:289-291.

45. Bollag U, Albercht E, Wingert W. *Medicated versus saline nose drops in the management of upper respiratory infection.* Helv Paediat Acta 1984;39:342-345.

46. Graham NM, Burrell CJ, Douglas RM, et al. *Adverse effects of aspirin, acetaminophen, and ibuprofen on immune function, viral shedding and clinical status in rhinovirus infected volunteers.* J Infect Dis 1990;162:177-182.

47. Sperber SJ, Hendley JO, Hayden FG, et al. *Effects of naproxen on experimental rhinovirus colds.* Ann Inter Med 1992;117:37-41.

48. Jones PN, Bigham RS, Manning PR. *Use of antibiotics in non-bacterial respiratory infections.* J Am Med Assoc 1953;153:262-264.

49. Hardy LM, Traisman HS. *Antibiotics and chemotherapeutic agents in the treatment of uncomplicated respiratory infections in children.* J Pediatr 1956;48:146-56.

50. Soyka LF, Robinson DS, Lanchant N, Monaco J. *The misuse of antibiotics for treatment of upper respiratory tract infections in children*. Pediatrics 1975;55:552-556.

51. Taylor B, Abbot GD, Kerr MMcK, Fergusson DM. *Amoxycillin and cotrimoxazole in presumed viral respiratory infections of childhood: Placebo-controlled trial.* Br Med J 1977;2:552-554.

52. Howie JGR. *Some non-bacteriological determinants and implications of antibiotic use in upper respiratory tract illness.* Scand J Infect Dis 1983;(Suppl)39:68-72.

53. Pauling L. *Vitamin C, the common cold and the flu.* San Francisco, CA: Freeman; 1976.

54. Caulehan JL. *Ascorbic acid and the common cold. Reviewing the evidence.* Post Grad Med 1979;66:153-160.

55. Carr AB, Einstein R, Lai LY, et al. *Vitamin C and the common cold; Using identical twins as controls.* Med J Aust 1981;2:411-412.

56. Sakethoo K, Januszkiewicz A, Sackner MA. *Effects of drinking hot water, cold water and chicken soup on nasal mucus viscosity and nasal airflow resistance.* Chest 1978;74:408-410.

57. Tyrrell D, Barrow I, Arthur J. *Local hyperthermia benefits natural and experimental common colds.* Br Med J 1989;298:1280-1283.

58. Macknin ML, Mathew S, VanderBrug Medendorp S. *Effect of inhaling heated vapor on symptoms of the common cold.* J Am Med Assoc 1990;264:989-991.

59. Eccles R, Morris S, Jawad MSM. *The effects of menthol on reaction time and nasal sensation of airflow in subjects suffering from the common cold.* Clin Otolaryngol 1990;15:39-42.

60. Eccles R, Jawad MS, Morris S. *The effects of oral administration of (-)menthol on nasal resistance to airflow and nasal sensation of airflow in subjects suffering from nasal congestion associated with the common cold.* J Pharm Pharmacol 1990;42:652-654.

61. Gwaltney JM. *Combined antiviral and antimediator treatment of rhinovirus colds.* J Infect Dis 1992;166:776-782.

62. Hayden GF, Henley GF, Henley JO. *Update: New developments in rhinovirus cold control.* J Respir Dis 1986;7:11-16.