Attempts to relieve the misery of the common cold have been made since long before current understanding of its viral origin. Although current symptomatic therapies provide some relief, any effective treatment must incorporate an antiviral to address the infection. Symptom production is related not only to viral cytopathic effect but also to the early activation of several inflammatory pathways. Antiviral treatment alone may not be able to prevent these events. Combining an antiviral with selected therapeutic agents that block these inflammatory pathways has been shown to improve the effectiveness of cold treatment. Early diagnosis and initiation of treatment combined with regular dosing until symptoms subside appears to be the most effective treatment strategy to maximize therapeutic outcomes. This strategy reduces viral shedding in nasal fluid, provides treatment for the period of maximum symptom burden, and may reduce the frequency and severity of the sinus disease that accompanies colds. Am J Med. 2002;112(6A):33S–41S. © 2002 by Excerpta Medica, Inc.

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he history of the common cold can be divided into several eras (Table 1).¹ These are the Era of Ignorance, the Era of Infection, the Viral Era, and the Molecular Era that we are in now. It is unclear when the first period began, but it is interesting that rhinovirus infects only the higher primates. The human line branched off from the other higher primates about 6 million years ago. This suggests that rhinovirus has been around for at least that long.

The cold treatments that people used in the Era of Ignorance were as ridiculous as some of those used today. The Roman scholar and naturalist, Pliny the Elder, prescribed rubbing the hairy muzzle of a mouse against the nose as a good cold treatment. Thomas Jefferson advised a friend to soak his feet in cold water every morning. Jefferson stated that he had not had a cold for many years owing to this practice. The second era, the Era of Infection, was introduced in 1914 by Dr. Walter Kruse at the Hygienic Institute in Leipzig. Dr. Kruse was the first investigator to perform nasal challenge studies, which he did by collecting nasal secretions from persons with colds, filtering the secretions to remove bacteria, and instilling them into the noses of volunteers. He produced the first experimental colds and proved that colds were an infection. By that time, the first nonsteroidal anti-inflammatory drug (NSAID), aspirin, was in use as a cold treatment, and decongestants such as ephedrine were available. Opiates had also been used to suppress coughing.

The Viral Era did not begin until 1956, when Dr. William Mogabgab discovered the first cold virus, the rhinovirus. It was not long before that, in the 1940s, that researchers discovered another effective treatment for cold symptoms: first-generation antihistamines. It has been only recently, however, that well-designed clinical trials were conducted on the use of antihistamines for the treatment of cold symptoms, and these trials clearly established the benefit of these drugs. The elucidation of the atomic structure of rhinovirus in 1986 by Dr. Michael Rossmann et al ushered in the Molecular Era. Novel experimental cold treatments based on this new information are now under study. These include soluble intracellular adhesion molecule–1 (ICAM–1), which as a treatment is designed to prevent attachment of rhinovirus to its receptor on nasal cells, and capsid binders and protease inhibitors, which are new compounds that interfere with viral replication. Another substance with anti–cold
virus activity still under study is interferon, which was discovered in the 1960s.

**PRINCIPLES IN TESTING COLD TREATMENTS**

Certain principles on which to base the testing of common cold treatments have emerged in recent decades. An obvious but still often ignored principle is that accurate information on the effectiveness of treatments for self-limited conditions requires testing under controlled and blinded conditions. This is especially true of the common cold, in which there is large variance in duration and severity of illness among individuals and a scarcity of objective measures of illness. Colds peak in severity on average by 3 days and then rapidly undergo spontaneous resolution. Thus, the opportunity to detect treatment effects is compromised unless individuals are enrolled for study in the early stage of illness, that is, within 24 hours. Many cold remedies that have been popular in the past or are currently in vogue have never undergone proper testing to determine if they are truly effective.

**Inflammatory Mediators**

Another important factor in developing cold treatments is the increasing evidence that cold symptoms are the result, in large part, of the action of inflammatory mediators rather than of direct viral cytopathology. Multiple inflammatory events occur simultaneously, and these processes may each have to be addressed therapeutically in order to secure optimum benefit.

The relief of the important symptoms of a common cold and their pathophysiologic causes represent treatment goals. Currently available treatments for cold symptoms are listed in Table 2. Dilation of blood vessels in the nose leads to swelling of the nasal turbinates, which causes nasal obstruction. Stimulation of the seromucous glands and opening of intercellular junctions of nasal cells lead to the collection of fluid in the nasal passages. Plasma exudation brings vascular inflammatory mediators, such as kinins, into the nasal passages. Also, goblet cell exocytosis contributes mucus to the nasal fluid. Stimulation of pain nerve fibers and the sneeze and cough reflexes accounts for the other respiratory symptoms of the common cold syndrome. Finally, mediators such as the prostaglandins are believed to be responsible for general symptoms such as malaise, headache, and myalgia. These systemic complaints, although present, are usually mild in colds. To successfully treat colds in their entirety, these various pathophysiologic events must be addressed.

**Symptomatic Cold Treatments**

Currently, several classes of drugs are available that are effective to a greater or lesser extent for the treatment of these various processes. These include decongestants, an-

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**Table 1. Historical Eras of the Common Cold**

<table>
<thead>
<tr>
<th>Title</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Era of Ignorance</td>
<td>Since the origination of the human species</td>
</tr>
<tr>
<td>The Era of Infection</td>
<td>1914</td>
</tr>
<tr>
<td>The Viral Era</td>
<td>1956</td>
</tr>
<tr>
<td>The Molecular Era</td>
<td>1986</td>
</tr>
</tbody>
</table>

Reprinted with permission from *Viral Infections: Diagnosis, Treatment and Prevention*, New York: Churchill Livingstone.¹

**Table 2. Cold Symptoms, Treatment Goals, and Available Treatments**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Treatment Goals</th>
<th>Available Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal obstruction</td>
<td>Shrink nasal turbinates</td>
<td>Decongestants</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>Reduce secretion of seromucous glands</td>
<td>Antihistamines (first generation)</td>
</tr>
<tr>
<td></td>
<td>Reduce exudation of plasma</td>
<td>Anticholinergics</td>
</tr>
<tr>
<td></td>
<td>Reduce goblet cell exocytosis</td>
<td>Antihistamines?</td>
</tr>
<tr>
<td>Sneezing</td>
<td>Suppress sneeze reflex</td>
<td>Antihistamine (first generation)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>Suppress pain reflex</td>
<td>Topical analgesics, NSAIDs?</td>
</tr>
<tr>
<td>Cough</td>
<td>Suppress cough reflex</td>
<td>Opiates</td>
</tr>
<tr>
<td></td>
<td>Block prostaglandins?</td>
<td>NSAIDs</td>
</tr>
<tr>
<td>Systemic (malaise, etc.)</td>
<td>Block responsible mediators</td>
<td>NSAIDs</td>
</tr>
<tr>
<td>All of the above</td>
<td>Stop viral replication</td>
<td>Antivirals</td>
</tr>
</tbody>
</table>

NSAID = nonsteroidal anti-inflammatory drugs.
ticholinergics, antihistamines, and NSAIDs. Lacking are drugs that are truly effective in lysing and/or evacuating mucus. Finally, because viral replication in the airway is the underlying pathologic problem, antiviral drugs must be an essential part of any cold treatment that has optimum effectiveness.

A comprehensive review of all prior clinical trials of cold treatments is not possible here, but a good review of this topic has been published.3 Some of the clinical trials used the rhinovirus challenge model. This model has an advantage over natural colds in studying cold treatments, because the signal-to-noise ratio in the model is higher.4 The modified Jackson method was used to diagnose illness and measure symptom severity.5 With the Jackson method, the subject is asked daily about the occurrence of a variety of symptoms, including sneezing, runny nose, nasal obstruction, scratchy/sore throat, cough, headache, malaise, myalgia, and chilliness. Symptoms are graded for severity on a scale of 1 to 3 or 1 to 4 (mild, moderate, severe, or very severe) over the period of the previous 24 hours. A positive diagnosis of a cold depends on a minimum total symptom score of 6 summed over the 5 days of observation plus the subjective impression of having had a cold and/or the presence of rhinorrhea for 3 days or more.

In several clinical trials, drugs representative of their class were tested in the rhinovirus challenge model using the Jackson method of scoring illness. Naproxen, as a representative of NSAIDs, was tested in doses of 200 or 500 mg 3 times a day.6 At the higher dose, significant reductions were observed in the severity of headache and malaise, and a strong, favorable trend occurred with chilliness (Figure 1). Also, severity of cough was reduced. Other studies have reported a beneficial effect of NSAIDs on cough.7,8 On the other hand, the severity of the nasal symptoms, sneezing, nasal obstruction, and rhinorrhea was not reduced. Viral concentrations in nasal secretions were the same in the naproxen and control groups.

Brompheniramine, as a representative of first-generation antihistamines, was also tested in the virus-challenge model.9 Large therapeutic effects were seen for sneezing severity and sneeze counts (Figure 2) and for rhinorrhea and nasal mucus weights (Figure 3). Also, cough severity and cough counts were reduced in the treated group (Figure 4). In contrast, no beneficial effect was observed for nasal obstruction, sore throat, malaise, or headache (Figure 5). Other clinical trials with first-generation antihistamines have found similar beneficial effects for sneezing and rhinorrhea but not for cough.10,11

Studies of first-generation antihistamine in patients with natural colds have shown benefit for sneezing and rhinorrhea, although effect sizes were smaller, as would be expected.12 Second-generation antihistamines have not been effective in treating colds, possibly because of

Figure 1. Mean (±SE) individual symptom scores and nasal mucus weights in 39 volunteers receiving naproxen (solid curve) and 40 volunteers receiving placebo (dashed curve). Subjects were evaluated using a modified method of Jackson. Obstruction = nasal obstruction. *P < 0.05; †P < 0.01. (Reprinted with permission from Ann Intern Med.6)
their lack of anticholinergic activity and failure to reach the central nervous system. First-generation antihistamines are safe, although in some people they cause drowsiness and should not be taken when driving or engaged in other activities that require being alert.

The effectiveness of decongestants in shrinking nasal tissue and relieving nasal obstruction is well documented. Most such studies have measured short-term effects of treatment in patients with natural colds. Much of this information is in the files of pharmaceutical companies, and few published studies have been given high validity scores. Only a small amount of information is available from clinical trials studying experimental colds that have evaluated decongestant effects over a period of 24 hours.

Computed tomography scans of the nasal passages and sinuses in adults with colds have demonstrated that decongestants mainly shrink the nasal turbinates and open the nasal passages and middle meatus. Drainage of sinus contents was not observed because of the high viscosity and adhesiveness of the exudate, which was not moved up to the ostia by mucociliary action. Also, decongestants would not be expected to open small-diameter drainage passages, such as the infundibulum, which is encased in bone. Even if shrinking of the thin epithelial lining of the infundibulum does occur, the passageway still has a diameter of no more than a few millimeters, which is too small for drainage of highly viscous material.

Figure 2. Mean (±SE) sneeze count (A) and sneeze severity scores (B) for volunteers with experimental rhinovirus colds who received either brompheniramine (open circles, n = 113) or placebo (solid circles, n = 112). The numbers on the horizontal axis refer to days after virus challenge. The bars under the horizontal axis refer to period of treatment. (Reprinted with permission from Clin Infect Dis.)

Antivirals
An important goal for treatment of colds has been to develop compounds with activity against the causative viruses. The initial hope that interferon would be an effective cold remedy was not fulfilled when put to the
test. Although interferon is effective in both experimental and natural colds when used prophylactically, it's chronic use in prophylaxis causes nasal irritation. As treatment, interferon did not reduce symptom burden sufficiently to have clinical value. In experimental colds, nasal symptom scores and production of nasal mucus was significantly reduced by treatment with intranasal interferon (Figure 6), but there was no therapeutic effect on other symptoms. 

Another approach has been to block viral attachment with synthetic ICAM-1. Intranasal application of multiple daily doses of ICAM-1 given prophylactically or therapeutically reduced the severity of experimental rhinovirus colds, but the magnitude of the therapeutic effect sizes observed was small.

Two other antiviral compounds with specific activity against rhinovirus—pleconaril, a capsid binder, and AG7088, a protease inhibitor—are currently being investigated. Published results of clinical trials with AG 7088 are not available, but pleconaril has been tested in adults with self-diagnosed natural colds. In two randomized double-blind, placebo-controlled multicenter trials, pleconaril 400 mg tid for 5 days was given to 1,046 patients and placebo to 1,050 patients. The effectiveness of treatment was analyzed in a subset of 681 pleconaril and 682 placebo patients who were positive for picornavirus RNA by reverse transcriptase polymerase chain reaction. Pleconaril treatment reduced the median duration of illness from 7.3 to 6.3 days and the total symptom severity score by 19%. Pleconaril administration has been associated
with gastrointestinal disturbance, increases in baseline in serum cholesterol value (5 mg/dL pleconaril, 4 mg/dL placebo), and breakthrough menstrual bleeding in women on oral contraceptives.

**Combination Antiviral Antimediator Treatment**

A new approach to cold treatment is based on combining an antiviral with drugs that block selected inflammatory events that occur in colds. The results of an earlier study in the rhinovirus challenge model that used a combination of intranasal interferon and ipratropium with oral naproxen support this concept. This has been followed by a recent randomized, controlled, double-blind, study in which adults with experimental colds were treated with intranasal interferon and oral chlorpheniramine and ibuprofen. During the 4 days of treatment, subjects on combination therapy had a reduction in daily mean total symptom score of 33% to 73% (range) compared with placebo. Treatment was associated with a significant reduction in viral excretion, nasal mucus weights, nasal tissue use, rhinorrhea, sneezing, nasal obstruction, sore throat, cough, and headache. Drowsiness (treatment 10%, placebo 0%) was associated with the treatment, which was otherwise well tolerated.

**Figure 4.** Mean (±SE) cough count (A) and cough severity scores (B) for volunteers with experimental rhinovirus colds who received either brompheniramine (open circles, n = 113) or placebo (solid circles, n = 112). The numbers on the horizontal axis refer to days after virus challenge. The bars under the horizontal axis refer to period of treatment. (Reprinted with permission from *Clin Infect Dis*.)
Figure 5. Mean (±SE) nasal obstruction (A), sore throat (B), malaise (C), and headache (D) severity scores for volunteers with experimental rhinovirus colds who received either brompheniramine (open circles, n = 113) or placebo (solid circles, n = 112). The numbers on the horizontal axis refer to days after virus challenge. The bars under the horizontal axis refer to period of treatment. (Reprinted with permission from Clin Infect Dis.9)

Figure 6. Nasal symptom scores and production of mucus in rhinovirus type-39–inoculated volunteers with HuIFN-α2 (white bars) or placebo (shaded bars) by nasal drops. Treatments were initiated on the first day after viral challenge at 4 PM. The nasal mucus weights on the first day after virus challenge represent 12-hour collections beginning at 8 PM. (Reprinted with permission from J Infect Dis.21)
**Early Treatment**

Another principle that appears to be important in obtaining maximum benefit from cold treatments is that treatment must be started early, at the first indication of a cold. There are at least 2 reasons that this is important. First, on average most of the symptom burden of colds occurs in the first 3 days of illness. After that, symptoms begin to resolve spontaneously. The second reason for early treatment is to limit buildup of nasal fluid, which may get blown into the sinuses, leading to viral and/or bacterial sinusitis. Also, because inflammatory mediators are activated early in the infection, it is important to block this event as much as possible by early treatment. The important principle is to not let the cold develop fully in the first place. This not only requires early treatment, but also continuation of the anti-inflammatory component of the treatment on a regular basis. Experience with the combined treatment suggests that when the cold is still active, sneezing, rhinorrhea, and cough begin to return 10 to 12 hours after the last dose, requiring continuing treatment. The early and regular dosing strategy is different from the way people currently tend to treat colds. The usual practice when a cold symptom appears is to wait and see what happens. After the cold is established, treatment is started. This approach misses the opportunity to obtain maximum benefit from the treatment. If treatment is begun early and it appears that the symptom(s) are not the result of a cold, then treatment can be discontinued. However, if it is a cold, then treatment should be continued for up to a week or until symptoms have resolved. This strategy conforms to the current recommendations for the diagnosis of secondary bacterial sinusitis, which is obtaining a history that a cold or a “flu-like” illness is no better or worse after a week to 10 days. This course of the illness may represent a secondary bacterial infection of the sinus, requiring antibiotic treatment. It is important to emphasize that the criterion is that the cold is no better or worse, not that some of the cold symptoms are still present after a week to 10 days. Many colds last that long but will be improving at the end of a week. Using this diagnostic strategy to distinguish colds from acute bacterial sinusitis can help to reduce the misuse of antibiotics.

The question of the early diagnosis of colds is important. If people cannot recognize when they are getting a cold and treat themselves early, then even the most effective cold treatment cannot be expected to provide much benefit. However, it appears that people are able to accurately self-diagnose a cold in the early stages. In one study, people were asked how long after they had their first symptom did they know that they had a cold. For 39%, the interval between their first symptom and the point at which they were fairly certain that they had a cold was reported to be less than 4 hours (Table 3). For 29.5%, the interval was 4 to 8 hours; for 15%, the interval was 8 to 16 hours; and for 16%, it was 24 hours. Thus, within 24 hours of the onset of the first symptom, recognition of the cold had occurred. These findings suggest that the problem in people not seeking early treatment for colds is not failure to recognize that a cold is starting. The problem is the behavior pattern that currently exists, in which people knowingly delay getting treatment. This behavior is understandable, given that available cold treatments are not very good and there is not a strong incentive to use them until the cold symptoms reach a certain level of discomfort. When better cold treatments become available, and with education, this behavior may change.

**SUMMARY**

Viral infection is the root cause of a cold, and a truly effective treatment—a real “cure”—must incorporate an antiviral to address the infection. Also, antiviral treatment reduces viral shedding in the nasal fluid and may reduce the chance of spread to other individuals. However, it appears that symptom production is related not only to viral cytopathic effect but also to the early activation of several inflammatory pathways, and antiviral treatment alone may not be able to prevent these events and thus give maximum clinical benefit.

The onset of symptoms occurs very soon after initiation of infection: it occurred within 10 to 12 hours in one study of rhinovirus colds. Combining an antiviral with selected therapeutic agents that block these inflammatory events has been shown to improve the effectiveness of cold treatment. Initiation of treatment at the earliest sign of a cold, combined with regular dosing until symptoms subside, appears to be the most effective treatment strategy. This strategy reduces viral shedding in nasal fluid, provides treatment for the period of maximum symptom burden, and may reduce the frequency and severity of the sinus disease that accompanies colds.

**Table 3. Time to Self-Diagnosis of Natural Rhinovirus Colds**

<table>
<thead>
<tr>
<th>Time to Diagnosis (hr)</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤4</td>
<td>108 (39)</td>
</tr>
<tr>
<td>4–8</td>
<td>81 (29.5)</td>
</tr>
<tr>
<td>8–16</td>
<td>41 (15)</td>
</tr>
<tr>
<td>24</td>
<td>44 (16)</td>
</tr>
</tbody>
</table>

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**References**


