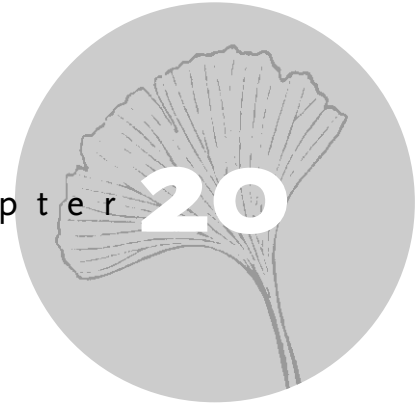




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Viral Upper Respiratory Infection

Bruce Barrett, MD, PhD

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Viral infection of the upper respiratory tract causes the common cold, humanity’s most common illness. Viral upper respiratory infection (URI) accounts for more than 25 million physician visits and 40 million lost days of school and work each year in the United States alone.¹ Total annual economic costs are estimated at around \$40 billion, making viral URI the seventh most expensive illness.² On average, children experience four to six colds per year. For adults, the average is two to three colds per year.³⁻⁵ Some people are especially prone to colds; others get them infrequently.

Although there is no proven cure for the common cold, a number of therapies have shown some benefit in various randomized, controlled trials (RCTs). Immunization strategies are impractical, because etiologic agents include hundreds of strains of a dozen or more types of viruses. However, prevention strategies such as hand washing, good nutrition, and exercise are highly likely to be beneficial.^{6,7}

Pathophysiology

As an experienced *illness*, the common cold is characterized by nasal congestion and drainage, sneezing, sore or scratchy throat, cough, and general malaise.⁸ Cough may or may not be present and tends to occur later in the disease, sometimes lasting for weeks after other symptoms have resolved. Severity of symptoms vary markedly, from barely noticeable to truly debilitating.⁹ Although true fever is not typical, feelings of feverishness and chilliness are common.¹⁰

As an infectious *disease*, viral URI is characterized by replication of viruses in oral, nasal, and upper respiratory epithelium¹¹ and by activation of local and systemic immune response.¹²⁻¹⁴ Viral replication within epithelial cells triggers cytokine-mediated local inflammatory reactions as well as recruitment of white blood cells. Parasympathetic neural pathways activate and coordinate local responses.

Blood vessels dilate and capillaries leak, causing edematous tissue swelling in the nasal passages.¹⁵ Mucous glands are activated, leading to copious discharge in some people. Inflammatory changes in the respiratory epithelium persist for days or weeks after viral shedding dies down. Nevertheless, it is possible to culture viruses out of occasional hosts weeks or even months after the initial infection. Activation of inflammatory mechanisms make viral URI the most important cause of asthma exacerbation.¹⁶

Rhinovirus is the single most common etiologic agent but accounts for less than half of all URIs.¹⁷⁻¹⁹ Other viruses include adenovirus, coronavirus, enterovirus, influenza virus, parainfluenza, and respiratory syncytial virus.^{20,21} Metapneumovirus has recently been discovered and added to the list.²² There may be others yet undiscovered, as even the best research laboratories fail to identify an etiologic agent in up to one quarter of people with obvious colds. A few bacteria, such as *Streptococcus* and *Hemophilus influenzae*, may cause illnesses with symptoms similar to common cold.

Respiratory viruses follow seasonal patterns. Influenza and respiratory syncytial virus only occurs during the winter months. Rhinovirus URIs tend to be in the fall and spring. Adenovirus appears year round. Parainfluenza miniepidemics are episodic. Outbreaks of atypical agents, such as the pertussis bacteria (*Bordetella pertussis*), may further complicate the picture.

The spectrum of illness varies greatly within and among agents. Influenza causes the most severe illness and hence is often classified separately from other viral URIs. Nevertheless, the majority of illness episodes caused by influenza are indistinguishable from those caused by other viruses, and a significant number of people infected with and shedding influenza have no symptoms or signs. Only a few present with the classic symptoms of rapid onset, fever, cough, headache, and myalgia. Unlike most viruses causing URI, influenza can lead to substantial epithelial denudation of the respiratory epithelium. Despite a coordinated system to provide influenza vaccine (“flu shots”) each fall, influenza is implicated in as many as 20,000 deaths each year.

Integrative Therapy

There are innumerable treatments for the common cold. Globally, botanical remedies have been the mainstay of treatment. Perhaps due to high illness prevalence, botanical therapies for common cold fill countless pages of notes and treatises by physicians, anthropologists, and ethnobotanists.²³⁻²⁶

Botanicals

Andrographis (*Andrographis paniculata*)

Andrographis (also known as *Justicia paniculata*) is indigenous to Asia, with traditional use most prominent in India. Of 28 *Andrographis* species, *A. paniculata* is most commonly used. According to Ayurvedic tradition,

andrographis is attributed many important medicinal properties, including constipation, digestion, fever, pain, sore throat, snake bite remedy, and blood cleanser. In the West, andrographis is most frequently used as a common cold treatment or preventive.

Various laboratories have reported antimicrobial,²⁷ antihyperglycemic,^{28,29} anti-inflammatory,³⁰ immunomodulatory,^{31,32} and psychopharmacologic³³ effects attributable to andrographolide, flavonoids,³⁴ and other photochemical constituents. There have now been at least seven trials ($N = 896$) testing various andrographis derivatives in URI, including pharyngitis.³⁵⁻⁴² Systematic reviews by Coon and Ernst⁴³ and Poolsup and associates⁴⁴ concluded the following:

Collectively, the data suggest that *A. paniculata* is superior to placebo in alleviating the subjective symptoms of uncomplicated upper respiratory tract infection. There is also preliminary evidence of a preventative effect.... *A. paniculata* may be a safe and efficacious treatment for the relief of symptoms of uncomplicated upper respiratory tract infection; more research is warranted.⁴³

Current evidence suggests that *A. paniculata* extract alone or in combination with *A. senticosus* extract may be more effective than placebo and may be an appropriate alternative treatment of uncomplicated acute upper respiratory tract infection.⁴⁴

Based on this positive albeit preliminary evidence, and with no indications of serious safety concerns, it seems reasonable for adults seeking relief from URI symptoms to try *Andrographis*-based cold remedies. There is not sufficient evidence to favor one product over another, any specific dosing regimen, or any particular standardization procedure for phytochemical content.

Dosage

Most clinical trials used products standardized to 4 or 5 mg of andrographolide. One reasonable dose regimen would be a 400-mg tablet, three times daily, for the first few days of a cold.

Precautions

For pregnant women and children, it seems prudent to recommend against use because there are little data from these populations and risk of harm may be present.

Astragalus (*Astragalus membranaceus*, *Astragalus mongholicus*)

Astragalus is an important medicinal plant in traditional Chinese medicine.⁴⁵ Although there are dozens if not hundreds of reported uses, astragalus extracts are commonly used as both treatment and prevention of the common cold.⁴⁶ Some antiviral activity has been reported, but immunomodulation is the purported mechanism of action. Indeed, several studies have reported immunoactivity from astragalus, from enhanced immunoglobulin production to restoration of lost T-cell activity.⁴⁷⁻⁵¹ Astragalus root contains astragaloside, flavonoids, and saponins, which are

thought to be involved in various hypothesized mechanisms of action. Unfortunately, because there are no human URI trials, no clear recommendations can be made for or against use as treatment or prevention of the common cold.

Dosage

2 to 6 gm daily

Precautions

Side effects are rare. Immunosuppression may occur with doses greater than 28 gm.

Chamomile (*Matricaria chomomilla*)

Chamomile has been used widely as a botanical remedy for centuries for a variety of purposes, including dysmenorrhea, gingivitis, hemorrhoids, infantile colic, indigestion, insomnia, nausea, vaginitis, and topically for a variety of skin conditions.⁵² In the United States, chamomile is most often used as calmativ or sedative and for irritable bowel syndrome. However, chamomile is also used for acute respiratory infection; hence, it merits inclusion in this review. As a common cold remedy, chamomile can be taken as an infusion (chamomile tea), or the flowering tops can be boiled and the vapors inhaled. One trial testing inhaled vapors from boiling chamomile reported benefit but was of insufficient quality to make firm conclusions.⁵³

Dosage

Although there is no good evidence, a cup or two of chamomile tea as supportive treatment for common cold is certainly safe and may be beneficial.

Precautions

Although there are no known dose-dependent adverse reactions, allergic sensitivity, including several cases of anaphylaxis, has been reported.⁵⁴

Echinacea (*Echinacea angustifolia*, *Echinacea purpurea*, *Echinacea pallidae*)

All dozen species from the genus *Echinacea* are indigenous to North America. Native peoples discovered dozens of medicinal uses, later transferring knowledge to European settlers.⁵⁵ In the 1920s, echinacea was introduced into Germany, where it has been popular ever since. Today, in America, Europe, and elsewhere, echinacea extracts are widely used, especially for prevention and treatment of common cold.⁵⁶ A considerable body of research exists regarding these uses, including 20 randomized trials with more than 3000 participants, and dozens of in vitro and animal studies.⁵⁷⁻⁶⁰ Although there is some consensus that echinacea extracts display immunologic activities such as macrophage activation and cytokine expression,⁶¹⁻⁶⁸ there is considerable disagreement concerning which of many echinacea-derived phytochemicals are involved. Various alkylamides, glycoproteins, polysaccharides and caffeic, cichoric and caftaric acids all are implicated. Differing extracts from all three species and from various plant parts have shown immunoactivity in laboratory models. No head-to-head,

dose-finding, or viral load outcome studies have been reported. One problem is that there are no clear mechanistic pathways linking immunoactivities to prevention or treatment of infection. While cytokine release assists in targeting and elimination of infected cells, these processes also enhance inflammatory pathways, yielding more severe symptoms. Disentangling symptom-generating pathways from virus-eliminating pathways remains the greatest challenge to development of any effective immunomodulating treatment for viral infectious disease.

Echinacea causes a tingling and numbness sensation on the tongue. This can be an indicator that the product used contains the active plant.

Double-blinded RCTs testing echinacea extracts for prevention and treatment of common cold were initially positive, with several reasonable-quality European trials reporting positive results from 1989 to 2001.⁶⁹⁻⁷⁶ More recent trials, including several in North America, have reported mixed results, with the better trials finding no benefit.⁷⁷⁻⁸¹ Nevertheless, current systematic reviews continue to be fairly positive, with the majority of trials reported as positive.⁵⁷⁻⁶⁰ A recent review with less positive conclusions argues that the positive trials may be due to inadvertent unblinding with either placebo effect or participant reporting bias contributing to false-positive results.⁸² A recent trial using *E. angustifolia* extracts in an induced cold model using inoculated rhinovirus found no effect, perhaps supporting this more negative view.⁸³ A comprehensive safety review notes a number of reported allergic reactions but suggests no dose-dependent adverse effects or major drug interaction concerns.⁸⁴

Given that echinacea extracts appear safe and that the majority of published trials remain positive, it seems reasonable to cautiously support use for adults, especially those with favorable personal experience.

Dosage

Positive trials have used differing formulations, with preparations made from herb and flower of *E. purpurea* used most widely. However, recent evidence suggests that alkylamides from roots of *E. purpurea* and *E. angustifolia* may have best bioavailability and immunoactivity.⁸⁵⁻⁸⁷ Although there is no consensus on standardization criteria, most experts do agree that echinacea extracts should be used as early as possible in the course of a cold, with multiple doses per day for the first few days of symptoms. One common liquid formulation (Echinagard) is dosed at 20 drops every 2 hours for the first day of symptoms, then three times daily for up to 3 days.

Precautions

My opinion is that use in children should be discouraged because the only pediatric RCT found no positive effects but did report a slight increase in rash among those randomized to echinacea.⁸⁸ Although there is a modest case control study finding no adverse effects in pregnancy,⁸⁹ I caution against this use because the theoretical risks are significant.

Garlic (*Allium sativum*)

Garlic is widely used as a food and flavoring. Medicinally, there are dozens if not hundreds of reported uses. The most prominent of these is moderation of cholesterol and other lipids, for which modest beneficial activity has been reasonably established.⁹⁰⁻⁹² Use as prevention or treatment of common cold is fairly widespread but less well researched.

In vitro studies have reported antibacterial and antiviral effects, but to my knowledge there has been only one relevant human trial: Josling reported a trial in which 146 participants were randomized to daily garlic or placebo capsule for 12 weeks.⁹³ Dramatic between-group differences were observed, with 65 colds in the placebo group and 24 in the garlic group ($P < 0.001$), with an average cold duration of 5.0 days among those taking placebo versus 1.5 days among those taking garlic ($P < 0.05$). Although the study was reported as double-blind, proof of blinding was not provided. The active treatment was “an allicin-containing garlic supplement” dosed at “one capsule daily.” No further information on extraction methods, phytochemical composition, or amount of garlic was provided. Nevertheless, it may be reasonable to tentatively support use because (1) side effect risks are low, (2) cardiovascular benefits are likely, and (3) garlic is tasty.

Dosage

My personal recommendation is to use fresh garlic in cooking as much and as often as palatable, keeping in mind positive expectations about cardiovascular and cold-prevention benefits.

Ginger (*Zingiber officinale*)

Ginger root is widely used as a food flavoring as well as for its medicinal properties. There is reasonable evidence supporting effectiveness as an anti-nausea agent^{94,95} and suggestions of effectiveness for vertigo⁹⁶ and knee osteoarthritis.⁹⁷ Unfortunately, virtually no research has been accomplished in the common cold setting. Nevertheless, because ginger is widely used as a treatment for colds and flu and I personally happen to enjoy this use when a cold is coming on, it is included here.

Dosage

Buy a nice ginger root at the local grocery store, shave off the peel, and then slice the root thinly using a sharp knife, being careful not to cut one's fingers. Drop the sliced ginger into boiling water and steep for 5 minutes, then add honey and lemon to taste. Sip slowly, and *feel* the ginger work!

Goldenseal (*Hydrastis canadensis*)

Goldenseal is among the top-selling botanicals in the United States. In addition to cold remedies, *Hydrastis* extracts are found in treatments for allergy, and in digestive aids, feminine cleansing products, mouthwashes, shampoos, skin lotions, and laxatives.⁵² Goldenseal accompanies echinacea in many cold therapies. However, there are currently no RCTs evaluating goldenseal either alone or in combination

with echinacea. Berberine-rich extracts are included in many traditional Chinese medicines. The demand for goldenseal has led to overharvesting and to the substitution of other plants containing berberine or similar compounds. Given these considerations, I do not recommend goldenseal to prevent or treat the common cold.

Precautions

The phytochemical constituent berberine is pharmacologically active and in overdose can cause significant toxicity, including cardiac arrhythmia and death.⁹⁸ Goldenseal is contraindicated in pregnancy and lactation.

Lemon (*Citrus limon*)

Originally from India, the lemon tree is now cultivated throughout the world, used as a food, flavoring, or botanical remedy. Medicinal uses include prevention or treatment of scurvy. Lemon is also used for malaria, rheumatic arthritis, fever, and numerous other indications. Lemon juice and lemon-flavored teas are used for prevention and treatment of colds, coughs, and flu. Although rigorous evidence of effectiveness is lacking, lemon's generally recognized safety and important nutritional value as a source of vitamin C (ascorbic acid) makes this a good choice for those who derive symptomatic comfort.

Peppermint (*Mentha piperita*)

Peppermint and other members of the mint family are widely used for a variety of medicinal purposes, including coughs and colds, as well as for gastrointestinal purposes. When treating colds, mint teas and infusions are taken internally; mint oils are applied topically. Peppermint oil is composed primarily of menthol, menthone, and menthyl acetate. Menthol especially has been extracted and included in various topical cold remedies we could classify as “menthol rubs.” Although neither mint teas nor menthol rubs have been subjected to rigorous RCTs for common cold, both applications seem reasonable from a cost, risk and potential benefit perspective, at least for adults. More concentrated preparations such as peppermint oil should not be applied to the mucosa of infants or young children because direct inflammatory toxicity can result. Bronchospasm, tongue swelling, and even respiratory arrest have been rarely reported.^{98,99}

Nutrition

Chicken Soup

Hot chicken soup is the epitome of traditional cold remedies and could no doubt be supported by many personal testimonies. Chicken soup as a cold remedy is also somewhat supported by at least two human studies, one reporting inhibited neutrophil chemotaxis,¹⁰⁰ the other suggesting increased nasal mucus velocity and decreased nasal airflow resistance.¹⁰¹ No RCTs using patient-oriented

outcomes are available. Personally, I would be much more enthusiastic if the chicken industry adopted more responsible sanitary, environmental, and animal welfare policies. In the meantime, use of soup made from free-range chickens and substantial quantities of wholesome organic vegetables can be cautiously supported.

Biomechanical

Hot Moist Air

One widespread traditional cold remedy involves the inhalation of hot moist air, often with a botanical or other additive. As noted earlier, benefits from inhalation of vapors from chamomile tea were reported from one clinical trial.⁵³ There are also at least two RCTs suggesting significant benefit for nasal inhalation of unadulterated hot moist air.^{102,103} However, two subsequent trials found no benefit.^{104,105} Although it seems eminently reasonable to recommend humidification when the air is dry, and perhaps advocate the inhalation of hot moist air for those that find it comforting, it should be noted that water boils around 100°C and that inhalation of vapors near this temperature may cause significant thermal damage. Be careful!

Nasal Saline

What could be more healthful and therapeutic than a mild saltwater rinse of the nasal cavities? While saline nasal lavage is a long-standing tradition in many cultures, it is only recently that Western biomedicine has begun to integrate this practice. Currently, there are a number of positive trials among people with allergic rhinitis and chronic sinus symptoms, including one here at the University of Wisconsin Department of Family Medicine.¹⁰⁶

To my knowledge there are only two RCTs of nasal saline among people with common cold. Adam and colleagues randomized 140 people to one of three groups: hypertonic saline, normal tonic saline, or no treatment (two squirts per nostril, three times per day). No significant differences among the groups were found in terms of duration or severity of symptoms.¹⁰⁷ Diamond and coworkers reported a trial in which 955 participants were randomized to one of three doses of nasal ipratropium, to the “placebo” saline vehicle, or to no treatment at all.¹⁰⁸ The nasal saline vehicle yielded greater benefit compared to no treatment than did any of the ipratropium doses when compared with saline.

Overall, nasal saline is a remedy with potential benefit and virtually no cost or significant risks.

Dosage

I suggest a mild salt water solution made with warm tap water and just enough salt to make it taste like tears ($\frac{1}{2}$ tsp of salt in 6 oz of warm water). To instill, the head and neck should be nearly horizontal, with one ear down, and the nose over a sink or basin. Using a Neti pot (small tea pot) or a bulb syringe, gently pour the saline into the higher nostril. The soothing, cleaning fluids will run through the nasal

cavity, coming to the other nostril and to the throat. Spit out any fluids from the mouth, and gently blow the nose with handkerchief or tissue. Repeat the process with the other ear down. I suggest twice daily treatment for the first few days of a cold.

Supplements

Vitamin C

The use of vitamin C (ascorbic acid) as prevention and treatment for common cold became widespread after two-time Nobel Prize–winner Linus Pauling promoted his belief in this therapy in the 1950s and 1960s.¹⁰⁹ By the early 1970s, three major trials conducted in Toronto by T. W. Anderson supported some preventive effectiveness.¹¹⁰⁻¹¹² Over the next few decades, more than 30 trials including more than 12,000 participants were reported.¹¹³ Approximately half reported positive results, far more than would be expected by chance but not enough to convince the more skeptical scientists. Although there is no clear consensus about why some trials found benefit and others did not, it seems reasonable to tentatively conclude some preventive effectiveness, as the most recent Cochrane systematic review has.

The consistent and statistically significant small benefits on duration and severity for those using regular vitamin C prophylaxis indicate that vitamin C plays some role in respiratory defense mechanisms.¹¹³

Dosage

The evidence supports modest preventive effectiveness for doses of 200 to 500 mg daily. Benefits of larger doses as prevention—or as treatment for new-onset colds—is supported by some trials and systematic reviews¹¹⁴ but not by others.¹¹⁵ Given the generally accepted safety of ascorbic acid at doses up to several grams per day over short periods, it seems reasonable to cautiously support use, especially among those with positive experiences and expectations. (Very high doses, such as the 18 gm/day that Linus Pauling was reportedly taking up to his death at age 93 in 1994, have not been tested in trials, hence cannot be supported.) Regular intake of vitamin C-rich foods and juices can be enthusiastically supported, because greater intake of fresh fruits and vegetables has no known risks and has been associated with many health benefits in dozens of large observational studies.

Precautions

Gastrointestinal side effects such as nausea, heartburn, cramping, and diarrhea are most common with high doses.

Zinc

In some ways, the story of zinc for colds is similar to that of vitamin C. Reportedly, the physician George Eby noticed the

rapid recovery from URI in a child hospitalized and given zinc for unrelated reasons. This observation was followed by a RCT that in 1984 reported positive results (but had several methodologic flaws).¹¹⁶ Since then, at least 10 trials with more than 1000 participants have been conducted using various zinc preparations.¹¹⁷⁻¹²⁰ As with vitamin C, only about half were positive, without clear indication of the reason for this disparity. As most zinc preparations have a distinctive taste, adequate blinding may be an issue, as more skeptical experts have argued.^{118,121} There is also some concerns over adverse effects, such as unpleasant taste and/or nausea. Although zinc is an essential mineral, with many known protective effects when ingested in foods in appropriate doses,^{122,123} use of relatively high doses during acute illness may or may not carry some risks. Advocates recommend frequent dosing (every 2 to 3 hours) for the first 2 or 3 days of a cold, a dosing regimen that some will not find convenient. More recently, nasal zinc preparations have been devised, and three out of four RCTs have reported benefits.^{121,124-126} Issues of specific preparation, dosing, and blinding complicate interpretation. Nasal irritation is common, and loss of sense of smell has been reported.¹²⁷ Large, well-designed trials are needed before the benefits of oral or intranasal zinc for common cold can be said to be proven. My personal recommendation is to tentatively support the use of oral or nasal zinc preparations among those who have experienced benefit and/or express positive feelings about the treatment but not to recommend use in children, women, or those who have not yet tried it.

Dosage

Zinc gluconate, 9 to 24 mg of elemental zinc every 2 hr while symptomatic

Mind-Body

As in virtually all illnesses, common cold includes both psychological and physiologic elements and is influenced by a variety of social factors. Numerous cross-sectional and prospective epidemiologic studies have provided consistent findings:³⁻⁵ Colds occur most frequently among the youngest people and among those in contact with them. Children who are in preschool day-care centers have more colds than those who are not, but they have fewer colds during subsequent school years, perhaps due to increased levels of specific immunity.^{128,129} Although moderate regular exercise protects against infection, excess activity such as running a marathon increases risk temporarily.^{7,130,131} Stress, both acute and chronic, increases risk.¹³²⁻¹³⁴ In a series of groundbreaking studies, Cohen and colleagues showed that a number of psychosocial variables predicted whether volunteers would become infected when exposed to rhinovirus. Childhood socioeconomic status,¹³⁵ number and quality of social relationships,¹³⁶ acute and chronic stress,¹³⁷ and certain psychological attributes^{138,139} measured prior to rhinovirus exposure all predicted subsequent infection and viral shedding as well as severity and duration of cold symptoms. Together, these observations suggest that maintenance of psychological and social health (positive attitude, healthy relationships) may be as important as maintenance of

physical health (exercise, nutrition) for preventing colds and moderating symptoms.

Placebo and Meaning

Over the several years that I have spent reviewing the hundreds of trials, systematic reviews, and other reports of cold research, I have increasingly become convinced of the importance of mind-body effects, otherwise described as placebo or meaning effects.¹⁴⁰⁻¹⁴² Positive thinking, suggestion, expectancy, and belief in the therapeutic value of a given remedy can be a powerful healing force. Although regular exercise, balanced nutrition, and tobacco cessation are clearly associated with fewer and less severe illness episodes, so too are positive mental health attributes such as favorable psychological profile and healthful social relationships. Sheldon Cohen's research has demonstrated that social and psychological attributes predict not only the severity and duration of symptoms but also resistance to experimental rhinovirus infection, inflammation as measured by cytokines, and degree and duration of viral shedding.¹³⁵⁻¹³⁹ Psychological predispositions, especially sociability and a positive emotional style, are predictive of both symptomatic and physiologic outcomes.^{138,143-145} For the integrative clinician, this means that understanding an individual's belief system may be a crucial part of the therapeutic encounter. If a patient already believes in a safe therapy, reinforcing that belief may enhance the therapeutic response. If she or he is wary of a remedy you mention, do not press the issue. Remember that reassurance, empathy, empowerment, and positive prognosis all can be usefully employed in the clinical encounter.

Conventional Therapies

Antihistamines

Drugs blocking the effects of histamine have been sold as cold remedies for more than a century but have been subjected to no more rigorous RCTs than alternatives such as vitamin C, zinc, and echinacea. Nevertheless, there is reasonable evidence of modest benefit, in terms of reduction of nasal drainage, for first-generation antihistamines such as diphenhydramine, clemastine fumarate, or chlorpheniramine.¹⁴⁶⁻¹⁴⁹ However, effects appear to be due more to anticholinergic mechanisms than to antihistamine effects because second-generation "nonsedating" antihistamines do not seem to provide benefit.¹⁵⁰ For adults who do not mind the potential sedating or membrane-drying effects, or for those where allergic response is involved, a first-generation antihistamine may be a reasonable choice. For children, where there is no positive evidence whatsoever, antihistamines should be reserved for allergic rather than infectious rhinitis.

Histamine plays a minimal role in URI symptoms. The therapeutic benefit from antihistamines comes from their anticholinergic effects.

Decongestants

The oral decongestant pseudoephedrine has been tested in several clinical trials and appears to have minor benefit in terms of reduction of nasal congestion and drainage.¹⁵¹⁻¹⁵⁴ Side effects including anxiety, dizziness, insomnia, and palpitations are fairly common. More worrisome is the potential of elevated blood pressure and cardiac arrhythmia. Phenylpropanolamine, for decades a popular over-the-counter decongestant, was taken off the market after studies suggested increased mortality, especially in the elderly.¹⁵⁵

The topical intranasal decongestant oxymetazoline (Afrin) has been shown to decrease nasal airway resistance as well as mucus production and drainage.¹⁵⁶⁻¹⁵⁹ Intranasal phenylephrine has been less extensively studied but likely has similar effects. Unfortunately, these proven benefits come at the risk of nasal membrane dryness and discomfort. Use no more than 4 days because rebound nasal congestion can occur.

Cough Suppressants

Dextromethorphan, the active ingredient in cough remedies designated with “DM,” is widely used as an over-the-counter cough suppressant. Codeine—and to a lesser extent hydrocodone—are prescribed for cough, and presumably work through similar opioid-mediated mechanisms, and as such have side effects including sedation, constipation, and, potentially, respiratory suppression. Although most patients and clinicians agree that these remedies work, there is considerable debate over effect size and mechanism of action, because little appropriate evidence is available.¹⁶⁰⁻¹⁶² The best systematic review of cough remedies for children and adults concludes that “there is no good evidence for or against the effectiveness of OTC medicines in acute cough.”¹⁶³ Benzonatate (Tessalon Perles) is licensed as a prescription antitussive but appears to have been given this indication without any good evidence.

Analgesics and Antipyretics

There is no doubt that acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, and naproxen are effective for pain and fever, which may accompany common cold. However, there is also some suggestion that viral shedding may be prolonged.^{164,165} Limited use for pain reduction is eminently reasonable; however, the widespread use of NSAIDs for general common cold symptoms is not justified because evidence-of-benefit is marginal, and many thousands of people die each year from NSAID-attributable gastrointestinal hemorrhage and congestive heart failure.¹⁶⁶⁻¹⁶⁸

Anticholinergics

Ipratropium nasal spray has been tested in several good-quality RCTs for amelioration of symptoms of infectious and allergic rhinitis.^{169,170} These trials, including a dose-response

trial among 955 with community-acquired common cold,¹⁰⁸ suggest definite benefit in terms of reduced nasal congestion and drainage. Common side effects include headache, uncomfortable nasal dryness, and nosebleed.

Combination Formulas

The \$4 billion cold remedy market is dominated by numerous products containing combination formulas. Loopholes in U.S. Food and Drug Administration regulations have allowed pharmaceutical companies to mix various decongestants, antihistamines, analgesics, and antitussives, then market them under a variety of brand names and strategies. Although there is some evidence of effectiveness from early trials combining a decongestant with an antihistamine,¹⁴⁶ few if any of currently marketed products have been tested in large, well-controlled RCTs. Personally, I recommend against using any combination cold formula, with a possible exception for those who are convinced that a specific formula works for them.

Antivirals

Dozens of phase I and II trials using experimental rhinovirus infection models have reported benefit for several different antiviral drugs.¹⁷¹⁻¹⁷⁵ None, however, have demonstrated safety and efficacy in community-acquired colds; hence, none can be recommended. Nevertheless, this is an active area of research, and it is quite possible that safe and effective antiviral cold treatments will be available some day.

There is actually more evidence regarding echinacea and vitamin C than any conventional therapy. Unfortunately, for every positive trial, there is a negative one.

Therapies to Consider

Hot Toddy

I have been impressed by the number of people, including several physicians, who have come up after a lecture to tell me that their favorite cold remedy was some form of a hot alcoholic beverage, such as a “hot toddy” or hot buttered rum. While to my knowledge no trials have tested any of these remedies, testimonies of symptomatic benefit should not be totally disregarded. At a societal level, there is a well-known inverse relationship between moderate regular consumption of alcoholic beverages and the number and severity of colds.¹⁷⁶ Those who consume one or two drinks daily have fewer and less severe colds than both those who drink heavily and those who drink not at all. One study found this relationship to be most pronounced for red wine.¹⁷⁷ Personally, I like to add a bit of rum to a cup of hot orange juice as a night-time cold remedy. However, this would be contraindicated among those with alcohol use disorders, in children, and among pregnant women.

PREVENTION PRESCRIPTION


- Eat a balanced nutritious diet, including foods containing vitamin C and zinc.
- Maintain a regular exercise and movement practice, being careful not to overtrain.
- Maintain supportive social relationships.
- Reduce exposure to people with colds.
- Reduce stressors and/or negative stress responses.
- Wash hands frequently.



THERAPEUTIC REVIEW

Below is a summary of therapeutic options for common cold. None are proven beyond reasonable doubt to be safe and effective. Nevertheless, these are all reasonable options given best current evidence of benefit and harm.


■ Botanicals

- Andrographis 400 mg tid as soon as symptoms appear. Continue for 3-4 days. 


- Echinacea 

Although no one product has been found to work better than another, consider using one of the following formulations tid or qid for the first 3-4 days of a cold.


1-2 mL of extract in juice or water or sublingually
 150-300 mg powdered extract
 1-5 mL of tincture (1:5 in ethanol)

- Astragalus, chamomile, garlic, ginger, lemon, and peppermint have limited evidence but have little potential harm and can be considered. 


■ Supplements

- Vitamin C 1000 mg tid for the first 3-4 days of symptoms 

Consider 200-500 mg daily to aid with prevention

- Zinc acetate or gluconate 23 mg tablets every 2 hr while awake. Zicam Nasal Gel one spray per nostril every 2-4 hr until symptoms subside. 


■ Pharmaceuticals

- First-generation (sedating) antihistamines can reduce nasal congestion but can cause drowsiness 

Diphenhydramine (Benadryl) 25-50 mg q 6 hr

Clemastine (Tavist) 1-2 mg bid to tid as needed

Chlorpheniramine (Chlor-Trimeton) 4 mg q 6 hr

- Intranasal decongestants reduce nasal congestion but can also cause nasal drying, irritation, insomnia, palpitations, and elevated blood pressure. 

Oxymetazoline nasal 0.05% 2 or 3 sprays in each nostril bid
Phenylephrine nasal 0.25% (Neo-Synephrine)* 1 or 2 sprays q 4 hr as needed

- Oral decongestants can also benefit nasal congestion but have similar risks as nasal decongestants.



Pseudoephedrine (Sudafed) 30-60 mg po q 4-6 hr

- Nasal ipratropium 0.03% (Atrovent) 2 sprays each nostril bid to tid. Also effective for nasal congestion but can



cause headache, nasal irritation, and nosebleeds

■ Biomechanical

- Consider the use of hot moist air via a humidifier. Limited evidence supports using the vapor from chamomile tea.
- Consider bid nasal irrigation with normal or hypertonic saline via bulb syringe, nasal spray, or a Neti pot.



*Don't use for more than 3 days since decongestants can cause rebound vasodilation.

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