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

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Problems and prospects of developing effective therapy for common cold viruses

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No effective treatment for common colds has yet been developed. Combination antiviral and anti-inflammatory therapies are the best hope for intervention after the onset of symptoms. Prophylaxis, especially in the form of vaccination, would have a major impact in disease prevention. These approaches offer new avenues for treating populations at risk and are of particular significance to those with asthma or chronic bronchitis.

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The search for a cure for common colds or, indeed, any reasonably effective treatment has been a focus of intensive research for 40–50 years, so far without very encouraging results. The chief obstacles to successful treatment are the enormous number of microorganisms associated with the syndrome (~200 different viruses or atypical bacteria, see Table 1) and the problem of diagnosis; for example, it is only recently that the importance of rhinoviruses has been appreciated[1], as the methods available in earlier epidemiological studies were not adequate to detect them. Other obstacles include the rapid mutation rates of some viruses, leading to the emergence of drug-resistant strains[2,3], the toxicity of many types of drugs, difficulties with drug delivery and vaccine development and problems of expense, efficacy, implementation and unwanted effects, including increases in disease severity. These problems have persuaded many pharmaceutical companies to abandon research programmes; however, there is renewed interest because of the advances made possible by molecular biological techniques. The most promising areas for future progress are vaccine design and intervention strategies directed by increased knowledge of the genetic makeup and protein structures of some of the viruses involved.

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Table 1. Agents associated with common colds

Agent[a]	Number of serotypes	Incidence (% of infections)	Comments
Viruses			
Rhinoviruses	100+	60%	All year round with autumn and spring peaks
Coronaviruses	2	15%	All year round, winter peaks
Influenza viruses	3	1–10%[b]	Epidemic
Parainfluenza viruses	4	1–10%[b]	All year round, winter peaks
Respiratory syncytial virus	2	1–10%[b]	Discrete yearly winter epidemic
Adenoviruses	47	1–10%[b]	Sporadic
Enteroviruses	40+	1–10%[b]	Sporadic
Atypical bacteria			
Mycoplasma pneumoniae	1	1–10%[b]	Five-yearly epidemic cycle
Chlamydia pneumoniae	1	1–10%[b]	New organism, true incidence uncertain

[a]Each agent has been reviewed in Ref. 59.
[b]Variable incidence depending on age, immunity and seasonality.

Epidemiology and complications

The common cold is probably the most frequent illness afflicting humankind and is certainly the main cause of consultations with primary-care medical practitioners in the developed world. It is also associated with significant industrial and school absenteeism. Based on current estimates, adults are thought to have an average of five illnesses per annum, school-age children have 8–12 illnesses per annum and infants probably suffer more frequently. There are numerous factors influencing the epidemiology of upper respiratory tract viral infections, including individual and community immunity, seasonal variation, smoking, psychological stress, socioeconomic factors, such as nutrition and population density, and, perhaps most importantly of all, family structure. It is well known that preschool and school-age children are the most frequent route by which new viruses are introduced into families.

In addition to the common cold, upper respiratory tract viral infections are associated with more-severe disease, particularly in the presence of other significant disease. Virus infections have been associated with as many as 85% of exacerbations of asthma in children[4] and 40–60% of exacerbations in adults[5]. Other common complications include otitis media[6] and sinusitis[7], although detailed epidemiological studies have not, as yet, been carried out to accurately quantify the risk for individual agents.

Mechanisms of virus-induced inflammation

The symptoms of the common cold principally involve rhinorrhoea, resulting from vascular leakage and, later, mucous secretion[8] and nasal blockage, chiefly a result of mucosal oedema, which is consequent upon vascular engorgement and inflammatory cell infiltration.

Inflammatory mediators

A sore throat, probably resulting in part from inflammatory mediator release, is also a common symptom. Several studies have looked for inflammatory mediators in upper respiratory tract infections; kinins[9], histamine (in atopic subjects)[8] and leukotriene C4 (Ref. 10) have been detected in nasal secretions. More recently, several cytokines, including interleukin 1 (IL-1), interleukin 6 (IL-6), interleukin 8 (IL-8), interleukin 11 (IL-11), tumour necrosis factor α (TNF-α), interferon α (IFN-α) and interferon γ (IFN-γ), as well as the chemokines RANTES (regulated upon activation normal T-expressed and secreted) and macrophage inflammatory protein 1α (MIP-1α), have been found in the nasal secretions of subjects with common colds[11–14].

Inflammatory cell infiltration

Neutrophil infiltration and peripheral blood leucopenia have long been recognized in upper respiratory tract infections; Levandowski demonstrated elevated numbers of lymphocytes in nasal secretions using flow cytometry[15]. However, studies on nasal biopsies have failed to demonstrate mucosal lymphocytosis during common colds[16,17]. This may be because of technical problems, such as the timing of the biopsy samplings, or because inflammatory cell infiltrates are not directly important in producing nasal congestion.

In contrast, in the lower airway, we have recently demonstrated $CD3^+$, $CD4^+$ and $CD8^+$ lymphocyte infiltration in the bronchial mucosa of normal subjects undergoing experimental nasal rhinovirus infection[18]. Eosinophils and eosinophil products, such as eosinophil cationic protein and major basic protein, have also been implicated in virus-associated wheezing episodes[19,20], and we have also demonstrated a bronchial mucosal eosinophilia during experimental colds in normal and asthmatic subjects[18].

Therapeutic options

Nonspecific therapies

Many therapies for the common cold have been tried, although none has been very successful so far. A recent review claims that consuming vitamin C can reduce the duration of illness by an average of 1 day[21], the inhalation of humidified hot air at 43°C has been shown to reduce the severity of symptoms[22] and zinc gluconate has also been shown to reduce symptom duration by 2 days; the mechanism is unknown, although it is

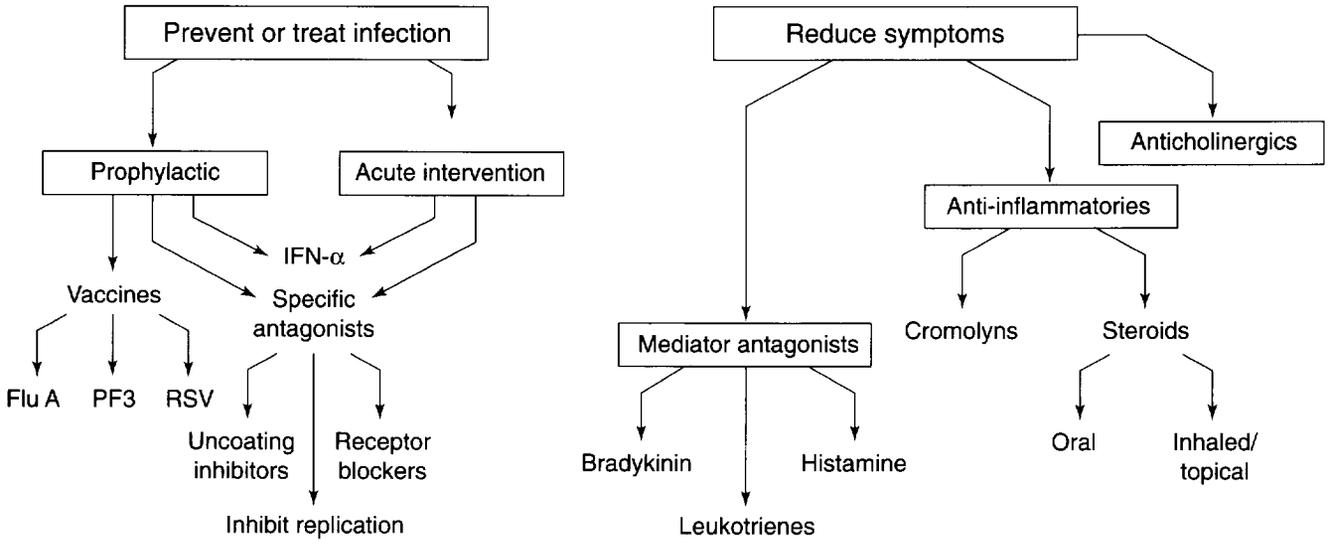

Fig. 1. Possible strategies for treating common colds. Abbreviations: Flu A, influenza virus type A; IFN-α, interferon α; PF3, parainfluenza virus type 3; RSV, respiratory syncytial virus.

possible that it has an antiviral effect[23]. However, for each of these treatments there are other studies with negative results. Thus, no treatment has been sufficiently effective to gain widespread acceptance. More specific avenues of treatment are summarized in Fig. 1.

Interferons

Nasal IFN-α, which was first tested over 20 years ago, has probably been the most successful treatment used. It is undoubtedly effective when given shortly before or after exposure to the virus, and also when given prophylactically to contacts in family outbreaks[24,25]. However, owing to several drawbacks, including the expense of production, the frequency of dosage and problems with local bleeding and discharge, it has not gained favour with pharmaceutical companies or clinicians.

Virus antagonists and inhibitors of virus uncoating

The only specific virus antagonists that are currently licensed for use are those principally active against influenza type A (amantidine and rimantidine) and respiratory syncytial virus (RSV) (ribavarin). Amantidine was discovered in 1964 and is an acyclic amine, whereas rimantidine is a methylated derivative that does not cross the blood–brain barrier and, therefore, does not possess the property of inducing 'jitteriness', which is sometimes associated with amantidine. Both compounds are thought to act after virus–cell attachment, but before uncoating, probably by interfering with ion flux mediated by the M_2 protein[26].

Amantidine and rimantidine are effective only against influenza type A and are recommended for use only in the presence of clear virological and epidemiological evidence of influenza A infection in the community. They should be used prophylactically for 6–8 weeks by at-risk populations, such as the elderly, those with other chronic afflictions (e.g. asthma or chronic bronchitis) and those within community groups, whether vaccinated or not. Therapy should be initiated in the first 24 h of symptoms and given for ten days. These drugs should not replace vaccination, as they are inactive against influenza type B.

Ribavarin is a nucleoside analogue that is active against RSV *in vivo*, but also against influenza and herpesviruses *in vitro*. Its mechanism of action is unknown, but there is evidence that it interferes with protein translation from mRNA, possibly by interfering with the 5′ cap. Ribavarin is relatively toxic and its use is therefore restricted to an aerosol in infants and children within the first three days of RSV bronchiolitis.

A major obstacle to the more widespread use of these antiviral therapies is their specificity, as specific antiviral therapies need to be used in the context of rapid viral diagnosis. For the majority of agents, especially the most common (rhinoviruses and coronaviruses), presently available diagnostic methods are inadequate. However, the development of the polymerase chain reaction (PCR) for viral diagnosis may make early diagnosis and appropriate specific treatment possible in the future[1,4].

With the exception of influenza type A epidemics and RSV bronchiolitis, treatment has to be given blind. The knowledge that rhinoviruses are responsible for ~60% of colds has made them a particularly attractive target for therapy. Thus, many compounds have been studied that inhibit rhinoviral infection by preventing virus uncoating or virus entry into the cell, or that inhibit various stages in virus replication once the virus has gained entry to the cell (Table 2). There are too many of such studies to mention them individually here but, suffice it to say, the fact that no effective drug has emerged so far is the result of a combination of factors. The most important of these are limitations to drug potency and delivery, drug toxicity (as viruses are dependent on host cell machinery to reproduce, compounds that are toxic to viruses can be toxic to humans) and the emergence of drug-resistant viruses[2].

Table 2. Antirhinoviral compounds and their modes of action[60]

Type of compound	Examples	Mode of action
Bendimidazole	Enviroxime	Inhibits viral RNA replication
Arildone	Dicloroflavans (WIN compounds)	Inhibit viral uncoating
	Chalcones (Ro 09-0410)	Bind within small canyon in the floor of the receptor-binding site in VP1, and stabilize virus coat[61,62]
Imidazole	SCH 38057	As for arildones
Pyridazinamine[a]	R 61837	Hydrophobic, insoluble in aqueous solutions
	R 77975 (pirodavir)	Delivery and residence in nasal epithelium difficult

[a]The only compounds so far shown to have clinical activity; see Ref. 63.

Vaccines

Vaccine development has long been thought to be potentially the most effective way of controlling virus-induced disease, but vaccine development programmes for respiratory viruses have had little success. Nevertheless, killed whole or split virus influenza vaccine is effective, despite antigenic drift and the requirement for intensive vigilance and annual revaccination.

RSV has been a priority for vaccine production, but a major setback occurred when, on subsequent natural exposure to the virus, formalin-inactivated vaccines were found to be associated with increased morbidity and mortality. Considerable research has been undertaken to determine why such adverse effects resulted from this vaccine (reviewed recently in Ref. 27), and present thoughts suggest that different RSV proteins are capable of inducing very different cellular immune responses[28,29]. The F protein and 22K produce a Th1-type response, with increased IFN-γ production and cytolytic activity, while the G protein favours a Th2-type response, with increased eosinophilia and decreased viral clearance[30]. Clinical studies with F subunit vaccines are now under way and it is hoped that a safe and effective vaccine is on the horizon. Initial trials are also being carried out with parainfluenza type 3 vaccines; recent progress with both vaccine types has been reviewed extensively elsewhere[31].

The other respiratory viruses have commanded relatively little attention. In particular, the rhinoviruses have been a very difficult target for vaccine design, as there are over 100 different serotypes, each of which is specific in its induction of neutralizing antibody. Recent work, however, has suggested that T-cell responses are relatively conserved across serotypes and this may be a fruitful area for future research[32].

Corticosteroids and over-the-counter medicines

Corticosteroids are known to have widespread anti-inflammatory effects, including the reduction of inflammatory cell infiltration and cytokine production, and their effectiveness has been assessed in randomized controlled trials. Although one study shows that they reduce inflammation and symptoms during the first two days of treatment, there appears to be a rebound effect when treatment is stopped, and no overall benefit has been demonstrated[33]. In a second recent study comparing oral prednisolone and placebo in experimental rhinovirus infections, steroids were reported to reduce sneezing and mucus weights on the first day, but there was no overall difference in symptoms. Steroids have even been associated with increased viral titres[34].

The use of high dose oral steroids for the common cold is not justified in view of the known side effects. However, steroids may have a more effective and logical place in the treatment of virus-associated wheezing illness. There have been several recent studies of the use of inhaled steroids in virus-associated wheeze in children of varying ages. High-dose-inhaled steroids used immediately with the onset of upper or lower respiratory symptoms have shown partial benefit[35,36], although no benefit was shown in other studies using lower dose prophylactic therapy[37].

Mediator antagonists

Although early studies failed to show any elevation of histamine levels in common colds, more recent studies have found an increase[38], particularly among atopic subjects[8]. However, antihistamine treatment for common colds has shown little benefit[39]. Since these studies, more-potent, non-sedating antihistamines have been introduced and, interestingly, one of these, loratadine, appears to reduce epithelial cell intercellular adhesion molecule 1 (ICAM-1) expression[40]. Given the role of ICAM-1 in inflammation and its role as the cellular receptor for 90% of rhinoviruses, it would be interesting to reassess this compound, particularly in virus-induced wheezing episodes.

Elevated levels of kinins have also been found in association with natural and experimental colds[41,42]; however, only one trial of a bradykinin antagonist has been carried out, unfortunately with negative results[43], although further studies with more-potent bradykinin antagonists are awaited. Anticholinergic nasal sprays have been shown to reduce rhinorrhoea and sneezing[44,45]. Leukotrienes have been implicated in virus-induced wheezing illness, but not in the common cold alone[11], and clinical trials with leukotriene antagonists in virus-induced wheezing illness are now under way.

Cromolyns

Cromolyns are anti-allergic and anti-inflammatory drugs that have effects on mast cells, eosinophils, epithelial cells and sensory nerves. There are two currently in clinical use and their mechanism of action is thought to involve inhibition of chloride channels[46]. Intranasal nedocromil sodium reduces symptoms and

Questions for future research

- Can a single or combined effective treatment/vaccine be designed that will combat all or most of the numerous agents causing common colds?
- Can a treatment for common colds be found that is effective enough to treat colds in normal individuals once they have developed symptoms, or should we be aiming at prophylaxis in at-risk populations?
- Would an appropriately formulated combination of already existing remedies be an effective treatment for common colds?
- Can new molecular techniques help to design new treatments to combat respiratory viral infections, for example by defining a common, important molecular mechanism and finding a way to block it?
- Will newer vaccine strategies, for example recombinant or DNA vaccines, be able to selectively induce protective rather than immunopathogenic responses?
- Will antiviral resistance prove to be as great a problem with antiviral therapies as it has with antimicrobial therapy?

improves psychomotor performance of subjects with experimental colds[47]. A recent study of intranasal and inhaled sodium cromoglycate in adults who have had common cold symptoms for less than 24 h showed that treatment with cromoglycate for 7 days produced swifter resolution of symptoms and reduced the severity of symptoms in the last 3 days of treatment. In addition, the treatment was very well tolerated with no significant side effects[48]. These studies are encouraging because they show an effect after symptoms have begun; however, the mechanisms involved in this protective effect are currently unknown.

Combination therapies

Recently, Gwaltney[49] proposed that for the effective suppression of common cold symptoms, a combined antiviral and anti-inflammatory effect would be required because neither agent appears very effective on its own. By administering intranasal IFN-α combined with intranasal ipratropium (an anticholinergic drug) and oral naproxen (a nonsteroidal anti-inflammatory drug) 24 h after experimental rhinovirus infection, virus shedding and the mean virus titre were significantly reduced, thus signifying an antiviral effect. The number of clinical colds, the mean symptom score, mucus secretion, cough and general malaise were all significantly reduced in treated subjects and the medications were well tolerated[49]. Interestingly, the symptom that was least effectively treated in this study was sneezing; however, as antihistamines are very effective at treating sneezing in allergic rhinitis, their addition to this cocktail may render it more effective.

Future avenues for treatment development

Molecular biological tools have increased our knowledge of respiratory virology and immunology enormously and have suggested several avenues that may profitably be explored in the search for new treatments.

Biological treatments

Following the identification of several cell surface proteins that act as virus receptors and are involved in virus entry into the cell, efforts have been targeted at blocking virus–receptor binding. One particular focus of attention has been rhinovirus and its binding to ICAM-1, which is the receptor for 90% of rhinoviruses. Blocking this interaction would treat ~50% of common colds (reviewed in Ref. 50). Trials with monoclonal antibodies and soluble ICAM-1 *in vitro* and in animal studies have been encouraging and clinical studies with these compounds are now planned or under way. However, the possible risk of emergence of resistant strains should be taken into account because although it had been thought that any mutations producing resistance would result in non-viability, as receptor binding is an essential step to virus replication, there is a report of the selection of strains of rhinovirus that are resistant to neutralization by soluble receptor *in vitro*[51].

Computer-aided drug design

The combination of a detailed knowledge of virus protein chemistry and structure with high-powered computational techniques is leading to the development of new antiviral compounds. There are now several examples of new antirhinoviral drugs that have been developed following the identification of a small hydrophobic pocket within the canyon region of the coat proteins of rhinoviruses (Table 2). This region is important for virus receptor binding and uncoating, once cell entry has been achieved. Drugs that fit within this pocket have been synthesized, with the aid of computer modelling techniques, to stabilize the coat proteins and thus prevent uncoating and release of viral RNA for replication. Some of these compounds are now in clinical trials.

Antisense oligonucleotides and 2–5A-antisense chimeras

It has long been known that virus-specific strands of DNA or RNA, complementary to viral messenger or genomic RNA, can anneal to viral RNA in virus-infected cells to produce an antiviral effect. The principal mode of action appears to be RNA degradation via RNase H. Inhibition of RSV replication has been shown *in vitro* using oligonucleotides directed at single-stranded regions of the RSV polymerase (L) gene[52].

The 2–5A pathway is involved in the antiviral actions of interferon[53], and the 2–5A-antisense concept is designed to enhance the efficiency of antisense oligonucleotides *in vivo* by specifically harnessing the activity of a ubiquitous intracellular RNase called 2–5A-dependent RNase (RNase L). In this strategy, an activator of 2–5A-dependent RNase is conjugated to the antisense oligonucleotides specific to the viral target. The result is highly specific and efficient cleavage of viral RNA. Studies *in vitro* have shown that this system works for nonviral RNA targets[54], and viral targets are currently being studied.

3C anti-proteinases

It has recently been discovered that picornaviruses (including all rhinoviruses) and human coronavirus 229E have similar 3C proteinases, which share several structural and functional characteristics[55]. These proteinases

are now in the process of being purified and their detailed structures and functions determined[56]. One attractive proposition would be the development of an antagonist that had functional activity against both proteinases, as this would be a single compound that was capable of treating 60–75% of common colds.

Recombinant/DNA vaccines

Analogous to rhinoviruses, T-cell responses to influenza viruses are also conserved across different virus strains. The generation of these T-cell responses normally requires endogenous expression of the antigen, as occurs in natural infection. A recent study has shown that plasmid DNA encoding the nucleocapsid protein of influenza type A evokes specific T-cell responses after injection into skeletal muscle in mice and also protects against subsequent challenge with a heterologous strain of influenza[57]. There is clearly a long way to go before a vaccine suitable for use in humans is developed, but the potential is exciting.

Targeting at-risk populations

The cure for common colds is still a long way off; however, as and when effective treatments become available, a productive approach is likely to target those populations most at risk. The elderly, the young and those with significant additional respiratory disease, such as asthma or chronic bronchitis, are most likely to benefit from treatment. They are also the groups most likely to be motivated to take treatments correctly, thereby giving the greatest chance of success.

As is currently the case for influenza vaccination, a strategy that should be encouraged is to concentrate treatment or prophylaxis regimens at the times of year when the risk is greatest: the winter months and, in particular, 2–4 weeks after children have returned to school after their holidays[58].

Conclusions

With perhaps the exception of the influenza vaccine, success in terms of prevention or treatment for common colds has so far evaded research and development. The major barriers to the development of effective treatments are the multiplicity of agents involved, difficulties with drug delivery, potency and toxicity, the fact that viral replication peaks just before or on the first day of symptoms and the emergence of drug-resistant strains. However, newer molecular methods and a better understanding of viral immunology are leading to encouraging developments in both vaccine research and the development of more-potent antagonists.

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