# Antiviral treatment of severe non-influenza respiratory virus infection

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**Abstract**

*Purpose of review:* Non-influenza respiratory virus infections are a frequent cause of severe acute respiratory infections, especially in infants, the elderly and the immunocompromised. We review here the current treatment options for non-influenza respiratory viruses and promising candidate antiviral agents currently in development.

*Recent findings:* Small molecule antiviral agents active against RSV such as ALS-8176 and GS-5806 show considerable promise in challenge studies and are undergoing late phase clinical trials in hospitalised adults and children.Monoclonal antibodies active against non-influenza respiratory viruses are broadly at a pre-clinical stage. Broad spectrum antivirals such as favipiravir and nitrazoxanide have potential utility in treating illness caused by non-influenza respiratory viruses but further definitive clinical trials are needed.

*Summary:* Severe non-influenza respiratory virus infection is common and current treatment is largely supportive. Ribavirin is used in immunocompromised patients but its use is limited by toxicity and the evidence for its efficacy is weak. Effective antiviral treatment for RSV may shortly become available, pending the results of ongoing clinical trials. For other non-influenza viruses effective treatments may become available in the medium term. Early detection of respiratory viruses with rapid molecular test platforms will be crucial in differentiating virus types and directing the prompt initiation of novel treatments when available.

## Keywords

Respiratory virus; antivirals; non-influenza respiratory virus; acute respiratory illness

**Introduction**

## Non-influenza respiratory viruses including respiratory syncytial virus (RSV), coronavirus, parainfluenza viruses, human metapneumovirus, rhinovirus and adenovirus cause severe disease in infants and the immunocompromised and are increasingly recognised as a common cause of severe acute respiratory illness among non-immunocompromised hospitalised adults [1,2]. There are currently very few therapeutic options available for non-influenza respiratory virus infections and management is largely supportive. This review examines the currently used antiviral agents for severe non-influenza respiratory virus infections, and promising antiviral agent currently in development. Table 1 lists the range of clinically important non-influenza respiratory viruses and summarises antiviral agents in development.

**Broad-spectrum antiviral agents**

The oral antiprotozoal drug Nitazoxanide has *in vitro* antiviral activity against a range of respiratory viruses including influenza, RSV and Middle East respiratory syndrome-coronavirus (MERS-CoV) [3,4] and also against non-respiratory viruses including hepatitis C, dengue virus, rotavirus and norovirus. Nitazoxanide is a small molecule drug that targets host-regulated processes involved in viral replication. It has been investigated as an oral treatment for a several viral infections, including influenza, viral gastroenteritis and chronic hepatitis C [3]. A large phase 2b/3 placebo controlled trial of nitazoxanide treatment in adolescents and adults with influenza-like illness in primary care showed a reduction in the duration of symptoms in adults with influenza and also in those with non-influenza respiratory virus infection [5].

Favipiravir (T-705) is an oral agent that inhibits the RNA-dependent RNA polymerase of wide range of RNA viruses including influenza, RSV and rhinoviruses as well as many non-respiratory RNA viruses [6] and was used as an experimental treatment for Ebola virus infection during the recent epidemic [7]. Clinical trials of favipiravir have been conducted in patients with uncomplicated influenza and it is approved for the treatment of influenza in Japan [8].

## Respiratory syncytial virus (RSV)

Ribavirin is a nucleoside analogue which interferes with RNA metabolism required for viral replication and has a broad-spectrum of activity against many RNA and DNA viruses [9]. It is mainly used in the aerosolised form for RSV infection but oral and intravenous formulations have also been used. Ribavirin has been used in infants with severe RSV induced bronchiolitis although trials have not shown consistent benefits and there are concerns over toxicity in this group [10]. In severely immunocompromised patients (principally haematopoietic stem cell transplant recipients) aerosolised ribavirin treatment is used to prevent RSV upper respiratory tract infection (URTI) progressing to a lower respiratory tract infection (LRTI) and to reduce mortality in RSV lower respiratory tract infection. Observational studies suggest that ribavirin reduces the risk of progression from URTI to LRTI and mortality, especially when commenced early in infection [11-13], however definitive proof of efficacy from high quality randomised controlled trials is lacking. The use of ribavirin is further limited by its toxicity and difficulties in safe administration of the aerosolised form. Ribavirin is teratogenic and occupational exposure of staff can occur, and its use has also been associated with respiratory deterioration. The oral and intravenous formulations are also associated with haematological toxicity and are contraindicated in renal impairment.

There have been two recent landmark human challenge studies of small molecule anti-RSV agents. GS-5806 (Presatovir) is an F-protein (fusion) inhibitor that inhibits RSV entry into cells by blocking viral-envelope fusion with the host-cell membrane. GS-5806 reduced RSV viral load by around 4-logs and reduced the severity of clinical symptoms compared to placebo in healthy adults infected with RSV in a human challenge study. Adverse events associated with GS-5806 included leukopenia and raised levels of alanine aminotransferase although these events were generally mild and the drug was well tolerated [13]. ALS-8176 (Lumicitabine) is a nucleoside analogue and inhibits of the L-protein, the RNA-dependent RNA-polymerase of RSV. It inhibits RSV replication within cells already infected and protects uninfected cells from infection. ALS-8176 was associated with a reduction in viral load to undetectable levels and reduced severity of clinical symptoms compared to placebo in an RSV human challenge study. Elevated levels of alanine aminotransferase were the most common adverse event and the drug was well tolerated [14]. Results of a completed phase 2b randomised controlled trial of GS-5806 in hospitalised adults with RSV infection are awaited [15] and a phase 2b trial in haematopoietic stem cell transplant recipients is underway [16]. A phase 2a trial of ALS 8176 in hospitalsied adults with RSV is currently underway [17] as is a trial in hospitalised infants [18]. It should be noted that a key limitation of the human challenge treatment model is that treatment is initiated very soon after the start of experimental infection and so the effects of prompt treatment may not be reproduced in clinical practice as patients hospitalised with respiratory virus infection generally present several days after symptom onset [1].

ALN-RSV01 (Asvasiran) is a small interfering RNA (siRNA) targeted against the mRNA of the RSV nucleocapsid. A human challenge study of intranasal ALN-RSV01 demonstrated that it prevented RSV infection, and at higher doses had a treatment effect. This trial established proof-of-concept for RNA interference as a therapeutic option for viral infection and warranting further study [19]. ALN-RSV01 has subsequently been shown to reduce the risk of bronchiolitis obilterans syndrome after RSV infection in lung transplant recipients [20, 21].

ALX-0171 is a trivalent inhaled ‘nanobody’ that binds to a conserved epitope of the RSV F-protein with high RSV neutralising potency and decreased capability to select escape mutants [22]. Results of clinical trials in hospitalised infants and children are awaited [23,24]. Another Fusion inhibitor AK0529, has completed phase I trials and is undergoing a phase 2 trial in hospitalised infants [25]. Other anti-RSV agents such as MEDI8897, a recombinant human RSV monoclonal antibody with a modified Fc region leading to a prolonged half-life have undergone early phase trials but are directed at prevention rather than treatment [26]. Another monoclonal antibody, motavizumab, evaluated as treatment in a clinical trial, failed to show any reduction in viral load, severity of illness or duration of hospitalisation in infants hospitalised with RSV infection [27]. Compassionate use of high-titre anti-RSV intravenous immunoglobulin in high-mortality-risk haematopoietic stem cell transplant recipients with RSV infection appears well tolerated and increased serum neutralising antibody titres to RSV in one retrospective study, however definitive evidence of efficacy from placebo controlled studies is lacking [28].

## Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV)

Despite a promising pre-clinical study, treatment of MERS-CoV with ribavirin and interferon in observational studies has not been associated with reduced mortality [29,30]. A meta-analysis of patients with SARS and influenza has suggested that treatment with blood products from convalescent patients may be associated with decreased mortality and so hyper-immune and convalescent plasma from patients who survived MERS-CoV infection could be a potential future therapy [31]. However, collection of sufficient quantity of such blood products may be an insurmountable barrier to developing a treatment [32]. Several neutralising monoclonal antibodies (mAbs) have been developed which bind to the viral surface spike (S) protein of MERS-CoV therefore preventing viral entry and membrane fusion. These mAbs have demonstrated potent inhibition of the virus in vitro and protection from lethal challange in animal models and are now in the stage of being taken forward into clincal stuidies in humans [33,34].

**Parainfluenza virus and Human metapneumovirus**

Ribavirin has been used in heavily immunocompromised patients with parainfluenza and human metapneumovirus infections but the evidence base for efficacy is weak and as detailed above its uses is limited by difficulties in administering the aerosolised form and by its toxicity. DAS181 (Fludase) is an inhaled sialidase that cleaves sialic acid from host respiratory epithelial cells, which is required for both influenza and parainfluenza virus to bind and therefore has antiviral activity against these viruses. DAS181 has undergone phase I trials and was found to be safe and generally well tolerated and is currently being evaluated for the treatment of parainfluenza infections in adults in a phase 2 placebo controlled trial in the USA [35]. DAS181 may also have activity against human metapneumovirus [36]. According to pipeline reports, AL-8176 (Lumicitabine) has been found to have activity against other paramyxoviruses including parainfluenza virus and human metapneumovirus and studies are undeway but are currenly at the pre-clincal stage [37]. An agent with broad spectrum antiviral activity agaist these viruses could represent a major advancement in the treatment of respiratory virus infections in high-risk populations.

**Picornaviruses**

Pleconaril is an oral viral capsid inhibitor with broad antiviral activity against picornaviruses, which includes rhinoviruses and enteroviruses. It was effective in reducing the duration and severity of common colds in adults caused by picornaviruses in two randomised controlled trials [38]. However, concerns over the potential for the emergence of antiviral resistance, drug interactions with the oral contraceptive pill and study populations being limited to healthy participants meant that pleconaril was not approved for clinical use [39] and it is not being devlopmed further. BTA798 (Vapendavir) is another small molecule capsid binding agent which was recently evaluated in a phase 2b trial in adults patients with rhinovirus-induced asthma exacerbations but failed to demonstrate efficacy [40].

The *ex-vivo* bronchial epithelium of asthmatic patients is associated with a defective innate immune response to rhinovirus infection which is restored by adding exogenous IFN-β [41]. A placebo controlled trial of inhaled IFN-β in asthmatic patients with cold symptoms did not meet its primary outcome measure but suggested that inhaled IFN-β was effective at attenuating exacerbations in a subset of patients with severe asthma [42]. A subsequent multicentre phase II trial of inhaled IFN-β in severe asthmatics patients administered at the onset of cold symptoms was recently ceased due to a very low number of reported exacerbations occurring during the trial, meaning that the primary outcome measure could not be reached. [43,44]. Inhaled beta interferon still remains a potential, therapeutic agent for respiratory virus infection and further clinical studies may be warranted.

**Adenovirus**

Adenovirus can occasionally cause severe acute respiratory illness in immunocompetent adults [45] but more commonly causes severe infection in heavily immunocompromised patients. Cidofovir is an intravenous nucleoside analogue that inhibits viral DNA polymerase and is used in immunocompromised patients with disseminated and progressive adenovirus infection or pre-emptively in patients with persistent replication [46, 47]. Its use is limited by toxicity, most notably nephrotoxicity. Brincidofovir is an oral lipid conjugate of cidofovir that increases it cellular uptake and is potentially more potent and less toxic. It has been used experimentally in a small number of immunocompromised patients with severe adenovirus disease and a larger number with asymptomatic adenovirus infection as a pre-emptive treatment, but larger-scale randomised controlled trials are needed [48,49].

## Conclusions

Non-influenza respiratory viruses are responsible for a large burden of severe disease. Respiratory virus testing in hospitalised patients with acute respiratory illness is currently underutilised but a routine testing strategy with rapid molecular diagnostic platforms has the potential to detect respiratory virus infection at presentation and direct the use of novel antiviral agents when available [50, 51]. Current therapeutic options for severe disease caused by non-influenza respiratory viruses are extremely limited. Aerosolised ribavirin is sometimes used in severe RSV infection in infants and in heavily immunocompromised adults but it use is limited by toxicity and by a lack of high quality evidence for its efficacy. Multiple novel candidate antivirals are undergoing clinical trials including some with some broad antiviral activity such as nitazoxanide and favipiravir. Several promising small molecule drugs active against RSV are in the late stages of development. Convalescent plasma and monoclonal antibodies may be future treatments for MERS-CoV infection.

## Key points

* Current antiviral treatment options for severe non-influenza respiratory virus infection are extremely limited.
* Ribavirin is used in severe RSV infection in young children and in severely immunocompromised adults but use is limited by toxicity and the evidence base for its efficacy is poor.
* GS-5806 and ALS-8176 appear to reduce clinical severity of RSV infection in human challenge studies and are promising candidate antivirals undergoing late stage clinical trials.
* Convalescent plasma and Monoclonal antibodies may be future therapeutic options for MERS-CoV infection.
* Broad spectrum antivirals such as nitazoxanide and favipiravir show promise in early studies across a range of respiratory viruses

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**Table 1**. Clinically important non-influenza respiratory viruses and key antiviral agents currently used or in development

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Antiviral** | **Mechanism** | **Target** | **Route** | **Phase** |
| Ribavirin | Multiple | Broad | Inhaled, oral, parenteral | N/A |
| GS-5806 (Presatovir) | F-protein inhibitor | RSV | Oral | 2b |
| ALS-8176 (Lumicitabine) | RNA polymerase inhibitor | RSV | Oral | 2a |
| AK0529 | F-protein inhibitor | RSV | Oral | 2 |
| ALN-RSV01(Asvasiran) | Small interfering RNA | RSV | Inhaled | 2b |
| ALX-0171 | F-protein binding 'nanobody' | RSV | inhaled | 1/2a |
| Hyper-immune /convalescent plasma | Neutralising antibodies  | MERS-CoV | Parenteral | 2 |
| Monoclonal antibodies | Spike protein binding antibody | MERS-CoV | Parenteral | 1 |
| T-705 (Favipiravir) | RNA polymerase inhibitor | Broad (influenza, RSV, rhino)  | Oral | N/A |
| DAS181 (Fludase)  | Sialidase | Broad (influenza, PIV, hMPV) | Oral | 2 |
| Nitazoxanide  | Multiple | Broad | Oral | 3 |
| Interferon-Beta | Enhanced innate antiviral response | Broad | Inhaled | 2b |
| Pleconaril | Capsid binder  | Rhinovirus | Oral | N/A |
| BTA798(Vapendavir) | Capsid binder  | Rhinovirus | Oral | 2b |
| Cidofovir | DNA polymerase inhibitor | Adenovirus | Parenteral  | N/A |
| Brincidofovir | Prodrug of cidofovir | Adenovirus | Oral  | 3 |

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