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INVITED REVIEW SERIES: INFECTIOUS DISEASES

Antiviral therapy for respiratory tract infections

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Abstract: Viruses are important pathogens causing respiratory tract infections both in the community and health-care facility settings. They are extremely common causes of morbidity in the competent hosts and some are associated with significant mortality in the compromised individuals. With wider application of molecular techniques, novel viruses are being described and old viruses are found to have new significance in different epidemiological and clinical settings. Some of these emerging pathogens may have the potential to cause pandemics or global spread of a severe disease, as exemplified by severe acute respiratory syndrome and avian influenza. Antiviral therapy of viral respiratory infections is often unnecessary in the competent hosts because most of them are self-limiting and effective agents are not always available. In the immunocompromised individuals or for infections caused by highly pathogenic viruses, such as avian influenza viruses (AIV), antiviral treatment is highly desirable, despite the fact that many of the agents may not have undergone stringent clinical trials. In immunocompetent hosts, antiviral therapy can be stopped early because adaptive immune response can usually be mounted within 5–14 days. However, the duration of antiviral therapy in immunosuppressed hosts depends on clinical and radiological resolution, the degree and duration of immunosuppression, and therefore maintenance therapy is sometimes needed after the initial response. Immunotherapy and immunoprophylaxis appear to be promising directions for future research. Appropriate and targeted immunomodulation may play an important adjunctive role in some of these infections by limiting the extent of end-organ damage and multi-organ failure in some fulminant infections.

Key words: antiviral, nosocomial, respiratory tract infection, virus.

INTRODUCTION

Viruses are common but often under-recognized causes of respiratory tract infections (RTI). In addition to the commonplace upper respiratory tract infections (URTI), they are increasingly being recognized as important pathogens in lower respiratory tract infections (LRTI), especially community-acquired pneumonia (CAP). In 30–60% of the cases of community-acquired LRTI, no specific pathogens were found.[1] With better viral diagnostics by molecular techniques, new viruses have been implicated in patients with different forms of RTI.

Common viruses associated with RTI are listed in Table 1. The majority of them cause community-acquired infections. A few of them, most notably cytomegalovirus, are primarily opportunistic pathogens affecting immunocompromised hosts. However, almost all of the pathogens have been associated with infections in the compromised individuals which may result in substantial morbidity and mortality. The pathology and pathogenesis of viral LRTI can involve both direct injuries by the viruses and immunopathological damages. In a number of viral pneumonias such as the severe acute respiratory syndrome (SARS) and avian influenza caused by influenza A/H5N1 virus, there is evidence that high viral loads at the respiratory tract is associated with worse prognosis or mortality.[2,3] Effective suppression of viral replication at an early stage of the infection would therefore be potentially beneficial. Chemoprophylaxis with antivirals has also been used in institutional settings (as in

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Table 1 Antiviral treatment of important viruses causing respiratory tract infections in humans

Family	Genus/species	Usual clinical setting†	Antiviral options‡	Usual adult dosage (adjustment for creatinine clearance is necessary for some drugs)	Duration of treatment
Adenoviridae	Human adenovirus	O	Cidofovir	Induction with 5 mg/kg i.v. once weekly for 2 weeks (weekly doses up to 6 weeks have been used), followed by 5 mg/kg i.v. once every two weeks. Probenecid (2 g p.o. 3 h before, then 1 g each at 2 and 8 h after cidofovir infusion for adults).	Until viral clearance.
			Ribavirin	Loading dose 33 mg/kg i.v. followed by 16 mg/kg i.v. q6h for 4 days, followed by 8 mg/kg i.v. q8h for 3 days.	7 days or until viral clearance is documented.
			Vidarabine	10 mg/kg/day i.v.	5 days and repeat the course if necessary.
Herpesviridae	Epstein–Barr virus	O	Unknown. Withdrawal or reduction of immunosuppression; may consider acyclovir, rituximab (anti-CD20).		
	Human cytomegalovirus	O	Ganciclovir	See Table 2.	See Table 2.
			Foscarnet	See Table 2.	See Table 2.
			Cidofovir	See Table 2.	See Table 2.
			Valganciclovir	See Table 2.	See Table 2.
	Herpes simplex viruses	O, N	Acyclovir	10 mg/kg i.v. q8h.	10 days.
			Foscarnet	40 mg/kg i.v. q8–12h.	
			Cidofovir	5 mg/kg i.v. once weekly.	
	Varicella-zoster virus	C, N	Acyclovir	10 mg/kg i.v. q8h.	10–21 days depending on clinical course.
			Foscarnet	40 mg/kg/day i.v. in 3 doses.	
			Vidarabine	10 mg/kg/day.	
	Human herpesvirus 6	O	Cidofovir	As for CMV.	
			Foscarnet	As for CMV.	
			Ganciclovir	As for CMV.	
Parvoviridae	Human bocavirus	C	Unknown		
Coronaviridae	Human coronaviruses OC43, 229E, NL63, HKU1	C, N	Unknown		
	SARS-coronavirus	C, N	Unknown. May consider:		
			Lopinavir/ritonavir in combination with ribavirin	Lopinavir 400 mg/ritonavir 100 mg p.o. q12h. Dosage of ribavirin below.	10–14 days.
			Nelfinavir	Not tested in clinical trials.	
			Interferon-α and -β	Alfacon-1: 9 μg/day subcutaneously for 2 days, then increase to 15 μg/day if not responding.	8–13 days.
			Convalescent plasma	200–400 mL.	
			Ribavirin	8 mg/kg i.v. q8h for 14 days; or 8 mg/kg i.v. q8h for 5 days followed by 1200 mg q8h p.o. for a total of 10–14 days; or 2 g i.v. loading followed by 1 g i.v. q6h for 4 days and then 500 mg i.v. q8h for 3 days.	7–14 days

Table 1 *Continued*

Family	Genus/species	Usual clinical setting[†]	Antiviral options[‡]	Usual adult dosage (adjustment for creatinine clearance is necessary for some drugs)	Duration of treatment
Orthomyxoviridae	Influenza viruses A, B, C	C, N	Neuraminidase inhibitors (oseltamivir, zanamivir); adamantanes (amantadine, rimantadine); convalescent plasma (for A/H5N1)	See Table 3.	See Table 3.
Paramyxoviridae	Measles virus	C	Ribavirin	Aerosolized: 6 g/day.Intravenous: 20–35 mg/kg/day.	5–7 days.
	Human metapneumovirus	C, N	Ribavirin	Loading dose 33 mg/kg i.v., followed by 16 mg/kg/day i.v. from days 2–5, followed by 8 mg/kg/day i.v.	Until viral clearance.
	Human parainfluenza viruses	C, N	Ribavirin	Aerosolized: 2 g three times a day for 7 days). Intravenous: 1.2 g i.v. q8h or 60 mg/kg/day in 4 divided doses.	Aerosolized: 7 days. Intravenous: 5–10 days.
	Human respiratory syncytial viruses	C, N	Ribavirin	Aerosolized: 6 g in 100 mL water over 2 h, three times a day; or 6 g in 300 mL water for 18 h a day. Oral: loading dose 10 mg/kg p.o., then 400 mg p.o. q8h for one day, then 600 mg p.o. q8h. Intravenous: loading dose 33 mg/kg, followed by 16 mg/kg q6h for 4 days, followed by 8 mg/kg q8h for 3 days or until viral clearance; or 33 mg/kg/day on first day followed by 20 mg/kg/day, all given q8h.	Immunocompetent hosts: 3–7 days. Immunocompromised hosts: 3 days to over 14 days or until clearance of virus.
			Palivizumab	15 mg/kg im one dose per month; up to 3 doses a month has been used.	
			IVIG	500 mg/kg i.v. every other day to weekly.	
Picornaviridae	Human parechovirus	C	Unknown		
	Human rhinovirus	C, N	Pleconaril	5 mg/kg p.o. q8h.	7–10 days.
Others	Mimivirus	C, N	Unknown		

[†] C, community-acquired infection in immunocompetent hosts; N, nosocomial transmission reported; O, opportunistic pathogen; exceptions do occur.

[‡] Antiviral options listed are based on *in vitro* susceptibility, animal studies, clinical case reports, and randomized controlled trials. Not all agents have been approved for the respective indications or tested in controlled clinical trials. The duration of therapy given are commonly reported in the literature. For treatment of the immunosuppressed hosts, the duration may need to be prolonged and guided by clinical, radiological, and virological progress. The efficacy of IVIG has not been proven by controlled clinical trials for most of the infections.

CMV, Cytomegalovirus; IVIG, intravenous Ig.

the case of influenza outbreaks) or following exposure to highly virulent viruses (such as influenza A/H5N1 virus).

Practicalities in antiviral therapy of viral RTI

Effective antiviral therapy for viral RTI is problematic. First, there are the inherent limitations in the number of available agents. Second, antiviral therapy is generally not recommended for healthy immunocompetent individuals because benefits on the clinical course of the disease are often limited. For example, while treatment of influenza by amantadine or neuraminidase inhibitors (NAI) does shorten the duration of illness, the benefit is a mere one day if only the antiviral are given within 48 h after the onset of disease. Clinical benefits of antiviral treatment are likely to be greater in immunocompromised patients with more severe diseases. Third, early institution of antivirals is essential to limit the multiplication of viruses and the concomitant tissue damage and activation of the pro-inflammatory response. Unfortunately, unlike most of the common bacterial pathogens in which aetiological identification and antibiotic susceptibility testing can be completed within a few days and proper empirical antibacterial coverage generally covers most of the relevant pathogens, rapid viral diagnosis is only possible for a handful of agents. Although PCR and RT-PCR broadened the range of pathogens that can be detected, these are still not widely available in most routine laboratories and they usually do not offer same-day testing results. Antiviral susceptibility testing is virtually non-existent under such settings, though genotypic testing for mutations conferring resistance can be done rapidly in some centres.

ANTIVIRAL THERAPY FOR SPECIFIC PATHOGENS

Adenoviridae

The 51 serotypes of human adenoviruses (HAdV) are classified into six species, human adenovirus A–F.[4] Adenoviruses are non-enveloped double-stranded DNA viruses and they are common causes of sporadic or outbreaks of community-acquired infections such as pharyngoconjunctival fever, keratoconjunctivitis and gastroenteritis. Severe or disseminated infections are extremely rare in the immunocompetent hosts,[5] and most of these cases have been associated with immunosuppression, including bone marrow transplantation (BMT), solid organ transplantation (SOT), HIV infection and underlying malignancies. Patients could have asymptomatic viraemia or shedding of the virus in stool or urine, or they may present with pneumonia, enteritis and colitis, haemorrhagic cystitis and nephritis, hepatitis, encephalitis, myocarditis or disseminated infection.[6] In immunocompromised patients, adenoviraemia (as detected by PCR) precedes the onset of systemic infection,[7] and the persistent presence of high-level viraemia is associated with worse outcomes and death.[8–10] In paediatric BMT recipients, the presence of viraemia in serum or plasma at levels above 10^6–10^7 copies/mL is considered to be a risk factor for severe complications.[10] In the setting of BMT, disease is more commonly seen in recipients of allogeneic transplantation, graft from unrelated donors, and among children as compared with autologous transplantation, graft from matched siblings and adults respectively.[11] Pneumonia (with or without other organ system involvement) is the presenting syndrome in 11–20% of BMT recipients who developed adenovirus infection.[11,12] Among the adult BMT recipients, mortality due to adenovirus infection is highest in those suffering from disseminated disease with pneumonia (80%), isolated pneumonia (75%) and disseminated disease without pneumonia (50%).[12]

Ribavirin, cidofovir and vidarabine have been used for the treatment of adenovirus infections. Vidarabine demonstrates *in vitro* activities against adenoviruses and has been used for the treatment of adenovirus-associated haemorrhagic cystitis.[13,14] It was ineffective in the treatment of adenovirus infection in the BMT setting.[15]

Ribavirin has been used for adenovirus pneumonia in immunocompromised patients delivered via oral, intravenous or nebulized routes, either alone or in combination with intravenous Ig (IVIG) or donor leucocyte infusion (in BMT recipients).[15–22] There are no controlled clinical trials to demonstrate the benefits of ribavirin. The major side-effect of ribavirin is haemolytic anaemia. Although clinical and virological response is seen in some patients, treatment failure is frequent and sometimes associated with increases in the plasma viral load.[15,20–22] No significant benefit was noticed in the small number of patients who received combination therapy with ribavirin and cidofovir.[21] Susceptibility to ribavirin is not uniform among all adenovirus isolates, with only HAdV C being susceptible.[23] The susceptibility of species C is also variable depending on the cell type used for *in vitro* susceptibility testing.

Cidofovir is superior to ribavirin in the treatment of severe adenovirus infections. Unlike ribavirin, susceptibility of HAdV to cidofovir is independent of the species.[23] The most significant adverse reaction to cidofovir is nephrotoxicity which occurs in about 25% of the patients who received the drug for cytomegalovirus infection.[24] To reduce the risk of nephrotoxicity, pre-hydration therapy with normal saline and probenecid are essential before each dose of cidofovir. Concomitant use of nephrotoxic drugs should be avoided if possible. Although there are no randomized controlled trials to determine the efficacy of cidofovir in adenovirus infections, results from previous case series have been favourable. The response rate ranged from 62.5% to 98%.[9,15,24–28] The occurrence of serious nephrotoxicity appeared to be uncommon when the necessary precautions were taken and it seldom requires cessation of treatment.[24,26] The use of IVIG in addition to other antiviral agents cannot be recommended at the moment.[27]

Two approaches to anti-adenovirus therapy have been suggested. The conventional approach is to start treatment when the patient develops laboratory-proven HAdV clinical disease. Another approach is pre-emptive therapy; antiviral therapy is started in asymptomatic individuals when virological surveillance is positive for HAdV.[15] There are no clinical trials on the preferred strategy of management, although pre-emptive therapy may be preferable because commencement of antiviral therapy at the time of overt clinical disease may not offer substantial improvement.[20] There is evidence that the level of viral load in peripheral blood is correlated with the presence and severity of disease.[26] Starting antiviral treatment at a time when the viral load is still low may prevent the development of more severe disease and end-organ damage. The duration of antiviral therapy has not been standardized. Patients have to be monitored for the clinical, radiological and virological progress. It has been suggested that treatment needs to be continued until adenovirus is negative on two to three consecutive specimens previously positive for adenovirus.[11,26] The duration is also determined by the level of immunosuppression, the severity of graft-versus-host disease or the presence of graft rejection in the transplant setting.

Herpesviridae

Epstein–Barr virus (human herpesvirus 4)

Primary Epstein–Barr virus (EBV) pneumonia is extremely rare but acute epiglottitis can be life-threatening. Few cases of pneumonitis had been reported in the immunocompetent patient complicating primary EBV infection and infectious mononucleosis.[29–32] Hypoxaemia is a prominent finding in many cases. Although the aetiological role of EBV has been questioned in some earlier reports, more recent cases have documented the presence of EBV in the lungs by *in situ* hybridization or quantitative PCR.[30,33] Even in the immunocompromised patients, EBV pneumonitis is rare, with cases occurring in the setting of severe aplastic anaemia, BMT or in association with post-transplant lymphoproliferative disease.[33–35] No recommendations on antiviral therapy of EBV pneumonitis can be made at the moment. Although acyclovir suppresses EBV shedding *in vivo*, no clinical benefits have been demonstrated in the treatment of EBV-associated infections such as infectious mononucleosis. In patients whose pulmonary disease is related to post-transplant lymphoproliferative disease, treatment should include withdrawal of immunosuppressants and rituximab (anti-CD20).[33–35] Some patients may develop respiratory tract manifestations such as acute epiglottitis as a complication of haemophagocytic lymphohistiocytosis. The treatment of EBV-related haemophagocytic lymphohistiocytosis involves the control of hypercytokinaemia (using corticosteroids and IVIG), immunosuppressants and chemotherapeutic agents (such as etoposides, cyclosporine A, antithymocyte globulin), with or without antiviral agents. A combination of acyclovir (3 g/day i.v.), IVIG (30 g/day for 5 days) and prednisolone (100 mg/day for 10 days) had been used with success in a patient with pneumonitis due to primary EBV infection.[31] The role of rituximab for EBV-related haemophagocytic lymphohistiocytosis has not been established.

Human cytomegalovirus (human herpesvirus-5)

Human cytomegalovirus (HCMV) pneumonitis is one of the most severe forms of viral LRTI seen especially among allogeneic BMT and lung or heart–lung transplant recipients in whom the incidences are 10–30%, 15–55% and 71% respectively.[36] The disease is almost uniformly fatal without treatment, and mortality can still be as high as 30–50% with antiviral therapy. In the BMT setting, seropositivity of the transplant recipient and the presence of acute graft-versus-host disease are important risk factors while for SOT, high risk of disease is seen in seronegative recipients of organs from seropositive donors, and in patients receiving antilymphocyte globulins. The disease is very rarely reported in immunocompetent patients.[37] Histopathology of the lungs and viral culture are the gold standards for diagnosis, though in recent years the diagnosis is mainly based on other tests such as pp65 antigenaemia and quantitative PCR to determine the viral load in peripheral blood and BAL.[38]

The key agents for antiviral therapy of HCMV pneumonitis are ganciclovir, foscarnet, cidofovir and more recently, oral valganciclovir (Table 2).[39] The main adverse reactions to ganciclovir and foscarnet are myelosuppression and nephrotoxicity respectively. These agents can be used for prophylaxis in at-risk patients, pre-emptive therapy, and treatment of established HCMV disease. Pre-emptive therapy rather than universal prophylaxis has become a widely accepted strategy for prevention as it limits the use of antiviral agents to those who are at highest risk of developing HCMV disease, thereby reducing the potential adverse reactions and cost.

Prevention of HCMV disease in seronegative BMT recipients should include the use of blood products from HCMV-negative donors or which have been leucocyte-depleted. Compared with placebo or no prophylaxis, antiviral chemoprophylaxis with acyclovir, valacyclovir and ganciclovir significantly reduces the risk for HCMV infection or disease and all-cause mortality in solid-organ transplant recipients.[40,41] For the prevention of HCMV disease, ganciclovir is more effective than acyclovir. Limited data showed that valacyclovir prophylaxis may have a role in preventing HCMV disease in BMT recipients.[42] Oral ganciclovir prophylaxis and valganciclovir pre-emptive therapy (both in renal transplant recipients) have also been effective.[43,44] Recent studies suggested that oral valganciclovir prophylaxis could be effective in preventing HCMV disease in solid-organ transplant recipients.[45–48] The potential toxicity of foscarnet and cidofovir limits their use for prophylaxis.

Pre-emptive therapy of HCMV infection is initiated when there is evidence of infection but without clinical disease. This strategy is based on the routine

Table 2 Antiviral options for human cytomegalovirus (HCMV) infection

	Prophylaxis[†]	Pre-emptive therapy[†¶]	Treatment of HCMV disease[†¶]
Acyclovir[‡]	500 mg/m^2 i.v. q8h; 800 mg p.o. q6h.	—	—
Valacyclovir[‡]	2 g p.o. q6h.	—	—
Ganciclovir[‡]	5 mg/kg i.v. q12h for 5 days, then 5 mg/kg i.v. q24h; or 6 mg/kg i.v. q24h.	Induction: 5 mg/kg i.v. q12h for 2–3 weeks. Maintenance: 5 mg/kg i.v. q24h.	Induction: 5 mg/kg i.v. q12h for 2–3 weeks. Maintenance: 5 mg/kg i.v. q24h for 3–4 weeks.
Valganciclovir[‡††]	900 mg p.o. q24h.	Induction: 900 mg p.o. q12h. Maintenance: 450 mg p.o. q12h.	Induction: 900 mg p.o. q12h for 2–3 weeks. Maintenance: 900 mg p.o. q24h for at least 2 weeks.
Foscarnet[‡]	60 mg/kg i.v. q24h.	Induction: 60–90 mg/kg i.v. q12h for 2 weeks. Maintenance: 90 mg/kg i.v. q24h.	Induction: 90 mg/kg i.v. q12h; or 60 mg/kg i.v. q8h. Maintenance: 90 mg/kg i.v. q24h.
Cidofovir[‡§]	—	Induction: 3–5 mg/kg i.v. once a week for 2 weeks. Maintenance: 3–5 mg/kg i.v. once every 2 weeks.	Induction: 3–5 mg/kg i.v. once a week for 2 weeks. Maintenance: 3–5 mg/kg i.v. once every 2 weeks.

[†] Normal adult dosages are given. Adjustment of dosage may be necessary in individual patients.
[‡] Dosage adjustment is necessary in the presence of renal impairment.
[§] Pre-hydration is necessary. See Table 2 for dosage of probenicid.
[¶] The duration of maintenance therapy is generally 2–3 weeks, but the need for maintenance therapy and its duration is generally guided by antigenaemia and depends on the degree of immunosuppression.
[††] With the availability of valganciclovir, oral ganciclovir has little place in the prophylaxis and treatment of CMV infection.

monitoring for HCMV activity, usually by pp65 antigenaemia. Intravenous ganciclovir is generally used as the first-line agent, though myelosuppression can occur in 20–30% of patients. Foscarnet and cidofovir are used when the patient is intolerant of ganciclovir or when ganciclovir resistance is suspected clinically or confirmed virologically. Foscarnet has similar efficacy as ganciclovir when used for pre-emptive treatment in BMT recipients.[48,49] Combined foscarnet and ganciclovir therapy for BMT recipients has been suggested but has not been widely used.[50] A study using half-doses of combined foscarnet and ganciclovir failed to show clinical benefits over conventional full-dose ganciclovir regimen.[51] Treatment of HCMV pneumonitis is different from other forms of HCMV disease in BMT recipients for whom high-dose IVIG (500 mg/kg q48h for 10 doses then 500 mg/kg twice a week for 8 doses) or HCMV hyperimmune globulin is often recommended in addition to antivirals.[52] The value of IVIG, however, has not been demonstrated in most series.[53]

Leflunomide is an immunosuppressive agent currently approved for the treatment of rheumatoid arthritis. It also possesses *in vitro* activities against HCMV and herpes simplex viruses (HSV).[54] A few BMT and renal transplant recipients had received leflunomide for the treatment of HCMV viraemia or disease (though none with pneumonitis) with resolution of viraemia and disease, though not all reports had a favourable outcome.[55–58] The place of leflunomide in the treatment of HCMV requires further studies. The antimalarial compound artesunate showed *in vitro* and *in vivo* activities on HCMV.[59,60] There is currently only one report of using artesunate for treating drug-resistant HCMV infection in a BMT recipient.[61]

Herpes simplex viruses

Herpes simplex viruses consists of two serotypes, HSV-1 and HSV-2, also known as human herpesvirus 1 and 2 (HHV-1 and -2) respectively. Primary HSV infection is followed by life-long latency of the virus in the sensory ganglia, with mucocutaneous reactivation and neurovirulence being the major characteristics of the viruses. Asymptomatic shedding of HSV-1 in the saliva can occur in 1–5% of healthy individuals.

Herpes simplex virus LRTI was thought to be a rare condition affecting mainly the immunosuppressed patients. However, with better and more widely available viral diagnostic methods, HSV is increasingly being found in LRT specimens with HSV-1 being the predominant serotype. Although HSV can be a primary respiratory pathogen causing tracheobronchitis or pneumonitis, the significance of finding HSV in LRT secretions, which can result from oropharyngeal contamination, has been controversial.[62] There are no pathognomonic clinical and radiological signs of HSV pneumonia, and clinical diagnosis is often based on a positive virological finding and exclusion of other pathogens. In the hospital setting, HSV haemorrhagic tracheobronchitis with or without pneumonitis is usually found in critically ill, severe burn or trauma patients, patients who have undergone major surgery, intensive care patients who had received prolonged mechanical ventilation (often with ARDS), and immunosuppressed patients such as

those with underlying malignancies or transplant recipients.[62–66] The incidence of finding HSV in the respiratory secretions in these situations ranged from 2% to 50%.[62] The presence of HSV in these patients has been associated with a higher mortality and more prolonged mechanical ventilation. Patients with HSV pneumonia tend to have higher viral loads in the respiratory tract and this parameter has been suggested to be useful in differentiating patients with genuine HSV infections of the lower respiratory tract.[64,67] Clustering of cases of HSV pneumonia in intensive care units has been reported.[68,69]

Intravenous acyclovir is the drug of choice for the treatment of serious HSV infections.[62,70] Oral valacyclovir may be considered in less severe diseases but there is little information on this agent in this setting. In the rare occurrence of acyclovir resistance, foscarnet and cidofovir may be used.[71] Cross-resistance to ganciclovir and famciclovir is usually complete in strains with thymidine kinase mutations. Treatment is usually recommended in patients with otherwise unexplained pneumonia, herpetic oral or mucocutaneous lesions, or in immunocompromised individuals with a positive virological finding.

Human herpesvirus 6 (roseolovirus)

Human herpesvirus 6 (HHV-6) and HCMV are both betaherpesviruses ubiquitous in all human populations. Acquisition of HHV-6 is common in infancy and childhood, with seroprevalence ranging from 70% to 100% in adults.[72] Primary infection usually presents as an acute febrile illness with or without rash (roseola infantum or sixth disease). Latency of the virus can be found in peripheral blood mononuclear cells and bone marrow progenitor cells. Reactivation and development of disease normally occurs in immunocompromised hosts such as transplant recipients and HIV-infected individuals. The disease can manifest as encephalitis or encephalopathy, pneumonitis, hepatitis, delayed engraftment, graft dysfunction and myelosuppression.[72,73] Pneumonitis is commoner following BMT than SOT and co-infection with other pathogens can occur.[74–78] HHV-6 pneumonitis is rare in immunocompetent individuals.[79–81]

Treatment of serious HHV-6 infections is similar to HCMV. *In vitro*, ganciclovir, foscarnet and cidofovir are active against HHV-6, with cidofovir and foscarnet having the best antiviral selectivity index.[82,83] Immunocompromised patients with HHV-6 diseases have commonly been treated with ganciclovir (dosages similar to that for HCMV diseases).[84] In BMT recipients, ganciclovir prophylaxis is effective in preventing reactivation of HHV-6 and is superior to acyclovir prophylaxis.[84,85]

Varicella-zoster virus (varicellovirus; human herpesvirus 3)

Varicella-zoster virus (VZV) is a common childhood infection that has a much higher incidence of complications in adults than in children. The commonest complications are secondary bacterial infection of the skin lesions and pneumonia in children and adults respectively. Symptomatic varicella pneumonia occurs in 1 in 200 000 cases in children and 1 in 200–400 healthy adults, but the incidence of asymptomatic pulmonary involvement as shown by radiological changes can be ten times commoner, with reported figures ranging from 5% to 50% of the patients.[86,87] Varicella pneumonia is the commonest cause of death associated with varicella in adults. The mortality rate in adults is 25 times higher than that in children, and in the UK and USA, adults accounted for 54.3–64% of total deaths due to varicella.[88] The mortality rate of varicella pneumonia in healthy non-pregnant adults is 5–23%, but ranges from 35% to 40% in pregnant women with a perinatal mortality rate of up to 65%.[88,89] Maternal mortality is highest during the third trimester. Primary infection in the first 20 weeks of pregnancy is also associated with the congenital varicella syndrome in 0.4–2% of life births.[90] Smokers, patients with chronic lung diseases and immunocompromised individuals are also at higher risk of developing varicella pneumonia and have higher mortality. At least five confirmed cases of pneumonia were caused by the vaccine strain of VZV.[91]

Although there were no randomized controlled trials of antiviral treatment for varicella pneumonia, acyclovir is considered to be the drug of choice.[88,92] Foscarnet is a possible alternative but few reported cases had received this agent.[92–94] Vidarabine is a third option and appeared to be effective in disseminated VZV infection including pneumonia.[92,95,96] Oral acyclovir, valacyclovir and famciclovir should be avoided for this serious infection.

The use of adjunctive corticosteroid in varicella pneumonia could be beneficial.[97–101] Corticosteroids may reduce the degree of pulmonary inflammation and hence results in more rapid improvement in oxygenation, shorter duration of mechanical ventilation and faster radiological improvement.

Parvoviridae

Human bocavirus

Human bocavirus (HBoV) was described in 2005 using molecular screening of respiratory samples from patients with RTI.[102] Since then studies showed that HBoV is globally prevalent in community-acquired infections.[103–105] Despite the associations with RTI, the causative role of HBoV has not been universally accepted because of the lack of a suitable animal model, frequency of co-pathogens found in clinical specimens and the detection of the virus in asymptomatic individuals.[106] Nevertheless, it appears that at least in some individuals with a high viral load (in both respiratory secretions and blood), HBoV is capable of causing clinical disease and seroconversion .[107] The susceptibility of HBoV to antiviral agents is unknown.

Mimiviridae

Mimivirus

Mimivirus is a novel nucelocytoplasmic large DNA virus found in association with the free-living amoeba *Acanthamoeba polyphaga*.[108] It has been associated with community- and hospital-acquired pneumonia diagnosed by detection of viral DNA and serology.[109,110] However, two recent surveys failed to detect the presence of mimivirus in respiratory specimens, suggesting that it may not be a prevalent cause of pneumonia.[111,112]

Coronaviridae

Severe acute respiratory syndrome coronavirus

The emergence of SARS coronavirus (SARS-CoV) in late 2002 led to a global epidemic involving more than 8000 cases and a case fatality ratio of 11%.[113] Recent studies suggested that bats are probably the reservoir of a related virus and various game animals served as the amplification host before transmission to human.[114] Nosocomial transmission to health-care workers was a prominent feature during the epidemic, with 21% of all the cases being health-care workers.[113]

Ventilatory support, in particular, the use of non-invasive ventilation under proper isolation facilities and appropriate antibacterial coverage to control secondary bacterial infections are essential. No randomized controlled trials have addressed the issue of optimal antiviral therapy for SARS. Based on serial viral load studies, effective antiviral therapy is important because the viral load in respiratory tract secretions is significantly correlated with subsequent organ dysfunction and death.[115,116] These studies also showed that the viral load in nasopharyngeal aspirate peaked at 10–15 days after the onset of disease; therefore, there is potentially a window of opportunity for antiviral therapy.[117]

Ribavirin was the earliest antiviral to be used for the treatment of SARS. Its *in vitro* activity on SARS-CoV is variable and is dependent on the cell type used.[118] Animal studies and efficacies in clinical series have been disappointing and was associated with significant adverse reactions such as haemolytic anaemia and electrolyte disturbances.[117,119–123]

Two other groups of compounds are more promising for the treatment of SARS. The first group is the protease inhibitors such as lopinavir/ritonavir and nelfinavir.[124,125] They inhibit the main protease $3CL^{pro}$ of SARS-CoV which is crucial for viral replication. Two studies in Hong Kong using lopinavir/ritonavir plus ribavirin demonstrated more favourable outcomes as compared with a regimen using ribavirin alone. These included overall death rate, intubation rate, incidence of ARDS, nosocomial infection, rate of use and mean dose of corticosteroids, viral load in nasopharyngeal aspirate and peripheral lymphocyte count.[126,127]

The second group of potentially useful agents are interferons.[124] Several interferons were active against SARS-CoV *in vitro*, with interferon-β1a and -β1b being the most active. In an uncontrolled clinical trial, the use of corticosteroids with interferon alfacon-1 (a synthetic interferon-α) resulted in improvements in oxygenation and more rapid resolution of chest radiograph abnormalities.[128]

Therapeutic use of convalescent plasma from SARS patients has been described.[129–131] Clinical and virological improvements were seen, including a decrease of plasma viral load from 10^5 copies/mL to undetectable levels after plasma transfusion.[131] A stock of convalescent sera from SARS patients was maintained by some centres such as the Hong Kong Red Cross Blood Transfusion Service.

Another issue in the therapy of SARS is the use of immunomodulatory agents to reduce the extent of tissue damage due to cytokine storm. Corticosteroids have not been found to be beneficial in the absence of an effective antiviral agent and was associated with an increase in the plasma viral load in some studies.[120,131] High doses of corticosteroids also led to the development of opportunistic infections and late complications such as avascular osteonecrosis of the hip.[132,133]

The current evidence suggests that ribavirin or corticosteroids alone are unlikely to be useful clinically. The use of protease inhibitors, interferons (alfacon-1, α-n1, α-n3, β-1a and β-1b) and convalescent plasma warrants further studies. These agents should also be evaluated for their efficacies in chemoprophylaxis in high-risk contacts, such as laboratory workers handling SARS-CoV who might have been accidentally exposed.

Human coronaviruses OC43 and 229E and other newly described coronaviruses

Human coronaviruses (HCoV) OC43 and 229E are the prototype human coronaviruses which typically cause URTI, especially the common cold. LRTI due to these viruses are rare. Following the SARS epidemic, two novel human coronaviruses, NL63 and HKU1, were discovered in respiratory specimens.[134,135] These viruses are common causes of RTI globally sand are often found in severe cases of CAP. The antiviral susceptibility of these non-SARS CoV is not known. Earlier studies showed that intranasal spray of interferon α-2b was effective for prophylaxis of colds due to coronaviruses.[136,137] Limited data showed that chloroquine possesses antiviral activities against both SARS-CoV and HCoV-229E *in vitro*.[138,139]

Orthomyxoviridae

Human and avian influenza viruses

Influenzavirus A, B and C (FLUAV, FLUBV, FLUCV respectively) are single-stranded negative-sense RNA viruses with a segmented genome. The viral key proteins involved in virological nomenclature, antigenic variation and antiviral targets are haemagglutinin (HA), neuraminidase (NA) and matrix proteins (M1,

M2). HA and NA are the antigenic determinants of FLUAV, which form the basis for their subtype classification. Among FLUAV, there are 16 HA (H1–16) and 9 NA types (N1–9). HA mediates viral attachment and entry into host cells by binding to cellular sialic acid receptors. NA cleaves the glycosidic linkages to sialic acid on host cells and the surface of the viral particles and therefore facilitates the spread of the virions in the host. M2 is an ion channel mediating the pH-dependent dissociation of matrix proteins from the nucleocapsid during viral uncoating and pH changes across the trans-Golgi network during maturation of HA molecules.

The natural reservoir of all the different HA and NA types of FLUAV are the waterfowls.[140] Most of the serotypes of influenza viruses exhibit a certain degree of host specificity. Human infection is most commonly caused by FLUAV A/H1N1, A/H3N2 and FLUBV. Other serotypes such as A/H1N2 are less commonly seen and A/H2N2 has not been circulating in human populations for five decades. Large-scale cross-species infection of human by AIV occurred in 1997 in Hong Kong which was caused by A/H5N1.[141] Since then, there is a steady increase in the number of cases of mainly poultry-to-human transmission in Asia and Africa, but the epicentre of the infection is now in Southeast Asia where the disease has become endemic. At the time of writing there were 382 human cases reported to the World Health Organization with 241 fatalities (case fatality rate, 63%) since 2003, with most of the cases (133) and deaths (108) being reported from Indonesia.[142] In addition, A/H5N1 has been spreading geographically to large areas of the Eurasian and African continents among the waterfowls and poultry.[143]

The clinical and epidemiological features of A/H5N1 infection in humans have been reviewed elsewhere.[144–146] The typical manifestation of the disease starts with an influenza-like illness (ILI), with rapid progression to pneumonia, ARDS and multi-organ failure. Diarrhoea is seen in up to 70% of the patients. Other types of AIV have also been found to cause human infections. The A/H9N2 virus had caused mild respiratory illnesses in Hong Kong.[147–149] In the Netherlands, the A/H7N7 virus had caused a major human outbreak associated with poultry with one fatal case.[150,151] Typical symptoms were conjunctivitis, an ILI and occasionally pneumonia. In 2004, an outbreak of human A/H7N3 infection associated with poultry occurred in British Columbia, Canada, and the symptoms were primarily conjunctivitis and an ILI.[152,153] In addition to AIV, clinically mild human infections due to other mammalian influenza viruses, such as the swine A/H1N1 and A/H3N2 viruses, have been reported.[154–156]

Seasonal human influenza is an extremely common cause of RTI in both the community and health-care settings. The disease ranges from a febrile URTI to fulminant primary viral pneumonia or secondary bacterial pneumonia. Primary viral pneumonia is typically seen in patients with underlying comorbidities such as chronic cardiopulmonary diseases, but 25% and 13% of the cases occur in otherwise healthy adults and pregnant women respectively. The disease can be rapidly fatal in 1–4 days. There is frequently a distinct seasonal pattern in temperate countries with the peak incidence in the winter months. In tropical countries the disease may be prevalent year round or have two yearly peaks in both summer and winter months.

Antiviral therapy for uncomplicated influenza in the immunocompetent host is not normally necessary. The reasons include the usual delay of more than 48 h from onset of illness to medical attention, difficulties in differentiating influenza from other viral RTI, potential for antiviral resistance, cost of the medications and potential adverse reactions to the drugs. Although antiviral treatment for influenza is available, all the currently available agents must be given within 48 h (preferably 36 h or less) after the onset of illness to be effective. This can be explained by the dynamics of viral multiplication and shedding of influenza viruses. Influenza is generally a very acute infection. Incubation period of influenza is about 48 h (ranges 24–96 h), and shedding of viruses from the respiratory tract peaks at 24–72 h after infection. This means that virus shedding is already substantial even before the onset of illness. Early diagnosis of influenza is therefore crucial if antiviral therapy is going to be effective. However, specific virological diagnosis is often not available in the primary care setting. The clinical diagnosis of influenza is usually made as ILI, the definition of which also varies between different studies and surveillance programmes. Agents other than influenza viruses and the proportion of ILI cases caused by influenza viruses are affected by the seasonality of different infections. The positive predictive value of ILI for confirmed influenza varies from 30% to 87% during influenza seasons, while the figure drops to 23–30% during off-seasons.[157–161] Thus, antiviral treatment of influenza is usually only recommended for at-risk patients and those who develop severe disease and complications.[162]

The two main groups of anti-influenza agents are the adamantanes and NAI (Table 3). Amantadine and rimantadine share similar clinical efficacies, the main difference is the adverse effect profile. Amantadine is noted for its neurotoxicity. Common adverse neurological effects include dizziness, confusion, disorientation, depression, seizures and insomnia. Amantadine is excreted by the kidneys. Dosage reduction is necessary in patients with renal impairment and in elderly people over 65 years of age. Amantadine is effective for prophylaxis and treatment of human influenza. When given within 48 h of onset of illness, it reduces the duration of symptoms for 1–2 days. Resistance emerges rapidly following therapeutic use of adamantanes in human influenza and the resistant viruses are fully transmissible and pathogenic. Up to 30% of patients with human influenza A being treated with amantadine may shed resistant viruses, sometimes as early as 2–3 days after treatment. The incidence of adamantane resistance among human influenza viruses (A/H3N2) is increasing in many parts of the world, especially in China.[163] For this reason, amantadine is no longer recommended as the first-line antiviral therapy for seasonal influenza.[162,164]

Table 3 Antiviral agents for influenza virus infection

	Prophylaxis	Treatment
Amantadine	200 mg/day p.o. (single or 2 divided doses); 100 mg q24h p.o. for elderly (>65 years)	200 mg/day p.o. (single or 2 divided doses); 100 mg q24h p.o. for elderly (>65 years)
Rimantadine	200 mg/day p.o. (single or 2 divided doses); 100 mg q24h p.o. for elderly (>65 years)	200 mg/day p.o. (single or 2 divided doses) for 5–10 days; 100 mg q24h p.o. for elderly (>65 years) for 5–10 days
Oseltamivir	75 mg q24h p.o. for 7–10 days	75 mg q12h p.o. for 5 days
Zanamivir	10 mg q24h by oral inhalation for 10–28 days	10 mg q12h by oral inhalation for 5 days

The efficacy of the adamantanes against AIV, in particular, A/H5N1 viruses, is unknown. There are no controlled clinical trials of any antiviral agent for the treatment of AIV infections. The prevalence of amantadine resistance among A/H5N1 viruses in poultry is very high in countries like China.[165] The situation is attributed to the extensive use of amantadine in poultry farming.[165] In Vietnam and Thailand, 95% of 638 A/H5N1 isolates are amantadine resistant.[166] Isolates of A/H5N1 from the Indochina clade in Cambodia-Thailand-Vietnam often carry mutations in the M2 gene conferring resistance to adamantanes. However, the China-Indonesia clade of viruses remains susceptible to amantadine.

Despite the problems and limitations, the role of adamantanes should not be completely dismissed. First, amantadine has an extremely long shelf life of over 25 years and is relatively inexpensive. Therefore, they are useful agents for stockpiling against pandemic influenza. As it is not possible to predict the nature of the viral strain responsible for future influenza pandemics, they may still have a role for therapy and prophylaxis. Second, *in vitro* synergistic antiviral effects were seen when rimantadine was combined with NAI.[167] Animal studies showed that when rimantadine is combined with oseltamivir for treatment of A/H3N2 infection, a synergistic effect was seen in preventing animal mortality.[168] Low-dose combinations of oseltamivir and amantadine for chemoprophylaxis against A/H1N1 and A/H3N2 infection in mice were effective.[169] Against the A/H5N1 virus, a protective effect was seen when mice were challenged by the virus 24 h after receiving an amantadine–oseltamivir combination.[170]

The adamantanes are commonly used in the control of institutional outbreaks of seasonal influenza. They are given to both patients or residents and staff for a minimum of 2 weeks or 1 week after the last new case appeared.[164] In the setting of influenza A outbreaks in long-term care facilities, it is important to initiate chemoprophylaxis within 5 days after the onset of the outbreak. Delayed initiation was associated with longer durations of outbreaks, higher incidence rates and case fatality rates.[171]

Susceptibility to the NAI may be variable according to the different NA types of FLUAV.[172] Oseltamivir is available orally while zanamivir is available as dry powders and delivered by oral inhalation. Both NAI are effective for treatment and prophylaxis (pre- or post-exposure) of human influenza infection in clinical trials.[173] As in the case of adamantanes, when the drugs are given within 36–48 h of onset of symptoms, a mean reduction of the duration symptoms for 1–2 days can be achieved. Early administration of oseltamivir (within 12 h after the onset of symptoms) appears to increase the effectiveness of therapy for both influenzas A and B. There are differences between the response of influenzas A and B towards oseltamivir. In Japan, the clinical response to oseltamivir is lower for influenza B than influenza A in terms of a longer duration of fever.[174] The effectiveness of oseltamivir on influenza B is also lower in the 2004–2005 season compared with the 2002–2003 season. Whether this is due to antigenic variation or reduced oseltamivir susceptibility is unknown.

The NAI are remarkably free from major side-effects. Reports from Japan suggested that oseltamivir might be associated with neurotoxicity in adolescents. Oseltamivir and its metabolites may have excitatory effects on the central nervous system of the rat, which may account for some of the neuropsychiatric side-effects noticed in the past few years with more widespread use of the drug.[175,176] The safety of these agents in infants and pregnant women is unknown. Oseltamivir and zanamivir are currently approved for children over 1 and 7 years of age respectively. Limited studies from Japan showed that oseltamivir is probably safe in infants under 1 year old.[177,178]

Both oseltamivir and zanamivir are effective in animal models in preventing death and improving survival following infection by A/H5N1 viruses. Early commencement of therapy (within 48 h of infection) is critical in improving the survival of animals. The length of this window of opportunity for human AIV infection is unknown. In Thailand, patients who survived A/H5N1 infection after oseltamivir treatment appeared to have received the agent earlier than those who subsequently died (4.5 vs 9 days after disease onset).[179] Nonetheless, therapeutic efficacy of oseltamivir in human A/H5N1 infection has not been favourable. The case fatality ratio remains extremely high at 63% and up to 81% in Indonesia even though oseltamivir has been used in most patients.[142] The lack of major beneficial effects is often attributed to the late presentation of the patients to medical treatment, high initial viral loads, poor oral bioavailability of oseltamivir, lack of parenteral preparations of NAI, a cytokine storm resulting in multi-organ failure and the emergence of oseltamivir resistance.

Primary resistance to the NAI among wild strains of human influenza viruses (A/H1N1, A/H3N2 and B) used to be extremely rare.[180] Development of

resistance following oseltamivir treatment occurred in 0.33–5.5% of the treated patients.[181–183] However, a worrying trend of oseltamivir resistance has been emerging. The first report came from Japan where oseltamivir resistance was encountered in up to 18% of A/H3N2 viruses from children being treated with oseltamivir.[184] In the 2004–2005 season, FLUBV with reduced susceptibility to oseltamivir was detected in Japan.[185] In the 2005–2006 season in France, two human A/H1N1 isolates were found to be resistant to zanamivir, one A/H1N1 isolate was resistant to oseltamivir but susceptible to zanamivir, and an FLUBV isolate was resistant to both zanamivir and oseltamivir.[186] In the 2007–2008 season, a high prevalence of oseltamivir resistance was reported among human A/H1N1 viruses in at least nine European countries; overall, 14% of 437 strains tested were resistant to oseltamivir (range 6–70%).[187] The H274Y mutation in the NA gene is responsible for some of the cases of oseltamivir resistance seen in Europe. The emergence of oseltamivir resistance among A/H5N1 viruses is also alarming. The first case was described in a Vietnamese girl who had received 4 days of post-exposure oseltamivir prophylaxis. The level of resistance apparently did not lead to treatment failure.[188] Subsequently, two more Vietnamese patients were found to have infection due to oseltamivir-resistant A/H5N1 viruses.[3] In the patients who died from oseltamivir-resistant A/H5N1 infections, a rising viral load was detected in their throat swabs.[189] A study involving A/H5N1 viruses of avian origins in Southeast Asia obtained in 2005 showed that while all the viruses were susceptible to zanamivir and all clade 1 isolates from 2004 were susceptible to oseltamivir, some clade 1 isolates from Cambodia and some clade 2 isolates from Indonesia in 2005 showed a 15- to 30-fold reduction in oseltamivir susceptibility.[190]

Resistance to the NAI occur as a result of mutations in the NA gene of the virus. A number of mutations have been described; a common mutation is H274Y, which is found in N1 viruses and confers high-level resistance to oseltamivir.[191,192] With few exceptions, most of the oseltamivir-resistant influenza viruses (including those with the H274Y mutation) remained susceptible to zanamivir. The lack of cross-resistance between these two NAI is due to the differences in their chemical structure and binding properties to the NA molecule.[193] Oseltamivir has a hydrophobic pentyloxy substitution at the C6 position while zanamivir has a polar glycerol group. Binding of oseltamivir to the wild-type NA molecule requires a conformational change in the NA to accommodate the hydrophobic side-chain, while such a change is not necessary for the binding of zanamivir. The H274Y mutation prevents this conformational change from occurring, thereby conferring resistance to oseltamivir but does not affect the binding of zanamivir. Earlier experiments demonstrated the reduced fitness of NAI-resistant viruses *in vitro* and in animal studies. A/H3N2 viruses with NA mutations of R292K and E119V as well as A/H1N1 with H274Y have lower transmissibility, infectivity and pathogenicity in ferrets, as well as reduced replication *in vitro*.[194–197] However, the loss in fitness and virulence is not a uniform characteristic of all NAI-resistant mutants, and close monitoring for their pathogenicity is essential.[198,199] In view of the increasing concern for oseltamivir-resistant influenza viruses, relative rarity of zanamivir-resistant isolates especially among A/H5N1, and the difficulty in administering zanamivir powder to the severely ill patient, other modes of therapy need to be explored. A special preparation of zanamivir in saline was used for nebulization in a study and was well tolerated.[200] Nebulized zanamivir may improve the delivery of drugs to the LRT in severely ill patients and those put on mechanical ventilation. In preclinical trials, intravenous zanamivir has been given at very high doses to volunteers and was well tolerated.[201,202] The availability of an intravenous formulation of zanamivir can prove life-saving in patients suffering from severe disseminated infections by yielding high drug concentrations both in the consolidated lungs and at other extrapulmonary foci of infection.

Ribavirin has activities against both FLUAV and FLUBV and it has been used for treatment and prophylaxis of influenza. The routes of administration include oral, intravenous and aerosolization.[203–206] Anecdotal reports have shown efficacy in the therapy against influenza A and B, including therapy in the immunocompromised hosts. Unfortunately, a consistent benefit has not been observed in all clinical trials and ribavirin is currently not considered to be a drug of choice for influenza. Data on the activity of ribavirin on AIV are limited.[207] An investigational agent is viramidine which is a carboxamidine analogue of ribavirin and it possesses anti-influenza activity *in vitro* and animal studies.[207]

Convalescent plasma is another potentially useful form of therapy for severe influenza and infection due to A/H5N1. Convalescent plasma has been used in one patient with A/H5N1 infection with good clinical and virological responses.[208] A meta-analysis on the use of convalescent blood products during the Spanish influenza pandemic showed that there was a survival benefit in those who received this treatment, and the benefit was greater if treatment was begun within 4 days of onset of pneumonia.[209]

Another approach to therapy of A/H5N1 infection is the use of immunomodulators in an attempt to limit the pro-inflammatory cytokine storm and the resultant tissue damage. Corticosteroids has been used in some cases but has not been shown to be beneficial.[210] A recent animal study showed that a combination of intraperitoneal zanamivir, celecoxib and mesalazine protects mice from a high inoculum of A/H5N1 viruses even if treatment was started 48 h after challenge.[211] To be effective, immunomodulators should be carefully chosen to target the detrimental pathways of the inflammatory cascade while preserving the protective immunity.

Paramyxoviridae

Measles virus

Pneumonia is the commonest serious complication of measles. Pneumonia associated with measles can

be a primary viral pneumonia (Hecht's pneumonia) or secondary bacterial pneumonia, the former being commoner in adults and the latter commoner in children. Symptomatic pneumonia is seen in 3–15% of healthy adults with measles, and it accounts for about 60% of the deaths due to measles.[212–214] With the decrease in the uptake of measles vaccine and the frequent community outbreaks of the disease in developed countries, one might expect to see more cases of measles pneumonia in the future.

Uncomplicated measles does not require antiviral therapy. In measles pneumonia, bacterial superinfection has to be excluded and antibacterial agents given if indicated. Few studies and case reports have addressed the issue of antiviral therapy of measles. Ribavirin possesses *in vitro* activities against measles virus and patients had been treated with this agent via the aerosolized or intravenous route.[215–219] Clinical benefits were seen in some cases although no definitive conclusions can be made at the moment. IVIG (400 mg/kg single dose) has also been used in some cases with ribavirin.[218] Recently, it was found that *in vitro* a two- to fivefold decrease in the 50% inhibitory concentration of ribavirin against measles virus was seen when ribavirin was complexed with α- or β-cyclodextrins.[220]

Human metapneumovirus

The human metapneumovirus (hMPV) was first described in 2001 and has a global occurrence.[221] There are two genetic lineages, A and B, in hMPV, each of which are further divided into sublineages 1 and 2.[222] Infection by hMPV is common, and most of the population would have been exposed to the virus by early adulthood.[223–225] Infection is especially common in children 3 years of age or younger. The prevalence of hMPV in children hospitalized for RTI ranged from 3% to 10%, often second only to RSV in prevalence.[226–231] The infection manifests as fever, URTI symptoms, croup, exacerbation of asthma, bronchitis, bronchiolitis or pneumonia.[232] The disease is not clinically distinguishable from other causes of viral RTI, though the severity may be less than RSV infection.[233,234] Community-acquired infection in immunocompetent children is usually uncomplicated. Severe pneumonia and even mortality have been reported in immunocompromised patients such as BMT and SOT recipients.[235,236] The viral load of hMPV is correlated with the disease severity in children.[237] Infected adults may develop an ILI, exacerbation of COPD, congestive heart failure, asthma and pneumonia. A recent prospective study showed that hMPV is the cause of CAP in 4% of adults, all of whom had underlying chronic heart and/or lung diseases.[238] It was the second commonest viral respiratory pathogen in a series of adult patients with haematological malignancies with or without BMT.[235,239] Outbreak of hMPV infection in elderly residents of a long-term care facility has also been reported.[240]

Like many other clinically important paramyxoviruses, hMPV is susceptible to ribavirin. *In vitro*, the activity of ribavirin against hMPV is similar to RSV.[241] In a mouse model of infection, ribavirin reduced the viral load in the lungs by 5 $\log_{10}$ after 5 days of treatment.[242] Although controlled clinical trials have not been performed, a lung transplant recipient with hMPV pneumonia had been treated with intravenous ribavirin and its use is recommended for severe infections in immunocompromised hosts.[243,244]

Human parainfluenza viruses

There are four human parainfluenza virus (HPIV) serotypes placed in two genera under the family *Paramyxoviridae*. These include *Respirovirus* (HPIV-1 and 3) and *Rubulavirus* (HPIV-2 and 4, also includes the mumps virus). They are enveloped, single-stranded, negative-sense RNA viruses. Most human infections are caused by HPIV-1, 2 and 3.[245] HPIV-4, which is not normally detected by rapid antigen assays, has been found to be associated with RTI and community outbreaks of RTI in recent years.[245–248]

Human parainfluenza viruses are very common causes of community-acquired RTI, especially in the paediatric population. Manifestations in children ranges from croup (for which HPIV are the commonest aetiological agents), bronchiolitis, tracheobronchitis, to pneumonia.[245] HPIV-1 and -2 are often associated with URTI such as croup, while HPIV-3 predominates in causing LRTI in very young infants.[245,249] HPIV infection in adults is generally less severe and often present with URTI. However, immunocompromised individuals, both children and adults, are prone to develop severe illness as a result of HPIV infection. Severe diseases are often seen among BMT and SOT (such as lung transplant) recipients, as well as those with haematological malignancies and congenital immunodeficiencies.[250–258] Prolonged (up to 121 days) and sometimes asymptomatic shedding of HPIV from the respiratory tract of the patients has been documented, potentially adding to the risk of transmission in health-care facilities.[254,258] Nosocomial acquisition or outbreaks of HPIV infection have also been reported among these compromised patients.[252,253] In some studies, a high viral load in the nasopharyngeal aspirate is associated with symptomatic infection and severity of disease.[258] In these compromised hosts, HPIV-3 is the commonest serotype causing severe LRTI. The mortality—up to 80% or above—is highest among those who developed pneumonia.[255] The mortality of HPIV-3 pneumonia in transplant recipients used to be very high with 30-day mortality of 35%, but some other series had a much lower 30-day mortality of 4%.[254,257]

Antiviral therapy of uncomplicated HPIV infection in the immunocompetent patients is not generally indicated. HPIV pneumonia in the immunocompromised host is usually treated with antivirals. As in the case of other paramyxoviruses, HPIV are susceptible to ribavirin, which is the commonest antiviral agent used clinically for severe infections. *In vitro* and in animal studies, ribavirin suppresses viral multiplication and improves survival of animals.[259–261] Immunocompromised patients with serious HPIV infections are treated with ribavirin given by the intravenous or

aerosolized routes, though its efficacy has not been studied in randomized controlled trials.[251,252,254,262] In at least two of the case series, aerosolized ribavirin did not result in improved clinical outcomes.[254,255] It is uncertain whether this ineffectiveness is due to the lack of *in vitro* activities of ribavirin against HPIV, poor penetration of the drug to the lower airways or late commencement of antiviral treatment.

Interestingly, HPIV are susceptible to NAI *in vitro*.[263] One of the surface glycoproteins of HPIV is the haemagglutinin-neuraminidase (HN) protein. The HN protein functions in attachment of the virions to the host cells and aids the release of newly formed virions from infected cells. The neuraminidase activity and receptor interaction of the HPIV-3 HN protein is inhibited by zanamivir *in vitro*.[263] There is no direct comparison between the activity of NAI on influenza and parainfluenza viruses. However, when plaque reduction assay was used to determine antiviral susceptibility, the IC_{50} of zanamivir on FLUAV was in the range of 4–14 nM while the value for HPIV-3 was 0.8 mM.[263,264] It is uncertain whether this inhibitory effect is clinically relevant.

Human respiratory syncytial viruses

Human respiratory syncytial virus (HRSV) is one of the species in the genus *Pneumovirus* under the family *Paramyxoviridae*. The species consists of two subtypes A and B and both subtypes often co-circulate in the community at the same time. HRSV shows a seasonality with the peak incidence commonly seen in winter and early spring in temperate countries.[265,266] The main burden of the disease is in young children in whom it is one of the more serious pathogens because of its propensity to cause LRTI such as bronchiolitis and pneumonia. In children, HRSV causes 50–90%, 5–40% and 10–30% of the hospitalizations for bronchiolitis, pneumonia and tracheobrochitis respectively.[267] Owing to the lack of a durable immunity, re-infection is common; the subsequent episodes are, however, less severe than the first attack. Risk factors for more severe disease in childhood include prematurity, presence of chronic lung diseases, congenital heart disease and congenital or acquired immunodeficiencies.[268] Persistent wheezing after HRSV infection is common but its role in causing asthma and atopy has not been conclusively demonstrated. HRSV is also the commonest virus causing outbreaks in paediatric wards.[265,269]

Human respiratory syncytial virus is a common but under-appreciated pathogen in the adults. In one of the studies, HRSV caused 1.0–4.4% of CAP in otherwise healthy adults, and was one of the four commonest pathogens identified. Patients with HRSV infection tend to have more wheezing and rhonchi compared with other pathogens.[270] Community-dwelling elderly and elderly individuals living in long-term care facilities have significant morbidity and mortality from HRSV infections.[271,272] Attack rates during outbreaks in long-term care facilities ranged from 12% to 89%. In a prospective study, HRSV infection occurred in 3–7% of healthy community-dwelling elderly and 4–10% of high-risk adults, and accounted for 10.6% of hospitalizations for pneumonia.[271] In elderly patients hospitalized for HRSV infection, the length of hospital stay, rate of intensive care use and mortality are similar to influenza A. Mortality is also high in the immunocompromised patients who develop HRSV pneumonia.[273,274]

Antiviral treatment of HRSV infection is traditionally based on ribavirin. Ribavirin is often given in the nebulized form via a SPAG-2 aerosol generator. A potential problem in giving nebulized ribavirin to intubated patients is the precipitation of the drug in the tubing, thereby causing malfunction of the ventilator. Another problem associated with the use of nebulized ribavirin is the teratogenicity of the drug; pregnant or potentially pregnant health-care workers must avoid close contacts with patients on this mode of therapy. Administration of nebulized ribavirin by the high-dose short-duration regimen (Table 1) may reduce environmental contamination by the drug.[275] Oral ribavirin has been used for a median duration of 16 days (range 4–64 days) in patients with haematological diseases.[276] Intravenous ribavirin has also been used in BMT and lung transplant recipients.[277,278] The optimal duration of ribavirin is unknown, courses of 3 days to over 14 days have been used.[279] IVIG (500 mg/kg q48h) is sometimes used in the immunocompromised patients together with ribavirin.[274,280] Although ribavirin is licensed for HRSV infection and has been shown to reduce the viral load in BMT patients, clinical trials have not been uniformly in favour of its efficacy.[281] Systematic reviews of the efficacy of ribavirin in HRSV infection in infants and young children showed a trend towards shorter duration of mechanical ventilation and duration of hospital stay in the ribavirin-treated group.[265,282] The current recommendation is that ribavirin should not be routinely given to patients with HRSV infection, but may be considered in high-risk patients such as the immunocompromised, those with significant comorbidities, or those with severe infections.[276,283,284]

Corticosteroids have also been commonly used for HRSV infection. Agents such as hydrocortisone, prednisolone, methylprednisolone, budesonide and dexamethasone have been given by mouth, by nebulization, intramuscularly or intravenously.[265] The results have been conflicting. In one of the meta-analyses, the use of corticosteroids in HRSV bronchiolitis infants lead to a statistically significant reduction of length of hospital stay—by only 0.43 day.[285] In mechanically ventilated patients, the steroid-treated patients overall tended to have a shorter duration of mechanical ventilation (by 1.6 days, statistically insignificant), the benefit is most prominent in the bronchiolitis group in whom the duration of mechanical ventilation was significantly shortened by 4.3 days.[286]

A major breakthrough in the management of HRSV infection is in immunoprophylaxis and possible immunotherapy of the disease. Immunoprophylaxis of HRSV infection in the high-risk individuals can be achieved using RSV immune globulin (RSVIG). RSVIG is given at a dose of 750 mg/kg i.v. once a month for up to 5 months during the peak HRSV

season. This has been shown to be highly effective in reducing the number of RSV hospitalization, duration of hospitalization and the severity of disease.[276] The disadvantages of RSVIG being the need for intravenous infusion, the use of human blood products and the high cost of the product. RSVIG is no longer produced by its manufacturer MedImmune since 2003. Subsequently, palivizumab was developed. Palivizumab is a humanized IgG mAb against the F (fusion) protein of HRSV and it is 50–100 times more potent than RSVIG. The F protein is conserved between different strains of HRSV and it serves the pivotal function of viral fusion with cell membrane as well as intercellular spread of the virus. Palivizumab is given at 15 mg/kg once a month by intramuscular injection for 5 months, starting 2 weeks before the HRSV season is expected to begin. Significant reduction in the hospitalization rate of palivizumab-treated high-risk infants (especially the premature and those with chronic lung diseases) was seen.[287] Compared with placebo, palivizumab reduces the incidence of hospitalization due to HRSV infection by 55%, compared with 41% by RSVIG. The reduction in premature infants without bronchopulmonary dysplasia was 78% while the figure for infants with bronchopulmonary dysplasia was 39%. Palivizumab also led to a significantly reduced admission rate to intensive care, shorter duration of hospital stay and shorter duration of moderate to severe respiratory illness. RSVIG and palivizumab have also been used for therapeutic purposes in a small number of patients.[274,288–293] Concrete benefits of using Ig for treatment of HRSV infection is lacking.[294]

Currently, another anti-RSV mAb, motavizumab, is being developed.[295,296] Motavizumab has a much higher affinity to the F protein of HRSV than palivizumab with significantly enhanced binding to F protein and *in vitro* neutralization of the virus.

Picornaviridae

Human parechoviruses

The human parechoviruses (HPeV) are non-enveloped viruses with a single molecule of linear positive-sense, single-stranded RNA. At least six types of HPeV have been described (HPeV-1 (formerly human echovirus 22), 2 (formerly human echovirus 23) and 3–6) based on serotypic and genotypic characteristics.[297–301] HPeV are sometimes detected in respiratory specimens and are associated with mild respiratory symptoms as well as otitis media (HPeV-1 and -3).[302–304] However, their exact role in the pathogenesis of RTI is currently uncertain. HPeV are also found in patients with gastroenteritis, neonatal sepsis and acute flaccid paralysis.[305–308] Nothing is known about their antiviral susceptibility. Although not specifically used for parechoviruses, pleconaril—the most promising agent against picornaviruses—had been used with IVIG in a case of acute flaccid paralysis caused by echovirus 19 but failed in another case of neonatal echovirus 7 infection.[309,310]

Human rhinovirus

The human rhinovirus (HRV) previously consists of two species, HRV-A and HRV-B, which in turn are made up of over 100 serotypes. The HRV-QPM strain was found to be associated with LRTI symptoms in about half of the cases and it is almost identical to the newly described species HRV-C.[311,312] The HRV are arguably the commonest of all known viral causes of RTI.[313] Although certain months of the year are characterized by a high prevalence of particular respiratory viruses (such as the 'flu season' in temperate countries), some studies showed that year-round, HRV are the cause of the majority of acute community-acquired viral RTI.[314]

Human rhinoviruses are typically stereotyped as the 'common cold viruses' because they accounted for over 50% of common colds. During the peak seasons of HRV infections—often in early spring and autumn—up to 90% of colds are due to HRV.[315] The infection is a self-limiting disease with a median duration of illness of 1 week, but a quarter of them can last for 2 weeks. It can occur in any age groups owing to the large number of serotypes. Involvement of the LRT by HRV has been less well studied until the past decade with the wider availability of better diagnostic techniques such as RT-PCR. It is now well documented that HRV causes LRTI, manifesting as bronchitis, bronchiolitis and pneumonia in both children and adults.[315,316] They are also important causes of exacerbations in patients with chronic airway diseases such as asthma, COPD and cystic fibrosis.[315] In children hospitalized for acute RTI, HRV can be detected in the nasopharyngeal aspirate in 35.4% of the individuals in one recent study, and pneumonia was diagnosed in 11.3% of the patients in that cohort.[317] Apart from the children, elderly individuals living in the community can also develop HRV-associated LRTI.[318,319] In another series which used RT-PCR to detect the viruses, HRV accounted for 57% of episodes of viral RTI among the elderly individuals in whom an aetiological agent was found. In the majority of these cases, HRV were the sole pathogens found.[318] Symptoms of LRTI were noted in 62.5% of the individuals. HRV are also important respiratory pathogens in the immunocompromised hosts, in particular the transplant recipients.[315,320] Patients who developed HRV pneumonia appeared to have a poor prognosis with 100% mortality reported in a series of BMT recipients.[320] While not as commonly reported as influenza viruses or HRSV as a cause of nosocomial infection, HRV has been associated with outbreaks in hospitals which can lead to substantial mortality in the compromised populations.[321,322]

No antiviral agent is currently licensed for the treatment of HRV infections. One of the earlier and more successful trials used intranasal interferon α-2 for rhinoviral colds. In double-blind placebo controlled trials involving healthy volunteers, the use of intranasal interferons were shown to be effective for prophylaxis in experimental infections with HRV.[323–325] Intranasal interferon was also effective for prophylaxis against natural infections and post-exposure prophylaxis.[326–328] This mode of delivery

was, however, ineffective for therapy of established infections.[329,330]

A large number of experimental agents have been tested for their anti-picornavirus activities and some had undergone early phases of clinical trials.[331–334] Pleconaril is the best studied of these agents. It binds to the hydrophobic pocket in the viral capsid VP1, thereby inhibiting the attachment, entry and uncoating of the virus.[334] Pleconaril is orally bioavailable and achieves excellent penetration into body fluids including cerebrospinal fluid. *In vitro*, most HRV are inhibited by pleconaril but at least seven serotypes belonging to HRV-B are resistant to pleconaril.[335] Resistance is related to the amino acid sequence at the binding site of the capsid pocket. Clinical trials with pleconaril have been performed on enteroviral meningoencephalitis, myocarditis and neonatal sepsis.[336] In the double-blind, randomized, placebo-controlled trials which investigated the efficacy of pleconaril for picornavirus colds in adults (in which 99% of the viruses detected were rhinoviruses), the use of pleconaril resulted in a 1.5-day reduction in the time to alleviation of illness and decreased viral load in the nasal mucus.[337] A 15-month-old leukaemia child who developed severe HRV pneumonia after BMT was being treated with pleconaril and had marked improvement clinically and radiologically.[336] Pleconaril may be the most promising agent for the treatment of severe HRV infections. Unfortunately, the drug is not yet routinely available for clinical therapy.

CONCLUSION

Viral RTI carry a substantial burden of disease and each pathogen shows specific clinical and epidemiological characteristics. Most of the agents are common causes of respiratory illness in the community affecting immunocompetent individuals. In this regard, the infants and children are frequently the commonest age group to develop symptomatic illness. Some are noted for their preponderance to cause severe infections in the immunosuppressed hosts (such as HCMV), while most of the rest produce more serious illnesses in the immunocompromised than the immunocompetent individuals. The influenza viruses are unique in their pandemic potential, and others are notable for having an animal reservoir (as in AIV and SARS-CoV). Nosocomial transmission of respiratory viruses is a common cause of outbreaks in hospitals and other health-care facilities. Diligent infection control measures (primarily contact and droplet precautions, with airborne precautions in some special situations) are crucial.

Antiviral agents are available for some of these pathogens. The herpesviruses are often susceptible to the guanosine analogues (such as acyclovir), ganciclovir, foscarnet and cidofovir. Ribavirin is a broad-spectrum agent active on many RNA and some DNA viruses. Influenza viruses are specifically targeted by the adamantanes and NAI. The interferons deserve more intensive investigations to assess their therapeutic and prophylactic roles. Unfortunately, only a few of these agents have undergone stringent clinical trials to assess their clinical efficacies. The choice of a specific agent is often based on *in vitro* susceptibility and clinical experience, sometimes supported by efficacies in experimental animal models. Randomized controlled trials are, however, not always feasible, especially in life-threatening infections. Immunological agents may become an important aspect in the therapy or prophylaxis of some infections. Examples include the use of convalescent plasma for the treatment of SARS and A/H5N1 infections. Palivizumab is a successful example in this respect. In general, life-threatening infections such as HCMV pneumonitis and A/H5N1 infections must be treated with antivirals despite the lack of clinical trials in some settings. For other respiratory viruses, antiviral treatment is often recommended only for immunocompromised individuals or for severe infections in the competent host. In some viral RTI, such as SARS and avian influenza infections due to FLUAV A/H5N1, immunopathological damage or excessive activation of the pro-inflammatory cascade is thought to contribute to the organ damage and mortality. Immunomodulating agents are used for these infections in the hope of reducing these tissue damages. Corticosteroids are the most commonly used of these agents because of the potency in suppressing inflammatory reactions. However, the value of corticosteroids has not been encouraging for most of theses infections. One possibility for the lack of beneficial effects of corticosteroids could be the broad and non-specific suppressive effects on the immune system, which may also inhibit the protective cellular immunity crucial to control viral multiplication. Corticosteroids or other immunomodulators should be used only when an effective antiviral agent is available, lest the immunosuppression may lead to uncontrolled viral replication. More targeted modulation of the immune system should be explored in the future.

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