

Respiratory Viruses Other than Influenza Virus: Impact and Therapeutic Advances

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INTRODUCTION

A desire for a “cure for the common cold” has been a perennial wish from a long-suffering populace. While not universally considered a high-priority medical need, upper respiratory tract infections (URTIs) cause countless sleepless nights and are responsible for vast economic losses due to missed work and school absences. The recent development of improved diagnostic techniques has greatly expanded our knowledge of the agents that cause this ubiquitous clinical syndrome and has also broadened our understanding of the epidemiology and medical impact associated with respiratory viruses (RVs) other than influenza virus.

These developments, however, have proven to be a double-edged sword for companies that would develop and license antiviral agents for URTIs. While the increased sensitivity of PCR-based diagnostics has greatly increased the probability of identifying the causal offender in patients with URTI, large-scale molecular screening for viral genome sequences continues to identify new agents that are also putatively responsible for this nonspecific clinical syndrome. Accordingly, the development of an antiviral with high specificity for a specific agent (a common goal of drug development programs) effectively targets an ever-shrinking proportion of subjects with symptoms of the common cold. Because syndrome-based therapy would expose many subjects to a drug who do not stand to benefit from it, the bar for safety of such an antiviral is high. Targeted therapy based upon the presence of the causative virus would be preferable; here, a revolution in simple, office-based diagnostics for identifying the viral cause of URTIs would significantly advance the field.

Here we discuss antivirals for RVs other than influenza virus (both those available and those currently under development), considering the epidemiology of such infections, the important role played by diagnostic testing in treatment, and the hurdles that are faced in development of these compounds.

TAXONOMY AND ANTIVIRAL TARGETS

Despite commonalities in disease presentation among many of the RVs, they are genetically and antigenically distinct (Table 1). The RNA viruses of the *Mononegavirales* order contain single-stranded genomes that are negative sense. This order is comprised of seven families, including *Orthomyxoviridae* (which contains the influenza viruses) and *Paramyxoviridae* (which contains the parainfluenza viruses (PIVs), human respiratory syncytial virus [RSV], and human metapneumovirus [hMPV]). Members of both families are enveloped; unlike viruses in the family *Paramyxoviridae*, the viral genomes from family *Orthomyxoviridae* are segmented.

The *Picornaviridae* are nonenveloped viruses with a single-stranded genome of positive polarity. The rhinoviruses are the most important members of this family causing respiratory diseases in humans; other viruses in this group that can cause respiratory disease are enteroviruses (such as coxsackieviruses and numbered enteroviruses). Over 100 serotypes of rhinovirus have been identified, a fact that has significantly hamstrung

the development of vaccines for this ubiquitous human pathogen. Viruses from the family *Coronaviridae* also contain positive-sense single-stranded RNA (ssRNA) but are enveloped. This family currently includes five members that are known to infect humans: human coronavirus (HCoV) 229E, HCoV OC43, the severe acute respiratory syndrome-associated CoV (SARS-CoV), and the recently described HCoV NL63 and HCoV HKU1 (174).

DNA viruses associated with human respiratory disease include the nonenveloped double-stranded DNA (dsDNA) viruses from the family *Adenoviridae* and the newly discovered ssDNA virus from the family *Parvoviridae* known as human bocavirus (HBoV).

EPIDEMIOLOGY

Respiratory viral infections are an important cause of morbidity and, in some settings, of mortality as well. For most RVs, the epidemiology is characterized by annual outbreaks during the winter and spring seasons; some RVs, however (e.g., PIVs), are prevalent throughout the year. The epidemiology of RVs in immunocompromised patients usually parallels that observed in the community, as these viruses circulate in immunocompetent individuals (including health care personnel, family members, and visitors).

The social and economic impact of respiratory viral disease is substantial. For instance, respiratory viral infections lead to more than 400,000 hospitalizations per year in children less than 18 years of age in the United States (81). Using RSV-specific diagnostic codes alone, an estimated 96,000 RSV hospitalizations occurred annually among children in the United States in 1997 to 2000 (21).

Immunocompetent Hosts

Seasonal colds. Seasonal colds represent a clinical syndrome of upper respiratory signs and symptoms, which include rhinorrhea, sore throat, sneezing, cough, and watery eyes. None of the symptoms are pathognomonic for any specific virus, as virtually all known RVs can cause any combination of these symptoms. While there are important differences in the symptoms between viruses (128, 162), none of these differences are sufficiently distinct to enable a definitive clinical diagnosis.

Bronchiolitis. Bronchiolitis is the most common cause of hospitalization of small infants in developed countries (112, 155, 220). RSV is the leading cause of bronchiolitis, but other RVs such as hMPV, influenza virus, and CoVs, have also been shown to cause this disease (59, 66, 149; H. Stempel, E. Martin, J. Kuypers, J. Englund, and D. Zerr, presented at the Infectious Diseases Society of America Annual Meeting, San Diego, CA, 4 to 7 October 2007.). A recent study showed that lytic viral infection of the bronchial tissue is the dominant pathogenic mechanism in children with bronchiolitis (222). Bronchiolitis is a cause of hospitalization in approximately 45 of 1,000 infants in the United States, with a rate of 126 outpatient visits per 1,000 infants (23, 139, 163). Certain populations, such as

TABLE 1. Classification of and key targets for human respiratory viruses other than influenza virus

Family (nucleic acid ^a)	Representative virus	Cellular receptor(s)	Viral target(s)	Cellular targets
<i>Paramyxoviridae</i> (– ssRNA)	RSV	Sialyl-glycoproteins, glycolipids	Fusion polypeptide, RNAi, N protein, L protein	Several ^b
	PIV	Sialyl-glycoproteins, glycolipids	HN, RNAi	
	hMPV	Sialyl-glycoproteins, glycolipids	F protein	
<i>Picornaviridae</i> (+ ssRNA)	Enteroviruses (coxsackievirus type A or B, echovirus)	ICAM-1, decay-accelerating factor (CD55), CAR, integrins	Viral capsid	CAR ^c or other cell-associated factors
	Rhinovirus	ICAM-1, sialic acid	Viral capsid, viral protease	
<i>Coronaviridae</i> (+ ssRNA)	HCoV	CD13 (HCoV 229E), ACE2 (HCoV NL63, SARS-CoV), CD209L (SARS-CoV, HCoV-229E)	Several (see the text)	
<i>Adenoviridae</i> (dsDNA)	Adenovirus	CAR, integrins	DNA polymerase	CAR or other cell-associated factors
<i>Parvoviridae</i> (+ or – ssDNA)	HBoV	Unknown (sialyl-glycoproteins?)	DNA polymerase	

^a –, negative sense; +, positive sense.

^b See the text.

^c CAR, coxsackievirus and adenovirus receptor.

American Indian and Alaska Native infants, have a significantly higher incidence (23, 163, 179). Prematurity is an important risk factor for severe RSV disease in children, but other factors, including chronic lung disease (e.g., bronchopulmonary dysplasia), congenital heart disease, and low socioeconomic status, are associated with more severe clinical manifestations. Ethnicity, male sex, and body mass of <5 kg are also important (179).

Acute otitis and sinusitis. RVs have been increasingly appreciated as causes of acute otitis media and sinusitis. Indeed, studies in children suggest that RSV is the cause of acute otitis media in approximately 15% of cases, and it accounts for one-third of viral causes (158, 176). Other viral causes include PIV, rhinovirus, adenovirus, enterovirus, and influenza virus (158). Rhinovirus was the predominant virus recovered in the middle ear cavities of children with asymptomatic otitis media with effusion in one study (28). Ear involvement of viral infections has also been seen in adults (129).

Sinusitis occurs in 10% of adult patients with acute RV infections (129). RSV, influenza viruses, and picornaviruses appear to be most commonly involved (129).

Croup. The majority of cases of viral croup are caused by PIVs. PIV type 1 appears to be more commonly involved than types 2, 3, and 4 (71, 110, 178). However, RSV, adenovirus, hMPV, and influenza virus can cause croup as well (43, 166, 231). Recently, CoV NL63 and HBoV have been described as causes of croup (4, 215).

Community-acquired pneumonia. RVs are increasingly recognized as a cause of community-acquired pneumonia in adults, especially the elderly, and children (50). Overall, studies published to date suggest that up to 20 to 25% of cases of community-acquired pneumonia in adults are due to RVs (94),

with influenza viruses and rhinoviruses the leading causes. The median age in the study by Jennings et al. (94), which evaluated RSV, PIV, adenovirus, rhinovirus, and CoVs in adult patients with community-acquired pneumonia, ranged from 51 years for adenovirus pneumonia to 81 years for PIV pneumonia. RSV, PIV, CoVs, adenovirus, enterovirus, HBoV, and hMPV have also been described as causes of community-acquired pneumonia in young immunocompetent adults as well as in the elderly (3, 53, 71). In addition, adenovirus is a well-known cause of pneumonia in military recruits (218).

Exacerbation of COPD or asthma. Historically, exacerbations of chronic obstructive pulmonary disease (COPD) have been thought to be caused by bacterial infection, which provides the rationale to administer antibiotics empirically. Recent evidence suggests that RVs are an important trigger for both COPD and asthma exacerbations (173, 183). Studies to date suggest viral causes in approximately 20% of exacerbations. In addition to influenza A and B viruses, CoVs, rhinoviruses, RSV, and hMPV are detectable in individuals with COPD exacerbations (53, 65, 104–106, 186). Persistence of RSV in the respiratory tract in subjects with COPD has been shown to be associated with airway inflammation and an accelerated decline in FEV1, thus representing a new potential target for therapeutic intervention (230). Rhinovirus has been associated with asthma exacerbations (65). There is a potential role of early RSV infection in childhood as a risk for subsequent asthma development (190).

Immunocompromised Hosts

Though the impact of RVs in the immunocompetent host is substantial, patients with compromised immune function are

far more likely to experience poor outcomes on a per-subject basis. Accordingly, the bulk of clinical data for the use of antivirals for RV infections has been accumulated from this population.

Hematologic malignancies and HCT. Among hematopoietic cell transplant (HCT) recipients and severely immunosuppressed nontransplant patients with hematologic malignancies (229), RSV URTI may progress to fatal pneumonia (73). During the RV season, the incidence of RSV infection may be as high as 10% (152, 192), though recent advances in infection control practices have reduced the attack rate at many centers. In a large study, winter season, male gender, and use of bone marrow as a stem cell source were identified as risk factors for the acquisition of RSV in HCT recipients (152). URTI precedes pneumonia in 80% of patients, and approximately one-third of patients with RSV URTI progress to pneumonia after a median of 7 days. The strongest risk factors for progression to pneumonia are older age and lymphopenia (15, 152).

There is some evidence that low-risk autologous HCT recipients with pretransplant RSV infection may be transplanted without adverse outcome (5). The outcome of RV infections may also be less severe with nonmyeloablative or reduced-toxicity conditioning regimens (J. Schiffer, K. Kirby, B. Sandmaier, D. Maloney, R. Storb, L. Corey, and M. Boeckh, presented at the Infectious Disease Society of America Annual Meeting, Toronto, Ontario, Canada, 12 to 15 October 2006), highlighting the importance of immune status in disease severity. Accordingly, pretransplant RSV infection should lead to a delay of allogeneic myeloablative HCT procedures until clearance of the virus in order to avoid fatal pneumonia during the time of most severe immunosuppression (161).

hMPV can cause URTI and fatal interstitial pneumonia in HCT recipients (48). Risk factors for acquisition and progression are poorly defined.

Of the four types of PIVs, PIV type 3 is most commonly detected in HCT recipients (~90% of cases), followed by serotypes 1 and 2. The incidence of 7% after HCT in two studies is higher than that reported for RSV (4%) with conventional detection methods (151, 226). Recent studies using PCR suggest that the incidence may be higher than 15% (162). Only HCT from an unrelated donor has been identified as a risk factor for acquisition of PIV (151). In T-cell-depleted patients, the resulting CD4 lymphopenia has been reported to increase the risk of all RV infections, including PIV (26). Similar to the case for RSV infection, URTI is the predominant presentation of PIV infection in this population. Progression to pneumonia seems to be less common than with RSV (151). The most important risk factors for the progression from URTI to pneumonia are the use of systemic corticosteroids and lymphopenia (26, 28, 151). Over half of HCT recipients with PIV 3 pneumonia have serious pulmonary copathogens such as *Aspergillus fumigatus* (151).

Adenovirus pneumonia can occur in HCT recipients, especially following in vivo or ex vivo T-cell depletion (56, 121, 241). Adenovirus pneumonia can occur as an isolated event or as part of disseminated disease and is often associated with high-level DNAemia (121).

Limited information is available on rhinovirus, CoV, and BoV infection after HCT (61). These viruses are relatively frequently detected, but their potential to cause lower respira-

tory tract disease is poorly defined (20, 63). Cases of lower respiratory tract disease with fatal outcome have been described with rhinovirus, often in the presence of copathogens (20, 63, 92).

SOT. Similar to the case for HCT recipients, RVs can cause major morbidity and also mortality in solid organ transplantation (SOT) recipients. Incident infection depends on virus exposure, but the disease severity appears to be different in different organ transplant settings. The setting with the most significant impact is lung and heart-lung transplantation, while liver and renal transplant recipients appear to be somewhat less affected (164, 191, 224). RVs have been implicated in pneumonia and chronic rejection in lung transplant recipients (9, 108, 225). The highest morbidity has been described with RSV, influenza virus, and PIV; however, there is probably a diagnostic bias, as more recently discovered viruses have not been studied to the same extent as these long-known viruses.

For RSV, most data come from lung, renal, and pediatric liver transplantation. In lung transplant recipients, RSV is associated with a high frequency of RSV pneumonia and with subsequent organ rejection and bronchiolitis obliterans (BO); direct mortality due to RSV infection, however, is low (225). RSV infections in pediatric liver transplant recipients have been associated with significant morbidity, including pneumonia (12, 170).

In a large study of lung transplant recipients, 5.3% of patients had PIV diagnosed by bronchoalveolar lavage or transbronchial biopsy after lung transplantation (217). The onset of PIV infection was at a median of 2 years posttransplantation (range of 0.6 to 5 years), and high rates of acute allograft rejection (82%) and BO (32%) were documented (217).

Adenovirus infection may result in pneumonia, hepatitis, hemorrhagic cystitis, nephritis, enterocolitis, and disseminated disease in SOT recipients (91). Incidence figures for adenovirus infection range from 6.5% to 8.3% (88). Patients often recover without specific treatment (88). However, more serious manifestations have been reported, including fatal cases of hepatitis or disseminated infection after liver transplantation (141); enteritis in small bowel transplant recipients and acute rejection and adenoviral enteritis in intestinal transplant recipients (97, 156, 168); pneumonia associated with graft loss, death, or progression to BO in lung transplant recipients (22, 156); and coronary vasculopathy and graft loss after heart transplantation (187).

Limited data exist on hMPV. In lung transplant recipients, hMPV infection may present as mild, self-limited infection (42) or as a serious infection with acute graft rejection (62, 109).

Human rhinovirus infection after SOT generally appears to be relatively mild, but persistent infection with graft dysfunction has been described in lung transplant recipients (95, 137).

All four human CoVs may cause pneumonia; however, most patients appear to clear the virus spontaneously (60, 61). Late airflow obstruction following CoV infections has been observed in lung transplant recipients; large cohort studies have not yet been conducted (108).

HIV/AIDS. Compared with that in pediatric cancer patients, the frequency of RV infections appears to be higher in human immunodeficiency virus (HIV)-infected patients (as might be expected because their higher exposure within the at-large

TABLE 2. Seasonality, symptoms, and diagnosis of infections with respiratory viruses other than influenza virus^c

Virus	Seasonality	Frequency of disease manifestation						Performance of diagnostic technique			
		URTI	Otitis media	Croup	Bronchiolitis	Pneumonia	Airflow obstruction and/or wheezing	Culture	Enzyme immunoassay	Fluorescent antibody/rapid cultures	PCR
RSV	++	+++	++	+	+++	+++	+++	+	+	++	+++
hMPV	+	+++	++	+	++	+++	++	Research	NA ^a	+	+++
PIV type 1	+	+++	+	+++	+	++	++	+	NA	+	+++
PIV type 2	+	+++	+	++	+	++	++	+	NA	+	+++
PIV type 3	+	+++	+	++	++	++	+++	+	NA	+	+++
PIV type 4	-	+++	+	+	+	+	+	+	NA	++	+++
Adenoviruses	+	+++	+	+	++	+	-	+	++	++	+++
Rhinoviruses	+	+++	+	+	+	+	+++	+	NA	NA	++
CoVs	+	+++	+	++	+	+	++	Research	NA	NA	+++
HBoV	+	+++	ND ^b	+	+	+	+	NA	NA	NA	+++

^a NA, not available.^b ND, no data.^c Symbols represent negative results or indicators (-) or levels of test utility or seasonality or disease manifestation frequency (+, ++, and +++).

community), but the clinical course appeared to be less severe (140). The burden of severe pneumonia due to RSV, influenza virus, PIV, and adenovirus was substantially higher in South African children infected with HIV than in non-HIV-infected children (132, 134, 135). In another South African study, PIV infection was associated with a higher mortality in HIV-infected children than in uninfected individuals (133). hMPV was identified as a possible cause of pneumonia in 3.7% of HIV-infected versus 9.1% of non-HIV-infected children and was the second most common RV associated with hospitalization (after RSV). The incidence and impact of CoV infection in HIV-infected children have not been systematically evaluated.

Elderly persons. Studies have only recently examined the full impact of RV infections other than influenza in the elderly. The best data exist for RSV. In a prospective study, RSV accounted for 10.6% of hospitalizations for pneumonia, 11.4% for COPD, 5.4% for congestive heart failure, and 7.2% for asthma (52). RSV and hMPV have also been reported to cause outbreaks in chronic care facilities (16, 51).

IMPORTANCE OF DIAGNOSTICS TO TARGETED THERAPY

One important feature of RV infections is the nonspecific nature of clinical signs and symptoms. Indeed, there are very few, if any, specific features that allow clinical diagnosis according to causal virus (Table 2). The high number of potential viral agents that may cause similar symptoms of respiratory illness presents formidable diagnostic challenges. The absence of broad diagnostic platforms that are office based and inexpensive (as well as the lack of effective outpatient treatment options) have prevented the widespread use of existing diagnostics. Currently, the following diagnostic tests are available.

Culture and Antigen Detection

Standard methods available for testing include viral cultures (results are available in several days), shell vial centrifugation cultures using virus-specific monoclonal antibodies (1 to 3 days), direct fluorescent-antibody (DFA) tests (2 h), and en-

zyme immunoassays (2 h). A problem with the rapid test methods is relatively low sensitivity in adults, where the viral load may be low (49–51).

Appropriate specimen handling is important for recovery of the virus via culture. Nasal wash specimens should be placed on ice or in the refrigerator immediately and transported to the laboratory without delay (49). Specimen setup in the laboratory should occur within 2 to 4 h. Isolation of rhinovirus requires lower incubation temperatures. On tissue sections from lung biopsy or autopsy specimens, virus-specific monoclonal antibody staining and viral cultures may be used.

PCR and Microarray Platforms

Molecular detection techniques are rapidly replacing traditional methods (39, 83, 242). Major efforts are under way to develop multiplex assays that can detect a large number of respiratory pathogens concurrently (114, 136, 153). A multiplex assay that detects seven RVs (Hexaplex) has shown excellent performance characteristics in various clinical settings (83, 98). Another multiplex platform (MultiCode-PLx system; EraGen Biosciences, Inc., Madison, WI), which detects 17 RVs simultaneously, showed significantly increased diagnostic yield compared to DFA or culture methods; this was caused mainly by improved detection of influenza A virus and viruses not readily detected by standard virologic methods, including hMPV, CoVs, and rhinoviruses (153). A 20-RV microbead-based assay also showed excellent sensitivity and specificity as well as an increased yield for detection of viruses that are difficult to detect by culture or DFA (136). Microarray and nanotechnology are also being explored to develop large-scale and efficient viral detection platforms (34, 57, 123).

ANTIVIRAL AGENTS: MODE OF ACTION AND SPECTRUM OF ACTIVITY

A wide variety of strategies have been investigated in an attempt to interrupt the replication of the RVs, though it is worth noting that ribavirin is the only FDA-approved agent for the treatment of RVs other than influenza virus. In this section we briefly summarize the most promising of those strategies

and highlight the antiviral activities of agents against the RVs that are currently marketed.

Inhibitors of Attachment and Entry

The first step in the viral life cycle that is amenable to interference is the attachment and entry of the virus into the susceptible host cell. RVs possess surface molecules that are critical for such attachment (Table 1); such molecules are frequently the prime antigenic components that elicit host neutralizing antibodies.

Accordingly, pooled human and humanized monoclonal antibody preparations have been developed to prevent (and potentially treat) infections due to RVs, most prominently those caused by RSV. Animal studies provided the proof of concept, demonstrating that passively administered polyclonal antibody preparations could prevent RSV lower respiratory tract infection when high serum neutralizing titers were achieved (223). RSV-IG (Respigam; MedImmune Inc., Gaithersburg, MD) was developed with these observations in mind by selecting and pooling conventional immune globulin that had high-titer activity against RSV. Clinical trials with high-risk infants demonstrated a significant reduction in hospitalizations due to RSV (68, 69); due to the polyclonal nature of the product, it also reduced infections due to other RVs and episodes of otitis media (189). However, this product is no longer manufactured.

The large volumes and prolonged infusion times associated with RSV-IG spurred development of monoclonal antibodies with specific activity against RSV. Palivizumab (Synagis; MedImmune Inc., Gaithersburg, MD), the first monoclonal antibody approved for clinical use as an anti-infective, is indicated for the prevention of serious lower respiratory tract disease caused by RSV in pediatric patients at high risk for RSV disease. Palivizumab targets the F (fusion) glycoprotein of RSV, preventing RSV binding to cells and the cell-to-cell fusion critical in disease pathogenesis. As a monoclonal preparation, however, the antiviral spectrum of palivizumab is limited to RSV.

Small-molecule inhibitors of viral entry are also undergoing development for the treatment and/or prophylaxis of RV infections. Most human rhinoviruses utilize the intracellular adhesion molecule ICAM-1 for attachment to susceptible cells within the nasal mucosa. Accordingly, soluble forms of ICAM-1 (e.g., tremacamra [Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT]) have been investigated as a decoy to occupy these sites and prevent binding. Capsid binding agents such as pleconaril (Viropharma Inc., Exton, PA) for human rhinovirus and fusion inhibitors against RSV (both discussed further below) are also undergoing development to prevent viral attachment and entry. However, there are no currently approved compounds that utilize this mechanism of action.

Nucleoside Analogues

The majority of approved drugs with antiviral activity act as nucleoside analogues, which act by inhibiting RV DNA or RNA polymerases. Specificity is a common issue with this approach; the compound must have greater affinity for viral than host polymerase in order to limit toxicities.

Ribavirin. Ribavirin (1- β -D-ribofuranosyl-1,2,4-triazole-3-carboxamide) (Virazole; ICN Pharmaceuticals Inc.) is the only antiviral approved by the FDA for the treatment of an RV other than influenza virus, that being for the treatment of hospitalized infants and young children with severe lower respiratory tract infections due to RSV. Though available in intravenous and oral formulations, for RSV infection it is administered as a small-particle aerosol using a tent, mask, or mechanical ventilator for 12 to 18 h daily or, alternatively, at higher doses over 2 h given three times daily. The precise mechanism of action is unknown but appears to be multifaceted. As a structural analogue of guanosine, it inhibits the enzyme IMP dehydrogenase; phosphorylated forms of the compound inhibit RSV RNA polymerase. Alternative explanations for clinical activity include immunomodulatory effects (80) or the triggering of lethal mutagenesis of the viral genome (205). In vitro, ribavirin has broad-spectrum activity against a wide variety of RVs, including RSV, PIV, and adenovirus (194); in vitro activity against the human rhinoviruses is variable according to serotype.

Ribavirin was developed first as an influenza drug and showed impressive reduction of mortality in mouse models of influenza (232, 238). In human trials, however, results were mixed (194); as a result, the U.S. Food and Drug Administration declined to approve the drug for influenza. The absence of approved agents to treat infections other than influenza has prompted the off-label use of aerosolized and systemic ribavirin for many RV infections in the immunocompromised host (as discussed below). Ribavirin's high cost, mode of delivery, side effect profile (potential for sudden deterioration of respiratory function when given via aerosol and dose-dependent anemia when administered systemically), and potential for teratogenicity, however, have restricted widespread use in the at-large community. Indeed, as discussed below, ribavirin is rarely used for the only population for which it is FDA approved: hospitalized infants and young children with severe lower respiratory tract infections due to RSV.

Cidofovir. Cidofovir [(S)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine] (Vistide; Gilead Sciences, Foster City, CA) is an acyclic nucleoside phosphonate that is converted into its active metabolite through two consecutive phosphorylation steps by cellular enzymes. The diphosphate form acts as a cytosine nucleoside analogue and is used as an alternative substrate by the viral DNA polymerase, for which it has a higher affinity than host DNA polymerase. Licensed only for the treatment of cytomegalovirus retinitis in patients with HIV/AIDS, it has broad in vitro antiviral activity that includes the human adenoviruses that cause respiratory illnesses in humans. However, renal impairment is a major dose-limiting toxicity with cidofovir; cases of acute renal failure resulting in dialysis and/or contributing to death have occurred with as few as one or two doses of cidofovir. As a result, cidofovir has been used clinically only among patients with severe adenovirus infections and/or those at high risk for adenovirus-related death (such as recipients of stem cell transplants), as discussed below.

Immunomodulatory Therapy

IFNs. The antiviral activity of interferon (IFN) has been known since 1957 (90). dsRNA is a potent inducer of endog-

enous production of IFN, indicative of its role in modulating viral infections. IFN acts by inhibiting protein synthesis (and thus host-directed synthesis of new viral particles), in addition to stimulating host defense mechanisms, including cellular and humoral immune responses. IFN- α (currently in its preferred pegylated form) has acquired a definitive place in the treatment of hepatitis C infections in combination with ribavirin.

However, despite pronounced antiviral effects in several animal models of RV infection, topically applied IFN has been ineffective for the treatment of RV infections such as rhinovirus, as discussed below. With side effects ranging from fever and malaise to severe thrombocytopenia and suicidality, the investigation of systemic IFN for the treatment of RV infections is presently limited to the highly pathogenic SARS-CoV.

Corticosteroids. It is logical that corticosteroids may offer clinical benefit against the inflammation accompanying RV illnesses, but data regarding virus-specific responses to steroids are lacking. A number of randomized controlled trials have documented the effectiveness of glucocorticoids in relieving symptoms of croup (11, 180). For bronchiolitis, studies suggest that approximately 25% of infants hospitalized with this diagnosis receive corticosteroids, but the data showing efficacy have been inconsistent and controversial (40). The most recent large meta-analysis and a subsequent large randomized trial found no benefit in bronchiolitis symptoms or length of stay for infants and young children treated with glucocorticoid therapy compared with placebo (40, 157). Steroids were commonly employed to treat patients with SARS-CoV; however, the treatment effects are difficult to interpret in the absence of randomized trials and because of frequent concomitant use of other agents (discussed below). There are few data specific to the immunocompromised host, but the receipt of steroids has been shown to be a significant dose-dependent risk factor for progression of PIV type 3 URTI to pneumonia in HCT recipients (151).

Oligonucleotide Approaches (Antisense/siRNA)

RNA interference (RNAi) is a normal cellular process by which dsRNA causes the silencing of the target mRNA. RNAi thus represents a normal posttranscriptional mechanism that leads to “knockdown” of gene expression. RNAi via the use of synthetic small interfering RNAs (siRNAs) holds the promise of specific antagonism of intrinsic host-derived disease-causing genes or of reducing the production of viral genomes. The therapeutic potential for RNAi as an antiviral strategy is particularly great, as the absence of host and viral gene homology ensures antiviral specificity. In addition, siRNAs hold an advantage over protein therapeutics given their ease of synthesis and the rapidity with which lead compounds can be identified and optimized. Like with protein therapeutics, delivery issues pose the greatest hurdle; topical application of siRNAs to the nasal or pulmonary mucosa may need to be coupled with techniques that allow intracellular penetration for antiviral efficacy. Potent prophylactic and therapeutic efficacies in mouse models of RSV and PIV have prompted further clinical development of this approach (discussed below).

While not the subject of this review, several alternative approaches have also been considered to decrease the impact of RV infections. Biopsy of the nasal mucosa after experimental

challenge with human rhinovirus reveals that infection with this common RV occurs in a small number of cells which retain their cellular integrity (169). These observations suggest that it is the host response to infection, rather than virus-induced cellular damage per se, that explains symptoms attributed to incident rhinovirus infection. Accordingly, approaches to suppress inflammation may have merit for certain RV infections in the immunocompetent host; combined antiviral and anti-inflammatory therapy may be required to effect the greatest clinical benefit in these patients.

THERAPY FOR SPECIFIC VIRAL INFECTIONS

RSV

Two drugs are approved for the management of RSV infection in the United States. Ribavirin is approved for the treatment of RSV bronchiolitis in children, while palivizumab is approved for prevention of RSV-associated hospitalization for high-risk infants.

Ribavirin. A recent Cochrane database review of ribavirin for RSV infection of the lower respiratory tract in young children showed a significantly shorter duration of mechanical ventilation and trends toward reduced mortality, less respiratory deterioration, shortened overall hospitalization, and a decrease in the long-term incidence of recurrent wheezing (216). However, another recent systematic review found that there was no evidence that ribavirin use led to consistent or more than transient improvements in clinical outcomes (101). Several problems were noted with the studies of aerosolized ribavirin for severe bronchiolitis, including small sample sizes and the absence of benefit for clinically meaningful outcomes (such as duration of hospitalization or duration of illness). The one study that did report differences in duration of mechanical ventilation and hospitalization (193) has been criticized for using sterile water in the placebo arm, which is a possible irritant to the airways compared with standard mechanical ventilation with humidified air. A further double-blind trial of aerosolized ribavirin that used an isotonic saline solution as the placebo could not demonstrate a positive effect of ribavirin on the same outcomes (138). Accordingly, the American Academy of Pediatrics currently recommends that ribavirin should not be used routinely in children with bronchiolitis, citing the “marginal benefit for most patients” and the “cumbersome delivery requirements, potential health risks for caregivers, and high cost” that serve as disincentives for use (2).

Since untreated RSV pneumonia may be associated with a high fatality rate in post-HCT patients and those with underlying hematologic malignancies (30, 73), however, ribavirin is used more frequently in these settings. Data supporting the use of ribavirin in immunocompromised patients are primarily in the form of nonrandomized studies. Intermittent, short-duration (2 g over 2 h three times per day), or continuous aerosolized ribavirin is considered the treatment of choice for RSV pneumonia in severely immunosuppressed patients, including allogeneic HCT recipients following myeloablative conditioning. With this regimen, the 30-day all-cause mortality is approximately 40% (128, 152); however, if treatment is started after respiratory failure, the outcome is almost uniformly fatal (228). There are several factors that may account for differ-

ences in outcome in the available cohort studies. Perhaps the most important factor is the timing of therapy initiation (128). Other factors such as the presence of lymphopenia at the time of diagnosis (15, 30, 125), the presence of copathogens (e.g., invasive molds or cytomegalovirus), and the use of immunosuppressive agents are also likely to be important. Systemic (e.g., oral and/or intravenous) ribavirin alone does not seem to be effective for the treatment of pneumonia, although studies are small in size (117, 196). Systemic ribavirin given at the URTI stage may be more effective (185). Whether combined oral and aerosolized ribavirin is more effective than aerosolized ribavirin alone has not been studied.

Due to the high mortality associated with RSV pneumonia in this population, aerosolized ribavirin has also been used preemptively for immunosuppressed patients with RSV URTI to prevent progression to pneumonia (30). A small randomized trial suggests that this approach is safe and that ribavirin reduces RSV viral load (14). Whether progression to pneumonia can be prevented by this approach remains an open question.

Immunoglobulin preparations and palivizumab. Palivizumab is an RSV-specific humanized monoclonal antibody that is licensed for use in at-risk pediatric patients. It has a long serum half-life, enabling its administration by intramuscular injection at monthly intervals during the RSV season. The pivotal randomized controlled trial with premature infants (≤ 35 weeks gestation) and pediatric subjects with underlying bronchopulmonary dysplasia showed that palivizumab reduced hospitalizations due to RSV infection by 55% (10.6% with placebo versus 4.8% with palivizumab), though hospitalizations were reduced by a greater degree for premature infants than for those with bronchopulmonary dysplasia (89). A subsequent randomized study of subjects with congenital heart disease demonstrated that palivizumab also decreased the rate of RSV-related hospitalization by 45% (from 9.7% for placebo recipients to 5.3% for the palivizumab group) (54). As recently reviewed by Cardenas et al., several postmarketing surveillance studies have confirmed the utility of palivizumab prophylaxis in these patient populations (25).

Despite the high attack rate and high mortality, there is no consensus on the role of antibody preparations, including palivizumab, in immunocompromised patients; this may be due to the large volumes (and thus high cost and questionable cost-effectiveness) required for adult prophylaxis. Uncontrolled data suggest that high-titer antibody preparations or palivizumab may be required if such adjunctive therapy is given (13, 46, 196). Nevertheless, palivizumab prophylaxis before and after HCT is often used in small children, analogous to its use in high-risk infants. Palivizumab is also used in combination with aerosolized ribavirin for treatment of documented pneumonia due to RSV in severely immunocompromised children and adults (13).

Drugs in development for RSV. Four compounds are in early clinical development for RSV infection. RSV-604 (A-60444) (Novartis, Basel, Switzerland) is a novel oral benzodiazepine that inhibits the RSV N protein (29). The compound is undergoing phase I/II testing in transplant recipients. The novel fusion inhibitor TMC353121 (Tibotec Pharmaceuticals, Mechelen, Belgium) is also undergoing phase I testing in stem cell transplant recipients (J. Bonfanti, T. Gevers, C. Meyer, P. Timmerman, R. Willebrords, P. Van Remoortere, P. Wiger-

inck, and K. Andries, presented at the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, 17 to 20 September 2007). Another fusion inhibitor is RS 637, also known as VP14637 (RSVCO, Inc., Gaithersburg, MD); the compound is in late-stage preclinical development. BTA9881 is an F-protein inhibitor under phase I clinical development by Biota/MedImmune (131). siRNAs (Alnylam Pharmaceuticals, Cambridge, MA) have also been developed for aerosol delivery (45); ALN-RSV01 is presently undergoing phase II testing in adults experimentally infected with RSV.

With regard to prophylaxis, MedImmune (now Astra Zeneca, London, United Kingdom) has recently developed motavizumab, a next-generation monoclonal antibody for RSV that was engineered to have increased potency compared to palivizumab. *In vitro*, motavizumab binds to the RSV F protein 70-fold better than palivizumab, and it was selected from among other candidates due to its favorable pharmacokinetics and lung penetration (236). In cotton rats, motavizumab was approximately three- to fourfold more potent in reducing RSV titers in the lung than palivizumab; unlike palivizumab, it was also able to significantly reduce viral titers in the upper respiratory tract (236). In a recently completed phase III pivotal study of 6,600 infants at high risk for serious RSV infection, motavizumab reduced the incidence of hospitalization due to RSV infection by 26% and achieved a 50% reduction in the incidence of RSV-specific medically attended outpatient lower respiratory infections compared to palivizumab; no differences in adverse effects were reported (X. Carbonell, G. Losonsky, M. Hultquist, E. Connor, et al., presented at the Pediatric Academic Societies' Annual Meeting, Toronto, Ontario, Canada, 5 to 8 May 2007). Given its effectiveness in the cotton rat model, MedImmune is also currently exploring the use of motavizumab for the treatment of children who are hospitalized with RSV infection.

Adenovirus

Adenoviruses are associated with a wide variety of illnesses, including epidemic respiratory infections in closed populations (such as military recruits). In the absence of vaccination, a safe and effective antiviral would be welcomed for these populations; however, currently available agents do not have favorable risk/benefit ratios for an illness that is usually self-limited. Antiviral therapy for adenovirus infections is thus utilized primarily in the severely immunocompromised host for whom the risk for adenovirus-related mortality is high. Though no agents have been approved for the treatment of adenovirus infection, cidofovir and ribavirin have activity *in vitro*; clinical experience with these agents is summarized below.

Ribavirin. Clinical responses to ribavirin therapy among severely immunocompromised hosts with established adenovirus infections have been disappointing (126); this perhaps is attributable to the finding that ribavirin activity *in vitro* may be restricted to subgroup C isolates (143). Preemptive therapy, in which high-risk subjects are monitored for the presence of early adenovirus infection by PCR of the plasma and treated with antivirals before symptoms emerge, has also been attempted with ribavirin: one group reported virologic responses with preemptive ribavirin alone or ribavirin plus cidofovir in 21 of 26 children treated in this fashion, with five deaths (19%)

attributed to disseminated adenovirus disease in the absence of immunologic recovery (96).

Cidofovir. Cidofovir appears to be more clinically active than ribavirin (147). Administered intravenously, two cidofovir dosing regimens have been used for the management of adenoviral disease: a “high-dose” regimen of 3 to 5 mg/kg weekly for several weeks followed by every-other-week dosing (in line with the approved schedule for the treatment of cytomegalovirus retinitis) or a lower-dose, “renal-sparing” regimen of 1 mg/kg three times per week (115, 148, 150, 219, 241). A recent review of the literature identified 70 HCT recipients with definite or probable adenovirus disease who were treated with ≥ 2 doses of cidofovir; the overall mortality was 19% among these subjects (150). A noncomparative cohort study of cidofovir given with the low-dose protocol showed that it was safe and potentially effective for the treatment of adenovirus hemorrhagic cystitis in HCT recipients, with clinical improvements in 71% of patients (148). Preemptive therapy with cidofovir has also been attempted; a recent cohort of 177 highly immunosuppressed pediatric recipients of allogeneic stem cell transplantation treated with this strategy had only 2% adenovirus-associated mortality (241). However, the most immunosuppressed subjects (e.g., those who have received T-cell-depleted HCT) may still fail to control adenovirus viremia and succumb to adenovirus disease despite active surveillance and preemptive therapy with cidofovir, as seen in a recent series of patients from Vienna, Austria (122).

The most problematic issue with cidofovir remains its toxic effects on renal function, particularly when given to transplant recipients, who very commonly receive concomitant nephrotoxic medications. In one large series of HCT recipients treated with cidofovir for adenovirus infection, approximately one-third of subjects developed treatment-emergent renal toxicity (127).

Recently, lipid esters of both cidofovir and a related compound, HPMPA [(S)-9-(3-hydroxy-2-phosphonylmethoxypropyl)-adenine], have been developed that have promise for the treatment of adenovirus, poxvirus, and human herpesvirus infections (116, 175). Interestingly, these compounds appear not only to have resolved the issues surrounding oral bioavailability but also to have a lower potential for nephrotoxicity than cidofovir itself due to reduced distribution to the kidney (36). High antiadenovirus activity of these compounds has been demonstrated *in vitro* (147).

Human Rhinovirus

Despite intensive research and development efforts, there are no agents approved for the treatment or prevention of human rhinovirus infections. Investigational approaches to date have included IFNs, inhibitors of viral attachment and entry, and inhibitors of viral protease. In the following sections, we also briefly summarize studies of the use of zinc and echinacea for treatment of the common cold.

IFNs. Several studies have evaluated the efficacy and safety of intranasal recombinant IFN- α 2b in the prevention or treatment of human rhinovirus infections. While modest efficacy was shown with prophylactic use (74, 197), long-term intranasal administration of natural or recombinant IFN was associated with nasal irritation that appears to be preceded by IFN-

induced mucosal histologic changes, particularly lymphocytic infiltration (79). Moreover, treatment of symptomatic rhinoviral infections with intranasal IFN was ineffective (77). Development of these compounds has thus halted.

Attachment and entry inhibitors. Tremacamra (Boehringer Ingelheim, Ridgefield, CT) was a soluble form of ICAM-1 that was designed to interfere with the attachment of rhinovirus to endogenous ICAM-1 on target host cells. Intranasally applied tremacamra demonstrated small but statistically significant effects on symptom scores when given either before or after experimental challenge with human rhinovirus (213); clinical drug development did not progress, however, due to concerns about efficacy (when given more than 12 h after viral challenge) and patient acceptability (given the six-times-daily administration schedule).

Several capsid binding agents have been designed and have undergone clinical evaluation. The “WIN” series from the legacy Sterling Winthrop Pharmaceuticals was the first to be extensively studied; WIN51711 failed to progress due to drug-induced crystalluria in human volunteers, while WIN54954 demonstrated poor efficacy after experimental challenge, likely due to poor drug levels at the nasal mucosa (159). Pleconaril (WIN63843) was subsequently developed and was the first rhinovirus-targeted antiviral submitted for approval to the U.S. FDA. In two phase II studies of 1,024 immunocompetent subjects who were treated within 36 h of the onset of symptomatic URTI, pleconaril reduced the time to resolution of symptoms by 1 to 1.5 days in the subgroup of subjects (42%) with proven rhinoviral infections (75). Comparable results were observed in the 65% of subjects ($n = 1,363$) who were positive for picornavirus in the placebo-controlled phase III studies (75). Though the magnitude of clinical benefit appeared to be small, these effects were projected to have enormous economic benefits in terms of recouping lost productivity due to sick leave (142). However, subsequent prophylaxis studies demonstrated that pleconaril was a cytochrome P450 inducer, which led to intermenstrual bleeding and pregnancy in some women who took the drug together with oral contraceptives (55, 76). Concerns for this and other drug interactions and transmitted drug resistance (167), in addition to the modest efficacy, prompted the Antiviral Drugs Advisory Committee of the FDA to vote against a recommendation for approval in 2002. Schering-Plough (Kenilworth, NJ), under license from Viropharma, has reformulated pleconaril for intranasal delivery and resumed development.

Protease inhibitors. A virus-encoded 3C protease is critical for rhinoviral replication, and thus presents a rational target for drug development. Rupintrivir (AG7088) was developed as an intranasally administered 3C protease inhibitor with demonstrated potent activity *in vitro* against all human rhinovirus serotypes (160); it demonstrated moderate antiviral and clinical efficacy after experimental human challenge (78). Lack of efficacy in natural infection studies, however, led to termination of further development (159). Compound 1 was subsequently identified as an orally bioavailable inhibitor of 3C protease; though safe and well tolerated in phase I studies with healthy volunteers, further clinical development of this compound is not planned, likely due to marginal pharmacokinetics (159).

Zinc and echinacea. Zinc salts have long been known to be weak inhibitors of rhinovirus replication in vitro (107), possibly by the binding of zinc ions to rhinovirus surface canyons, thus inhibiting viral interaction with its surface receptor (154). The results of individual studies of oral zinc salts have been conflicting, and meta-analyses of clinical trials have shown no evidence of benefit (93). Perhaps this is unsurprising, since serum zinc concentrations are well below those required for a direct antiviral effect. However, trials of intranasally applied zinc have also shown mixed results (8, 145, 211). Preparations of echinacea are also widely used for the prevention and treatment of the common cold, with results that have been as varied as the number and nature of the preparations (212). A recent meta-analysis has concluded that though there is some evidence that preparations based on the aerial parts of *Echinacea purpurea* might be effective for the early treatment of colds in adults, results are not fully consistent (120).

HCoV

There is no specific antiviral therapy available for HCoV infections. The emergence of SARS-CoV has triggered the largest thrust of antiviral research for CoVs; therefore, we will review antivirals specific to SARS-CoV (67).

The sudden and severe nature of the SARS outbreak in 2002 and 2003 necessitated the use of empiric treatment strategies. A number of antiviral agents have been used to treat SARS, including ribavirin, lopinavir-ritonavir, and oseltamivir, but none were given in a controlled fashion, and the efficacy of these drugs has not been established. CoVs rely on a main 3C-like proteinase to process viral polyproteins for replication, which provides a prime target for the development of antivirals, aided by knowledge of the crystal structure (240). The polymerase, helicase, spike protein, and other proteases offer additional drug targets.

Ribavirin. Although ribavirin has not been shown to effectively inhibit SARS-CoV replication at high concentrations in Vero cells (38, 201), the use of other SARS-CoV-permissive animal and human cell lines has demonstrated inhibition of viral replication, particularly when ribavirin was used in combination with type I IFN (144). A number of reports describe the clinical use of ribavirin during the SARS outbreak. Although ribavirin was often administered, most studies employed other agents, including steroids and IFNs, making it difficult to determine specific antiviral effects of ribavirin (85, 113, 165, 209, 210, 221, 244). A recent systematic review of 30 studies describing the use of ribavirin treatment for SARS determined that 26 studies were inconclusive regarding treatment efficacy and that 4 publications presented evidence of possible harm (200). Hemolytic anemia, liver dysfunction, and electrolyte abnormalities were the main adverse events described, although the lack of control groups and concomitant treatment with other drugs make it difficult to determine causality (18, 103, 204, 233).

Protease inhibitors. The protease inhibitor combination lopinavir-ritonavir has been shown to have in vitro antiviral activity against SARS-CoV (31, 35). Two main clinical studies evaluated the effects of lopinavir-ritonavir during the SARS outbreak, which suggest that initial treatment with this drug was associated with a significantly lower risk of death and

development of acute respiratory distress syndrome than control treatment (27, 35). However, the antiviral effect was confounded by possible bias in the selection of the control group and treatment allocation (27, 35, 200). Other protease inhibitor compounds have been shown to inhibit SARS-CoV replication in vitro, including nelfinavir and calpain inhibitors (7, 239).

Attachment, entry, and fusion inhibitors. The membrane-associated carboxypeptidase angiotensin-converting enzyme 2 (ACE2) is a cellular receptor for SARS-CoV and interacts with the spike protein (119). ACE2 binding agents, neutralizing antibodies, or soluble forms of the receptor therefore offer options for candidate drugs (41, 87, 203). In animal models, administration of immune serum and monoclonal antibodies have demonstrated a reduction in SARS-CoV replication and reduced severity of disease (177, 202, 208). Data from clinical studies during the SARS outbreak using either convalescent plasma or intravenous immune globulin were inconclusive with regard to a beneficial effect (33, 84, 195, 200, 221). Fusion inhibitors against the SARS-CoV spike protein are also promising therapeutic candidates (19, 102, 124). Another target is cathepsin L, a lysosomal protease, which has been shown to be required for in vitro SARS-CoV infection. Inhibitors of cathepsin L blocked infection by SARS-CoV, but not HCoV-NL63, of ACE2-expressing cells (86, 188).

Steroids and IFNs. Systemic steroids were used extensively for therapy during the SARS outbreak in 2002 and 2003, generally in combination with ribavirin. Due to this concomitant drug use, it is difficult to determine whether steroids had a beneficial effect, and most studies are deemed inconclusive (200). Type I IFN compounds have been shown to inhibit SARS-CoV virus replication in vitro and in vivo in animal models (6, 37, 70, 82, 201, 206). IFN- β was shown to be more potent than IFN- α , and synergistic effects were reported for IFN- α with ribavirin, IFN- β with ribavirin, and IFN- β with IFN- γ (31, 144, 181, 182, 198). Two reports described the use during the SARS outbreak of IFN- α given with steroids and/or ribavirin, but the results in both cases are confounded by choice of control group, treatment bias, and lack of consistent treatment regimens (130, 244).

Other. The use of siRNAs targeting the spike gene and replicase 1A gene of SARS-CoV has inhibited gene expression and viral replication in SARS-CoV-infected cells (127, 243) and shown efficacy in SARS-CoV-infected macaques (118). In vitro studies suggest that additional compounds, such as glycyrrhizin (a component of licorice roots) (38), nitric oxide (99), niclosamide (235), cinanserin (a serotonin antagonist) (32), adamantane-derived bananins (207), and plant lectins (100) inhibit in vitro SARS-CoV replication. Existing drugs, natural products, and synthetic compounds continue to undergo high-throughput testing for evidence of anti-SARS CoV activity.

PIV, hMPV, and HBoV

There are no agents approved for the treatment of the PIVs, hMPV, or HBoV. Ribavirin is active against PIV in vitro and in animal models (64) and has thus been used for the treatment of pneumonia in immunocompromised hosts. Only anecdotal reports of the benefit of aerosolized or systemic ribavirin have been published; responses have been highly variable, reflecting

the confounding effects of illness severity, level of immunosuppression, and underlying disease (47, 58, 151, 227, 234). Indeed, in retrospective series of HCT recipients treated with aerosolized ribavirin with or without intravenous immunoglobulin, mortality was similar among subjects treated with ribavirin and those who were given only supportive care (151, 227). Promising targets for drug development exist, however; the viral hemagglutinin-neuraminidase (HN) that mediates binding and the adjacent fusion protein that HN activates after binding has occurred are particularly interesting targets. Now that the three-dimensional crystal structure for the human PIV type 3 HN has been elucidated (111), structure-function mapping is under way (171, 172) and HN inhibitors are being screened and tested in animal models. A novel HN inhibitor has been shown to effectively inhibit cell binding, neuraminidase activity, and growth of PIVs in tissue culture and in the lungs of infected mice (1). In addition, RNAi represents a promising strategy for PIV infections (10).

Though no agents are currently in development for the treatment of hMPV infections, ribavirin has shown activity in vitro (237) and in mouse models (72). Antibodies directed against the hMPV F protein have also been shown to protect hamsters against infection with hMPV (214), suggesting that passive immunoprophylaxis (analogous to that used for RSV infection) could be used to prevent severe hMPV infections in infants at greatest risk. As for RSV and PIV, RNAi may be an option for therapy of hMPV infections in the not-too-distant future (146).

Antivirals active against HBoV have not been described to date.

FUTURE DIRECTIONS

Given the high burden of disease in both immunocompetent and immunocompromised hosts, there remains a clear unmet medical need for antiviral drugs that target RV infections. The lack of rapid, sensitive, and inexpensive diagnostic tests that can distinguish a wide variety of respiratory pathogens at the point of care has been a key factor in slowing down interest in drug development. The absence of diagnostic platforms makes it difficult and time-consuming to assess the true burden of disease in various settings, but perhaps more importantly, it also restricts the ability to conduct clinical trials in settings other than highly specialized transplant centers. Although studies with transplant recipients are feasible, they are complex due to slow enrollment and are difficult to interpret due to confounding by underlying disease. Fortunately, recent technologic advances make it more likely that rapid and affordable multiplex testing will soon be available at the point of care, where the burden of disease is the greatest. Also, a recently developed human volunteer infection model for RSV has shown consistent infection rates and clinical disease following standardized inoculation (J. Devincenzo, J. Cehelsky, R. Meyers, A. Vaishnav, S. Nochur, K. Foote, T. Wilkinson, P. Meeking, A. Mann, E. Moane, J. Oxford, R. Studholme, P. Dorsett, and R. Lambkin-Williams, presented at the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, 17 to 20 September 2007). Proof-of-concept testing of new antiviral compounds in settings other than transplant

recipients may thus become easier; it is hoped that this will stimulate drug discovery and development.

There are also other ways to address the broad spectrum of possible pathogens that can cause clinical disease. One is the development of broad-spectrum antivirals. While respiratory symptoms are characteristically nonspecific and the spectrum of possible agents in cases of bronchiolitis, COPD exacerbation, or pneumonia is large, there are clearly a few pathogens that are both virulent and common. These may include RSV, PIVs, and possibly hMPV and the recently described CoVs. While these viruses do not share targets that are amenable to inhibition by a single small molecule, the use of combinations of safe and specific agents (including topically or systemically administered antibodies or siRNA) could be envisaged as a future approach.

Several alternative approaches are also possible. Nonspecific potentiators of the host response could be investigated, the failure of topical IFN notwithstanding. On the other hand, nonspecific attenuators of the host response (e.g., novel anti-inflammatory agents such as Toll-like receptor or chemokine antagonists) could be more effective than current analgesics in providing symptomatic relief from the common cold. Unfortunately, such immune modulation is not likely to be effective for those who are already immunocompromised.

Given that vaccines are not available for RVs other than influenza virus (and are not likely to be forthcoming for rhinovirus, the most prevalent etiologic agent, due to the multitude of serotypes), it is hoped that discovery and clinical development efforts continue for agents that may treat and prevent this common human condition, the "common cold."

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