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

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Antiviral Agents in the Critically Ill Child

Flor M. Munoz, MD

The treatment for most viral infections in children primarily is supportive. Severe viral illnesses and significant secondary complications that require treatment in the intensive care unit may occur in immunocompromised patients and also in infants and children who were previously healthy. Antiviral agents with specific activity against certain respiratory viruses, herpesviruses, and enteric viruses are available. New drugs are under development, and their use in pediatric patients is a subject of active research. The clinician's knowledge of the mechanisms of action, spectrum of activity, and side effects of these drugs is an important tool for their judicious use in the treatment of the critically ill child.

Copyright © 2000 by W.B. Saunders Company

Children are susceptible to infections caused by a variety of viral pathogens that result in a wide spectrum of disease manifestations. Infants and children who are previously healthy may have viral illnesses severe enough to require care in the pediatric intensive care unit. Viral infections might result in respiratory failure (eg, those caused by respiratory syncytial virus [RSV], influenza, parainfluenza, adenovirus), altered mental status associated with encephalitis or meningitis (eg, herpes simplex virus [HSV], enterovirus, arbovirus), dehydration and shock from severe gastroenteritis (eg, rotavirus, enterovirus), hepatitis and liver failure (hepatitis viruses B and C), or multiorgan involvement. Immunocompromised children are susceptible to common viruses and develop more severe local or disseminated disease. These viruses include members of the herpesvirus family such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), and varicella-zoster virus (VZV). This review describes the antiviral agents currently available and their use in the treatment of common viral infections in critically ill children. The treatment of human immunodeficiency virus (HIV) infection is beyond the scope of this review. Table 1 summarizes the most important causes of viral illnesses in children admitted to the intensive care unit and current options for treatment or prophylaxis.

Respiratory Infections

Viral respiratory infections are a leading cause of morbidity, mortality, and significant economic expense throughout the world. In the United States, acute viral respiratory disease requires medical attention in 80 percent of children younger than 5 years and almost 50 percent of those 5 to 17 years of age. In children hospitalized for an acute respiratory illness, RSV is the pathogen most frequently encountered, followed by parainfluenza 1, 3, and 2, and influenza A and B viruses. The pathogenesis of disease caused by these viruses involves direct epithelial cell injury of bronchioles, edema, and mucus plugging of the airways. Other important pathogens include adenovirus, rhinovirus, and respiratory coronaviruses. Infection with these viruses may result in severe lower respiratory tract disease or may precipitate acute exacerbations of underlying pulmonary conditions such as asthma and cystic fibrosis. In a recent survey, 80 to 85 percent of episodes of acute asthma in school children were associated with a respiratory virus infection, and rhinovirus accounted for 50 percent of the isolates.

The treatment of most viral infections essentially is supportive, and the number of efficacious antiviral drugs currently available is limited (Table 2). Aerosolized ribavirin has been used to treat RSV infections, and oral amantadine and rimantadine are available for the treatment and prophylaxis of influenza A infection. Newer agents with activity against both influenza A and B viruses, the neuraminidase inhibitors, have become available recently but are not licensed for use in children yet. Newer compounds active against paramyxoviruses, rhinoviruses, and other picornaviruses are under investigation. No proven efficacy of any drug in the treatment of adenovirus infections has been shown.

Antiviral Drugs Against Respiratory Viruses

Ribavirin

Ribavirin is a synthetic nucleoside analogue of guanosine and inosine. It is converted by cellular enzymes to active monophosphate and triphosphate forms. Its exact mechanism of action is unknown. Ribavirin exhibits in vitro activity against many RNA and DNA viruses and has been reported to have clinical efficacy against RSV and influenza A and B viruses, hantavirus, and Lassa fever virus. Aerosolized ribavirin currently is indicated for treating RSV lower respiratory tract infection in selected high-
risk populations. Conditions associated with high risk during RSV infection include complicated congenital heart disease, underlying chronic lung disease, primary or acquired immunosuppression, prematurity, age less than 6 weeks, certain debilitating conditions (eg, neuromuscular disease), and severe illness requiring mechanical ventilation. Administration early in the course of RSV disease in immunocompromised and high-risk patients may be beneficial, the efficacy of ribavirin in critically ill children who previously were healthy has not been proved. Ribavirin is not licensed for the treatment of influenza. Anecdotal reports indicate efficacy against measles and adenovirus infections (aerosol and intravenous forms), but no controlled trials have been performed to date. Oral ribavirin in combination with interferon alfa is indicated for treating hepatitis C. This combination also inhibits the replication of subacute sclerosing panencephalitis virus infection in vitro and results in improved survival of infected hamsters, but no clinical studies have been performed.

Administration of ribavirin for inhalation requires the use of a small particle (<4 µm) aerosol generator (SPAG) and a delivery rate of 12.5 L/min. The daily recommended dose (6 g/d) can be administered at a standard concentration (20 mg/mL) over 12 to 18 hours or at higher concentrations (60 mg/mL) over shorter periods (eg, 2 h three times/d) for a total duration of 3 to 6 days. When given to children who require mechanical ventilation, aerosolized ribavirin does not significantly affect the respiratory system mechanics. However, malfunction of ventilator delivery systems can occur because of drug crystallization and precipitation. Potential side effects include induction of bronchospasm, headache, rash, and conjunctivitis in both patients and caretakers. When used systemically, loading and maintenance doses are necessary, and ribavirin can cause anemia, resulting from extravascular hemolysis (at low doses) or bone marrow suppression (at high doses), and hyperbilirubinemia. Teratogenicity has been documented only in animal species. Resistance has not been described.

**Table 1. Etiology of Viral Infections in the Critically Ill Pediatric Patient and Current Antiviral Treatment Options**

| Typical Disease                          | Virus              | Antiviral Agent                                      |
|-----------------------------------------|--------------------|------------------------------------------------------|
| **Respiratory tract infections**        | RSV                | Ribavirin, protease inhibitors (AG7088)†             |
|                                        | Influenza viruses A and B | Amantadine, rimantadine,* neuraminidase inhibitors (zanamivir* and oseltamivir†) |
|                                        | Parainfluenza 1, 2, 3 | Paramyxovirus fusion protein inhibitors†             |
|                                        | Adenovirus         | NA                                                   |
|                                        | Rhinovirus         | Protease inhibitors (AG7088),† pleconaril†          |
| **Central nervous system infections**   | HSV                | Acyclovir, valacyclovir,* famcyclovir,* pencyclovir,* foscarnet,* cidofovir* |
|                                        | Enterovirus        | Pleconaril†                                         |
|                                        | Arbovirus          | NA                                                   |
| **Systemic infections**                 | CMV                | Ganciclovir, foscarnet,* cidofovir*                  |
|                                        | EBV                | Cidofovir,* foscarnet,* interferon-α†               |
|                                        | VZV                | Acyclovir, valacyclovir,* famcyclovir,* pencyclovir,* foscarnet* |
| **Gastrointestinal tract infections**   | Hepatitis C        | Interferon α + ribavirin*                            |
|                                        | Hepatitis B        | Interferon alfa                                     |
|                                        | Rotavirus/enterovirus | NA                                             |
|                                        | Enterovirus        | Pleconaril†                                         |

*Not licensed for use in children.
†Investigational drug.

**Table 2. Antiviral Drugs Active Against Respiratory Viruses and Picornaviruses**

| Antiviral Drug | Mechanism of Action | Indication/Comment                                      |
|---------------|---------------------|--------------------------------------------------------|
| Ribavirin     | Not fully defined, related to interference with viral mRNA formation and inhibition of protein synthesis | Aerosolized form: High-risk RSV lower respiratory tract disease
| Amantadine    | Blockage of H* channel reduces intracellular acidification necessary for fusion of influenza A virus to host cell endosome and release of viral RNA | Intravenous: Lassa fever
| Rimantadine   |             | Oral: Hepatitis C
|               |             | Resistance not identified                              |
| Zanamavir     | Inhibition of neuraminidase | Prophylaxis and treatment of influenza A, without effect on B
| Oseltamivir   | Inhibition of 3C protease | Rapid and frequent resistance because of point mutations of M2 protein
| AG7088        |             | Treatment of influenza A and B
| Pleconaril    | Inhibition of viral replication by blocking virus attachment or uncoating through capsid binding | Resistance very rare
|               |             | In vitro efficacy against picornavirus, particularly rhinovirus
|               |             | Oral compound active against picornavirus; clinical studies in progress |
**Paramyxovirus Fusion Protein Inhibitors**

RSV, parainfluenza, and measles viruses belong to the Paramyxovirus family. These viruses contain two major surface glycoproteins: a receptor binding protein that facilitates attachment to host cells and a fusion protein required for release of the genome-containing nucleocapsids into the cell cytoplasm. Active peptides derived from specific regions within the transmembrane fusion protein of RSV and parainfluenzae 3 virus have been identified. These active peptides exhibit antiviral activity against paramyxoviruses in vitro and against RSV in vivo in a cotton rat model. A potential for the development of synthetic active peptides against paramyxoviruses exists, as similar compounds have been developed against HIV-1.

**Amantadine/Rimantadine**

Amantadine (1-adamantanamine hydrochloride) and its α-methyl derivative, rimantadine, are primary symmetrical amines that interfere with the transmembrane transport of hydrogen (H⁺) initiated by the influenza A membrane protein M2. They inhibit the uncoating and replication of all human influenza A virus subtypes (H1N1, H2N2, H3N2), but they have no effect on influenza B viruses. Oral formulations have been shown to be efficacious in reducing the severity and duration of influenza A illness when administered within the first 48 hours of the onset of symptoms and have been licensed in the United States for the prophylaxis and treatment of influenza A infection. Rimantadine has not been approved by the Food and Drug Administration (FDA) for use in children, but frequently it is preferred because it exhibits fewer side effects than does amantadine and its longer half-life allows once-a-day dosing. Side effects are similar to those induced by antihistamines (nausea, vomiting, drowsiness, difficulty concentrating, agitation), and both may induce seizures in individuals with a history of seizure disorders. Resistance to both drugs develops frequently and rapidly during therapy because of a single amino acid mutation of the RNA sequence encoding for the influenza A M2 protein. This phenomenon has been described in hospitalized pediatric populations and is a concern, particularly because of the risk of transmission of resistant strains of influenza A to susceptible patients within hospital units such as the intensive care unit. In outbreak situations within a hospital unit, amantadine and rimantadine can be used for the prophylaxis of children at risk who cannot be immunized with inactivated influenza vaccine.

**Neuraminidase Inhibitors**

Neuraminidase is a viral enzyme that cleaves terminal sialic acid residues from glycoconjugates, enabling the release of influenza viruses from infected cells and preventing viral aggregation and inactivation by respiratory mucus. The enzyme’s active site is highly conserved in the surface of influenza A and B viruses. Two neuraminidase inhibitors active against both influenza A and B are now available for clinical use: inhaled zanamavir and oral oseltamivir (GS4104), the ethyl ester prodrug of GS4071, which is the active compound.

Inhaled zanamavir has been well tolerated and very effective (>80%) in preventing infection and febrile illness in animal and human experimental influenza A infection. In a recent randomized, placebo-controlled trial, zanamavir administered once daily during the influenza season in healthy adult volunteers was 67 percent efficacious in preventing culture-confirmed clinical influenza and 84 percent efficacious in preventing culture-confirmed febrile illness. Clinical studies are investigating the use of zanamavir for postexposure prophylaxis in institutions and for the prevention of nosocomial influenza.

When administered within the first 30 hours of illness to ambulatory adults with acute influenza, zanamavir reduces the duration of symptoms by up to 3 days. Similar results are observed in patients as young as 12 years with underlying lung disease. The use of nebulized zanamavir in hospitalized patients with influenza lower respiratory tract disease is being studied in controlled clinical trials. This nebulized preparation has been given to patients receiving mechanical ventilation through a compassionate use protocol. Inhaled zanamavir is approved for the treatment of influenza A and B infections in patients 12 years of age and older. Zanamavir has a potential role as a prophylactic agent for nonimmunized and high-risk individuals, but further studies in the latter population are necessary. The use of zanamavir in children deserves consideration as well, particularly because treatment with this drug is associated with a lower incidence of middle ear pressure abnormalities during influenza illness, but the current method of drug delivery might be problematic in the younger patients.

Oseltamivir, the prodrug of GS41071, a potent carbocyclic transition state analogue inhibitor of influenza neuraminidase, has the advantages of a good oral bioavailability (70%) and a long plasma half-life (7-9 hours) that allows less frequent dosing. The active compound provides protection against experimental influenza in animal and human studies and against natural infection in healthy adults (>80% efficacy) given a once-daily dose during the influenza season. When used as treatment within the first 36 hours of onset of illness, oseltamivir reduces the severity and the duration of influenza symptoms by 1.5 days. The use of oseltamivir in high-risk populations and children is being studied. Resistance to neuraminidase inhibitors can occur by mutations (amino acid substitutions) in either of the two major surface glycoproteins, hemagglutinin or neuraminidase. Albeit rare, this phenomenon occurred in vivo in an immunocompromised child with influenza B pneumonia after 7 days of treatment with zanamavir.

**Protease Inhibitors and Antipicornavirus Agents**

Human rhinoviruses belong to the Picornaviridae family. Picornaviruses are a known cause of conjunctivitis, lower respiratory tract disease, acute gastroenteritis, aseptic meningitis, and encephalitis, in addition to the common cold. Currently, no antiviral agents are available to treat diseases caused by picornaviruses, but potential drugs are being developed.

AG7088 is an irreversible, peptidomimetic inhibitor of 3C protease, an enzyme present in rhinoviruses and several related picornaviruses, responsible for the cleavage of viral precursor polyproteins into structural and enzymatic proteins. In vitro,
AG7088 has been found to potently inhibit the replication of 48 rhinovirus serotypes, coxsackieviruses A21 and B3, enterovirus 70, and echovirus 11 in a dose-dependent fashion. A formulation for intranasal administration has been developed, and clinical studies are expected in the near future.

Pleconaril is an investigational compound that inhibits viral replication and shows in vitro activity against all picornaviruses. Pleconaril binds to the capsid of viruses, inhibiting attachment and virus uncoating. It is readily absorbed by the oral route with a bioavailability of 70 percent, reaching higher drug concentrations in the meninges, liver, and nasal epithelium than in plasma because of its lipophilic properties. In studies of experimental respiratory infection and in placebo-controlled studies of viral meningitis in adults and children, pleconaril has been shown to reduce the severity and duration of symptoms when administered within 48 hours of onset of illness. Controlled clinical trials of pleconaril in the treatment of rhinovirus diseases and enteroviral meningitis in children are in progress.

Central Nervous System and Disseminated Viral Infections

Human herpesviruses are common causes of mucocutaneous infections in immunocompetent and immunocompromised children. HSV-1 is the most important cause of sporadic viral central nervous system infection, followed in frequency by seasonal viruses such as enteroviruses and arboviruses. Herpesviruses are not uncommon causes of severe, life-threatening conditions in previously healthy children who develop complications or dissemination of initially localized infections (such as VZV) and in immunocompromised children, who are also more susceptible to extensive disease caused by other herpesviruses such as CMV, EBV, and human herpesvirus 6 (HHV-6).

Antiviral Drugs for Herpesviruses

Numerous antiviral agents are available for the treatment and prophylaxis of herpesvirus infections. In general, the agents are categorized in two major classes: the nucleoside analogues, which include most anti-herpesvirus drugs, and the pyrophosphate analogue foscarnet (Table 3). Nucleoside analogues require conversion to monophosphate, diphosphate, or triphosphate forms by cellular or viral kinases to selectively inhibit viral replication; foscarnet does not.

Acyclovir/Valacyclovir

Acyclovir is a synthetic acyclic purine nucleoside analogue of guanosine. Valacyclovir is the L-valyl ester of acyclovir and is three to five times more bioavailable than is acyclovir. Hydrolysis of valacyclovir to acyclovir occurs in the intestinal wall and the liver. Acyclovir is catalyzed by herpesvirus thymidine kinase to acyclovir monophosphate and then transformed to the active compound acyclovir triphosphate by cellular kinases. The active drug inhibits viral DNA polymerase by acting as an immediate DNA chain terminator. Acyclovir is active against HSV-1 (most sensitive virus), HSV-2 (twofold less susceptible than HSV-1), and VZV (requires higher doses than HSV) but has limited activity against CMV, EBV, and HHV-6, which lack thymidine kinase.

Oral, topical, and intravenous preparations of acyclovir are available and efficacious for the treatment of children with HSV mucocutaneous disease, encephalitis, and neonatal infection, and primary and recurrent VZV infections. Intravenous administration is required for treating any invasive disease and preventing dissemination of mucocutaneous infection in immunocompromised hosts. Administration early in the course of the disease is more beneficial. Valacyclovir is available only in a tablet form, and its safety and effectiveness have not been

| Antiviral Drug | Mechanism of Action | Indication/Comment |
|---------------|---------------------|--------------------|
| Nucleoside analogues | DNA chain terminator and inhibition of DNA polymerase | Most useful in the treatment of HSV and VZV infections |
| Foscarnet | Inhibition at pyrophosphate binding site of DNA polymerase or reverse transcriptase | Acyclovir-resistant HSV, ganciclovir-resistant CMV |
| Valacyclovir | DNA chain terminator | Resistance: mutations of thymidine kinase |
| Penciclovir | DNA chain inhibitor and inhibition of DNA polymerase | Oral formulations licensed for adults only |
| Famciclovir | DNA chain inhibitor and inhibition of DNA polymerase | Topical treatment for adults only |
| Trifluridine | Inhibition of DNA polymerase | Resistance: similar to acyclovir |
| Idoxuridine | - | Significant toxicity |
| Ganciclovir | DNA chain terminator and inhibition of DNA polymerase | Most useful against CMV |
| Vidarabine | DNA chain terminator and inhibition of DNA polymerase | Resistance: mutations of DNA polymerase, phosphoryl transferase, and thymidine kinase |
| Cidofovir | Inhibition of DNA polymerase or DNA chain terminator | Alternative for acyclovir-resistant HSV and ganciclovir/foscarnet-resistant CMV |

Table 3. Antiviral Drugs Active Against Herpesviruses
established in children. When administered intravenously, acyclovir can crystallize and precipitate in the renal tubules. This can be minimized by slowing infusion rates and by ensuring adequate hydration. Other side effects include local phlebitis, elevation of blood urea nitrogen (BUN) and serum creatinine levels, neutropenia, nonspecific gastrointestinal symptoms (nausea, vomiting, diarrhea), and encephalopathic changes (obtundation, seizures). Adjustment of dose is required with impaired renal function. Resistance to acyclovir occurs by mutations that result in deficiency or alterations of thymidine kinase or viral DNA polymerase. Resistance is more likely to occur with prolonged exposure or suboptimal dosing and in immunocompromised patients. Foscarnet or cidofovir are alternatives for acyclovir-resistant HSV and VZV.

**Famciclovir/Penciclovir**

Famciclovir is the synthetic acyclic guanine derivative prodrug of penciclovir. Famciclovir is readily absorbed after oral administration and is converted to the active triphosphate form penciclovir by viral thymidine kinases like acyclovir. Unlike acyclovir, penciclovir is not an obligate DNA chain terminator, but it effectively inhibits DNA chain elongation. It also exhibits a less powerful inhibition of viral DNA polymerases. However, famciclovir’s higher oral bioavailability and longer intracellular half-life ensure more prolonged antiviral activity and allow for lower and less frequent dosing. Clinical indications, adverse events, and mechanisms of resistance of these drugs are similar to those of acyclovir and valacyclovir. Safety and efficacy data are not available for children.

**Trifluridine and Idoxuridine/Vidarabine**

Trifluridine and idoxuridine are thymidine nucleoside analogues used for the topical treatment of HSV infections such as primary keratoconjunctivitis and recurrent epithelial keratitis. Both require phosphorylation to an active triphosphate form and have significant side effects and toxicity (local irritation, corneal and conjunctival edema, increased intraocular pressure, and photophobia). Only trifluridine is licensed for use in the United States. This compound also has been used topically for the treatment of acyclovir-resistant chronic mucocutaneous genital HSV infections in HIV-infected patients.

Vidarabine (adenine arabinoside or Ara-A) has antiviral activity against HSV-1 and HSV-2, vaccinia virus, and VZV. Intravenous vidarabine is rapidly deaminated in vivo to a less active compound, arahypoxanthine, and is associated with significant toxicity, which limits its use. Trifluridine is preferred for the treatment of HSV keratoconjunctivitis because vidarabine can cause significant local eye irritation. Resistance to this agent has not occurred in the clinical setting.

**Ganciclovir**

Ganciclovir is a nucleoside analogue of guanine that can undergo transformation to ganciclovir monophosphate by two viral-specific enzymes: a phosphotransferase encoded by the UL-97 gene of CMV and the thymidine kinase of HSV. Activation to its triphosphate form is accomplished by cellular kinases. Ganciclovir inhibits viral DNA synthesis by directly terminating viral DNA elongation and by competitive inhibition of DNA polymerase. Although ganciclovir has in vitro activity against HSV and VZV, it is 100 times more potent against CMV.

Ganciclovir is indicated for the treatment of CMV retinitis, encephalitis, pneumonitis, esophagitis, hepatitis, and colitis; it is used in the prophylaxis of CMV retinitis and in selected CMV-seropositive immunocompromised patients (ie, bone marrow and solid organ transplant recipients). Limited data in children suggest safety and efficacy similar to those in adults. The combination of ganciclovir with CMV immune globulin intravenously has been used for treatment and prophylaxis of CMV disease in immunocompromised patients. Ganciclovir also may have a role in the prophylaxis of EBV lymphoproliferative disease in transplant recipients. The use of ganciclovir in congenital CMV disease is under investigation and not routinely recommended. Antiviral treatment in this population is unlikely to have an effect on tissue injury that occurred antenatally.

Significant toxicity that commonly occurs with intravenous administration of ganciclovir includes bone marrow depression (granulocytopenia, anemia, and thrombocytopenia), elevation of hepatic transaminases and serum BUN and creatinine levels, and, less frequently, nonspecific gastrointestinal complaints, headache, and rash. Dose adjustment is required with impaired renal function. Concomitant use of nephrotoxic drugs increases ganciclovir nephrotoxicity. Immune compromised patients often require prolonged therapy with ganciclovir, increasing the chances of toxicity and development of resistance. Resistance occurs through mutations of the genes encoding for viral DNA polymerase, CMV phosphotransferase, or HSV thymidine kinase. Therefore, ganciclovir-resistant CMV may not be susceptible to treatment with acyclovir and requires the use of agents with different mechanisms of action, such as cidofovir and foscarnet.

**Cidofovir**

Cidofovir is a new acyclic nucleoside monophosphate derivative. Because of the presence of a phosphonate group, initial phosphorylation by viral-specific enzymes is not required. Cidofovir is phosphorylated by host cell enzymes to its active diphosphate form, which selectively inhibits viral DNA polymerase through competitive inhibition or DNA chain termination. Cidofovir is a potent inhibitor of viral replication, with activity against CMV and other herpesviruses (including HSV, VZV, and EBV). Given that initial phosphorylation by viral enzymes is bypassed by cidofovir, it is the drug of choice for acyclovir-resistant HSV and ganciclovir- or foscarnet-resistant CMV. The active diphosphate form has a long intracellular half-life, allowing for long intervals of administration between doses (once weekly). Cidofovir is additive or synergistic against CMV in vitro when combined with acyclovir, ganciclovir, and foscarnet. The most significant adverse effect is nephrotoxicity (proximal tubular dysfunction), which can be reduced by oral probenecid and adequate hydration before treatment. Other adverse reactions include neutropenia, peripheral neuropathy, and ocular hypotonia. Viral resistance conferred by mutations in DNA polymerase has been shown in vitro but has not occurred in patients treated with cidofovir.
**Foscarnet**

Foscarnet (trisodium phosphonoformate) is an organic analogue of inorganic pyrophosphate. Phosphorylation by viral or host cell kinases is not required for activation of this compound. Its mechanism of action is preventing elongation of DNA chains through selective inhibition at the pyrophosphate binding site of viral DNA polymerase and retroviral reverse transcriptase, at concentrations that do not inhibit cellular DNA polymerase. Foscarnet has antiviral activity against HSV-1 and HSV-2 (including acyclovir-resistant strains), VZV, CMV (including ganciclovir-resistant strains), EBV, HHV-6, hepatitis B virus, and HIV-1.

Foscarnet currently is indicated for treatment of CMV retinitis in HIV-infected patients and for acyclovir-resistant HSV infections in immunocompromised hosts. Acyclovir-resistant VZV also has been treated successfully with foscarnet. Its use should be limited because of the occurrence of significantly more adverse events than occur with ganciclovir. Intravenous administration of foscarnet commonly results in phlebitis, nausea and diarrhea, anemia and granulocytopenia, nephrotoxicity, electrolyte disorders (hypocalcemia, hypokalemia, hypomagnesemia, hypophosphatemia or hyperphosphatemia), and seizures. The excretion of the drug in urine may result in genital ulceration. Concomitant administration of nephrotoxic drugs should be minimized, and serum calcium levels should be monitored closely in patients receiving intravenous pentamidine. In animal studies, foscarnet has been shown to affect the development of tooth enamel and bones. Because resistance to foscarnet may develop by mutations in the viral DNA polymerase, acyclovir-resistant HSV and ganciclovir-resistant CMV viruses that have these mutations might also develop resistance to foscarnet.

**Viral Infections of the Gastrointestinal Tract**

Most viral infections that cause gastroenteritis are self-limited and require only supportive therapy. Hepatitis viruses can cause acute and chronic disease in children. Children younger than 19 years account for 10 percent of patients with primary hepatitis B virus (HBV) infection each year. The epidemiology of hepatitis C virus (HCV) infection in children is less well characterized in the United States, but its incidence is likely to be similar or less. The majority of children with HBV or HCV infection are asymptomatic. However, 20 to 50 percent of children and 90 percent of neonates infected with HBV have persistent infection, and the majority of children infected with HCV have chronic infection that may progress to cirrhosis. Both viruses are associated with the development of hepatocellular carcinoma. Risk factors for HBV and HCV infection include parental exposure to blood products, parenteral drug use, hemoglobinopathies, heterosexual or homosexual activity, and maternal infection during pregnancy. Numerous potential drugs are available for the treatment of hepatitis B and C (Table 4). Of these, interferon alfa has been modestly efficacious, with increased efficacy when used in combination with ribavirin.

**Antiviral Drugs for Hepatitis B and C Viruses**

**Interferon Alfa/Ribavirin**

Interferons are cytokines released by virus-infected host cells. Uninfected cells acquire resistance to RNA and DNA viruses by binding and internalizing interferons. Although their exact mechanism of action is not totally understood, interferons activate cellular mechanisms that induce the release of enzymes causing degradation of viral mRNA and inhibition of viral protein synthesis.

Recombinant interferon alfa-2b is licensed in the United States for the treatment of chronic HBV infection in adults and children. Subcutaneous administration three times a week for 6 months results in normalization of liver transaminase levels and seroconversion (presence of antibody to hepatitis B e antigen [HBeAb] and absence of hepatitis B e antigen [HBeAg]) in 40 to 50 percent of adult patients. Controlled clinical trials suggest similar response rates (range, 20% to 58%) in children living in Western countries but lower response rates in Asian children. The response rate is lower in those who acquire HBV in the neonatal period and higher with higher doses of interferon. Response rates (defined as absence of HCV DNA in serum) are similar when interferon alfa is used in the treatment of adults with hepatitis C, but a relapse rate of 30 percent occurs after completion of therapy (net persistent response rate of 5% to 20%). Nonresponders show no improvement with repeated treatment, higher doses, or longer duration of therapy. Clinical studies in children are limited, but as with HBV, similar response and relapse rates are observed in children with HCV. When used in combination with orally administered ribavirin, the persistent response rate of interferon alfa in the treatment of HCV increases to 49 percent. Interferon alfa might also be useful in the treatment of EBV lymphoproliferative disease.

| Table 4. Antiviral Drugs Active Against Hepatitis B and C Viruses |
| --- |
| **Antiviral Drug** | **Mechanism of Action** | **Indication/Comment** |
| Interferon alfa-2a | Inhibition of viral protein synthesis through activation of host cellular enzymes that degrade viral mRNA | Investigational |
| Interferon alfa-2b | Inhibition of viral protein synthesis through activation of host cellular enzymes that degrade viral mRNA | Chronic and recurrent HBV and HCV infection |
| Interferon alfa-n3 | Inhibition of DNA polymerase | Chronic and recurrent HBV and HCV infection |
| Lamivudine and ribavirin | Inhibition of DNA polymerase | Investigational |
| Famciclovir | Inhibition of DNA polymerase | Investigational |
| Tenofovir | Inhibition of DNA polymerase | Investigational |
| Adefovir | Inhibition of DNA polymerase | Investigational |
Side effects of interferon therapy that are frequent but transient include fever, headache, malaise, thrombocytopenia, and leukopenia. Less frequently, alopecia, prolonged fatigue, and depression may occur. The need for repeated parenteral administration and the lack of sustained response in most patients implies an adequate selection of subjects that should receive treatment with interferon. In the case of HBV, better response rates are observed in non-Asian children with infection acquired beyond the neonatal period, who have mild pretreatment elevations of liver enzymes and liver histology, and lower baseline serum HBV DNA or hepatitis B core antigen (HBcAg) concentrations.

**Lamivudine and Other Compounds**

Nucleoside analogues such as lamivudine, famciclovir, adefovir, and tenofovir inhibit HBV replication in vitro by inhibiting DNA polymerase. Although these agents have been efficacious in experimental animal studies and reduce HBV DNA levels in patients with chronic HBV infection, long-term treatment is required, which in turn has been associated with the development of resistant mutations in HBV DNA polymerase (with the exception of adefovir). Combination therapy is under investigation.

**Summary**

Viral infections are the most common cause of morbidity in pediatrics. The majority of children have viral illnesses that do not require hospitalization. However, severe illness, complications, and secondary bacterial infections that require treatment in the pediatric intensive care unit also occur. Infants, young children, and patients with certain underlying conditions are more commonly admitted to the intensive care unit. Prevention through immunization is possible for influenza and hepatitis B virus infections, and it should be encouraged, particularly in high-risk populations. Passive prophylaxis with intravenous immunoglobulin for high-risk groups is available for RSV and CMV, and monoclonal antibody products are now available for RSV as well. The number of drugs becoming available for treating severe viral infections in children is increasing. However, it is important to keep in mind that their efficacy might be limited by the need for administration early during the course of disease (and therefore for adequate diagnostics), their frequent toxicity, and the development of resistance. Adequate supportive therapy continues to be the cornerstone in the treatment of severe viral infections in children. The knowledge of the currently available antiviral agents and their particular indications and side effects, along with a selective and judicious use of these drugs, will enhance the clinician’s capability to achieve a successful outcome in the critically ill child.

**References**

1. Acute respiratory infections: The forgotten pandemic. Communique from the International Conference on Acute Respiratory Infections. Canberra, Australia, 7-10 July 1997. Int J Tuberc Lung Dis 2:2-4, 1998
2. Kaiser L, Couch RB, Galasso GJ, et al: First International Symposium on Influenza and Other Respiratory Viruses: Summary and overview. Kapalua, Maui, HI, December 4-6, 1998. Antiviral Res 42:149-176, 1999
3. Update: Respiratory syncytial virus activity—United States, 1997-1998 season. MMWR 47:1043-1045, 1998
4. Johnston SL, Pattermore PK, Sanderson G, et al: Community study of role of viral infection in exacerbations of asthma in 9-11 year old children. BMJ 310:1225-1229, 1995
5. American Academy of Pediatrics Committee on Infectious Diseases: Reassessment of the indications for ribavirin therapy in respiratory syncytial virus infections. Pediatrics 97:137-140, 1996
6. Moler FW, and the Pediatric Critical Care Study Groups: Effectiveness of ribavirin in otherwise well infants with respiratory syncytial virus associated respiratory failure. J Pediatr 128:422-428, 1996
7. Takahashi T, Hosoya M, Kimura K, et al: The cooperative effect of interferon alpha and ribavirin on subacute sclerosing panencephalitis (SSPE) virus infection, in vitro and in vivo. Antiviral Res 37:29-35, 1998
8. Jefferson LS, Coss Bu JA, Englund JA, et al: Respiratory system mechanics in patients receiving aerosolized ribavirin during mechanical ventilation for suspected respiratory syncytial viral infection. Pediatr Pulmonol 20:117-124, 1999
9. Janai HK, Marks MI, Zaleska M, et al: Ribavirin: Adverse drug reactions, 1986 to 1998. Pediatr Infect Dis J 9:209-211, 1990
10. Hunt-Fujigaki A, Murray DL: Adverse reactions to ribavirin. Pediatr Infect Dis J 19:680-681, 1990
11. Reichard O, Schwarcz R, Weiland O: Therapy of hepatitis C: Alpha interferon and ribavirin. Hepatology 26:1088-1118, 1997 (suppl 1)
12. Joshi SB, Durie RE, Lamb RA: A core trimmer of the paramyxovirus fusion protein, parallels to influenza virus hemagglutinin and HIV-1 gp120. Virology 248:20-34, 1998
13. Wild C, Greenwell T, Matthews T: A synthetic peptide from HIV-1 gp21 is a potent inhibitor of virus mediated cell-cell fusion. AIDS Res Hum Retroviruses 9:1051-1053, 1993
14. Van Loris LP, Newell PM: Antivirals for the chemoprophylaxis and treatment of influenza. Semin Respir Infect 7:61-70, 1992
15. Belshé RB, Burk B, Newman F, et al: Resistance of influenza A virus to amantadine and rimantadine: Results of one decade of surveillance. J Infect Dis 139:430-435, 1979
16. Munoz FM, Campbell JR, Atmar RL, et al: Influenza A virus outbreak in a neonatal intensive care unit. Pediatr Infect Dis J 18:411-415, 1999
17. Hayden FG, Belshé RB, Clover RD, et al: Emergence and apparent transmission of rimantadine resistant influenza A virus in families. N Engl J Med 321:1686-1702, 1989
18. Hayden FG, Gwaltney JM: Viral infections, in Murray JF, Nadel JD (eds): Textbook of Respiratory Medicine. Philadelphia, PA, Saunders, 1994, pp 977-1035
19. Ryan DM, Teichhurst J, Dempsey MH, et al: Inhibition of influenza virus replication in mice by GG167 (4-guanidino-2,4-dideoxy-2,3-dehydro-N-acetylenuraminic acid) is consistent with extracellular activity of viral neuraminidase (sialidase). Antimicrob Agents Chemother 38:2270-2275, 1994
20. Hayden FG, Treanor JJ, Betts RF, et al: Safety and efficacy of the neuraminidase inhibitor GG167 in experimental human influenza. JAMA 273:295-299, 1996
21. Monto AS, Robinson DP, Herlocher ML, et al: Zanamivir in the prevention of influenza among healthy adults. A randomized controlled trial. JAMA 282:31-35, 1999
22. Hayden FG, Osterhaus ADME, Treanor JJ, et al: Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza virus infections. N Engl J Med 337:674-679, 1997
23. The MIST (Management of Influenza in the Southern Hemisphere Trialists) Study Group. Randomised trial of efficacy and safety of
inhaled zanamavir in treatment of influenza A and B virus infections. Lancet 352: 1877-1881, 1998

24. Walker JB, Hussey EK, Treanor JJ, et al: Effects of the neuraminidase inhibitor zanamavir on otologic manifestations of experimental human influenza. J Infect Dis 176:1417-1422, 1997

25. Li W, Escarpe PA, Eisenberg EJ, et al: Identification of GS4104 as an orally bioavailable prodrug of the influenza virus neuraminidase inhibitor GS4071. Antimicrob Agents Chemother 42:640-646, 1998

26. Sidwell RW, Huffman JH, Barnard DL, et al: Inhibition of influenza virus infections in mice by GS4104, an orally effective influenza virus neuraminidase inhibitor. Antiviral Res 37:107-120, 1998

27. Hayden FG, Lobo M, Treanor JJ, et al: Efficacy and tolerability of oral GS4104 for early treatment of experimental influenza in humans. Program and Abstract of the 37th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto, Canada, Soc Microbiol 1997 (abstr LB-26)

28. Hayden FG, Atmar RL, Schilling M, et al: Safety and efficacy of oral GS4104 in long term prophylaxis of natural influenza. Program and Abstracts of the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, CA, Soc Microbiol, 1998, (abstr LB-6)

29. Treanor JJ, Vrooman PS, Hayden FG, et al: Efficacy of oral GS4104 in treating acute influenza. Program and Abstracts of the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy. San Diego, CA, Soc Microbiol, 1998, (abstr LB-4)

30. Guhaare LV, Matrosovich MN, Brenner MK, et al: Evidence for zanamavir resistance in an immunocompromised child infected with influenza B virus. J Infect Dis 178:1257-1262, 1998

31. Dragovich PS: Structure-based design, synthesis, and biological evaluation of irreversible human rhinovirus 3C protease inhibitors. 4. Incorporation of P1 lactam moieties as L-glutamine replacements. J Med Chem 42:1213-1224, 1999

32. Abdel-Rahman SM: Single-dose pharmacokinetics of a pleconaril derivative (VP63843) oral solution and effect of food. Antimicrob Agents Chemother 42:2706-2709, 1998

33. Sawyer MH, Saez-Llorenz X, Aviles CL, et al: Oral pleconaril reduces the duration and severity of enteroviral meningitis in children. Pediatric Academic Societies Annual Meeting, San Francisco, CA, 1999, (abstr 1012)

34. Whitley RJ, Guann JW Jr: Acyclovir: A decade later. N Engl J Med 327:782-789, 1992

35. Acosta EP, Fletcher CV: Valacyclovir. Ann Pharmacother 31:183-191, 1997

36. Hwang CBC, Ruffner KL, Coen DM: A point mutation within a distinct conserved region of the herpes simplex DNA polymerase gene confers drug resistance. J Virol 66:1774-1776, 1992

37. Vere Hodge RA: Famciclovir and penciclovir. The mode of action of famciclovir including its conversion to penciclovir. Antiviral Chem Chemother 4:67-84, 1993

38. Cirelli R: Famciclovir: Review of clinical efficacy and safety. Antiviral Res 29:141-151, 1996

39. Bean B: Antiviral therapy: Current concepts and practices. Clin Microbiol Rev 5:146-182, 1992

40. Hodinka RL: What clinicians need to know about antiviral drugs and viral resistance. Infect Dis Clin North Am 11:946-967, 1997

41. Faulds D, Heel RC: Ganciclovir. A review of its antiviral activity, pharmacokinetic properties and therapeutic efficacy in cytomegalovirus infections. Drugs 39:597-638, 1990

42. Canpolat C, Culbert S, Gardiner M, et al: Ganciclovir prophylaxis for cytomegalovirus infection in pediatric allogeneic bone marrow transplant recipients. Bone Marrow Transplant 17:389-393, 1996

43. Couchoud C, Cuchear M, Haugh M, et al: Cytomegalovirus prophylaxis with antiviral agents in solid organ transplantation: A meta analysis. Transplantation 63:641-647, 1998

44. Nigro G, Krzyztofiak A, Bartmann U, et al: Ganciclovir for cytomegalovirus associated liver disease in immunocompetent or immunocompromised children. Arch Virol 142:573-580, 1997

45. Ginevri F, Losurdo G, Fontana I, et al: Acyclovir plus CMV immunoglobulin prophylaxis and early therapy with ganciclovir are effective and safe in CMV high-risk renal transplant pediatric patients. Transpl Int 11:303-13, 1998 (suppl)

46. King SM, Suprimer R, Andrews W, et al: Randomized comparison of ganciclovir plus intravenous immune globulin (IVIG) with IVIG alone for prevention of primary cytomegalovirus disease in children receiving liver transplants. Clin Infect Dis 25:1173-1179, 1997

47. McDiarmid SV, Jorda S, Lee GS, et al: Prevention and preemptive therapy of posttransplant lymphoproliferative disease in pediatric liver transplant recipients. Transplantation 66:1604-1611, 1998

48. Erice A: Resistance of human cytomegalovirus to antiviral drugs. Clin Microbiol Rev 12:296-297, 1999

49. Lea AP, Breyson HM: Cidofovir. Drugs 52:225-230, 1996

50. Wastgaff AJ, Breyson HM: Foscarnet. A reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic use in immunocompromised patients with viral infections. Drugs 48:199-226, 1994

51. Centers for Disease Control and Prevention: Viral Hepatitis Surveillance Program 1993. Hepatitis Surveillance Report No. 56, April 1996

52. American Academy of Pediatrics: Hepatitis B, hepatitis C, in Peter G (ed): 1997 Red Book: Report of the Committee on Infectious Diseases (ed 24), Elk Grove Village, IL, American Academy of Pediatrics, 1997, pp 247-264

53. Centers for Disease Control and Prevention: Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. MMWR 47 (No RR-19), 1998

54. Ng VL, Balistreri WF: Hepatitis B. Clinics in Liver Disease. 3:267-290, 1999

55. Fishman LN, Jonas MM, Levine JE: Update on viral hepatitis in children. Pediatr Clin North Am 43:57-74, 1996

56. Hutchinson JG, Gordon SC, Schiff ER, et al: Interferon alpha-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. N Engl J Med 339:1485-1492, 1998

57. Nakai Y, Oba H, Tonegawa Y, et al: Interferon alpha therapy for chronic hepatitis B virus infection. Antimicrob Agents Chemother 39:1935-1938, 1995

58. DeClerq E: Perspectives for the treatment of hepatitis B virus infections. Int J Antimicrobial Agents 12:81-95, 1999