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ANTIVIRAL THERAPY (NON-HIV)

JOHN H. BEIGEL

Although some viral infections are self-limited, others can cause significant morbidity and mortality. Effective therapy is available for many of these infections. Emerging viral diseases such as coronavirus and influenza, concern about viral agents of bioterrorism, and treatment of chronic viral diseases such as hepatitis B and hepatitis C have reinvigorated the search for new antiviral agents. This chapter reviews currently available antiviral agents for the treatment of infections caused by viruses other than human immunodeficiency virus (HIV). Not all agents discussed are presently licensed in all countries.

MECHANISM OF ACTION

Currently available agents can be classified into those that directly inhibit viral replication at the cellular level (antivirals), those that modify the host response to infection (immunomodulators), and those that directly inactivate viral infectivity (antibodies, virucides, or microbicides). Antiviral agents can be further classified into two general mechanisms. First—and most numerous—are nucleic acid analogues that inhibit viral DNA or RNA synthesis by competing with endogenous nucleic acids for incorporation into the viral genome by viral DNA polymerase or RNA transcriptases. The second mechanism is inhibition of the functions of other essential viral enzymes or proteins, including those responsible for attachment to or release from cells. For example, the principal antivirals for influenza viruses inhibit viral proteins responsible for either uncoating (M2 protein) or release and spread (neuraminidase).

Antiviral strategies that are not covered in this chapter include local destructive measures that destroy both host tissues and virus simultaneously, such as cryotherapy, laser, and podophyllin treatment of warts. Although effective, such measures are useful only for discrete or localized mucocutaneous infections.

ANTIVIRALS FOR HERPESVIRUS INFECTIONS

Acyclovir and Valacyclovir

Acyclovir, which is an acyclic analogue of the nucleoside guanosine, is converted to its active form through initial monophosphorylation by a virus-encoded thymidine kinase (TK). Although normal human cells possess TK, the affinity of acyclovir for viral TK is approximately 200 times greater than for human TK. The monophosphate then undergoes two additional host cell enzyme-mediated phosphorylations to acyclovir triphosphate (acycloguanosine triphosphate), which preferentially inhibits viral DNA polymerase, competitively and through chain termination. The higher concentrations of the activated form in infected cells and its affinity for viral polymerases result in low toxicity to normal host cells.

Valacyclovir is the L-valyl ester prodrug of acyclovir. Addition of the L-valyl ester fosters greater oral absorption, after which valacyclovir is converted to acyclovir; the prodrug provides three to five times greater bioavailability than oral acyclovir.

Clinical Uses

Acyclovir and valacyclovir are used principally to treat infections caused by herpes simplex virus (HSV; Chapter 382) and varicella-zoster virus (VZV; Chapter 383). Depending on country, acyclovir is available in a topical ointment and cream, oral capsules, and intravenous and ophthalmic formulations. Valacyclovir is available only as an oral capsule.

Oral acyclovir or valacyclovir decreases the duration of symptoms by approximately 50% and reduces the duration of viral shedding by about 90% in initial episodes of genital herpes. Two or 3 days of therapy appears to be sufficient for recurrent genital herpes. Chronic suppression is highly effective in reducing clinical and viral recurrences, and valacyclovir reduces the risk of transmission of genital HSV between heterosexual partners by 48%. For herpes labialis (cold sores), 1 day of therapy with oral valacyclovir improves time to healing and reduces pain, whereas acyclovir ointment has no consistent clinical benefit.

Parenteral acyclovir is indicated for the initial treatment of mucosal or cutaneous HSV infection in immunocompromised patients, neonatal HSV infections, and disseminated or organ-invasive infections in immunocompetent patients. A subsequent switch to oral valacyclovir is possible in some circumstances. High-dose parenteral acyclovir is the therapy of choice for treatment of HSV encephalitis.

Acyclovir is also effective treatment of VZV infections, although higher doses are needed than for mucosal HSV infections (see Table 368-1). In adults treated within 24 hours of the development of a varicella rash, acyclovir decreases the severity of disease and number of lesions, but oral valacyclovir may be more effective than oral acyclovir. Intravenous acyclovir is warranted for initial treatment of varicella and zoster in immunocompromised hosts. Both acyclovir chemoprophylaxis and valacyclovir chemoprophylaxis reduce the incidence of recurrent HSV in recipients of stem cell and solid organ transplants, but valacyclovir is superior for prevention of cytomegalovirus (CMV) disease.

Toxicity

Acyclovir and valacyclovir have excellent safety profiles and are generally well tolerated. Common side effects include nausea, vomiting, and headaches. Major adverse effects include renal dysfunction and central nervous system (CNS) toxicity. Dehydration and preexisting renal dysfunction predispose to the development of renal impairment. Neurologic side effects include tremor, myoclonus, confusion, lethargy, agitation, and hallucination. Renal dysfunction predisposes to the development of neurotoxicity. Neutropenia and other signs of bone marrow toxicity have also been reported rarely.

Antiviral Resistance

Despite widespread use of acyclovir, the development of HSV resistance in immunocompetent subjects is uncommon (prevalence <1%). However, antiviral resistance is higher in immunocompromised subjects, including those with HIV infection (prevalence of 5%) or bone marrow transplants (prevalence of up to 30%). Drug-resistant, refractory VZV infections can occur in highly immunocompromised patients. Intravenous foscarnet or cidofovir may be effective for infections caused by acyclovir-resistant viruses.

Penciclovir and Famciclovir

Penciclovir is an acyclic guanine analogue that unlike acyclovir is not an obligate chain terminator and may be incorporated into DNA. Penciclovir is phosphorylated by viral TK to penciclovir monophosphate, which is then converted to penciclovir triphosphate. Penciclovir demonstrates in vitro activity against VZV and HSV comparable to that of acyclovir. The bioavailability of penciclovir after oral administration is less than 2%. In contrast, famciclovir is an oral prodrug that is deacetylated and oxidized in the liver to form penciclovir; the bioavailability of penciclovir averages 77% after administration of famciclovir.

Clinical Uses

Penciclovir and famciclovir are used to treat HSV and VZV infections. Penciclovir is available as a topical cream and in some countries as an intravenous formulation. Famciclovir is available as a capsule.

Frequent applications of topical penciclovir reduce herpes labialis pain and lesions by about 1 day. Famciclovir is approved for the treatment of recurrent HSV labialis and genital infections and for herpes zoster, for which it is as effective as valacyclovir. It is also as effective as acyclovir when it is used to treat initial genital HSV infection.

Toxicity

Penciclovir is well tolerated as a topical cream; the majority of adverse reactions are local irritation and mild erythema. Adverse effects of oral famciclovir include headache, dizziness, nausea, and diarrhea.

TABLE 368-1 ANTIVIRALS FOR HERPESVIRUS INFECTIONS

VIRAL INFECTION	DRUG	ROUTE	USUAL ADULT DOSAGE
HERPES SIMPLEX VIRUS			
Genital herpes			
First episode	Acyclovir	PO	400 mg tid or 200 mg 5 times/day for 7-10 days
	Famciclovir	PO	250 mg tid for 7-10 days
	Valacyclovir	PO	1 g bid for 7-10 days
Recurrent	Acyclovir	PO	800 mg tid for 2 days, or 400 mg tid or 200 mg 5 times/day for 5 days
	Famciclovir	PO	1000 mg bid for 2 doses
	Valacyclovir	PO	500 mg bid for 3 days or 1 g/day for 5 days
Suppression	Acyclovir	PO	400 mg bid or 200 mg tid
	Famciclovir	PO	250 mg bid
	Valacyclovir	PO	500 mg/day or 1 g/day (10 or more episodes/year)
Orolabial herpes	Penciclovir 1%	Topical	Apply cream every 2 hr while awake for 4 days
	Acyclovir 5%	Topical	Apply cream 5 times/day for 4 days
	Docosanol 10%	Topical	Apply cream 5 times/day until healing
	Valacyclovir	PO	2 g q12h × 2 doses
	Acyclovir	PO	400 mg 5 times/day for 5 days
	Famciclovir	PO	1500 mg single dose
Mucocutaneous disease	Acyclovir	IV	5 mg/kg/8 hr for 7-14 days
	Acyclovir	PO	400 mg 5 times/day for 7-14 days
	Valacyclovir	PO	500 mg or 1 g bid for 7-10 days
Encephalitis	Acyclovir	IV	10 mg/kg/8 hr for 10 days
Neonatal	Acyclovir	IV	10-20 mg/kg/8 hr for 14-21 days
Keratoconjunctivitis	Trifluridine	Topical	1 drop of 1% solution q2h up to 9 drops/day
	Vidarabine	Topical	½-inch ribbon of 3% ointment 5 times daily
Acyclovir-resistant HSV	Foscarnet	IV	40 mg/kg q8-12 h until healed.
CYTOMEGALOVIRUS			
CMV retinitis	Ganciclovir	IV	Induction: 5 mg/kg/12 hr for 14-21 days (maintenance: 5 mg/kg/day)
	Valganciclovir	PO	Induction: 900 mg bid for 21 days (maintenance: 900 mg/day)
	Cidofovir	IV	5 mg/kg once weekly × 2, then every other week (maintenance: 5 mg/kg q2wk)
	Foscarnet	IV	60 mg/kg/8 hr or 90 mg/kg q12h for 14-21 days (maintenance: 90-120 mg/kg daily)
	Fomivirsen	Intravitreal	330 µg q2wk × 2, then q4wk (maintenance: 330 µg every month)
HIV infection, CMV colitis or esophagitis	Ganciclovir	IV	5 mg/kg/12 hr for 14-28 days (until symptoms resolved)
Prophylaxis (transplantation)	Ganciclovir	IV	5 mg/kg/12 hr for 7-14 days, then 5 mg/kg IV once a day
	Valganciclovir	PO	900 mg qd
Prophylaxis (advanced HIV infection)	Ganciclovir	IV	5 mg/kg daily
VARICELLA-ZOSTER VIRUS			
Varicella	Acyclovir	PO	800 mg qid for 5 days
Varicella in immunocompromised hosts	Acyclovir	IV	10 mg/kg/8 hr for 7-10 days
Herpes zoster in immunocompromised hosts	Acyclovir	IV	10 mg/kg/8 hr for 7-10 days
Herpes zoster in normal hosts	Acyclovir	PO	800 mg 5 times daily for 7-10 days
	Valacyclovir	PO	1 g tid for 7 days
	Famciclovir	PO	500 mg tid for 7 days

TABLE 368-2 MECHANISMS OF EXCRETION AND THRESHOLDS FOR DOSE ADJUSTMENT

	MAJOR ROUTE OF ELIMINATION	THRESHOLD FOR ADJUSTMENT IN RENAL INSUFFICIENCY OR FAILURE	ADJUSTMENT FOR HEPATIC FAILURE	ADJUSTMENT FOR OBESITY
Acyclovir IV	Renal	CrCl < 50 mL/min	No adjustment	Dose by ideal body weight
Acyclovir PO	Renal	CrCl < 25 mL/min	No adjustment	Dose by ideal body weight
Valacyclovir	Renal	CrCl < 50 mL/min	No adjustment	Unknown
Famciclovir	Renal	CrCl < 60 mL/min	No adjustment	Unknown
Foscarnet	Renal	CrCl < 1.4 mL/min/kg	No adjustment	Unknown
Ganciclovir IV	Renal	CrCl < 70 mL/min	No adjustment	Unknown
Valganciclovir	Renal	CrCl < 60 mL/min	No adjustment	Unknown
Cidofovir	Renal	CrCl < 55 mL/min	No adjustment	Unknown

Antiviral Resistance

Penciclovir resistance in HSV has been uncommon in immunocompetent subjects but, like acyclovir resistance, more frequent in immunocompromised hosts (2.1%). Most acyclovir-resistant HSV isolates are cross-resistant to penciclovir.

Ganciclovir and Valganciclovir

Ganciclovir is an acyclic deoxyguanosine analogue with antiviral activity against multiple herpesviruses, including HSV, VZV, CMV (Chapter 384), Epstein-Barr virus (EBV; Chapter 385), and human herpesvirus 8. It is much more active than acyclovir against CMV and EBV.

TABLE 368-3 DRUG-DRUG INTERACTIONS

	COADMINISTERED DRUG	RISKS OR TOXICITIES	POSSIBLE MECHANISM
Acyclovir	Fosphenytoin	Decreased phenytoin plasma concentration	Decreased phenytoin absorption
	Meperidine	Increased risk for CNS stimulation and excitation	Increased meperidine metabolites
	Mycophenolate	Increased plasma concentration of acyclovir	Competition for renal secretion
	Valproic acid	Decreased valproic acid plasma concentration	Decreased valproic acid absorption
	Varicella vaccine	Decreased varicella vaccine effectiveness	Inhibition of VZV
	Zidovudine	Increased lethargy and fatigue	Unknown
Valacyclovir	Mycophenolate	Increased risk for neutropenia	Unknown
Ganciclovir	Didanosine	Increased didanosine toxicity (neuropathy, diarrhea, pancreatitis)	Increased didanosine bioavailability
	Imipenem	Increased risk for CNS toxicity (seizures)	Unknown
	Mycophenolate	Increase in plasma concentration of ganciclovir	Competition for renal secretion
	Probenecid	Increase in plasma concentration of ganciclovir	Competition for renal secretion
	Tacrolimus	Increased risk for nephrotoxicity	Additive nephrotoxicity
	Zidovudine	Increased risk for hematologic toxicity (anemia, neutropenia)	Unknown
Valganciclovir	Probenecid	Increase in plasma concentration of ganciclovir	Competition for renal secretion
	Zidovudine	Increased risk for hematologic toxicity (anemia, neutropenia)	Unknown
Cidofovir	Aminoglycosides	Nephrotoxicity	Additive nephrotoxicity
	Foscarnet	Nephrotoxicity	Additive nephrotoxicity
	Pentamidine	Nephrotoxicity	Additive nephrotoxicity
Foscarnet*	Drugs that prolong QRS	Torsades de pointes	Additive toxicity, prolongation of QRS
	Renal toxic drugs	Nephrotoxicity	Additive nephrotoxicity
Idoxuridine	Boric acid	Eye irritation	Formation of precipitate

*Many classes of drugs have added toxicity when they are administered with foscarnet. Consult a pharmacologist if you are uncertain about possible interactions.

TABLE 368-4 SIGNIFICANT ADVERSE EFFECTS (U.S. FDA BLACK BOX WARNING)

DRUG	BLACK BOX SYNOPSIS
Cidofovir	Renal impairment, including renal failure; prehydrate and use probenecid Neutropenia May be carcinogenic and teratogenic and may cause hypospermia or aspermia
Foscarnet	Nephrotoxicity; prehydrate Seizures related to minerals and electrolyte disturbances
Ganciclovir	Neutropenia, anemia, thrombocytopenia May be carcinogenic and teratogenic and may cause hypospermia or aspermia
Valganciclovir	Neutropenia, anemia, thrombocytopenia May be carcinogenic and teratogenic and may cause hypospermia or aspermia

The bioavailability of oral ganciclovir is less than 10%. After the oral administration of valganciclovir, which is an L-valyl prodrug of ganciclovir, bioavailability of ganciclovir averages 60%.

Clinical Uses

Ganciclovir is available as an oral capsule, a parenteral injection, and an ocular implant; valganciclovir is available only as a tablet. Ganciclovir and valganciclovir are effective for treatment of CMV retinitis, for which they are comparably active. In the absence of immune reconstitution, long-term suppression therapy is necessary.

They are also used for life-threatening CMV diseases in patients with acquired immunodeficiency syndrome (AIDS) and other immunocompromised conditions and for prevention of CMV disease in transplant patients. For immunocompromised patients with organ-invasive CMV infections, intravenous ganciclovir provides clinical response rates of 70 to 90%, although response rates are lower for CMV pneumonitis after stem cell transplantation or CMV encephalitis in patients with AIDS. Oral valganciclovir provides long-term outcomes similar to those of intravenous ganciclovir for the treatment of CMV disease.[2]

Long-term prophylaxis with ganciclovir or valganciclovir reduces the incidence of CMV disease after solid organ and stem cell transplantation, but this therapy has substantial side effects, including bone marrow suppression. These drugs can also be used as preemptive therapy for patients who have CMV viremia or antigenemia. In the prevention of CMV disease, preemptive valganciclovir therapy may be equally effective to chronic valacyclovir prophylaxis.[3] Intravenous ganciclovir is the recommended agent for treatment of herpesvirus B infections, particularly those involving the CNS.

Toxicity

The most common adverse effect with ganciclovir and valganciclovir is bone marrow suppression, particularly neutropenia and thrombocytopenia, which occur in up to 50% of patients given intravenous ganciclovir. Fever, edema, phlebitis, headache, neuropathy, disorientation, nausea, anorexia, rash, and myalgias have also been reported with ganciclovir therapy. Intravitreal ganciclovir implants may cause vitreous hemorrhage and retinal detachment.

Antiviral Resistance

Ganciclovir resistance secondary to mutations in CMV kinase and sometimes DNA polymerase is related to the length of ganciclovir exposure and the degree of immunosuppression. Resistance may be associated with progressive disease during continued ganciclovir use; foscarnet and cidofovir are alternative treatments.[4]

Cidofovir

Cidofovir, which is an acyclic phosphonate derivative of cytosine, is phosphorylated to its active diphosphate form by host cellular enzymes. Cidofovir diphosphate competitively inhibits viral DNA polymerase and viral DNA synthesis. Despite a short serum half-life, the antiviral effects are protracted because of prolonged intracellular concentrations of the phosphorylated metabolite.

Clinical Uses

Cidofovir is commercially available as an intravenous infusion. Investigational uses have included topical gel and intravitreal and intralesional injection.

Intravenous cidofovir is indicated in AIDS patients for CMV retinitis for which ganciclovir or foscarnet therapy is failing. Limited data suggest that intravenous cidofovir may be effective in other CMV infections (pneumonitis, gastroenteritis), acyclovir- or foscarnet-resistant HSV infections, certain forms of human papillomavirus disease, invasive adenoviral infections in transplant recipients, and possibly BK virus infection in renal transplant patients. In addition, in vivo and animal data suggest efficacy of cidofovir against smallpox, vaccinia, and monkeypox infections, although clinical trials are lacking.

Toxicity

Dose-related nephrotoxicity, characterized by increased serum creatinine, proteinuria, and tubular dysfunction, is the main side effect of intravenous cidofovir. Adequate hydration and concomitant oral probenecid reduce the

risk. Other common side effects include diarrhea, asthenia, nausea, vomiting, neutropenia, fever, and rash. Iritis, intraocular pressure changes, loss of visual acuity, and uveitis have been reported with intravenous cidofovir. Intravitreal cidofovir is effective but locally toxic.

Antiviral Resistance

Sustained exposure to cidofovir does not easily induce resistance, although resistance has infrequently been described in HSV and CMV.

Foscarnet

Foscarnet is a pyrophosphate analogue that acts as a noncompetitive inhibitor of many viral RNA and DNA polymerases. When a nucleotide is incorporated into a DNA or RNA strand by a polymerase, pyrophosphate is released. Foscarnet directly inhibits viral polymerases without phosphorylation, so TK-deficient acyclovir-resistant HSV and VZV are susceptible to this agent.

Clinical Uses

Foscarnet is as effective as ganciclovir for the treatment of CMV retinitis in patients with AIDS, and combination therapy with ganciclovir may be superior to monotherapy with either agent for recalcitrant retinitis. For extraretinal CMV disease, foscarnet has demonstrated efficacy similar to that of ganciclovir. The choice of agent may be dictated by the side effect profile. Foscarnet is also effective for the treatment of acyclovir-resistant HSV and VZV infections.

Toxicity

Nephrotoxicity with azotemia and proteinuria is dose limiting and occurs in more than a third of patients. A slow infusion rate and saline hydration reduce the risk. Other common side effects include anemia (30 to 50% of patients), granulocytopenia, diarrhea, nausea, vomiting, fever, seizures, paresthesias, headache, and genital ulcers. Marked electrolyte disturbances may develop, including hypophosphatemia, hypocalcemia, hypokalemia, and hypomagnesemia. Foscarnet can prolong the QT interval and be associated with cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, and torsades de pointes.

Antiviral Resistance

The development of CMV resistance to foscarnet as a result of mutations in viral DNA polymerase is uncommon, except after prolonged administration. In AIDS patients with retinitis, foscarnet resistance is detectable in 13% of patients at 6 months and in 37% at 12 months.

Fomivirsen

Fomivirsen, which is an antisense oligonucleotide that inhibits CMV replication, is currently available as an intravitreal injection that is effective for both newly diagnosed CMV retinitis and CMV retinitis failing usual therapies, although direct comparisons with other agents are lacking. Intravitreal administration of fomivirsen may cause increased intraocular pressure, iritis, vitreitis, and cataracts in 10 to 20% of patients.

Brivudine

Brivudine, also known as bromovinyldeoxyuridine, is a thymidine analogue that is currently licensed for the treatment of herpes zoster in several European Union countries but not in the United States. Its efficacy is comparable to that of acyclovir, with similar time to crusting and cessation of pain. Common side effects include nausea, vomiting, abdominal discomfort, and anorexia.

Docosanol

Docosanol, which is a 22-carbon saturated fatty alcohol that inhibits intracellular penetration of lipid enveloped viruses, is approved as a cream for the treatment of herpes labialis. Frequent topical applications have shown reductions in time to cessation of pain and healing, but direct comparison to other agents is lacking. Local reaction, rash, and pruritus are common side effects.

Idoxuridine and Trifluorothymidine

Idoxuridine and trifluorothymidine (trifluridine) are thymidine analogues that are phosphorylated by both viral and cellular TKs to active triphosphate derivatives that inhibit both viral and cellular DNA synthesis. The result is antiviral activity but also host cytotoxicity, which prevents safe systemic use. However, the tolerability of these compounds is adequate for topical use. Both idoxuridine and trifluorothymidine are available as ophthalmic formulations and are licensed for the treatment of herpetic keratitis. In direct comparison, trifluridine appears to be the more efficacious of these compounds. In addition, idoxuridine in dimethyl sulfoxide has been used topically in some countries for treatment of mucosal herpes infections. The most frequent adverse effects with trifluridine are transient burning or stinging on instillation and palpebral edema. Irritation and punctate corneal defects have been reported with idoxuridine.

Vidarabine

Vidarabine, an adenosine analogue, is now available only as an ophthalmic ointment indicated for acute keratoconjunctivitis and recurrent epithelial keratitis secondary to HSV. Its clinical activity appears to be superior to that of idoxuridine. Toxicities of the ointment include conjunctival injection, burning, and irritation.

ANTIVIRALS FOR INFLUENZA VIRUS INFECTIONS

Adamantanes (Amantadine, Rimantadine)

Amantadine and rimantadine are symmetrical tricyclic amines with activity against many influenza A viruses (Chapter 372). By inhibiting the ion channel function of the M2 protein of influenza A, they interfere with uncoating of the virus and release of the viral genome.

Clinical Uses

Amantadine and rimantadine (Tables 368-5 to 368-7) decrease the length and severity of uncomplicated influenza A virus infection by susceptible strains if they are initiated within the first 2 days after the onset of symptoms, but it is uncertain whether they reduce the risk for complications. Both drugs are formulated for oral administration: capsules for amantadine and tablets for rimantadine as well as pediatric syrups. In recent years, marked increases in antiviral resistance in community isolates have limited the utility of these drugs.

Both rimantadine and amantadine are effective when they are used for prophylaxis against influenza A illness (overall 66% average for rimantadine and 74% for amantadine). In persons who take the drug for prophylaxis, subclinical infections may still develop and elicit immune responses that will protect them when they are exposed to antigenically related viruses.

Amantadine is also used in the treatment of parkinsonism, for drug-induced extrapyramidal reactions, and in the management of multiple sclerosis symptoms.

Toxicity

Amantadine causes CNS side effects in 10 to 30% of healthy young adults who take the standard adult dose of 200 mg/day; the frequency is significantly lower with rimantadine. Neuropsychiatric side effects include anxiety, nervousness, insomnia, and, particularly in the elderly or those with renal insufficiency, hallucinations, confusion, disorientation, and psychosis or coma. Amantadine or less often rimantadine is associated with an increased risk for seizures. Both drugs cause gastrointestinal side effects. Orthostatic hypotension occurs in 1 to 5%. Anticholinergic side effects, including dry mouth, occur in amantadine recipients.

TABLE 368-5 ANTIVIRALS FOR INFLUENZA VIRUS INFECTIONS

VIRUS	DRUG	ROUTE	USUAL ADULT TREATMENT DOSAGE
Influenza A and B virus	Oseltamivir	PO	75 mg bid for 5 days
	Zanamivir	Inhalation	10 mg bid by inhaler for 5 days
Influenza A virus	Amantadine	PO	100 mg bid or 200 mg qd for 5 days
	Rimantadine	PO	100 mg bid for 5 days

TABLE 368-6 MECHANISMS OF EXCRETION AND THRESHOLDS FOR DOSE ADJUSTMENTS

	MAJOR ROUTE OF ELIMINATION	THRESHOLD FOR ADJUSTMENT IN RENAL INSUFFICIENCY OR FAILURE	ADJUSTMENT FOR HEPATIC FAILURE	SPECIAL ADJUSTMENT FOR THE ELDERLY
Amantadine	Renal	CrCl < 50 mL/min	No adjustment	>65 yr: 100 mg daily
Rimantadine	Hepatic and renal	CrCl < 10 mL/min/1.72 m^2	100 mg daily	100 mg daily
Oseltamivir	Renal	CrCl < 30 mL/min/1.72 m^2	No adjustment	
Zanamivir	Renal	No adjustment	No adjustment	

TABLE 368-7 DRUG-DRUG INTERACTIONS

	COADMINISTERED DRUG	RISKS OR TOXICITIES	POSSIBLE MECHANISM
Amantadine	Anticholinergics	Dry mouth, constipation, decreased urination, sedation, blurred vision	Additive anticholinergic effect
	Benztropine	CNS toxicity (confusion, hallucinations)	Unknown
	Bupropion	Nausea, vomiting, excitation, restlessness, postural hypotension	Unknown
	Triamterene	Incoordination, agitation, visual hallucinations	Decreased amantadine clearance
	Trimethoprim	CNS toxicity (insomnia, confusion)	Decreased amantadine clearance

Antiviral Resistance

Single point mutations in M2 confer high-level resistance to these drugs and make them ineffective. Such resistant variants emerge commonly during treatment and are transmissible. In 2005-2006, the frequency of resistance in influenza A (H3N2) viruses was as high as 92% in the United States. Resistance is also present in some seasonal H1N1 and many H5N1 and pandemic H1N1 viruses.

Neuraminidase Inhibitors (Oseltamivir, Zanamivir, Peramivir)

Zanamivir, oseltamivir, and peramivir are sialic acid analogues that inhibit influenza virus neuraminidases by competitively interacting with the active enzyme site of influenza A and B viruses, including adamantine-resistant strains. Influenza neuraminidase cleaves terminal sialic acid residues and destroys the receptors recognized by viral hemagglutinin. These drugs inhibit this action, which is essential for release of virus from infected cells, prevention of viral aggregates, and spread within the respiratory tract.

Oseltamivir is administered orally as the phosphate prodrug, which is rapidly absorbed and hydrolyzed to the active form oseltamivir carboxylate. The oral bioavailability of zanamivir is poor, and it is currently licensed to be delivered as an orally inhaled powder. Peramivir, an intravenous neuraminidase inhibitor, is not licensed but was previously made available for use under an emergency use authorization, a mechanism by which the U.S. Food and Drug Administration (FDA) allows the use of an unapproved medical product during certain types of emergencies, such as pandemic influenza.

Clinical Uses

Oseltamivir and zanamivir are effective for the treatment and prophylaxis of acute influenza A and B infections. Early treatment in adults decreases the duration and severity of illness and reduces lower respiratory tract complications, antibiotic use, and, with oseltamivir, hospitalizations. In cohort studies, treatment with oseltamivir has been associated with a significant reduction in death (odds ratio, 0.21). Zanamivir is also effective in alleviating symptoms and decreasing the risk for lower respiratory complications. Both zanamivir and oseltamivir are highly effective for the prevention of influenza. Peramivir may be useful in patients who are not responding to either oseltamivir or zanamivir antiviral therapy.

Toxicity

The most common side effects with oseltamivir are nausea and vomiting. It may also be associated with headache, rash, and possibly abnormal transaminases. Zanamivir is generally well tolerated, but bronchospasm (sometimes severe) has been reported primarily in patients with underlying airway disease. The most common side effects of peramivir are nausea, diarrhea, and mild neutropenia.

Antiviral Resistance

Oseltamivir resistance as a result of neuraminidase mutations has been detected during treatment of seasonal influenza, more often in children than in adults and recently in H5N1- and H1N1-infected patients. In the immunocompromised host, and possibly in individuals with H5N1 or H1N1, the development of resistance is associated with treatment failure. Zanamivir retains clinical effectiveness against the most common oseltamivir-resistant variant.■

TABLE 368-8 ANTIVIRALS FOR HEPATITIS VIRUS INFECTIONS

VIRAL INFECTION	DRUG	ROUTE	USUAL ADULT DOSAGE
Chronic hepatitis C*	PEG-interferon alfa-2a *or* PEG-interferon alfa-2b	SC	180 µg weekly for 48 wk
	plus ribavirin	SC	1.5 µg/kg weekly for 48 wk
		PO	800-1200 mg/day, depending on weight
Chronic hepatitis B	Interferon alfa-2b	SC, IM	5 MU/day or 10 MU 3 times weekly for 16-24 wk
	PEG-interferon alfa-2a	SC	180 µg weekly for 48 weeks
	Entecavir Naive virus	PO	0.5 mg daily; optimal duration of therapy is unknown
	Lamivudine resistant virus	PO	1 mg daily; optimal duration of therapy is unknown
	Lamivudine	PO	100 mg/day
	Adefovir	PO	10 mg/day
	Telbivudine	PO	600 mg/day

*Genotypes 2 and 3 may tolerate shorter treatment.

ANTIVIRALS FOR HEPATITIS VIRUS INFECTIONS

Adefovir

Adefovir, an acyclic analogue of adenosine monophosphate, is administered orally as a prodrug, adefovir dipivoxil, which is rapidly converted enzymatically to adefovir in intestinal epithelium.

Clinical Uses

In chronic hepatitis B (Chapter 151), prolonged administration of adefovir is effective in improving histologic abnormalities of the liver, decreasing hepatitis B virus (HBV) DNA levels, and normalizing biochemical (alanine aminotransferase) markers in patients with hepatitis B e antigen (HBeAg)–positive and HBeAg-negative chronic hepatitis B (Tables 368-8 to 368-11). Adefovir has been shown to be effective against chronic hepatitis B resistant to lamivudine. The combination of lamivudine and adefovir may decrease the emergence of resistant virus but does not have additive or synergistic antiviral activity.

TABLE 368-9 MECHANISMS OF EXCRETION AND THRESHOLDS FOR DOSE ADJUSTMENT

	MAJOR ROUTE OF ELIMINATION	THRESHOLD FOR ADJUSTMENT IN RENAL INSUFFICIENCY OR FAILURE	ADJUSTMENT FOR HEPATIC FAILURE	SPECIAL ADJUSTMENT FOR ELDERLY
Adefovir	Renal	CrCl < 50 mL/min	No adjustment	
Entecavir	Renal	CrCl < 50 mL/min	No adjustment	
Lamivudine	Renal	CrCl < 50 mL/min	No adjustment	
Tenofovir	Renal	CrCl < 50 mL/min	No adjustment	
Ribavirin	Renal	CrCl < 50 mL/min	No adjustment	
PEG-interferon alfa-2a	Renal	CrCl < 50 mL/min	Progressive rise in alanine transaminase	>60 yr: consider reduction
Telbivudine	Renal	CrCl < 50 mL/min	No adjustment	

TABLE 368-10 DRUG-DRUG INTERACTIONS

	COADMINISTERED DRUG	RISKS OR TOXICITIES	POSSIBLE MECHANISM
Lamivudine	Ribavirin	Lactic acidosis	Unknown
	Sulfamethoxazole	Increased risk for lamivudine adverse effects	Competition for renal secretion
	Trimethoprim	Increased risk for lamivudine adverse effects	Competition for renal secretion
	Zalcitabine	Increased zalcitabine and lamivudine exposure	Inhibition of phosphorylation
Tenofovir	Atazanavir	Decreased atazanavir concentration or increased tenofovir levels	Unknown
	Didanosine	Increased didanosine plasma concentration and risk for toxicity	Increased didanosine bioavailability
	Lopinavir	Increased tenofovir bioavailability	Unknown
	Ritonavir	Increased tenofovir bioavailability	Unknown
Ribavirin	Nucleoside analogues	Lactic acidosis	Unknown
	Interferon alfa-2b	Worsening mental depression, anger, and hostility	Unknown
Interferon alfa-2	Angiotensin-converting enzyme inhibitors	Hematologic abnormalities (granulocytopenia, thrombocytopenia)	Unknown
	Colchicine	Decreased interferon alfa-2a effectiveness	Unknown
	Theophylline	Theophylline toxicity (nausea, vomiting, palpitations, seizures)	Unknown
	Ribavirin	Worsening mental depression, anger, and hostility	Unknown

TABLE 368-11 SIGNIFICANT ADVERSE EFFECTS (U.S. FDA BLACK BOX WARNING)

DRUG	BLACK BOX SYNOPSIS
Adefovir	Severe acute exacerbations of hepatitis B may occur with cessation of therapy Nephrotoxicity may occur in patients at risk for or undergoing renal dysfunction Lactic acidosis and severe hepatomegaly with steatosis
Entecavir	Lactic acidosis and severe hepatomegaly with steatosis; severe acute exacerbations of hepatitis B may occur with cessation of therapy
Lamivudine	Severe acute exacerbations of hepatitis B may occur with cessation of therapy Lactic acidosis and severe hepatomegaly with steatosis
Ribavirin	Monotherapy for hepatitis C is not effective Hemolytic anemia Teratogenic and embryocidal
Interferon alfa	May cause or aggravate neuropsychiatric, autoimmune, ischemic, and infectious disorders
Telbivudine	Severe acute exacerbation of hepatitis B may occur with cessation of therapy Lactic acidosis and severe hepatomegaly with steatosis

Toxicity

The major adverse effect is nephrotoxicity, manifested by increased serum creatinine and sometimes hypophosphatemia, both of which are usually reversible with discontinuation of the drug. Common side effects include asthenia, headache, nausea, vomiting, and diarrhea. In addition, severe exacerbations of hepatitis B have been observed after cessation of therapy.

Antiviral Resistance

Adefovir resistance secondary to point mutations in HBV polymerase develops in about 6% of patients after 3 years of adefovir therapy. Lamivudine generally retains activity against adefovir-resistant variants.

Entecavir

Entecavir, which is a deoxyguanosine nucleoside analogue with specific antiviral activity for hepadnaviruses, is more potent than lamivudine and also retains some activity against lamivudine-resistant HBV variants. It is well absorbed after oral administration, and its prolonged half-life (128 to 149 hours) allows once-daily dosing.

Clinical Uses

Entecavir is approved for the treatment of chronic hepatitis B in adults with evidence of active viral replication and either persistent elevations in serum aminotransferases or histologically active disease. Compared with lamivudine, entecavir is more efficacious in reducing HBV DNA levels and normalizing serum aminotransferases as well as in improving histologic abnormalities.[368] Higher doses and longer durations of therapy are indicated for lamivudine-resistant infections. Entecavir is not recommended in patients who have HIV/HBV coinfection and who are not receiving concurrent highly active antiretroviral therapy because of the risk of resistance to HIV nucleoside reverse transcriptase inhibitors.

Toxicity

Adverse effects reported during entecavir therapy include headache, fatigue, dizziness, nausea, abdominal pain, rhinitis, fever, diarrhea, cough, and myalgia. Lactic acidosis and severe hepatomegaly with steatosis have been reported. Severe exacerbations of hepatitis B have been observed after cessation of therapy.

Antiviral Resistance

Entecavir resistance, caused by specific mutations in HBV polymerase, appears to be uncommon, with no evidence after more than 1 year of drug exposure.

Lamivudine

Lamivudine is a deoxycytidine nucleoside analogue active against retroviruses and hepadnaviruses. The triphosphate inhibits HBV polymerase, and its incorporation into viral DNA results in termination of the DNA chain.

Clinical Uses

Prolonged lamivudine administration to patients with chronic hepatitis B suppresses viral replication, improves histologic abnormalities of the liver, reduces progression of fibrosis, and decreases the risk for late complications, but monotherapy with lamivudine appears to be inferior to monotherapy with interferon for sustained control of HBV replication. Combination therapy with lamivudine and interferon has shown inconsistent benefit compared with either drug alone.

Toxicity

Adverse effects of lamivudine include diarrhea, headache, and elevated liver enzymes. Severe post-treatment exacerbations of hepatitis B, including fatalities, have occurred with discontinuation of lamivudine, more commonly in patients coinfected with HBV and HIV.

Antiviral Resistance

Lamivudine resistance, caused by mutations in HBV polymerase, is common during prolonged treatment of hepatitis B and emerges in about 20% of treated patients annually. Resistance is associated with increases in viral replication and aminotransferases.

Tenofovir

Tenofovir is a nucleotide analogue of adenosine monophosphate. The commercially available agent, tenofovir disoproxil fumarate, is an ester prodrug of tenofovir and gives an effective tenofovir bioavailability of 25%.

Clinical Uses

Treatment with tenofovir is more effective than adefovir in producing histologic improvement and viral suppression in patients with HBeAg-negative or HbeAg-positive chronic hepatitis B.■ In HBV-HIV coinfection, combination antiretroviral therapy that includes tenofovir leads to significantly reduced HBV DNA levels compared with combination therapy with adefovir.

Toxicity

Tenofovir is generally well tolerated; the most common side effects are nausea, diarrhea, vomiting, and anorexia. Lactic acidosis with hepatic steatosis has been reported, primarily when it is used in combination with other nucleoside analogues. Acute exacerbations of hepatitis B have been reported after discontinuation of tenofovir in patients who are coinfected with HIV and HBV.

Antiviral Resistance

Mutations in HBV polymerase that confer reduced susceptibility to tenofovir occur during prolonged use (>12 months), although the clinical significance of these mutations remains to be defined.

Telbivudine

Telbivudine is a synthetic thymidine nucleoside analogue with activity against HBV, including some lamivudine-resistant variants. The triphosphate form competitively inhibits the HBV DNA polymerase (reverse transcriptase).

Clinical Uses

Telbivudine is used for the treatment of chronic hepatitis B. In comparative trials against lamivudine or adefovir, telbivudine demonstrated greater virologic response at week 52 (60% vs. 40% of subjects HBV DNA negative by polymerase chain reaction analysis).

Toxicity

Common side effects include headache, nausea, and vomiting. Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-HBV therapy. Myopathy, manifested by muscle aches or weakness with increased creatine kinase, has rarely been reported.

Ribavirin

Ribavirin is a purine nucleoside with antiviral activity against some DNA viruses and many RNA viruses, including influenza A and B, parainfluenza, measles, respiratory syncytial virus (RSV), retroviruses, arenaviruses such as Lassa virus, and some hantaviruses.

Clinical Uses

Monotherapy with ribavirin for chronic hepatitis C (Chapter 151) has been shown to decrease serum alanine aminotransferase but not hepatitis C virus RNA levels. However, combination therapy with ribavirin and various interferons, most recently pegylated interferons, is superior to interferon monotherapy, improves viral clearance and liver histologic responses, and reduces complications, including mortality. Ribavirin plus pegylated interferon has become the standard treatment of chronic hepatitis C.

Aerosol administration of ribavirin has been used to treat RSV bronchiolitis and pneumonia in children and to treat influenza A and B infections. Limited benefit has been seen with oral ribavirin in uncomplicated influenza. Aerosol ribavirin combined with intravenous immune globulin, particularly with the anti-RSV monoclonal antibody palivizumab, appears to reduce the mortality of RSV infection in bone marrow transplant and other highly immunocompromised patients.

Systemic ribavirin reduces the mortality associated with Lassa fever and Asian (Korean) hemorrhagic fever with renal syndrome (Chapter 389), although not mortality in patients with hantavirus-associated cardiopulmonary syndrome. It appears to have activity in Congo-Crimean hemorrhagic fever and in Nipah virus infections. Ribavirin is often recommended as treatment of hemorrhagic fevers of unknown etiology or secondary to arenaviruses or bunyaviruses in the event that these viruses are used as biologic weapons.

Toxicity

Aerosol delivery may cause bronchospasm. Systemic ribavirin is frequently associated with hemolytic anemia (in up to 61% in some series) and sometimes with electrolyte abnormalities, including hypocalcemia and hypomagnesemia. Arrhythmias, pruritus, rash, nausea, and myalgia have been reported, as have neurologic side effects, including insomnia and irritability. Ribavirin is gonadotoxic and teratogenic in multiple species.

Emtricitabine

Emtricitabine is an analogue of cytidine. It is currently licensed only for the treatment of HIV infection. However, in a large study of patients with chronic hepatitis B, monotherapy with emtricitabine led to significantly better histologic response (62% vs. 25%) and virologic suppression (54% vs. 2%) at 48 weeks compared with placebo.

Interferons

Interferons are glycoprotein cytokines with a complex array of antiviral, immunomodulating, and antineoplastic properties. Interferons are currently classified as α, β, or γ; the natural sources of these classes, in general, are leukocytes, fibroblasts, and lymphocytes, respectively. Each type of interferon can now be produced through recombinant DNA technology. Although the full mechanism of interferon's action is not defined, interferons generally induce synthesis of new cellular RNA and proteins that mediate antiviral effects through multiple different mechanisms.

Interferons generally require administration daily or several times per week. However, the combination of interferon with polyethylene glycol to form pegylated interferon significantly prolongs absorption, decreases elimination, and provides higher, more sustained plasma levels that enable administration once weekly.

Clinical Uses

In chronic active hepatitis B, treatment with interferon alfa leads to loss of HBV DNA and biochemical and histologic improvement in about 25 to 40% of patients. Administration of PEG-interferon alfa-2a or alfa-2b for 48 weeks converts about 30% of patients to seronegative status after 6 months of treatment. Combination therapy with interferon and lamivudine is not clearly superior to interferon alone.

In contrast to hepatitis B, combination therapy is the mainstay of treatment of hepatitis C. Subcutaneous administration of PEG-interferon alfa-2a plus daily ribavirin for 48 weeks results in a sustained virologic response in about 55% of treated patients, compared with less than a 30% response with interferon monotherapy. Patients with hepatitis C genotype 1 have lower levels of response than do patients with genotype 2 or 3 (46% vs. 76%). Patients with genotypes 2 and 3 may need only 24 weeks of combination therapy. Shorter durations of therapy (14 weeks) have lower sustained virologic response.

Toxicity

Common side effects of interferon administration include influenza-like symptoms (fever, chills, headache, and malaise), but these symptoms usually become less severe with repeated treatments; tolerance develops in most patients within several weeks. Major toxicities have included bone marrow

suppression, primarily granulocytopenia, and thrombocytopenia, which are generally reversible when therapy is discontinued. Neuropsychiatric disturbance may be manifested by depression, anxiety, somnolence, confusion, and behavioral disturbance. Other side effects include profound fatigue and anorexia, weight loss, hypothyroidism or hyperthyroidism, alopecia, and cardiotoxicity with arrhythmias and reversible cardiomyopathy.

OTHER ANTIVIRALS

Imiquimod

Imiquimod and the related compound resiquimod are topical immune response modifiers that lack direct antiviral effects. Instead, these agents induce activation of immune cells (monocytes, macrophages, natural killer cells) to produce antiviral cytokines, particularly interferon-α and tumor necrosis factor-α.

Topical imiquimod cream is approved for the treatment of anogenital warts (Chapter 381). In immunocompetent patients, imiquimod leads to complete clearance of warts in 37 to 52% of patients. It may also be beneficial in patients with refractory cutaneous leishmaniasis (Chapter 356) and for molluscum contagiosum (Chapter 380). It is administered as a topical cream three times weekly for a maximum of 16 weeks and is washed off 6 to 10 hours after application.

Side effects are primarily local and include erythema, irritation, tenderness, and, less often, erosion. The side effects usually resolve with cessation of the drug.

Grade A

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SUGGESTED READINGS

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