H CONT. as soon as possible in hospitalized patients because some observational studies have shown decreased adverse outcomes. Treatment initiation should not be delayed while waiting for the results of confirmatory testing.

Neuraminidase inhibitors are active against influenza A and B and can be given orally (oseltamivir), intranasally (zanamivir), or, more recently, intravenously (peramivir). Antiviral therapy is recommended for patients with severe disease, including all hospitalized patients, and those at high risk for complications with confirmed or suspected influenza infection. Antiviral therapy should be given for at least 5 days, but in severely ill or immunosuppressed patients, a longer duration should be considered with repeat follow-up testing to document clearance. Immunosuppressed patients are at risk for neuraminidase inhibitor resistance during or after therapy. H

Widespread influenza vaccination is the most important preventive intervention; all persons aged 6 months or older without contraindications and all health care personnel should be vaccinated (see MKSAP 18 General Internal Medicine). Oral oseltamivir and inhaled zanamivir are FDA approved for chemoprophylaxis (zanamivir is not approved in patients with chronic lung diseases) to contain outbreaks in institutional settings (such as long-term care facilities) and hospitals in conjunction with droplet precautions and vaccination. Chemoprophylaxis is given for at least 2 weeks, continuing at least 1 week after the last identified infection. Good hand hygiene and face masks can prevent secondary infections in households.

KEY POINTS

- Widespread influenza vaccination is the most important preventive intervention; all persons aged 6 months or older without contraindications and all health care personnel should be vaccinated.
- Antiviral therapy should be started within 48 hours of symptom onset but can be initiated up to 5 days after symptom onset in hospitalized patients; treatment should not be delayed while awaiting testing.

H Novel Coronaviruses

Coronaviruses are RNA viruses that cause respiratory and gastrointestinal diseases. Six known types infect humans, with some infecting animals as well. Two novel coronaviruses, severe acute respiratory syndrome–coronavirus (SARS-CoV) and Middle East respiratory syndrome-coronavirus (MERS-CoV), can infect animals and also cause severe disease and epidemics in humans. In 2002, SARS-CoV emerged in China, causing an acute pneumonia epidemic with a mortality rate of approximately 10%. No infections have been reported since 2004. Treatment is supportive. MERS-CoV emerged in 2012 in Saudi Arabia in humans and camels, with most infections occurring in the Arabian Peninsula. MERS-CoV causes pneumonia, diarrhea, and kidney failure with a mortality rate of approximately 40%. Because all types of coronaviruses may spread from human to human, contact and airborne precautions should be implemented for hospitalized patients with suspected infection. H

KEY POINT

- Middle East respiratory syndrome–coronavirus infection occurs primarily in the Arabian Peninsula and can cause severe pneumonia with diarrhea, kidney failure, and death.

Human Herpesvirus Infections

Human herpesviruses (HHVs) are a group of eight DNA viruses (**Table 68**). In humans, infection with HHV results in lifelong viral latency with the possibility of reactivation and oncogenesis. HHV can be transmitted by physical or sexual contact during active infection or through asymptomatic shedding of the virus (in saliva, semen, or cervical secretions); other routes include blood transfusion, organ transplantation, or maternofetal transmission. Varicella-zoster virus (VZV) is the only HHV that can be transmitted by the airborne route; it is also the only HHV with a vaccine that produces protective humoral immunity. Antivirals are available for some HHVs, and immunoglobulin therapy is available for cytomegalovirus and VZV.

Herpes Simplex Virus Types 1 and 2 H

Herpes simplex virus (HSV) type 1 infection is transmitted by oral-oral or oral-genital contact. It typically causes oral ulcers and affects 90% of adults (see MKSAP 18 Dermatology). During stress, severe illness, or immunosuppression, patients may experience recurrence of oral stomatitis or esophagitis. The incidence of primary genital infection by HSV-1 is increasing (see Sexually Transmitted Infections). HSV-1 is the most common cause of viral encephalitis (see Central Nervous System Infections).

HSV-2 is sexually transmitted and typically causes genital and rectal ulcers with or without proctitis. HSV-2 affects approximately one sixth of adults in the United States and can also cause recurrent benign lymphocytic meningitis (Mollaret meningitis), myelitis, sacral radiculopathy, and neonatal infection or death (maternofetal transmission in primary genital infection). HSV-1 and HSV-2 can cause herpetic whitlow (on fingers), herpes gladiatorum (a skin infection typically associated with contact sports), keratoconjunctivitis, retinitis, and erythema multiforme.

HSV-1 and HSV-2 infections can be treated and suppressed with oral nucleoside analogues (acyclovir, valacyclovir, and famciclovir). Topical antiviral agents (trifluridine and vidarabine) are used for herpetic keratitis. Intravenous acyclovir is used for severe mucocutaneous disease, disseminated infections in immunosuppressed persons, esophagitis, and suspected HSV encephalitis. H

TABLE 68. Human Herpesviruses and Associated Manifestations

Type	Synonym	Subfamily	Manifestations	Latency Site
HHV-1	Herpes simplex virus 1	α	Primary infection: oral and/or genital herpes (predominantly orofacial: gingivostomatitis, pharyngitis, herpes labialis) Reactivation: Bell palsy, viral encephalitis; other sites, including skin and eye (recurrent herpes labialis)	Nerve ganglion
HHV-2	Herpes simplex virus 2	α	Primary infection: oral and/or genital herpes (predominantly genital); meningitis, sacral radiculopathy, and transverse myelitis	Nerve ganglion
HHV-3	Varicella-zoster virus	α	Varicella (chickenpox), herpes zoster (shingles)	Nerve ganglion
HHV-4	Epstein-Barr virus	γ	Infectious mononucleosis, nasopharyngeal carcinoma; in immunocompromised patients: Burkitt lymphoma, central nervous system lymphoma (in patients with AIDS), posttransplant lymphoproliferative disease, hairy leukoplakia	B cell
HHV-5	CMV	β	CMV mononucleosis; in immunocompromised patients: CMV retinitis, leukopenia and thrombocytopenia, pneumonitis, colitis, esophagitis, or hepatitis	Monocyte, lymphocyte, endothelial cell, epithelial cell
HHV-6 (6A and 6B)	Roseolovirus, herpes lymphotropic virus	β	Mononucleosis-like syndrome, roseola (sixth disease, exanthema subitum) in children; may affect various organ systems in transplant patients	T cell
HHV-7	Roseolovirus	β	Usually asymptomatic; may be associated with pityriasis rosea; roseola (sixth disease, exanthema subitum) in children	T cell
HHV-8	Kaposi sarcoma–associated virus	γ	Kaposi sarcoma, PEL, multicentric Castleman disease	B cell, endothelial cell

CMV = cytomegalovirus; HHV = human herpesvirus; PEL = primary effusion lymphoma.

KEY POINTS

- Herpes simplex virus (HSV) type 1 is the most common cause of viral encephalitis, and the incidence of primary genital infection caused by HSV-1 is increasing.
- Intravenous acyclovir is used for severe mucocutaneous herpes, disseminated infections in immunosuppressed persons, esophagitis, and suspected HSV encephalitis.

Varicella-Zoster Virus

Overview

VZV (HHV-3) is transmitted by inhalation and colonization of the respiratory tract, with subsequent viremic dissemination to skin, liver, spleen, and sensory ganglia (varicella, or chickenpox). VZV establishes latency in the ganglia and can later reactivate, causing herpes zoster (shingles), especially in adults older than 60 years or in immunosuppressed patients. Contact and airborne precautions should be used for all hospitalized patients with varicella, for patients with disseminated herpes zoster, and for those with dermatomal zoster who are immunosuppressed.

Clinical Features and Diagnosis

Primary varicella infection (chickenpox) presents with a febrile pruritic vesicular rash affecting the skin and mucocutaneous surfaces (oropharynx, conjunctiva, genitals); the rash commonly begins on the face and trunk, then spreads to the extremities (centrifugal distribution). Lesions may comprise macules, papules, vesicles, and scabs in different stages of development. Skin lesions may become superinfected with *Streptococcus pyogenes* or *Staphylococcus aureus* (impetigo). Most children recover without sequelae, but adults may develop pneumonia, encephalitis, hepatitis, and cerebellar ataxia.

Herpes zoster typically causes a painful vesicular rash that follows a dermatomal distribution that does not cross the midline (see MKSAP 18 Dermatology). Young patients presenting with herpes zoster should be tested for HIV. Immunosuppressed patients can present with multiple dermatomes affected or with disseminated disease. Postherpetic neuralgia, defined as neuropathic pain lasting more than 1 month after resolution of the vesicular rash, is the most significant complication of herpes zoster. Other complications

H CONT. include herpes zoster ophthalmicus with visual loss, Ramsay-Hunt syndrome (vesicular rash in external ear associated with ipsilateral peripheral facial palsy and altered taste), pneumonia, hepatitis, and central nervous system complications such as meningitis, encephalitis, myelitis, and stroke caused by vasculitis (see Central Nervous System Infections).

Varicella or herpes zoster can be diagnosed clinically by the typical vesicular rash and confirmed with VZV PCR testing of the base of a vesicular lesion. VZV is underdiagnosed in the absence of a rash (zoster sine herpete); in such cases, cerebrospinal fluid serologic (VZV IgM and IgG) and PCR testing can be used to diagnose the infections. H

Management

H Antiviral therapy (acyclovir, valacyclovir, and famciclovir) speeds recovery and decreases the severity and duration of neuropathic pain if begun within 72 hours of VZV rash onset. Intravenous acyclovir should be used for immunosuppressed or hospitalized patients and those with neurologic involvement. H

Vaccination is the most important preventive strategy (see MKSAP 18 General Internal Medicine). Postexposure prophylaxis should be provided to susceptible persons (VZV IgG negative); postexposure varicella vaccination is appropriate in immunocompetent persons, and varicella-zoster immune globulin should be used in immunocompromised adults and in pregnant women.

KEY POINTS

- The rash of primary varicella infection (chickenpox) commonly begins on the face and trunk, then spreads to the extremities (centrifugal distribution) and may comprise macules, papules, vesicles, and scabs in various stages of development.
- In immunosuppressed patients, herpes zoster (shingles) can affect multiple dermatomes or present with disseminated disease; young patients presenting with herpes zoster should be tested for HIV.
- Postexposure varicella vaccination is appropriate in immunocompetent persons, and varicella-zoster immune globulin should be used in immunocompromised adults and pregnant women.
- Antiviral therapy speeds recovery and decreases the severity and duration of neuropathic pain if begun within 72 hours of VZV rash onset.

Epstein-Barr Virus

Epstein-Barr virus (EBV) (HHV-4) is highly prevalent; serologic studies show evidence of previous EBV infection in almost all adults. It is most commonly transmitted by saliva and is the main cause of infectious mononucleosis in children and adolescents. Patients present with fever, severe fatigue, exudative pharyngitis, cervical and axillary lymphadenopathy, and splenomegaly. Atypical lymphocytosis and aminotransferase level elevations are clues to the diagnosis, which is established by the presence of heterophile antibodies (Monospot test) or IgM to the EBV viral capsid antigen. The Monospot test result may be negative in the first week of illness. Treatment is supportive, with no role for acyclovir; glucocorticoids may be given to patients with autoimmune hemolytic anemia, central nervous system involvement, or tonsillar enlargement with a compromised airway. EBV is associated with the development of T-cell and B-cell lymphomas, Hodgkin and Burkitt lymphoma, nasopharyngeal carcinoma, and posttransplant lymphoproliferative disease in solid organ transplantation.

KEY POINTS

- Epstein-Barr virus infection, the primary cause of infectious mononucleosis, presents with fever, severe fatigue, exudative pharyngitis, cervical and axillary lymphadenopathy, and splenomegaly.
- The diagnosis of Epstein-Barr virus is established by the presence of heterophile antibodies on the Monospot test, although this test result may be negative during the first week of illness.

Human Cytomegalovirus

H Cytomegalovirus (HHV-5) infections are most commonly asymptomatic but may present with a mononucleosis-like syndrome without pharyngitis and with negative heterophile antibody results. Cytomegalovirus may be transmitted through the placenta (congenital cytomegalovirus), breastfeeding, saliva, blood transfusion, or organ transplantation (cytomegalovirus-positive donor to cytomegalovirus-seronegative recipient). Approximately 60% to 90% of adults have latent cytomegalovirus infection with reactivation of disease more common in immunosuppressed persons (those with AIDS, transplant recipients, those receiving glucocorticoid therapy). Cytomegalovirus can cause retinitis, pneumonitis, hepatitis, bone marrow suppression, colitis, esophagitis, and adrenalitis in immunocompromised persons. Immunocompetent patients occasionally also present with colitis.

Because cytomegalovirus can cause a myriad of clinical manifestations, a high index of clinical suspicion is important. Diagnosis is commonly confirmed with molecular tests, such as PCR testing of serum, bronchoalveolar lavage fluid, or cerebrospinal fluid, or by demonstrating typical cytopathic "owl's-eye" intracellular inclusions on biopsy specimens (**Figure 25**). Pathologic diagnosis is confirmed by cytomegalovirus immunostains. Serologic assays have limited diagnostic utility because most adults are seropositive; however, they are performed routinely in pretransplant evaluations to assess the risk of cytomegalovirus reactivation after transplantation and to determine appropriate prophylaxis.

Antiviral therapy with intravenous ganciclovir or oral valganciclovir is used in immunocompromised patients or in immunocompetent patients with severe disease. Oral valganciclovir is also used as prophylaxis or pre-emptive therapy (treat if the PCR serum testing result is positive) in transplant

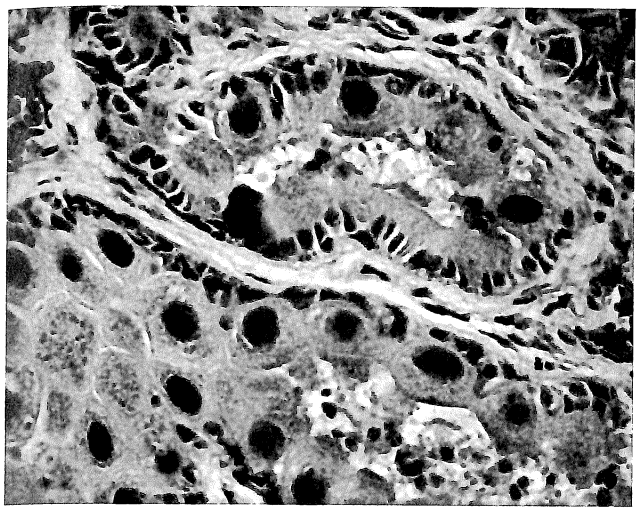

FIGURE 25. Under a magnification of 500X, a photomicrograph of a sample of kidney tissue reveals the presence of what are referred to as cytomegalic inclusion cells. With enlarged, darkly stained nuclei, such cells are also known as owl's-eye inclusion cells and are caused by cytomegalic inclusion disease resulting from cytomegalovirus.

CONT. recipients. Foscarnet and cidofovir can be used in instances of ganciclovir resistance or intolerance.

KEY POINTS

- Serologic assays for cytomegalovirus have limited diagnostic utility because most adults are seropositive; however, they are performed routinely in pretransplant evaluations to assess the risk of cytomegalovirus reactivation following transplantation and to determine appropriate prophylaxis.
- Diagnosis of cytomegalovirus is confirmed with molecular tests of infected fluids, by demonstrating typical cytopathic "owl's-eye" intracellular inclusions on biopsy specimens, or by cytomegalovirus immunostaining of pathologic samples.

Stewardship and Emerging Resistance

Introduction

Emergence of antibiotic resistance is potentiated by all antibiotic use. Careful antibiotic use is essential to preserving the armamentarium. Among outpatient visits, 12.6% are associated with antibiotic prescriptions, and 30% of those prescriptions are considered inappropriate. Most prescriptions are for acute respiratory infections (usually caused by viruses) and asymptomatic bacteriuria not requiring antibiotic treatment. One fifth of emergency department visits for adverse drug events are related to antibiotics. Inpatient antibiotic use accounts for 38.5% of all antibiotic use; half of hospitalized patients receive antibiotics, and half of these medications are considered unnecessary or inappropriate. The World Health Organization has named carbapenem-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa* and carbapenem-resistant and extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae as priority-one pathogens, for which new antibiotics are critically needed.

Antimicrobial Stewardship and the Value of Infectious Disease Consultation

Antibiotic stewardship refers to coordinated interventions to improve antibiotic use and clinical outcomes by promoting optimal antibiotic regimens. Goals include minimizing adverse events (5% risk per antibiotic per patient), risk of *Clostridium difficile* infection, and emergence of resistance. A key aspect of stewardship is avoiding antibiotic administration when not indicated. Antibiotic selection, dosing, therapy duration, and route of administration are also considered. Furthermore, antimicrobial stewardship programs include simplifying unnecessary combination therapy, avoiding redundant double anaerobic coverage, converting intravenous to oral agents, streamlining de-escalation, and minimizing duration of therapy.

Combination therapy does not prevent the emergence of resistance. However, it may be considered in specific circumstances, such as empiric therapy regimens, to broaden the spectrum of activity or provide coverage for potential antimicrobial-resistant organisms pending culture and susceptibility results. Antibiotic combination therapy may also provide synergistic activity in limited situations, such as enterococcal endocarditis and bacteremia caused by carbapenem-resistant Enterobacteriaceae (CRE).

Conversion from an intravenous to an oral antimicrobial agent should be considered for ease of administration and to limit intravenous catheter access and use, thereby decreasing the risk of catheter-related bloodstream infection. Factors supporting readiness for conversion include a temperature of 38 °C (100.4 °F) or less, an improving leukocyte count, clinical stability and improvement of signs and symptoms related to infection, a functioning gastrointestinal tract and ability to swallow medications or having a nasogastric tube in place, no diagnostic indication for intravenous therapy (endocarditis, *Staphylococcus aureus* bacteremia), and availability of a suitable oral alternative with good oral bioavailability (fluoroquinolones, oxazolidinones, metronidazole, clindamycin, trimethoprim-sulfamethoxazole, fluconazole, doxycycline, voriconazole).

Antimicrobial stewardship programs use various interventions to optimize antimicrobial use. Interventions that have been shown to be effective in improving outcomes, decreasing resistance, and decreasing costs include preauthorization and prospective audit with feedback to the