Pathogens

Chapter 2

Viruses

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Abstract Viral infections are an important and often unrecognized component of disease in immunocompromised patients. The diagnosis and management of viral infections have expanded largely because of new quantitative molecular diagnostic assays. Well-recognized pathogens such as herpes simplex virus (HSV), cytomegalovirus (CMV), and respiratory viruses have been joined by newly recognized pathogens such as BK virus, human herpesvirus-6 (HHV-6), and human metapneumovirus in this highly susceptible patient population. The role of Epstein-Barr virus (EBV) and Human herpesvirus-8 (HHV-8) in lymphoproliferative diseases also continue to be clarified. As a result, the management of viral infections in patients with hematologic malignancies continues to be a growing challenge for the clinician.

Keywords Antivirals • Cytomegalovirus • Herpes viruses • Hematological malignancy • Respiratory viruses • Epstein-Barr virus • Polyoma virus • Adenovirus • Viral infections

1. Herpesviruses

The herpesviruses are large, enveloped double-stranded DNA viruses that produce a lifelong infection within the host. The ability to establish latency makes these viruses a common and potentially life-threatening challenge in patients with hematologic malignancies or in those who have undergone hematopoietic stem cell transplantation (HSCT). Herpesvirus infection should be considered a dynamic interaction between latent virus and the immune system of the individual patient. In the immunocompromised host, latent infection reactivates leading to invasive disease, immune-mediated complications or, Epstein-Barr virus (EBV) and human herpesvirus-8 (HHV-8), malignancy.

There are eight known human herpesviruses that are traditionally divided into three subfamilies based on genomic organization, homology, and location of latency (Table 2-1).

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Table 2-1. Classification of the herpesviruses.

Virus	Subfamily	Location of latency
Herpes simplex virus, type 1	α	Dorsal root ganglia
Herpes simplex virus, type 2	α	Dorsal root ganglia
Varicella-zoster virus	α	Dorsal root ganglia
Cytomegalovirus	β	Bone marrow myeloprogenitor cells
Human herpesvirus-6	β	Bone marrow myeloprogenitor cells
Human herpesvirus-7	β	Bone marrow myeloprogenitor cells
Epstein-Barr virus	γ	B lymphocytes
Human herpesvirus-8 (Kasposi's sarcoma herpesvirus)	γ	B lymphocytes

2. Herpes Simplex Virus, Type 1 and 2

Herpes simplex viruses, type 1 and 2 (HSV-1 and HSV-2), are transmitted through intimate or mucocutaneous contact including the oral mucosa, genitalia, ocular epithelium, anal mucosa, respiratory tract, and bloodstream. HSV-1 is classically associated with herpes labialis, infection of the oral mucosa. HSV-2 is classically associated with herpes genitalis, infection of the genital tract. Both are common throughout the United States. Previous studies have suggested that as many as 62% of healthy adults have serologic evidence of previous infection with HSV-1, and 21% with HSV-2 [1]. Recent trends suggest an overall decrease in the incidence of HSV-2, though HSV-1 may be becoming a more common cause of genital herpes infection [2]. Clinically, the two viruses are indistinguishable.

2.1. Clinical Syndromes

Localized reactivation of HSV-1 or -2 can lead to cutaneous herpes lesions or keratoconjunctivitis through distribution of the involved nerve fibers from the dorsal root ganglia where the virus remains latent. With the loss of cellular immunity in the setting of hematologic malignancy, disseminated disease has been reported [3]. Diffuse cutaneous eruptions covering multiple dermatomes may occur, or may involve other organs with or without concomitant cutaneous lesions (Table 2-2).

Tonsillar abscess formation due to HSV has also been reported in a patient with a history of chronic myelogenous leukemia who underwent HSCT [9]. In patients with chronic lymphocytic leukemia, a syndrome of generalized lymphadenopathy has been attributed to HSV alone [10] and with coinfection of HSV-1, HSV-2, and EBV [11]. Localized lymphadenopathy due to HSV may be seen in individuals with oral or genital infections that may be asymptomatic in the severely compromised host. Necrotizing spinal myelopathy has been reported in a patient with T-cell leukemia, confirmed with immunohistochemical staining [12]. These presentations are uncommon.

Table 2-2. HSV-1 and HSV-2 syndromes.

Anatomic location/syndrome	Symptoms/presentation
Mucocutaneous	
Oral/peri-oral Genital Disseminated	Vesicle formation with or without ulceration in affected skin areas, usually followed by crusting of the visible lesions
Esophagitis	Odynophagia, dysphagia, retrosternal chest pain [4]
Hepatitis	Fever, abdominal pain, leucopenia, nausea/vomiting, with or without cutaneous lesions [5]
Pneumonitis	Dyspnea, cough, fever [6]
Central/Peripheral Nervous System	
Meningitis	Fever, headache, nausea/vomiting, photophobia, stiff neck
Encephalitis	Fever, headache, impaired consciousness, seizures, other focal neurologic deficits
Radiculopathy (myelitis)	Autonomic dysfunction [7], radiculopathy, possibly transverse melts [8]
Ocular	
Keratoconjunctivitis	Pain, decreased vision, characteristic dendritic corneal lesions
Chorioretinitis	Decreased vision, acute retinal necrosis with blindness
Immunologic	
Erythema multiforme	Distinctive eruption on affected skin with characteristic histology (T-cell infiltration)

HSV Herpes simplex virus

2.2. Diagnosis

The diagnosis of HSV can often be made clinically for limited oral, peri-oral, or genital infections with characteristic vesicles or ulcerations. The use of the classic Tzanck smear looking for viral cytopathic effect can be useful although the study is limited by lack of specificity and the need for expert interpretation. Molecular techniques and immunostaining provide increased speed, sensitivity, and specificity and are gaining wider use (Table 2-3).

Mucocutaneous disease is often diagnosed with fluorescent immunostaining of cell scrapings taken from the lesions. This allows testing for other herpesviruses that may cause a similar clinical picture (e.g., varicella-zoster virus), and to exclude HSV involvement in the evaluation of oral lesions that could result from other causes such as drug toxicity. Esophagitis, pneumonitis and hepatitis are also frequently best diagnosed through the use of immunohistochemical staining for HSV-specific antigens on biopsy specimens. In these settings, HSV may be a part of a dual infection (e.g., with *Candida* species, other viruses). Cultures are of little value in disease involving organs beyond the mucocutaneous barrier. Cultures from respiratory specimens, in particular, can be misleading if positive, given the frequency of asymptomatic shedding of the virus from the oropharynx in immunocompromised individuals. Disease involving the central nervous system (CNS) is frequently diagnosed by molecular amplification assays such as polymerase chain reaction (PCR)

Table 2-3. HSV-1 and -2 Diagnostics.

Diagnostic test	Description	Comments
Serology	Evaluation of the serum for presence of HSV-1 and HSV-2-specific IgG and IgM antibodies	Can be negative in acute infection or in patients with hypogammaglobulinemia; indicates only past infection
Culture	Swabs taken from the lesions or biopsies from tissue samples grow HSV in cell culture media; results in 24–48 h depending on viral titer	Dependent on proper processing of specimen (viral culture media and transport and storage at 4°C); sensitivity decreases if lesions are over 48 h old; may give false positive results from respiratory specimens
PCR	Molecular gene amplification specific for HSV; commonly used on CSF, tissue lesions or vitreous fluid	Assay not standardized, but high sensitivity and specificity
Routine pathological examination	Histopathology of biopsies with routine H&E staining or from Tzanck smears reveal giant multinucleated cells, cytopathic effect or intranuclear inclusions	Cellular changes from tissue can be seen with other herpesviruses (VZV, CMV, etc.); dependent on quality of sample and local expertise
Fluorescent or immunohistochemical staining	Slides of cells prepared from scrapings of lesions or tissue biopsies; HSV-specific monoclonal antibodies with indirect fluorescence or direct immunostaining	Proper cell handling technique required

HSV Herpes simplex virus; *PCR* Polymerase chain reaction; *CSF* Cerebrospinal fluid; *H&E* Hematoxylin and eosin; *VZV* Varicella-zoster virus; *CMV* Cytomegalovirus

of cerebrospinal fluid (CSF) samples. The sensitivity and specificity of HSV PCR from CSF is thought to be close to 95% [13], though specimens taken early or late in the clinical course may be more likely to be falsely negative [14]. Brain biopsy with immunohistochemical staining remains definitive for HSV encephalitis if PCR is unrevealing and diagnosis is essential. Ocular disease is often made on clinical examination, though PCR of cell scrapings in keratoconjunctivitis or vitreous fluid in the case of retinal disease may also play a role [15].

2.3. Therapy

Treatment should be considered in all patients with active HSV infection and underlying hematologic malignancy or HSCT. Immunocompromised hosts are at a greater risk for severe disease and dissemination. Minor herpes labialis infections can spread rapidly to the pharynx, the esophagus, and via the bloodstream to multiple organs and cutaneous dermatomes. The most widely available agents for treatment of HSV infections are nucleoside analogues that inhibit the synthesis of HSV viral DNA. The most frequently used agent by far is acyclovir, though valacyclovir, famciclovir, vidarabine, and foscarnet can be used depending on the clinical scenario (Table 2-4). Intravenous therapy should be considered as initial therapy for progressive or disseminated infection in immunocompromised hosts.

Valacyclovir is an L-valine ester prodrug of acyclovir. After absorption, it is metabolized into acyclovir by the liver. This prodrug form of acyclovir can achieve higher plasma levels than equivalent doses of oral acyclovir, and thus less frequent dosing can be used for similar therapeutic levels of drug (bid vs. 5/day).

Table 2-4. HSV therapeutics.

Syndrome	Therapeutic options
Mucocutaneous HSV	Acyclovir 400 mg po 5x/day Acyclovir 5 mg/kg IV q 8 h Valacyclovir 500 mg to 1 g po bid Famciclovir 500 mg po bid
Disseminated HSV	Acyclovir 10 mg/kg IV q 8 h
Esophagitis	Acyclovir 5 mg/kg IV q 8 h
Hepatitis	Acyclovir 5–10 mg/kg IV q 8 h
Pneumonitis	Acyclovir 5–10 mg/kg IV q 8 h
Encephalitis/meningitis	Acyclovir 10 mg/kg IV q 8 h
Keratoconjunctivitis	Topical therapy with either: 3% acyclovir gel 3% vidarabine ointment 1% trifluorothymidine drops
Chorioretinitis or acute retinal necrosis	Acyclovir 10 mg/kg IV q 8 h
Erythema multiforme	Treat as localized mucocutaneous disease

HSV Herpes simplex virus

Famciclovir is the diacetyl ester prodrug of penciclovir and is rapidly converted by the body. Vidarabine was the first antiherpesvirus drug to be of proven value, but is rarely used in clinical practice due to inferiority in clinical trials to acyclovir and significant toxicities, including neurotoxicity with parasthesias, ataxia, seizures, and rarely coma [16, 17]. Foscarnet is a direct noncompetitive inhibitor of herpesvirus DNA polymerase and has in vitro activity against all herpesviruses. Foscarnet undergoes little intracellular metabolism, and is not dependent on the herpetic thymidine kinase (required to phosphorylate acyclovir to the active state) and therefore may be used in the treatment of acyclovir-resistant strains of HSV that arise due to mutations in the viral thymidine kinase. The utility of foscarnet is limited by nephrotoxicity, symptomatic hypocalcemia, and other electrolyte (magnesium, potassium) losses that require co-infusion with a large amount of fluid.

With the exception of the topical ocular antiviral agents, dosages of all agents listed in Table 2-4 are modified in the setting of renal insufficiency. Length of therapy is usually for 7–14 days, with the exception of disease involving the CNS, wherein therapy is often extended to a total of 14–21 days because of risk for recurrence [18, 19]. For acyclovir resistance, foscarnet is generally used at doses of 40 mg/kg IV every 8 h for 14–21 days, depending on clinical response [20].

Patients with hematologic malignancies have a higher incidence of HSV shedding in their saliva, are at increased risk for reactivation of HSV with intensified immunosuppression, and are at increased risk of atypical manifestations and dissemination of disease. In the setting of HSCT, HSV-seropositive individuals may have a reactivation rate of 65–90% [21]. Thus, the routine implementation of prophylaxis has been advocated in any patient who has evidence of prior infection with HSV (HSV-1 or -2 seropositive) with hematologic malignancy undergoing chemotherapy or HSCT. Suppression can be

in the form of acyclovir 400 mg po bid or higher, valacyclovir 500 mg po qd or bid, or famciclovir 250 mg po bid beginning on the day of conditioning or induction and continuing until resolution of neutropenia or 6 weeks, whichever is longer. If patients cannot tolerate oral therapy, then IV acyclovir 250 mg/m^2 IV every 12 h is also effective [22].

3. Varicella-Zoster Virus

Varicella-zoster virus (VZV) is the third member of the α-subfamily of human herpesviruses. Classically, VZV is associated with two clinical syndromes: varicella, known as chickenpox, and herpes zoster, known as shingles. As with HSV, the patient with an underlying lymphoproliferative disorder or HSCT is at higher risk for dissemination of disease and systemic involvement, blurring the clinical entities. Although frequently considered a benign childhood illness in the immunocompetent population, VZV carries an overall case fatality rate of 2–4 deaths per 100,000, with greatest risk among older adults and infants [23]. Older estimates before the era of effective antiviral therapy and zoster immunoglobulin put the mortality in those children with acute lymphocytic leukemia who developed primary VZV at 7% [24]. Compared to HSV, however, infection is even more ubiquitous, with over 90% of people in temperate climates infected before adolescence [25]. Infection is typically spread via the respiratory tract during acquisition of primary infection, or by physical contact with mucocutaneous lesions. Due to the great infectivity of VZV, attack rates can be as high as 100% in the susceptible host [26].

3.1. Clinical Syndromes

Primary infection, or varicella, presents with fever and often the simultaneous development of a characteristic cutaneous vesicular rash that can involve mucosal surfaces (oropharynx, conjunctiva, genitourinary tract, etc.). It begins with small macular erythematous lesions that progress to a vesicular stage before crusting-over during a 1-2 day period. The lesions evolve at different times so that some lesions may be healing while fresh lesions emerge.

Primary infection in patients with leukemia or in patients who have undergone HSCT occurs most often in children and can lead to dissemination with involvement of multiple organs, including the CNS as meningitis, encephalitis, or vasculitis of the intracranial vessels. In the immunocompromised or immunologically naïve host, infection produces skin lesions that persist for longer periods, and may be associated with hepatitis, cholangitis, pneumonitis, uveitis, or cause a sepsis-like syndrome with disseminated intravascular coagulation [24]. Bacterial superinfection of skin lesions can occur with organisms including *Staphylococcus aureus*, leading to cellulitis, deeper soft-tissue involvement, and sepsis [27].

3.2. Diagnosis

Often, the diagnosis of routine varicella or zoster can be made based on physical examination when a characteristic rash and distribution is observed or when exposure in the case of primary infection is present. The differential

includes other viral infections such as HSV or enteroviruses, both of which can have atypical presentations in the immunocompromised host. Again, as with HSV, the Tzanck smear of cell scrapings from a cutaneous lesion may be useful, but lacks sensitivity and specificity. Use of specific molecular techniques is common for diagnosis of VZV (Table 2-5).

There is some serological cross-reactivity between VZV and HSV-1 due to similarities in the viral glycoprotein B [28]. Multiple methods exist to measure antibodies to VZV, including fluorescent antibody to membrane antigen (FAMA) methods, enzyme-linked immunosorbent assays (EIA), latex agglutination methods, complement fixation assays, and other immunofluorescent assays. Individual laboratories may vary in their approach. Overall, serologic tests are not as clinically useful in rapidly diagnosing VZV as PCR and antigen detection. Most cases of VZV in the immunocompromised occur as a result of viral reactivation; serologic testing to determine those at risk for primary infection is not 100% reliable in these hosts [29]. Though the exact sensitivity and specificity of PCR from CSF for VZV is unclear, PCR is becoming relied upon by more and more physicians for diagnosing CNS infections due to herpesviruses in general. The VZV PCR assay is likely most useful earlier in the patient's clinical course, particularly if primary infection is suspected and seroconversion may be delayed [30, 31]. PCR can also be used to distinguish infection between wild-type VZV and that of the vaccine strain [32].

Table 2-5. VZV diagnostics.

Diagnostic test	Description	Comments
Serology	Evaluation of the serum for presence of VZV-specific IgG and IgM antibodies	Can be negative in acute infection or in patients with hypogammaglobulinemia; indicates past infection
Culture	Swabs from mucocutaneous lesions or biopsies can grow VZV in cell cultures in 3–5 days	Dependent on proper processing of specimen (requires transport and storage at 4°C); difficult to isolate from nasopharynx
PCR	Molecular gene amplification specific for VZV; used on CSF, tissues or skin lesions	Sensitive and specific, but not universally available
Routine pathological examination	Pathological examination from biopsies with routine H&E staining or from Tzanck smears can reveal giant multinucleated cells, cytopathic effect or intranuclear inclusions	Most cellular changes also seen with other herpesviruses (HSV, CMV, etc.); dependent on quality of sample, local expertise
Fluorescent or immunohistochemical staining	Slides of cells from scrapings of lesions or biopsies; VZV-specific monoclonal antibodies for indirect fluorescence or immunostaining	Proper cell handling technique required

VZV Varicella-zoster virus; *PCR* Polymerase chain reaction; *CSF* Cerebrospinal fluid; *H&E* Hematoxylin and eosin; *HSV* Herpes simplex virus; *CMV* Cytomegalovirus

3.3. Therapy

In the non-immunocompromised population, primary infection with VZV is self-limited and usually treated with symptomatic intervention only. Antiviral therapy is indicated for reactivation disease such as shingles, or for diffuse disease in immunocompromised individuals. Intravenous acyclovir (10 mg/kg every 8 h) is considered first-line therapy for any patient with a hematologic malignancy or HSCT who develops primary infection or reactivation of VZV. Patients improving on this regimen may be converted to oral therapy with either acyclovir at 800 mg po 5x/day or valacyclovir 1 g po tid to complete the course. Famciclovir at a dose of 500 mg po tid may also be of value in this setting. The latter agents (famciclovir and valacyclovir) have better oral bioavailability than acyclovir. Most experts recommend extending therapy for at least 2 days beyond crusting of all lesions. Resistance is rare, reported most often in patients with underlying HIV infection [26]. Foscarnet may be an alternative agent when resistance develops. All of these medications require dose reduction with renal insufficiency.

Patients with hematologic malignancies or HSCT, regardless of serostatus, should avoid exposure to persons with active VZV infections [29]. Use of VZV immunoglobulin (VZIG) should be considered in the prevention of infection in seronegative patients and as a means to possibly reduce the risk for severe disease in patients with hematologic malignancies exposed to VZV. Vaccination with the live VZV vaccine should be considered in advance of immune suppression but cannot be used in immunocompromised hosts. In VZV-seronegative patients, administration of VZIG as soon as possible within 96 h after exposure is indicated [33]. Some experts also report using those VZIG in HSCT patients with a significant exposure who are already known to be seropositive, but are often hypogammaglobulinemic. Significant exposures include contacts with individuals with chicken pox or who received the live VZV vaccine and subsequently developed a varicella-like rash with the risk of transmitting the vaccine-related strain of VZV [33]. Dosing of VZIG is 125 international units per 10 kg of body weight with a maximum dose of 625 units and a minimum dose of 125 units given intramuscularly. Administration after 96 h from the exposure is of unclear value.

In order to prevent the spread of VZV infection to other immunocompromised individuals or VZV-seronegative individuals in the hospital setting, patients with VZV disease should be placed under airborne and contact precautions [34]. Although intravenous acyclovir over several months and oral acyclovir dosed at 800 mg po bid for up to 1 year have been shown to prevent VZV in patients undergoing HSCT [35], long-term acyclovir prophylaxis to prevent VZV is not routinely recommended [33]. Prevention in most immunocompetent individuals is now through the use of the live, attenuated VZV vaccine. Though different formulations exist, all vaccines use the Oka strain of VZV isolated from a healthy child with varicella and then attenuated through sequential passage in cell culture [26]. Currently, live vaccine is contraindicated for use among HSCT recipients and other immunocompromised individuals. Further research is needed to determine the efficacy and safety of the VZV vaccine in this population. Ideally, however, all healthcare workers, family members of patients, or other household contacts who are VZV-seronegative should be immunized as soon as the decision is made to perform HSCT.

Completion of the vaccine should be done 4 or more weeks before the conditioning regimen begins [33]. An inactivated vaccine is under development.

4. Cytomegalovirus

Cytomegalovirus (CMV) is a member of the β-subfamily of herpesviruses. Infection in the United States population is common, with an age-adjusted estimate of 58.9% [36]. Risk increases steadily throughout an individual's lifetime, and lower socioeconomic status as well as ethnic background may play a role in the risk of infection. Spread of the virus is usually through mucocutaneous or intimate contact, as well as through congenital acquisition or transplantation of organs and transfusion of blood products. In the immunocompromised patient population, coinfection with multiple strains have been reported [37]. CMV is one of the most important viruses in immunocompromised patients. Primary infection acquired through HSCT or blood products, or reactivation of latent virus can lead to significant morbidity.

4.1. Clinical Syndromes

Primary infection of CMV is classically associated with a mononucleosis-like syndrome that results in fever, lymphadenopathy, and leucopenia, often with a relative lymphocytosis similar to primary infection with EBV. In the case of CMV, the frequently used heterophile agglutinin test in EBV will be negative, however. In the immunocompromised patient, or in the patient with underlying inflammatory disorder, CMV viral replication can lead to invasive tissue or end-organ disease (Table 2-6).

Virtually, all organ systems can be affected by invasive CMV infection. Aside from the syndromes listed in Table 2-6, CMV has also been blamed for causing a hemorrhagic cystitis in patients after HSCT [42, 43]. T-cell function is the primary determinant for control of CMV infection. Aggressive chemotherapy and use of T-cell depleting agents such as alemtuzumab increase the risk for CMV disease in patients with hematologic malignancy. Alemtuzumab in particular has been associated with rates of CMV viremia in patients with lymphoproliferative disorders of 15–44% [44–46].

4.2. Diagnosis

The development of sensitive molecular techniques to diagnose active CMV infection has revolutionized the approach to CMV management in the immunosuppressed population. Identifying patients at risk who will require preemptive or prophylactic therapy is becoming a more prominent approach to HSCT care in particular. Quantitative assays to measure the viral load in the blood have impacted management of infection (Table 2-7).

Serologies are most useful in determining past exposure and in identifying patients at risk for reactive disease when immunosuppressed. If negative, the patient may be at high risk for acquiring CMV infection if transplanted from a CMV seropositive donor. Cell culture techniques using human fibroblast cell lines are time-consuming, with results in 10 days to as long as 4–6 weeks in order to detect the cytopathic changes indicative of a positive assay. Shell vial cultures allow detection of CMV antigens prior to the development of

Table 2-6. CMV syndromesa.

Anatomic location/syndrome	Symptoms/presentation
Mononucleosis	Fever, lymphadenopathy, leucopenia with relative lymphocytosis
Pneumonitis	Most severe complication of CMV infection with cough, dyspnea, interstitial infiltrates on chest radiography superinfection [38]
Gastrointestinal	
Esophagitis/gastritis	Odynophagia, dysphagia, retrosternal chest pain, anorexia, nausea, vomiting
Enteritis/colitis	Fever, watery diarrhea (occasionally bloody), plaque-like pseudomembranes, erosive or ulcerative disease
Hepatitis/cholangitis	Fever, abdominal pain, leucopenia, nausea/vomiting, elevated transaminases (bacterial co-infection)
Pancreatitis	Fever, abdominal pain, and peritonitis, infection of the biliary tract [39]
Myocarditis	Congestive heart failure
Central/Peripheral Nervous System	
Meningoencephalitis	Vasculitis with fever, headache, nausea/vomiting, photophobia, impaired consciousness, seizures, focal neurologic deficits
Polyradiculopathy	Hyporeflexia, limb weakness, parasthesias and possibly sensory loss, myelitis [40]
Guillain–Barré syndrome	Progressive ascending paresis [41]
Ocular	
Retinitis	Decreased vision, acute retinal necrosis with blindness
Hematologic	
Disseminated intravascular coagulation	Consumptive coagulopathy with thrombocytopenia and hemolytic anemia usually in the setting of fever and sepsis-like syndrome

CMV Cytomegalovirus
[a]Non-exclusive syndromes

cytopathic changes. The overall sensitivity and specificity are limited by the frequency of asymptomatic shedding in immunocompromised hosts in respiratory, urinary, and gastrointestinal sites [47]. Molecular-based techniques such as antigenemia assays, nucleic acid amplification, and hybrid capture assays are commonly used in the diagnosis of active CMV disease. The antigenemia assay is limited in the setting of profound neutropenia because of the lack of circulating granulocytes. Though exact predictive values of these tests may vary depending on what study is referenced, all appear to have a high sensitivity and specificity in immunocompromised patients [48–50] and in patients who have undergone allogeneic HSCT [51]. PCR from whole blood tends to be a more sensitive assay than the others, but less specific than plasma when used for molecular amplification. The pp65 antigenemia assay, when not limited by neutropenia, may be the most specific in terms of predicting active disease [51]. PCR, the hybrid capture assay, and the antigenemia assay are all likely useful in monitoring a patient's response to therapy. Viral loads may take several weeks to become undetectable on therapy, however [52, 53], and retesting a patient less than 1 week after initiation of treatment is generally not advised.

Table 2-7. CMV diagnostics.

Diagnostic test	Description	Comments
Serology	Evaluation of the serum for presence of CMV-specific IgG and IgM antibodies	Determines risk for latent CMV reactivation, past infection; may be negative in acute infection and with hypogammaglobulinemia or immunosuppression
Culture	Shell vial culture of CMV with human fibroblasts for detection of immediate early antigens	Shell vial technique can be positive in 2–3 days; lacks specificity for detecting active CMV disease
Antigenemia assay	Rapid detection of CMV-specific proteins (pp65) in peripheral blood leukocytes, correlates with total viremia	Semi-quantitative; requires circulating peripheral blood polymorphonuclear cells
Hybrid capture assay	Signal amplification with RNA probe for CMV DNA; detection with antibodies specific for RNA:DNA hybrids	Semi-quantitative; range of ~1,400–600,000 copies of CMV/mL
Nucleic acid amplification	PCR of DNA with gene amplification specific for CMV; nucleic acid sequence-based amplification (NASBA) for immediate-early and late gene expression	Few data on immunocompetent hosts; various assays are not comparable; highly sensitive with detection level ~500 copies/mL or less
Pathologic inspection with or without immunohistochemical staining	H&E stain can reveal "owl's eye" intranuclear inclusions; sensitivity can be increased with staining for CMV-specific proteins	Proper cell handling technique required

CMV Cytomegalovirus; *PCR* Polymerase chain reaction; *H&E* Hematoxylin and eosin

4.3. Therapy

Although the nucleoside analogue acyclovir has some activity against CMV in vitro, the related purine analogue ganciclovir has become the gold standard for management of CMV disease. Acyclovir has been used in prophylaxis, but lacks the potency required for treatment of established CMV disease [54]. Other antivirals that have clinical utility for the treatment of CMV include valganciclovir, which is the prodrug of ganciclovir, foscarnet, and cidofovir. The latter two are generally reserved for infections caused by ganciclovir-resistant strains of CMV because they can cause significant nephrotoxicity and other side effects. Other agents are less well-studied; use of ancillary agents may have benefit in certain clinical scenarios (Table 2-8).

Both valganciclovir and ganciclovir are capable of inducing hematologic abnormalities including neutropenia, anemia, and thrombocytopenia. Valganciclovir is the L-valyl ester prodrug of ganciclovir, and as such has a 1.7-fold greater bioavailability than oral ganciclovir. A 900 mg dose of valganciclovir is able to achieve a systemic exposure of IV ganciclovir dosed at 5 mg/kg [57], and has now replaced oral ganciclovir in clinical practice [54]. Ganciclovir resistance among CMV isolates is frequently due to a mutation of the phosphatase UL 97 gene, or less commonly the DNA polymerase UL 54 gene [58]. New resistance mutations are under study. In cases of resistance, either documented or presumed due to no decrease in viral load after up to 3 weeks of therapy,

Table 2-8. CMV therapeutics.

Agent	Dose	Comments
Ganciclovir	5 mg/kg IV every 12 h for 7–14 days, followed by 5 mg/kg IV once daily	Induction therapy used initially followed by maintenance; length of therapy varies (treat to negative assay)
	1–1.5 g po tid	Oral formulation generally avoided as initial therapy for active CMV disease due to poor bioavailability
Valganciclovir	900 mg po bid for initial therapy, followed by 900 mg po qd or 450 mg po bid	Data are limited on use as initial therapy for active CMV disease; some failures in GI disease
Foscarnet	40–60 mg/kg IV every 8–12 h, or 90 mg/kg IV every 12 h	Dosing and duration of therapy less well-studied; given with saline hydration and electrolyte (Mg, K) replacement (renal toxicity)
Cidofovir	5 mg/kg IV once weekly	Given with saline hydration and probenecid (renal toxicity)
Other agents		
CMV immune globulin	150 mg/kg IV	Clinical utility likely limited to HSCT patients with CMV pneumonitis [55] or hypogammaglobulinemia
Fomivirsen	330 μg intravitreally	Used for the treatment of CMV retinitis only
Maribavir	Under study (orphan drug)	Novel anti-CMV agent currently undergoing active investigation
Leflunomide	100–200 mg po qd for up to 7 days, followed by 20–60 mg po qd (not approved for this indication); ideal dosing parameters unclear [56]	Immunosuppressive agent; induction therapy followed by maintenance; monitor serum levels (goal 60–80 mcg/mL) to avoid toxicity (liver); experimental use with failure of other antiviral agents; clinical benefit for active CMV disease unclear

CMV Cytomegalovirus; *IVIG* Intravenous immunoglobulin; *HSCT* Hematopoietic stem cell transplant

foscarnet or cidofovir or combination therapy is recommended. All of these antiviral agents require dose reduction in the setting of renal insufficiency. Foscarnet and cidofovir may provoke significant renal toxicity.

Although the use of CMV-negative and leukocyte-depleted blood products can help prevent CMV infection in seronegative patients, the risk is never reduced to zero. Prophylaxis and preemptive treatment have reduced the significant morbidity and mortality associated with CMV disease in this population. Late CMV disease post-HSCT remains a significant risk for mortality and likely reflects ongoing immune dysfunction and ineffective T-cell control of viral replication [59]. Risk factors include ongoing pharmacological immunosuppression such as high-dose corticosteroids, graft versus host disease (GVHD), need for donor lymphocyte infusions, and previous CMV disease. Prophylaxis with IV ganciclovir for up to 100 days post-transplant has been effective in preventing reactive CMV infection in seropositive HSCT recipients [60], as has use of oral acyclovir and valacyclovir [61, 62]. Many centers, however, advocate the preemptive approach in order to avoid unnecessary toxicity from prolonged antiviral drug use. Testing the blood of at-risk patients on a regular basis using molecular amplification or antigen detection techniques can often uncover low-level asymptomatic viremia that may be

amenable to antiviral therapy before symptomatic CMV disease can evolve. IV ganciclovir and valganciclovir have been used, though there are no large randomized, comparative studies completed in the HSCT population regarding valganciclovir for this purpose [63].

5. Human Herpesvirus-6 and -7

The role of the β-herpesviruses, human herpesvirus-6 (HHV-6) and human herpesvirus-7 (HHV-7), in causing disease among immunosuppressed patients remains unclear; prospective studies are needed to define the effects of reactive infections in patients with hematologic malignancies. Both viruses infect most individuals at a young age, occasionally causing a self-limited childhood febrile illness with or without skin rash. Primary infection in adults is rare, though a mononucleosis-like syndrome caused by HHV-6 has been described in a few case reports [64, 65]. Among HSCT recipients, HHV-6 has also been associated with a syndrome of pneumonitis, hepatitis, encephalitis, bone marrow suppression, as well as asymptomatic viremia of unclear significance [66–73]. HHV-7 has been associated with meningitis and encephalitis and other neurologic dysfunction [74–76] with a possible role in bone marrow suppression uncertain [77].

Diagnostic assays for HHV-6 and -7 are evolving. All, unfortunately, still have limitations in differentiating active disease from latent virus (Table 2-9).

Serology can be performed using a variety of assays such as EIA, radioimmunoassays, or indirect fluorescence assays. Because most adults are seropositive, only paired sera showing a ≥ 4-fold rise in titers can be considered diagnostic. IgM antibodies in HHV-6 may be limited by the presence of false positives in the general population [78]. Older HHV-7 serology assays are also limited by cross-reactivity with HHV-6 [79]. These tests are not widely available and have little clinical utility. PCR assays have been performed on serum, plasma, whole blood, CSF, and tissue. Cell-free samples such as serum,

Table 2-9. HHV-6 and HHV-7 diagnostics.

Diagnostic test	Description	Comments
Serology	HHV-6 or HHV-7-specific IgG and IgM antibodies	Indicates presence of past infection; may be negative in acute infection or with hypogammaglobulinemia; paired samples for diagnosis
PCR	Quantitative amplification of HHV-6 or HHV-7-specific DNA from tissue or body fluid	PCR may not distinguish latent virus from active infection
Immunohistochemical antigen staining	Staining of tissues with monoclonal antibodies to HHV-6 or HHV-7 antigens	Proper cell handling technique required

HHV-6 Human herpesvirus-6; *HHV-7* Human herpesvirus-7; *PCR* Polymerase chain reaction

plasma, or CSF may be better at differentiating active infection from the presence of latent virus [80]. Immunohistochemical staining of tissue samples for HHV-6 or HHV-7 can also be limited, and does not necessarily separate active from latent virus. PCR and antigen staining assays for HHV-7 have not been found to have much clinical utility to date and are frequently unavailable for routine testing outside of the research setting.

The need for, and the activity of, antiviral therapy in HHV-6 and, in particular HHV-7, remain unclear. Both ganciclovir and foscarnet have been used in the treatment of presumed HHV-6 infections [69, 70]. In vitro reports of resistance to ganciclovir among HHV-6 isolates have been reported [81]. There are no prospective studies to guide management with these agents. As of yet, there are no convincing clinical scenarios in which therapy of HHV-7 infection is warranted [82]. In vitro, both foscarnet and ganciclovir inhibit HHV-7 replication [83].

6. Epstein-Barr Virus

Epstein, Achong, and Barr first described the infectious agent isolated from the cells of Burkitt's lymphoma in 1964 [84]. The relationship between EBV and heterophile-positive infectious mononucleosis is well-established. The relationship between EBV and malignancies such as Burkitt's lymphoma, nasopharyngeal carcinoma, post-transplant lymphoproliferative disorder (PTLD), Hodgkin's disease, and others is an area of active investigation. Seroprevalence studies indicate EBV infection to be present in greater than 90% of adults in most populations.

6.1. Clinical Syndromes

Primary infection with EBV in childhood is often asymptomatic. In adolescence or adulthood, it can frequently result in infectious mononucleosis, causing fever, lymphadenopathy, and pharyngitis. Virtually, every organ system may be affected by active EBV infection. The role of EBV in the pathogenesis of malignancies and lymphoproliferative disorders is particularly challenging in patients with hematological disorders (Table 2-10).

In the setting of infectious mononucleosis, diverse complications have been reported, including the classic association of splenic rupture and hematologic dysfunction. Hemolytic anemia, thrombocytopenia, and disseminated intravascular coagulation have all been reported. Oral hairy leukoplakia is an uncommon benign lesion most frequently associated with human immunodeficiency virus (HIV) infection. Although reported in the setting of HSCT, it is exceptionally rare [90]. The development of post-transplant lymphoproliferative disorder (PTLD) is the most often encountered and most feared complication of EBV infection after HSCT. Risk is greatest among those who are EBV-seronegative prior to transplant.

6.2. Diagnosis

Infectious mononucleosis can be a clinical diagnosis in an immunocompetent patient in the right clinical setting. Supportive evidence in the form of atypical lymphocytes seen on peripheral blood smear and the presence of heterophile antibodies are sometimes employed. In the immunocompromised individual, serology may not be detectable, particularly in acute infection.

Table 2-10. EBV clinical syndromes.

Anatomic location/syndrome	Symptoms/presentation
Infectious mononucleosis	Fever, lymphadenopathy, pharyngitis, splenomegaly
Neurologic syndromes	
Meningitis/encephalitis	Fever, confusion, headache, and cerebral edema [85]
Transverse myelitis	Back pain, sensory loss, areflexia, ataxia, and difficulty with bowel and bladder function [86]
Optic neuritis	Visual loss, possibly in combination with other neurologic deficits [87]
Pneumonitis	Lymphocytic interstitial pneumonitis commonly with pediatric HIV/AIDS [88]
Myocarditis	Congestive heart failure [89]
Nephritis	Reports of tubulointerstitial nephritis, membranous nephropathy, and glomerulonephritis
Rash	Diffuse morbilliform rash associated with administration of penicillins in the setting of primary infection
Oral hairy leukoplakia	White linear plaques usually on lateral surface of the tongue
Lymphoproliferative disorders	
Hemophagocytic lymphohistiocytosis	Unusual syndrome of fever, lymphadenopathy, hepatosplenomegaly, hepatitis, pancytopenia, coagulopathy and T-cell, and histiocyte proliferation with hemophagocytosis in bone marrow, spleen and lymph nodes
X-linked lymphoproliferative disorder	An inherited mutation of the X chromosome that leads to fulminant infectious mononucleosis after EBV infection with high mortality
Post-transplant lymphoproliferative disorder	Largely B-cell proliferation after solid organ or HSCT with extranodal presentations and risk for malignant B-cell lymphomas; T-, NK-, and null cell tumors – role of EBV variable
Malignancies	
Burkitt's lymphoma	Lymphoma typically arising in the jaw; most frequently in Africa; both malaria and EBV may be cofactors
Nasopharyngeal carcinoma	Tumor strongly associated with EBV, most frequently in southern China
Hodgkin's disease	EBV gene expression has been consistently detected in Reed-Sternberg cells associated with Hodgkin's disease; exact rates/role of EBV varies by region
Non-Hodgkin's lymphoma	EBV may be related to non-Hodgkin's lymphomas of HIV-infected population, as well as the post-transplant patient
Leiomyomas/sarcomas	EBV associated with smooth muscle tumors in patients with HIV, children

HIV Human immunodeficiency virus; *AIDS* Acquired immunodeficiency syndrome; *EBV* Epstein-Barr virus; *HSCT* Hematopoietic stem cell transplant

The myriad complications of EBV infection in this patient population and their atypical presentations have made use of molecular diagnostics essential for the diagnosis and management of active EBV infections (Table 2-11).

Serologic assays for heterophile antibodies, anti-viral capsid antigen IgM, IgG, early antigen IgG, and nuclear antigen IgG can be performed independently through indirect immunofluorescence, EIA, or in combination simultaneously with a multiplexed bead assay [92]. Serologic assays are of

Table 2-11. EBV diagnostics.

Diagnostic test	Description	Comments
Serology		
Heterophile antibody	Serologic test for antibodies to antigens on erythrocytes of other animal species; rapid Monospot assay uses latex agglutination	Frequently negative in leukemia or HSCT; monospot assay has a sensitivity of 85% in immunocompetent individuals [91]
Viral capsid antigen antibody	Serum assay for IgM or IgG antibodies specific to the EBV viral capsid antigen	IgM levels typically become undetectable after 3 months; may not develop with primary infection in immunocompromised host; IgG levels indicate past infection
Early antigen antibody	Testing of serum IgG for two subsets of early antigens: anti-D and anti-R	Often present in acute infection, but may not develop in immunosuppressed patients
Nuclear antigen antibody	Testing of the serum for IgG toward EBV nuclear antigen	Usually not present during acute infection, but develop after 1–2 months, and may persist throughout life
Culture	Culture of EBV from oropharyngeal washings or blood	Not routinely available; asymptomatic shedding prevents separation of active versus latent infection
PCR	Quantitative amplification of EBV-specific DNA from tissue or body fluid	Does not distinguish latent EBV infection from active invasive disease; PCR of blood can detect active viral replication; optimal cut-off values for each assay unclear
Immunohistochemical staining	In-situ hybridization of tissue samples for EBV-encoded small ribonucleic acid (EBER) using oligonucleotide probes	Highly sensitive and specific for EBV gene expression from tissue samples

HSCT Hematopoietic stem cell transplant; *EBV* Epstein-Barr virus; *PCR* Polymerase chain reaction

little value in diagnosing acute infection in the immunocompromised host as humoral responses may be delayed or absent. There is often a lag in the development of anti-viral capsid and anti-nuclear antigen IgG. Anti-viral capsid antigen IgM and anti-early antigen IgG may fail to appear altogether [93]. Quantitative PCR assays differ between laboratories, but a single assay in an individual should be used for patient management. There is no agreement as to the significance of quantitative values other than within an individual. In studies of HSCT recipients, 1,000 copies/mL has been used to assess risk for the development of PTLD [94]. In situ hybridization of biopsy samples using abundant, small EBV-encoded RNA (EBER) oligonucleotides has become the standard for detecting EBV in lymphoproliferative disorders and malignancies [95].

6.3. Therapy

In the absence of severe complications, there is usually no indication for therapy other than supportive care in primary infection with EBV in the immunocompetent individual. The use of corticosteroids to reduce tonsillar swelling and airway compromise is sometimes necessary [96]. Steroids and

antiviral therapy may be employed with other life-threatening complications such as hepatitis and possible liver failure, hematologic crises including aplastic anemia or hemolysis, though there are no prospective studies to support their use. In the immunocompromised individual, therapeutic modalities are diverse and are frequently indicated to either prevent or treat the lymphoproliferative complications and risk for malignancy from EBV. Both acyclovir and ganciclovir have in vitro activity against lytic replication of EBV, with ganciclovir having slightly greater efficacy [97]. However, there are few data to suggest that antivirals have a significant effect on the outcome of infection. EBV-related lymphoproliferative disorders and malignancies in immunocompromised hosts are thought to be dependent on latent infection that relies on cellular enzymes for EBV episomal DNA synthesis, and thus are not inhibited by the routine anti-herpesvirus nucleoside analogues [96]. Both acyclovir and ganciclovir have been used for prophylaxis in patients after solid organ transplantation, with meta-analyses suggesting a benefit to universal prophylaxis against CMV in preventing PTLD [98]. However, no firm conclusions can be drawn because of the small size and heterogeneity of the patient populations and non-randomized nature of these studies. Induction of the EBV thymidine kinase gene through the use of compounds such as arginine butyrate has been attempted in order to induce susceptibility to antiviral therapy with a mixed degree of success [99, 100]. Another antiviral that has been investigated in in vitro assays and in case reports is high-dose zidovudine (AZT) [101]. Maribavir, a newer compound being investigated for the use of treating CMV, also has in vitro activity against EBV through a different mechanism of action than the nucleoside analogues [102]. Yet, there are no trials investigating its use in EBV infection.

Once PTLD is established, therapeutic approaches include reduction of immunosuppression to the degree possible, surgery for isolated lesions, traditional chemotherapy, radiation (especially for CNS lesions), and the use of rituximab, a monoclonal antibody directed toward the CD20 antigen frequently found on B cells, the main site of EBV infection and latency [103]. The use of antiviral therapy in established disease may be used to reduce active viral replication and resultant immunosuppression but does not appear to directly impact tumor progression. In solid organ transplant recipients, CMV is a co-factor for PTLD, and prevention or treatment of CMV may be of benefit. The use of rituximab as a preemptive approach in HSCT to prevent PTLD in patients with otherwise asymptomatic but persistent EBV viremia has not always yielded persistent control in many patients [104]. Investigative approaches include infusion of EBV-primed autologous or allogeneic cytotoxic T-cells and anti-cytokine therapies [103].

7. Human Herpesvirus-8 (Kaposi's Sarcoma Herpesvirus)

HHV-8 is the most recently discovered member of the herpesvirus family, having been isolated in 1994 from a patient with Kaposi's sarcoma and co-infection due to HIV [105]. HHV-8 is a recognized cofactor in Kaposi's sarcoma and in the development of a variety of lymphoproliferative and malignant disorders. The virus is endemic in the Mediterranean region, in central and southern Africa, and much of South America although the route of

transmission remains unclear and may vary depending on the population being analyzed [106]. In endemic areas, prevalence increases after 2 years of age, consistent with transmission from family members or close contacts. In low-seroprevalence areas such as the United States, infection is highest among men who have sex with men, suggesting possible sexual transmission [107, 108]. Increased numbers of sexual partners and HIV coinfection also increase risk, though heterosexual transmission and the risk in other HIV-risk groups such as injection drug users appear to be much lower [106]. Among patients with underlying hematologic disorders, there is a suggestion that infection may be higher compared to the general population [109].

7.1. Clinical Syndromes

Primary infection with HHV-8 among immunocompetent children has been associated with a mononucleosis-like syndrome, while in adults, it is a milder illness and frequently asymptomatic. In immunocompromised patients, primary infection has been associated with a wide array of clinical presentations, including mononucleosis in patients with non-Hodgkin's lymphoma after autologous HSCT [110], bone marrow suppression after renal transplantation or autologous HSCT [111], hemophagocytic syndrome in a patient after renal transplantation and others with HIV infection [112, 113], and in one report of an infant with DiGeorge syndrome, disseminated disease with hepatitis, enterocolitis, and pneumonitis [114].

Disease associated with latent or reactivated infection from HHV-8 includes Kaposi's sarcoma, and also primary effusion lymphoma and multi-centric Castleman disease. Kaposi's sarcoma is a mesenchymal neoplasia of the blood and lymphatic vessels with varying presentations and outcomes in different patient populations. Castleman disease, a lymphoproliferative disorder, can lead to HHV-8-positive plasmablastic lymphoma. Other possible associations with HHV-8 that have not been well validated include multiple myeloma and germinotropic lymphoproliferative disorders, as well as non-lymphoid malignancies such as cardiovascular disease, pemphigus vulgaris, and the autoimmune disorder sarcoidosis [115].

7.2. Diagnosis

Current HHV-8 diagnostics may not be available in many clinical centers, and the optimal use of such assays is unclear [115]. The lack of a gold standard test, the inability to assess individual risk for infection among different patient populations, and, in particular, ignorance about the natural history of HHV-8 are barriers to proper management. Among the available assays (Table 2-12), PCR is most commonly used.

HHV-8 antibodies are measured by various techniques, including EIA, immunofluorescence, and Western blot. Sensitivity and specificity vary among these tests, although EIA is technically easier to perform and has been used in large-scale seroprevalence studies [116]. PCR of whole blood has not been well studied and may not offer any value in diagnosing patients with Kaposi's sarcoma or other malignancies with HHV-8 infection. PCR assays vary widely in terms of sensitivity and specificity in diagnosing primary HHV-8 infection. Sensitivity is closer to 100% for detection of HHV-8 in tissue samples such as Kaposi's sarcoma lesions [117].

Table 2-12. HHV-8 diagnostics.

Diagnostic test	Description	Comments
Serology	Presence of HHV-8-specific IgG and IgM antibodies	Presence of past infection; may be negative in acute infection and with hypogammaglobulinemia. Sensitivity and specificity vary by target population
PCR	Quantitative or qualitative amplification of HHV-8-specific DNA from blood, tissue, or body fluid	Sensitivity and specificity vary by tissue studied and clinical syndrome
Immunohistochemical staining of tissue or cells	Staining of fixed cells using antibodies specific to HHV-8 antigens	Detects HHV-8-specific gene expression for diagnosis of Kaposi's sarcoma and other HHV-8-related malignancies

HHV-8 Human herpesvirus-8; *PCR* Polymerase chain reaction

7.3. Therapy

Antiviral therapy with acyclovir, ganciclovir, foscarnet, and cidofovir appears to have activity against HHV-8 viral replication in vitro. Acyclovir may be less active compared to the others [118]. As for EBV, antiviral therapy does not alter latent gene expression, limiting the clinical value of these drugs. There are case reports of antiviral therapy, but no general conclusions are merited [112, 119]. For established Kaposi's sarcoma and lymphoproliferative disorders due to HHV-8, chemotherapy and radiotherapy have been used with some success. Intralesional injections of cidofovir have had little effect in Kaposi's sarcoma compared with the benefit of liposomal doxorubicin, though recurrence and resistant disease have been described with the latter [120]. For primary effusion lymphomas, resistance to traditional chemotherapy is common, and response rates are lower [121]. Therapies targeting latent viral gene expression are under study. Activation of lytic gene expression to make the virus more sensitive to traditional antiviral therapies, similar to EBV, is also under investigation. Hydroxyurea may have activity against latently infected cells in some cases, although resistance has developed frequently [122]. Use of interferon ($-\alpha$ or $-\gamma$) may be able to trigger cell death in infected HHV-8 cells in vitro, but has not undergone clinical evaluation [123]. In HIV infection, immune reconstitution through the use of highly active antiretroviral therapy (HAART) has had a salutatory effect on the treatment and prevention of Kaposi's sarcoma and HHV-8. Immune reconstitution through decreased immunosuppression may also be of benefit in patients with HHV-8-related disease post-transplant.

8. Respiratory Viruses

The viruses primarily affecting the respiratory tract include some closely- and not so closely-related viruses. Adenovirus, influenza, parainfluenza, respiratory syncytial virus (RSV), the other less studied or less clinically significant infections such as rhinovirus, coronavirus, and the relatively newly described metapneumovirus are included in this section. Measles, mumps, and rubella also may cause respiratory syndromes. These viruses spread through the community by air-borne droplet inhalation, physical contact with environmental

fomites, or ingestion, and are easily transmitted to patients with hematologic malignancies. Infection control measures, vaccination, and proper hand hygiene for healthcare workers and household contacts is a crucial component in preventing the spread of these infections and their potentially lethal complications in immunocompromised hosts. Reduction in immune suppression and immune reconstitution remains keys to successful outcomes in immunocompromised hosts.

Respiratory viruses cause more severe disease with more frequent complications in immunocompromised individuals. The true incidence of asymptomatic respiratory viral infection is unknown. Atypical presentations often go unrecognized. Although infections limited to the upper respiratory tract are rarely fatal, there is a higher mortality associated with lower respiratory tract infections particularly in allogeneic HSCT recipients.

9. Adenovirus

Adenovirus is a double-stranded, DNA-based, non-enveloped virus associated with diverse clinical findings. Current classification of the virus distinguishes a total of 51 distinct serotypes divided into six subgroups (A–F) based on DNA homology [124]. Infection is usually acquired by inhalation of respiratory droplets, ingestion, or direct contact with the conjunctiva. Infection occurs year-round with no particular peak season, other than that noted in military recruits within the first 4 weeks of fall basic training [125]. Immunocompromised hosts are at high risk for severe disease and dissemination of the virus, leading to significant morbidity and mortality. A case fatality rate has been reported to be as high as 60% among pediatric and young adult HSCT recipients [126].

9.1. Clinical Syndromes

Infection with adenovirus results in upper respiratory tract infection that is usually benign and self-limited. Other clinical syndromes are common, particularly in the immunocompromised host (Table 2-13). Allogeneic HSCT recipients are at the greatest risk for infection and disease due to adenovirus, though complications are reported in patients with other underlying hematologic malignancies.

Risk for infection among HSCT-recipients is reported to be as high as 29%, with the respiratory tract being the most common location of virus isolation. Risk for complicated disease includes GVHD, young age, and presence of other opportunistic infections [130]. Not surprisingly, patients who are more heavily immunosuppressed and who are suffering from other immunologic and infectious complications of transplant are at higher risk for infection and disease due to adenovirus. Mortality is most strongly associated with pneumonia, with or without evidence of dissemination [131].

9.2. Diagnosis

Standard culture-based and serologic methods for detection of adenovirus infection are commonly available but may have limited clinical utility. The availability of newer molecular techniques for diagnosis of active infections may offer opportunities for earlier intervention (Table 2-14) [132].

Table 2-13. Adenovirus Clinical Syndromes.

Anatomic location/syndrome	Symptoms/presentation
Upper respiratory tract infection	Pharyngitis and coryza, laryngitis or otitis media with fever and malaise
Conjunctivitis	Usually with pharyngitis; epidemic form associated with subgroup D and painful bilateral conjunctivitis and blurring of vision
Pneumonitis	Dyspnea, cough and fever, with or without upper respiratory tract signs and symptoms accompanied by often diffuse bilateral pulmonary infiltrates; significant mortality in immunocompromised, especially with bacterial or fungal superinfection
Gastroenteritis	Acute diarrheal illness with fever or other systemic signs and symptoms
Hepatitis	Fever, elevated hepatic transaminases, hepatic necrosis, and fulminant hepatic failure in patients after HSCT [127]
Nephritis	Renal failure with possible prodrome of fever, hematuria, and flank pain after HSCT [128]
Hemorrhagic cystitis	Fever, gross hematuria, anemia, pain
Meningoencephalitis	Fever, headache, and confusion reported in children during an adenovirus outbreak [129]

HSCT Hematopoietic stem cell transplant

Table 2-14. Adenovirus diagnostics.

Diagnostic test	Comments	Limitations
Serology	Adenovirus-specific IgM and IgG antibodies	High prevalence of antibodies in the population limits diagnostic utility for acute infection
Culture	Epithelial cell culture assays with characteristic adenovirus cytopathic effect	Excretion of virus may persist in the stool or urine for months after acute infection; culture can be positive after only 2 days, but may take up to 28 days depending on serotype
Antigen assay	Rapid detection of adenoviral antigens through either direct immunofluorescence or enzyme-linked immunosorbent assays	Not serotype-specific; lacks sensitivity depending on source of specimen
PCR	Molecular amplification and detection of adenovirus-specific DNA	Highly sensitive and specific; not universally available
Pathology with or without immunohistochemical staining	On tissue biopsy, intranuclear inclusions and occasional obscuring of the nuclear membrane, resulting in "smudge cells"	Findings can be nonspecific and not always appreciated; changes confused with other viral processes, particularly CMV; immunohistochemical staining to increase sensitivity and specificity

PCR Polymerase chain reaction; *CMV* Cytomegalovirus

EIA assays for serologic testing are replacing older tests and are likely more sensitive. To diagnose a recent infection with antibodies, however, acute and convalescent sera for testing are required in order to document a ≥ 4-fold increase over time. Serotype-specific neutralizing antibody assays may be useful in therapeutic decision-making. Cultures can be performed on samples from the respiratory tract, conjunctiva, stool, urine, CSF, or other sites. Samples from the stool and urine, in particular, need to be interpreted with caution. Ongoing shedding in asymptomatic immunocompromised individuals

limits the utility of culture-based diagnostics. Antigen detection assays can be much more rapid, but lag in sensitivity. Tests for use in conjunctival samples suggest an overall sensitivity of 38%, though this rate was higher when taken earlier in the illness [133]. Among respiratory specimens, the sensitivity of antigen testing may also be relatively low compared to testing for other respiratory viral pathogens. The specificity and predictive values remain close to 100%, however, and ultimately the value of the test is most likely dependent on the adequacy of the sample taken [134]. PCR is emerging as the method of choice for detecting active adenoviral disease from any infected site. Although further studies are needed, there is an association of viremia with end-organ disease and mortality [132]. Asymptomatic viremia appears to be more common than is generally appreciated.

9.3. Therapy

There are no controlled clinical trials regarding the treatment of adenovirus infection to date. There are only limited in vitro susceptibility assays and uncontrolled clinical reports (Table 2-15).

The exact role of antiviral therapy in adenovirus disease remains unclear. Reduction in immune suppression and immune reconstitution is important when feasible. The two most commonly used agents, cidofovir and ribavirin, have significant toxicities. Cidofovir has significant nephrotoxicity, while ribavirin has bone marrow toxicity, risk for anemia, and is a teratogen. Cidofovir appears to be the most active agent against adenovirus in vitro, and clinical experience suggests the capacity to reduce viremia and viruria with subsequent clinical improvement in some patients. Various serotypes differ in response to cidofovir. Dosing and length of therapy remain unclear.

Table 2-15. Adenovirus Therapeutics.

Agent	Comments
Cidofovir	Cidofovir has in vitro activity against all serogroups of adenovirus; case reports and uncontrolled case series suggest clinical effect [135–140]
DLI	Donor lymphocyte infusions have been associated with clearance of adenovirus in a case report of gastroenteritis after HSCT [141] and in a case report of life-threatening hemorrhagic cystitis after HSCT [142]
Ganciclovir	Ganciclovir may have in vitro activity against adenovirus at high levels (which may not be clinically achievable); studies in HSCT patients receiving ganciclovir for CMV prophylaxis may have shown a protective effect [143]
IVIG	Combined use of IVIG with ribavirin or other agents has been reported in at least two cases [144, 145]
Ribavirin	In vitro, ribavirin has mixed activity against adenovirus [146]; case reports are mixed in clinical effect; the largest case series showed no association of ribavirin with survival in HSCT recipients with adenovirus infection [131]
Vidarabine	In vitro activity appears marginal; used in case reports for the treatment of hemorrhagic cystitis [147, 148]
Zalcitabine (ddC)	ddC with some in vitro activity [149]; animal model of adenovirus infection with some efficacy in preventing pneumonia [150]

DLI Donor lymphocyte infusions; *HSCT* Hematopoietic stem cell transplant; *CMV* Cytomegalovirus; *IVIG* Intravenous immunoglobulin

Doses of 5 mg/kg given IV once weekly for two to three doses, followed by infusions every other week, has been most often cited [138]. Cidofovir is usually given concomitantly with probenecid to help prevent some of the renal toxicity of the drug. Hemorrhagic cystitis may be relapsing with immune function, and hydration with urine flow is an essential component of care in these individuals. Despite some case reports, topical administration of antiviral agents has not proven very helpful in therapy of this common syndrome.

10. Influenza, Parainfluenza, and Respiratory Syncytial Virus

The spread of influenza and RSV occurs in outbreaks and epidemics throughout the winter. Parainfluenza infection occurs throughout the year, with epidemics arising occasionally in the fall and spring. For all three, spread within families and household contacts, as well as in the nosocomial setting, is common. Although much emphasis is placed on influenza, RSV is the single most common cause of lower respiratory tract infection in children, and both RSV and parainfluenza infections are likely under-recognized in the elderly and immunocompromised patient populations [151].

Influenza virus A and B are capable of invasive infection in patients with hematologic malignancies. Influenza A is most closely associated with changes in the two major glycoproteins:hemagglutinin (H) and neuraminidase (N). Antigenic shifts in these glycoproteins are associated with epidemics and worldwide pandemics of influenza A, while the role of minor changes, so called antigenic drifts, is more closely associated with localized outbreaks. Influenza B has a lesser propensity for antigenic changes. Parainfluenza is in the paramyxoviridae family and is divided into four major serotypes: Parainfluenza 1–4. Parainfluenza-3 is the most prevalent serotype and is also associated most strongly with the development of pneumonia and bronchiolitis. RSV is also a member of the paramyxoviridae family. There are two subtypes described: A and B. Both can be present simultaneously in community outbreaks, though subtype A typically causes more severe disease [152]. Influenza, parainfluenza, and RSV are all associated with a more prolonged clinical course, risk of pneumonia, co-infection with other pathogens, and death in patients with hematologic malignancies [153].

10.1. Clinical Syndromes

Among immunocompetent non-elderly adults, influenza, parainfluenza, and RSV tend to be self-limited upper respiratory tract illnesses or febrile syndromes. In the setting of hematologic malignancies, the frequency of lower respiratory tract involvement increases dramatically with a risk of dissemination and systemic complications (Table 2-16).

Cardiac and CNS involvement have been reported in parainfluenza, complicating the diagnosis of pulmonary infiltrates with infection and heart failure. Involvement of the lower respiratory tract increases the risk for bacterial or fungal superinfection including *Streptococcus pneumoniae* and *Staphylococcus aureus*.

Table 2-16. Influenza, parainfluenza, and RSV syndromes.

Virus	Syndrome	Symptoms
Influenza	Uncomplicated	Fever, myalgias, malaise, cough, sore throat
	Complicated	
	Pneumonia	Fever, dyspnea, and hypoxia with symptoms of uncomplicated influenza; Superinfection, bacterial and fungal, is common and increases risk for sepsis and death [154]
	Myocarditis	Scattered reports of involvement of influenza with the myocardium during acute illness, leading to congestive heart failure
	Meningoencephalitis	Fever, encephalopathy and seizure with abnormal CSF findings, and a positive PCR for influenza in some children [155]
	Myositis	Myalgia with tenderness of the affected muscles (most commonly the legs), with elevation of serum creatinine phosphokinase, myoglobinuria, and renal failure
Parainfluenza	Upper respiratory tract infection	Fever, cough, sore throat, rhinorrhea, otitis media
	Lower respiratory tract infection	Fever, cough, dyspnea, and hypoxia, with bronchiolitis or pneumonia
RSV	Upper respiratory tract infection	Fever, cough, conjunctivitis, rhinorrhea, sinusitis, otitis media
	Lower respiratory tract infection	Fever, cough, dyspnea, with concomitant bronchospasm and respiratory failure

CSF Cerebrospinal fluid; *PCR* Polymerase chain reaction; *RSV* Respiratory syncytial virus

10.2. Diagnosis

The availability of molecular assays and viral antigen detection testing has altered the clinical approach to respiratory viral infection. Viral culture remains necessary for susceptibility testing, viral typing, and identification of new pathogens. However, laboratories are increasingly utilizing rapid testing methods for identification of respiratory viruses. None of the rapid antigen tests have been well studied in immunocompromised hosts, though in immunocompetent patients, they likely have a sensitivity and specificity in the 80–99% range. Adequacy of the respiratory specimen provided for testing can be a limiting factor [134]. The sensitivity of these assays may also be limited when compared with newer molecular assays (Table 2-17). Rapid diagnostics have significant implications for successful therapy, however.

10.3. Therapy

Therapy for these viruses varies in terms of both efficacy and clinical data. Early diagnosis, and the early initiation of antiviral therapy for influenza, and likely RSV, is of importance. Delaying chemotherapy or HSCT in patients with hematologic malignancy with respiratory viral infections may improve outcomes [160], emphasizing the importance of appropriate and rapid diagnosis (Table 2-18).

Table 2-17. Influenza, parainfluenza, and RSV diagnostics.

Virus	Diagnostic test	Comments	Limitations
Influenza	Serology	Testing of serum for influenza-specific antibodies	Can only diagnose disease retrospectively; requires fourfold increase in titers from both acute and convalescent sera
	Culture	Respiratory samples (sputum, nasal swabs or washings, bronchoalveolar lavage fluid or throat swabs) used on epithelial cell culture assays	48–72 h positive result with rapid shell vial technique, otherwise 5–10 days; remains the "gold standard" of diagnosis
	Antigen assays	Immunofluorescent antigen–antibody staining of respiratory samples (DFA); more rapid, diverse commercially prepared kits for testing of respiratory samples for influenza antigens using enzyme immunoassays	Rapid antigen assays may not test for both influenza A and B, or distinguish between the two (as for DFA and some rapid tests); sensitivity and specificity of rapid tests range from 72–95% and 76–84%, respectively [156]
	PCR	Influenza A- or B-specific molecular amplification of viral RNA from body fluid, nasopharyngeal aspirates, bronchoalveolar lavage fluid, or throat swabs	Highly sensitive and specific, but not available routinely; expensive to perform
Parainfluenza	Serology	Testing of serum for parainfluenza-specific antibodies	Not routinely available, lacks specificity due to some cross-reactivity, and can only diagnose retrospectively (need both acute and convalescent serum to demonstrate at least a fourfold rise)
	Culture	Growth of parainfluenza from respiratory specimens on cell culture lines	Specific assay, though possibly limited sensitivity depending on source and timing of collection [157]
	Rapid antigen assays	Immunofluorescent assays using parainfluenza-specific antibodies for antigen detection in cell samples or tissue	Most readily available sensitive and specific assay
	PCR	Parainfluenza-3-specific molecular amplification of viral RNA has been developed	No clinical experience to clarify its potential role in diagnosing active parainfluenza-3 infection [158]
RSV	Culture	Growth of RSV on cell culture lines using respiratory secretion samples	Culture can take anywhere from 4 to 14 days, limiting clinical utility
	Rapid antigen assays	Detection of RSV-specific antigens on cell surfaces taken from respiratory samples using immunofluorescent antibody techniques	Rapid and widely available; sensitivity may vary depending on patient and quality of sample
	PCR	RSV-specific molecular amplification using respiratory specimens	Sensitive and specific; may be superior to antigen detection in patients with hematologic malignancy [159]

RSV Respiratory syncytial virus; *PCR* Polymerase chain reaction

Table 2-18. Influenza, parainfluenza, and RSV therapeutics.

Virus	Drug	Dosing
Influenza	Oseltamivir	75 mg po bid75 mg po qd (for CrCl<30 mL/min)
	Zanamivir	Two inhalations (5 mg) bid
	Amantidine	100 mg po bid or 200 mg po qd200 mg po x 1, then 100 mg po qd (for CrCl of 30–50 mL/min) 200 mg po x 1, then 100 mg po qod (for CrCl of 15–29 mL/min) 200 mg po every 7 days (for CrCl<15 mL/min)
	Rimantidine	100 mg po bid100 mg po qd (for CrCl < 10 mL/min and for severe liver disease)
	Ribavirin	Dosing unclear, inhalation anecdotally effective in immunocompetent individuals, while oral therapy likely not [161]
Parainfluenza	Ribavirin	Dosing unclear, but reports of using 15–20 mg/kg/day in three divided doses with or without another 6 g/day inhaled therapy has been reported in HSCT recipients [162, 163]
RSV	Ribavirin	Dosing unclear, but reports of using 2 g aerosolized three times daily has been reported in patients with hematologic malignancies and HSCT [164]
	Palivizumab	15 mg/kg IM q monthly during winter season (November through April) for prophylaxis only; no benefit seen in therapy

RSV Respiratory syncytial virus; *CrCl* Creatinine clearance; *HSCT* Hematopoietic stem cell transplant; *IM* Intramuscularly

Oseltamivir has emerged as the most commonly used antiviral therapy for influenza because of its ease of administration and tolerance. Being a neuraminidase inhibitor like zanamivir, it has efficacy against both influenza A and B. Usual treatment in the immunocompetent individual is for 5 days, but in the immunocompromised patient, particularly in HSCT recipients or patients with complicated disease, more prolonged therapy may be warranted [63]. Data specifically in HSCT recipients suggest that early therapy using oseltamivir can possibly reduce viral shedding and risk for pneumonia [165]. The adamantanes, amantidine, and rimantidine, are classified as M2 inhibitors and are efficacious against influenza A only. Although they are less expensive than the neuraminidase inhibitors, they are limited by increasing rates of resistance. In January of 2006, the Centers for Disease Control (CDC) issued an alert to avoid the use of M2 inhibitors during the 2005–2006 influenza season in the United States due to unacceptably high rates of resistance seen in the H3N2 strain circulating at the time. The same precaution has been recommended for the 2006–2007 season as well, until further more definitive susceptibility testing can be established. All of the above agents have also been used for prophylaxis during outbreaks, though dosing, length of therapy, and susceptibilities of circulating strains may vary.

Immunization is a central component of influenza control. Use of the annual trivalent inactivated influenza vaccine among HSCT recipients, healthcare workers, and household contacts may decrease the attack rate both in the community and in the nosocomial setting [165]. Vaccine responses are generally reduced among patients with hematologic malignancies or HSCT, but the potential benefits of prevention far outweigh any risks incurred by administering the vaccine. Accordingly, annual vaccination is recommended in this patient population. The newer live-attenuated influenza vaccine that is

administered intranasally has been approved for use in the United States for individuals aged 5–49 years [166] but has not been recommended in immunocompromised individuals or in their household contacts because of risk of transmission [167].

For parainfluenza, the efficacy of therapy is less clear, and there are no established or proven agents. Ribavirin (orally, IV and aerosolized) with and without intravenous immunoglobulin has only anecdotal efficacy. The largest study that evaluated the use of ribavirin in HSCT did not note any difference in mortality or virus shedding, particularly with parainfluenza-3 [163].

Treatment for RSV appears moderately effective in some studies. The use of inhaled ribavirin has not been proven effective in immunocompetent children, while there are data to suggest efficacy in the adult HSCT population [164, 168]. Early diagnosis and intervention may be the key to improving outcomes in this particular group [168]. Repletion of antibodies in hypogammaglobulinemic hosts may be useful. Currently, palivizumab, a monoclonal antibody directed toward RSV, has only been studied as a prophylactic agent in children at risk of respiratory complications from RSV infection. Trials investigating its use as a therapeutic agent in combination with ribavirin are reportedly ongoing [168]. It is well-tolerated in the HSCT population [169] and was successful at treating RSV pneumonitis in combination with corticosteroids in a case report of a women with relapsed Hodgkin's disease after autologous HSCT [170].

11. Human Metapneumovirus

Human metapneumovirus (hMPV) is a recently described respiratory virus in the paramyxovirus family [171]. hMPV is a ubiquitous pathogen, accounting for a substantial portion of respiratory tract illnesses in normal children [172]. Recent studies suggest that hMPV was an unrecognized pathogen for as long as serologic samples have been available. hMPV is not as common as RSV but more common than parainfluenza [173], with a propensity for the winter months [172]. Many questions remain regarding the role of this agent in immunocompromised individuals, the mechanism of spread in the community and prevention and therapy.

hMPV is a likely cause of upper respiratory tract infection as well as bronchiolitis and pneumonia in infants, the elderly and immunocompromised individuals, particularly HSCT recipients. Upper respiratory tract prodromal symptoms are common prior to the onset of lower respiratory tract disease [174]. Death as a result of lower respiratory tract disease has been described in the setting of HSCT, and it may be a relatively common outcome of hMPV pneumonia [174].

PCR for viral RNA is the only established assay for diagnosis. Testing of respiratory secretions or tissue biopsy samples via PCR is sensitive, although the true incidence of asymptomatic viral shedding remains unclear [175]. Biopsies of lung tissue in patients with pneumonia presumably caused by hMPV show changes consistent with viral pneumonitis, but are otherwise non-specific. These changes may include diffuse alveolar damage and mononuclear cell infiltration, but there are no definite viral inclusions [174].

Although there are no clinical data to guide therapy, ribavirin appears to have in vitro activity against hMPV equivalent to that of RSV [176]. A mouse

model of hMPV infection suggests that ribavirin may be efficacious in vivo [177]. Prospective clinical studies are needed.

12. Other Respiratory Viruses

Other respiratory pathogens include the rhinoviruses, coronaviruses, measles, mumps, and rubella. Rhinoviruses and coronaviruses are associated with the common cold. Symptoms are generally self-limited and consist of upper respiratory tract-related complaints: rhinorrhea, sinus congestion, pharyngitis and cough. Although these viruses are thought to be limited to the upper respiratory tract for replication, reports isolating them from the lower respiratory tract do exist [178–180]. The outcome of infection due to rhinoviruses or coronaviruses in patients with hematologic malignancies is not well characterized. The incidence of severe infection due to rhinoviruses is unknown. Fatal pneumonia has been attributed to infection from rhinoviruses in patients who have undergone HSCT [181]. Use of reverse-transcriptase PCR (RT-PCR) for rhinoviruses and coronaviruses in bronchoalveolar lavage samples from patients who have undergone HSCT suggests that isolation of rhinoviruses from lower respiratory tract samples is associated with co-infection from other pathogens (e.g., bacteria, fungi and other viruses) [180]. The validity of RT-PCR in respiratory samples remains unclear. Most laboratories do not have the culture techniques or PCR available for the detection of these viruses in clinical samples. There is no established antiviral therapy for these infections.

Measles, mumps, and rubella are uncommon pathogens in the US due to an effective vaccine program. The vaccine is a live attenuated virus vaccine involving all three pathogens. Because it is a live virus vaccine, it is generally avoided in immunocompromised individuals, though it is considered safe and effective in children who had acute lymphoblastic leukemia after they have been effectively treated with chemotherapy [182]. Sporadic cases of all three viruses occur. Measles, or rubeola, is typically associated with cough, coryza, fever, and a maculopapular rash. There are limited data on measles in immunocompromised patients. Cumulative case reports suggest that the case-fatality rate among oncology patients is as high as 70% [183]. Complications from the infection, including pneumonitis and encephalitis, may be more common. The typical rash of measles may be absent in immunocompromised patients, complicating the diagnosis. Serology, culture and RT-PCR can be used to diagnose measles. Serology is commonly available. Acute and convalescent sera are required to demonstrate the requisite fourfold increase over time to confirm the diagnosis. There is no known effective treatment for measles once infection is established. High-dose vitamin A when used in children has been reported to decrease the severity of the disease [184]. Ribavirin remains of unproven benefit [185].

Mumps, a member of the paramyxovirus family, is most commonly associated with parotitis, though its clinical manifestations can be diverse and include meningitis, encephalitis, hearing loss, orchitis, oophoritis, myocarditis, arthritis, and others. Like measles, mumps is usually a rare illness, though a large outbreak in the United States was recently characterized [186]. From January through October of 2006, a total of 5,783 cases of confirmed or probable mumps were reported, involving a total of 45 states. Most cases came from Iowa, Kansas, Wisconsin, and Illinois, and clustered around college campuses. The natural

history of this illness in immunocompromised individuals remains unclear. Diagnosis is usually through standard serologic methods. EIA is most often used due to ease of performance and reliability. Therapy is entirely supportive.

Rubella, or German measles, is a member of the Togaviridae family. Although most often associated with only mild, innocuous infections in adults and children, congenital acquisition can have devastating effects on unborn fetuses. Thanks to broad use of the live-attenuated vaccine; rubella is no longer endemic in the United States, with less than 25 cases reported annually among foreign-born persons [187].

12.1. Enteroviruses

Enteroviruses are a heterogeneous group of viruses that along with the rhinoviruses, aphthoviruses, cardioviruses, and Hepatitis A virus, make up the picornaviridae family. The enteroviruses are further subclassified into different groups and 67 total serotypes (Table 2-19). There tends to be a peak season of infection in temperate climates during the summer and autumn months. Spread is generally via the fecal-oral route, though respiratory transmission may be possible. Although cell-mediated immunity generally plays an important role in viral immunology, humoral immunity is thought to be of particular importance in controlling enteroviral infections, and some of the most severe outcomes have been noted in patients with agammaglobulinemia [188, 189].

12.2. Clinical Syndromes

In the immunocompetent host, the vast majority of enteroviral infections produce a completely asymptomatic infection. Occasionally, a mild febrile illness with or without upper respiratory tract symptoms may be present. Other symptoms are rarer, but have been well-characterized (Table 2-20). In patients who have undergone HSCT, fatal complications have been documented [189–196]. Occasionally, these viruses appear to precipitate gastrointestinal GVHD.

Most cases of protracted and fatal enteroviral infections have been among patients with severe B-cell dysfunction, such as hereditary forms of agammaglobulinemia. In these particular clinical scenarios, enterovirus RNA can sometimes be persistently recovered over months to years from multiple anatomic sites such as the CSF, lung, myocardium or bone marrow [188]. In HSCT, the combination of underlying T-cell dysfunction combined

Table 2-19. The enteroviruses.

Virus subgroup	Serotypes
Polio	1–3
Coxsackie A	1–22, 24
Coxsackie B	1–6
Echovirus	1–9, 11–27, 29–33[a]
Enterovirus	68–71[b]

[a]Echovirus 34 is the same virus as a genetic variant of coxsackie
[b]Hepatitis A is often classified as enterovirus 72

Table 2-20. Enteroviral syndromes.

Syndrome	Symptoms
Upper respiratory tract infection	Fever, rhinorrhea, pharyngitis
Pneumonitis	Fever, cough, possibly dyspnea
Rash	Fever, erythematous macular or maculopapular exanthems, with or without other syndromes; occasionally purpuric resembling meningococcemia
Hand-foot-and-mouth syndrome	Fever, oral vesicular lesions and cutaneous maculopapular lesions on the hands, feet, and buttocks
Herpangina	Vesicular lesions on the tonsils and soft palate similar to herpes labialis, sore throat, fever
Conjunctivitis/keratitis	Ocular pain, injection, blurring of vision
Gastroenteritis	Fever, diarrhea
Pericarditis/myopericarditis	Chest pain, congestive heart failure
Aseptic meningitis	Fever, headache, photophobia, nausea/vomiting, meningismus
Pleurodynia	Fever and chest pains with spasms of chest and abdominal muscles that mimic pulmonary emboli
Paralytic poliomyelitis	Weakness or paralysis of one or more extremities following aseptic meningitis

with suppressed humoral responses may contribute to more profound infection as well. However, the true incidence of enteroviral infections in this population remains unclear. Some estimate the incidence of enteroviral infections among HSCT recipients at 10%, though mortality is thought to be low overall and associated with coinfection of other pathogens. No clear independent risk factors for infection among HSCT recipients have been identified [196].

Diagnosis

Diagnosis of enteroviral infections involves the use of serology, culture, or PCR (Table 2-21). Because of many limitations in the other two methods, PCR is becoming a more favored approach.

Microneutralization serologic assays offer the benefit of being serotype-specific. Other methods such as immunofluorescent assays and EIA may show some cross-reactivity between the serotypes. The specificity of measuring serotypes also hampers the clinical utility of these tests. With 67 different serotypes known, routine diagnosis of enteroviruses with serology is not always realistic. Serologies are most useful when looking for evidence of polio infection. Culture can be labor-intensive and can require multiple cell lines to be effective [197]. Because excretion of enteroviruses from the gastrointestinal tract can persist after infection for as long as 8 weeks, [198, 199] isolation of the virus from stool, rectal swabs or possibly the oropharynx may result in a falsely positive assay. The same holds true for PCR when used in samples taken from these anatomic locations. Most experiences with PCR comes from CSF samples in cases of suspected aseptic meningitis where the sensitivity may be higher than culture and much more clinically useful [200].

Table 2-21. Enterovirus diagnostics.

Diagnostic test	Comments	Limitations
Serology	Measurement of IgG and IgM antibodies specific to enteroviruses	Both acute and convalescent sera are required to make a diagnosis; may not be able to determine acute infection in a clinically relevant time period; can be limited in patients with agammaglobulinemia; are serotype specific; cross-reactivity can exist
Culture	Growth of the virus in cell culture, looking for a characteristic cytopathic effect	May take up to 1 week for identification; sometimes may detect carriage of virus rather than true infection
PCR	Reverse transcriptase molecular amplification of RNA specific to enteroviruses	Highly sensitive and specific; not available in all labs; does not identify specific serotypes; sometimes may detect carriage of virus rather than true infection

PCR Polymerase chain reaction

12.3. Therapy

There is no established treatment for enteroviruses [196]. Intravenous immunoglobulin (IVIG) has been used with mixed success in various case reports of patients with persistent meningitis and in children with myocarditis when compared to historical controls [188, 189, 201]. Antibody responses to enterovirus are serotype-specific, and because of this, IVIG may not be clinically useful in all cases [202]. There are no data regarding dosing and duration of use with IVIG. Previous investigations of specific antiviral therapy against enteroviruses resulted in the development of a compound known as pleconaril. Pleconaril acted by binding to the viral capsid antigen, impairing viral binding and uncoating [203]. Clinical trials and various case reports of pleconaril use in aseptic meningitis have shown only modest to no clinical benefit, and its further development was put on hold [189, 204].

Control of polio via vaccination has virtually eliminated wild polio viral infections in the Western hemisphere. Loss of immunity to poliovirus is well-documented in patients after allogeneic HSCT [205, 206], and has led to recommendations for revaccination with inactivated poliovirus vaccine after transplantation [207]. Live virus, vaccines should be avoided in immunosuppressed patients, and the live attenuated oral poliovirus vaccine is no longer available in the United States due to the rare but severe complication of vaccine-associated paralytic polio. Since the implementation of the inactivated vaccine, vaccine-associated paralytic polio has been eliminated in the United States [208].

13. Viral Hepatitides

Viral hepatitis A, B and C are unrelated viruses capable of inducing acute or both acute and chronic liver disease. Hepatitis B virus (HBV) and hepatitis C virus (HCV) are of particular importance because of their abilities to establish chronic infection and reactivate with immunosuppression.

14. Hepatitis A

Hepatitis A is a member of the picornaviridae family that is transmitted via the fecal-oral route from one individual to another. Though most infections are mild, fulminant hepatitis with significant mortality has been reported. However, there are currently no reports of hepatitis A disease in HSCT patients, making the true risk and incidence of infection in this population unknown [209]. Transmission can result from person-to-person contact, sexual contact or ingestion of contaminated food or water. There are also rare reports of transmission via blood products [210]. Once ingested, the virus replicates in the gastrointestinal epithelium and then produces transient viremia, leading to infection of and further replication in the hepatocytes. The average incubation period is close to 4 weeks [211].

Symptoms of infection usually include fever, malaise, and hepatitis with or without jaundice. The differential diagnosis includes numerous infectious and non-infectious etiologies, including other viruses such as CMV, EBV, HSV, VZV, and the other hepatitides. The diagnosis is usually made via the measurement of serum anti-hepatitis A IgM antibodies, in the right clinical setting. These antibodies can usually be detected by 1 week into the illness and persist in immunocompetent individuals for several months. Detection of viral RNA via PCR is only available only in the research setting. Treatment is supportive with no available antiviral therapy. Immune globulin specific for hepatitis A can be administered intramuscularly to provide short-term protection, though long-term prevention is ideally through the use of vaccination. Some groups have recommended that post-HSCT seronegative patients who live in or are traveling to endemic areas receive the inactivated hepatitis A vaccine [212].

15. Hepatitis B

HBV, along with HCV, has the ability to establish chronic infection and occasionally cause a fatal post-transplant hepatitis in HSCT recipients [213]. Despite the availability of an effective vaccine, HBV continues to be an important cause of morbidity and mortality in the United States. Patients from higher-prevalence areas such as Southeast Asia, China and sub-Saharan Africa are at greater risk of exposure to the virus in the perinatal period, and are at greater risk of chronic infection and subsequent complications. The incidence of acute HBV in the United States seems to be declining among pediatric patients, reflecting most likely, the efficacy and implementation of universal vaccination. Among adults, acute infection continues to increase [214]. Among HSCT recipients, the prevalence of HBV infection in the United States is estimated to be about 1% [215]. The most common risk factors for infection include having a history of multiple sex partners, men who have sex with other men and injection drug use. Aside from the usual inoculation by intimate mucocutaneous contact and perinatal infection, transfusion of infected blood products and transplantation of infected organs are well-described modes of transmission.

15.1. Clinical Syndromes

The majority of patients with acute HBV infection are asymptomatic despite active viral replication and elevated hepatic chemistries. The incubation period

can last up to 4 months during which time patients may experience constitutional symptoms. About one-third develop icteric hepatitis. Fulminant hepatitis with hepatic failure is unusual with HBV (~1%) [216], and is likely due to immune-mediated complications rather than virally-mediated hepatic necrosis. The risk for developing chronic infection is inversely related to a patient's age, with perinatal infection carrying the highest risk. Chronic infection is diagnosed by persistent (>6 months) elevation of hepatic chemistries, particularly the alanine aminotransferase (ALT) level. Most patients with chronic disease are asymptomatic unless they develop cirrhosis and complications thereof. Immune complex-mediated complications outside the liver can include membranous and membranoproliferative glomerulonephritis as well as polyarteritis nodosa.

15.2. Diagnosis

The diagnosis of HBV is usually with serologies and antigen-detection, with nucleic acid amplification which is now being commonly used. Immunohistochemical staining of liver biopsies are of use to assess hepatic injury and viral replication (Table 2-22).

Hepatitis B surface antigen testing has been the primary marker for identifying acute and chronic infection, and can be detected as early as 9 days into infection with modern automated EIA tests [217]. Occasionally, patients with active infection are found to have a negative hepatitis B surface antigen assay. These patients will usually have serologic evidence of hepatitis B core antibodies and low-level HBV DNA levels. This phenomenon is more common in patients with HBV and HIV coinfection [218]. The development of real-time PCR assays has created the most sensitive assays available for detecting HBV. HBV DNA levels as measured by PCR can be directly correlated to the risk of liver disease, death, and drug resistance in patients on therapy. Though baseline values may vary from individual to individual, monitoring on a regular basis may be useful, particularly in those patients on therapy. Although different algorithms exist, checking a patient's HBV viral load by PCR two to four times yearly while on therapy may provide an assessment of their response. Failure of an antiviral agent to achieve a 1 log or more decrease in viral load over 3 months, or a rebound of viral replication of 1 log or greater after an initial response is often considered evidence of failure [219]. Standardization of quantification in international units (IU)/mL will enhance comparison of different molecular assays [220].

15.3. Therapy

For lamivudine, loading doses of 35–100 mg in the setting of decreased renal function are often given during the first day before starting a lower daily dose. Entacavir doses at the higher end of the range are generally reserved for lamivudine-refractory disease. Other agents being evaluated for treatment of HBV, but less-studied at this time, include emtricitibine (FTC), tenofovir (TDF), telbivudine, valtorcitabine and clevudine [221]. Tenofovir and emtricitibine are currently used in the treatment of HIV infection and have shown particular promise in the setting of HIV and HBV coinfection [222]. Although not studied in detail in the HSCT recipient population, numerous case reports exist regarding the efficacy of these antivirals as both prophylactic agents and as primary therapeutics in chronic carriers and in recipients of HBV positive

Table 2-22. Hepatitis B Diagnostics.

Diagnostic test	Comments	Acute/chronic infection	Limitations
Serology assays			
Hepatitis B surface antibody	IgG antibody	Recovery phase of acute infection and in chronic disease	Immunity due to vaccine or from past exposure; found in acute and chronic infection
Hepatitis B core IgM antibody	IgM antibody	Early acute infection and occasionally during flares of chronic infection	Usually indicates acute infection, but can persist in serum for up to 2 years; increase with flares may be misleading
Hepatitis B core IgG antibody	IgG antibody	Latter part of acute infection (recovery phase), and persist during chronic infection	In combination with hepatitis B surface IgG usually indicates past exposure, but not yet chronic infection
Hepatitis B early antibody	IgG antibody	Latter part of acute infection (recovery phase), and persist in low-level non-replicating chronic infection	Delayed seroconversion can occur in patients who develop chronic infection
Antigen assays			
Hepatitis B surface antigen	Protein found in the viral envelope	Appears early in acute infection; persistence beyond 6 months implies chronic infection	May be absent in brief window period of anti-hepatitis B surface IgG seroconversion in acute infection
Hepatitis B early antigen	Secretory protein from the HBV precore protein	Early acute infection and associated with high levels of HBV DNA replication; occasionally persists into chronic infection when seroconversion (HBV early IgG) does not occur	Perinatally acquired infection may be hepatitis B early antigen positive with normal serum ALT; seroconversion does not always indicate resolution of acute infection
DNA assays			
Hepatitis B viral DNA PCR	Molecular amplification and detection of HBV-specific DNA	Usually detectable in immediate acute infection and throughout chronic infection	Heterogeneity of PCR techniques and absence of standardization
Hepatitis B hybrid capture	Capture oligonucleotide amplification of HBV-specific DNA	Usually detectable very early in acute infection, and can be persistently positive in chronic disease	Less sensitive than PCR, and generally fails to detect <5,000 copies/mL

HBV Hepatitis B virus; *ALT* Alanine aminotransferase; *PCR* Polymerase chain reaction

donor stem cells. Optimal length of therapy is yet to be well-established with many of the agents listed in Table 2-23, and the development of resistance may vary with any of the individual agents.

Implementation of the routine universal immunization protocol is the most effective means of preventing spread of HBV. In patients undergoing allogeneic HSCT, HBV immunization can result in an effective antibody response, though systemic re-immunization of recipients may be necessary to maintain long-term immunity [223].

Table 2-23. Hepatitis B therapeutics.

Drug	Class	Dosing	Limitations
Interferon-α	Immunomodulator	5 million units sq qd, or 10 million units sq tiw	Major side effects
Lamivudine (3TC)	Nucleoside analogue	100 mg po qd for normal CrCl 50 mg po qd for CrCl 30–49 mL/min 15 mg po qd for CrCl 5–14 mL/min 10 mg po qd for CrCl <5 mL/min	Bone marrow suppression
Adefovir	Nucleotide analogue	10 mg po qd for normal CrCl 10 mg po qod for CrCl 20–49 mL/min 10 mg po q 72 h for CrCl 10–19 mL/min 10 mg q week for patients on hemodialysis	Renal insufficiency
Entecavir	Nucleoside analogue	0.5–1 mg po qd for normal CrCl 0.25–0.5 mg po qd for CrCl 30–50 mL/min 0.15–0.3 mg po qd for CrCl 10–29 mL/min 0.05–0.1 mg po qd for CrCl <10 mL/min	Development of resistance poorly understood
Pegylated interferon-α-2a	Immunomodulator	180 μg sq q week	Major side effects; may be better tolerated than interferon-α

16. Hepatitis C

Acquisition of HCV during HSCT has virtually disappeared due to effective testing of donors. HCV, like HBV, causes both acute and chronic infection, and acute infections are frequently asymptomatic. HCV leads to chronic infection in most patients. After HSCT, individuals acquiring HCV have an increased incidence of chronic infection and rapid progression to cirrhosis compared to otherwise healthy controls [224]. Symptoms of acute infection may include malaise and nausea, with or without jaundice. Chronic HCV infection is often asymptomatic with fluctuating transaminase levels. Patients undergoing HSCT who acquire HCV infection rarely develop signs or symptoms of decompensated liver disease during the first 10 years after transplant [225]. Beyond the 10-year mark, a significant portion of HSCT recipients develop cirrhosis and often hepatocellular carcinoma [224].

16.1. Diagnosis

HCV diagnostic testing is based on quantitative molecular assays, though serologic assays are most often used for screening. The second-generation EIA test is widely used with greater sensitivity than the first-generation assay [226]. A third-generation EIA can detect an additional HCV antigen, providing an advantage in high-prevalence settings and in detecting acute infections before seroconversion [227, 228]. Previously, confirmation of HCV infection in the setting of a positive serology was done through the use of a recombinant

immunoblot assay (RIBA-2). This immunoblot technique uses the same antigens detected by the second-generation EIA. The RIBA-2 increases the specificity of a positive EIA and reduces false positive results in low-prevalence settings or in patients with normal hepatic chemistries. More commonly now, detection of HCV RNA through the use of molecular amplification is used for confirmation and in patient management. Since patients with acute leukemia after HSCT may be less likely to develop antibody responses to HCV, PCR has significant advantages as a diagnostic tool [229]. Various molecular methods are not directly comparable, but single quantitative assays should be used in individuals. Commercially available assays include both RT-PCR and branched chain PCR methods. Branched chain PCR for HCV is technically easier, but less sensitive than standard RT-PCR techniques. A small percentage of patients with chronic infection have low-grade viremia that may not be detected [230]. PCR assays also have clinical utility in monitoring patients on therapy. Successful virologic response is generally defined as at least a 2 log decline from baseline levels 12 weeks into therapy, whereas those patients who do not experience the same decline are defined as nonresponders. Eradication of infection, or sustained virologic response, is also measured by use of the PCR assay and is defined by undetectable viral levels after completion of therapy and again 6 months later [231].

16.2. Therapy

Patients with chronic HCV infection after HSCT should be considered for therapy. Options are limited, and the current combination of interferon-α plus ribavirin is poorly tolerated. Pegylated interferon may be better tolerated, though the prolonged half-life may be of concern in patients with hematopoietic toxicity [232]. Interferon may be an instigator of reactivation of GVHD as well. Dosing regimens depend on variables such as type of interferon used and patient tolerance. For HCV genotypes 1 and 4, ribavirin is typically dosed at 1,000 mg a day in two divided doses for individuals ≤ 75 kg and 1,200 mg a day in two divided doses for those > 75 kg. With genotypes 2 and 3, 800 mg in two divided doses is likely to be sufficient.

17. Retroviruses

Retroviruses are a group of RNA viruses with a common genetic profile and reproductive machinery using the viral-specific enzyme reverse transcriptase to convert the RNA genome into an integrated DNA sequence within the host genome. The clinically significant retroviruses in human infection include human immunodeficiency virus1- and -2 (HIV-1 and -2), and human T-cell lymphotropic virus-I and -II (HTLV-I and -II).

18. Human Immunodeficiency Virus

HIV infection increases the risk of non-Hodgkin's lymphoma of which diffuse large B-cell lymphoma and Burkitt's lymphoma are the two most common forms [233]. Primary effusion lymphomas and EBV-related polymorphic lymphoproliferative disorders are also well described [234, 235].

18.1. Diagnosis

Testing for HIV infection is via EIA serologic assay from blood with confirmation by Western blot and quantitative molecular assay. The standard third-generation EIA used in clinical practice utilizes recombinant DNA proteins from immunodominant regions of HIV-1 and HIV-2. Some detect both IgM and IgG with a sensitivity in the 96–99% range and a specificity of up to 99% [236]. False negative EIA tests may occur between the time of viral transmission and seroconversion and in hypogammaglobulinemia, replacement transfusions, infection with HIV-1 subtype O [237] or infection with HIV-2 (if an HIV-2 specific-assay is not used) [238].

A positive EIA is confirmed through Western blot using proteins derived from the three major genetic domains of retroviruses (*gag, pol* and *env*). Possible explanations for false positive EIA assays include hematologic malignancies, autoimmune disorders, positive rapid plasma reagin (RPR) tests or infection with syphilis, HIV-2 infection (if an HIV-2 specific western blot is not used) and vaccination. If bands from at least two of the three major proteins are identified, the test is scored as positive. If only a single band is identified, then the test is frequently interpreted as indeterminate. The patients from the latter group usually are not true positives, and represent cross-reactivity due to other retroviruses, autoantibodies, heterophile antibodies, vaccination (most common) or lab error. Rarely, it is reflective of early primary HIV-1 infection prior to full seroconversion. In the presence of primary infection, antibodies to HIV are usually detectable an average of 3–7 weeks after infection. This is occasionally delayed, though 95% have detectable circulating IgG by 6 months [239].

Quantifying cell-free HIV RNA in plasma is now a critical part of assessing and monitoring disease progression and response to therapy. Current RT-PCR techniques can detect viral loads as low as 50 copies/mL and are thought to shorten the window period of HIV detection to within 2–14 days [240]. New rapid serologic tests have been developed in order to increase routine testing [241]. The CDC has recommended that positive tests with these assays be confirmed (usually via western blot) [242].

19. Human T-Cell Lymphotropic Virus

HTLV-I is a member of the retrovirus family known to infect as many as 20 million people worldwide. HTLV-I is a cause of adult T cell leukemia and lymphoma, as well as HTLV-I-associated myelopathy or tropical spastic paresis [243]. HTLV-II has not been consistently linked to any significant disease process. Similar to HIV in that there is a tropism for CD4-positive T cells, HTLV does not lead to cell death, but rather promotes proliferation and transformation. It is endemic in Japan, Indonesia, the Middle East, and parts of the Caribbean, South America and Africa. Prevalence rates are less than 1% in nonendemic areas such as the United States. Transmission is thought to be primarily through breastfeeding, although spread via blood transfusion, transplantation, and sexual contact are factors in endemic areas.

Diagnostic assays for HTLV are similar to those for HIV. Screening is primarily carried out via EIA assays to detect circulating HTLV-specific antibodies. Confirmation can be done with western blot analysis. Western

blot confirmation can also distinguish between HTLV-I and HTLV-II [244]. PCR testing is available to detect proviral DNA in whole blood. Treatment for HTLV infection is usually not indicated for asymptomatic patients. In the setting of adult T cell leukemia, the combination of zidovudine, a nucleoside reverse transcriptase inhibitor, and interferon-α have been used with some possible benefit [245]. Once lymphoma is established, use of non-Hodgkin's lymphoma chemotherapy regimens are moderately successful. Allogeneic HSCT has also been reported [246].

20. Polyomaviruses

The two polyomaviruses known to cause infection in humans include JC virus and BK virus. These are both small, non-enveloped, double-stranded DNA viruses closely related to the papillomaviruses. Both groups of viruses are in the Papovaviridae family. JC and BK virus were each first isolated and described in 1971 [247, 248]. JC virus is the cause of progressive multifocal leucoencephalopathy (PML), a demyelinating disease of the central nervous system. PML is best described in patients with acquired immunodeficiency syndrome (AIDS), though it is rarely seen in solid organ and HSCT recipients, and in other immunosuppressed individuals, including patients with hematologic malignancies and in individuals receiving some forms of immunosuppressive antibody therapies. BK virus is associated with nephropathy and ureteric stenosis in renal transplant recipients and with hemorrhagic cystitis in HSCT recipients.

21. JC Virus

JC virus infection is usually acquired during childhood and is not associated with any known illness during the acute phase. Most adults are seropositive, and PML is related to reactivation of the latent virus during significant periods of immunosuppression [249]. Although it has the strongest association with AIDS, PML was originally described in the setting of lymphoproliferative disorders and is thought to have a low prevalence of 0.07% overall among patients with hematologic malignancies [250]. PML presents as a subacute neurologic disease, affecting multiple systems depending on the location of the CNS lesions. Changes in a patient's mental status, ataxia, and motor deficits involving one or more extremities have been described. Infection of the oligodendrocytes by JC virus leads to demyelination of the white matter and the subsequent neurologic consequences. The disease itself is progressive with a median survival of roughly 6 months in patients with AIDS, and probably less than that in non-HIV infected patients with hematologic malignancies [251].

21.1. Diagnosis

The diagnosis is frequently made based on clinical findings. In patients with HIV infection and AIDS, a compatible magnetic resonance imaging (MRI) scan of the head demonstrating one or more white matter lesions without obvious contrast enhancement or mass effect suggests the diagnosis. Computed tomography (CT) scans tend to be less sensitive than MRI scanning [252]. Confirmation of PML and active JC virus infection is made through use of

brain biopsy or JC virus molecular testing in CSF. Demyelination with intranuclear inclusions seen in the oligodendrocytes is typical, with or without necrosis and inflammation. In situ hybridization using JC virus DNA probes can increase the sensitivity and specificity of the biopsy findings [253]. Testing for circulating IgG antibodies is of little diagnostic value due to the ubiquity of infection. Likewise, routine CSF analysis is often unhelpful and may or may not reveal any changes consistent with active inflammation such as elevation of cell counts and protein levels. PCR analysis of CSF for JC virus DNA in immunocompromised patients with a consistent clinical history and radiographic findings is most often used to make the diagnosis. CSF PCR for JC virus has a sensitivity close to 90% and a high specificity [254]. Brian biopsy may be needed in the face of a negative CSF PCR to confirm a diagnosis.

21.2. Therapy

There are no therapies with significant value in treating PML. Reversal of immune deficiency is the main modality of therapy. Cidofovir, which has limited in vitro activity against JC virus, has not shown any benefit in clinical trials of patients with HIV infection and PML [255]. Another agent, cytarabine, with some in vitro activity against JC virus [256], has also not been shown to be of benefit in comparative trials in patients with HIV infection and PML. However, a non-comparative, open-label study evaluating non-HIV infected individuals with PML found that cytarabine dosed at 2 mg/kg IV for 5 days had an association with stabilization of neurological function in 36% of individuals [257]. In AIDS the use of highly active antiretroviral therapy (HAART) has been of benefit in some series.

22. BK Virus

BK virus infection in adults has an estimated prevalence of over 80%. Infection is usually acquired during childhood, and tends to be asymptomatic. The route of transmission remains unclear, though respiratory acquisition is postulated. After primary infection, the virus remains latent in the urogenital epithelium, as well as in some lymphoid tissue and circulating leukocytes. Viral reactivation can occur during periods of immunosuppression.

22.1. Clinical Syndromes

BK virus induces in vitro transformation of rodent cells but does not do so as often in human cells. Definitive evidence of a relationship with oncogenesis in humans has not been proven [258]. BK virus has been implicated as a cause of pneumonia in a patient with AIDS and in at least two patients with underlying hematologic malignancies [259–261]. BK virus has a central role in the development of BK nephropathy (polyomavirus nephropathy or PVAN) and ureteral stenosis in renal transplant recipients [262] and in post-engraftment hemorrhagic cystitis of HSCT recipients [263]. The latter syndrome is increasingly being recognized (often in patients previously thought to have adenovirus infection). Symptoms range from microscopic hematuria to painful and severe hemorrhage, with or without bladder obstruction [263]. These symptoms can be persistent in the neutropenic or immunocompromised individual.

22.2. Diagnosis

Though numerous methods may be available to diagnose BK viral infection (Table 2-24), urine cytology and molecular assays are often used as diagnostic tools for hemorrhagic cystitis after HSCT.

Detection of BK viruria with PCR can correlate with active disease, but is limited somewhat by a lack of specificity. Asymptomatic BK viruria can be documented in other non-renal solid organ transplant recipients, elderly patients not on immunosuppression, HIV-infected patients, pregnant women and otherwise healthy individuals [266–270]. BK viruria is uncommon in general and tends to be lower in quantity than in HSCT recipients with hemorrhagic cystitis [271, 272]. HSCT patients with hemorrhagic cystitis have high level viruria (100,000,000–10,000,000,000 copies/mL), and levels of 10,000,000 copies/mL correlate with risk for hemorrhagic cystitis in this patient population [271]. The pattern of BK viruria is also thought to be of potential significance. In one prospective cohort, some patients who went on to develop hemorrhagic cystitis invariably experienced a peaking of their BK viruria as measured by PCR in the 2–3 week period after HSCT, and before clinical hemorrhagic cystitis [273]. Measurement of plasma with PCR for the presence of BK virus may also show a correlation with the development of hemorrhagic cystitis. Levels greater than 10,000 copies/mL strongly correlated with post-engraftment hemorrhagic cystitis in a case-control study among HSCT recipients [274].

22.3. Therapy

Most clinical strategies for hemorrhagic cystitis in HSCT recipients have not been successful. Reduced immunosuppression through the use of related donors or reduced-intensity conditioning regimens may reduce the risk post-HSCT

Table 2-24. BK virus diagnostics.

Diagnostic test	Description	Comments
Serology	BK virus-specific IgG antibodies in serum	Test not commonly available, evidence of prior exposure
Culture	In vitro	Not commonly available and requires weeks to months [264]
Urine cytology	Detection of "decoy cells," uroepithelial cells shed in the urine with changes consistent with active BK virus infection (enlarged nucleus with a large intranuclear inclusion)	Nonspecific, and these changes can possibly be seen with other viral infections (e.g., adenovirus) or malignancy; highly sensitive for screening.
PCR	Quantitative real-time amplification of polyomavirus-specific DNA sequence from either plasma or urine	Highly sensitive assay limited in specificity (see text); real-time assays distinguish JC and BK virus by analysis of the melting curves [265]
Biopsy with in situ hybridization	Viral changes of uroepithelium with in situ hybridization or immunofluorescence increases sensitivity and specificity	Hemorrhagic cystitis often prevents biopsy; often with thrombocytopenia
Electron microscopy	Electron microscopy of viral particles in urine sediment or biopsy specimens	Not widely available

PCR Polymerase chain reaction

[275]. Other factors may contribute to risk including chemotherapy and irradiation injury to bladder mucosa, thrombocytopenia, neutropenia and co-infection with adenovirus or CMV. Reduction of BK viruria or viremia has not been well correlated with reduced incidence or severity of hemorrhagic cystitis.

In vitro suppression of BK viral replication is possible with some fluoroquinolone antibiotics or related compounds that inhibit DNA gyrase [276, 277]. Other in vitro data have suggested that the selectivity index for fluoroquinolones and the inhibition of BK virus replication is too low to be of any clinically significant value [278]. Well-designed clinical trials are needed to validate these data.

Cidofovir has in vitro inhibitory effects on BK virus [279–281]. It has been used in case reports both systemically and through bladder instillation to treat BK virus-related hemorrhagic cystitis [282, 283]. Use of bladder instillation has not been very effective in patients and systemic therapy has been limited by renal toxicity [283].

Leflunomide is an immunosuppressive agent that inhibits CMV, HSV and BK replication in vitro [284]. It has been used to treat PVAN in small numbers of renal transplant recipients in combination with a reduction in immunosuppression [284, 285]. No studies have described its use in HSCT recipients with hemorrhagic cystitis.

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