Viral Lower Urinary Tract Infections

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Lower urinary tract infections (UTIs) are common among the general population and are most often caused by bacterial pathogens. Viruses are an uncommon cause of UTIs in an immunocompetent host; however, viruses are increasingly recognized as the cause of lower UTI, especially hemorrhagic cystitis, among immunocompromised patients. BK virus, adenovirus, and cytomegalovirus are predominant pathogens involved in hemorrhagic cystitis after stem cell and solid organ transplantation, and their early diagnosis and treatment may prevent significant morbidity of hemorrhagic cystitis. The diagnosis of viral lower UTI is based on molecular techniques, and real-time polymerase chain reaction is often the method of choice because it allows for quantification of viral load. Cidofovir is becoming a drug of choice in viral UTIs because it is active against the most common viral pathogens. This review discusses the epidemiology, pitfalls in diagnosis, and current treatment of viral UTIs.

Introduction

Lower urinary tract infections (UTIs) are commonly seen in urologic practice, and most urologists are familiar with typical bacterial pathogens and current treatment paradigms; however, viral pathogens, which can cause lower UTIs, are less known. Viral infections of the lower urinary tract are usually seen in immunocompromised patients, especially in solid organ and stem cell transplantation recipients, and are the most common cause of hemorrhagic cystitis in this group of patients [1••,2,3••] Anatomically lower UTIs can be divided into cystitis, prostatitis, seminal vesiculitis, and urethritis; however, bladder and ureter are most commonly affected by viral lower tract UTIs.

One of the main differences between bacterial and viral pathogens affecting the lower urinary tract is that no bacteria should be found in the urine of healthy people, especially in men. The same can not be assumed with viruses because some of them (eg, BK virus [BKV]) can be found in healthy, asymptomatic, immunocompetent patients. Therefore, viral infection is defined as a presence of an identifiable viral organism with inflammatory symptoms. The symptoms of lower UTI include hematuria, genital or lower abdominal pain, urgency, frequency (secondary to inflammatory response and irritation of the bladder wall), pyuria, and hematospermia. In rare instances of prostatic abscess, the obstructive voiding symptom and urinary retention can be found.

The presentation, as well as the natural history of lower UTIs, depends on existing anatomic abnormalities and (more importantly) on the immune status of the host.

With the emergence of new medications and protocols to treat systemic diseases (such as leukemia, lymphoma, chronic renal insufficiency, and rheumatologic disease) bone marrow transplantation, chemotherapy, immune modulators, and immunosuppressants are commonly used and add to the number of immunocompromised patients. The immunologic status of the patient dramatically changes one's ability to fight the infection and alters clinical course. Mortality among immunocompetent patients with lower UTI is extremely low; however, viral UTI with high viral load can be associated with high mortality in immunocompromised patients because of associated viremia and multiorgan viral infections and failure. Antivirals themselves have significant side effects, and their use may induce organ rejection [4]. Thus, lower urinary tract symptoms in an immunocompromised patient should be diagnosed and treated promptly.

This review brings the reader up-to-date with typical viral pathogens that can cause lower UTI and provides information on clinical management.

Epidemiology

The most common presenting symptom of viral UTI is hemorrhagic cystitis. Recently, hemorrhagic cystitis was considered a complication of chemotherapy, especially with alkylating drugs such as busulfan. However, with improved methods of viral detections, it was found that viral infections are a common cause of hemorrhagic cystitis. In a prospective study of more than 100 children who underwent bone marrow transplantation, hemorrhagic cystitis occurred in 25.5%, and viral cause was identified in more than 95% of children with hemorrhagic cystitis.

Table 1. Syndromes and conditions associated with increased risk of viral lower tract urinary tract infection

Condition	Mechanism of increased risk of viral infections
Bone marrow transplantation	Immunosuppression and chemical bladder irritation
Solid organ transplantation	Immunosuppression
Hematopoietic malignancies	Abnormal function of immune system, immunosuppression
Chemotherapy for malignancies	Myelosuppression, chemical bladder damage
HIV infection	Immunosuppression
Congenital immunodeficiency	Abnormal function of immune system
Wiskott-Aldrich syndrome	Abnormal function of immune system
Wegener's granulomatosis	Abnormal function of immune system
Rheumatologic diseases and their treatment	Immunosuppression
Pregnancy	Abnormal function of immune system, changed hormonal status
Diabetes, alcoholism, malnutrition, liver cirrhosis	Abnormal function of immune system

Polyoma BKV was detected in the urine of 21 patients (80.8%), adenovirus (AdV) was detected in four (14.4%), and JC virus was detected in one patient (3.8%). The high-dose chemotherapy conditioning was the best predictor of developing viral hemorrhagic cystitis [5••]. Male sex and unrelated or mismatched donor are additional risk factors for hemorrhagic cystitis [4].

Viral hemorrhagic cystitis can also occur after renal transplantation, but its prevalence is lower than in bone marrow transplantation recipients, which may be attributed to lower risk of BKV reactivation rate after renal transplantation. This is thought to be secondary to less pronounced suppression of cellular immune response, which is needed to prevent rejection in solid organ transplantation [6]. BKV and AdV are the most common viral pathogens isolated in hemorrhagic cystitis after renal transplantation. BKV can cause interstitial nephritis, ureteral stenosis, and hemorrhagic cystitis and is almost always treated with antivirals [7]. Adenoviral hemorrhagic cystitis is usually self-limiting, and treatment depends on clinical picture. Detection of AdV in urine in patients with hemorrhagic cystitis is pathognomonic of adenoviral cystitis [5••,8,9].

Symptoms and Signs

Lower abdominal pain, dysuria, frequency, urgency, and lack of high-grade fever are common symptoms of lower UTI among the immunocompetent population, regardless of type of pathogen (Table 1). The symptomatology is altered by the immune status of the host and gross hematuria; fever and malaise are seen more commonly in immunocompromised patients with lower UTI. The majority of UTIs are caused by bacteria with *Escherichia coli* and *Enterococcus* [10]. Thus, bacteriologic cultures have to be obtained in every patient; however, in patients not improving clinically (despite antibiotic treatment) or in patients who are at high risk of viral UTI (ie, bone marrow transplantation recipients, patients undergoing treatment with a multidrug regimen for leukemia or lymphoma), the diagnosis of viral UTI has to be strongly considered. Early diagnosis may prevent rejection.

Diagnosis of Viral UTI

Diagnosis of viral UTI is more challenging because viruses are small organisms, and they can not be visualized with even the best optical microscope. The culture of viruses may take up to 14 to 28 days, and often it is too late to treat a patient with disseminated multiorgan viral infections at that time. Thus, molecular and immunofluorescence techniques are used more commonly.

The reliability of diagnosis depends on adequate technique, obtaining and transporting the specimen as well as technique of detection. Clinicians should be familiar with commonly used methods of virus detection: culture, direct immunofluorescence of organism, serologic- and antigen-based assays, and genomic amplification (quantitative or qualitative).

Viruses are too small to be detected by direct light microscopy after staining the specimen. Viruses live in the host cells, and the presence of some viruses (cytomegalovirus [CMV], BKV) may be suspected by characteristic changes on urine cytology [11]. Otherwise, a virus has to be grown in culture, and the type of virus is determined based on characteristic cytopathologic changes of cell culture inoculated with the specimen. This diagnostic method is cumbersome and prone to false-negative results. Not all viruses can be cultured. AdV, CMV, enteroviruses, herpes simplex virus (HSV), influenza, mumps, parainfluenza, respiratory syncytial virus, and varicella-zoster virus can be cultured, but this technology is not applicable for detection of Coxsackie A viruses, hepatitis viruses, arbovirus, parvovirus, human papillomavirus, reovirus, measles virus, and gastrointestinal viruses. To increase detection, 1 mL of body fluids

or tissues have to be placed in a special transportation medium (eg, M4) as soon as possible and placed at 4°C until they reach the laboratory. Medium can not be frozen and most laboratories will not accept specimen obtained on a bacterial transportation swab. Because each of the viruses requires specific cell line, media, and method of detection, it is especially important to provide adequate clinical information and to be specific about the type of virus to be detected. Unlike bacterial specimens, one can not order a general "viral culture."

Because of the cost and time required for diagnosis using culture, most laboratories have shifted to other techniques, which can be generally divided into methods detecting the presence of pathogen (antigen), such as direct immunofluorescence and enzyme-linked immunosorbent assay (ELISA); methods detecting genetic material (DNA or RNA), which is a specific finger print of the virus; and methods detecting antibodies in the serum or central nervous system, such as ELISA or competitive ELISA. Each of these techniques differs by their cost, specificity, and sensitivity.

In direct immunofluorescence, the pathogen is detected in the spun body fluid (or cells). The antibody against the antigen specific for virus (eg, HSV or BKV) is used and then detected under fluorescent microscope by secondary antibodies coupled with fluorochrome [12]. The method is relatively simple and fast; however, it is not a quantitative method and can not be used for viruses with rapidly changing antigens. This test is most commonly used to detect HSV by scraping from the genital ulcers, but it can also be performed on urine specimen [13,14]. For collection, one would use a dacron swab to collect the cells from the ulcer and then smear the cells on two clean slides with the patient's name and medical record number. After the cells have air-dried the test can be transported to the virology laboratory.

ELISA and competitive ELISA are used to detect viral antigens and antibodies against the viruses in the specimen. The antibodies against the antigen are immobilized on the styrene plate, and secondary antibodies are then applied to detect the antigen. The plates are washed to remove excess antibody and chemiluminescence, or colorimetric detection reagents are added. The darker the color in the well, the more antigens (viral particles) present in the specimen. In competitive ELISA, the tracer antigen competes with the specimen antigen for a set number of binding sites. In this assay, the lighter color after developing reaction means that there is a higher concentration of virus in the patient's sample. ELISA is also used in the detection of antibodies. In this assay, the antibody is an antigen. ELISA is a relatively simple and fast technique that is often used in automatic assays; however, small changes in volumes of sandwich antibodies or developer will affect the results (pipetting error). In automatic instrumentation, the chemicals are dispensed from prefilled containers, and "carry-over" contamination between different runs of assay can easily occur. This is a known problem; hence, if the results do not match the clinical picture, one should contact the laboratory and inquire about recent quality-control problems or controls.

Because the amount of primary antibody is fixed per well, the concentrations of antigens or tracer can not be too high because they will occupy all of the binding sites by chance, and the assay results can be outside of the linear standard curve. Given that each assay uses a different (and often) proprietary amount of antigen and antibodies as well as tracers, the results between different assays may differ, and it is preferable to use the same assay from a single supplier.

Serologic methods detect changes in titers of antibody against the known pathogen. Because developments of antibodies against a virus take time and use of immunosuppressants may modulate immune response, lack or presence of antibodies may not exclude or confirm current infection. This is especially true in viruses, such as HSV, CMV, and BKV, with a high prevalence (17%, > 60%, and > 90%, respectively) among an immunocompetent population in the United States [15,16]. HSV and BKV are especially important in urology. To find out if a patient was ever exposed to HSV, one can measure immunoglobulin G against HSV levels, which should be elevated. During acute or recent infection, the immunoglobulin M titer allows for differentiation of new viral infection versus history of exposure in the past. Immunoglobulin M increases within 2 weeks of exposure. The results for antibodies are reported as titers, and increasing titers make it more likely that the patient has current infection. Because of some nonspecific binding of a patient's antibodies to the antigen, good quality laboratories stratify their titers into negative, undetermined, and positive. Undetermined titers can be a result of nonspecific binding or of current infection when the host has not yet produced enough antibodies to be detected. If levels of antibodies are within an undetermined level, the assay should be repeated in 2 to 4 weeks, or direct method of detection should be used.

Because of problems with detection of antibodies and poor correlation between the viral load and the ELISA, as well as the fact that many viruses are present in immunocompetent hosts, the current state-of-the-art detection techniques are based on molecular techniques [17]. These techniques are based on polymerase chain reaction (PCR), which allows for specific and fast amplification of a small region of viral genome. Because the genome of most of the clinically important viruses is known, it is relatively easily to amplify viral DNA or RNA and to detect amplicon by gel electrophoresis, chromatography, or real-time PCR. Real-time PCR allows for relative or absolute quantification of viral load. The results are reported as number of virions per mL or number of units per mL of specimen. Commercially available BKV tests are able to detect 500 copies of BKV in 1 mL of urine.

Although PCR is a sensitive diagnostic method and even a minute amount of virus can be detected, its sensitivity is also one of its drawbacks. The genome of some viruses is not stable, and one needs to choose the most stable "conserved" sequence that can identify the virus of interest with high specificity. Even a single change in the nucleotide sequence can affect the binding of primers, and if the annealing temperature is high, the presence of a virus may not be detected (false-negative result). The viruses also occur in multiple genotypes (example HPV or AdV); thus, often one assay is not able to detect all genotypes. Because the PCR reaction produces millions of copies of viral DNA "amplicon," it is easy to obtain false-positive results from airborne amplicon contamination. Therefore, in many laboratories, the preparatory and analytic areas are physically separated, and high-performance flow hoods are used when amplified samples are handled. The real-time PCR, which eliminates transferring of amplified product to the gel, avoids many of the contamination problems and has become a method of choice for molecular detection of clinically important viruses. Real-time PCR and quantification of viral load has significant prognostic value in predicted clinical outcomes [18].

Most Common Viral Pathogens Causing Lower UTI

Classification of clinically important viruses is somehow difficult because viruses with quite different biochemical and genomic properties may cause similar diseases. Generally, viruses are divided based on type of nuclei acid that they are made from (DNA or RNA), and subsequently, they are divided into groups based on replication properties such as single- or double-strand. The most commonly used classification is called the Baltimore classification (coined for its creator, American biologist and Nobel laureate, Dr. David Baltimore), and it divides viruses into seven groups. Clinically, viruses are often group-based on clinical picture, though viruses with different biochemical properties can lead to a similar pathology (Table 2). Basic knowledge of viral classification is useful because the majority of antiviral drugs are active against viruses with similar biochemical and molecular properties (Table 3).

Human polyomavirus (BKV)

The human polyomavirus (BKV) is a subgroup of papovavirus and is a common and normally nonpathogenic virus, with approximately 97% of the adult population having antibodies against it [19]. BKV has a significant homology to a neurotropic virus, causing progressive multifocal leukoencephalopathy, or JCV. BKV was first identified in the urine of a renal transplantation recipient with the initials B.K. (by Dr. Sylvia D. Gardner in 1971). The BKV virus has a urotheliotropic nature and can be identified in the collecting system epithelium and transitional epithelium. The typical cytopathologic changes of BKV are often found in a healthy person, and it is believed to represent transient shedding of virions in urine, most likely secondary to stress or decreased immune response. The patient's cytopathologic changes resolve within 3 months, and there seems to be no clinically significant sequelae of BKV-positive cytology in immunocompetent people [20]. High-grade transitional cell carcinoma can be difficult to distinguish from BKV on cytology, and follow-up cytology may be considered in patients with risk factors for transitional cell carcinoma [21]. Up to 0.3% of the healthy population and 3% of pregnant women will have BKV-positive urine cytology [22]. The interest in BKV paralleled development in potent immunosuppressants and the discovery of an association between reactivation of BKV in patients with renal transplantation and progressive nephropathy and allograft loss–polyomavirus-induced nephropathy [23]. The BKV is commonly found in the urine of patients with hemorrhagic cystitis and ureteral strictures, especially after bone marrow and solid organ transplantations [6,24]. Fifteen of 90 patients developed late-onset BKV hemorrhagic cystitis 16 to 95 days after bone marrow transplantation in the study by Giraud et al. [3••]. Most of these patients (10 of 15; 67%) developed hemorrhagic cystitis within 30 days after transplantation. The hemorrhagic cystitis was severe in more than 80% of the patients. Reduced conditioning decreases risk of BKV-related hemorrhagic cystitis [3••].

Diagnosis of BKV infection

BKV infection should be suspected in a patient with immune deficiencies (Table 1) who presents with hemorrhagic cystitis, microscopic hematuria, hydronephrosis, and an increase in creatine. Most BKV infections occur within 1 to 6 months after transplantation (Table 4). The clinical diagnosis needs to be confirmed by detecting the virus in the urine or blood. Recipients of renal transplantation may also have associated graft dysfunction, and renal biopsy may show typical interstitial nephritis with characteristic changes in tubules. The presence of BKV in renal parenchyma may be detected by commercially available antibodies. Because of the high prevalence of positive antibodies in the serum and lack of a reliable viral cell culture, the diagnosis of BKV lower UTIs requires molecular techniques, such as quantitative real-time PCR, which allows for the detection of BKV and an estimation of the number of viral copies per mL of urine or blood [25]. BKV DNA is rarely detected in the urine of a healthy individual. Urine cytology can be indicative of BKV infection by identifying so-called "decoy" cells; however, sensitivity of decoy cells in diagnosis of BKV infection in hemorrhagic cystitis is low [26]. Real-time PCR tests and quantification of viral copies seem to have prognostic value and can be used to monitor response to therapy. BKV is detected in 87% of patients with hemorrhagic cystitis after bone marrow transplantation, and the prevalence of BKV is statistically higher than in patients without hemorrhagic

Table 2. Clinical and biologic classification of viruses (clinical picture and/or mode of treatment)

Clinical classification of viruses*
Adenovirus (upper respiratory infection, hemorrhagic cystitis)
Coronavirus (SARS)
Enterovirus (meningitis)
Hemorrhagic fever viruses
Congo-Crimean hemorrhagic fever (ribavirin successful)
Ebola virus (supportive treatment, no antiviral available)
Hantavirus (pulmonary syndrome; ribavirin)
Dengue hemorrhagic fever (intravenous colloids, support)
West Nile virus (may be transmitted by blood products, breast feeding; no specific treatment)
Yellow fever virus (vaccination effective)
Hepatitis A, B, C
Herpesviruses
Cytomegalovirus
Epstein-Barr virus (mononucleosis)
Human herpes virus-6 (roseola)
Human herpes virus-7
Human herpes virus-8 (Kaposi's sarcoma, lymphoma)
Herpes simplex virus type 1 (Bell palsy, encephalitis, mucocutaneous herpes)
Herpes simplex virus type 2 (genital herpes)
Herpes varicella-zoster virus (varicella [chickenpox], herpes zoster)

*Clinical classification is based on syndromes or pathology caused by viruses.
†Baltimore classification is based on genomic methods of replication and was created by Dr. David Baltimore.
AMV—avian myeloblastosis virus; BKV—BK virus; HIV-1—human immunodeficiency virus type 1; JCV—JC virus; M-MLV—Moloney murine leukemia virus; SARS—severe acute respiratory syndrome.

Table 2. Clinical and biologic classification of viruses (clinical picture and/or mode of treatment) *(Continued)*

Clinical classification of viruses*
Influenza A and B
Measles virus
Human metapneumovirus (upper respiratory infection)
Monkeypox (chickenpox-like syndrome; cidofovir)
Norovirus (gastroenteritis; no specific therapy)
Papillomaviruses (anogenital warts; vaccine available for females)
Parvovirus B19 virus (arthritis and anemia, intravenous immunoglobulin-antibodies against parvo B19 [only in anemia])
Papovavirus/polyoma virus
BKV
JCV
Rabies (rabies vaccine before onset of symptoms otherwise 100% fatal)
Respiratory syncytial virus (pneumonia in children and adults; no treatment so far successful)
Rhinovirus (common cold; no specific treatment)
Smallpox (smallpox vaccine and antiserum)
Baltimore classification of viruses†
Group I: double-stranded DNA: adenoviruses, herpesviruses, human papilloma Virus, polyoma viruses (BKV), smallpox, molluscum contagiosum virus
Group II: single-stranded DNA: parvoviruses (parvovirus B19)
Group III: double-stranded RNA: reoviruses, birnaviruses (rotaviruses)
Group IV: positive-sense single-stranded RNA: picornaviruses; togaviruses (coronavirus, SARS, West Nile virus, hepatitis A, E, and C, rubella virus, polio virus)
Group V: negative-sense single-stranded RNA: orthomyxoviruses, rhabdoviruses (influenza, mumps, measles viruses, rabies virus)
Group VI: reverse-transcribing RNA: retroviruses (HIV-1, AMV, M-MLV)
Group VII: reverse-transcribing DNA: hepadnaviruses (hepatitis B virus)

*Clinical classification is based on syndromes or pathology caused by viruses.
†Baltimore classification is based on genomic methods of replication and was created by Dr. David Baltimore.
AMV—avian myeloblastosis virus; BKV—BK virus; HIV-1—human immunodeficiency virus type 1; JCV—JC virus; M-MLV—Moloney murine leukemia virus; SARS—severe acute respiratory syndrome.

Table 3. Common antivirals: spectrum, use, and therapeutic implications*

Name, function	Viral activity	FDA-approved use	Typical dose	Comments
Acyclovir, inhibits viral DNA polymerase and incorporates into viral DNA	HSV-1, HSV-2 herpes simiae, VZV; acyclovir is more active against HSV-1 than HSV-2 than VZV, respectively; potential activity against EBV	Genital HSV: primary, acute	200 mg PO 5×/d for 10 d	Adjust for renal and liver function; contraindicated with cidofovir (increased risk of nephrotoxicity); avoid aminoglycosides, clofarabine, and gallium nitrate
		Genital HSV, recurrent	200 mg PO 5×/d for 5 d	
		Genital HSV, suppression	400 mg PO BID×12 mo	
		Herpes zoster	800 mg PO 5×/d for 10 d	
		HSV encephalitis	10 mg/kg IV Q8h for 10 d	
		Varicella, primary	800 mg PO QID for 5 d	
Famciclovir, inhibits DNA polymerase	HSV-1 and HSV-2, VZV; limited activity against EBV and HBV	Herpes zoster	500 mg PO Q8h for 7 d	Adjust for renal function; monitor digoxin levels if used together; may increase digoxin level
		Genital HSV, primary and recurrent	250 mg PO TID for 10 d	
Valacyclovir, inhibits DNA polymerase	HSV-1 and HSV-2, VZV	Genital herpes, primary	1000 mg PO BID×10 d	Adjust for renal function; adequate hydration; avoid carboplatin, cimetidine, entecavir, and phenytoins
		Genital herpes, recurrent	500 mg PO BID×3 d	
		Genital herpes, suppression	1000 mg PO QD, may start at 500 mg PO QD	
		Reducing transmission in discordant couples	500 mg PO QD together with safe sex practices	
		Herpes zoster	1000 mg PO TID×7 d	
Ribavirin, mechanism of action unknown	HCV; in vitro activity against herpesviruses, adenoviruses, and poxyviruses, hemorrhagic fever viruses, influenza, measles, mumps, and RSV; clinical activity is limited and does not correlate with in vitro activity	Hepatitis C in combination therapy	Dose depends on genotype of virus; used in combination with interferon α-2B	Risk of hemolytic anemia, fatal myocardial infarctions; highly teratogenic and may persist up to 6 mo in organism after last dose; both females and males advised to use two forms of reliable contraception for minimum of 6 mo after last dose and during therapy; multiple drug interactions

*The treating physician should be familiar with multiple drug interactions and FDA labeling for each drug because many of the antiviral drugs have well-proven teratogenic and reproductive side effects in animals.

BID—twice daily; CMV—cytomegalovirus; EBV—Epstein-Barr virus; FDA—US Food and Drug Administration; HBV—hepatitis B virus; HCV—hepatitis C virus; HSV-1—herpes simplex virus type 1; HSV-2—herpes simplex virus type 2; IV—intravenous; PO—by mouth; Q—every; QD—every day; QID—four times daily; RSV—respiratory syncytial virus; TID—three times daily; VZV—herpes varicella-zoster virus.

Table 3. Common antivirals: spectrum, use, and therapeutic implications* ***(Continued)***

Name, function	Viral activity	FDA-approved use	Typical dose	Comments
Entecavir, inhibits reverse transcriptase, incorporates in viral DNA	Active against hepatitis B only, no activity against HIV	Hepatitis B, chronic	0.5 mg PO QD	Lactic acidosis; severe hepatomegaly; hepatitis B exacerbation; monitor liver and renal function and multiple drug interactions
Lamivudine, inhibits reverse transcriptase	Retroviruses: HIV and hepatitis B	Hepatitis B, chronic HIV, in combination therapy	100 mg PO QD	Lactic acidosis; severe hepatomegaly; hypertensive crisis with phenylpropanolamine; check HIV status (emergence of resistance)
Adefovir, inhibits reverse transcriptase	Active only against hepatitis B; converted to diphosphate in cells	Hepatitis B, chronic	10 mg PO QD	Nephrotoxicity; exacerbation of hepatitis B and HIV (drug resistance); lactic acidosis; monitor renal and liver function
Ganciclovir, inhibits DNA polymerase	CMV, HSV-1, HSV-2, EBV, VZV; very active against CMV and HSV; requires intracellular conversion to triphosphate	CMV: prophylaxis, transplantation	5 mg/kg IV Q12h ×7–14 d then 5 mg/kg IV Q24h 1000 mg PO TID	Granulocytopenia; anemia; thrombocytopenia; carcinogenic and teratogenic in animal studies; causes azoospermia; adjust for renal function; do not use with cidofovir; multiple drug interactions and adverse effects
		CMV prophylaxis, HIV-related	1000 mg PO TID	
		CMV retinitis	5 mg/kg IV Q12h ×14–21 d	
Foscarnet, selectively inhibits viral DNA polymerase, reverse transcriptase inhibitor	CMV, HSV-1, HSV-2, EBV, VZV, herpes virus-6; limited data on activity for hepatitis B and HIV	CMV retinitis in AIDS	90 mg/kg IV Q12h × 3 wk then Q24h	Renal toxicity: severe seizures (ciprofloxacin [contraindicated]); exacerbates electrolyte abnormalities; multiple drug interactions; adjust for renal function
		HSV and VZV infections mucocutaneous, resistant to other agents	40 mg/kg IV Q12h × 3 wk	
Valganciclovir, inhibits DNA polymerase	CMV, HSV-1, HSV-2, EBV, VZV; very active against CMV and HSV	CMV retinitis in AIDS	900 mg PO BID × 21 d then 900 mg PO QD	Granulocytopenia; anemia; thrombocytopenia; carcinogenic and teratogenic in animal studies; causes azoospermia; adjust for renal function; do not use cidofovir; adjust for renal function
		Solid organ transplantation, CMV prophylaxis	900 mg PO QD for 3 mo	
Cidofovir, active intracellular metabolite; cidofovir diphosphate, inhibits viral polymerase	CMV, adenovirus, HSV-1 and HSV-2, VZV, EBV	CMV retinitis in AIDS	5 mg/kg IV Q7d for 14 d then 5 mg/kg IV Q14 d, use probenecid before injection 1–2 gm	Acute renal failure; death; highly nephrotoxic and concomitant use of nephrotoxic drugs to be avoided; hydrate well; probenecid prevents nephrotoxicity

*The treating physician should be familiar with multiple drug interactions and FDA labeling for each drug because many of the antiviral drugs have well-proven teratogenic and reproductive side effects in animals.

BID—twice daily; CMV—cytomegalovirus; EBV—Epstein-Barr virus; FDA—US Food and Drug Administration; HBV—hepatitis B virus; HCV—hepatitis C virus; HSV-1—herpes simplex virus type 1; HSV-2—herpes simplex virus type 2; IV—intravenous; PO—by mouth; Q—every; QD—every day; QID—four times daily; RSV—respiratory syncytial virus; TID—three times daily; VZV—herpes varicella-zoster virus.

cystitis [3••]. BKV is more prevalent than AdV in patients with hemorrhagic cystitis [5••,27]. Urine should be sent for BKV and AdV detection by PCR for every patient with hemorrhagic cystitis who is immunocompromised.

Treatment

Until recently, the treatment of the BKV infection and its urologic complications focused on supportive measures (hydration, correction of coagulopathy, bladder irrigation), reduction in immunosuppression, and leflunomide with an overall poor response [28]. Acyclovir, ganciclovir, brivudine, ribavirin, foscarnet, and cytarabine have poor antiviral activity against BKV in in vitro studies [29]. Over the past few years, cidofovir, administered intravenous (IV) or intravesical, proved to be effective therapy against BKV with a relatively low rate of side effects [5••,30,31].

In the case of hemorrhagic cystitis, hydration, correction of coagulopathy, and bladder irrigation may be followed by cidofovir intravesical instillation, 5 mg/kg in 60 mL of saline instillation for 1 hour once a week [30]. Cidofovir can also be given IV at a similar dose; however, bladder instillation may avoid nephrotoxic complications of the drug. Cidofovir is active against the CMV and AdV, though it is less active against BKV, and by itself, it can cause nephropathy. Thus, intravesical instillation may be a better option for hemorrhagic cystitis, especially because the AdV plays a role in some of the patients with hemorrhagic cystitis, and cidofovir may be active against both organisms [1••,32,33••,34]. The response to treatment is measured by quantitative real-time PCR and resolution of hematuria. Although BKV is (without a question) the dominant viral cause of cystitis, only 50% of patients with BKV viruria will develop hemorrhagic cystitis, and prophylactic treatment with cidofovir may not be necessary. However, preemptive management—starting therapy as soon as the patient develops cystitis—may be beneficial, taking into account the high morbidity associated with hemorrhagic cystitis after bone marrow transplantation. One study showed that ciprofloxacin prophylaxis decreased the viral load of BKV as compared with cephalosporin. The mechanism of this finding is unclear [35].

It is important to remember that BKV is associated with an increased risk of bladder cancer, and follow-up cytologic studies (once hematuria resolves) may be indicated [36]. It is unknown if BKV is a cause or one of the modulators that increase the chance of neoplastic transformation.

Adenoviruses (AdV)

AdV are double-strand DNA viruses with at least 51 serologic subtypes. AdV are known to cause upper respiratory, gastrointestinal, and conjunctival infections in healthy people and children; however, their pathogenicity is altered by the immunologic status of the host, and in immunocompromised patients, AdV can affect many other systems [32]. Normally, the AdV causes asymptomatic infection of lymphoepithelial tissues, but in the immunocompromised patient, they can reactivate the latent infection or cause de novo infection. The adenoviral infections are more common in stem cell transplantation and solid organ transplantations. AdV can be detected in 10% of urine samples after transplantation, and over 12 months of follow-up, adenoviral UTIs occurred in 9% of patients [37]. Children, recipients of allogeneic versus autogeneic stem cell graft, and patients with graft versus host disease are much more prone to adenoviral diseases, which is a reflection of a more pronounced immunosuppression used in the above conditions. Immunocompetent patients have limited disease that hardly ever leads to serious mortality or morbidity.

Table 4. Most common causes of viral infections at different time periods after solid organ transplantation

1 mo-HSV, hepatitis
1–6 mo-CMV, EBV, VZV, influenza, RSV, adenovirus, BKV
> 6 mo-CMV, papillomavirus, post-transplant lymphoproliferative disease

BKV—BK virus; CMV—cytomegalovirus; EBV—Epstein-Barr virus; HSV—herpes simplex virus; RSV—respiratory syncytial virus; VZV—herpes varicella-zoster virus.

Diagnosis

Adenoviral cystitis can present as gross and microscopic hematuria in up to 20% of patients [38]. History of solid organ or bone marrow transplantation and use of immunosuppressants aids in diagnosis because AdV cystitis occurs almost exclusively in immunocompromised patients [8]. Most cases of AdV-related hemorrhagic cystitis occur within 12 months of transplantation [8]. Hemorrhagic cystitis is most commonly caused by immunotype 11, and presence of AdV in urine is almost exclusively seen in hemorrhagic cystitis [39]. The adenoviral infection can often coexist with aspergillosis and CMV in immunocompromised patients, and broad cultures should be obtained.

AdV are never detected in healthy patients. Presence of AdV in the urine of an immunocompromised patient is always associated with cystitis, but only 50% of BKV viruria will present clinically as cystitis. Cystitis is the most common clinical presentation of AdV infection of the genitourinary tract. Infection with AdV is defined as presence of virus in culture, presence of viral antigen by immunofluorescence, or presence of AdV DNA by PCR, irrespective of symptoms. The diagnosis using molecular techniques is faster because the culture can take up to 21 days.

Adenoviral disease refers to presence of virus and symptoms of invasive disease. In stem cell transplantation patients, AdV can cause hepatitis, hemorrhagic colitis, hemorrhagic cystitis, or pneumonitis and often leads to disseminated disease and death [40]. Adenoviral infections are associated with significant mortality and morbidity, and some advocate preemptive treatment and a high level

of suspicion in immunocompromised patients, especially if AdV can be detected in the blood by PCR [40,41].

Treatment
Unfortunately, until recently there was no single antiviral drug that would be potent and devoid of drug toxicity. Cidofovir is becoming an optional treatment of adenoviral infections and should be considered a first-choice antiviral to treat AdV cystitis. Lower dose (1 mg/kg three times per week for 3 weeks) is used in renal transplantation patients because of concern of nephrotoxicity of cidofovir, but this regimen fails to prevent HSV or CMV infections, and a higher dose (5 mg/kg once a week, IV or intravesical) may be a better choice [33,42,43]. It is possible that the nephrotoxicity of cidofovir is a result of often reduced immunosuppression and rejection and not the result of cidofovir itself, and a higher dose with continued immunosuppression may result in less long-term complications. Ribavirin, which has relatively poor activity against AdV, has been more successful in treating human leukocyte antigen–matched bone marrow recipients. Ribavirin is less successful in decreasing mortality in children [44–46]. Ganciclovir is mostly used for prevention of CMV infection; however, it has been used in the treatment of hemorrhagic cystitis in transplantation patients [47]. Vidarabine (10 mg/kg/day for 5 days) has been successfully used in the treatment of hemorrhagic cystitis and may be a viable alternative to cidofovir, but it is less active in generalized AdV infections [45,48–50]. Vidarabine and its metabolite achieve a high concentration in urine, which may explain its success in treatment of AdV hemorrhagic cystitis [48].

Cytomegalovirus (CMV)
CMV infection is common, and more than 60% of adults are seropositive. CMV belongs to a large group of herpes viruses that are of limited pathologic significance in immunocompetent patients. CMV reactivation or new infection is common in transplantation patients, and it can cause significant mortality and morbidity; hence CMV prophylaxis is commonly employed in patients after transplantation. CMV is a relatively rare cause of lower UTIs; however, circumferential evidence supports the association between CMV and hemorrhagic cystitis [51]. Reports of resolution of hematuria after treatment with IV ganciclovir have added further evidence linking CMV and hemorrhagic cystitis [51]. Although rare, CMV cystitis can also occur in immunocompetent patients [52]. Hemorrhagic cystitis has been clearly associated with reactivation of CMV [53,54]. CMV is also believed to cause ureteritis and ureteral stenosis [55].

Diagnosis
CMV can be detected by seroconversion in a previously negative host and increase in immunoglobulin M and immunoglobulin G antibodies titers [56••], but a high prevalence of latent CMV infection makes serologic diagnosis difficult, and detection of CMV antigen (pp65), RNA, or DNA is commonly used. Recently the pp65 antigenemia and real-time PCR have been compared with each other, and real-time PCR seems to correlate better with the clinical picture [57].

Treatment
Most patients receive prophylaxis with ganciclovir after solid organ transplantation; however, in active diseases, other drugs, such as foscarnet, 60 mg/kg IV twice daily for 14 days, can be used because they are active against CMV [58]. Cidofovir is active against both BKV and CMV and has been used if both viruses are detected [59]. For this reason, cidofovir may become a drug of choice in patients who present with hemorrhagic cystitis after solid organ or bone marrow transplantation.

Herpes simplex virus type-1 and -2
HSV type-2 is a common cause of genital ulcers in immunocompetent hosts, but bladder involvement is rare. HSV cystitis can occur in immunocompetent patients who have some other predisposing factors, such as diabetes mellitus or rheumatologic disorders [60,61]. Hemorrhagic cystitis can be a sign of disseminated HSV infection in immunocompromised patients [62].

Diagnosis
Diagnosis is relatively easy because HSV can be detected by serology, direct immunofluorescence, or cell culture.

Treatment
Treatment of HSV infection depends on the host's age and immune and serologic status. Neonates who are born of mothers with primary HSV infection are at high risk of transmission and central nervous system complications, and they are treated with IV acyclovir for 14 days. Acyclovir or valacyclovir is commonly used in symptomatic subjects with primary infection for 10 to 14 days using oral medications. Suppression is recommended in patients with recurrent flare-ups or in discordant couples to decrease risk of infection [63•].

Other viruses that are important in urology are the human papillomavirus, poxvirus causing molluscum contagiosum, and HIV; however, they do not (per se) cause lower UTIs and thus are outside the scope of this review.

Conclusions
Viral infections of the genitourinary tract are associated with significant morbidity and suffering, including increased mortality in immunocompromised patients. As urologists we need to include the most recent developments in genitourinary virology in our practice because knowledge of viral biology and clinical pathology may

prevent viral transmission (HSV and human papillomavirus), and early management of viral cystitis may decrease mortality related to disseminated viral infections of the lower urinary tract in selected patients.

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References and Recommended Reading

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