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Management of common infections in solid organ transplant recipients in British Columbia

Because transplant recipients remain on lifelong immunosuppression, physicians must be aware of the common infections they may face, and consult with infectious diseases and transplant infectious diseases specialists to support the ongoing health of this unique patient population.

ABSTRACT: Solid organ transplantation is becoming increasingly common in British Columbia, and infectious complications in these immunosuppressed patients are being seen with increasing frequency by community providers. Some infections, such as *Pneumocystis* pneumonia and cytomegalovirus infection, commonly affect all transplant recipients, whereas some infections are more specific to certain transplant types, such as cholangitis in liver transplant recipients, urinary tract infections in renal transplant patients, and pulmonary mold infections in lung transplant recipients. Numerous protocols and procedures exist to identify and mitigate infectious risk in transplant patients, as do specific treatment strategies. This article provides an overview of the epidemiology, diagnosis, treatment, and prevention of common infections in transplant patients, with a focus on community practitioners caring for this ever-increasing population.

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The number of solid organ transplant recipients is steadily increasing in British Columbia. In 2020, 253 kidney transplants, 71 liver transplants, 32 heart transplants, and 51 double lung transplants were performed in BC.[1] These transplant recipients reside throughout the province; therefore, all health care providers should have a general understanding of common issues this population may face. Infections are a major complication of transplantation and are associated with significant morbidity and mortality.[2]

We review risk periods for infections and chemoprophylaxis, with particular attention to management of cytomegalovirus. Additionally, we focus on management of the most common community onset infections, including recurrent urinary tract infections in kidney transplant recipients, intra-abdominal infections in liver transplant recipients, and mold and respiratory virus infections in lung transplant recipients.

Infection risk and prophylaxis

In solid organ transplantation, in general, the post-transplant period is divided into three risk periods: early (first month), intermediate (1 to 6 months), and late post-transplant (beyond 6 months)[3,4] **[Table 1]**. All solid organ transplant recipients receive perioperative antibacterial prophylaxis to reduce the risk of surgical site infection. In addition, the 2019 American Society of Transplantation Infectious Diseases Community of Practice candidiasis guidelines recommend *Candida* prophylaxis for adult liver transplant recipients with one or more of the following risk factors: prolonged or repeat operation, retransplantation, renal failure requiring dialysis, high transfusion requirement, hepaticojejunostomy, and *Candida* colonization during the perioperative period.[5] For lung transplant recipients, ischemia at the bronchial anastomosis, receipt of a single-lung transplant, hypogammaglobulinemia, cytomegalovirus infection, and pre-/post-transplant colonization of the airways with *Aspergillus* spp. are considered high-risk situations for post-transplant mold infections.[6]

In all solid organ transplant recipients, trimethoprim-sulfamethoxazole prophylaxis against *Pneumocystis jirovecii* pneumonia is recommended for a minimum of 1 year post-transplant, and in BC, it is often continued for the duration of the recipient's life due to infrequent but severe cases of late *P. jirovecii* pneumonia, which have occurred in the British Columbia transplant program. **Table 2** summarizes the current recommendations in BC for antiviral prophylaxis against the most common viral pathogens encountered in solid organ transplant recipients.[7]

Cytomegalovirus

Cytomegalovirus is the most frequently occurring opportunistic viral infection following solid organ transplant. It affects all organ transplants and is a major infectious cause of morbidity and mortality in transplant recipients.[8] In addition to having direct effects of end organ disease, cytomegalovirus has a number of indirect effects, including increased risk of bacteremia and invasive fungal infections in solid organ transplant recipients. It has also been associated with an increased risk for Epstein-Barr virus-mediated post-transplant lymphoproliferative disease, increased risk of acute rejection, and chronic allograft dysfunction.[8]

The primary infection with cytomegalovirus may be asymptomatic or it may cause a self-limited febrile illness in immunocompetent individuals.[8] After primary infection, cytomegalovirus establishes a lifelong latent infection that can periodically reactivate and cause shedding of an infectious virus.[9]

Cytomegalovirus infection is the presence of cytomegalovirus replication in tissue, blood, or other bodily fluids, regardless of symptoms. Conversely, cytomegalovirus disease is cytomegalovirus infection with clinical symptoms. The latter is subdivided into cytomegalovirus viral syndrome, with fever, malaise, lymphocytosis, leukopenia, or thrombocytopenia, or cytomegalovirus end-organ disease, including retinitis, pneumonitis, hepatitis, enteritis, nephritis, and others.[8]

Cytomegalovirus serologic status of donor and recipient are the key predictors of cytomegalovirus disease after transplantation. Thus, all donors and recipients should

TABLE 1. Timeline of infection after solid organ transplant (adapted from Fishman[3]).

Early (< 1 month)	Intermediate (1–6 months)	Late (> 6 months)
Perioperative infections: aspiration pneumonia, ventilator-associated pneumonia/hospital-acquired pneumonia, catheter-associated urinary tract infections, central line–associated bloodstream infections, surgical site infection *Clostridioides difficile,* methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, *Candida* spp. **Donor-derived infections:** HIV, rabies, West Nile virus Bacterial infections; e.g., bacteremia	**With *Pneumocystis* and antiviral (cytomegalovirus/herpes simplex virus, hepatitis B virus) prophylaxis:** BK virus nephropathy, respiratory viral infection, *Cryptococcus, Mycobacterium tuberculosis,* aspergillosis **Without prophylaxis:** *Pneumocystis jirovecii* pneumonia, herpes viruses (cytomegalovirus, varicella zoster virus, herpes simplex virus, Epstein-Barr virus), hepatitis B virus, *Nocardia,* toxoplasmosis, strongyloidiasis	Community-acquired pneumonia Urinary tract infection Late cytomegalovirus infection, late *Pneumocystis jirovecii* pneumonia Aspergillosis

TABLE 2. Antiviral prophylaxis for solid organ transplant recipients (adapted from BC Transplant medication guidelines[7]).

Virus	Donor	Recipient	Risk	Management
Cytomegalovirus	–	–	Low	No prophylaxis for kidney/kidney-pancreas/liver or lung
Cytomegalovirus	±	+	Intermediate	Valganciclovir if recipient is to receive lymphocyte-depleting agent; 3 months for kidney/kidney-pancreas/liver/heart; 6 months for lung
Cytomegalovirus	+	–	High	Valganciclovir for 6 months for kidney/kidney-pancreas; 3 months for liver and heart; 1 year for lung
Herpes simplex virus/varicella zoster virus	n/a	+	n/a	Prophylaxis with valacyclovir 500 mg orally twice daily × 1 month for patients receiving lymphocyte-depleting agent and not receiving cytomegalovirus prophylaxis
Hepatitis B virus in liver transplant recipient	HBc Ab+	HBc Ab+ or –	High	Lamivudine for life
	HBc Ab–	HBc Ab+	Intermediate	Monitor for hepatitis B virus reactivation* No prophylaxis
	Any hepatitis B virus status	HBs Ag+	High	Hepatitis B virus immunoglobulin for 1 year and hepatitis B virus antivirals (e.g., entecavir, tenofovir) for life
Hepatitis B virus in nonliver transplant recipient	HBc Ab+ and hepatitis B DNA detectable	Any hepatitis B virus status	High	Start lamivudine and refer to hepatologist
	HBc Ab+ and hepatitis B DNA undetectable	HBc Ab– regardless of HBs Ab status	Intermediate	Monitor for hepatitis B virus reactivation* No prophylaxis
	HBc Ab–	HBc Ab+	Intermediate	Monitor for hepatitis B virus reactivation* No prophylaxis

*Monitor for hepatitis B virus reactivation every 3 months for 1 year, then every 6 months thereafter. Tests to be done: hepatitis B surface antigen, hepatitis B core antibody, hepatitis B surface antibody, and hepatitis B DNA.

be screened for Cytomegalovirus-IgG before transplantation. Populations at higher risk are Cytomegalovirus-seronegative organ recipients of seropositive donors (Cytomegalovirus D+/R– aka Cytomegalovirus mismatch), and Cytomegalovirus-seropositive recipients who receive lymphocyte-depleting therapy, such as antithymocyte globulin.[10] If Cytomegalovirus-IgG is indeterminate, providers should assume the highest-risk scenario (e.g., the cytomegalovirus-indeterminant donor is assumed to be positive).[8]

Post-transplant, molecular tests that detect cytomegalovirus DNA in blood are the preferred methods for cytomegalovirus monitoring and for diagnosing cytomegalovirus infection. The diagnosis of tissue-invasive disease depends on the presence of positive findings by histopathology. Importantly, the degree of cytomegalovirus viremia may not necessarily correlate with the severity of tissue-invasive disease. This is most commonly seen in cytomegalovirus enteritis.[8,10]

There are two main approaches to cytomegalovirus management post-transplant: cytomegalovirus prophylaxis and cytomegalovirus monitoring with pre-emptive therapy.[10] These approaches are generally managed by transplant teams during the first year post-transplant when recipients are at greatest risk of cytomegalovirus viremia and disease. Late cytomegalovirus disease can occur beyond 1 year post-transplant, and if clinical concern exists for this entity, community providers can send blood for cytomegalovirus polymerase chain reaction (PCR) testing. In BC, all cytomegalovirus PCR testing is sent to and performed at St. Paul's Hospital's virology laboratory. Importantly, ordering providers must specify that cytomegalovirus PCR or viral load is what is desired because the default lab test for cytomegalovirus in blood is serologic testing, which is of no utility in the diagnosis being sought.

For cytomegalovirus prophylaxis, valganciclovir 900 mg orally once daily is currently used for the highest-risk groups **[Table 2]**. The main side effect of valganciclovir is cytopenias. If this occurs, valganciclovir should be discontinued and pre-emptive monitoring instituted. The dose of valganciclovir should not be lowered to manage cytopenias because it increases the risk of resistance. Letermovir is a novel agent against cytomegalovirus that does not cause significant cytopenias. There is an ongoing randomized controlled trial of letermovir versus valganciclovir for prophylaxis of cytomegalovirus in high-risk D+/R– kidney transplant recipients (ClinicalTrials.gov identifier: NCT03443869).

Pre-emptive therapy is the administration of an antiviral only to those who develop evidence of rising cytomegalovirus DNA that surpasses a given threshold on PCR monitoring. Treatment is with valganciclovir 900 mg orally twice daily, and cytomegalovirus PCRs should be monitored weekly. Therapy is discontinued and weekly monitoring is continued after two sequential negative cytomegalovirus PCRs spaced 1 week apart.

Cytomegalovirus disease is treated with IV ganciclovir 5 mg/kg every 12 hours or oral valganciclovir 900 mg twice daily, adjusted based on renal function. Both are equally effective for mild to moderate disease. IV ganciclovir is the drug of choice in severe or life-threatening cytomegalovirus disease. Second-line agents may include foscarnet or cidofovir, but their use is limited by renal toxicity and IV-only formulations. The duration of treatment of cytomegalovirus disease depends on the resolution of clinical symptoms and two sequential negative cytomegalovirus DNA levels. Patients with cytomegalovirus disease who fail to respond to therapy after more than 2 weeks of full-dose antiviral therapy should be assessed for the possibility of drug-resistant cytomegalovirus in consultation with specialists in infectious diseases or transplant infectious diseases.

Management of common community onset infections by organ group

Intra-abdominal infections in liver transplant recipients

Risk of intra-abdominal infection following liver transplantation is relatively high[11] due primarily to the technically complicated nature of liver transplantation, particularly regarding biliary anastomoses.[12] Most liver transplantation is performed using one of two techniques: choledococholedocostomy (duct-to-duct anastomosis) or Roux-en-Y hepaticojejunostomy.[13] The duct-to-duct approach is preferred because it results in a more natural anatomy with preservation of the sphincter of Oddi, which is important in reducing reflux of intestinal contents into the transplanted organ. However, duct-to-duct procedures are not always feasible. Roux-en-Y procedures involve direct juxtaposition of the small intestine with the biliary system and significantly increase the risk of reflux. Vascular complications, including hepatic artery and portal vein thrombosis, also predispose transplant recipients to intra-abdominal infection due to hepatic necrosis and bile duct ischemia.[12] Prompt recognition of intra-abdominal infection following organ transplantation is important, and the early initiation of empiric antimicrobial therapy coupled with source control, potentially requiring surgical intervention, is necessary to optimize outcomes.[12] An additional factor that complicates intra-abdominal infection in solid organ transplant recipients is increased rates of colonization by multidrug-resistant organisms, which affects the choice of empiric antimicrobial coverage **[Table 3]**.[14-16]

Infections of surgical incisions should be suspected in patients presenting with pain, erythema, discharge, or dehiscence of wounds, typically within the first 30 days following transplantation.[17] Patients presenting with incisional infections should receive imaging to evaluate for the presence of deeper infection requiring more aggressive surgical debridement. These patients should undergo bedside or operative inspection of their wound to facilitate diagnosis of additional complications, collection of microbiologic specimens for culture, and thorough washout and debridement if applicable. Ultimately, choice and duration of antimicrobial therapy will be dictated by careful consideration of microbiologic testing and clinical response.[12,17]

Abdominal solid organ transplant recipients presenting with clinical signs of peritonitis should receive evaluation by medical and surgical teams, as this may signify perforation or anastomotic leak.[18] Given the immunosuppression used in solid organ transplant, patients with leaks or perforation may not manifest the usual signs and often present with fever alone; a high degree of clinical suspicion should be maintained, particularly in the first 3 months

following transplantation.[12] Blood and surgical site culture collection, initiation of empiric antimicrobial therapy **[Table 3]**, acquisition of abdominal imaging, and prompt surgical exploration when indicated are important for optimizing outcomes.

Definitive management will be dependent on radiographic and/or operative findings. Antimicrobials should be tailored based on microbiologic results and should be continued until source control has been obtained.[12] Following definitive source control, the duration of antimicrobial therapy is not clearly established. The STOP-IT trial demonstrated equivalent outcomes in patients who received short courses (~4 days) of antimicrobials following source control versus those who received longer courses (~8 days); however, the trial did not include solid organ transplant recipients.[19] Optimal duration in this population is unknown. In general, 1 to 2 weeks of antibiotics are given following source control; longer durations are used if residual collections remain.

Liver transplant patients are predisposed to developing intrahepatic infections.[12] Biliary strictures, whether anastomotic or nonanastomotic, contribute to patients developing recurrent cholangitis, while biliary leaks contribute to the formation of bilomas and hepatic abscesses. These infections do not occur in isolation: biliary ischemia can result in both strictures (predisposing to cholangitis) and duct perforation (resulting in biloma formation). Bilomas may become infected and result in hepatic abscess formation. Both bilomas and abscesses may compromise blood flow and result in further bile duct ischemia and additional stricturing or leaks.

TABLE 3. Empiric antimicrobial recommendations for intra-abdominal infections in solid organ transplant recipients based on multidrug-resistant colonization status (adapted from Haider and colleagues[12]).

Colonizing organism	Recommended antimicrobial	Alternatives and additional considerations
No known multidrug-resistant organisms	Piperacillin-tazobactam or ceftriaxone + metronidazole	Vancomycin may be added for enterococcal coverage when using cephalosporin-based regimens if high clinical concern For patients with severe ß-lactam allergies, ciprofloxacin and metronidazole ± vancomycin can be used
Extended-spectrum ß-lactamase	Meropenem or imipenem	Ertapenem is not active against *Pseudomonas* or *Enterococcus*
Carbapenemase-producing organism	Consult infectious diseases/ transplant infectious diseases specialists High-dose, extended-infusion meropenem plus colistin, tigecycline, or fosfomycin (choose two additional drugs, guided by susceptibilities) ± aminoglycoside or fluoroquinolone if susceptible	Ceftazidime-avibactam or meropenem-vaborbactam Requires Health Canada Special Access Program approval—consult infectious diseases specialist
Multidrug-resistant *Pseudomonas*	Consult infectious diseases/ transplant infectious diseases specialists Ceftolozane-tazobactam or high-dose, extended infusion Meropenem ± aminoglycoside/ ciprofloxacin	Empiric choice will depend on patient-specific resistance patterns
Methicillin-resistant *Staphylococcus aureus*	Vancomycin (in addition to gram-negative coverage as above)	Daptomycin, linezolid, ceftobiprole
Vancomycin-resistant *Enterococcus*	Daptomycin or linezolid (in addition to gram-negative coverage as above)	Liver transplant patients with vancomycin-resistant *Enterococcus* colonization are at highest risk
Antifungal coverage	Fluconazole or micafungin	May be added in the case of suspected bowel perforation or anastomotic leak or severe sepsis from intra-abdominal infection

Urinary tract infections in kidney transplant recipients

Urinary tract infection is the most common infectious complication among kidney transplant recipients.[20] These infections most commonly occur in the first year after transplantation but may occur at any time.[21] Urinary tract infections have been shown to be associated with increased mortality and renal allograft loss.[22] Even a single urinary tract infection after transplantation is enough to increase the risk of impaired allograft function.[23] Urinary tract infections also increase the risk of acute cellular rejection.[24] Almost one-third of patients who develop a urinary tract infection after kidney transplantation will experience recurrent infection.[21]

In most studies, kidney transplant recipients shared the same classic risk factors for recurrent urinary tract infection as the general population: female gender and prior recurrent urinary tract infection or urological abnormalities.[25] Prolonged use of Foley catheter, presence of a ureteral stent, increased age of recipient, and delayed graft function are risk factors for early urinary tract infection.[24] Ureteric reflux disease and cadaveric donors also represent a higher risk.[26] Kidney transplant recipients also have unique risk factors, including anatomical and functional abnormalities, as well as immunosuppression.[27] The placement of the renal allograft into the pelvis alters the distance and angle of the ureter in relation to the bladder and kidney, which contributes to increased risk of renal allograft infection **[Figure]**.

Most urinary tract infections after transplantation are caused by *Escherichia coli*. Other common uropathogens include other members of the Enterobacterales, as well as *Enterococcus* spp., *Pseudomonas aeruginosa*, and *Staphylococcus saprophyticus*. Unusual uropathogens include *Candida* spp. Emerging drug resistance due to extended-spectrum ß-lactamase carbapenemase-producing organisms and other multidrug-resistant organisms are of particular significance because they have been shown to increase the risk of recurrent urinary tract infection in kidney transplant recipients and often require treatment with IV antibiotics and treatments that have greater side effects.[27]

In order to diagnose and treat urinary tract infection, it is critical to differentiate asymptomatic bacteriuria from symptomatic urinary tract infection. Urinary symptoms with or without systemic symptoms such as fever, chills, malaise, hemodynamic instability, leukocytosis, flank/allograft pain, or bacteremia are key for diagnosis of a urinary tract infection. If the urinary tract infection is symptomatic, the best next step is to collect a midstream urine sample or use straight catheterization to assess pyuria, followed by culture and sensitivity testing. For patients who have had indwelling catheters for more than 2 weeks, the Infectious Diseases Society of America recommends removing the catheter and collecting urine by either a midstream void or a newly placed urinary catheter.[27]

The management of recurrent urinary tract infections in kidney transplant patients requires a proper diagnosis of the underlying mechanism.[28] Management of recurrent urinary tract infections is summarized in **Table 4**.

Mold infections in lung transplant recipients

Invasive fungal infections are a serious cause of morbidity and mortality in lung transplant patients, and both diagnosis and therapy can be challenging. Numerous factors predispose lung transplant recipients to invasive fungal infections, including constant exposure to environmental spores and hyphal elements, lack of normal ciliary action, lack of innervation and cough reflex, and airway ischemia, particularly at the anastomosis. While yeasts (*Candida* spp.) are the most common cause of invasive fungal

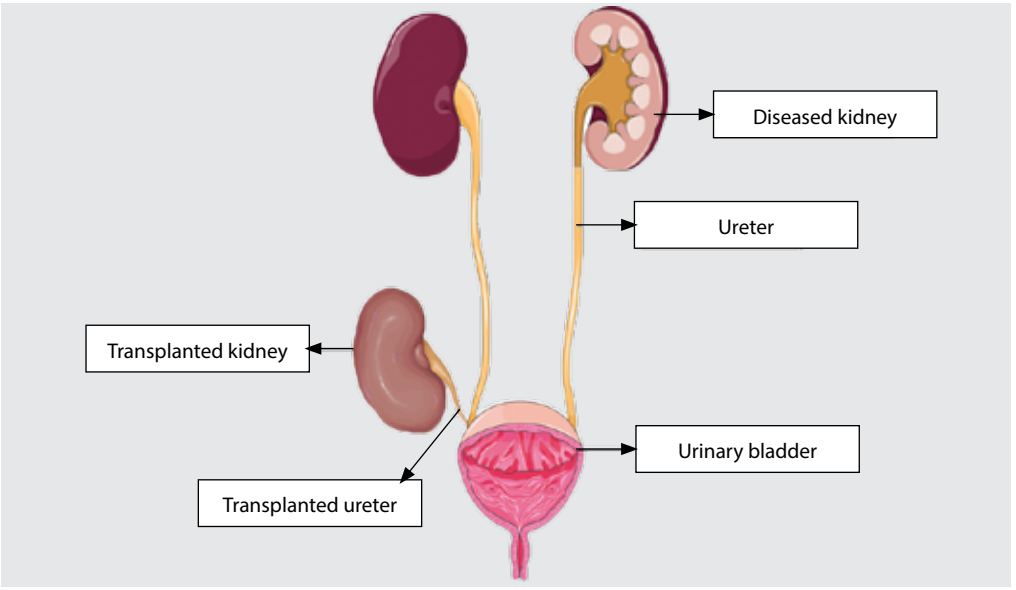

FIGURE. Anatomy of the genitourinary tract after kidney transplantation. The placement of the renal transplant in the recipient pelvis as opposed to the site of the native kidneys, termed heterotopic, causes increased risk of infection due to unique anatomic considerations (image created using Servier Medical Art).

TABLE 4. Management of recurrent urinary tract infections in kidney transplant recipients.

Medical management	Anatomical/functional assessment	Lifestyle modification
Adequate diabetes control Intravaginal estrogen **Antibiotic regimens:** Pill-in-pocket approach • Patients are provided with an antibiotic course to have on hand based on previous cultures susceptibilities • When symptoms of urinary tract infection develop, patient can collect urine culture and self-initiate antibiotics Postcoital antibiotics • Single postcoital dose of an antibiotic • The choice of antibiotic should be based on the susceptibility patterns of the strains causing the patient's previous urinary tract infection, the patient's history of drug allergies, and potential for interactions with other medications Prophylactic antibiotics • Daily administration of antibiotics to prevent the development of urinary tract infections • Generally avoided due to the risk of resistance, particularly in the transplant population **Adjunctive therapies:** Methenamine • Converts to formaldehyde in urine, making bladder inhospitable to uropathogens • Not available in BC; consult infectious diseases specialist Cranberry supplements • Limited evidence; proposed to prevent binding of *E. coli* to bladder epithelium D-mannose • Limited evidence; proposed to impair uropathogen binding to bladder epithelium	Assessment of postvoid residual Imaging by ultrasound or CT scan, cystourethrography, cystoscopy, or urodynamic studies if postvoid unrevealing Surgical intervention for benign prostatic hyperplasia/stricture Ureteric stents should be removed as early as possible to remove infection nidus	Wiping front to back Hydration Frequent timed voiding Postcoital voiding

infections among all solid organ transplant recipients (causing 49% to 85% of cases), lung transplant patients have higher rates of infection due to *Aspergillus* (44%) and other filamentous fungi (27%) than to *Candida* (23%).[29]

Risk factors for invasive aspergillosis that are unique to lung transplant patients include airway ischemia, single-lung transplant, pre- or post-transplant airway colonization with *Aspergillus* spp., cytomegalovirus infection, hypogammaglobulinemia, and episodes of rejection or augmented immunosuppression within the previous 3 months.[6,30,31]

Diagnosis of invasive aspergillosis is often challenging and is based on clinical, radiographic, and microbiologic characteristics. Diagnostic criteria for pulmonary invasive fungal infections are summarized in **Table 5**.[32] CT findings consistent with invasive aspergillosis include ground-glass opacities, peribronchial consolidation, nodules, or dense consolidation; the classical halo sign (dense consolidation surrounded by ground-glass opacification) occurs less commonly in solid organ transplant than in hematologic malignancies.[6] Tracheobronchial aspergillosis, occurring mainly at the anastomosis, accounts for approximately half of *Aspergillus* infections in lung transplant recipients and is both immediately dangerous and a precursor to invasive aspergillosis.[33] Direct inspection through bronchoscopy is needed because early tracheobronchial aspergillosis may be radiographically silent; microbiologic samples should also be collected, including cultures and galactomannan.

Therapeutic options recommended for the treatment of invasive aspergillosis are listed in **Table 6**. Therapy is typically continued for at least 3 months and until there is resolution of clinical, radiologic, and microbiologic signs of disease.[6] Azoles are CYP3A4 inhibitors and increase levels of common immunosuppressants used in solid organ transplant, including calcineurin inhibitors (e.g., tacrolimus) and mTOR inhibitors (e.g., sirolimus). Careful monitoring of tacrolimus levels is indicated while patients are receiving azoles and sirolimus is contraindicated. When an azole is discontinued, it results in reduced immunosuppressant levels and may precipitate rejection unless anticipated and proactively managed.

TABLE 5. Diagnostic criteria for invasive pulmonary aspergillosis (adapted from Donnelly and colleagues[32]).

Proven invasive pulmonary aspergillosis (IPA)	Histopathologic evidence of fungal invasion of tissue or Culture of organism from sterile site		
	Host factors	**Clinical features (CT)**	**Mycological evidence**
Probable IPA (host factor + clinical feature + mycological evidence) **Possible IPA** (host factor + clinical feature)	• Recent neutropenia • Hematologic malignancy • Solid organ transplant or hematopoietic stem cell transplantation recipient • Prolonged corticosteroids (> 0.3 mg/kg for > 3 weeks) • Treatment with T- or B-cell immunosuppressants • Severe inherited immunodeficiency • Acute graft versus host disease	• Dense, well-defined consolidation ± halo sign • Air-crescent sign • Cavity • Wedge-shaped and segmental, or lobar consolidation	Any of the following positive tests on samples obtained from nonsterile sites: • Fungal culture • Fungal elements observed • Galactomannan

TABLE 6. Antifungal agents recommended in the treatment of invasive pulmonary aspergillosis in solid organ transplant recipients (adapted from Husain and Camargo[6]).

Medication	Dose	Comments
First-line therapy		
Voriconazole	Loading dose: • 6 mg/kg orally/IV every 12 hours × 2 Maintenance dose: • 4 mg/kg orally/IV every 12 hours	• Trough level on day 7 (target 1.5–5 mcg/L) • Monitor liver enzymes, calcineurin inhibitor levels • Possible visual disturbances and hallucinations, transient following doses, attenuate over time
Second-line therapies		
Isavuconazole (dosage of prodrug isavuconazonium sulfate)	Loading dose: • 200 mg (372 mg) orally/IV every 8 hours × 6 Maintenance dose: • 200 mg (372 mg) orally/IV every 24 hours	• Monitor liver function and calcineurin inhibitor levels
Posaconazole (oral dosing based on delayed release oral tablet; liquid suspension also available but not recommended due to frequent dosing and poor absorption)	Loading dose: • 300 mg orally/IV every 12 hours × 2 Maintenance dose: • 300 mg orally daily	• Target trough > 1 mcg/L • Monitor liver function and calcineurin inhibitor levels
Liposomal amphotericin B	• 3–5 mg/kg IV daily	• Risk of renal toxicity; monitor electrolytes, renal function
Additional therapies		
Nebulized amphotericin B	• 25 mg inhaled twice daily	• For tracheobronchial aspergillosis, adjunctive therapy or prophylaxis
Echinocandins (micafungin, caspofungin)	• Micafungin: 100 mg IV every 24 hours • Caspofungin: 70 mg IV × 1, then 50 mg IV every 24 hours	• Used as combination therapy • Use as monotherapy should be considered only in consultation with transplant infectious diseases specialist

Solid organ transplant recipients should minimize exposure to soil and decaying organic material by avoiding gardening, landscaping, raking leaves, and construction or excavation sites. If avoidance is not possible, wearing gloves and a mask (N95 if on construction sites) is recommended.

Viral respiratory tract infections in lung transplant recipients

In solid organ transplant recipients, particularly lung transplant patients, viral respiratory tract infections can lead to serious morbidity and precipitate organ rejection.[34] Common pathogens include influenza, parainfluenza, respiratory syncytial virus, human metapneumovirus, rhinovirus/enterovirus, and coronaviruses, including SARS-CoV-2. Immunocompetent patients infected with these viruses typically have only upper respiratory tract involvement (with the exception of influenza and SARS-CoV-2). In lung transplant recipients, these viruses can cause a wide array of symptoms, ranging from mild symptoms, such as nasal congestion and rhinorrhea, to severe disease, including tracheobronchitis, bronchiolitis, and pneumonia. Seasonal patterns in these viruses exist.[34]

There are no clinical features that are useful for distinguishing disease caused by different viruses, but molecular diagnostics using PCR have played an increasingly important role. Establishing a diagnosis is particularly important because medical therapies are available for a few, but not all, of these viruses, and infection can both mimic and potentially precipitate rejection.[35,36] Many viruses are also associated with secondary bacterial or fungal pneumonias.[34,37] Nasopharyngeal swabs are most commonly used to collect samples for testing. Lower tract sampling may be indicated if clinical suspicion is high and upper tract samples are negative. Given the transmissibility of these pathogens, transplant wards must take care to appropriately isolate patients with confirmed or suspected infection to prevent spread to other vulnerable patients.

Influenza and, more recently, SARS-CoV-2 are the only viruses in this group for which vaccines and targeted therapy are available. Solid organ transplant recipients who contract influenza are at higher risk of complications relative to the general population, including pneumonia (22% to 49%) and ICU admission (11% to 16%).[34,38] Receipt of annual vaccination in solid organ transplant patients has been associated not only with reduced incidence (from 25.0% to 1.3% in a single study on lung transplant patients) but also with a decrease in disease severity in patients who develop influenza despite being immunized.[39,40] Risk factors for the development of severe influenza in solid organ transplant recipients include diabetes, bacterial or fungal pneumonia, use of antilymphocyte globulins, and acquisition of infection in the first 3 months following transplantation.[39]

Annual vaccination with inactivated influenza vaccine is strongly recommended (live-attenuated vaccines are contraindicated in solid organ transplant recipients); for patients who are unable to be vaccinated, prophylactic oseltamivir 75 mg orally daily for 10 days can be considered following high-risk exposures.

Transplant patients who develop influenza should be treated with oseltamivir 75 mg orally twice daily, regardless of symptom duration, and treatment should be continued for a minimum of 5 days and possibly extended up to 10 days in patients with severe disease or persistent symptoms. Importantly, oseltamivir does not have any significant drug–drug interactions with antirejection medications used in solid organ transplant, although it does require renal dose adjustment.[34]

Early data indicate that solid organ transplant recipients are infected with SARS-CoV-2, the virus causing COVID-19, at twice the rate of the general population, though it is unclear whether this is due to immunosuppression, increased comorbidities, or increased exposure.[41] Independent risk factors for mortality among solid organ transplant patients with COVID-19 have been reported to be lung transplantation, older age, and nosocomial acquisition.[41,42] The increased mortality in lung transplant recipients is likely due to similar factors that predispose them to other severe viral respiratory infections; the type of baseline immunosuppression does not seem to affect mortality. There are currently insufficient data to provide strong, evidence-based recommendations on the treatment of COVID-19 in solid organ transplant recipients. However, there is no indication that treatment should differ from that for the general population; consideration should be made for drug–drug interactions, and management should involve transplant physicians, particularly when alteration of immunosuppression is being considered.[43] Transplantation should be deferred if either the donor or recipient is SARS-CoV-2 positive;[43,44] potential transplant recipients who test positive may be considered on a case-by-case basis, depending on the urgency of transplantation, in consultation with an infectious diseases or transplant infectious diseases physician.

Both Canadian and BC guidelines recommend vaccination against SARS-CoV-2 in solid organ transplant recipients.[45,46] Major caveats in the transplant population include a recommendation to complete vaccination 2 weeks before transplant (though not to delay necessary transplant while awaiting vaccination), and to delay vaccination by at least 1 month following transplantation or following treatment of acute rejection, and by 3 months following rituximab therapy. The purpose of delaying vaccination in these scenarios is to ensure vaccine efficacy in the setting of increased immunosuppression, rather than due to concerns about safety. The efficacy of vaccination in this population is unknown, and strict adherence to public health measures must be maintained regardless of vaccination status.

Summary

Due to the success of solid organ transplant programs in BC, more transplant recipients are living in the community. These recipients remain on lifelong immunosuppression and are at ongoing risk for infectious complications. It is important for physicians working in communities throughout BC to have an awareness of some of the common infections these patients may face and to consult with colleagues in infectious diseases and transplant infectious diseases as required to support the ongoing health of this unique patient population. ■

Competing interests

Dr Mah is on the advisory board and/or has received research support from Avir, Merck, and Verity. Dr Belga has received fees for speaking from Merck and grants from Vancouver Coastal Health

Research Institute, Transplant Research Foundation of BC, and the COVID-19 Immunity Task Force. Dr Wright received fees for attending a one-time advisory board meeting for letermovir (mentioned in the article as it is the only agent of the two approved by Health Canada and available in BC).

References

1. Transplant BC. Current statistics, by program. 2021. Accessed 9 May 2021. www.transplant.bc.ca/Documents/Statistics/Current_Stats2104.pdf.
2. Blumberg EA, Danziger-Isakov L, Kumar D, et al. Foreword: Guidelines 3. Am J Transplant 2013;13(suppl 4):1-2.
3. Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med 2007;357:2601-2614.
4. Green M. Introduction: Infections in solid organ transplantation. Am J Transplant 2013;13(suppl 4):3-8.
5. Aslam S, Rotstein C. Candida infections in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant 2019;33:e13623.
6. Husain S, Camargo JF. Invasive aspergillosis in solid-organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant 2019;33:e13544.
7. BC Transplant Provincial Health Services Authority. Medication guidelines for solid organ transplants. 2019. Accessed 9 May 2021. www.transplant.bc.ca/Documents/Health%20Professionals/Clinical%20guidelines/Clinical%20Guidelines%20for%20Transplant%20Medications.pdf.
8. Razonable RR, Humar A. Cytomegalovirus in solid organ transplant recipients—Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant 2019;33:e13512.
9. Cannon MJ, Schmid DS, Hyde TB. Review of cytomegalovirus seroprevalence and demographic characteristics associated with infection. Rev Med Virol 2010;20:202-213.
10. Kotton CN, Kumar D, Caliendo AM, et al. The third international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. Transplantation 2018;102:900-931.
11. Romero FA, Razonable RR. Infections in liver transplant recipients. World J Hepatol 2011;3:83-92.
12. Haidar G, Green M. Intra-abdominal infections in solid organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant 2019;33:e13595.
13. Kochhar G, Parungao JM, Hanouneh IA, Parsi MA. Biliary complications following liver transplantation. World J Gastroenterol 2013(19):2841-2846.
14. Garzoni C, Vergidis P. Methicillin-resistant, vancomycin-intermediate and vancomycin-resistant Staphylococcus aureus infections in solid organ transplantation. Am J Transplant 2013;13(suppl 4):50-58.
15. Patel G, Snydman DR. Vancomycin-resistant Enterococcus infections in solid organ transplantation. Am J Transplant 2013;13(suppl 4):59-67.
16. van Duin D, van Delden C. Multidrug-resistant gram-negative bacteria infections in solid organ transplantation. Am J Transplant 2013;13(suppl 4):31-41.
17. Abbo LM, Grossi PA. Surgical site infections: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant 2019;33:e13589.
18. Pungpapong S, Alvarez S, Hellinger WC, et al. Peritonitis after liver transplantation: Incidence, risk factors, microbiology profiles, and outcome. Liver Transpl 2006;12:1244-1252.
19. Sawyer RG, Claridge JA, Nathens AB, et al. Trial of short-course antimicrobial therapy for intraabdominal infection. N Engl J Med 2015;372:1996-2005.
20. Alangaden GJ, Thyagarajan R, Gruber SA, et al. Infectious complications after kidney transplantation: Current epidemiology and associated risk factors. Clin Transplant 2006;20:401-409.
21. Hollyer I, Ison MG. The challenge of urinary tract infections in renal transplant recipients. Transpl Infect Dis 2018;20:e12828.
22. Abbott KC, Swanson SJ, Richter ER, et al. Late urinary tract infection after renal transplantation in the United States. Am J Kidney Dis 2004;44:353-362.
23. Ariza-Heredia EJ, Beam EN, Lesnick TG, et al. Impact of urinary tract infection on allograft function after kidney transplantation. Clin Transplant 2014;28:683-690.
24. Lee JR, Bang H, Dadhania D, et al. Independent risk factors for urinary tract infection and for subsequent bacteremia or acute cellular rejection: A single-center report of 1166 kidney allograft recipients. Transplantation 2013;96:732-738.
25. Ariza-Heredia EJ, Beam EN, Lesnick TG. Urinary tract infections in kidney transplant recipients: Role of gender, urologic abnormalities, and antimicrobial prophylaxis. Ann Transplant 2013;18:195-204.
26. Chuang P, Parikh CR, Langone A. Urinary tract infections after renal transplantation: A retrospective review at two US transplant centers. Clin Transplant 200519:230-235.
27. Goldman JD, Julian K. Urinary tract infections in solid organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant 2019;33:e13507.
28. Bodro M, Linares L, Chiang D, et al. Managing recurrent urinary tract infections in kidney transplant patients. Expert Rev Anti Infect Ther 2018;16:723-732.
29. Pappas PG, Alexander BD, Andes DR, et al. Invasive fungal infections among organ transplant recipients: Results of the Transplant-Associated Infection Surveillance Network (TRANSNET). Clin Infect Dis 2010;50:1101-1111.
30. Aguilar CA, Hamandi B, Fegbeutel C, et al. Clinical risk factors for invasive aspergillosis in lung transplant recipients: Results of an international cohort study. J Heart Lung Transplant 2018;37:1226-1234.
31. Husain S, Silveira FP, Azie N, et al. Epidemiological features of invasive mold infections among solid organ transplant recipients: PATH Alliance registry analysis. Med Mycol 2017;55:269-277.
32. Donnelly JP, Chen SC, Kauffman CA, et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. Clin Infect Dis 2020;71:1367-1376.
33. Singh N, Husain S. Aspergillus infections after lung transplantation: Clinical differences in type of transplant and implications for management. J Heart Lung Transplant 2003;22:258-266.
34. Manuel O, Estabrook M. RNA respiratory viral infections in solid organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant 2019;33:e13511.
35. Peghin M, Hirsch HH, Len Ó, et al. Epidemiology and immediate indirect effects of respiratory viruses in lung transplant recipients: A 5-year prospective study. Am J Transplant 2017;17:1304-1312.
36. Vu D-L, Bridevaux P-O, Aubert J-D, et al. Respiratory viruses in lung transplant recipients: A critical review and pooled analysis of clinical studies. Am J Transplant 2011;11:1071-1078.
37. van de Veerdonk FL, Kolwijck E, Lestrade PPA, et al. Influenza-associated aspergillosis in critically ill patients. Am J Respir Crit Care Med 2017;196:524-527.
38. Kumar D, Ferreira VH, Blumberg E, et al. A 5-year prospective multicenter evaluation of influenza infection in transplant recipients. Clin Infect Dis 2018;67:1322-1329.
39. Kumar D, Michaels MG, Morris MI, et al. Outcomes from pandemic influenza A H1N1 infection in recipients of solid-organ transplants: A multicentre cohort study. Lancet Infect Dis 2010;10:521-526.
40. Schuurmans MM, Tini GM, Dalar L, et al. Pandemic 2009 H1N1 influenza virus vaccination in lung transplant recipients: Coverage, safety and clinical effectiveness in the Zurich cohort. J Heart Lung Transplant 2011;30:685-690.
41. Coll E, Fernández-Ruiz M, Sánchez-Álvarez JE, et al. COVID-19 in transplant recipients: The Spanish experience. Am J Transplant 2021;21:1825-1837.
42. Kates OS, Haydel BM, Florman SS, et al. Coronavirus disease 2019 in solid organ transplant: A multicenter cohort study. Clin Infect Dis 2021;73:e4090-e4099.
43. Canadian Society of Transplantation and Canadian Blood Services. Consensus guidance and recommendations for organ donation and transplantation services during COVID-19 pandemic. Last updated 4 November 2021. Accessed 5 March 2022. https://professionaleducation.blood.ca/sites/default/files/2021-11-04_covid-19_consensus_guidance_en.pdf.
44. National Institutes of Health (US). Special considerations in solid organ transplant, hematopoietic stem cell transplant, and cellular immunotherapy candidates, donors, and recipients. 2020. Accessed 9 May 2021. www.covid19treatmentguidelines.nih.gov/special-populations/transplant.
45. Lun E, Khoo D, Wright A, et al. Clinical guidance on COVID-19 vaccines for solid organ transplant recipients. BC Centre for Disease Control, 2021. Accessed 9 May 2021. www.bccdc.ca/Health-Info-Site/Documents/COVID-19_vaccine/Transplant_Clinical_Guidance.pdf.
46. Canadian Society of Transplantation. National transplant consensus guidance on COVID-19 vaccine. 2021. Accessed 9 May 2021. www.cst-transplant.ca/_Library/Coronavirus/National_Transplant_Consensus_Guidance_on_COVID_vaccine-20210123_FINAL-DK.pdf.