Chapter 8
Infections in the Adult Solid Organ Transplant Recipient

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Introduction

There is a clear mortality benefit from solid organ transplantation with an average of 4.3 years of life gained per organ transplant [1]. Solid organ transplantation necessitates immunosuppression that is intense immediately following transplantation and, in most cases, decreases over time. Improvements in immunosuppression management have reduced the incidence of acute rejection and improved graft survival. However, infection remains a significant risk for all solid organ transplant recipients and can shorten life expectancy as well as shorten the life of the graft [2]. The nature of such infections varies depending on time since transplantation, degree of immunosuppression, type of transplant, unique donor and recipient characteristics, and environmental exposures. This chapter reviews both common and serious infections, as well as explores diagnostic and therapeutic considerations in this unique population. Given the complexities of this population including the potential for unusual pathogenic organisms, increased risk for rapid evolution of infections, and the need to still consider antimicrobial stewardship, consultation with a transplant infectious disease specialist should be considered when treating infections in solid organ transplant recipients.

Timeline of Immunosuppression and Related Infection Risk

The time elapsed since solid organ transplantation affects the susceptibility to infection. Infectious risks can be divided into the early, intermediate, and late post-transplant periods (See Table 8.1).
The early post-transplant period (0–1 month)

This period confers increased risk for nosocomial infections and immediate donor-borne infection transmission with patients being cared for in intensive care unit (ICU) and hospital settings. Surgical complications such as wound infections, anastomotic leaks, as well as ICU-related illness including central venous catheter infections, urinary catheter infections, and ventilator-associated pneumonias are common. Donors are screened for viral hepatitis, human immunodeficiency virus...
(HIV), herpes simplex virus (HSV), as well as with bacterial and fungal blood and urine cultures in most cases. However, donor-derived infections do occur, and while they are likely at low rates, the exact incidence is unknown due to limited reporting data. Donor-derived infections may result from variation in donor infection screening protocols as well as the limited time window in which to assess potential donors [4]. While primary care providers are most likely not involved in the care of solid organ transplant recipients during this early period, it can be helpful to review the patient’s early transplant course for a history of prior infectious complications.

**The intermediate post-transplant period (1–6 months, up to 12 months)**

This period is characterized by maximal effects of immunosuppression dosing. These medications suppress both T- and B-cell immunity and increase the risk for opportunistic infections similar to the risk in patients with HIV. Prophylaxis against cytomegalovirus (CMV) includes valganciclovir or ganciclovir for 3–12 months depending on CMV status and type of transplant [5]. Those who are CMV-negative for both donor and recipient (D−/R−) and therefore not receiving CMV prophylaxis should be considered for antiviral prophylaxis against HSV and VZV. Antiviral therapy to prevent HSV reactivation is recommended in solid organ transplant recipients who are HSV seropositive (and not receiving CMV prophylaxis) for at least 1 month post-transplant [6]. Prophylaxis against varicella zoster virus (VZV) is recommended in seropositive recipients who are not already receiving prophylaxis against CMV or HSV—however, this situation is less common and the optimal duration is uncertain due to limited data [7].

Protocols for antiviral prophylaxis vary by center, and prophylaxis is typically re-initiated even in the later post-transplant period if patients are treated for rejection, especially if T-cell depleting therapies are used. Prevention of reactivation of hepatitis B virus (HBV) is important in liver transplant recipients, who will receive immunoglobulin plus lamivudine or entecavir. Non-liver solid organ transplant recipients who are positive for HBV are monitored for HBV reactivation for 3–6 months after transplantation.

The incidence of *Pneumocystis jirovecii* pneumonia (PJP) in solid organ transplant recipients has decreased due to the use of routine prophylaxis [8]. Trimethoprim-sulfamethoxazole is the preventive drug of choice in patients without a sulfa allergy. Trimethoprim-sulfamethoxazole is also effective against nocardia, toxoplasmosis, and listeria. It has lesser protection for acute cystitis, sinusitis, and pneumococcal pneumonia. In the setting of a true sulfa allergy, dapsone, atovaquone, and pentamidine are alternatives [9]. Lung transplant recipients are at higher risk and are recommended for lifelong therapy. Other solid organ transplant recipients typically receive 6–12 months of PJP prophylaxis, although it may be modified by the presence of
other risk factors such as graft dysfunction, low CD4 counts, neutropenia, concurrent CMV disease, and corticosteroid dosing [8].

Other fungal infections in the early and intermediate periods post-transplantation can be severe. Azole and other antifungal therapy may be utilized for prophylaxis against *Candida* and *Aspergillus* in higher risk patients [10]. While practice varies by transplant center, in general, lung transplant recipients are at higher risk of *Aspergillus* and often receive 3–6 months of prophylactic antifungal therapy after transplantation [11]. In other solid organ transplant recipients, the use of prophylaxis against *Aspergillus* is limited by lack of sufficient data; patients may be given prophylaxis based on risk factors for invasive disease [11]. There is also practice variation in prophylaxis against *Candida* species, with some guidelines preferring prophylaxis in gastrointestinal site transplantations (liver, pancreas, small intestine), while in other sites prophylaxis against *Aspergillus* may be more important [12]. In addition to *Candida* and *Aspergillus* species, reactivation of endemic mycosis may occur, and its incidence can be as high as 6.9% for coccidioidomycosis. Reactivation is more severe and occurs earlier (within 3 months) from donor-derived infections. Recipient reactivation usually occurs within 1 year. Symptoms can include fevers, chills, pleurisy, and cough, though severe pneumonia and multiorgan failure are possible [13]. Prophylaxis may be considered against reactivation of endemic mycoses if recipients have a history of disease prior to transplantation. In most cases, the transplant team, in consultation with a transplant infectious disease specialist, will determine the appropriate prophylaxis against invasive fungal infections. The primary care provider should be aware of possible prophylactic regimens as well as the presentation of clinical disease.

Despite usual prophylaxis, solid organ transplant recipients are susceptible to other viruses including BK virus, hepatitis C (HCV), adenovirus, and influenza. Vaccination for influenza (intramuscular inactivated vaccine), and vigilance for the other at-risk viruses is needed. In this period, solid organ transplant recipients are at risk for bacterial infections including healthcare- and hospital-acquired pneumonia as well as community-acquired pneumonia. Providers must be wary of atypical pneumonia, tuberculosis, and gastrointestinal infection with *Clostridioides difficile* (Cdiff).

Common prophylaxis regimens are shown in Table 8.2.

**The late post-transplant period** typically starts >6–12 months after transplant. By this time, immunosuppression is being tapered and solid organ transplant recipients are living in their home community under the care of their primary care providers in conjunction with their transplant center. Community-acquired infections are more likely and pattern similarly to the general population with pneumonia, urinary tract infections (UTI), and infectious diarrhea being common. The risk for opportunistic infections is higher if patients experience organ rejection and require intensification of immunosuppression. Unique infections affecting solid organ transplant recipients include late CMV reactivation/infection, HSV, HBV and HCV reactivation, and less commonly JC and BK virus infections. BK virus is a particular concern in renal transplant recipients in whom it can be a major cause of graft failure.
Key Considerations in Diagnosis

Solid organ transplant recipients require lifelong immunosuppression resulting in a reduction of usual signs and symptoms of inflammation that accompany infections [3]. The pragmatism and parsimonious approach we strive for in usual practice must be set aside when assessing the solid organ transplant recipient for infection. While symptoms may be muted, the actual infection may evolve rapidly and progress to a more severe infection in these immunosuppressed patients. Infections may be the result of polymicrobial infections and/or from multi-drug-resistant organisms. Comprehensive testing and more rapid escalation to invasive testing are appropriate [3].

Immunosuppression reduces the sensitivity of tests that rely on the patient’s immune system such as serological tests for antibodies. Instead, direct detection of pathogens using culture, polymerase chain reaction (PCR), and similar tests of optimal specimens is preferred. This may require more invasive testing such as biopsy of infected tissue [3, 14].

| Infection                  | Prophylaxis                                                                 |
|----------------------------|----------------------------------------------------------------------------|
| Cytomegalovirus (CMV) [5]  | Ganciclovir (IV), valganciclovir (PO)                                     |
| D+/R−                      | Lung: 0–12 months; some centers extend >12 months                         |
|                            | Heart: 3–6 months                                                          |
|                            | Liver: 3–6 months                                                          |
|                            | Kidney: 6 months                                                           |
| R+ (any donor status)      | Lung: 6–12 months                                                          |
|                            | Heart, liver, kidney: 3 months                                             |
| D−/R−                      | No prophylaxis (but should have HSV/VZV prophylaxis)                       |
| HSV                        | If recipient is positive for HSV (1 or 2) and not receiving CMV prophylaxis, then at least 1 month is recommended. (e.g., acyclovir, but regimens vary) |
| VZV                        | Provide if recipient is positive for VZV and negative for HSV and CMV, and not already receiving prophylaxis against CMV or HSV; optimal duration uncertain |
| Fungal                     | Invasive (Aspergillus, Candida species):                                   |
|                            | Varies by transplant center and patient risk factors; prophylaxis against Aspergillus often given in lung transplant recipients; against Candida in liver transplant recipients |
|                            | Endemic                                                                    |
|                            | Varies by patient risk factors, e.g., history of prior endemic mycotic disease |
| Pneumocystis jirovecii     | Lung: lifelong                                                             |
|                            | Other organs: 6–12 months, may vary if risk factors present                |
Respiratory Infections

**Case**

A 60-year-old woman with a history of bilateral lung transplantation 2 years prior presents to the primary care clinic in the winter season with 3 days of subjective fevers, nasal congestion, rhinorrhea, dry cough, and myalgias. She is adherent to her immunosuppression regimen and has not had any episodes of rejection in the last year. On exam, her temperature is 38.0 °C, heart rate 98, blood pressure 125/70, respiratory rate 22, and oxygen saturation 97% on ambient air. Her exam reveals mild erythema of the oropharynx but no tonsillar hypertrophy and no exudate. Her lungs are clear and she has no lymphadenopathy. She received the inactivated influenza vaccine in October.

**Comment:**

This patient is presenting with symptoms of an upper respiratory tract infection during influenza season. She has a low-grade fever with mild tachycardia and an elevated respiratory rate. Although the patient received the influenza vaccine, not all viral subtypes are covered equally, and she is still at risk of influenza infection. Infection with other respiratory viruses including rhinovirus, coronavirus, and respiratory syncytial virus (RSV) is also possible. This patient should undergo testing with a viral respiratory PCR panel, or a rapid influenza test if the extended panel is not available. Because of the presence of cough and fever during influenza season, she should be treated empirically for influenza with oseltamivir unless contraindicated.

The absence of lymphadenopathy and sore throat make bacterial pharyngitis unlikely. Community-acquired pneumonia is also less likely without clear signs of lower respiratory tract involvement. Opportunistic infections due to mycobacterial and fungal etiologies, as well as reactivation of latent diseases, such as CMV, typically present more gradually and would not be consistent with the acuity of symptom onset in this case. Nonetheless, a chest X-ray should be obtained to evaluate for new consolidation or nodules.

Respiratory infections after solid organ transplantation are common and account for significant morbidity and mortality in this population. Bacterial pneumonia remains the most common cause of lower respiratory tract infections, with one study identifying community-acquired pneumonia (CAP) in 40.7% and healthcare-associated pneumonia (HCAP) in 38.9% of solid organ transplant recipients treated for pneumonia [15]. Solid organ transplant recipients are at higher risk of developing lower respiratory tract disease from common respiratory viruses and often develop more severe symptoms than immunocompetent hosts [16]. Solid organ transplant recipients are also more likely to develop invasive fungal pneumonia as well as bacterial and fungal co-infection in the setting of a viral respiratory illness [15]. Primary care providers must be aware of the risk factors and possible presentations of respiratory infections in solid organ transplant recipients to appropriately triage, diagnose, and treat these patients in the outpatient setting. Table 8.3 shows common respiratory infections in solid organ transplant recipients.
| Category of respiratory infections | Common pathogens | Common diagnostic evaluation | Treatment | Prevention |
|-----------------------------------|------------------|-----------------------------|-----------|------------|
| **Viral**                        |                  |                             |           |            |
| Influenza                        | PCR-based nasopharyngeal swab | Neuraminidase inhibitor | Oseltamivir | Zanamivir | Influenza vaccination with either inactivated influenza vaccine (IIV) or recombinant influenza vaccine (RIV) Prophylaxis with oseltamivir for close contacts with influenza exposure |
| Parainfluenza                    | PCR-based nasopharyngeal swab | Supportive care | Consider reduction in immunosuppression +/− ribavirin +/- IVIg (mixed data, only in consultation with an infectious disease specialist) | Hand hygiene | No vaccination or prophylaxis available |
| Human metapneumovirus            |                  |                             |           |            |
| Respiratory syncytial virus (RSV) |                  |                             |           |            |
| Adenovirus                       | PCR-based nasopharyngeal swab | Supportive care | +/− cidofovir, only in consultation with an infectious disease specialist | Hand hygiene | No vaccination or prophylaxis available |
| **Bacterial**                    |                  |                             |           |            |
| Streptococcus pneumoniae         | Sputum culture | Antibiotics tailored to causative agent | If no pathogen identified, treat empirically with: Respiratory fluoroquinolone, or Amoxicillin-clavulanate + macrolide | Hand hygiene | Vaccination for Haemophilus influenzae (Hib) and Streptococcus pneumoniae (PPSV23) |
| Haemophilus influenzae            |                  |                             |           |            |
| MSSA/MRSA                        |                  |                             |           |            |
| Nocardia species                 |                  |                             |           |            |
| Chlamydia pneumoniae             |                  |                             |           |            |
| Moraxella catarrhalis            |                  |                             |           |            |
| Legionella species               |                  |                             |           |            |
| Pseudomonas aeruginosa           |                  |                             |           |            |
| Category of respiratory infections | Common pathogens | Common diagnostic evaluation | Treatment | Prevention |
|-----------------------------------|------------------|-----------------------------|-----------|-----------|
| Mycobacterium tuberculosis        | AFB sputum stain and culture | Antibiotics tailored to causative agent, in consultation with an infectious disease specialist | Pre-transplant testing for latent TB |
| Non-tuberculous mycobacterium (NTM) | | | |
| Fungal                            | Sputum stain and culture | Antifungal therapy, typically voriconazole, in consultation with an infectious disease specialist | Prophylaxis with voriconazole early in post-transplant course (protocols vary) |
| Aspergillus species               | Galactomannan assays on sputum and serum | | |
| Endemic mycoses (histoplasmosis, coccidioidomycosis, blastomycosis) | Sputum or BAL culture or histopathologic/cytopathologic identification of organisms | Antifungal therapy, often fluconazole or itraconazole, in consultation with an infectious disease specialist | None |
| Pneumocystis jirovecii            | Immunofluorescence stain on induced sputum or bronchoscopy sample | TMP-SMX, +/− steroids depending on degree of hypoxemia | TMP-SMX, variable duration depending on organ transplanted; lifelong after lung transplantation |

*Also consult with transplant team due to common drug interactions between azoles and immunosuppressant medications
*The COVID-19/SARS-CoV-2 pandemic is ongoing as of this publication. Testing and treatment should follow up to date public health guidelines for high-risk populations, including solid organ transplant recipients
All solid organ transplant recipients who present with a suspected respiratory viral infection should undergo evaluation with a nasopharyngeal sample tested by PCR for respiratory viral pathogens [16]. Most respiratory viral infections are restricted to the upper respiratory tract; however, solid organ transplant patients are at higher risk of developing lower respiratory tract infection and subsequent complications, including superimposed bacterial pneumonia, due to impaired cellular and humoral immunity [17]. In lung transplant recipients, development of lower respiratory tract disease may be associated with increased risk of chronic lung allograft dysfunction, though the relationship with episodes of acute rejection has not been established [18]. Identifying common viral infections, such as non-epidemic coronavirus or rhinovirus, as a cause of lower respiratory tract infection may reassure the clinician that additional evaluation is not necessary and improve antibiotic stewardship.

In a solid organ transplant recipient with lower respiratory tract symptoms, the primary care provider should strongly consider obtaining chest imaging. Focal infiltrates on chest X-ray are most consistent with a bacterial pneumonia, whereas diffuse lung disease and multifocal infiltrates are more likely to represent a viral infection or non-infectious process. With a relevant exposure history and characteristic tempo of symptom onset, nodular opacities on chest X-ray may suggest a fungal etiology [19].

Chest imaging, while helpful, cannot definitively rule in or rule out bacterial, viral, or fungal etiologies of respiratory symptoms; imaging must be combined with a thorough history and the provider’s best clinical judgment to determine a diagnosis. The primary care provider should have a low threshold to consult with an infectious disease specialist or a pulmonologist when interpreting the chest X-ray findings in a solid organ transplant recipient with a suspected infectious respiratory illness. Chest CT and even bronchoscopy may be indicated to differentiate infection from non-infectious causes of respiratory symptoms, including rejection in lung transplant patients, and drug fever [2]. Lung transplant recipients in particular should receive consultation with the transplant pulmonologist, both to expedite the appropriate workup and to avoid empiric treatment that may make subsequent diagnostic tests less accurate (See Chap. 7). Patients who present to clinic with signs of impending respiratory failure, hypoxemia, or any other unstable vital signs due to a suspected respiratory infection should be admitted to the hospital for inpatient evaluation and treatment. Even patients who are clinically stable may benefit from an emergency department evaluation or inpatient stay if they have higher risk for severe infection, including earlier time period since transplantation, higher level of immunosuppression, history of organ failure or chronic illness, and other risk factors, as solid organ transplant recipients can decompensate quickly.

See Chap. 9, for a broader discussion of differential diagnoses of respiratory symptoms, including non-infectious causes. Specific infectious entities are discussed below.
Respiratory Viral Illness

Influenza is an acute, febrile illness that typically manifests with respiratory symptoms or may be asymptomatic. While influenza infection is usually self-limited in immunocompetent individuals, solid organ transplant recipients may have variable presentations of influenza, ranging from atypical, non-respiratory symptoms to severe respiratory compromise [15]. Common non-respiratory symptoms of influenza infection in solid organ transplant recipients include gastrointestinal distress, sore throat, low-grade fever, or even lack of fever. Solid organ transplant recipients are also more likely to shed the influenza virus for a longer period of time than immunocompetent hosts due to inability to clear the virus, prolonging their risk of complications and possible transmission to others [15, 20, 21]. Risk of influenza infection is highest among lung transplant recipients, followed by patients with liver and kidney transplants [15]. Rates of severe influenza infection are reported between 16 and 20% in lung transplant recipients, with mortality ranging from 4 to 8% in this population [15]. Mortality is higher among solid organ transplant recipients during influenza outbreaks and was reported at 21% for lung transplant recipients in an Australian study during the 2009 H1N1 influenza epidemic [15].

If a solid organ transplant recipient presents to the primary care setting with fever and upper respiratory symptoms or cough during influenza season, the primary care provider should have a high index of suspicion for influenza infection. While it is often appropriate to treat immunocompetent hosts for influenza empirically, the Centers for Disease Control and Prevention (CDC) recommends that providers should attempt to diagnose influenza infection in solid organ transplant recipients to target therapy. While rapid influenza antigen tests are specific for influenza infection, they lack appropriate sensitivity in immunocompromised hosts [16]. More sensitive tests, including the viral respiratory PCR panels, are considered the gold standard in many institutions, and can identify the influenza subtype, which may be important in epidemic years or in cases of treatment failure. Because influenza testing varies by institution, primary care providers will need to know which tests (e.g., rapid antigen, nucleic acid amplification, PCR) are available in their location, the tests’ performance characteristics, and how quickly results will be known. If a rapid influenza antigen test is negative for a solid organ transplant recipient who presents with suspected influenza and the PCR panel is not available, the patient should receive empiric influenza treatment unless contraindicated [22]. Pooled analyses of randomized controlled trials evaluating the efficacy of oseltamivir treatment in high-risk individuals have shown a decrease in the rates of hospitalization due to influenza from 3.2% to 1.6% (relative risk reduction, 50%) [23].

There are two main classes of antiviral therapy available to treat influenza infections: adamantanes (amantadine and rimantadine) and neuraminidase inhibitors (oseltamivir and zanamivir) [22, 23]. Historically, amantadanes have been active against most influenza A strains, but not influenza B. However, widespread resistance to influenza A (H3N2) and more limited resistance to influenza A (H1N1) has been reported since 2006. The neuraminidase inhibitors are active against both influenza A and B viruses, though oseltamivir resistance among certain influenza A (H1N1) strains has also been identified [23]. With these resistance patterns, the
CDC recommends oseltamivir 75 mg BID for 5 days for treatment of influenza in immunocompromised hosts; amantadines are no longer considered first-line therapy. Providers caring for solid organ transplant patients living outside the United States should review local epidemiology and resistance patterns, and consult with local experts to guide treatment strategies. Some patients may benefit from a longer course of therapy if not significantly improved after initial treatment, particularly if levels of immunosuppression are particularly high; in this case, primary care providers should consider discussing with an infectious disease specialist. There is no data however to support doses of oseltamivir higher than 75 mg daily, though clinicians may consider increasing the duration of therapy to 75 mg daily for 10 days (or longer) in solid organ transplant patients due to prolonged viral shedding and clearance [2, 24]. Influenza changes seasonally and may have pandemic strains—it is important to follow local public health reporting and updated guidelines.

Baloxavir is a novel cap-dependent endonuclease inhibitor approved by the United States FDA in October 2018 for the treatment of acute uncomplicated influenza in patients 12 years of age and older within 2 days of symptom onset [25, 26]. Baloxavir is administered as a single-dose oral medication. In randomized controlled trials comparing baloxavir to placebo and oseltamivir, baloxavir was superior to both placebo and oseltamivir in reducing viral load 1 day after initiating treatment, with the implication that transmission rates may be reduced [27]. The role of baloxavir in treating immunosuppressed patients has not been established, although local institutions may use it in select patients, particularly if there is concern for oseltamivir resistance.

If the patient develops worsening lower respiratory symptoms including productive cough or pleuritic chest pain while on oseltamivir, one should obtain chest imaging to evaluate for bacterial co-infection or even consider treating empirically for a concomitant bacterial pneumonia. (In a lung transplant recipient, one should consult early with the transplant pulmonologist, preferably before starting antibiotics—See Chap. 7.)

Vaccination against influenza with an inactivated influenza vaccine is indicated for solid organ transplant recipients before and after transplantation [16]. However, the vaccine should be withheld in the first 2 months after transplant due to the likelihood of inadequate response [28]. Either the trivalent or quadrivalent inactivated influenza vaccine (IIV) or the recombinant influenza vaccine (RIV) may be administered intramuscularly; the live attenuated influenza nasal vaccine (LAIV) is contraindicated in solid organ transplant recipients [29]. There is no evidence indicating that solid organ transplant recipients derive additional benefit from the high-dose influenza vaccine [30, 31]. Nevertheless, some infectious disease specialists recommend the high-dose influenza vaccine in solid organ transplant recipients because of limited evidence of increased immune response, although no clinical outcome data are yet available.

In addition to influenza, infection with other viral respiratory pathogens, including respiratory syncytial virus (RSV), parainfluenza virus, human metapneumovirus, rhinovirus, and adenovirus, is common in solid organ transplant recipients [15, 17]. Similar to influenza, these respiratory viruses are spread by direct contact with aerosolized droplets [15]. The clinical syndrome is similar to infection with influenza and includes fever, cough, rhinorrhea, and myalgias, though development of lower respiratory tract symptoms with bronchiolitis and pneumonia is more
common in solid organ transplant recipients than in immunocompetent individuals [17]. Nasopharyngeal swab or wash should be collected in the clinic and sent for PCR-based assays, which remain the gold standard for diagnosing respiratory viral infections in solid organ transplant recipients [2, 15]. Supportive care is the mainstay of treatment for non-influenza respiratory infections. If the patient develops hypoxia, they should be promptly admitted to the hospital. In severe cases, the transplant team should be informed; in some circumstances, the transplant team may consider whether a reduction in immunosuppression is warranted [15]. Antiviral drug therapy for certain viral pathogens in solid organ transplant recipients, including RSV and adenovirus, is under investigation [15, 17]. There are currently no accepted guidelines for the use of ribavirin in the treatment of RSV; practices vary by institution and it is typically only used in hospitalized patients with lower respiratory tract disease and a significantly depressed absolute lymphocyte count.

Infection with cytomegalovirus (CMV) can cause significant respiratory illness in solid organ transplant recipients. While infection with CMV can occur as a primary or secondary infection, the majority of cases in this patient population represent reactivation of a latent reservoir. CMV disease can manifest as either CMV syndrome, characterized by fever, malaise, and myelosuppression, or as CMV tissue-invasive disease, which can be isolated to the allograft or involve multiple organs simultaneously [32, 33]. Symptoms of CMV pneumonia are non-specific and are typically characterized by subacute onset of fevers, cough, and hypoxemia, accompanied by a range of radiographic findings including bilateral infiltrates, nodules, and areas of consolidation. Lung transplant recipients are at particularly high risk for CMV pneumonia; diagnosis requires the presence of signs or symptoms of pulmonary disease combined with the detection of CMV in bronchoalveolar lavage or lung tissue samples [34]. Because of the non-specific presentation, primary care providers should maintain a high index of suspicion for CMV pneumonia in lung transplant recipients and closely collaborate with the patient’s transplant physicians to expedite evaluation and coordinate care.

Emerging respiratory infections such as COVID-19 (SARS-CoV-2) may be particularly severe in solid organ transplant recipients. At the time of this book’s publication, this virus continues to be studied during the worldwide pandemic. Testing should be initiated promptly depending on local epidemiology and public health guidelines. Consultation with infectious disease specialists is indicated in a solid organ transplant recipient with suspected or confirmed COVID-19 infection.

Bacterial Pneumonia

Community-Acquired Pneumonia (CAP) is common in solid organ transplant recipients, although evidence is mixed as to whether CAP occurs more frequently in these patients compared to the general population [35, 36]. While solid organ transplant recipients are at risk for CAP from typical organisms including Streptococcus pneumoniae, Legionella pneumophila, and Haemophilus influenza, they are also at increased risk of infection with Nocardia spp, Staphylococcus aureus, Pseudomonas aeruginosa, and other gram-negative rods (GNRs) [16]. Abrupt onset of fever
accompanied by cough productive of sputum should raise concern for CAP. A focal infiltrate on chest X-ray may be useful in confirming suspicion for CAP, but should not be used to rule in or rule out disease.

IDSA guidelines (2019) include recommendations for the treatment of CAP in patients with comorbidities (which include chronic heart, lung, liver, and renal disease, as well as asplenia). For solid organ transplant recipients, CAP treatment options include monotherapy with a respiratory fluoroquinolone or combination therapy with a beta-lactam (amoxicillin-clavulanate) or a cephalosporin plus either doxycycline or a macrolide [16, 37]. This treatment regimen should only be used for stable outpatients. Drug interactions are common with antibiotics and immunosuppressant medications—if starting a new antibiotic, especially a macrolide, the transplant team should be notified (See Chap. 3). The typical treatment duration is 5 days, though providers may treat longer if symptoms are not improving. However, if symptoms persist without response to antibiotic therapy, consultation with a pulmonologist should be obtained to consider additional diagnostic testing and alternate diagnoses.

Hospital admission should be expedited for any patient with CAP and unstable vital signs, and considered for certain solid organ transplant recipients who, although stable, are high risk for decompensation. Validated clinical prediction scores to stratify the need for hospitalization may be used, but only in combination with clinical judgment in this population.

As discussed above, the primary care provider who is treating a lung transplant recipient with suspected CAP should contact the patient’s lung transplant specialist. Lung transplant recipients may be at risk for opportunistic infections and resistant bacteria, may already be receiving macrolides chronically for anti-inflammatory therapy, and may need an expedited evaluation for rejection.

Infection with mycobacterium, including Mycobacterium tuberculosis, mycobacterium avian complex (MAC), and other non-tuberculous mycobacterial (NTM) species, is an important diagnostic consideration in the solid organ transplant recipient who presents with subacute to chronic onset of respiratory symptoms. The incidence of pulmonary tuberculosis (TB) in solid organ transplant recipients depends on the incidence in the general population, epidemiologic risk factors, and new or ongoing TB exposures [38]. The frequency of active TB among solid organ transplant patients is estimated to be 20–74 times higher than the general population, with higher prevalence rates in endemic areas [39]. Rates of active TB are highest in lung transplant patients compared to other solid organ transplant recipients. Approximately two-third of active TB infections occur within the first post-transplant year, with the majority reflecting reactivation of prior disease [40]. All solid organ transplant recipients should undergo TB testing prior to transplantation to identify cases of latent tuberculosis infection (LTBI); however, not all LTBI may be identified due to anergy with end stage organ failure [41]. One-third to one-half of all cases of active TB in solid organ transplant recipients are disseminated or occur at non-pulmonary sites—thus primary care providers must maintain a high index of suspicion for pulmonary as well as disseminated disease. Active pulmonary TB in solid organ transplant recipients may manifest with non-specific symptoms such as fevers, weight loss, and fatigue, as well as productive cough, hemoptysis, and dyspnea. If the physician suspects pulmonary TB, standard TB evaluation should be pursued with a chest X-ray.
and sputum samples sent for acid-fast bacilli (AFB) staining and culture. Primary care providers should communicate with an infectious disease specialist and a pulmonologist to determine if more invasive diagnostic testing is warranted and to determine a treatment course if pulmonary TB is identified. Importantly, treating pulmonary TB in solid organ transplant recipients requires medication adjustment to avoid interactions between rifamycins and calcineurin inhibitors [41].

In comparison to pulmonary TB, NTM infections in solid organ transplant recipients typically occur later in the post-transplant course. However it is important to note that these infections have been described in the days to months after transplant as well [42]. NTM infections involve the lung in more than 50% of cases, with heart and lung transplant recipients being more susceptible than kidney and liver transplant recipients [2]. Manifestations of respiratory NTM infections include pulmonary infiltrates, solitary pulmonary nodules, abscesses, and cavitary lesions. Symptoms of pulmonary NTM infections are non-specific and may include chronic cough, sputum production, and less often, hemoptysis. Importantly, systemic symptoms such as fever and night sweats, may not be present [43]. In solid organ transplant recipients with suspected NTM infection, a pulmonologist should be involved early to help direct the evaluation, which may include bronchoscopy and requests for special staining, culture, and histopathology. While these pathogens are less common than other bacterial and viral causes of respiratory infection in solid organ transplant patients, they are important diagnostic considerations due to difficulty in making the diagnosis, the need for long-term, multi-drug antibiotic regimens, and potential interaction of these antibiotics with drugs used for immunosuppression [44].

**Fungal Pneumonia**

Invasive fungal pneumonia, particularly with *Aspergillus* species, is of concern in solid organ transplant recipients and disproportionately affects lung transplant recipients, with complicated infections affecting up to 13% of patients [45]. As opposed to the rapid symptom onset characteristic of viral or bacterial pneumonia, respiratory illness due to fungal infection usually develops over weeks or even months. Additionally, the incidence of invasive fungal infections is higher 6–12 months after transplant and mold infections, such as invasive aspergillosis, often occur >1 year after transplant [19]. Solid organ transplant recipients are also at higher risk for infection with endemic mycoses, including histoplasmosis, coccidioidomycosis, and blastomycosis, and providers should take a thorough travel history to assess risk of these infections [46]. Finally, invasive candidiasis is an important cause of infection in the solid organ transplant recipient, though it presents less commonly as pneumonia [2]. Diagnosis and treatment of invasive fungal pneumonia require the assistance of an infectious disease specialist or a pulmonologist and are often performed in the inpatient setting—thus early recognition by the primary care provider and coordinating early with specialty care are critical.

Pneumonia due to *Pneumocystis jirovecii* peaks during the first 6 months after transplantation when immunosuppression is highest. Additional risk factors include increased intensity of immunosuppression (as occurs with treatment of rejection
episodes), inadequate adherence to prophylaxis, a history of CMV viremia, and lung transplantation which confers a sustained increase in risk compared to other organ transplants, leading to lifelong prophylaxis for most lung transplant recipients. *Pneumocystis jirovecii* pneumonia is typically acute or subacute in onset; however, compared to patients with HIV infection, the time course of disease presentation in solid organ transplant recipients may be more rapid. Clinicians should have a high index of suspicion for *Pneumocystis jirovecii* infection in solid organ transplant recipients who present with hypoxemia out of proportion to radiologic findings, particularly in patients who are no longer taking or who are not adherent to *Pneumocystis jirovecii* prophylaxis.

*Pneumocystis jirovecii* pneumonia may be diagnosed either by performing immunofluorescence on sputum samples or lower respiratory secretions. Compared to HIV-infected individuals, solid organ transplant recipients may have lower burden of organisms thus reducing the sensitivity of microscopy. PCR may be used as an alternative means to make a diagnosis of *Pneumocystis* pneumonia if the index of suspicion is high, though it does not reliably exclude airway colonization in the solid organ transplant population [47]. While evaluation for *Pneumocystis* pneumonia can be performed as an outpatient if the patient is stable and resources are readily available, often the patient will require admission for a more expedient workup, including evaluation for other causes of respiratory illness. Treatment with trimethoprim-sulfamethoxazole (TMP-SMX) is the preferred course of therapy. Low-dose daily prophylaxis with TMP-SMX, if tolerated, has the additional benefit of helping to prevent infection with *Toxoplasma* and *Nocardia* species, as well as other common causes of urinary and respiratory tract infections [19].

**Gastrointestinal Infections**

**Case**

A 54-year-old woman with a history of kidney transplantation presents with 3 weeks of diarrhea and decreased appetite. She has 3–5 loose stools daily without hematochezia, melena, or change in frequency or severity. Her immunosuppression medication dosing and adherence have not changed. She has no recent travel or change in diet or water sources. Her CMV serostatus is D+/R-. On exam, she has normal vital signs, is not orthostatic, and has a normal abdomen exam. What is the next appropriate step in her care?

*Comment: This patient appears to be clinically stable, and it may be feasible to continue her evaluation as an outpatient. Initial testing should include kidney function, complete blood counts, a serum CMV PCR, and stool testing for enteric pathogens. Initial stool testing at a minimum should include common bacterial enteric pathogens and *Clostridioides difficile* PCR. Depending on a patient’s known exposures and clinical course, testing for norovirus and parasitic infections such as *cryptosporidium* and *giardia* may be tested up*
In solid organ transplant recipients, the most common presentation of gastrointestinal infections is diarrhea, and it affects 20–50% of patients. The Infectious Disease Society of America (IDSA) defines diarrhea as >3 soft or loose stools per day. Acute diarrhea is present for <14 days, persistent diarrhea for 14–29 days, and chronic diarrhea for >30 days. Risk factors for diarrhea in solid organ transplant recipients include being female, using tacrolimus or tacrolimus plus mycophenolate [48].

**Differential Diagnosis of Infectious Causes of Diarrhea**

The causes of diarrhea in solid organ transplant recipients is similar to that of the general population, including non-infectious and infectious etiologies. As in immunocompetent populations, *norovirus*, food-borne bacterial and viral illness, medications, and *Clostridioides difficile* (Cdiff) are common. However, solid organ transplant recipients are more likely to have opportunistic infections and more likely to have persistent infectious diarrhea.

**Diagnostic Considerations**

A good history is important when assessing diarrhea in solid organ transplant recipients. Fever more commonly indicates a viral, or invasive bacterial etiology, and rarely is caused by parasitic infections. Blood in the stool can be caused by invasive bacterial infections, *cytomegalovirus* (CMV) or Entamoeba. Watery diarrhea with or without emesis suggests viral or medication-induced diarrhea [48].
In both immunosuppressed and immunocompetent patients, fecal studies have a low overall diagnostic yield, but are often a necessary part of the evaluation. The American Society of Transplantation Infectious Diseases Community of Practice recommends a tiered approach to testing for solid organ transplant recipients presenting with diarrhea (Fig. 8.1) [48, 49]. Initial recommendations including stopping any non-immunosuppressive medications that could contribute to diarrhea and performing bacterial stool culture or, if available, stool multiplex polymerase chain reaction (PCR), Cdiff stool PCR, and serum CMV PCR or nucleotide acid

![Fig. 8.1 Diagnostic approach to diarrhea in solid organ transplant](image-url)
amplification test (NAAT). If diarrhea persists and an etiology is not identified, then additional testing should be considered for norovirus, ova and parasites, giardia stool enzyme-linked immunosorbent assay (EIA), cryptosporidium stool EIA, as well as considering a breath test for small intestine bacterial overgrowth (SIBO). If the diarrhea persists and an etiology is still not obtained, then these guidelines recommend considering discussing a potential adjustment in immunosuppressive medications that may be contributing to diarrhea, as well as colonoscopy, upper endoscopy, evaluation for malabsorption, and empiric treatment with antimotility agents or probiotics [48].

This algorithm should be adjusted for local epidemiology, the overall clinical likelihood of infectious versus non-infectious cause of diarrhea, the severity of a patient’s presentation, the pattern of diarrhea (duration, relationship with intake), and the availability of a stool multiplex assay (which often tests for bacterial pathogens, norovirus, rotavirus, cryptosporidium, giardia, and Cdiff). For further discussion, see Chap. 9.

Specific Etiologies

_Clostridiodes difficile_ (Cdiff) is a spore-forming anaerobic bacterium that causes infectious diarrhea in solid organ transplant recipients on the order of 1–33% depending on the type of transplant, with lowest incidence in renal transplant recipients and highest in multiorgan or heart/lung transplant recipients [50]. Cdiff infection occurs most frequently in the immediate post-transplant period; however, solid organ transplant recipients are at increased longitudinal risk. Antibiotics, notably penicillins, cephalosporins, clindamycin, and fluoroquinolones, increase risk of Cdiff infection, especially if there are multiple or prolonged courses. Specific risk factors for Cdiff in solid organ transplant recipients include age >55, repeat transplantation status, liver transplant, and treatment using anti-thymocyte globulin [48]. In solid organ transplant recipients who develop Cdiff infections, 5–16% will have a fulminant infection and the mortality rate is 2.3–8.5% [48, 50]. Cdiff is also known to increase morbidity in other infections including CMV and pneumonia, as well as cause organ dysfunction and longer hospital stays.

Diagnosis of Cdiff infections is based on both clinical and laboratory data. There is an increasing number of people who are colonized with Cdiff, and no current laboratory tests can distinguish between colonization and infection. Hence, the diagnosis of Cdiff is made when a patient experiences new onset or unexplained, clinically significant (3 loose stool/day) diarrhea in the presence of laboratory confirmation of free Cdiff toxin (toxin A or B via EIA), or toxigenic
Cdiff bacteria (Cdiff NAAT) in the stool. In the 2019 American Society of Transplantation Community of Practice guidelines for Cdiff in solid organ transplant recipients, additional recommendations include not automatically repeating negative Cdiff tests, and not “testing for cure” after an infection. Uncommonly, Cdiff may present without diarrhea, and this infection should be also considered in solid organ transplant recipients who present with fever, leukocytosis, abdominal pain, and ileus. If there is negative Cdiff standard testing and a high clinical suspicion for Cdiff infection, then further workup should be considered, including abdominal/pelvic CT imaging, colonoscopy, and repeat standard testing [50].

Treatment of Cdiff is similar in solid organ transplant recipients and immune competent patients. Treatment as of 2018 IDSA guidelines no longer uses metronidazole. First-line treatment is vancomycin 125 mg PO Q6H or fidaxomicin 200 mg BID × 10 days. Fulminant Cdiff, characterized by hypotension, ileus, or megacolon, will be managed inpatient, and is treated with vancomycin 500 mg PO Q6H plus metronidazole 500 mg IV Q8H, +/- rectal vancomycin, and possible surgery consultation. In patients with hypogammaglobulinemia (tested with quantitative immunoglobulins), treatment with IgG may reduce the risk for recurrent Cdiff infection [48]. Solid organ transplant recipients have an 8–16% risk for relapsing Cdiff infections. Treatment of recurrent Cdiff infections is well described in IDSA guidelines and includes fidaxomicin, tapering or pulsed courses of vancomycin, or vancomycin followed by rifaximin. Bezlotoxumab (10 mg/kg IV) is a human monoclonal antibody targeting Cdiff toxin B. The 2019 guidelines recommend consideration for its use in first infections and recurrences to prevent recurrent Cdiff infections [50]. Transplant infectious disease and/or gastroenterology specialists should be involved in the care of solid organ transplant recipients with recurrent Cdiff.

Fecal microbiota transplant (FMT) has been used in immunosuppressed and solid organ transplant recipients in limited studies. In immunosuppressed patients, cure rates range 78–89% but with 15% experiencing serious adverse events which included hospitalizations and 2 deaths [48]. A single-center study of 94 solid organ transplant recipients with recurrent Cdiff (78%) or severe fulminant Cdiff (22%) found an overall cure rate of 91% with FMT, and a 3-month primary cure rate of 58.7%. Adverse events were experienced in 22% consisting of mostly self-limited diarrhea, abdominal pain, FMT-related diarrhea. However, 3.2% experienced severe adverse events including 2 hospitalizations for flare of inflammatory bowel disease (IBD). The same study found that in solid organ transplant recipients with IBD, 25% experienced post FMT IBD exacerbations. In CMV-seropositive patients, 14% experienced reactivation of CMV after FMT. Notably, patients in the study also experienced severe complications of the Cdiff infection itself including death [51]. Based on this study, 2019 guidelines
recommend FMT for recurrent Cdiff infections in solid organ transplant recipients [50]. Given these potential risks, it is advisable to consult a transplant infectious disease specialist when considering FMT.

Cytomegalovirus (CMV) is a double-stranded DNA virus that is part of the herpes virus family. It has varying gastrointestinal manifestations that can include esophagitis, gastritis, enteritis, colitis, and typically presents with diarrhea, abdominal pain, and fever. It can also cause hepatitis, cholangitis, and pancreatitis. Solid organ transplant recipients are at highest risk for CMV infections when the donor’s serostatus is positive and recipient’s serostatus is negative. Other risks include the degree of immunosuppression, acute rejection, advanced age, allograft dysfunction, and the type of transplant, with renal transplants being of highest risk [48].

As per the guidelines for work-up of diarrhea in solid organ transplant recipients, serum CMV testing with either PCR or quantitative nucleic acid amplification testing (QNAT) is a first-line test. There are some data that suggest a stool CMV PCR may be highly specific (but not sensitive), but this test is not widely available [52]. Older (2013) guidelines recommend quantitative nucleic acid amplification testing (QNAT) for both diagnosis and monitoring of CMV infections, although this test has largely been supplanted by PCR, if available. The pp65 CMV antigenemia test has historically been used for diagnosis and monitoring of CMV infections but is less standardized and more labor-intensive. Repeat serological testing is not needed after transplant, though it can help with determining susceptibility to community-acquired CMV infections in CMV-negative recipients. Viral culture of the blood and urine have poor sensitivity and specificity, respectively. Tissue invasive disease is diagnosed via CMV inclusion bodies or CMV antigens detected via immunohistochemistry on biopsy specimens obtained during colonoscopy/endoscopy. Tissue cultures and QNAT can be difficult to interpret as both infection and shedding can create positive results but may have a limited role in diagnosis [34]. Tissue diagnosis via colonoscopy should be pursued if needed to confirm the diagnosis even with a positive change in serum PCR (e.g., if there are competing diagnoses, or the patient tolerates anti-CMV therapy poorly, or if empiric therapy against CMV was attempted and the patient did not respond), or if the serum CMV PCR is negative but the clinical suspicion of CMV gastrointestinal disease is still high.

Solid organ transplant recipients with CMV gastrointestinal disease should receive consultation with an infectious disease specialist. Initial treatment is with oral valganciclovir, whereas IV ganciclovir is used for more life-threatening cases. Renal function must be monitored carefully, and doses adjusted accordingly. Treatment duration is dependent on weekly CMV viral loads. Recommendations are for 1–2 consecutive negative viral loads with a minimum treatment duration of 2 weeks. Failure to improve viral loads with therapy over the course of 6 weeks should raise the suspicion for drug resistance. Foscarnet is used if there is concern for resistance, and dose reduction or
changes to immunosuppressive medications may be necessary. In some cases, genotype testing for resistance has a role [34]. After treatment, there is no evidence for benefit of secondary prophylaxis of CMV to prevent recurrent infections.

**Norovirus** is a single-stranded RNA virus that causes 90% of non-bacterial diarrhea, resulting in 19–21 million cases per year in the United States. Routes of infection include fecal/oral, inhalation of aerosolized emesis, or direct contact. Most immunocompetent people experience a self-limited acute diarrhea followed by up to 2 weeks of asymptomatic shedding. While some solid organ transplant recipients may present similarly, several studies suggest that chronic diarrhea is also a common presentation [53–55].

Norovirus in solid organ transplant recipients contributes to dehydration, renal insufficiency, graft dysfunction, and chronic diarrhea; it rarely causes mortality. Treatment is supportive and focuses heavily on rehydration and anti-motility agents. Reducing immunosuppressive medications has not improved the recovery for norovirus chronic diarrhea.

**Other important causes of infectious diarrhea in solid organ transplant recipients** include parasitic infections. Parasitic infections beside Entamoeba and giardia include cryptosporidium, cytomega simplex, cyclospora, and microsporidium. Cryptosporidium is a water-borne parasite, which has been known to infect immunosuppressed and solid organ transplant recipients in epidemic outbreaks from environmental exposures. Avoidance of exposure to water sources that could be contaminated by waste products should be encouraged for all solid organ transplant recipients [56].

The COVID-19 (SARS-CoV-2) virus may present with gastrointestinal symptoms, including diarrhea. This emerging pandemic virus should be considered in the differential diagnosis of diarrhea in a solid organ transplant recipient, depending on local epidemiology and public health guidelines. The presentation, testing strategies, and treatment for solid organ transplant recipients with COVID-19 infections continues to be evaluated at the time of this book’s publication. Transplant infectious disease specialists should be consulted when considering COVID-19 in a solid organ transplant recipient.

There are many non-infectious causes of diarrhea in a solid organ transplant recipient. Immunosuppressive and other medications commonly cause diarrhea—mycophenolate causes dose-dependent, direct enterocyte toxicity, while calcineurin inhibitors such as tacrolimus cause diarrhea via a macrolide promotility effect. Calcineurin inhibitors further complicate matters when diarrhea causes dehydration, leading to increased calcineurin inhibitor blood levels and renal toxicity. Sirolimus and everolimus cause diarrhea infrequently [48]. Non-immunosuppressive medications may also cause diarrhea and a thorough medication history should be gathered. Less common causes include graft versus host disease (GVHD) and post-transplant lymphoproliferative disorder. GVHD is generally rare in solid organ transplantation except for in small bowel transplants. It presents with chronic diarrhea, abdominal pain, fevers, and sometimes rash. Post-transplant lymphoproliferative disorder
(PTLD), when it involves the gastrointestinal tract, may present with chronic diarrhea, weight loss, abdominal pain, gastrointestinal bleeding, and anorexia. Risk for PTLD, from EBV activity, is thought to increase with increased immunosuppression, and is highest in multiorgan and intestinal transplants, and lowest in renal and liver transplants. Mortality rates historically for PTLD in solid organ transplantation are 50–70% [57]. (See Chaps. 9 and 10).

**Urinary Tract Infections**

**Case**
A 44-year-old woman who received a deceased donor kidney transplant 11 months ago presents with fatigue and dysuria. She was taken off of trimethoprim-sulfamethoxazole for PJP prophylaxis at 6 months post-transplant. Her post-transplant course has been complicated by a catheter-related UTI during her initial hospitalization, but none since. She had a ureteral stent post-operatively that has been removed. She has not had any episodes of rejection.

On exam she is afebrile, with otherwise normal vital signs. She has no tenderness over her transplanted kidney in the right lower quadrant, and no costovertebral angle tenderness. A urine dipstick is positive for leukocyte esterase, nitrites, and protein.

In addition to sending the urine sample for a formal urinalysis and reflexive bacterial culture, checking a complete blood count and chemistry panel, what empiric treatment should be started?

**Comment:**
This patient has no history of structural genitourinary tract disease, no history of resistant UTI, and no signs or symptoms concerning for a systemic infection. Her examination is reassuring without tenderness over her graft or native kidneys and she did not experience nausea or vomiting. Her diagnosis is consistent with a simple cystitis in a kidney transplant recipient.

Empiric therapy choices include fluoroquinolones, third-generation oral cephalosporins, or amoxicillin-sulbactam. Because she is past 6 months post-transplant, her duration of treatment can be 5–7 days. Longer treatment courses have not shown benefit in cases of simple cystitis. Empiric therapy with trimethoprim-sulfamethoxazole should be avoided given the risk for resistance to this antibiotic with recent use for prophylaxis. Antibiotics may be narrowed based on culture results.

If the patient develops fever, tenderness or pain over the allograft, flank pain, or vomiting, she should present to the Emergency Department as she may need volume resuscitation, IV antibiotics, and potentially urgent assessment of her allograft.
Urinary tract infections (UTIs) are common in solid organ transplant recipients, as they are in the general population. Kidney transplant recipients have higher risk for UTIs due to surgical manipulation of the genitourinary tract and the associated risk related to foreign bodies such as ureteral stents. A study of 4388 solid organ transplant recipients followed for at least 1 year found that UTI incidence varied based on the type of transplant. The overall rate of UTIs was 4.4% over the study period; the incidence of UTIs (expressed as the number of UTIs per 1000 transplant-days) was highest in kidney transplant recipients (0.45), followed by kidney-pancreas (0.22), heart (0.07), liver (0.06), and lung (0.02) [58]. The highest incidence of UTIs occur in the first 3–6 months post-transplant. Bacteremia is due to UTIs in over one-third (37%) of cases in kidney transplant recipients [59]. The wide prevalence quoted in studies of UTIs in kidney transplant recipients, 7–80%, is due to the lack of standardized diagnostic criteria, variable use of prophylactic antibiotics, and uneven follow-up duration [60].

**Risk Factors**

Risk factors for UTI include demographic factors, history of genitourinary diseases, and transplant-specific risks. In a study of nearly 29,000 kidney transplant recipients, 17% of men and women in the first month post-transplant developed UTIs. By 3 years after kidney transplantation, female transplant recipients experienced more UTIs than male transplant recipients, 60% versus 47%. Factors that increased risk for UTI in kidney transplant recipients were female sex, older age, indwelling catheters, diabetes, neurogenic bladder, and renal calculi [61]. Specific transplant-related risks include ureteral stents or urological structural abnormalities, vesicoureteral reflux, acute cellular rejection, and deceased-donor graft. Risks for later-onset (>6 months post-transplant) UTIs include prednisone dose >20 mg/day and serum creatinine of >2 mg/dL. However, the type of long-term immunosuppressive is not clearly associated with UTI risk [61].

UTIs in kidney transplant recipients result in serious health consequences. Blood stream infections occur in kidney transplant recipients at 40 times the annual rate of the general population. UTI caused 30–73% of blood stream infection in kidney transplant recipients and 80% of those UTIs are from gram-negative rods. In a retrospective study of 116 hospitalizations for blood stream infections in kidney transplant recipients, 83% occurred after the first year of transplant and 71% were community acquired. In this study, 57% of blood stream infectious were from a UTI source, followed by GI and surgical site infection sources. Sixty-five percent of bacteremic kidney transplant recipients developed acute kidney injury [62]. A 4-year retrospective study of kidney transplant recipients with severe UTIs requiring hospitalization found that *Klebsiella* and *E. coli* were the most common pathogens, and between a quarter and a third of those bacteria produced extended-spectrum beta-lactamase (ESBL). In these hospitalized kidney transplant recipients with UTIs, 41% experienced acute kidney injury, 3.6% experienced graft loss, and there was a 1.2% 1-year mortality [63].
Table 8.4  Classification of asymptomatic bacteriuria (AB) and urinary tract infection (UTI) in renal transplant recipients

| Classification                     | Description                                                                 | Laboratory investigations of urine |
|------------------------------------|-----------------------------------------------------------------------------|-----------------------------------|
| Asymptomatic bacteriuria           | No urinary or systemic symptoms of infection                                | >10⁵ CFU/mL uropathogen⁴          |
| Acute simple cystitis              | Dysuria, urinary urgency/frequency, or suprapubic pain; but no systemic symptoms and no ureteral stent/ nephrostomy tube/chronic urinary catheter | >10 WBC/mm³ ³   >10⁴ CFU/mL uropathogen⁴ |
| Acute pyelonephritis/ complicated UTI | Fever, chills, malaise, hemodynamic instability, or leukocytosis (without other apparent etiology); flank/allograft pain; or bacteremia with same organism as in urine Dysuria, urgency, frequency, suprapubic pain may or may not be present | >10 WBC/mm³ ³   >10⁴ CFU/mL uropathogen⁴ |
| Recurrent UTI                      | ≥ 3 UTIs in prior 12-month period                                           | As above                          |

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WBC white blood cell, CFU/mL colony-forming units/milliliter

⁴While routine treatment of AB is not recommended (see Treatment section), if considering treatment of AB (e.g., in the immediate post-transplant period), a repeat urine culture is recommended (with care to minimize contamination) to assess persistence of the same uropathogen. Spontaneous resolution is common

⁵Staphylococcus epidermidis (except if ureteral stent), Lactobacillus, and Gardnerella sp. are unlikely to be uropathogens. Regarding CFU/mL: while most patients with UTI will have >10⁵ CFU/mL of a uropathogen in a midstream urine sample, some patients with pyelonephritis may have only 10⁴–10⁵ CFU/mL of a uropathogen, and some patients with cystitis may have even fewer CFU/mL (most data on cystitis with low CFU/mL is only for E. coli). Not all labs report <10⁴ CFU/mL.

While not an absolute criteria (depending on the performance characteristics of the urinalysis or presence of neutropenia), <10 WBC/mm³ should prompt consideration of a diagnosis other than UTI

Definitions

Clinical providers must be precise in their nomenclature when describing and diagnosing urinary infections. Guidelines for classification of urinary tract infections in kidney transplant recipients are shown in Table 8.4. Other guidelines also exist for urinary tract infections in solid organ transplant recipients in general, and use similar definitions [64]. Overuse of antibiotics for asymptomatic bacteriuria can be avoided, and appropriate therapy in the setting of complicated UTIs can be selected.

Differential Diagnosis

Gram-negative rods (GNRs), with E. coli being most common, account for >70% of UTIs in solid organ transplant recipients. Enterobacteriaceae, Enterococci, Pseudomonas, Staphylococcus saprophyticus, Streptococcus species including group B or viridans can cause infections but more commonly are colonizers. Solid organ transplant recipients are at higher risk for MDR organisms. Less commonly viral and fungal urinary infection can also occur.
Specific Organisms

Carbapenem-resistant Klebsiella pneumonia (CRKP) and extended-spectrum beta-lactamase producing Klebsiella pneumonia (ESBL-KP) are concerning pathogens for UTIs in solid organ transplant recipients. A 2015 study of kidney transplant recipients with UTI found CRKP UTI were associated with ICU admissions, longer hospital stays, and failure of antibiotic interventions compared to susceptible klebsiella pneumonia UTIs [65].

More unusual pathogens include Mycobacterium tuberculosis, Salmonella, CMV, and adenovirus which mainly causes hemorrhagic cystitis. Corynebacterium urealyticum may be a pathogen in the setting of obstructive uropathy. Rarely Mycoplasma hominis and Ureaplasma urealyticum can cause intra-renal or perinephric abscess or graft pyelonephritis in kidney transplant recipients. Staphylococcus epidermidis, Lactobacillus, Gardinella vaginalis are unlikely pathogens. Candida species are usually asymptomatic colonizers. Rarely, they can cause upper tract infections including candidemia and ureterovesicular fungal balls [61]. A urine culture with mixed flora represents contamination.

Special consideration should be given to BK virus in solid organ transplant recipients. It is a polyomavirus that is ubiquitous in the environment and causes both animal and human infections. The median age of infection is 4–5 years old. Primary infection is usually a self-limited respiratory infection and rarely presents as acute cystitis. BK virus develops a lifelong latency in renal cells and transitional epithelial cells of the genitourinary tract. Immunosuppression triggers viremia that in some cases results in invasive renal infections. In kidney transplant recipients, the reactivation occurs in native kidneys and can cause a high level of renal graft failure, as high as 50–80% within 2 years of transplant. BK virus nephropathy is much rarer in non-renal solid organ transplantation, although when it does occur it tends to lead to end stage renal disease (ESRD) and significant mortality. The most common manifestations of BK virus reactivation infections are BK nephropathy and hemorrhagic cystitis. The gold standard for diagnosis of BK nephropathy is renal biopsy, although BK viral loads in the blood and urine as well as the presence of decoy cells (virally infected epithelial cells seen on cytology) assist in diagnosis and are used in screening. The key treatment of BK virus nephropathy/re-activation infections is reduction in immunosuppression [66].

Diagnostic Considerations

In solid organ transplant recipients, the presentation of UTI may lack usual lower urinary tract symptoms such as frequency, urgency, and dysuria. Instead, symptoms such as fever, malaise, and non-specific sepsis symptoms as well as leukocytosis may be the main presentation. Because of denervation of the allograft, the transplanted kidney may not be tender to palpation. Pyuria >10 WBC/mL is usually present, and lack of pyuria in the setting of UTI symptoms should spur evaluation
for alternative etiologies. Notably, *E. coli* UTI in solid organ transplant recipients may only have $10^4$ CFUs and still be considered a UTI by transplant infectious disease specialists [61].

**Therapeutic Considerations**

The Infectious Disease Community of Practice of the American Society of Transplantation guidelines (2019) recommend the following [61]: Routine urine testing in asymptomatic solid organ transplant recipients should not be performed after the first 2 months post-transplant. In the setting of asymptomatic bacteriuria, the recommendation is to observe for symptoms without treatment. However, if there is persistent asymptomatic bacteriuria with an associated creatinine rise, there is a weak recommendation for treatment with antibiotics. Simple cystitis should be treated for 5–10 days, and never for 3 days in solid organ transplant recipients. Treatment of complicated UTI/pyelonephritis should be for 14–21 days with an effort to narrow antibiotics based on urine culture data. However, the course should be extended for a longer duration if source control (such as in the setting of perinephric abscesses that require incision and drainage) is only achieved partway through the antibiotic course [61].

**Specific Treatment Recommendations by Condition**

**Simple cystitis** should be treated empirically with fluoroquinolones, amoxicillin-clavulanate, or an oral third-generation cephalosporin. Providers should be wary of the risk for trimethoprim-sulfamethoxazole resistance in patients who have received this antibiotic for prophylaxis. Empiric antibiotics should be narrowed as much as possible based on the culture results. While 7–10 days of antibiotic therapy should be utilized in the first 6 months post-transplant, 5–7 days can be considered for simple cystitis after 6 months [61].

**Pyelonephritis/complicated UTIs** in stable patients can be treated with ceftriaxone, ampicillin-sulbactam, or ciprofloxacin as long as prior cultures do not show antibiotic resistance. Patients with nausea and vomiting or other signs of clinical instability should be admitted to the hospital, and empiric therapy with piperacillin/tazobactam, cefepime, or a carbapenem should be initiated. Detailed inpatient management is beyond the scope of this book, but in general, consultation with a transplant infectious disease specialist is often indicated, as multi-drug-resistant organisms are increasing; the transplant team will also need to be involved, especially in severe infections (e.g., septic shock) in which reduction of immunosuppressive medications is recommended; and advanced imaging may be required to assess for upper tract disease such as renal abscess or structural abnormalities that could lead to obstruction in order to ensure source control. Treatment duration
should be 14–21 days, and antibiotics should be narrowed to reflect coverage of culture results [61].

For recurrent UTI treatment, interventions have not been adequately tested in solid organ transplant recipients. Recommendations for solid organ transplant recipients with recurrent UTIs are identical to those for immunocompetent patients. Behavioral interventions including hydration, timed voiding, front to back wiping in females, and avoidance of serial anal and vaginal intercourse is recommended. Vaginal estrogen for post-menopausal women decreased the frequency of recurrent UTIs from 6 in the placebo group to 0.5 per year in the treatment group. Post-coital antibiotics in females, and assessment for BPH with obstruction and prostatitis in males are also recommended. Non-antimicrobial interventions such as cranberry juice and probiotics are not well supported [61]. Additionally, given the higher risk of UTIs in the solid organ transplant population, primary care providers should strongly consider consultation with an infectious disease specialist.

**Early postoperative infections are usually addressed by the transplant team.**

For donor-derived infections trimethoprim-sulfamethoxazole used for PJP prophylaxis in the first 6–12 months will effectively serve as dual prophylaxis against many UTI organisms in kidney transplant recipients. One study showed a two-third reduction in UTIs for those receiving trimethoprim-sulfamethoxazole versus no antimicrobial prophylaxis. In patients who cannot tolerate trimethoprim-sulfamethoxazole, some authors recommend fluoroquinolones or Fosfomycin specifically for UTI prophylaxis, and guidelines are to limit such prophylaxis to the first post-transplant month [61].

Ureteral stents are utilized in kidney transplant recipients to reduce the risk of ureterovesicular anastomosis stenosis. However, ureteral stents may increase the risk for UTI, and they are typically removed within 2 weeks of transplantation to decrease the risk for UTI [61].

### Infections of the Central Nervous System

**Case**

A 45-year-old man who underwent liver transplant 18 months prior is brought to the primary care clinic by his family who is concerned about confusion. They noticed that he has become progressively more confused and fatigued over the last 10 days. They note word-finding difficulties, trouble remembering the names of his children, and being confused about the time of day. He has been sleeping more and taking naps in the afternoon, which is unusual for him. Yesterday morning, he began complaining of a headache, and this morning he was difficult to rouse from sleep. In the office, his temperature is 38.1 °C, heart rate 92, blood pressure 104/54, respiratory rate 16, and oxygen saturation 98% on ambient air. He is sleepy but arousable and able to
Infections of the central nervous system (CNS) are less common in solid organ transplant recipients than in prior years due to more tailored immunosuppressive regimens and routine surveillance. The current incidence of opportunistic CNS infections in this population is estimated to be 1–2%, down from 7% in previous studies [67]. However, CNS infections remain a significant cause of morbidity for solid organ transplant recipients, with some studies suggesting mortality rates as high as 44–77% [68]. Further, mortality rates with CNS fungal infections after solid organ transplantation may be as high as 90% percent. Solid organ transplant recipients may not present with typical symptoms of CNS infection, and therefore clinicians should have a high index of suspicion in a patient with fever, headache, and/or altered mental status [68]. Like most infectious complications in solid organ transplant recipient, the risk for different CNS infections varies according to time after transplantation (See Tables 8.1 and 8.5) [69].

**Diagnostic Considerations**

A solid organ transplant recipient with onset of fever and altered mental status should undergo a rapid evaluation including CBC, peripheral blood cultures, and a lumbar puncture (LP) to evaluate for CNS infection. Diagnostic studies from the LP...
should include cell count, glucose, total protein, gram stain and bacterial culture, and measurement of the opening pressure [70]. For most solid organ transplant recipients undergoing evaluation for CNS infection, the CSF should also be sent for viral PCR including enteroviruses, HSV, VZV, EBV, and CMV. If there is concern for a fungal etiology, providers should consider sending a CSF cryptococcal antigen and India ink staining for Cryptococcus [71].

Solid organ transplant recipients are at higher risk for development of bacterial or fungal brain abscesses than immunocompetent hosts. Any solid organ transplant recipient presenting with cranial nerve deficits requires urgent brain imaging [71]. A space-occupying lesion identified on brain imaging in a solid organ transplant recipient warrants immediate neurosurgical and infectious disease consultation to direct additional evaluation and consideration of early treatment. In the case of a space-occupying lesion, the decision to pursue an LP is done in conjunction with radiology, neurosurgery, or infectious disease, depending on the resources available, due to the concern for herniation if the intracranial pressure is elevated. If analysis of the CSF is unrevealing for patients with a space-occupying lesion, brain biopsy with pathologic examination may be indicated.

**Bacterial Infections of the CNS**

There is a sevenfold increase in the incidence of bacterial meningitis among solid organ transplant recipients compared to the broader population [72]. Patients after solid organ transplantation who develop bacterial meningitis may not manifest typical symptoms of high fevers and meningeal symptoms due to impaired inflammatory
response from immunosuppressing medications [68]. Solid organ transplant recipients are also at higher risk of CNS infection with opportunistic bacteria including *Nocardia spp*, *Mycobacterium*, and *Listeria spp*. These infections often begin as a respiratory illness and result in meningitis due to hematogenous spread of the organism [72].

If there is concern for bacterial meningitis, the solid organ transplant recipient should be evaluated in an emergency department or inpatient setting to undergo lumbar puncture and rapid administration of antibiotics until diagnostic studies return. Of note, solid organ transplant recipients with significant bacterial CNS infections may have a lower pleocytosis than immunocompetent hosts on evaluation of the cerebral spinal fluid (CSF), so providers should have a low threshold to administer antibiotics until further consultation with an infectious disease specialist is available.

**Viral Infections of the CNS**

Viral infections of the CNS most commonly present 1–6 months after transplantation. Herpes viruses are the most common causes of viral CNS infection in solid organ transplant recipients, including VZV, HSV, CMV, EBV, and HHV-6 [68]. Patients may present with symptoms of either a meningitis or encephalitis. A solid organ transplant recipient who presents with altered mental status, personality changes, seizures, or speech or gait disturbance should be evaluated for viral encephalitis with lumbar puncture and PCR-based assays on the CSF. As with bacterial infections, evaluation will typically require an emergency department evaluation and likely hospitalization.

EBV rarely causes encephalitis but is associated with post-transplant lymphoproliferative disorder (PTLD) in the CNS [72]. While more commonly seen in patients receiving immunomodulating drugs for rheumatologic or neurologic disease, infection with JC virus can cause progressive multifocal leukoencephalopathy (PML) in solid organ transplant recipients late in the post-transplantation course [2].

**Fungal Infections of the CNS**

Infection with cryptococcus is by far the most common cause of fungal meningitis and meningoencephalitis in patients after solid organ transplantation. The onset of cryptococcus infection is late in the post-transplant course, often occurring 16–21 months after transplantation [71]. Cryptococcus infection occurs after inhalation through the respiratory tract and is typically thought to represent reactivation of the infection in immunocompromised hosts, although primary infections do occur. Importantly, fever is present only 50% of the time in solid organ transplant recipients with cryptococcus meningoencephalitis. Testing for cryptococcus antigen in the CSF and the serum is the gold standard for diagnosing cryptococcus
infection and is more commonly used in institutions across the United States than India ink testing. Treatment regimens vary and may involve induction therapy for 2 weeks with liposomal amphotericin B and flucytosine, followed by consolidation therapy with fluconazole for 8 weeks, and finally a lower dose maintenance regimen of fluconazole for an additional 6–12 months [71].

Aspergillus is the most common fungal etiology causing cerebral abscesses in solid organ transplant recipients [2]. Mortality for solid organ transplant recipients with aspergillus abscesses is greater than 50%, even with voriconazole or amphotericin B treatment. Providers should also be aware that Toxoplasma gondii, a parasitic infection, may cause brain abscesses in solid organ transplant recipients and requires prolonged antimicrobial therapy [70].

### Skin and Soft Tissue Infections

**Case**

A 67-year-old patient with history of kidney transplantation presents to the primary care clinic with 4 days of worsening erythema, edema, and pain of the right lower extremity. The patient first noticed erythema and swelling around his great toe, which progressed to the foot and then the lower leg in the following days. Yesterday evening, he had trouble going to sleep due to pain. He does not have fever or chills. He had no trauma to the foot and does not walk barefoot. On exam, he is afebrile and vital signs are normal. His right lower extremity has erythema and edema extending from the distal foot up the knee, with increased erythema and induration medially compared to laterally. There are no areas of purulence or fluctuance. There is dryness and cracking of the skin between his toes with evidence of tinea pedis. There is no pain in the joints of the ankle or foot with range of motion.

**Comment:**

This patient has uncomplicated cellulitis of the lower extremity. There are no signs of systemic infection and no areas of purulence. He likely developed a bacterial superinfection of his foot due to underlying tinea pedis, which causes skin breakdown and creates a portal of entry for skin flora. A swab for bacterial culture is only indicated if purulence is present; in the absence of purulence, a skin culture is not helpful due to contamination from skin flora. In the absence of purulence or signs of an abscess, empiric treatment should be tailored to cover Streptococcus species and methicillin-sensitive S. aureus (MSSA). If there are areas of purulence, the antibiotic spectrum should be extended to cover methicillin-resistant S. aureus (MRSA); common regimens include a first-generation cephalosporin combined with antibiotic active against MRSA including doxycycline, trimethoprim-sulfamethoxazole, or clindamycin. When considering antibiotics in a solid organ transplant...
Skin and soft tissue infections (SSTIs) are extremely common in solid organ transplant recipients due to ongoing immunosuppression and may affect up to 20% of patients at some time in the post-transplant period [73]. Similar to immunocompetent hosts, SSTIs in solid organ transplant recipients may be caused by bacteria, mycobacteria, fungi, viruses, and parasites, although immunocompromised individuals are more susceptible to severe morbidity and mortality. Common skin infections may present atypically in solid organ transplant recipients because of defects in cellular and humoral immunity and may reflect either localized or disseminated disease. When assessing SSTIs in solid organ transplant recipients, providers should use a similar approach to evaluation and management of SSTIs in immunocompetent hosts, first determining if the lesion is purulent or non-purulent (see Fig. 8.2) as this directs initial diagnostic and management strategies. In immunosuppressed hosts, cutaneous lesions are commonly vesicular, drug interactions should be checked, as well as dose adjustment for chronic kidney disease, a common metabolic complication. If an abscess is present, it should be treated with incision and drainage as well as an antibiotic active against MRSA. Cellulitis may be treated for a little as 5 days though the treatment course may be extended up to 14 days, depending on the individual and degree of improvement.

Signs of systemic infection from a skin and soft tissue infection should prompt immediate referral to the emergency room for laboratory evaluation, blood cultures, imaging, and possible surgical consultation. If there is concern for concomitant deep vein thrombosis, then venous duplex imaging should be obtained.

Skin and soft tissue infections (SSTIs) are extremely common in solid organ transplant recipients due to ongoing immunosuppression and may affect up to 20% of patients at some time in the post-transplant period [73]. Similar to immunocompetent hosts, SSTIs in solid organ transplant recipients may be caused by bacteria, mycobacteria, fungi, viruses, and parasites, although immunocompromised individuals are more susceptible to severe morbidity and mortality. Common skin infections may present atypically in solid organ transplant recipients because of defects in cellular and humoral immunity and may reflect either localized or disseminated disease. When assessing SSTIs in solid organ transplant recipients, providers should use a similar approach to evaluation and management of SSTIs in immunocompetent hosts, first determining if the lesion is purulent or non-purulent (see Fig. 8.2) as this directs initial diagnostic and management strategies. In immunosuppressed hosts, cutaneous lesions are commonly vesicular,
nodular, or ulcerative, and the patient’s travel and exposure history becomes critically important in driving the differential diagnosis. Other, non-infectious diagnostic considerations for skin findings in a solid organ transplant recipient include drug eruptions, erythema multiforme, Sweet syndrome, and underlying malignancy [74].

**Diagnostic Considerations**

Appropriate diagnostic evaluation of SSTIs in solid organ transplant recipients depends on the appearance of the skin lesion, concern for disseminated disease, and the patient’s exposure history. If the lesion is purulent, providers should have high suspicion for typical or atypical bacterial infection and should obtain a swab of the purulent material to send for gram stain and bacterial culture. While non-bacterial pathogens can cause purulent-appearing lesions, bacterial culture is the most appropriate first step. Blood cultures are rarely indicated in the evaluation of SSTI except when fever is present, in patients who use recreational injection drugs, and patients presenting in shock. When there is concern for disseminated infection either because of the presence of systemic symptoms or multiple similar-appearing cutaneous lesions at distant sites, providers should consider ordering both bacterial and fungal blood cultures. Vesicular lesions should be unroofed with samples sent for viral PCR to detect infection with herpes simplex virus (HSV) or varicella zoster virus (VZV) infection. Nodules or ulcerative lesions, either solitary or grouped, may be difficult to identify by visual inspection alone and referral to a surgeon or dermatologist for skin biopsy may be indicated. Tissue specimens should be sent to both the microbiology lab for culture and the pathology lab for histologic evaluation [74, 75]. Special stains and culture media may be required depending on the exposure history and differential diagnosis; primary care providers should communicate early with an infectious disease specialist and a dermatologist to ensure that appropriate testing is performed.

**Cellulitis and Abscesses**

Cellulitis remains the most common clinical SSTI syndrome with an incidence of 2 cases per 1000-patient years. Cellulitis is a non-necrotizing, superficial skin infection involving the epidermis and dermis. Immunosuppression is an important risk factor for SSTIs; risk increases when other conditions are present including chronic skin inflammation, poor venous or lymphatic circulation, diabetes mellitus, and obesity [75]. Furuncles, carbuncles, and cutaneous abscesses represent isolated collections of pus in the dermis and deeper tissues that require incision and drainage to fully control the source of infection. Abscesses typically present as tender, erythematous, indurated nodules, often with fluctuance and surrounding skin erythema [76]. Cellulitis and abscesses are not distinctly different entities in solid organ transplant
recipients compared to immunocompetent hosts. The most important principles in diagnosis include vigilance when assessing possible cutaneous infection, understanding that the syndromes may present more subtly in solid organ transplant recipients and may progress more rapidly than in immunocompetent individuals.

Beta-hemolytic streptococci remain the most common cause of cellulitis in immunocompetent and immunocompromised hosts, followed by community-acquired *S. aureus*, including MRSA. In some studies, *S. aureus* (MSSA and MRSA) is the predominant pathogen involved in purulent cellulitis and remains the leading causes of SSTIs overall, especially in cases involving abscesses [76].

Other pathogens, including GNRs, are encountered less frequently and most often in the setting of bacteremia. Infection with atypical bacteria, such as nocardia or non-tuberculous mycobacteria, are infrequent causes of cellulitis; skin manifestations of these pathogens may also present as pustules, nodules, ulcers, and abscesses [77]. Other rare causes of SSTIs have been associated with certain exposures, such as an outbreak of nontuberculous mycobacterium after exposure to fish markets in New York City [78, 79].

The IDSA has established clear guidelines for the diagnosis and management of SSTIs; yet, rates of misdiagnosis, inappropriate antibiotic use, and hospitalization remain high [75, 80]. Of note, fever has been shown to be an unreliable indicator for the need for admission, despite traditional practice [81]. Further, other physical exam findings consistent with severe infection, such as bullae and lymphatic streaking, do not correlate with fever. Risk prediction tools for SSTI also have poor performance, lacking sensitivity in the identification of severe infections in elderly patients and populations with elevated risk, such as solid organ transplant recipients. Thus, providers must remain vigilant in their assessment of cellulitis and abscess, with low threshold for diagnostic sampling and treatment.

In typical cases of cellulitis without systemic signs of purulence, the IDSA recommends antibiotic therapy targeted at streptococci. If purulence is present or suspected, therapy should be extended to cover MRSA. Providers should choose antibiotics based on local susceptibility patterns and institutional antibiograms; typical oral regimens that cover both streptococci and MRSA include a penicillin or first-generation cephalosporin, combined with trimethoprim-sulfamethoxazole, doxycycline, or clindamycin. If a patient is already receiving trimethoprim-sulfamethoxazole for prophylaxis, an alternative agent should be selected to cover MRSA. When used for a short duration to treat purulent cellulitis, there are no particular concerns about these antibiotics interacting with immunosuppression regimens. Linezolid is another oral antibiotic active against *S. aureus*; however, its use is typically reserved for patients who cannot tolerate or have demonstrated resistance to first-line agents. Use of linezolid is also limited by cost and interactions with other common medications including selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). Note that cytopenias caused by linezolid develop with long antibiotic courses and are of less concern when it is used for a short course to treat cellulitis.

Some clinicians treat both streptococci and MRSA initially, particularly in solid organ transplant recipients, although clear guidance on this approach is lacking. Recommended treatment duration for cellulitis is 5 days and may be extended if the
patient is not improving as expected. While prior evidence held that abscesses could be treated with incision and drainage alone, a large randomized controlled trial demonstrated that cure rate for abscesses increased with the addition of trimethoprim-sulfamethoxazole to incision and drainage compared to incision and drainage alone, particularly in settings where MRSA is prevalent [82]. The IDSA makes a strong recommendation for clinicians to consult with an infectious disease specialist or a dermatologist in the treatment of cellulitis in solid organ transplant recipients, particularly if complicating factors are present [75].

**Necrotizing Skin Infections**

Necrotizing soft tissue infections (NSTIs) remain a relatively rare cause of SSTIs overall, and there is a paucity of data on NSTIs in immunocompromised patients. NSTIs are associated with high mortality rates (15–50%), and early recognition and diagnosis can be challenging. Common pathogens included GNRs, anaerobes, coagulase-negative *Staphylococcus* species, *S. aureus* species, beta-hemolytic streptococcal species, and *Enterococcus* species; however, in a single-center study on NSTIs in immunocompromised hosts, wound cultures revealed polymicrobial growth in 58.7% of cases [83]. In this study, more immunocompromised patients had positive blood cultures in the setting of NSTIs compared to immunocompetent hosts. Immunocompromised patients also had increased rates of in-hospital death associated with NSTI infection compared to immunocompetent hosts (39.1% vs. 19.4%). Additional findings included a lower WBC counts (often in the normal range) and absence of fever among immunocompromised hosts. These findings highlight the high index of suspicion needed among triaging physicians to ensure early identification and appropriate referral to an emergency care setting [84].

**Vesicular Eruptions**

The presence of vesicular lesions in a solid organ transplant recipient should raise suspicion for infection with a herpes virus. Reactivation of herpes simplex virus (HSV) and varicella zoster virus (VZV) are most common; however, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and human herpes virus 6 (HHV-6) may cause vesicular lesions as well, though cutaneous manifestations are less common in these diseases.

HSV accounted for the vast majority of mucocutaneous infection in solid organ transplant recipients (>80%) before the introduction of antiviral prophylaxis; since then, incidence has dropped dramatically [84]. Infection with HSV produces painful, grouped vesicles on an erythematous base that coalesce into shallow ulcerations on surfaces of mucous membranes. HSV lesions in solid organ transplant recipients may take longer to heal than in immunocompetent hosts, in part due to impaired cellular immunity and prolonged viral shedding [74]. HSV-1 tends to cause
oropharyngeal lesions, whereas HSV-2 has a predilection for anogenital eruptions; however, both serotypes may affect any mucocutaneous surface, particularly in solid organ transplant recipients.

Reactivation of VZV is common among solid organ transplant recipients, with shingles, or “zoster,” affecting 6–7% of individuals [74]. VZV reactivation presents with grouped vesicles on an erythematous base and typically affects a single dermatome. Disseminated zoster, defined as reactivation of VZV affecting 3 or more dermatomes, is more common in immunocompromised individuals and may take longer to respond to antiviral therapy. Primary infection with VZV, also called chicken pox, is relatively uncommon in adults due to almost universal exposure during childhood. Solid organ transplant recipients should have varicella titer testing prior to transplantation, and the varicella vaccine should be considered for anyone who is seronegative for anti-varicella antibodies. It is important to note that the current VZV vaccine is a live, attenuated vaccine, and administration is contraindicated post-transplantation [85].

If HSV or VZV infection is suspected, providers should obtain a swab of vesicular lesions and send the sample for PCR testing (see above). While awaiting testing results, empiric treatment with acyclovir or valacyclovir may be initiated to reduce duration and severity of symptoms. First-line therapy for herpes labialis includes acyclovir 400 mg 5×/day for 5 days. Genital herpes may be treated with acyclovir 400 mg 5×/day for 10 days or valacyclovir 1000 mg 3×/day for 10 days. Patients with recurrent HSV could experience asymptomatic shedding for days before an outbreak occurs; thus, there may be a role for twice-daily suppressive therapy with acyclovir or valacyclovir in individuals with more than 3 outbreaks per year to reduce risk of transmission. Herpes zoster should be treated with a higher dose of acyclovir, 800 mg 5×/day for 7–10 days or valacyclovir 1000 mg 3×/day for 7 days [85]. Severe HSV or VZV infection may require hospitalization and administration of IV acyclovir. Famciclovir is also active against HSV and VZV and may be used in the treatment of these infections, though treatment duration varies.

Disseminated CMV may cause a maculopapular, vesicular, or even ulcerative eruption in solid organ transplant recipients. Cutaneous manifestations of CMV typically affect 10–20% of solid organ transplant recipients with systemic CMV disease and portend a poor prognosis [85]. Infection with HHV-6 typically causes a self-limited febrile illness with a maculopapular rash, though manifestations may be more severe in solid organ transplant recipients. Cutaneous lesions associated with EBV infection are most commonly seen in the setting of post-transplant lymphoproliferative disorder (PTLD).

**Nodular and Ulcerative Lesions**

Numerous bacterial and fungal pathogens can cause nodular cutaneous lesions in solid organ transplant recipients, and these lesions may or may not indicate disseminated infection. In solid organ transplant recipients, defects in cellular immunity predispose to mycobacteria, atypical bacteria, certain zoonoses (*Brucella, Bartonella*), and parasites (Leishmaniasis), all of which may present with cutaneous...
nODULES OR ULCERS. AS AN EXAMPLE, UP TO 32% OF SOLID ORGAN TRANSPLANT RECIPIENTS WITH DISSEMINATED NOCARDIA INFECTION DEVELOPED SKIN MANIFESTATIONS [78]. SOME NON-TUBERCULOUS MYCOBACTERIA (NTM) MAY PRODUCE LOCALIZED NODULES OR ULCERATED LESIONS (E.G., MYCOBACTERIUM FORTUITUM), WHILE INFECTIONS WITH MYCOBACTERIUM ABSCESSUS OR CHELONAE ARE MORE LIKELY TO RESULT IN PUSTULAR, NODULAR, OR POPULAR LESIONS IN ASSOCIATION WITH DISSEMINATED INFECTION.

THE MOST COMMON CLINICAL PRESENTATION OF CANDIDIASIS IN SOLID ORGAN TRANSPLANT RECIPIENTS IS MUCCUTANEOUS DISEASE, INCLUDING THRUSH AND ESOPHAGEAL CANDIDIASIS [86]. HOWEVER, CANDIDA REMAINS THE MOST COMMON CAUSE OF DISSEMINATED FUNGAL INFECTIONS IN SOLID ORGAN TRANSPLANT RECIPIENTS; SKIN LESIONS OCCUR IN 10% OF THESE PATIENTS AND MAY BE THE PRESENTING SYMPTOM IN 13–36% OF CASES [74]. IN COMPARISON, DISSEMINATED ASPERGILLUS INFECTION IS A RARE CAUSE OF CUTANEOUS LESIONS IN SOLID ORGAN TRANSPLANT RECIPIENTS AND IS UNLIKELY TO BE A PRESENTING SYMPTOM FOR PCPs.

ENDEMIC FUNGAL INFECTIONS, INCLUDING HISTOPLASMOSIS, COCCIDIOIDOMYCOSIS, AND BLASTOMYCOSIS, TYPICALLY CAUSE PRIMARY PULMONARY INFECTIONS. PRIMARY INOCULATION WITH THESE PATHOGENS CAUSING ISOLATED SKIN DISEASE IS UNCOMMON. SOLID ORGAN TRANSPLANT RECIPIENTS INFECTED WITH AN ENDOMIC MYCOSES ARE AT HIGHER RISK FOR DISSEMINATED DISEASE DUE TO IMPAIRED CELLULAR IMMUNITY, AND MAY DEVELOP PAPULES, PLAQUES, PUSTULES, NODULES, OR ULCERS. SKIN DISEASE IS THE MOST COMMON EXTRA-PULMONARY MANIFESTATION OF BLASTOMYCOSIS AND MAY PRESENT AS EITHER VERRUCOUS OR ULCERATIVE LESIONS [87].

IF THERE IS CONCERN FOR AN ENDOMIC FUNGAL INFECTION, A THOROUGH EXPOSURE HISTORY IS CRITICAL. IN THE UNITED STATES, HISTOPLASMOSIS IS NATIVE TO THE OHIO AND MISSISSIPPI RIVER VALLEYS AND REMAINS THE MOST COMMON OF THE ENDOMIC FUNGAL INFECTIONS OVERALL. COCCIDIOIDOMYCOSIS IS ENDOMIC TO THE SOUTHWESTERN UNITED STATES INCLUDING CENTRAL CALIFORNIA, AS WELL AS AREAS OF WASHINGTON STATE AND NORTHERN MEXICO [88]. BLASTOMYCOSIS IS FOUND PREDOMINANTLY IN SOUTHERN AND SOUTHEASTERN STATES BORDERING THE OHIO AND MISSISSIPPI RIVER VALLEYS, AS WELL AS UPPER MIDWESTERN STATES IN THE GREAT LAKES REGION. TAKING A DETAILED HISTORY TO CLARIFY RECENT TRAVEL TO ENDOCIME AREAS, AS WELL AS EXPLORATION OF CONCOMITANT PULMONARY SYMPTOMS, WILL HELP CLARIFY THE DIAGNOSTIC POSSIBILITIES. WORLDWIDE PATTERNS VARY—KNOWING LOCAL AND REGIONAL PATTERNS OF ENDOCIME MYCOSES CAN AID IN THE DIAGNOSIS OF CUTANEOUS FUNGAL INFECTIONS.

DIAGNOSIS OF NODULAR AND ULCERATIVE LESIONS TYPICALLY REQUIRES BIOSPY, EITHER WITH A DERMATOLOGIST OR A SURGEON, DEPENDING ON THE DEPTH OF THE WOUND. THESE SAMPLES SHOULD BE SENT FOR MICROBIOLOGIC AND PATHOLOGIC EVALUATION. EMPIRIC THERAPY IS NOT RECOMMENDED; RATHER, PROVIDERS SHOULD AVOID CULTURE OR PATHOLOGY RESULTS AND CONSIDER CONSULTATION OR REFERRAL TO AN INFECTIOUS DISEASE SPECIALIST TO DETERMINE TREATMENT.

PREVENTION

IN ADDITION TO THE MEDICATIONS FOR PROPHYLAXIS AGAINST VIRUSES AND PNEUMOCYSTIS JIROVECTI, SOLID ORGAN TRANSPLANT RECIPIENTS ARE EDUCATED TO TAKE OTHER MEASURES TO PREVENT INFECTION, INCLUDING HAND HYGIENE, AVOIDING SICK CONTACTS, FOODS THAT HAVE HIGHER RISK OF BACTERIAL CONTAMINATION, AND TRAVEL TO LOCATIONS WITH ENDOCIME INFECTIOUS DISEASES. DURING THE COVID-19/SARS-COV-2 PANDEMIC, SOLID ORGAN TRANSPLANT
recipients are in the highest risk category and should limit their exposure by following public health guidelines. The primary care provider can assist by keeping vaccinations up to date (Table 8.6; see also Chap. 12). Solid organ transplant recipients should be reminded not to accept live vaccines. Additionally, the recombinant herpes

| Vaccinations                                      | Pre-transplant | Post-transplant | Comments                                                                 |
|--------------------------------------------------|----------------|----------------|--------------------------------------------------------------------------|
| Measles Mumps Rubella (MMR—live)                 | Yes            | No             | Recommended to be given prior to transplantation. This live attenuated vaccination is contraindicated after transplant |
| Zoster (Zostavax ®—live)                         | Yes            | No             | Live attenuated virus vaccine can be given prior to transplant           |
| Zoster (Shingrix ®—recombinant antigen)          | Yes            | Yes only in low-dose immunosuppression | ACIP recommends it for patients on low-dose immunosuppression (<20 mg prednisone/day) or anticipating higher immunosuppression or recovering from higher dose immunosuppression. Subjects on moderate or high-dose immunosuppression were excluded from efficacy studies. Consult with transplant team if considering. |
| Varicella (live)                                 | Yes            | No             |                                                                          |
| Prevnar ® vaccine (PCV13)                        | Yes            | Yes            | At least 1 year after PPSV23                                           |
| Pneumococcal vaccine (PPSV23)                    | Yes            | Yes            | At least 8 weeks after PCV13. Booster 5 years after first PPSV23 dose if <65 years of age. A last dose is given at 65 or older, again 5 years after the last PPSV23 dose |
| Hepatitis A vaccine                              |                |                | Recommended in ESLD                                                     |
| Hepatitis B vaccine                              |                |                | Recommended in ESLD, ESRD                                                |
| Tetanus/diphtheria (Td)                          | Yes            | Yes            | Every 10 years                                                          |
| Tetanus/ diphtheria/ pertussis (Tdap)            | Yes            | Yes            |                                                                          |
| Influenza (inactivated)                         | Yes            | Yes            |                                                                          |
| Influenza (live)                                 | Yes            | No             | Not within 2 weeks of transplant                                         |
| Meningitis (N. meningitidis)                     | Yes            | Yes            |                                                                          |
| Polio (inactivated)                              | Yes            | Yes            |                                                                          |
| Polio (live)                                     | Yes            | No             |                                                                          |
| HPV                                              | Yes            | Yes            |                                                                          |
zoster vaccine is currently not recommended—although it is not a live vaccine, there is a theoretical risk of precipitating acute rejection, and the use of this vaccine is still under investigation in this population. Vaccine guidelines change regularly—it is important to regularly check updated recommendations, and if in doubt, discuss with the transplant team.

**Conclusion**

Infection remains a significant risk in solid organ transplant recipients. A knowledge of the time course of immunosuppression and potential pathogens will assist in the evaluation and management of the solid organ transplant recipient who presents to the primary care setting with potentially infectious symptoms. Signs and symptoms of infection may present subtly in solid organ transplant recipients due to immunosuppression; hence, primary care providers must maintain a high index of suspicion when evaluating these patients in clinic. A higher level of care is often required for more severe infections because of the increased risk for complications and monitoring required due to immunosuppression, and consultation with the transplant team and an infectious disease specialist is often indicated. With timely and appropriate care, infections may be treated successfully in the solid organ transplant recipient.

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