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Chapter 8

Complications of Kidney Transplantation: Effects of Over-Immunosuppression

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1. Introduction

Kidney transplantation is a relatively young field within medicine which continues to experience rapid advances in several areas. The number of immunosuppressive medications available to prevent and treat immunologic rejection of the transplanted organ has increased significantly since the late 1990's, however, there continues to be a great need for developing novel, less toxic medications. The fine balance between over- and under-immunosuppression is difficult to achieve in many transplant recipients, particularly as candidacy for kidney transplantation has expanded to include the elderly, patients with HIV and/or Hepatitis C infection, and sensitized transplant candidates. The relationship between infection and rejection remains closely intertwined, and can be a vicious cycle, with reduction of immunosuppression to manage infection potentially triggering rejection, and increased immunosuppression in the setting of rejection potentially leading to infectious complications. This chapter will focus on post-transplant complications resulting from over-immunosuppression, specifically infection and malignancy.

2. Infection

The occurrence of infection after transplantation is a significant determinant of transplant outcome [1]. The incidence of infections after solid-organ transplantation is dependent on several factors, including the degree of immunosuppression, the type of organ transplanted, technical or surgical complications, need for additional antirejection therapy, environmental exposures, and the time frame after transplantation. A comprehensive list of factors contributing the 'net state of immune deficiency' can be found in reference [2]. Most recent United States data shows that infectious complications cause 20.9% of kidney transplant recipient death with a functioning allograft [3]. Infection also accounts for a significant proportion of death-censored graft loss, accounting for 7.7% of graft losses in the U.S.

between 1990 and 2006 [4]. Using the leading cause of allograft loss, chronic rejection as a reference, risk factors for infection-related graft loss included prior acute rejection and utilization of any induction therapy. Older transplant recipients (> 65 years at transplant) had a higher risk of infection related graft loss (14.1%). In this series, the infections leading to graft loss were caused by infections associated with urological complications and polyomavirus associated nephropathy [4]. Other infections that directly contribute to death-censored graft loss include pyelonephritis and acute kidney injury in the setting of sepsis/critical illness.

The occurrence of infection after transplantation usually falls within 3 general time frames: the first month, the second through the sixth month, and more than 6 months after transplantation [2, 5, 6]. Infections that occur during the first month after transplantation are generally the same nosocomial infections seen in non-immunosuppressed patients after surgery. These infections include bacterial and candidal urinary tract infection (UTI), wound/surgical site infections, catheter-related infections, and pneumonia.

The period from the second to sixth month after transplantation is the time during which opportunistic infections "classically" associated with transplantation occur [1] , although the patterns have changed thanks to the availability of antimicrobial prophylaxis against some infections [2]. The most common infections during this period include cytomegalovirus (CMV), *Pneumocystis (carinii) jiroveci*, *Aspergillus* species, *Nocardia* species, *Toxoplasmosis*, *Listeria monocytogenes,* and fungal infections. In addition, reactivation of immunomodulating viruses will begin to manifest a clinically significant effect. These viruses include Epstein Barr virus (EBV), CMV, hepatitis B virus (HBV), hepatitis C virus (HCV), human herpesvirus type 6 (HHV-6), and human immunodeficiency virus (HIV) [1, 6]. Multi-drug resistant (MDR) bacteria such as *Klebsiella*, *Pseudomonas*, *Acinetobacter*, *Staphylococcus*, and *Enterococcus* can also be problematic during this period [5, 7-9].

More than 6 months after transplantation, most transplant recipients (80%) are doing well [6], and can be classified into one of three risk groups [5]:

1. Patients who have done well and immunosuppression is being tapered
2. Patients who have required increased immunosuppression exposure due to rejection
3. Patients at risk for late progressive viral reactivation (polyomavirus, CMV, HBV, HCV, HPV)

The most common infections seen during this period mimic those seen in the general community [6]. Such infections include influenza virus, UTIs, and pneumococcal pneumonia. Although opportunistic infections are rarely observed during this time period, reactivation of varicella zoster virus (VZV) or CMV can occur. In addition, transplant recipients who have had multiple rejection episodes requiring additional antirejection may be predisposed to opportunistic infections more commonly seen 2 to 6 months after transplantation. It is recommended that patients being treated for acute rejection be placed back on opportunistic infection prophylaxis [10]. Transplant recipients experiencing chronic infection due to HBV, HCV, CMV, EBV, or HIV, resulting in a greater degree of morbidity,

are subsequently at an increased risk for other infections [1, 6]. In patients who undergo repeat transplantation, the typical timetable of infections may be altered. Infections characteristic of 1 of the 3 conventional time periods may occur simultaneously and with an increased severity [11]. In addition, modern immunosuppressive agents, as well as availability of prophylaxis against some infections has led to an altered timeline for many patients.

Although not addressed in this chapter due to space constraints, transplant centers should be aware of the newer emerging infectious diseases that may affect transplant recipients [12]. This is also a great concern due to increasing rates of transplant tourism, where patients travel to foreign countries to receive a transplant and may be exposed to infectious complications not typically seen in their home country, where they will receive their follow-up care. In addition, transplant recipients travelling for leisure should consult with a travel medicine specialist when possible [13].

2.1. Bacterial infection

Some of the most prevalent microbial pathogens observed after organ transplantation are bacteria. The specific bacterial infections that occur after transplantation can be divided into 4 categories [14]:

- Infections due to surgical or technical complications,
- Infections related to prolonged hospitalization (nosocomial infections),
- Infections associated with the degree of immunosuppression (opportunistic infections), and
- Infections occurring months after transplantation when the transplant recipient resumes normal activity (community-acquired infections).

Although transplant recipients are susceptible to common bacterial pathogens observed in normal hosts, the immunosuppressed state of the recipient after transplantation predisposes the patient to bacterial pathogens not commonly observed in the normal host. These opportunist pathogens include *Legionella* species, *Nocardia* species, *Rhodococcus* species, *L monocytogenes*, and *Mycobacteria* species. Following transplantation, disruption of anatomic barriers is commonly associated with bacterial infections. For instance, the upper airway is normally colonized with bacteria, and the lower respiratory tract is normally sterile. Endotracheal intubation creates a conduit between the upper and lower respiratory tract, introducing bacteria to the lower respiratory tract and resulting in disease of the bronchial tubes or lung parenchyma. Indwelling urinary and vascular catheters may become colonized with nosocomial bacteria or cutaneous flora and introduce these pathogens into the urinary tract, transplant kidney, or bloodstream.

2.1.1. Urinary tract infection

The most common infections occurring after kidney transplantation are UTIs, which may include asymptmatic bacteriuria, cystitis, and/or pyelonephritis. The reported incidence of

UTI in kidney recipients is 7.3% to to 90% [15-18] with the variation likely due to differences in definitions of infection and prophylactic strategies. Predisposing factors include renal insufficiency, ischemic changes of the graft, decreased urine flow through the urinary epithelium, prolonged urinary catheterization, ureteral stenting, post-transplant diarrhea, and underlying medical conditions such as diabetes mellitus, female gender, urinary tract abnormalities, bladder dysfunction, and bladder outlet obstruction [17-20]. In pediatric kidney transplant recipients, age less than 5 at the time of transplant and lower urinary tract abnormalities may be risk factors for post-transplant UTI [21]. Studies analyzing whether the utilization of double-J ureteral stents during a kidney transplant procedure increases the risk of post-transplant UTI have produced conflicting results [22-24]. It has been suggested that a shorter duration (3 weeks versus 6 weeks) of ureteral stent placement may reduce the incidence of UTI [24].

The most common pathogens implicated in UTIs include *E. coli*, *Staphylococci*, *Enterococci*, *Enterobacter* and *Pseudomonas aeruginosa* [20, 25]. Despite routine treatment of asymptomatic bacteriuria, patients still develop symptomatic cystitis and pyelonephritis, and recurrent asymptomatic bacteriuria has been shown to be an independent risk factor for transplant pyelonephritis [16]. Recurrent UTI can also contribute to inflammation and fibrosis of the allograft [16, 26]. Bloodstream infections, the majority (75%) of which were due to a urinary source (*E. Coli* in 50% of infections) have also been shown to lead to allograft failure (either directly or by causing death) and all-cause mortality [27]. It is recommended that all UTI's in kidney transplant recipients be considered complicated, and thus short-term treatment regimens are not recommended [20].

2.1.2. Clostridium difficile associated diarrhea and colitis

Clostridium difficile associated diarrhea (CDAD) and *C. difficile* colitis are an increasingly important cause of morbidity and mortality after solid organ transplantation, with reported incidence of 0.5% to 16.0% of kidney transplant recipients [28-30]. CDAD tends to occur early in the post-transplant period, although later cases related to exposure to antibiotics or increased immunosuppression due to allograft rejection also occur. Transplant recipients are also at higher risk for fulminant *C. difficile* colitis as compared to the general population. CDAD is often difficult to eradicate completely, leading to recurrent infection, due to the fact that it is a spore forming bacterium.

Risk factors for CDAD include older age, antimicrobial exposure, and rabbit anti-thymocyte globulin induction therapy [30, 31]. For patients developing fulminiant CDAD, risk factors identified include peak leukocyte count of 25,000/mm^3 or greater and evidence of pancolitis on CT scan. For those developing fulminant CDAD, colectomy has been associated with improved patient and graft survival when compared to patients managed with medical therapy alone [30]. Medications that suppress gastric acid production, commonly used in transplant recipients, may also increase risk of CDAD [31].

The most commonly utilized diagnostic test for CDAD is *C. difficile* toxin detection in the stool via ELISA [31]. Antimicrobial management of CDAD includes oral metronidazole (first

line for mild to moderate CDAD) or oral vancomycin (for severe CDAD), with intravenous (IV) metronidazole added in severe cases [31]. It is important to note that IV vancomycin does not penetrate the intestinal lumen, and is therefore ineffective for managment of CDAD. The removal or reduction in other antibiotics is an important adjunctive step. Surgery is often necessary in fulminant cases, in order to avoid colonic rupture. Other adjunctive therapies sometimes employed but with less supporting data include vancomycin enema, *Lactobacillus* probiotic supplementation, and intravenous immune globulin (IVIG) [5, 31]. An algorithm for management of patients with *C. difficile* infection can be found in reference [31].

2.1.3. Tuberculosis

Worldwide, the estimated incidence of tuberculosis (TB) (*Mycobacterium tuberculosis*) in kidney transplant recipients is 20 to 70 times that of the general population [32]. Treatment of active TB infection in transplant recipients is complicated due to drug interactions, antimicrobial resistance, and toxicity of the antimicrobials used for treatment of TB. Extrapulmonary involvement, atypical presentation, and limitations of the tuberculin skin test make diagnsois difficult. Although newer methods are available, which measure release of interferon γ (such as Quantiferon Gold), more data is needed regarding utilization of these assays in kidney transplant candidates and recipients [33].

Identification of high risk patients (those living in endemic areas or those with prior infection or exposure) is essential in order to administer prophylaxis with isoniazid (INH). A meta analysis of INH prophylaxis in kidney transplant recipients found that the relative risk of TB infection was significantly reduced, while risk of toxicity (hepatitis) did not differ between patients that did or did not receive prophylaxis [33]. Current European [34] and U.S. [35] guidelines recommend 9 months of INH prophylaxis for those with latent TB infection, however, the optimal timing of prophylaxis is unclear, particularly for patients awaiting a deceased donor transplant. When treating transplant recipients with active tuberculosis, close monitoring of calcineurin inhibitor levels with concomitant dose increase is needed due to presence of rifampin or related drugs in the anti-tuberculosis regimen [35].

2.1.4. Prophylaxis of bacterial infection

Trimethoprim/sulfamethoxazole (TMP/SMX), traditionally used for prophylaxis against *Pneumocystis jiroveci* pneumonia, has proven efficacy in reducing the incidence of UTIs, as well as bacteremias after transplantation [36, 37], although resisitance to common urinary tract pathogens is increasingly common in more recent years [16, 38]. TMP/SMX is also effective in preventing infections by *L monocytogenes*, *Nocardia* species, and *Toxoplasmosis gondii*, leading to recommendations for its use in all patients without contraindication to its use [2]. Therapy should continue for at least 6 months after transplantation, although the duration varies from center to center. In sulfa-allergic patients, alternatives to TMP/SMX include atovaquone, pentamidine, and dapsone. For patients not on TMP/SMX, ciprofloxacin (x 3 to 6 months) has been recommeded as UTI prophylaxis [20].

To prevent surgical wound and abdominal infections, the local perioperative antibacterial prophylaxis should be administered. The prophylactic antibiotic of choice should be determined by the resident flora of the transplanted, the prevalent bacterial flora identified in wound infections and the institutional antibiotic susceptibility pattern [39]. In kidney transplant recipients, the target pathogens include uropathogens and staphylococci; hence either a first-generation cephalosporin or ampicillin/sulbactam is an appropriate prophylactic agent. More recently, it has been suggested that due to the low incidence of surgical site infection observed in the absence of peri-operative antimicrobial prophylaxis, prophylaxis should only be used in higher risk patients (> 65 years of age and/or obese (defined as body mass index > 35)) in order to reduce resistance, adverse events, and cost [40]. Obesity, an established risk factor for wound complications, is often targeted prior to transplant. Interestingly, significant pre-transplant weight loss has also been identified as a risk factor for wound complications, attributed to body contour changes resulting in an unfavorable abdominal panniculus [41].

2.1.5. Treatment of bacterial infection

The antibiotic of choice for the treatment of infection after renal transplantation is largely dependent on the susceptibility of the bacteria identified in the urine, blood, or wound culture, and is very important due to increasing bacterial resisitance to commonly used antimicrobials. Fluoroquinolones, cephalosporins, or penicillins are commonly used to treat UTIs. For infections due to coagulase-negative staphylococci or ampicillin-resistant enterococci, vancomycin is utilized. Critically ill patients require intial broad spectrum antimicrobials, which should then be narrowed as culture results become available. Nephrotoxic agents (such as aminoglycosides) should be avoided whenever possible, relying on effective non-nephrotoxic alternatives instead.

Treatment duration depends on the origin and severity of infection. Wound infections and most UTIs require treatment for 5 to 7days, whereas pyelonephritis usually requires 2 weeks of therapy or longer. Imaging to rule out obstruction or anatomic abnormalities should be considered in cases of recurrent UTIs. In addition, wound infections may require debridement with an adjunctive antibiotic regimen. Patients with neutropenic fever may receive granulocyte colony stimulating growth factors, which have been shown not to increase the risk of acute rejection [5]. Depending on the severity of the infection, reduction in immunosuppression, with close monitoring of graft function, may also play an important role in clearing the infection.

2.2. Fungal infection

Invasive fungal infections are a significant infectious complication among solid-organ transplant recipients and remain a major cause of morbidity and mortality. Among all solid-organ transplant recipients, kidney transplantation is currently associated with the lowest rate of fungal infections, with a one-year cumulative incidence of 1.3% [46]. *Candida, Aspergillus,* and *Cryptococcus* are the most common fungal pathogens in solid-organ

transplantation [42]. The Transplant-Associated Infection Surveillance Network (TRANSNET) reports that leading invasive fungal infections are candidiasis (49%), Cryptococcus (15%), Aspergillosis (14%), and endemic mycoses (10%) [43]. In this report, Pneumocystis represented only 1% of invasive fungal infections, likely demonstrating the effectiveness of prophylactic strategies.

Pneumocystis jiroveci pneumonia (PJP) usually occurs within the first 6 months after transplantation without prophylaxis. Risk factors for PJP include prior CMV infection, underlying pulmonary disease, allograft dysfunction, net state of immunosuppression, allograft rejection, and prolonged neutropenia [44, 45]. Recently, a nosocomial cluster of PJP was reported, spread via exposure in clinic waiting areas [44]. Universal prophylaxis against PJP is recommended for 6 to 12 months after transplant [45].

The most common pathogen is the *Candida* species, mostly *Candida albicans* or less commonly, *Candida glabrata, C. tropicalis, or C. parapsilosis* [43, 46]. Identifying the species of *Candida* is important for choosing appropriate antifungal agents, and *C. glabrata* should be tested for antifungal susceptibility, especially in areas with known resistance or if the infection is not responding to the initial therapy [43]. The majority of these infections occur within the first 2 months after transplantation, and occur as candidemia, UTI, or peritonitis [43]. Asymptomatic candiduria is generally not treated unless the patient is neutropenic or will be undergoing a urologic procedure, while symptomatic candiduria is usually treated [43, 47]. Imaging of the transplant kidney to rule out abscess in the collecting system or presence of fungus ball(s) is also recommended [43, 47]. Fluconazole is the only azole to concentrate in the urine, and so has an important role in the treatment of *Candida* UTI's.

Infections due to endemic fungi typically occur in the mid to late posttransplantation period, although some do occur within 2 months of transplant. Endemic fungal infections are associated with pathogens like *Histoplasma capsulatum*, *Blastomyces dermatitidis,* and *Coccidioides immitis*. For detailed review of the various types of fungal infections in solid organ transplantation, the reader is referred to references [42, 45, 46, 48-51]. Although rare, donor-derived fungal infections are important to consider; recent guidelines outline occurrence and management of such infections [48].

2.2.1. Prevention and treatment of fungal infections

Systemic prophylaxis of fungal infection is generally not required for kidney transplant recipients. Prevention of oral candidiasis is achieved through use of topical nystatin or clotrimazole. Multiple options are available for the treatment of invasive fungal infections in solid-organ transplantation, including amphotericin B (liposomal formulations preferred due to less nephrotoxicity), azole antifungals (fluconazole, itraconazole, voriconazole, posiconazole) and echinocandins (caspofunginm micafungin, anidulafungin). The optimal regimen should be based on antifungal susceptibility testing. Detailed review of these agents is beyond the scope of this chapter, however, a brief discussion of drug-drug interactions between antifungal agents and immunosuppressants is warranted, as well as mention of toxicities of concern in kidney transplant recipients (see Section 2.5).

2.3. Viral infection

Many factors affect the development of viral infection after solid-organ transplantation. These factors include recipient and donor serostatus, recipient comorbidities (eg, diabetes mellitus), immunosuppression regimen, organ(s) transplanted, ischemia-reperfusion injury to graft, and community-acquired infection. Viral infection can be particularly devastating to transplant recipients because of the immunosuppressive properties of the viral pathogens themselves, which may increase the patients' susceptibility to other opportunistic infection (particularly fungal infection), or posttransplant lymphoproliferative disease (PTLD).

2.3.1. Cytomegalovirus

Cytomegalovirus (CMV), a herpesvirus, is the most important viral infection in solid-organ transplantation because of its broad effects on immunocompromised patients [6]. Active infection produces not only signs and symptoms associated with the viral syndrome itself, but also has other widespread effects associated with cytokine-mediated inflammatory response and generation of cross-reactive T cells [52]. These effects may lead to allograft injury and/or acute rejection, systemic immunosuppression from the virus, and EBV-associated PTLD [6]. Risk factors for CMV infection/disease include CMV donor-positive/recipient-negative (D+/R-) serostatus pairs, recent treatment for acute rejection, recent completion of prophylactic antiviral therapy, and rabbit anti-thymocyte globulin induction therapy [53, 54]. In CMV D+/R- pairs, there may be an association between the use of CMV prophylaxis and improved graft survival and lower acute rejection rates [55].

Clinical Manifestations

Differentiation between CMV infection and CMV disease is important when assessing a patient for CMV. A patient with CMV infection has active viral replication in the blood or other body fluids, but does not necessarily experience systemic signs and symptoms such as malaise, fever, and pancytopenia. Patients with CMV disease, however, most commonly have a viral syndrome with fever or have invasive infection that has affected an organ system, such as colitis, hepatitis, or pneumonitis [56].

Diagnosis and Monitoring

CMV serology of the donor and recipient are useful for estimating the recipient's risk of CMV developing after transplantation, but is not useful for diagnosing CMV infection/disease because seroconversion often does not occur until after symptoms are resolved [10, 53, 57]. Rather, methods that quantify the extent of the CMV infection are necessary to make the diagnosis. Two common methods include CMV antigenemia (stain circulating neutrophils for CMV antigen) and CMV DNA polymerase chain reaction (PCR) (quantitative viral load) [58]. A major limitation of antigenemia is the need for sufficient quantities of neutrophils to perform the test, which is often not possible because of the neutropenia caused by the CMV virus itself. Therefore, the CMV viral load is a key diagnostic tool; trends in viral loads are more valuable than individual levels [57]. Viral load assays vary between laboratories, however, and assay standardization is needed. Another

limitation includes the fact that peripheral viral load may be undetectable in patients with invasive CMV disease, particularly when the gastrointestinal tract and lungs are sites of infection. In these cases, biopsy of the infected tissue and/or bronchial alveolar lavage is often necessary to confirm diagnosis [57].

Prevention

Several strategies have been used to prevent and treat CMV. Some centers routinely provide antiviral prophylaxis (called universal prophylaxis) to patients at risk for CMV (particularly D+/R- pairs), whereas others employ preemptive strategies, in which patients are routinely monitored and receive prophylaxis only if laboratory markers become positive. Each method has benefits and drawbacks. Benefits of universal prophylaxis include preventing both CMV and other herpes viruses and lack of need for intensive monitoring. Drawbacks include the risk of developing ganciclovir-resistant CMV (although a small risk), adverse effects of the medications, the fact that late CMV disease may occur despite early prophylaxis (delayed onset), and the fact that the disease may have atypical features.

For preemptive strategies, benefits include decreasing the use of antivirals and their associated adverse effects and costs. However, the logistically demanding monitoring schedule, requirement for strict compliance to the costly surveillance methods, potential to develop CMV disease before detection, and development of drug resistance are disadvantages of preemptive strategies [57]. CMV-related morbidity is also a significant risk when adherence to monitoring guidelines is poor [59]. Drug resistance can occur if ganciclovir is used in a patient with active viral replication, owing to its poor oral bioavailability. A recent prospective randomized trial of pre-emptive therapy versus valganciclovir prophylaxis in CMV serostatus positive kidney transplant recipients found that both CMV infection and CMV disease were significantly higher in the pre-emptive group, in particular for D+/R+ patients [60]. The general consensus is that the highest risk patients (D+/R-) should receive universal prophylaxis [10, 61].

With the introduction of valganciclovir, a prodrug of ganciclovir with superior oral bioavailability, interest has focused on use of this agent to prevent and treat CMV infection and disease. For outpatients, valganciclovir 900 mg per day or ganciclovir 1000 mg three times per day are commonly used to prevent CMV [10]. Pharmacokinetic studies show that oral valganciclovir administration at 450 mg (given once daily) gives exposure that is equivalent to the standard oral regimen of ganciclovir (1 g administered 3 times a day) [62]. The manufacturer-recommended dose of valganciclovir for CMV prophylaxis is 900 mg/day, and this dose appears to be equivalent in efficacy to oral ganciclovir, with an increased incidence of neutropenia compared with ganciclovir [56]. In several studies, researchers have retrospectively evaluated the efficacy of low-dose valganciclovir (450 mg daily) as prophylaxis for CMV in kidney transplant recipients [63]. An analysis comparing 3 months of standard ganciclovir versus low dose valganciclovir in the prophylaxis of CMV in 129 kidney or pancreas transplant recipients revealed a 14% incidence of CMV disease at 1 year after transplantation (10% noninvasive and 4% invasive) [63]. The incidence was similar between patients receiving ganciclovir and valganciclovir, and risk factors for

development of CMV disease included CMV D+/R- serostatus and use of thymoglobulin as part of immunosuppression regimen (incidence 25% in patients receiving thymoglobulin). The same investigators later reported outcomes in 37 kidney or pancreas recipients who received thymoglobulin induction and an extended course (6 months) of CMV prophylaxis with low-dose valganciclovir [64]. The incidence of CMV disease decreased in thymoglobulin-treated patients from 25% to 8% when prophylaxis was extended from 3 months to 6 months.

The duration of CMV prophylaxis also remains controversial; current recommendations suggest a minimum of 3 months of therapy [10]. Several studies have demonstrated a lower incidence of CMV disease after transplantation in patients receiving prophylaxis for 6 months, particularly in patients at highest risk for developing CMV [53, 64-67]. From a pharmacoeconomic perspective, prolonged (200 days vs. 100 days) valganciclovir prophylaxis for high-risk patients (D+/R-) has been shown to be cost-effective [68].

Treatment

Patients with CMV infection/disease should be treated with IV ganciclovir or oral valganciclovir; IV ganciclovir should be used in severe/life-threatening cases, and when gastrointestinal symptoms (such as diarrhea) may limit absorption of valganciclovir [10]. Ganciclovir (IV) is the gold standard for treatment due to the large body of experience with it and its lack of nephrotoxicity, which limits the use of other antiviral agents such as cidofovir and foscarnet. The treatment dose of 5 mg/kg IV every 12 hours must be adjusted for renal function; this adjustment should be done carefully, as subtherapeutic ganciclovir exposure in the setting of high CMV viral load may promote the development of resistance [57]. Because the bone marrow–suppressive effects of ganciclovir may further compound the neutropenia caused by the CMV virus itself, care should be exercised in adjusting the dose of ganciclovir to avoid these effects. Rather, use of white blood cell growth factors may be preferable in order to avoid the subtherapeutic ganciclovir exposure [57]. At a dose of 900 mg, valganciclovir provides exposure similar to that of 5 mg/kg body weight of IV ganciclovir, and can also be administered twice per day for treatment of active CMV infection [10, 62]. Thus, the cost of treating active CMV infection could be substantially lowered by its potential to treat with oral valganciclovir in the outpatient setting, for mild to moderate cases in patients not experiencing significant gastrointestinal symptoms (ie. diarrhea) [10]. Another key component of managing patients with CMV disease includes careful reduction in immunosuppression, taking into consideration patient and organ-specific factors. CMV immunoglobulin may also have an adjunctive role in treatment of severe CMV disease [10, 57].

Close monitoring of viral load is necessary to assess response to therapy; monitoring should begin 1 week after initiation of therapy and treatment should be continued until the viral load has been undetectable for 1 week [57]. The role of secondary prophylaxis after treatment is not clearly defined. When secondary prophylaxis is employed, viral load should be monitored for potential development of resistance and use of valganciclovir may be preferable owing to its superior bioavailability [57]. CMV disease recurs in approximately

15% to 35% of patients. Recurrence is due to incomplete suppression of CMV rather than the development of resistance. Patients at higher risk for recurrence include D+/R- pairs, multisystem CMV disease, those who receive treatment for acute rejection, patients with high viral loads at the time of initial diagnosis of the infection, and those who had a detectable viral load at the end of therapy for the initial infection [57].

Ganciclovir-resistant strains of CMV have developed in recent years, and are attributed to mutation of the UL97 +/- the UL54 gene(s), with the combined mutations leading to a high-level of ganciclovir resistance [10, 69]. Patients at highest risk for developing ganciclovir-resistant CMV include D+/R- pairs, as well as kidney-pancreas transplant recipients [57]. Utilization of pre-emptive strategies in D+/R- patients has been associated with development of GCV-resistance in more than 10% of patients [70]. Treatment of ganciclovir-resistant strains includes high-dose IV GCV, combination therapy with ganciclovir plus foscarnet, and CMV hyperimmunoglobulin [10, 57]. Increasing the ganciclovir dose (up to 10 mg/kg every 12 hours) with careful monitoring for toxic effects may also be useful in these patients [57]. An algorithm for management of ganciclovir resistance can be found in reference [10].

2.3.2. Varicella zoster virus

The adult seroprevalence rate for varicella zoster virus (VZV) in the United States is greater than 90%. Primary varicella infection is a risk for seronegative transplant recipients; adults are more likely to experience severe infection leading to complications such as hepatitis, pneumonitis, and encephalitis. In an analysis of herpes zoster (shingles) infection in the setting of modern immunosuppression, researchers evaluated 869 solid-organ transplants performed between 1994 and 1999, and the incidence of varicella zoster was 7.4% in kidney recipients. Herpes zoster infection occurred at a median of 9.0 months after transplantation and resulted in significant morbidity; 62.7% of cases were within 1 year of transplant. Independent risk factors for infection included induction therapy and antiviral therapy (other than >6 weeks of CMV prophylaxis with acyclovir or ganciclovir) [71].

Clinical Manifestations

Cutaneous scarring, defined as skin disfigurement (scarring or hypopigmentation), occurred in 18.7% of patients with herpes zoster, usually following a dermatomal pattern. Postherpetic neuralgia, defined as pain persisting more than 30 days after rash development, occurred in 42.7% of patients [71]. More serious manifestations of VZV infection may include pneumonitis, hepatitis, or encephalitis. This is especially true in primary infections, where morbidity and mortality may be high.

Diagnosis and Monitoring

Diagnosis of VZV infection typically involves clinical examination of skin lesions. Viral cultures, direct fluorescent antibody assays, or PCR testing may be used to confirm diagnosis when necessary [72].

Prevention

CMV prophylaxis with ganciclovir will most likely prevent VZV, although acyclovir is effective for those patients not receiving ganciclovir [72]. Patients who are VZV seronegative before transplantation should be vaccinated against varicella whenever possible, although pre-transplant administration of the herpes zoster vaccine, Zostavax is not recommended at this time due to a higher live-virus content [72]. The varicella vaccine should not be administered to patients receiving immunosuppressants, because the varicella vaccine is a live, attenuated vaccine that may cause infection in immunocompromised patients. After transplantation, seronegative patients exposed to VZV should receive postexposure prophylaxis, although this is not guaranteed to prevent infection. Postexposure prophylaxis consists of varicella zoster immunoglobulin if the patient arrives for treatment within 96 hours of initial exposure (preferred), or antiviral therapy if that 96-hour window has passed. However, the immunoglobulin preparation is no longer widely available to transplant centers, so IVIG may be utilized [72]. Although some centers have reported administration of the varicella vaccine after liver transplantation with minimal adverse effects [73], others have reported development of infection [74]. Therefore, this practice remains controversial and is not supported by existing guidelines [72].

Treatment

Patients with active, serious VZV infection should be treated with IV acyclovir, whereas less serious infections may be treated with oral acyclovir, valacyclovir, or famciclovir. In rare cases of acyclovir resistance, foscarnet may be used [72].

2.3.3. Herpes simplex virus 1 and 2

Adult seroprevalence rates for herpes simplex virus 1 and 2 in the U.S. are 62% and 22%, respectively. Most infections after transplantation are due to reactivation of latent virus.

Clinical Manifestations

Infection with herpes simplex virus generally is manifested by orolabial lesions or genital/perianal lesions, although more serious systemic infection can result in esophagitis, hepatitis, or pneumonitis.

Diagnosis and Monitoring

Diagnosis of infection with herpes simplex virus 1 or 2 typically involves clinical examination of skin lesions. Culture of scrapings/tissue from lesions may be necessary to confirm diagnosis in some cases, and PCR assays are increasingly being used [75].

Prevention and Treatment

CMV prophylaxis with ganciclovir will most likely prevent HSV; acyclovir is effective for those patients not receiving ganciclovir [59]. HSV infections are usually treated with oral acyclovir, valacyclovir, or famciclovir [75]. In more serious infections, IV acyclovir may be employed, although alternative therapy such as foscarnet may be required in cases of acyclovir resistance [75].

2.3.4. Human herpesvirus 6, 7 and 8

Human herpesvirus (HHV) 6 and 7 are viral pathogens that can cause significant morbidity and mortality in transplant recipients. Although HHV 6 infection has been most commonly reported among stem cell transplant recipients, cases have also been reported in solid-organ transplant recipients [76-78]. As with CMV, HHV 6 and 7 appear to have immunomodulatory effects and may predispose patients to secondary infection. Indeed, the mortality associated with HHV 6 appears to be related primarily to the development of secondary fungal infection [77, 78]. HHV 8 is also known as Kaposi sarcoma–associated herpesvirus because development of Kaposi sarcoma is driven by this virus. The seroprevalence of HHV 8 exhibits geographic variation; it is most common in the Mediterranean, Middle East, and some areas of Africa.

Clinical Manifestations

Transplant recipients with HHV 6 infection commonly have fever, bone marrow suppression, interstitial pneumonitis, and/or encephalitis. In addition, hepatitis and cutaneous rash have also been found in patients infected with HHV 6. Severe cases may progress to aplastic bone marrow and secondary infection with fungal and/or other viral pathogens. Symptoms associated with HHV 7 are not as well documented. Patients with HHV 8 may have cutaneous lesions, fever, and evidence of bone marrow suppression.

Diagnosis and Monitoring

Patients who are HHV 6–negative before transplantation appear to have a higher incidence of infection, although most cases are reactivations because more than 90% of patients are seropositive by adulthood. As with other viral illnesses, quantitative PCR is useful in diagnosis and in monitoring patients with this infection. HHV 8 serostatus of the donor and recipient may be assessed on the basis of geographic location. Patients who are seropositive before transplantation, who are at risk for primary infection, or who have Kaposi sarcoma can then be monitored after transplantation by means of HHV 8 viral loads [79].

Prevention and Treatment

Routine prophylaxis for HHV is not recommended [79]. Symptomatic patients may be treated with ganciclovir, foscarnet, or cidofovir, in combination with immunosuppression reduction [79]. For patients with Kaposi sarcoma, reduction and/or withdrawal of immunosuppression is first-line therapy, and conversion from calcineurin inhibitor therapy to sirolimus is also recommended due to regression of KS lesions after conversion [79]. Surgery, irradiation, and chemotherapy may be required in patients who do not respond to the reduction in immunosuppression.

2.3.5. Epstein Barr virus

EBV is a herpesvirus that infects most people at a young age and causes infectious mononucleosis. In immunocompromised patients, primary EBV infection or reactivation of latent infection can cause PTLD, a feared consequence of immunosuppressive therapy. Risk

factors for the development of early PTLD include EBV seronegativity at the time of transplantation (leaving children at higher risk than adults), type of organ transplanted, type and degree of immunosuppression, CMV donor/recipient mismatch, CMV disease, and lymphocyte depleting antibody induction, while late PTLD may be related to duration of immunosuppression, type of organ transplanted, and older age of the recipient [80]. Kidney transplant recipients are considered low risk for development of PTLD (~1%). PTLD affects the transplant allograft in approximately 30% of cases. Lesions in the central nervous system are the most difficult to treat. In general, early occurrence of PTLD is polyclonal and easier to treat, whereas late PTLD is often monoclonal, and infected B cells may lose CD20 expression, making treatment difficult.

Clinical Manifestations

Signs and symptoms of PTLD may include those of a primary EBV infection/infectious mononucleosis, specifically fever, malaise, and swollen lymph nodes in the neck, tonsils, axilla, and/or groin. In addition, patients may have other nonspecific symptoms, depending on the type of organ transplanted.

Diagnosis and Monitoring

Diagnosis of PTLD is a combination of clinical assessment, blood tests, EBV-related blood tests, radiographic imaging, histology, and other adjunctive tests [80]. Pathological examination of tissue is the gold standard for the diagnosis of PTLD; excisional biopsies are preferred over needle biopsies. No specific staging system exists for PTLD; however, the current recommendation is to use the Ann Arbor staging classification system with Cotswold's modifications, which is used to stage non-Hodgkin lymphoma. Diagnosis is based on morphological classification, origin cell type, presence of EBV, and presence of CD20+ cells [80, 81].

Prevention

Because no definitive methods to prevent PTLD are known, diligent monitoring of high-risk patients is needed; this is done by performing serial EBV PCR. Risk is defined as high in D+/R- pairs, children, and patients receiving high dose and/or intensity immunosuppression [80, 81]. Utilization of ganciclovir/valganciclovir for CMV prophylaxis may give some protection, as ganciclovir has greater in vitro activity against EBV than acyclovir.

Treatment

Unfortunately, controlled trials in the treatment of PTLD are generally lacking. Key strategies for the management of patients with PTLD include reduction in immunosuppression, surgical resection, and local irradiation [80]. Secondary treatments may include antivirals, immunoglobulin, and monoclonal antibodies against B cells [80]. Anti-CD20 antibody (rituximab) is promising as first-line therapy after immunosuppression reduction because of its high specificity for B cells with a low adverse event profile. Cytotoxic chemotherapy (such as CHOP) is often used when first- and second-line therapies fail. Patients with CNS lesions may be treated with local radiotherapy, intrathecal anti-CD20

antibody, and/or interferon α [80]. EBV-specific cytotoxic T lymphocytes (CTL) may also have a role in the treatment of PTLD [82]. Patients may receive another transplant after successful treatment of PTLD; however, careful examination of patient-specific factors must occur.

2.3.6. Adenovirus

A concern mostly in children, adenovirus is a virus with many different serotypes that may cause diverse signs and symptoms during acute illness. Adenovirus is transmitted through respiratory secretions, fecal-oral route, and fomites; donor transmission has also been postulated in several reported cases. Adenovirus infection may occur in transplant recipients of any age; however, complications occur more commonly, and infections may be more severe in children [83].

Clinical Manifestations

Symptomatic disease can vary greatly, ranging from self-limiting febrile illness, to hemorrhagic cystitis or gastroenteritis, to severe infection with necrotizing hepatitis or pneumonia.

Diagnosis and Monitoring

The gold standard for diagnosis of adenovirus is by culture or antigen detection. In patients with invasive disease, tissue specimens can be examined for histology ("smudge cells" signaling cytopathic inclusions; the gold standard) or adenovirus PCR may be performed on the specimen [83].

Prevention and Treatment

No specific preventative measure is available, other than avoiding the spread of the virus via droplet and contact precautions for infected patients [83]. Supportive care, in conjunction with a decrease in immunosuppression is the standard of care for these patients. The use of antiviral agents such as ribavirin, ganciclovir, cidofovir, and respiratory syncytial virus immunoglobulin have been reported [83]. Cidofovir has the best data supporting its use, however its nephrotoxicity is an important concern in renal transplant recipients [83].

2.3.7. Human parvovirus B19

By adulthood, 30% to 60% of people are seropositive for parvovirus B19, an infection that usually is asymptomatic or manifests as a mild illness called erythema infectiosum in school-aged children and is commonly acquired through infected respiratory secretions. Parvovirus infects erythroid precursor cells, causing areticulocytic anemia in patients with severe infection.

Clinical Manifestations

Parvovirus infection develops in approximately 1% to 2% of transplant recipients, resulting in a pure red cell aplasia with a low or absent reticulocyte count. Other manifestations of the infection may include fever, arthralgia, rash, pancytopenia, and hepatitis.

Diagnosis and Monitoring

In transplant recipients, parvovirus B19 immunoglobulin M is a marker for ongoing infection, and parvovirus B19 DNA PCR may also be useful. Both have limitations, however, because transplant recipients may not be able to mount a response, making the serologic findings a less than ideal marker, whereas PCR may remain positive for up to 9 months after the initial infection. Therefore, the best diagnostic tool appears to be a positive PCR in a patient with pure red cell aplasia. Bone marrow biopsy may be considered for patients with signs and symptoms but negative serology and PCR [84].

Prevention and Treatment

No strategies are available to prevent parvovirus B19 infection in transplant recipients, although a vaccine is being developed [84]. The treatment of choice for parvovirus B19 infection is IVIG, although the optimal dosing regimen and duration of therapy are not clear. Current guidelines recommend 400 mg/kg/day for 5 days, possibly in conjunction with immunosuppression reduction [84].

2.3.8. Human papilloma virus

Patients with human papillomavirus (HPV) infection have an increased risk of cervical intraepithelial neoplasia (CIN) and cervical cancer, as well as risk for squamous cell cancers (SCC) of the anus, vulva, vagina, and penis [85]. The role of HPV in skin and oropharyngeal SCC is less clear [85]. The virus, in combination with exposure to ultraviolet radiation and the degree and length of immunosuppression are important factors in the development of cutaneous lesions. Viral warts may progress to these cancers in immunocompromised patients, with HPV DNA being found in 70% to 90% of cutaneous tissue in patients with SCC. Many strains of HPV exist, with HPV 5 and HPV 8 appearing to have a higher prevalence in transplant recipients with skin cancers.

Clinical Manifestations

Infected patients have cutaneous and anogenital warts (verruca vulgaris). Although less common, HPV may also be manifest as a respiratory tract infection.

Diagnosis and Monitoring

Diagnosis is made by examination of cutaneous warts during physical examination. Warts that look suspicious (eg, discolored) should be sampled by biopsy because of the known risk of malignant transformation of these lesions. In addition, suspicious anogenital warts should also be sampled, particularly as these lesions may be clinically indistinguishable from squamous epithelial lesions. Renal transplant candidates and recipients should have a pap smear yearly due to the increased risk of cervical cancer in this population [85]. HPV viral load by PCR is also utilized on clinical specimens.

Prevention

Patients with preexisting lesions should receive treatment before transplantation. An HPV vaccine has been developed, although its role prior to transplantation remains to be

determined. Currently, it is recommended for use pre-transplant in the FDA-approved patient populations [85]. After transplantation, high-risk patients (those with a history of warts, keratoses, skin cancer, or long-term immunosuppression) should be followed up by a dermatologist every 3 to 6 months. Patients must be educated to avoid excessive sun exposure, to wear protective clothing when in the sun, and to use sunscreen to protect them. For those patients (or their partners) with anogenital lesions, sexual transmission should be avoided by abstinence or condoms (although condoms do not provide complete protection).

Treatment

It is recommended that warts causing physical and/or psychological signs or symptoms be treated with cytotoxic agents that destroy the infected epidermis, such as salicylic acid, lactic acid, or cryotherapy. In addition, surgical removal and physical ablation are often employed; a more rare treatment includes stimulation of the local immune response in the infected area [85].

2.3.9. Polyomavirus

Polyomavirus nephropathy (PVN) is a significant cause of morbidity and graft loss in renal transplant recipients, and is described in great detail in another chapter of this textbook.

2.3.10. Hepatitis B

Chronic hepatitis B virus (HBV) infection was traditionally considered a risk factor for poorer patient and graft survival after kidney transplantation [86]. In the more recent era, which is distinguished by the availability of oral anti-viral agents, analysis of OPTN/UNOS data has shown equivalent patient and graft survival in HBV(+) versus HBV(-) kidney transplant recipients [87]. The risk of liver failure does, however, continue to be increased in HBV(+) patients [87].

Diagnosis and Monitoring

HBV(+) patients on anti-viral therapy should be monitored every three months after transplantation, specifically for viral load (HBV DNA) and ALT, both to monitor efficacy as well as assess for development of resistance [88]. In addition, those with cirrhosis should be monitored yearly for development of hepatocellular carcinoma (HCC) via hepatic ultrasound and alpha fetoprotein [88].

Prevention and Treatment

All patients should be vaccinated against HBV, preferably before beginning dialysis due to poorer immune response to the vaccine in dialysis and transplant patients [89]. Re-vaccination should occur when hepatitis B surface antibody titers fall below 10 mIU/mL [88]. Utilization of nucleoside or nucleotide analogues to suppress HBV viral load in HBV-infected kidney transplant recipients has led to reduction in mortality, although development of hepatocellular carcinoma still exists and requires routine monitoring [90]. All HBV surface antigen positive transplant recipients should receive prophylaxis with

tenofovir, entecavir, or lamivudine, although concerns over lamivudine resistance limit its use [88]. Use of interferon therapy after transplant is not recommended due to risk of precipitating rejection [88].

2.3.11. Hepatitis C

Hepatitis C is the leading indication for liver transplantation in the United States, and up to 38% of kidney transplant recipients worldwide have hepatitis C infection [91]. Hepatitis C infection is associated with poorer patient and graft survival after kidney transplantation as compared to Hepatitis C(-) patients, however, outcome after transplant is better than remaining on dialysis [92]. As with hepatitis B, it is important to clear the virus or decrease viral load before transplantation due to risk of rejection with post-transplant interferon.

Monitoring

After transplant, the ALT of HCV(+) patients should be monitored monthly for 6 months, and then every 3 to 6 months thereafter [88].

Treatment

Use of interferon therapy after kidney transplantation is not recommended due to risk of precipitating rejection, and should be used only when benefit clearly outweighs the risk of rejection [88]. This may include patients with fibrosing cholestatic hepatitis or life-threatening vasculitis. The use of newer oral agents for hepatitis C (including telaprevir and boceprevir) is contraindicated in transplant recipients due to lack of research studies [93]. Pharmacokinetic studies conducted in healthy volunteers have demonstrated significant drug interactions between telaprevir and cyclosporine or tacrolimus, which could lead to life-threatening toxicity [93, 94].

2.3.12. Less common but significant viral infections after transplantation

Novel Influenza A (H1N1) is a swine-origin influenza A virus that became a pandemic in 2009. In kidney transplant recipients, H1N1 caused significant morbidity and mortality [95-98], and mortality is higher in transplant recipients compared to the general population [97]. More severe cases develop pneumonia and may require ICU admission and ventilator support. Poorer outcomes are associated with delayed introduction of treatment; oseltamivir has been used to successfully treat transplant recipients with H1N1 [96-98].

West Nile Virus (WNV) is a single-stranded RNA virus of the Flaviviridae family that is transmitted to humans by mosquitoes. Since 1999, an increasing number of cases have occurred in North America. A limited number of severe cases have been reported in solid-organ transplant recipients, causing morbidity and mortality. Compared with the general population, where the infection rate for WNV was 5 per 100,000, the rate in transplant recipients was 200 per 100,000 ($P < .001$) [99]. A seroprevalence study found a 0.25% seroprevalence and a resultant 40% risk of meningoencephalitis in a transplant patient with community acquired WNV [100]. Similar studies of immunocompetent persons estimate the

risk of meningoencephalitis to be less than 1%. Transmission through infected blood transfusion and/or transplanted organ is a risk [101]. Clinical signs and symptoms of infection in transplant recipients included fever, confusion, headache, weakness, encephalitis, and meningitis [99].

Based on the limited number of cases of WNV infection in transplant recipients, it appears that delayed seroconversion due to immunosuppression may occur, leading to delayed diagnosis. Other diagnostic methods such as PCR may be used, although that method is not useful in all patients [99]. Transplant recipients should be educated about the risks of WNV infection, particularly in endemic areas. Patients should be encouraged to use insect repellant and to avoid the outdoors during the periods of dawn and dusk, when mosquitoes are most active. Treatment of WMV in recipients of solid-organ transplants has generally been empiric and supportive. Both interferon and ribavirin have in vitro activity against WNV, but available data are not sufficient to associate use of these agents with clinical outcome. In addition, IVIG may be useful. Reduction or discontinuation of immunosuppression, based on the clinical situation, is most likely important adjunct treatment.

Lymphocytic choriomeningitis virus (LCMV) is a rodent-borne, Old World arenavirus. Four clusters of LCMV infection in solid-organ transplant recipients have been reported, with some cases specifically linked to donor transmission of the virus [102, 103]. Liver function and coagulation abnormalities, transplant organ dysfunction, fever, rash, diarrhea, hyponatremia, thrombocytopenia, hypoxia, and renal failure are manifestations of the infection that develop in transplant recipients of infected organs. The mortality rate is high. LCMV is very rare; no routine screening is performed on organ donors. LCMV antibodies, immunohistochemistry, PCR, and viral culture may be used for diagnosis in suspected cases [102]. Treatment with IV ribavirin, in combination with reduction in immunosuppression, may have been beneficial in the 1 surviving patient of the outbreak described in reference [102].

2.3.13. Vaccination in solid-organ transplant candidates and recipients

Because of the likelihood of poor response to vaccines after transplantation due to inability to mount an optimal effective response, it is very important to have all vaccinations up to date before transplantation, and to carefully consider timing of administration in the post-transplant period [104]. Influenza (inactivated) and pneumococcal vaccines should be given at their recommended schedules after transplantation, in order to confer as much protection to the patient as possible [105]. Household contacts of transplant patients should also receive the inactivated influenza vaccine on an annual basis. Live vaccines should be avoided in transplant recipients, however their household contacts may receive live vaccines if necessary, with the exception of smallpox and oral-poliovirus vaccines [105]. More details about vaccination can be found in other chapters within this book.

2.4. Parasitic infection

Reactivation of latent parasitic infection in previously infected patients or de novo infection by natural means or through the donated organs is of increasing concern in the transplant

community. Multiple factors are contributing to increased incidence, including the presence of transplant centers in endemic areas, donor and/or recipient travel from endemic areas to Western countries for transplant, transplant tourism, immigrants with latent infection, leisure travel by recipients, and use of non-cyclosporine based immune regimens [106]. Parasitic diseases affecting transplant recipients are outlined in Table 1.

Classification	Parasitic Infection	Clinical Presentation in Transplant Recipients	Comments
Protozoa: Non-Intestinal	Toxoplasmosis (*Toxoplasma gondii*)	Brain abscess, chorioretinitis, pneumonitis, disseminated disease	PJP prophylaxis with TMP/SMX covers Toxoplasmosis
	Chagas Disease *Trypanosoma cruzi*	Panniculitis or other subcutaneous involvement; myocarditis and encephalitis less common	Donors from indiginous areas should be tested
	Leishmania (Old World and New World)	Visceral: fever, enlarged spleen, pancytopenia, malabsorption, interstitial pneumonitis	Mortality usually related to bacterial superinfection
	Malaria (*Plasmodium* species)	Fever, hemolysis, thrombocytopenia	Identification of species important for treatment due to resistance patterns
	Babesiosis *(Babesia* species)	Fever, malaise, hemolytic anemia, possible adult respiratory distress syndrome	May be difficult to distinguish babesiosis from malaria; morphology and DNA testing used to distinguish
	Acanthamoeba	Keratitis, granulomatous amoebic encephalitis, pulmonary lesions, cutaneous lesions, sinusitis, disseminated disease	Biopsy diagnosis of cutaneous lesions and cerebrospinal fluid examination essential for diagnosis
Protozoa: Intestinal	*Blastocystis hominis, Cryptosporidium, Cyclospora, Giardia, Isospora belli, Microsporidia*	Gastroenteritis, eosinophilia	Difficult to eradicate; reduction in immunosuppression may be important in clearing infection. Reduce risk by drinking only municipal or bottled water
	Entamoeba histolytica	Amebic colitis, liver abscess; less commonly pulmonary, cardiac, brain involvement	Reduce risk by drinking only municipal or bottled water
Intestinal Nematode	*Strongyloides stercoralis*	Pulmonary involvement, bacterial sepsis/meningitis (Gram negative GI organisms), acute, severe abdominal disease, eosinophilia	Difficult to eradicate; high mortality with disseminated infection

Classification	Parasitic Infection	Clinical Presentation in Transplant Recipients	Comments
Trematodes	Schistosomiasis (*Schistosoma* species)	Abdominal pain, anorexia, diarrhea; hematuria, dysuria, urinary frequency; fibrosis of liver or bladder and ureters	Reduce risk by avoiding fresh water in endemic regions
Cestodes	Echinococcosis *(Echinococcus)*	Liver failure; possible extrahepatic involvement in lungs, brain	May be difficult to distinguish from hepatic malignancy

Table 1. Parasitic diseases affecting transplant recipients

2.5. Drug-drug interactions and toxicities of anti-infective agents

There are a number of clinically significant drug interactions and toxicities that must be considered when treating infection in the transplant population (see Table 2). Drug levels of several of the primary immunosuppressants must therefore be monitored frequently and dose adjustment is needed to achieve the desired level of the immunosuppressant [107]. This is important to remember both when initiating and discontinuing therapy.

Anti-Infective Agent/Class	Drug Interactions or Important Toxicities in the Transplant Population	Additional Information
Azole Antifungals (systemic)	Increase levels of cyclosporine, tacrolimus, sirolimus and everolimus via Cytochrome P450 3A4 inhibition	Empiric dose adjustment of immunosuppressant is recommended when initiating azole therapy
Clotrimazole (topical) [108, 109]	Increase levels of tacrolimus (and possibly others) via Cytochrome P450 3A4 inhibition in the gut	Dose adjustment often necessary
Amphotericin B	Enhanced nephrotoxicity	When therapy needed for invasive fungal infection, liposomal formulations preferred to reduce risk of nephrotoxicity
Aminoglycosides	Enhanced nephrotoxicity	Avoid when possible
Macrolide antibiotics	Increase levels of cyclosporine, tacrolimus, sirolimus and everolimus via Cytochrome P450 3A4 inhibition Effect most pronounced with erythromycin and clarithromycin; more rare with azithromycin	Empiric dose adjustment of immunosuppressant is recommended when initiating macrolide therapy, particularly erythromycin or clarithromycin

Anti-Infective Agent/Class	Drug Interactions or Important Toxicities in the Transplant Population	Additional Information
Rifamycins	Decrease levels of cyclosporine, tacrolimus, sirolimus and everolimus via Cytochrome P450 3A4 induction	Empiric dose adjustment of immunosuppressant is recommended when initiating rifamycin therapy
Ganciclovir, Valganciclovir	Enhanced bone marrow suppression	Monitor WBC and platelet counts
Foscarnet, Cidofovir	Enhanced nephrotoxicity	Avoid when possible

Table 2. Important Drug Interactions and Toxicities with Anti-Infective Agents and Immunosuppressants

3. Malignancy

The net state of immunosuppression also affects the development of post-transplant malignancy. This includes not only *de novo* malignancy, but also recurrence of pre-transplant lesions. As seen in Table 3, a significant number of cancers are related to oncogenic viral infections. The Transplant Cancer Match Study assessed cancer risk in more than 175,000 solid organ transplant recipients, as compared to the general population [97]. It is important to note that this analysis includes only patients transplanted in the U.S., and the importance of biliary tract and bladder cancers due to parasitic infection outside of the U.S. are not represented in the analysis. In addition, non-melanoma skin cancers are not included in the analysis. Overall, transplant recipients had a cancer risk twice that of the general population. For kidney transplant recipients, the standardized incidence ratio for the most common malignancies seen across all transplant recipients regardless of organ was highest for kidney cancer (6.66), non-Hodgkin lymphoma (6.05) and lung cancer (1.46).

Non-melanoma skin cancers are the most common malignancy seen in the organ transplant population, and the incidence of these cancers is 3 to 5 times that of the general population. Although both basal (BCC) and squamous cell carcinoma (SCC) occur, SCC tends to occur more frequently in transplant recipients, as compared to a predominance of BCC in the general population. Both SCC and BCC occur at a younger age when compared to the general population. In addition, SCC tends to be more aggressive in transplant recipients as compared to the course in the general population [110]. This includes an increased number of primary tumors, deep tissue spread, perineural and lymphatic invasion, recurrence, and need for radiation or chemotherapy [110]. Guidelines for the management of transplant patients with SCC were published in 2004 [111]. Recurrent, de novo and donor-transmitted melanoma are also a concern in transplant recipients [112]. Guidelines for proposed reduction in immunosuppression for transplant patients with skin cancers are available [113].

Renal cell carcinoma (RCC) of the native kidney(s) is diagnosed in 0.3% to 4.8% of kidney transplant recipients [114, 115], and in the transplant kidney in approximately 0.2% [116].

Patients with pre-transplant cystic lesions are more likely to develop RCC by three years after transplant compared to those without (2.3% vs. 0.7%, respectively) [115]. Risk factors for developing RCC after transplant have included pre-transplant cystic disease/lesions, male gender, African-American race, older recipients (> 65 years at transplant), longer time on dialysis prior to transplant, older donor age (> 55 years), and treatment of acute rejection within 1 year of transplant [114, 115]. Most cases of RCC have papillary or clear cell histology, and RCC in one kidney is associated with RCC in the contralateral native kidney. Most cases are diagnosed incidentally, are low-grade, and are managed by native nephrectomy. More aggressive tumors may require chemotherapy, minimization or change in immunosuppression, and/or radiation. Interestingly, the mTOR inhibitor everolimus is FDA-approved as second line therapy for advanced RCC, and thus may be a preferred immunosuppressant in this setting.

Historically, post-transplant lymphoproliferative disorder (PTLD) has been a major concern for solid organ transplant recipients. A recent analysis of Scientific Registry of Transplant Recipients (SRTR) data for 156,740 kidney transplant recipients found an incidence of 0.7% at 5 years and 1.4% at 10 years [117]. This analysis, similar to prior reports, showed a clear distinction between early (less than 2 years after transplant) and late-onset (more than 2 years) PTLD. Risk factors for early PTLD on multivariate analysis include age 19 or younger at transplant, non-Hispanic white ethnicity, EBV negative serostatus at transplant, and CMV negative serostatus at transplant, while risk factors for late PTLD include age 19 or younger or 50 years or older at transplant and non-Hispanic white ethnicity. The use of induction therapy, including when the analysis was limited to T cell depleting agents, did not increase the risk of PTLD. In addition to PTLD, elderly transplant recipients are at increased risk for various hematologic malignancies [118]. Treatment of PTLD may include reduction in immunosuppression, surgery, anti-viral therapy, chemotherapy (including immunochemotherapy (rituximab)), and/or radiation.

Infectious Agent	Associated Sites/Types of Cancer
Epstein Barr Virus (EBV)	Non-Hodgkin Lymphoma, Hodgkin Lymphoma, PTLD, Nasopharyngeal
Human Papillomavirus	Cervix, Vulva, Vagina, Penis, Anus, Oropharynx
Hepatitis B and Hepatitis C	Liver
Human Herpesvirus 8 (HHV8)	Kaposi sarcoma
Helicobacter pylori	Stomach

Table 3. Oncogenic Infectious Agents

4. Conclusion

In summary, complications of over-immunosuppression after solid-organ transplantation can lead to significant morbidity and mortality if not promptly diagnosed and treated. However, the growing armamentarium of knowledge, diagnostic tools and therapeutic agents available for the prevention and treatment of these infections and malignancies will continue to improve the quality of care for these patients.

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