Infectious Diseases in Solid-Organ Transplant Recipients

A practical approach

Oriol Manuel
Michael G Ison
Editors

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Part I

General Transplant Infectious Diseases

1 The Epidemiology of Infection in Solid Organ Transplant Recipients: A Practical Timeline

Nicolas J. Mueller and Jay A. Fishman

Abbreviation

CMV Cytomegalovirus

1.1 Definitions and Concepts

The *net state of immunosuppression* is the sum of all factors relevant for the individual risk (Table 1.1) [1, 2]. Attempts to measure the "overall" level of immunosuppression have yielded conflicting results, notably when relying on commercially available assays. Thus, the clinician will need to consider the contribution of various risk factors on an individual patient basis. The most important factor is usually the immunosuppressive therapy. Table 1.2 shows the common associations of immunosuppressive agents and infectious syndromes.

The *environmental or epidemiologic exposures* include the infections present in the donor or recipient at time of transplantation (usually latent infections) and transmittable pathogens found in a health-care setting (nosocomial) or in the community (Table 1.3).

Nosocomial infections are acquired at a health-care institution and are often the result of necessary posttransplant interventions, such as mechanical ventilation,

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Table 1.1 Factors contributing to the "net state of immunosuppression"[a]

• Immunosuppressive therapy: type, temporal sequence, and intensity
• Prior therapies (chemotherapy or antimicrobials)
• Mucocutaneous barrier integrity (catheters, lines, drains)
• Neutropenia, lymphopenia, and hypogammaglobulinemia (often drug-induced)
• Technical complications (graft injury, fluid collections, wounds)
• Underlying immune defects (e.g., genetic polymorphisms, autoimmune disease)
• Metabolic conditions: uremia, malnutrition, diabetes, alcoholism/cirrhosis, and advanced age
• Viral infection (herpesviruses, hepatitis B and C, HIV, RSV, influenza)

[a]From Ref. [3], with permission

Table 1.2 Common associations of immunosuppression and infectious syndromes[a]

Antilymphocyte globulins (lytic depletion):
• T-lymphocytes: activation of latent viruses, fever, and cytokines
• B-lymphocytes: encapsulated bacteria
Plasmapheresis: encapsulated bacteria and line infections
Co-stimulatory blockade: unknown; possible increased risk for EBV/PTLD
Corticosteroids: bacteria, fungi (PCP), hepatitis B, and wound healing
Azathioprine: neutropenia and possibly papillomavirus
Mycophenolate mofetil: early bacterial infection, B-cells, and late CMV
Calcineurin inhibitors: enhanced herpesviral replication, gingival infection, and intracellular pathogens
mTOR inhibitors: wound healing, excess infections in combination with other agents, and idiosyncratic interstitial pneumonitis

[a]From Ref. [3], with permission

Table 1.3 Epidemiologic exposures relevant to transplantation[a,b]

• Virus
– Herpes group (CMV, EBV, HHV6, 7, 8, HSV, VZV)
– Hepatitis viruses (HAV, HBV, HCV, HEV)
– Retroviruses (HIV, HTLV-1 and 2)
– Others: West Nile (WNV), chikungunya, Zika, dengue, lymphocytic choriomeningitis virus, and rabies
• Bacteria
– Gram positive and Gram negative bacteria (*Staphylococcus* species, *Pseudomonas* spp., Enterobacteriaceae, antimicrobial-resistant organisms), *Legionella* spp.
– Mycobacteria (tuberculosis and nontuberculous)
– *Nocardia* species
• Fungus
– *Candida* species
– *Aspergillus* species
– *Cryptococcus* species
– Geographic fungi (*Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitidis*, *Paracoccidioides* species) and opportunistic molds (*Scedosporium*, *agents of* mucormycosis, phaeohyphomycoses)

Table 1.3 (continued)

• Parasites
– *Toxoplasma gondii*
– *Trypanosoma cruzi*
– *Strongyloides stercoralis*
– *Leishmania* species
– *Balamuthia* species
• Nosocomial exposures
– Methicillin-resistant staphylococci
– Antimicrobial-resistant enterococci (vancomycin, linezolid, daptomycin quinupristin-dalfopristin)
– Multidrug-resistant Gram-negative bacilli
– *Clostridium difficile*
– *Aspergillus* species
– *Candida* non-albicans strains
• Community exposures
– Food and water-borne (*Listeria monocytogenes*, *Salmonella* spp., *Cryptosporidium* spp., hepatitis A, *Campylobacter* spp.)
– Respiratory viruses (RSV, influenza, parainfluenza, adenovirus, metapneumovirus)
– Common viruses, often with exposure to children (Coxsackie, Parvovirus)
– Polyomavirus, Papillomavirus
– Atypical respiratory pathogens (*Legionella* spp., *Mycoplasma* spp., *Chlamydia*)
– Geographic fungi and *Cryptococcus*, *Pneumocystis jirovecii*
• Parasites (often distant)
– *Strongyloides stercoralis*
– *Leishmania* species
– *Toxoplasma gondii*
– *Trypanosoma cruzi*
– *Naegleria* spp.

[a]Both known and unrecognized infections from organ and in recipient
[b]From Ref. [3], with permission

intravenous lines, or urinary catheters. The spectrum is similar to those infections observed in critically ill patients undergoing major surgical procedures other than transplantation. Community-acquired respiratory viral infections and *C. difficile* colitis may also be nosocomially acquired. *Postoperative infections* are related to the surgical procedure and are included in the nosocomial infections. However, given the vulnerability of anastomoses between the donor organ and the recipient (e.g., vascular, biliary, tracheal, ureteric) to ischemia or leaks with fluid collections, such infections are common.

Donor-derived infections have a likely or confirmed source in the organ donor and are discussed in detail in Chap. 3 [4, 5].

Opportunistic infections are otherwise uncommon infections in a immunocompetent host. They are responsible for the wide spectrum of unusual pathogens observed in the transplant recipient; the most common may be targeted by antimicrobial prophylaxis.

Fever is considered the hallmark of an infectious process. In immunocompromised patients, fever can be absent in up to 40% of documented infections, while 20% of patients with fever have noninfectious causes (e.g., graft rejection). Clinical presentations are often subtle, despite the presence of advanced infection [6, 7].

1.2 Timetable of Infections

Infections follow a pattern after transplantation based on the immunosuppressive regimen and local epidemiology (Figs. 1.1 and 1.2) [1, 3]. The timetable serves as an instrument to develop a differential diagnosis for a patient suspected of having infection can be used to establish protocols for preventative measures and helps with recognition of unusual patterns of infection related to over-immunosuppression, environmental pressures, or failures of preventive strategies. When applying the timetable to any given patient, it is paramount that individual risk factors be considered. Prophylactic strategies, the net state of immunosuppression, and epidemiologic exposures will all have a great impact and may change the approach considerably. Three periods can be distinguished: the immediate postoperative period from the day of transplantation to 30 days after transplantation, the period from 1 month to approximately 12 months, and the time beyond 1 year after transplantation.

1.3 Period 1: Transplantation to 30 Days

This period is dominated by nosocomial infections, especially surgical site infections. The spectrum of pathogens is similar to that of major surgical procedures in similar anatomic areas and in other critically ill patients. Bacterial infections dominate followed by *Candida* species. A smaller but increasingly recognized group are those suffering donor-derived infection, which generally cause clinical symptoms early after transplantation, often dominated by graft dysfunction or cryptic fevers. Viral infections must be considered among donor-derived infections and unusual pathogens based on the epidemiology of the donor.

Superficial and deep surgical site infections, in some instances caused by anastomotic leaks or organ injury, are responsible for the surgical nosocomial infections, while pneumonia, line infections, and urinary tract infections are common as for other surgical patients. Recognition of nosocomial microbial resistance patterns and unusual hazards (e.g., construction) will guide empiric antimicrobial therapies. Hospital infection prevention measures (e.g., early extubation, decontamination) play a key role in this period.

1.4 Period 2: 1 Month Posttransplant to 12 Months Posttransplant

This phase is the most challenging in terms of spectrum of infections. While some infections are still related to the surgical procedure, pharmacologic immunosuppression is the main determinant of infectious risk and results in opportunistic infections

Fig. 1.1 The timeline of infections following organ transplantation. The pattern of common infections following organ transplantation varies with the net state of immunosuppression and the epidemiology of infectious exposures. Development of disease is delayed, but not eliminated by prophylaxis including vaccinations and antimicrobial agents. Individual risk modified by events including treatment for graft rejection or malignancy. Thickness of line indicates relative risk. Bold type indicates infections potentially preventable by prophylaxis. *PML* progressive multifocal leukoencephalopathy, *PTLD* posttransplant lymphoproliferative disorder. From: Fishman JA. Infection in Organ Transplantation. Am J Transplant. 2017;17(4):856–79

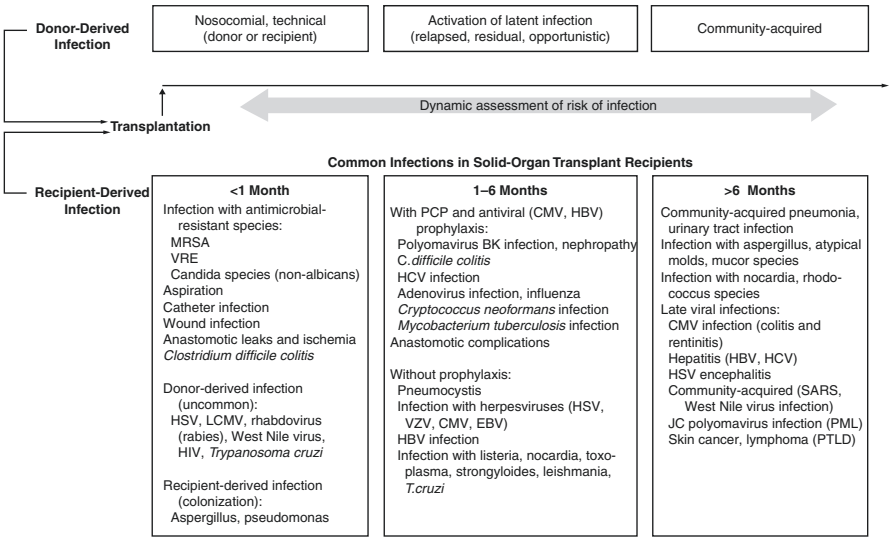

Fig. 1.2 Management of common infections requires continuous assessment of immune function and epidemiologic challenges for each organ recipient. From: Fishman J. N Engl J Med 2007;357:2601–2614

rarely observed in a normal host. Viral infections, resulting from reactivation of latent infections or primary infection through transmission by the graft into a naïve recipient, are an important contributor. Fungal infections include molds, endemic yeasts (e.g., histoplasmosis, paracoccidioidomycosis), and *Cryptococcus*, as well as *Pneumocystis jirovecii* and bacterial, opportunistic infections such as nocardiosis, or tuberculosis, must be included in the differential diagnosis. Parasitic infections, including toxoplasmosis and endemic pathogens (e.g., leishmaniasis, Chagas disease), must be considered.

The pattern observed in terms of involved sites and specific pathogens differs by the organ transplanted: clinically relevant viral respiratory infections will be found most often in lung transplant recipients, while BK virus reactivation is rare outside kidney transplantation. In the pioneering days of transplantations, these infections resulted in a very high morbidity and mortality. The implementation of preventive strategies has changed the patterns of infection considerably. Prevention of herpesviral infections has reduced the incidence not only of cytomegalovirus infections but of other herpesviruses as well. Trimethoprim-sulfamethoxazole-based prophylaxis has made *Pneumocystis* pneumonia and toxoplasmosis uncommon and protect against many additional bacterial infections such as listeriosis and nocardiosis.

1.5 Period 3: Beyond 12 Months

In patients with a satisfactory or good allograft function, immunosuppression can be lowered, and while an increased risk for infections persists compared to a normal host, the spectrum and severity of infection are driven by the community-derived

epidemiologic exposure; a careful clinical history is often the clue. Travel, gardening, or cleaning dusty rooms (barns) may hint to a source of infection and guide the differential diagnosis. Knowledge of the local circulating respiratory viruses including influenza helps in choosing diagnostic tests and empirical therapy, if indicated. Posttransplant lymphoproliferative disorder can mimic an infectious process.

The patients posing the greatest challenge in this period are those in need of a higher- maintenance immunosuppression. Often, acute and chronic rejection results in reduced graft function and necessitates more intense immunosuppression, enhancing the risk for infection. In terms of the differential diagnosis, this subgroup never progresses from the second to the third period. Consequently, the expected spectrum of potential pathogens remains large. Most guidelines limit prevention strategies to the first 6 months to 1 year. In these high-risk patients, however, prolonged prevention, including for herpesviruses, may be beneficial [8].

1.6 Assessment and Management of a Recipient with Suspected Infection

The differential diagnosis of a recipient with a suspected infection will vary according to the time elapsed since transplantation and involves the consideration of the net state of immunosuppression combined with the local epidemiology. A structured approach can never replace experience and intuition but ensures that no relevant aspects are missed. Some principles outlined below may be useful in the daily clinical work:

- In severely ill patients: Start with broader-spectrum empiric therapy based on the individual's known infectious risks (e.g., cytomegalovirus or colonization with antimicrobial-resistant organisms)—de-escalate as soon as possible.
- Consider ongoing prophylactic strategies in the differential diagnosis.
- Invasive means to achieve a specific microbiological diagnosis are often warranted and reduce therapy-related toxicities.
- Always ask: Can immunosuppression be reduced and balanced against the risk for immune reconstitution?
- Consider noninfectious causes (PTLD, rejection).
- Be aware of drug interactions.

1.7 Recent Changes in the Timeline

Since the first description of the timetable, the basic concepts have held up with a high reliability. Three changes merit consideration. First, the implementation of preventive strategies has resulted in a shift of observed infections most notably in period 2, as outlined in Fig. 1.2. Thus, when developing a differential diagnosis, active prophylactic measures need to be considered. Whether prevention has resulted in fewer opportunistic infections remains unclear, but the reduction of cytomegalovirus and *Pneumocystis jirovecii* infections was a major milestone in the care of these patients. Second, one new infection has emerged on a larger

scale: BK virus reactivation or primary infection in the kidney recipient, resulting in the development of new diagnostic tools and prevention measures. Third, donor-derived infections are increasingly recognized, in part due to the development of molecular diagnostic tools.

1.8 Current Challenges and Future Developments

Individualized Risk Assessment Most prevention guidelines will list some individual factors informing the clinician about pathogen-specific risks in defined patient populations. The donor-recipient CMV serological status is such an example. While helpful on an epidemiological level, it does not predict on an individual level which recipient will experience viral reactivation or primary infection. An individualized, reliable risk assessment will likely be a combination of factors, including genetic polymorphisms and pathogen-specific cellular immunity. The goal is to tailor prevention for common pathogens for each individual recipient [9, 10].

Microbiota The interplay between the microbiota, its role as a regulator of the immune system, and the impact of infections, their treatment, and prevention is being intensely explored. In the future, the benefit of any pharmacologic antimicrobial prevention will be weighed against its potential role on microbiota homeostasis, not only its ecologic impact on increasing resistance [11].

Antimicrobial Resistance After the relative success at preventing opportunistic infections, one of the major challenges is the worldwide emergence of antibiotic resistance. Not all geographical areas have been affected similarly, but the pressure affects all transplant programs. Some programs have started to routinely screen donors for the presence of multidrug- resistant organisms and have adapted the perioperative prophylaxis accordingly. The best approach is not known, specifically the nature of colonization of the donor that would constitute a relative or absolute contraindication for transplantation [12, 13].

Emerging Infections Increasing world travel has facilitated the spread of local endemic and epidemic infections, and the shift in vectors, such as mosquitos, will result in some tropical infections becoming endemic in temperate zones. Transplant infectious disease specialists need to track these changes, as the vulnerable transplant population could be affected disproportionally [14].

Microbiological Diagnosis Development of molecular assays has changed the diagnosis and management of viral infections including PTLD. The need for invasive diagnosis (e.g., biopsies to differentiate BK nephropathy from graft rejection or for fungal pneumonia) may be reduced, and the demonstration of antimicrobial resistance documented with further advances in next-generation sequencing technologies.

1.9 Conclusion

The prevention and treatment of infection remains a key component of successful organ transplantation. Infection often occurs without common signs or symptoms of infection. Specific microbiological diagnosis is required to optimize antimicrobial therapy and to avoid drug toxicities. The timeline for infectious risk incorporates considerations of the recipient's epidemiologic exposures and immunosuppression. However, management of transplant recipients will increasingly depend on molecular diagnostic tools, assays of pathogen-specific immune function, and risk stratification based on genetic polymorphisms controlling immune function. Emerging infections continue to challenge the transplant practitioner. New approaches will support the individualization of transplant care.

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Risk Assessment of Infections in SOT Recipients

2

Mario Fernández-Ruiz and Nicole M. Theodoropoulos

2.1 Introduction

When evaluating a solid organ transplant (SOT) recipient for infection, there are a large number of factors that should be considered. Since these patients are immunosuppressed, they often do not express the same signs and symptoms as a fully immune competent host. For instance, pulmonary infections may not present with cough or shortness of breath. Often, patients may not have fever or leukocytosis with infection. Skin and soft tissue infections may not have all the typical signs of erythema, induration, tenderness, and warmth.

On the other hand, the occurrence of certain opportunistic infections, especially those due to polyomaviruses or herpesviruses, may act as an indicator that the patient is over immunosuppressed. The functional impact on the host's response of the most commonly used immunosuppressive drugs is quite heterogeneous across patients. Unfortunately, there is no gold standard to assessing how immunosuppressed a given patient is. The amount of time that has elapsed since the transplant surgery is also critical in assessing the types of infections a patient is most at risk for. Usually, the longer the time from transplant, the less immunosuppressed a SOT recipient is, but this is not the case in patients suffering from graft rejection episodes requiring enhanced immunosuppression. Surgical complications and anatomical alterations from surgery need to be considered. Making a diagnosis, instead of empirically treating, is

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critically important in post-transplant patients, as the differential diagnoses may be broad. Invasive procedures and biopsies are often necessary to narrow on a definitive diagnosis.

2.2 Time from Transplant

Since many organ transplant recipients receive induction therapy at the time of transplant, their immunosuppression is often at its peak within a month from transplant. The deleterious effects of these induction therapies—specifically those including T-cell-depleting agents (e.g., polyclonal antithymocyte globulins or the anti-CD52 monoclonal antibody alemtuzumab)—on the cell-mediated immunity have been reported to last up to 1–2 years post-transplant [1, 2]. The more time that passes from transplant, the lower the risk for rejection and often maintenance immunosuppression medications are tapered.

As discussed in Chap. 1, early infections (i.e., those occurring within the first post-transplant month) are typically related to surgery or are donor-derived. Sometimes these events are related to an infection already active before the transplant procedure. The intermediate period (i.e., months 1 through 6 post-transplant) tends to be the time of highest immunosuppression when most opportunistic infections are seen. The typical timeline of infections is altered by the use of antimicrobial prophylaxis and by periods of augmented immunosuppression [3, 4]. Donor-derived infections usually present early after transplant but can be detected up to 1 or more years post-transplant in some cases. Any unknown infection within 6-month post-transplant should involve a look at donor factors and a review of the other recipients of organs from the donor.

2.3 Pre-transplant Recipient Factors

When evaluating a post-transplant patient for infection early after transplant, a review of their pre-transplant history is important, especially noting any history of infections or colonization with fungi or drug-resistant organisms, their pre-transplant serologies, vaccination status, and history of comorbidities. Patients with a history of uncontrolled diabetes mellitus, autoimmune disease or splenectomy, or chronic malnutrition have a unique increased risk for infection [3]. Special evaluation of issues with previous infection or colonization of the system requiring transplant is important. For example, many lung transplant recipients will have prior respiratory infections or colonization and will, therefore, be at risk for recurrence of these infections post-transplant, especially in the case of cystic fibrosis patients.

2.3.1 Donor Factors

Donor infectious disease screening test results need to be reviewed. Most providers understand that recipients that are seronegative for cytomegalovirus (CMV) or

Epstein-Barr virus (EBV) who receive a seropositive donor organ are at high risk for infectious complications from these viruses. However, the impact of donor/recipient serological mismatch for other pathogens such as *Toxoplasma gondii* or the remaining herpesviruses is less characterized. For instance, toxoplasmosis has been reported to be transmitted from donor to recipient after heart transplantation but also occasionally in other transplant populations [5–7].

Additionally, some organ procurement organizations screen deceased donors for West Nile virus, human T-lymphotropic virus-1/2, *Strongyloides stercoralis*, and Chagas (*Trypanosoma cruzi*) antibodies [8]. These test results need to be interpreted and acted on by the recipient transplant teams when appropriate. Donor blood, urine, and sputum are sent for culture at the time of procurement, and results of these cultures are reported several days later. These should be checked as a routine but also in the case of evaluation of a recipient for an early post-transplant infection. Detailed discussion about donor-derived infections will be included in Chap. 3.

2.3.2 Surgical Factors

With the transplant surgery, many details need to be understood by the physicians taking care of the transplant recipient as they can increase risk of infection. The type of anastomosis is essential to understand [9]. Anastomoses that involve bowel place the patient at risk for leakage and peritonitis. Some centers perform pancreas transplants with vesicular anastomoses, and this increases the risk of cystitis. Lung transplant patients are at risk for ischemia at the site of their tracheal anastomosis, and this can increase the risk of fungal and bacterial infections at this site.

Intra-abdominal surgeries are sometimes complicated by splenic injury and subsequent splenectomies. This will increase the risk of severe infections with encapsulated bacteria in the recipient. Other factors that will increase the risk of infection, especially fungal infection in liver transplant recipients, are return to the operating room, need for renal replacement therapy, and large intraoperational volume blood loss [10, 11].

Stents are sometimes placed in the ureter or biliary system in kidney and liver transplant operations, respectively. These foreign bodies need to be assessed and possibly removed earlier than planned when infections arise in these areas post-transplant.

2.4 Post-transplant Factors

In addition to pre-transplant and surgery-related factors, the susceptibility to infection among SOT recipients is modulated by a number of post-transplant variables that must be taken into account in the risk assessment process. Of note, most of them have a dynamic behavior that justifies continuous monitoring throughout the post-transplant period (in particular during the first 12 months).

2.4.1 Community and Healthcare-Associated Exposures

Causative agents of post-transplant infection may be endogenous in nature (posing the risk of reactivation of a latent infection), derived from the donor or the preservation fluid and transmitted through the graft itself or acquired from an exogenous source (through environmental, vector, or human-to-human exposure). Overall, the latter group represents the most usual mechanism of infection during the entire life span of SOT recipients.

Environmental pathogens to which these patients are particularly susceptible comprise of bacteria (*Pseudomonas aeruginosa*, *Legionella* spp.) and both ubiquitous (e.g., *Aspergillus* spp., *Cryptococcus* spp.) and geographically restricted fungi (e.g., *Histoplasma capsulatum*, *Blastomyces dermatitidis*, or *Coccidioides immitis*) [12, 13]. Gardening activities and exposure to potting mixes and compost-derived products are associated with infections due to *L. longbeachae* and dematiaceous (dark-pigmented) fungi [14, 15]. *Listeria monocytogenes* constitutes the most relevant foodborne pathogen in the SOT population [16], although *Salmonella* spp., *Vibrio* spp., or *Cryptosporidium* spp. must be also borne in mind [17]. The incidence of vector-borne infection may be theoretically considered comparable to that of the immunocompetent host. Nevertheless, it has been reported that post-transplant immunosuppression contributes to increase the severity of certain diseases such as babesiosis, ehrlichiosis, or rickettsiosis. Human-to-human transmission can result from direct contact with an infected person or indirectly through an intermediate object. *Mycobacterium tuberculosis* and respiratory viruses (e.g., influenza virus, adenoviruses, or respiratory syncytial virus) are relevant pathogens transmitted from infected individuals, usually but not exclusively in the community setting. Varicella-zoster virus (VZV) is also transmitted by direct contact, droplets or aerosols from vesicular lesions, or respiratory tract secretions.

Healthcare-associated exposure deserves particular attention, since SOT recipients usually have longer hospital and ICU stays, have more requirements for invasive diagnostic and therapeutic procedures, and are more commonly exposed to broad-spectrum antibiotics than other patient groups. Thus, the incidence of healthcare-associated and nosocomial bacterial infection is increased, as is the causative role of multidrug (MDR) Gram-negative bacilli (such as extended-spectrum β-lactamases [ESBL]-producing or carbapenem-resistant *Enterobacteriaceae*), methicillin-resistant *Staphylococcus aureus*, or vancomycin-resistant *Enterococcus*. The frequent use of indwelling devices (e.g., intravascular or urinary catheters or biliary stents) poses an additional risk of biofilm-associated infections. Antibiotic exposure and other factors (e.g., use of proton pump inhibitors or post-transplant hypogammaglobulinemia) explain the particular susceptibility of SOT recipients to *Clostridium difficile* infection, which may entail particularly deleterious effects on graft outcome [17].

2.4.2 Net State of Immunosuppression

Coined by Fishman, the concept of "net state of immunosuppression" refers to the additive measure of factors contributing to the individual susceptibility to infection

Table 2.1 Factors contributing to the "net state of immunosuppression" in SOT recipients (modified from Fishman [18])

Induction therapy (use of T-cell-depleting agents, cumulative dose)
Maintenance immunosuppressive therapy (regimen type, temporal sequence, dose, duration)
Prior immunosuppressive (e.g., chemotherapy) or antimicrobial therapies
Pre-transplant underlying immunodeficiency (e.g., adrenal insufficiency, systemic lupus, complement deficiencies)
Peri-transplant life-support procedures (e.g., vasoactive drugs, renal replacement therapy, invasive mechanical ventilation, ECMO)
Administration of blood-derived products
Disruption of mucocutaneous barrier (e.g., intravenous and urinary catheters, surgical procedures)
Metabolic conditions (e.g., uremia, malnutrition, diabetes, alcoholism, cirrhosis, vitamin D deficiency)
Cytopenias (drug-induced neutropenia or lymphopenia)[a]
Post-transplant de novo hypogammaglobulinemia
Chronic or latent viral infections (CMV, hepatitis B and C, EBV)

CMV cytomegalovirus, *EBV* Epstein-Barr virus, *ECMO* extracorporeal membrane oxygenation
[a]Typically due to mycophenolate mofetil, azathioprine, (val)ganciclovir, or trimethoprim-sulfamethoxazole

in each SOT recipient [18]. It results from the combination of a number of factors, including the nature, dose, and duration of immunosuppressive therapy, the use of invasive life-support techniques, the evolution of graft function, or the deleterious effect on the host's immune response of chronic or latent viral infections, among others (Table 2.1). In addition, the surgical issues related to the transplant procedure contribute to fluid leaks (blood, lymph, urine) and collections, as well as devitalized tissues at the surgical site.

Due to its multifaceted nature and dynamic course, the measurement of the net state of immunosuppression constitutes a clinical and methodological challenge, and it is unlikely that a single biomarker could accurately account for the multiplicity of immune and nonimmune factors involved. The ultimate would be to define a quantitative measure conceptually similar to the area under the curve, which would encompass the multiple contributing variables at a given point. At the present time, therapeutic drug monitoring (TDM) of immunosuppressive agents constitutes the most widely used approach to the immune status in SOT recipients. However, TDM is limited by its unidimensional nature, which does not take into account the synergistic effect of multidrug regimens or the impact of induction therapies with monoclonal or polyclonal antibodies, resulting in a relatively poor correlation with clinical events.

2.4.3 Strategies for Immune Monitoring

From a clinical perspective, the strategies for the immune monitoring in the setting of SOT may be categorized into nonpathogen-specific or pathogen-specific [19]. The first of these approaches evaluates the functionality of a given arm of

the immune system by means of assays (or biological parameters) with no antigen specificity. The nature of the biomarker used, in turn, may be quantitative (e.g., concentration of serum immunoglobulins or complement factors) or provide a functional assessment (e.g., intra-lymphocytic release of adenosine triphosphate [ATP] upon stimulation with phytohemagglutinin [PHA]) (Table 2.2). On the contrary, the pathogen-specific immune monitoring strategies are based on antigen-specific assays that estimate the magnitude and functionality of adaptive immune responses generated by T-cells or B-cells against a defined pathogen. Most of them measure the production of Th_1 effector cytokines (usually interferon [IFN]-γ) after stimulation with a known viral antigen (individual peptide, peptide library, whole virus lysate, or infected dendritic cells). Although there have been progresses in the assessment of specific immunity against VZV, EBV, or polyomavirus BK, the only currently approved assays for clinical use are aimed at measuring CMV-specific cell-mediated immune responses (Table 2.3) [20]. There are different clinical scenarios in which this approach has been clinically explored and that would constitute preferential applications of CMV-specific immune monitoring (Table 2.4) [21]. However, interventional studies based on these nonpathogen-specific or pathogen-specific immune assays are still scarce [22].

2.4.4 Antimicrobial Prophylaxis

As expected, the administration of antimicrobial prophylaxis modulates the incidence and timing of infectious complications in SOT recipients and must be taken into account in the risk assessment. The high efficacy exhibited by certain regimens, such as trimethoprim-sulfamethoxazole for *Pneumocystis jiroveci* pneumonia (PCP) or (val)ganciclovir for CMV, renders very unlikely the occurrence of breakthrough infection while on prophylaxis and modifies the conventional scheme proposed for infection according to the post-transplant period (early, intermediate, and late). Therefore, the period at risk would be displaced to a later phase, once prophylaxis has been discontinued, posing the potential for delayed diagnosis due to low clinical suspicion or diminished awareness [23]. It should be also noted that the impact of some prophylactic strategies is not limited to the primarily targeted pathogen. For instance, anti-CMV prophylaxis with (val)ganciclovir has been proven to be effective in preventing herpes simplex virus (HSV) and VZV reactivation [24], whereas the use of trimethoprim-sulfamethoxazole prophylaxis reduces, in addition to PCP, the incidence of listeriosis, urinary tract infection (UTI), or staphylococcal infection (although appears to have minor effect on the risk of nocardiosis). On the other hand, caveats of current prophylaxis practices include the development of atypical forms of disease (e.g., extrapulmonary *Pneumocystis* infection in patients receiving inhaled pentamidine) or the emergence of antimicrobial resistance (e.g., quinolone-resistant uropathogens or azole-resistant *Aspergillus calidoustus* associated with the widespread use of ciprofloxacin and voriconazole prophylaxis, respectively [25, 26]).

Table 2.2 Summary of methods for nonpathogen-specific immune monitoring (modified from Fernández-Ruiz et al. [19])

Characteristic	Serum immunoglobulins	Serum complement factors	Peripheral blood lymphocyte subpopulations	Soluble CD30	EBV or TTV viremia	iATP in $CD4^+$ T-cells	QuantiFERON-monitor
Required sample	Serum	Serum	Whole blood	Serum	Whole blood, PBMCs, or serum	Whole blood	Whole blood
Assay	Nephelometry	Nephelometry or ELISA (C3, C4, MBL)	Flow cytometry	ELISA	Quantitative PCR	Quantification of iATP release in PHA-stimulated $CD4^+$ T-cells	Quantification of IFN-γ release upon stimulation with anti-CD3 and R848
Functional analysis	No	No	No	Yes	Yes	Yes	Yes
Advantages	Economical and easy to perform. Potential for replacement therapy with IVIG	Economical and easy to perform. Potential for genotyping of *mbl2* gene variants	Easy to perform (automatized methods)	Easy to perform. Commercial assay. Low volume (25 μL) of serum required	Comprehensive assessment of the T-cell response	Only FDA-approved commercial assay (ImmuKnow® assay, Cylex, Columbia, MD). Highly standardized. Large volume of studies	Joint assessment of both innate and adaptive immunity. Commercial test (QuantiFERON-Monitor®; Qiagen, Hilden, Germany)
Disadvantages	Lack of standardized cutoff values. No information on the functionality of the humoral response	Lack of standardized cutoff values. No information on the functionality of the complement system	Lack of standardized cutoff values. No information on the functionality of the cellular response	Only few studies on predicting infection with discordant findings	Only preliminary studies. Lack of technical standardization. Potentially biased by antiviral prophylaxis (EBV)	Only modest PPV and NPV in studies to date. Relatively high cost. Potentially biased by sample storage time	Only preliminary studies

EBV Epstein-Barr virus, *ELISA* enzyme-linked immunosorbent assay, *FDA* Food and Drug Administration, *iATP* intracellular adenosine triphosphate, *IFN-γ* interferon γ, *IVIG* intravenous immunoglobulins, *MBL* mannose-binding lectin, *NPV* negative predictive value, *PBMCs* peripheral blood mononuclear cells, *PCR* polymerase chain reaction, *PHA* phytohemagglutinin, *PPV* positive predictive value, *TTV* Torque Teno virus

Table 2.3 Summary of methods for monitoring of CMV-specific T-cell-mediated immune response (modified from Fernández-Ruiz et al. [19])

Characteristic	MHC-tetramer staining	Intracellular cytokine staining	ELISpot	QuantiFERON-CMV
Required sample (volume)	PBMCs (0.5–1 mL)	PBMCs or whole blood (1–2 mL)	PBMCs (10 mL)	Whole blood (3–5 mL)
Turnaround time	1–2 h	8–10 h	24–48 h	24 h
Antigen	Individual peptide (pp65, IE-1, pp50)	Individual peptide/peptide library/whole virus lysate/ CMV (VR-1814)-infected immature dendritic cells	Individual peptide/peptide library/whole virus lysate/ CMV (VR-1814)-infected immature dendritic cells	Pool of 22 different peptides mapped within pp65, pp50, IE-1, IE-2, and gB
Functional analysis	No (unless associated with intracellular cytokine staining)	Yes	Yes	Yes
Phenotypic characterization	Yes	Yes	No	No
Differentiation between $CD8^+$ and $CD4^+$ responses	Yes	Yes	No	No (detects mostly $CD8^+$ T-cells)
Required knowledge on epitope	Yes	No	No	No
Required knowledge on individual HLA-type	Yes	No	No	No
Commercially available test	CE-approved test recently commercialized (Dextramer CMV® Kit; Immudex ApS, Copenhagen, Denmark)	No	CE-approved commercialized (T-Track CMV®; Lophius Biosciences, Regensburg, Germany)	CE-approved test with increasing clinical experience (QuantiFERON-CMV®; Qiagen, Hilden, Germany)

Table 2.3 (continued)

Characteristic	MHC-tetramer staining	Intracellular cytokine staining	ELISpot	QuantiFERON-CMV
Advantages	High specificity. Short turnaround time	Gold standard. Most existing literature based on this technique. Potential for freeze PBMCs and ship to reference laboratory for testing	Potential for freeze PBMCs and ship to reference laboratory for testing	Simple to perform and highly standardized
Limitations	Labor intensive. Lack of technical standardization. Need for purified PBMCs and access to a flow cytometer	Labor intensive. Lack of technical standardization. No commercial test. Need for access to flow cytometer	Lack of technical standardization. No defined cutoff values. Need for purified PBMCs and access to an ELISpot reader. No differentiation between $CD8^+$ and $CD4^+$ responses	Not differentiation between $CD8^+$ and $CD4^+$ T-cells. Sensitive to lymphopenia (high rate of indeterminate results in patients treated with ATG). Limited to widespread HLA types

ATG antithymocyte globulin, *CE Conformité Européenne*, *CMV* cytomegalovirus, *ELISpot* enzyme-linked immunosorbent spot assay, *HLA* human leukocyte antigen, *MHC* major histocompatibility complex, *PBMCs* peripheral blood mononuclear cells

2.4.5 Antirejection Therapy

The treatment for acute graft rejection may substantially modify the expected timetable of post-transplant infection, since it augments the overall amount of immunosuppression over a short period of time. In addition to the increase in the daily dose of those drugs contained in the maintenance immunosuppression regimen, antirejection therapy usually comprises the administration of steroid boluses, T-cell-depleting agents (e.g., polyclonal antithymocyte globulins) or, in the case of antibody-mediated rejection, agents targeting the B-cell (rituximab). These therapies are frequently associated with the development of lymphopenia (mostly affecting $CD4^+$ T-cell counts) and hypogammaglobulinemia. Recent developments in the approach to steroid-resistant forms of antibody-mediated rejection also include the use of eculizumab (a recombinant humanized monoclonal antibody that targets complement protein C5 and prevents the formation of the terminal membrane attack complex)

Table 2.4 Scenarios with available clinical information supporting the monitoring of CMV-specific T-cell-mediated immune response after SOT (modified from Fernández-Ruiz et al. [19])

Clinical scenario	Predicted event	Monitoring method	Proposed intervention
High-risk patients (D^+/R^-, T-cell-depleting antibodies, lung transplantation) during antiviral prophylaxis	Late-onset disease[a]	QuantiFERON-CMV, ELISpot	Prolong antiviral prophylaxis or close monitoring for viremia if inadequate response
High-risk patients (D^+/R^-) after discontinuing antiviral prophylaxis	Late-onset disease[a]	QuantiFERON-CMV	Prolong antiviral prophylaxis or close monitoring for viremia if inadequate response
Pre-transplant assessment in intermediate-risk patients (R^+ with no other factors)	Post-transplant viremia and/or disease	QuantiFERON-CMV, ELISpot	Initiate antiviral prophylaxis in patients with inadequate response
Intermediate-risk patients (R^+) on preemptive therapy with no concurrent viremia	Subsequent viremia and/or disease	ICS, QuantiFERON-CMV, ELISpot, MHC-tetramer staining	Reduce the frequency and/or discontinue monitoring of viremia if adequate response
Intermediate-risk patients (R^+) on preemptive therapy with asymptomatic viremia	Spontaneous clearance	QuantiFERON-CMV	Withhold antiviral therapy if adequate response
Active CMV infection or disease after discontinuation of antiviral treatment	Post-treatment relapse	ICS	Initiate secondary prophylaxis if inadequate response

CMV cytomegalovirus, *ELISpot* enzyme-linked immunosorbent spot assay, *ICS* intracellular cytokine staining, *MHC* major histocompatibility complex

[a]Refers to the occurrence of CMV disease after discontinuing antiviral prophylaxis with (val) ganciclovir

and bortezomib (a proteasome inhibitor), which increase the risk of neisserial infection and HSV and VZV reactivation, respectively. It should be noted the late-onset rejection usually takes place once antimicrobial prophylaxis has been discontinued, thus rendering the patient particularly susceptible to opportunistic infection [27].

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3 Pre- and Peri-transplant Period: Screening and Treatment of Infections in the Pretransplant Period, Donor-Derived Infection

Christian Garzoni and Daniel R. Kaul

3.1 Introduction

Optimal donor and recipient screening and selection must minimize the risk of disease transmission from donor to recipient and avoid unnecessary rejection of uninfected donors due to false-positive testing. False-positive tests become more likely when applied universally to a population at low risk of the tested infection. Risk mitigation relies on more than laboratory testing, and a comprehensive strategy is ideally based on three aspects:

- Donor medical, social, and epidemiological history
- Physical and radiological donor examination
- Microbiological testing

A previously proposed risk grading system for both donor and potential recipient factors classified the risk of donor-derived infection into one of five categories globally [1] (modified from Len and Garzoni, with permission [2]:

- Unacceptable risk includes absolute contraindication, with the exception of some lifesaving transplantation procedures in the absence of other therapeutic options on a case-by-case basis.

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- Increased but acceptable risk includes cases where transmissible microorganisms or diseases are identified during the evaluation process of the donor, but organ utilization is justified by the specific health situation of the recipient or the severity of its clinical condition.
- Calculated risk includes all cases where, even in the presence of transmissible diseases, transplantation is allowed for recipients with the same disease or with a protective serological status, in cases with broad-spectrum antibiotic therapy of a minimum duration (24 h) and those with documented bacteremia who have started targeted antibiotic therapy.
- Not assessable risk includes cases where the evaluation process does not allow an appropriate risk assessment for transmissible diseases.
- Standard risk includes cases where the evaluation process did not identify a transmissible disease.

Recently, both the European and the US approaches are abandoning this "grading system," and donors are classified using a dichotomous system:

– Standard risk donor: donor with no evidence of increased disease transmission risk beyond the average population-adjusted risk for undetectable disease.
– Nonstandard or increased risk donor: donor presents an increased risk for disease transmission beyond the average population-adjusted risk for undetectable diseases.

In the case of the nonstandard risk donor, an individualized risk-benefit analysis is needed to decide if transplantation of a given organ into a given recipient is justifiable. In this circumstance, informed consent of the recipient is mandatory, and all reasonable strategies for risk reduction should be employed.

This chapter will discuss mandated screening protocols for donor-derived infection in both the USA and Europe, as well as discuss potential screening for geographically and seasonally limited diseases in both deceased and living donors. Further, we will discuss important selected potential donor findings (either on screening or clinically) and discuss treatment intended to mitigate risk and help readers classify into the categories described above.

3.2 Definitions and Epidemiology

Expected donor-derived disease occurs frequently, with Epstein-Barr virus (EBV) and cytomegalovirus (CMV) being the most common pathogens, and defined management strategies are employed. Unexpected donor-derived disease transmission, the focus of this chapter, is rare complicating less than 1% of transplants [3]. Outcomes can be poor, with mortality rates of up to 25% in affected recipients [3]. In a 10-year review of donor-derived infections reported to the US Organ Procurement and Transplantation Network (OPTN) and Disease Transmission Advisory Committee (DTAC), which manages a required but passive reporting system, viral

infections accounted for 24% of infected recipients, bacteria 19%, mycobacteria 2.4%, fungus 16%, and parasites 12%. The remaining donor-transmitted diseases—malignancies and other non-infectious conditions—accounted for 34% of infected recipients [3]. Epidemiology will vary from region to region based on screening practices and the prevalence in the donor population of transmissible infection. For example, the transmission of intermediate stage Chagas disease would be much more likely in South America than in Europe, and cases of donor-derived infection with West Nile virus (WNV) would be seasonally limited. Most disease transmissions are caused by infections that may be difficult to screen for or recognized in the infected donor, including rabies virus, WNV, lymphocytic choriomeningitis virus, tick-borne encephalitis, as well as parasitic pathogens such as *Balamuthia mandrillaris*.

3.3 Timelines

In general, most donor-derived infections cause symptoms early after transplantation. In one report, 67% developed symptoms within 30 days of transplantation and 88% within 90 days [4]. Bacterial infections are almost always recognized within 30 days and rarely become apparent after 45 days. Nonetheless, some pathogens, particularly those with a long clinical latency, may present months after transplantation, including *M. tuberculosis*, *Strongyloides*, *Toxoplasma*, *Balamuthia*, *Histoplasma*, human immunodeficiency virus (HIV), viral hepatitis, *Microsporidium*, and rabies [5]. Early recognition and notification is critical to allow preventative measures to be instituted to protect other recipients of the source donor.

3.4 Diagnosis and Screening

3.4.1 Clinical Screening

In addition to the required and targeted screening tests discussed above, careful clinical screening is essential to identify donor risk factors for infection with a transmissible pathogen. For deceased donors, the cause of death should be reviewed to determine if an unidentified but transmissible pathogen may be present. For example, a number or clusters of potentially fatal donor-derived disease have involved donors with meningoencephalitis of unknown etiology. Transmitted pathogens have included *Balamuthia mandrillaris*, *Cryptococcus neoformans*, and lymphocytic choriomeningitis virus [6]. Generally, a potential donor with meningoencephalitis of unknown cause should be rejected. In addition to reviewing the cause of death, other clinical information should be considered. For example, the presence of multidrug-resistant organism in certain circumstances (e.g., sputum of a lung transplant donor, blood of any organ donor, urine of a kidney donor) may be transmitted to the recipient, and careful management strategies are required to mitigate risk.

3.4.2 Required Donor Laboratory Screening

Required screening strategies differ slightly between the USA and different European countries. In the USA, the OPTN sets required minimum standards for screening (Table 3.1). Further, the Public Health Service (PHS) classifies some donors as increased risk for undetected infection with HIV, hepatitis B, or hepatitis C based on behaviors or other exposures that put the patient at risk for recent or "window period" infection with the aforementioned blood-borne viruses (Table 3.2) [7]. In addition to the required serologic and nucleic acid testing (NAT) for hepatitis C, these donors must undergo NAT or antigen-antibody combination testing for HIV. As a practical matter, nearly all donors in the USA are tested by NAT for HIV, hepatitis C, and hepatitis B. The NAT window, or "eclipse," period, where tests may be negative but transmission of virus possible, is about 5–10 days for HIV, 6–9 days for HCV, and 20–26 days for HBV. Up to 25% of donors in the USA are identified as increased risk donors, but the risk of window period infection is likely less than 1%, and a thoughtful informed consent process is necessary to ensure that potential recipients understand the meaning of increased risk donor and of the generally low risk associated with these donors [8, 9].

Table 3.1 Routine donor screening tests (living and deceased)

Condition	Test	Comment
Human immunodeficiency virus	Antibody p24 or NAT	HIV+ donors may be eligible for donation to HIV + recipients NAT reduces window period to 5–10 days
Hepatitis C	Antibody and NAT	HCV+ may be used in HCV + recipients and investigational use in HCV− NAT reduces window period to 6–9 days
Hepatitis B [1]	Surface antigen Core antibody HBV NAT	NAT-negative core antibody-positive non-hepatic organs at low risk for transmission
CMV	IgG antibody	Needed to plan preventative strategy
EBV	IgG antibody	Needed to plan preventative strategy
Bacteremia	Blood cultures	Bacteremia typically not a contraindication, treat recipient
Urinary tract infection	Urine culture	UTI not a contraindication, treat kidney recipients
Pulmonary infection	Sputum culture BAL with culture Chest radiograph	Most relevant for lung recipients
Syphilis	Treponemal or non-treponemal test	No contraindication to transplant, treat recipient
Toxoplasmosis	IgG antibody	Prophylaxis in heart D+R−

HIV human immunodeficiency virus, *NAT* nucleic acid test, *HCV* hepatitis C virus, *HBV* hepatitis B virus, *CMV* cytomegalovirus, *EBV* Epstein-Barr virus, *UTI* urinary tract infection, *BAL* bronchoalveolar lavage, *D+R−* donor positive-recipient negative

Table 3.2 Public Health Service criteria defining donors at increased risk for recent infection with HIV, HBV, and HCV

• Any of the following behaviors in the preceding 12 months
– Men who have had sex with men
– Drug injection by intravenous, intramuscular, or subcutaneous route for nonmedical reasons
– Sex in exchange for money or drugs
– People who have had sex with partners meeting any of the above criteria
– People who have had sex with persons known or suspected to have HIV, HBV, or HCV infection
– New diagnosis with or treatment for syphilis, gonorrhea, chlamydia, or genital ulcers (with the exception of known recurrent HSV)
– People who have been on hemodialysis
– Child 18 months or younger born to a mother known to be infected with or at increased risk for HIV, HBV, and HCV
– Child who breastfed from a mother known to be infected with or at increased for HIV infection

3.4.3 Geographically or Seasonally Limited Infections

In addition to required testing for routine infections (e.g., blood and urine cultures) and blood-borne viruses, screening for geographically or seasonally limited infections may be appropriate in certain circumstances [10]. For example, during an outbreak of WNV, screening deceased donors with NAT may be reasonable. Such testing optimally would utilize highly specific assays to avoid false-positive tests which could lead to wastage of uninfected organs since confirmatory testing generally cannot be performed routinely given the time constrains of organ donation. Further, application of screening tests that have not been tested or approved in deceased donors, such as interferon-gamma release assay testing for TB, may provide tests with unexpected high false-positive or false-negative results. Even when the results of testing performed on deceased donors cannot reliably be obtained prior to the decision to procure the organ, the test may still be useful. For example, a positive donor serology for *Strongyloides* would prompt recipient treatment even if the result is learned after the transplant procedure has occurred. For living donors, there is a much greater opportunity to obtain a careful history of geographic risk, occupational risk, hobbies, and exposures to zoonotic infections. Appropriate testing can then be obtained including confirmatory tests if required. Table 3.3, adapted from an OPTN guidance document, lists some of agents for which testing could be considered in living donors [11].

3.5 General Approach

The following sections will discuss considerations for use and risk mitigation strategies for various categories of organisms and associated clinical situations.

Table 3.3 Screening for seasonally and geographically limited diseases

Disease	Signs/symptoms in potential donor	Known risk factors	Potential testing	Use in deceased donors
Human T-cell lymphotropic virus (HTLV-1)	Most asymptomatic, T-cell leukemia, or myelopathy	Residence in Asia (particularly Japan), Caribbean, South America, West Africa	Serology – Confirmatory testing required	False-positives common
Histoplasmosis	Fever, night sweats, lymphadenopathy, cough, noncalcified pulmonary nodules or cavities	Residence in Midwestern states, Mississippi, or Ohio river valleys	Serology – Complement fixation – Immunodiffusion – EIA – Urine or serum antigen testing	Consider if evidence of histoplasmosis (lung nodule with organism)
Coccidioidomycosis	Fever, joint pains, cough, neck stiffness, headaches, pulmonary nodules or cavities, reticulonodular infiltrates	Residence in desert areas of the southwestern USA	Serology – Enzyme immunoassay – Complement fixation – Immunodiffusion – Urine or serum antigen testing	Universal testing may be appropriate in endemic areas
Chagas	Most asymptomatic; symptomatic chronic infection may present with cardiomyopathy, cardiac conduction abnormalities, megaesophagus, megacolon	Born or resided in endemic areas of South and Central America, child of woman who lived in endemic area, received blood transfusion in endemic area	Serology testing	Consider if risk factors
Strongyloides	Donors may have chronic abdominal pain, intestinal symptoms, and/or eosinophilia, or could be entirely asymptomatic	Soil exposure in tropical/warm climates. Walking barefoot, contact with human sewage, or contaminated soil. Exposure risk may persist for decades	Donors could be tested by serology (preferable) and/or stool examination, specifically looking for *Strongyloides*	Consider if epidemiological risk factors

Tuberculosis	Fever, night sweats, weight loss, cough, recurrent pneumonia, exudative pleural effusion of unknown etiology, lymphadenopathy, noncalcified pulmonary nodules or cavities	Born outside USA/Europe, prolonged residence outside USA/Europe, homeless, alcohol or other substance abuse, jail/prison time, healthcare worker, known TB exposure	Positive tuberculin skin test (TST) or interferon-gamma release assay (IGRA); sputum/BAL AFB smear, culture, nucleic acid amplification, TB PCR; AFB smear, culture, PCR on tissue	Performance of latent TB testing in deceased donors unknown
West Nile virus	Often asymptomatic; 20% develop acute febrile illness; <1% encephalitis, myelitis	Mosquito exposure, blood transfusion; risk varies by season and location	Nucleic acid test (NAT) and IgM serology	Consider during outbreak

Adapted from Recognizing Seasonal and Geographically Endemic Infections in Organ Donors: Considerations during Living Donor Evaluation, OPTN Guidance Document) https://optn.transplant.hrsa.gov/media/1138/seasonal_disease_guidance.pdf

3.5.1 Bacterial Organisms

3.5.1.1 Routine Bacterial Infections

Bacterial infection or colonization is commonly detected in potential donors. While bacterial infections can be transmitted to recipients, most routine donor infections are not considered to be contraindications to transplantation. For example, kidney recipients of donors with bacteria isolated in the urine can generally be treated with 5–7 days of antibiotics based on resistance testing with no clinically significant transmission of infection. Similarly, most lung transplant centers treat recipients with 7–14 days of antibiotics guided by donor sputum or bronchoalveolar lavage culture results. In the case of donors with bacterial meningitis, organ procurement is considered safe after at least 48 h of effective antibiotic therapy, and recipients should receive 7 days of treatment posttransplantation. Donors with bacteremia due to *Staphylococcus aureus*, coagulase-negative *Staphylococcus*, and gram-negative organisms can often be used with donor and recipient treatment.

3.5.1.2 Multidrug-Resistant Bacteria

Colonization or infection of donors with gram-negative or gram-positive multidrug-resistant bacteria (MDR) presents a unique challenge. In one report, a donor with methicillin-resistant *Staphylococcus aureus* (MRSA) receiving appropriate antibiotics and with resolution of bacteremia transmitted recurrent and difficult to treat MRSA to two recipients despite prophylactic antibiotics [12]. In that case, however, the donor had endocarditis, and the extensive seeding of the organs likely played a role in the recalcitrant nature of the infection. Major complications may occur when donors infected or colonized with vancomycin-resistant enterococci (VRE), carbapenemase-producing bacteria, pan-resistant *P. aeruginosa*, and other pan-resistant gram-negative bacteria are used, and reports described poor outcomes in this circumstance [13]. In some cases, abdominal organs can be soiled with MDR organisms in donors with trauma and open abdomens. Knowledge of potential MDR colonization is highly relevant to target peri-transplant antibiotic prophylaxis, and one report does describe successful use of donors with MDR gram-negative organisms with careful application of active antibiotics after transplant [14]. In general, these donors should be used very cautiously in conjunction with transplant infectious disease consultation.

3.5.2 Fungal Organisms

3.5.2.1 Candida

As is the case for routine bacterial organisms, colonization of donors with *Candida* is common. Donor urinary colonization with *Candida* is typically treated with 7–14 days with an antifungal drug (typically fluconazole if sensitive) for kidney recipients. While no consensus exists on the need to routinely culture

preservation fluid, if cultures are done and *Candida* has grown, 7–14 days of antifungal treatment would be reasonable. There have been few reports describing recipients outcomes in donors with candidemia. These donor should be used with caution, and the recpient should be treated with an appropriate antifungal for 7–14 days. *Candida* can occasionally infect the bronchial anastomotic site of lung transplant recipients, and *Candida* is a frequent colonizer of sputum in potential donors. Many lung transplant centers routinely use antifungal prophylaxis after lung transplantation.

3.5.2.2 Endemic Fungi and Cryptococcus

Except in extreme cases of recipient need, active infection with endemic fungi should be considered a contraindication to organ donation [15]. Occult and asymptomatic donor infection, however, may be unrecognized with resultant transmission to recipients. Among the endemic fungi, coccidioidomycosis has been the most frequently reported. In the largest available report which included 6 donors, 9 of 21 exposed recipient developed active infection, and 6 of these recipients died. Notably, no recipient receiving preventative or early treatment died of coccidioidomycosis [16]. In endemic areas, prophylaxis is commonly given to recipients of donors with suspected or proven coccidioidomycosis, and many centers practice universal prophylaxis to reduce the risk of both donor-derived and environmentally acquired infection. Histoplasmosis had been less commonly reported, although in endemic areas granulomatous lesions in the lung or mediastinal lymph nodes are common and generally do not require any recipient treatment. When possible, however, serological and antigen testing of the donor can be used to guide therapy with management options including itraconazole treatment or antigen monitoring of the recipient [17]. As is true of donors with active endemic fungi, organ from donors with active infection with *Cryptococcus* should rarely if ever be transplanted. If donor-derived cryptococcal disease is discovered after transplant, all recipients should be tested for cryptococcosis using both antigen testing and culture. In the absence of detection of *Cryptococcus* in the recipient, a minimum 6-month course of fluconazole would be a reasonable course. If recipient disease is detected, guidelines for treatment should be followed [18].

3.5.3 Environmental Molds

Reports of rapid fatal dissemination of *Aspergillus* from colonized or infected donors suggest that potential donors known to be infected with *Aspergillus* or other pathogenic environmental methods should not be used [19]. Sources of these molds may include preservative fluids, environmental contamination during the procurement process, and drowning/submersion victims. Extended treatment with a mold-active antifungal is recommended if donor-derived mold infection (perhaps with the exception of lung colonization) is discovered posttransplant.

3.5.4 Mycobacteria

Medical and epidemiological history and chest imaging are mandatory to determine the risk for tuberculosis. Active disseminated tuberculosis is a contraindication for organ donation. Organs, with the exception of the lung in case of residual visible changes, can be used in cases of past tuberculosis treated for at least 6 months. History of latent TB or positive IGRA test without a sign of active infection is not a contraindication, but preventive therapy for all recipients should be considered (see Chap. 20).

3.5.5 Viral Infections

This chapter will not address *Cytomegalovirus* or EBV as these are expected donor-derived diseases with specific management strategies addressed in Chaps. 6 and 7.

3.5.5.1 Human Immunodeficiency Virus

Since widespread donor HIV testing became available, in the USA only two instances of donor-derived HIV infection have been reported. In one case a living donor contracted HIV between his initial testing and transplant. In the second case, a donor with a history of intravenous drug use in the serological window period transmitted HIV and hepatitis C to multiple recipients [20, 21]. Outside of the USA, a living donor in India likely in the window period transmitted HIV to her recipient, and human error in transcription of a positive HIV donor test result in Italy led to a cluster of donor-derived cases [22, 23]. Early diagnosis of donor-derived HIV is critical as early treatment may be lifesaving; recipients of donors with risk factors for window period HIV infection should undergo NAT testing 1 to 2 months posttransplant. Currently, in several European countries and since the passage of the HOPE Act in the USA, organs from HIV-infected donors who meet certain criteria can be transplanted into HIV-positive recipients, in some countries as part of research protocols. Several guidelines have been published for transplantation in HIV-positive recipients, and generally the following requirement for the recipient should be met: CD4 > 200 ul, efficacious HAART, documented aviremia, and absence of active opportunistic infections. Please refer to national guidelines and legal rules for more details [24].

3.5.5.2 Hepatitis B and Hepatitis C

Donor-derived hepatitis C has occurred from donors in both the serological and NAT window period [25]. While the hepatitis C NAT window period is only 6–9 days, the increase in the number of donors with active intravenous drug results in a larger donor pool with negative screening antibody and NAT tests at risk for recent and transmissible infection with hepatitis C. Modeling studies and limited data from DTAC suggest that the risk of NAT window period donor hepatitis C infection in an intravenous drug user is likely less than 3% [8, 25]. This risk may increase significantly in the setting of a local outbreak of hepatitis C. Similar to HIV, early

diagnosis of donor-derived hepatitis C is critical to avoid fibrosing hepatitis; NAT testing at 1–2 months after treatment will detect virtually all cases, and new antiviral therapy is highly effective. In immunosuppressed patients posttransplant, seroconversion may not occur and thus serologic testing is not reliable.

Window period hepatitis B transmission has occurred as well, and screening of recipients of donors at increased risk for recent hepatitis B is reasonable; a second test at 6–12 months is recommended. For HBV NAT-negative donors who are core antibody positive, the risk of transmission from non-hepatic organs is low, particularly if recipients are hepatitis B surface antibody positive. Hepatitis C seropositive donors can be divided into two categories based on NAT status. Those who are NAT positive are likely to transmit hepatitis C to the recipient of hepatic and non-hepatic organs. NAT-negative donors may have naturally cleared hepatitis C virus or received successful medical treatment for hepatitis C. While these donors would generally not be expected to transmit hepatitis C to seronegative recipients, one report describes that 4 of 25 recipients of hepatitis C seropositive/NAT-negative liver donors developed probable donor-derived hepatitis C. All four donors died from drug overdose, and it is unclear whether the hepatitis C transmission was due to occult hepatitis C infection or new donor eclipse period infection [26]. Chapter 10 provides further details on the treatment and prevention of viral hepatitis after transplant.

3.5.5.3 Other Viruses

Human T-cell lymphotropic virus 1 (HTLV-1) is endemic in the Caribbean, parts of South America, West Africa, and parts of Asia particularly Japan. Prevalence is very low in the USA and Europe, and universal screening is not required as false-positive tests resulted in significant organ wastage [27]. Donor-derived cases with the rapid development of HTLV-1-associated disease have been reported, and screening of donors from endemic areas is reasonable [28]. The effect of immunosuppression on the natural history of HTLV-1 remains unclear, and while HTLV-1-positive recipient status is not an absolute contraindication to transplantation, HTLV-1 disease has been reported after transplantation, and no effective antiviral treatment is available [29]. Other viruses associated with encephalitis and without effective treatment with described donor transmission and fatal outcomes in recipients have included WNV, lymphocytic choriomeningitis virus, tick-borne encephalitis virus, and rabies virus, and donors with suspected active infection with these pathogens should not be used [30].

3.5.6 Selected Parasitic Infections

Strongyloides is endemic throughout the world, but more common in tropical regions and the Mediterranean basin. Asymptomatic infection may persist for years, and donor-derived infection often with fatal outcomes has been well described [31]. Recipients with suspected infection or receiving organs from potentially infected donors should receive treatment with ivermectin, and with the exception

of hyperinfection in the donor concern for *Strongyloides*, infection should not delay transplantation or exclude infected donors or recipients.

Prevalence of infection with *Toxoplasma gondii* varies throughout the world but exceeds 70% in some regions. Since the parasite encysts in the heart muscle, the major concern has been transmission from positive heart donors to negative heart recipients, and prophylaxis is recommended in that setting. As disease development has been reported in seronegative non-cardiac recipients not receiving TMP/SMX prophylaxis, awareness of the potential for donor-derived disease in that circumstance is prudent.

Infection with *Trypanosoma cruzi*, the cause of Chagas disease, is endemic in parts of Mexico and much of Latin and South America. Intermediate stage Chagas disease is typically asymptomatic, and transmission to recipients may occur. Recipients of donors seropositive for Chagas disease should receive periodic blood microscopy and if possible, NAT testing available at the CDC (consultation with Division of Parasitic Diseases, CDC 770-488-7775) or local tropical disease reference centers. A suggested protocol for testing and treatment if transmission occurs is available [32].

3.5.7 Selected Relevant Guideline References

Guidelines advising on donor screening and recipient and donor management have been published and serve as an excellent reference [7, 10, 33].

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4 Prevention of Bacterial, Viral, Fungal, and Parasitic Infections During the Early Post-transplant Period

Camille Nelson Kotton and Christian van Delden

4.1 Evaluating the Pre-transplant Risk of Post-transplant Infections

The risk of infections in the first month post-SOT depends on the type of transplant, potential colonization of donor and recipient with multidrug resistant (MDR) bacteria, and the prolonged maintenance of indwelling vascular lines, chest or abdominal drainage tubes, and intubation devices [1]. Pre-transplant recipient conditions that impact the risk of infection include the underlying illnesses causing organ failure, their severity, and potential immunosuppressive role before transplant. For example, high MELD score (>30) liver transplant candidates have a significantly higher risk for post-transplant infections as compared to low MELD score liver transplant candidates. Chronic malnutrition predisposes to early post-SOT infections, and all efforts should be taken to correct nutritional defects before SOT. Pre-transplant use of steroids or occupational or recreational exposure to fungal pathogens (i.e., farming, gardening) might increase the risk for pre-transplant respiratory tract colonization by filamentous fungi. Similarly, the pre-transplant exposure of both donor and recipient to antibiotic therapies might lead to colonization by multidrug resistant (MDR) bacteria and yeasts and increase the subsequent risk of infection by these pathogens. In recent years, donor-derived infections with MDR bacteria have led to reports of devastating early post-SOT infections in the absence of specific prophylaxis [2]. As a consequence, both donor and recipient evaluation and screening for colonization by MDR pathogens may be indicated in order to tailor specific

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prophylactic measures for the recipient. This includes serologies for latent infections (i.e., *Treponema pallidum*, CMV, EBV, HSV, HIV, and, when indicated, *Toxoplasma gondii, Coccidioides, Trypanosoma cruzi*, *Strongyloides*); interferon gamma release assay (i.e., T-SPOT.TB or QuantiFERON-TB) testing for *Mycobacterium tuberculosis*; rectal, nares, and skin swabs to detect colonization with MDR bacteria; and transplant-specific cultures such as bronchial cultures for lung and urine cultures for kidney transplants. A careful travel history should be obtained whenever feasible to identify risks for infections with endemic pathogens. Table 4.1 summarizes the most frequent risk factors.

Pre-transplant evaluation should provide the opportunity to give vaccines (especially those live vaccines that can't be given after transplant, such as MMR or varicella), prophylaxis (i.e., latent tuberculosis), and treatment (i.e., latent syphilis, hepatitis B or C) when indicated.

Table 4.1 Risk factors for early post-transplant infections

Donor and recipient pre-transplant risk factors	Recipient per-transplant risk factors	Recipient early post-transplant risk factors
Colonization: – MDR bacteria (ESBL, CRAB, MRSA, VRE, etc.) – Yeasts (resistant *Candida* species) – Filamentous fungi (*Aspergillus*, *Mucor*, etc.) – Endemic fungi (*Histoplasma*, etc.) – *Pneumocystis jirovecii* – Respiratory viruses (influenza, RSV, etc.) Latent infections: – *Mycobacterium tuberculosis* – *Mycobacterium abscessus* – Viruses (CMV, HSV, EBV, HBV, HCV, West Nile virus, HIV, etc.) – *Toxoplasma gondii* Recipient specific: – Chronic malnutrition – Advanced organ failure (high MELD score) – Exposure to immunosuppressive agents (steroids, anti-TNF agents, etc.) – Palliative surgery – Mechanical ventilation, indwelling catheters, and drainage tubes	– Prolonged surgery – Extensive bleeding and high number of blood transfusions – Choice of surgical technique (Roux-en-Y biliary anastomosis for liver transplantation) – Technical problems affecting the transplant's functional integrity and vascular supply – Liver: hepatic artery thrombosis – Pancreas: duodenal leaks, splenic artery thrombosis – Kidney: vesicoureteral reflux – Heart: mediastinal bleeding – Lung: bronchial anastomotic leaks, etc.)	– Prolonged intubation and mechanical ventilation – Indwelling vascular catheters (central line catheters) – Abdominal and chest drainage tubes – Ureteral catheters – Persistent hematomas – Undrained collections – Persistent leaks (biliary, urinary, bronchial, etc.) – Prolonged renal replacement therapies (hemodialysis) – Repeated open surgery – Intense immunosuppression – Prolonged broad-spectrum antibiotic therapy – Nosocomial exposure (respiratory viruses, MDR pathogens, filamentous fungi, etc.)

The risk for reactivation of latent pathogens and infections with opportunistic infections diminishes gradually after transplant, with recovery from induction and gradual tapering of immunosuppression toward maintenance therapy. Treatment of rejection with increased immunosuppression augments the risk of infection, however, and prophylaxis against such infections may need to be reinitiated in such instances for some period of time, according to the type and intensity of immunosuppression.

4.2 Prevention of Bacterial Infections

Prophylaxis of bacterial infections is provided during the first days after transplant to prevent infections linked to the surgical act, amplified by the immunosuppression (Table 4.2). Usually antibiotic prophylaxis is kept as short as possible (24–72 h post-transplant) to avoid selection of resistant pathogens and only continued further in the case of patient-specific risks. This prophylaxis is targeted on the recipient's local flora and also potentially based on donor colonization by specific pathogens (MDR) [3]. Carbapenems should only be used in prophylaxis with documented colonization by ESBL-producing *Enterobacteriaceae* [4]. Some centers use organ transport fluid cultures as a means to target antibiotic prophylaxis. This should probably not apply for cultures growing potential contaminants (i.e., coagulase-negative *Staphylococci*). The common use of trimethoprim-sulfamethoxazole (TMP-SMX) to prevent *Pneumocystis jirovecii* infections may provide sufficient antibacterial prophylaxis to kidney transplant recipients against urinary tract infections; some centers add 24 h of prophylaxis with either a quinolone or a second-generation cephalosporin. For liver, heart, and lung transplants, reasonably broad Gram-positive and Gram-negative coverage (such as that provided by a second-generation cephalosporin or a penicillin with a beta-lactamase inhibitor) for 72 h might be sufficient in the absence of colonization by MRSA, VRE, or resistant Gram-negative bacilli. In case of pre-transplant colonization of kidney and liver recipients by carbapenem-producing *Enterobacteriaceae* (CPE), data about the benefit-risk of tailored prophylaxis is

Table 4.2 Prevention of early post-transplant bacterial infections

Transplant	24–96 h post-transplant[a]
Kidney	Ciprofloxacin or cefuroxime or cefazolin
Pancreas	Piperacillin-tazobactam + metronidazole for 5–7 days
Intestinal	Piperacillin-tazobactam or cefepime + metronidazole for 4 weeks
Liver	Cefuroxime or piperacillin-tazobactam
Lung	Cefuroxime
	Adapt to recipient/donor bronchial cultures
Heart	Cefuroxime or cefazolin

[a]Always adapt to local epidemiology, as well as pre- and per-transplant culture results of recipient to target patient-specific colonization. Keep duration of prophylaxis as short as possible

lacking. Therefore recent guidelines did not recommend targeted prophylaxis, except in centers with high incidence of surgical site infections [3]. For lung transplant recipients, the prophylaxis should be based on recipient pre-transplant cultures and adapted as soon as cultures of both donor and recipient main bronchi are available [5]. This is of particular importance in the case of cystic fibrosis (CF) recipients, frequently colonized pre-transplant by *Pseudomonas aeruginosa*, *Staphylococcus aureus* (MSSA and MRSA), *Burkholderia cepacia,* non-tuberculous *Mycobacterium* (NTM), and other potential pathogens. After transplant, these pathogens tend to seed the allograft from the recipient sinuses and lead to early severe infections in the absence of aggressive preemptive therapy [6]. Frequently patient-specific antibiotic therapy has to be provided for a few days post-transplant to such patients. In the case of NTM such as *Mycobacterium abscessus*, specific therapy is recommended for up to 12 months [7]. For liver transplant recipients in case of pre-transplant intra-abdominal infections, the prophylaxis should cover the previously identified pathogens. In the case of recurrent pre-transplant biliary infections (i.e., primary sclerosing cholangitis), the risk of peri-surgical intra-abdominal bacterial seeding is substantial and might require a targeted antibiotic prophylaxis for a few days post-transplant. In institutions with a high rate of VRE infections, specific prophylaxis might be used. For pancreas transplant recipients, most programs provide prophylaxis covering both Gram-positive and Gram-negative bacteria, as well as anaerobes for a few days. Intestinal transplant recipients have an extremely high risk of bacterial translocation due to the extensive mucositis during the first month following transplant. Broad-spectrum antibiotic prophylaxis (such as piperacillin-tazobactam or cefepime with metronidazole) is routine in these patients for 4 weeks post-transplant.

During the first few weeks after transplant, bacterial infections occur essentially as consequence of surgical wound infections and technical problems such as anastomotic leaks, urethral reflux, and biliary, bronchial, or urethral stenosis. Source control, including drainage of all accessible sites, is essential. Secondary prophylaxis might be required in the case of recurrent infections but should always be targeted and timely restricted to its minimum to avoid selection of resistant pathogens.

4.3 Prevention of Viral Infections

Prevention of viral infection after SOT may involve either routine monitoring of viral loads by periodic blood testing or prophylaxis with an antiviral agent or immunoglobulin (i.e., hepatitis B virus (HBV) immunoglobulin, cytomegalovirus (CMV) immunoglobulin; these are used less frequently in the era of directly acting antiviral therapy). For those recipients with donors at increased risk of transmission of HBV, hepatitis C virus (HCV), and HIV, routine post-transplant testing by both serology and nucleic acid testing in the first year is recommended [8].

Vaccination prior to transplant can help prevent many viral infections, including hepatitis A virus (HAV) and HBV, measles, mumps, rubella, varicella/zoster virus

(VZV), polio, human papilloma virus, and, for travelers and those with risk for certain exposures, rabies, yellow fever, and Japanese encephalitis. After transplant, non-live vaccines may be given, although they generally have less immunogenicity. The live viral vaccines that should generally be avoided after transplant include measles, mumps, rubella, varicella, zoster (live; recombinant may be safe), polio (oral), rotavirus, and yellow fever.

The human herpes viruses (HHV) are the most common viral infections after transplant and are the predominant preventable viral pathogens, primarily herpes simplex virus (HSV), VZV, and CMV; Table 4.3 summarizes details of routine prophylaxis. For CMV, some groups use preemptive therapy for prevention, with frequent (often weekly) blood checks for several months and initiation of treatment-dose antivirals when a certain threshold is reached [9]; to prevent varicella zoster

Table 4.3 Human herpes virus prophylaxis after kidney, liver, heart, or pancreas transplant [9]

Induction agent	Donor CMV antibody	Recipient CMV antibody	Prophylaxis	Monitoring with CMV viral load
Antithymocyte globulin	Positive	Positive	Valganciclovir × 3 months	Monitoring while on prophylaxis only if clinically indicated by symptoms; consider weekly monitoring after prophylaxis × 8–12 weeks in higher-risk patients and those on more potent immunosuppression
	Negative	Positive		
	Positive	Negative	Valganciclovir × 6 months (plus consider weekly monitoring afterward × 8–12 weeks in higher risk D+R− on more potent IS)	
	Negative	Negative	Acyclovir, famciclovir, or valacyclovir × 3 months[a]	
Basiliximab None	Positive	Positive	Valganciclovir × 3 months	
	Negative	Positive		
	Positive	Negative		
	Negative	Negative	Acyclovir, famciclovir, or valacyclovir × 3 months[a]	

Notes on viral prophylaxis:

- Dosages of all antiviral agents need to be adjusted for renal function. The eGFR or creatinine clearance should be used (not simply the serum creatinine)
- For prophylaxis, the first doses may be oral valganciclovir or intravenous ganciclovir, converting IV to oral as soon as patient tolerating oral medications There is recent data supporting the safety and efficacy of either approach in the treatment (not prophylaxis) setting [23, 24]
- While most kidney transplant recipients (given lower GFR) will need valganciclovir 450 mg a day (or less), some may have GFR > 60 and need valganciclovir 900 mg a day. Minidosing not recommended
- Lung transplant prophylaxis would be similar, although generally with longer courses of prophylaxis

[a]In case of either HSV or VZV, D+ or R+; if all are negative, no need for prophylaxis

and herpes simplex viruses, clinicians may wish to add acyclovir, valacyclovir, or famciclovir. Other HHV, such as Epstein-Barr virus (EBV), HHV-6, and HHV-8, are less amenable to prophylaxis. Vaccination with varicella and live viral zoster vaccines should be done before the onset of immunosuppression [10]; the recombinant zoster vaccine may be useful after transplantation.

EBV infection augments the risk of EBV-positive post-transplant lymphoproliferative disease (PTLD), especially in those who are EBV D+R− and those who undergo multivisceral/small bowel and thoracic transplants. In these EBV D+R− recipients, post-transplant monitoring periodically for the first 1–2 years can identify those at higher risk for PTLD; when possible, reduction of immunosuppression may sometimes help diminish the viremia [11]. Antiviral medication has not been found to be effective in either preventing or decreasing EBV viremia.

HBV can be prevented by pre-transplant diagnostic testing, including HBV core and surface antibody (both IgG), surface antigen, and sometimes viral load (to detect the rare cases when the surface antigen is negative but viral load positive). If any of those are positive, additional studies can be sent (HBVe antigen and antibody, hepatitis D antibody and antigen). Pre-transplant vaccination is recommended for all nonimmune organ transplant recipients; higher doses of vaccine are more likely to provide protection in those with chronic organ disease. Antiviral treatment can be given for acute or chronic active infection or when there is a risk of reactivation or transmission from the donor (i.e., HBV core antibody positive) [12].

HCV management has changed rapidly in recent times, given the advent of highly active therapies. Although some recipients are treated prior to transplant, some are now treated after transplant, in part to allow them to undergo transplant from donors with HCV, which may shorten the waiting time for organs and provide access to organs from younger donors with fewer comorbidities [13]. Numerous programs are now using HCV-positive donors in recipients without HCV and treating after transplant (often initiating therapy immediately, and primarily in research settings); early work demonstrates acceptable outcomes [14]. Prevention approaches for HCV involve both monitoring by viral load and serology and use of various treatment methods when indicated.

Hepatitis E virus (HEV) causes acute and chronic hepatitis in SOT recipients, especially in endemic regions, where pre-transplant screening of donors and recipients may be useful.

BK polyomavirus (BKPyV) causes nephropathy primarily in kidney transplant recipients and often reflects relative over-immunosuppression. Over 85% of adults have prior exposure and latent viral infection. Prevention is best done through periodic (every several months) urine and/or blood viral load testing during the first 2 years after transplant [15, 16]. Urine viral loads are often positive before blood. When a certain threshold has been achieved, clinicians may wish to reduce immunosuppression, as the best method to help clear BKPyV infection. With extensive, unremitting infection, some programs use antiviral therapy [16].

4.4 Prevention of Fungal Infections

In recent years, efforts have been made to identify risk factors for post-transplant fungal infections allowing risk stratification and to tailor antifungal prophylaxis individually to each recipient [17]. This takes into account center-specific epidemiologic data, potential pre-transplant and post-transplant environmental exposure to filamentous or endemic fungi, and pre-transplant colonization (Table 4.4).

Table 4.4 Prevention of fungal infections

Transplant	Fungus	Risk factors	Prophylaxis	Suggested duration[a]
Kidney	*Pneumocystis* *Candida* *Aspergillus*	All patients Candiduria Proven colonization, high-dose steroids, acute rejection, CMV infection	TMP-SMX Fluconazole Aerosolized amphotericin B, voriconazole	6 months 10–14 days 4–6 weeks
Pancreas	*Pneumocystis* *Candida* *Aspergillus*	All patients All patients Proven colonization, high-dose steroids, acute rejection, CMV infection	TMP-SMX Fluconazole, echinocandin Aerosolized amphotericin B, voriconazole	12 months 14 days 4–6 weeks
Intestinal	*Pneumocystis* *Candida* *Aspergillus*	All patients All patients Proven colonization, high-dose steroids, acute rejection, CMV infection	TMP-SMX Fluconazole, echinocandin Aerosolized amphotericin B, voriconazole	12 months 4 weeks 4–6 weeks
Liver	*Pneumocystis* *Candida* *Aspergillus*	High MELD score (>30), ATG, CMV disease, second transplant >2 risk factors: broad-spectrum antibiotics >5 days, yeast colonization >3 body sites, ICU >5 days, post-transplant hemodialysis, retransplantation or need for second surgery, choledocojejunostomy, high transfusion requirement, and pancreatitis Proven colonization, high-dose steroids, primary allograft failure or severe dysfunction, hemodialysis, retransplantation, acute rejection, CMV infection	TMP-SMX Echinocandin followed by fluconazole IV or Aerosolized amphotericin B, mold-active azoles (voriconazole, posaconazole, or isavuconazole)	6–12 months 2–4 weeks 4–6 weeks

(continued)

Table 4.4 (continued)

Transplant	Fungus	Risk factors	Prophylaxis	Suggested duration[a]
Lung	*Pneumocystis* *Candida* *Aspergillus*	All patients None All patients or according to risk factors: proven colonization, high-dose steroids, retransplantation, acute rejection, CMV infection	TMP-SMX – Aerosolized amphotericin B, voriconazole	12 months, lifelong – 4–6 weeks, lifelong
Heart	*Pneumocystis* *Candida* *Aspergillus*	All patients None Proven colonization, high-dose steroids, primary allograft failure or severe dysfunction, hemodialysis, retransplantation, acute rejection, CMV infection	TMP-SMX – Aerosolized amphotericin B, voriconazole	12 months, lifelong (depending on toxoplasma status) – 4–6 weeks

[a]Suggested durations from the University Hospitals Geneva, Switzerland

Except for low-risk liver transplant recipients, prophylaxis against *P. jirovecii* is recommended for all SOT recipients for 6–12 months, and some centers provide livelong prophylaxis for lung transplant recipients. Most centers use TMP-SMX (also providing protection against *Toxoplasma*, *Nocardia*, and urinary tract infections). In case of intolerance, oral atovaquone, dapsone, and aerosolized pentamidine are alternatives.

Candida sp. infections mainly occur as nosocomial infections during the first month post-transplant. Lung, heart, and kidney transplant recipients do not generally require systemic yeast prophylaxis; oral amphotericin B or nystatin is frequently provided to prevent thrush. Liver transplant recipients should be evaluated in a risk stratification to decide whether systemic anti-yeast prophylaxis is justified. Prophylaxis is given in the presence of more than two of the following risk factors: broad-spectrum antibiotics for more than 5 days, yeast colonization of more than three body sites, ICU for more than 5 days, post-transplant hemodialysis, retransplantation or need for second surgery, choledocojejunostomy, high transfusion requirement, and pancreatitis [17]. Early after liver transplant, an echinocandin might be preferred, once the liver function has recovered, and taking into account local epidemiology, a switch toward fluconazole might be considered. The duration should take into account the persistence of the risk factors. Pancreas and intestinal transplant recipients are at highest risk and should receive systemic anti-yeast prophylaxis for 2 and 4 weeks, respectively, post-transplant.

Aspergillus and *Mucor* infections are a serious concern following SOT because of their high-associated mortality. Given the toxicity, side effects, and drug interactions of antifungal prophylaxis, efforts should be made to identify SOT recipients at increased risk for invasive fungal infections. Recipients colonized at the time of transplant should receive prophylaxis for at least 4–6 weeks. Risk factors common

to all transplants include proven colonization, high-dose steroids, primary allograft failure or severe dysfunction, hemodialysis, retransplantation, acute rejection, and CMV infection. Lung transplant recipients, especially CF patients, are at high risk for *Aspergillus* infections. Some centers provide universal prophylaxis with either aerosolized amphotericin B or mold-active azoles (voriconazole, posaconazole, or isavuconazole); others prefer to give prophylaxis only in the presence of documented colonization or other risk factors. Voriconazole has been associated with a higher incidence of skin cancer in lung transplant recipients [18]. The strategy should be adapted according to local epidemiology.

Cryptococcus neoformans infections may occur before (especially with liver disease) or after transplant; prophylaxis with fluconazole is only recommended in the presence of positive cryptococcal antigen detection or with a documented history of disease. Similarly, those at risk for *Coccidioides* after transplant should be given prophylaxis with fluconazole.

4.5 Prevention of Parasitic Infections

Parasitic infections are less common after transplant and may be more challenging to diagnose. Acknowledging the risk of reactivation and donor-to-recipient transmission, based on donor and recipient exposures, may be the first step in preventing these infections. While most transplant recipients would be given *Toxoplasma* prevention, prevention of *Trypanosoma cruzi*, *Schistosoma*, *Leishmania*, malaria, *Babesia*, and others would only occur when risk was identified.

Symptomatic toxoplasmosis has been well described, primarily after heart transplant, and may present with myocarditis, brain abscess, pneumonitis, or disseminated disease. Without prophylaxis, those who are D+/R− have a 50% to 75% risk of symptomatic infection within the first few months. While rates of positivity are low in the United States, they can be much higher in Europe, Brazil, and elsewhere [19]. TMP-SMX is the most common prophylaxis. While pyrimethamine with sulfadiazine is effective and has been used for high-risk cardiac recipients, it does not seem to be essential based on clinical data and experience, as TMP-SMX alone has been sufficient and better tolerated; Table 4.5 outlines further details.

Strongyloides infections can be latent for decades, due to the autoinfection loop, and develop into clinically significant disease, from gastrointestinal to disseminated [20]. Both donors and recipients from endemic regions should be screened, with a plan to initiate treatment with ivermectin, thiabendazole, or albendazole if needed. In deceased donors, screening usually involves serology; there have been numerous cases of donor-derived infection [21]. Living donors and recipients may be screened by serology or by several stool specimens, as the sensitivity of an individual stool study is low. Those who have concomitant microfilarial disease and who are given ivermectin may experience the Mazzotti reaction, with fever, adenopathy, pruritus, abdominal pain, and even angioedema; it is best to screen those from endemic regions within the past 5–7 years (primarily Africa and Asia) for microfilaria by

Table 4.5 Duration of toxoplasmosis prophylaxis after heart transplant based on serologic combinations (Massachusetts General Hospital)

Serologic combination (donor/recipient)	Risk group	Treatment and dosing	Duration of therapy
D+R−	Highest risk	TMP-SMX DS[a] (some centers use SS) every day (if DS dose reduce to Bactrim SS q day if GFR < 30) × 12 months and then TMP-SMX SS every day (no need for dose reduction with renal insufficiency even ESRD/dialysis)[b]	Lifetime, if possible (otherwise discuss with infectious disease)
R+ (D+ or D−)	Moderate risk	TMP-SMX SS[a] every day (no need for dose reduction with renal insufficiency even ESRD/dialysis)	Can stop at 1 year, or when on low-dose immunosuppression (i.e., prednisone 5 mg a day), whichever is *later/longer* Restart during intensification of immunosuppression (i.e., pulse-dose steroids, ATG, or Rx of AMR) for same period as after transplant
D−R−	Lowest risk	Same as for R+ for *Pneumocystis* and other preventions, although not needed for toxoplasmosis	

[a]Trimethoprim-sulfamethoxazole (TMP-SMX) DS (double strength) is sulfamethoxazole 800 mg and trimethoprim 160 mg, while TMP-SMX SS (single strength) is half that dose
[b]If true TMP-SMX allergy documented, second-line prophylaxis would be with atovaquone1500 mg a day or dapsone 100 mg a day. With dapsone, breakthrough toxoplasmosis infection could occur, as could methemoglobinemia, and G6PD should be checked before starting treatment to avoid hemolysis if deficient

blood smear. For latent *Strongyloides* infection, ivermectin is often given as one or two daily doses, with a repeat series 2 weeks later, due to the autoinfection cycle and the efficacy of ivermectin at only certain stages in the parasite lifecycle; the optimal regimen has not been defined [20]. Those who are seropositive for HTLV are at risk for recurrent *Strongyloides,* sometimes necessitating repeat treatment; HTLV serology should be checked when positive *Strongyloides* serology is found.

Chagas disease is caused by *Trypanosoma cruzi* and generally occurs in those from Central and South America or who have received organs or blood products from infected people. Pre-transplant serologic testing of donors and recipients from endemic regions is recommended [22]. Rates of transmission from positive donors to recipients are significant; acceptance of hearts from positive donors is not recommended, and recipients of other organs from positive donors should undergo transplant only after informed consent. If either are positive, post-transplant screening by blood PCR or smear weekly for the first few months may detect early infection, at which point preemptive treatment with benznidazole (or nifurtimox) would be indicated [22]. Prophylaxis with these agents is not generally done, due to lack of efficacy data and significant toxicity.

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5 Late Posttransplant Period: Posttransplant Vaccination, Travel Advice, Foodborne Infections

Deepali Kumar and Elisa Cordero

5.1 Foodborne Diseases

5.1.1 Definitions and Epidemiology

Foodborne diseases are diseases caused by ingestion of food contaminated with microorganisms or chemicals at any stage in the process from food production to consumption.

Immunosuppressed patients are more susceptible to foodborne diseases and have a greater risk of severe illness [1, 2]. Besides immunosuppression, SOT recipients have other predisposing factors such as liver or kidney dysfunction, use of antacids and antimicrobials, and nutrition deficiencies. The inoculum of organisms needed to cause symptomatic disease is likely lower in this population [3].

The causes of foodborne diseases can be classified mainly in two categories: Chemical hazards, including chemical contaminants as well as natural toxins and infectious agents, the most frequent cause of foodborne diseases. Pathogens can cause different types of foodborne illness: (a) foodborne infections, when the pathogen causes disease directly when ingested; (b) foodborne intoxication, when the illness is caused by toxins produced in the food by pathogens; and (c) foodborne toxin-mediated infection, when the pathogens produce toxins in the body after being ingested.

The top five infections that cause foodborne illness in Western countries are norovirus, *Salmonella* spp., *Clostridium perfringens*, *Campylobacter* spp., and *Staphylococcus aureus*. Other microorganisms, such as *Clostridium botulinum*,

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Listeria, and Shiga toxin-producing *Escherichia coli* O157, seldom cause illnesses, although they usually are life-threatening.

Noroviruses are highly resistant to harsh environmental conditions, with an infectious oral dose <20 viral particles. Infected food workers are frequently the source of the outbreaks. Other sources of infection are foods (oysters, fruits, and vegetables) or touching the mouth after contact with contaminated objects or persons infected with norovirus [4].

Campylobacter spp. is the most common bacterial cause of human gastroenteritis in the world. It is generally associated with the consumption and handling of chicken and, less commonly, with the consumption of raw milk, red meat, contaminated water, or transmission from household pets or farm animals.

Salmonella spp. are a major cause of foodborne illness throughout the world. The bacteria are generally transmitted to humans through consumption of contaminated food of animal origin, mainly meat, poultry, eggs, and milk. Person-to-person transmission can also occur through the fecal-oral route.

Although *C. perfringens* may be normal intestinal flora, illness is caused by ingestion of food contaminated with large numbers of bacteria that produce enough toxins in the intestines to cause illness. Beef, poultry, and dried or precooked foods are common sources of *C. perfringens* infections [5].

Escherichia coli infection is usually transmitted through the consumption of contaminated water or food, such as undercooked meat products, raw milk, and fecal contamination of vegetables. Some strains such as the Shiga toxin-producing *E. coli* (STEC) can cause severe foodborne disease. *E. coli* STEC is heat-sensitive; therefore cooking food thoroughly can avoid transmission.

Staphylococcal food poisoning occurs when eating uncooked foods contaminated with toxins produced by *Staphylococcus aureus*.

The main source of hepatitis E virus transmission is the consumption of raw or undercooked, infected meat or direct contact with infected animals. For SOT patients exposed to HEV, infection can become chronic, with rapidly progressing liver disease.

5.1.2 Diagnosis

History is very important when evaluating a patient with a suspicion of foodborne disease. The clinician must consider the history, epidemiologic features, the symptoms, and signs. The most common clinical presentation of foodborne disease is diarrhea. However, such diseases can have other serious consequences such as kidney and liver failure, neural disorders, reactive arthritis, and death. None of the symptoms of foodborne illness are specific, although they may vary depending on the etiology (Table 5.1).

Contrary to immunocompetent adults, norovirus gastroenteritis in SOT recipients frequently results in chronic symptoms that persist weeks to months [6, 7]. In these patients, norovirus infection is accompanied by weight loss, dehydration, and renal insufficiency; symptoms last considerably longer than most other etiologies [8].

Table 5.1 Foodborne diseases

Etiology	Incubation period	Symptoms	Food sources
Bacillus cereus	10–16 h	Nausea, abdominal pain watery diarrhea, vomiting	Cereal products, rice, vanilla sauces, eat
Campylobacter jejuni	2–5 days	Diarrhea (bloody sometimes), severe abdominal pain, fever, bacteremia	Poultry, beef lever, raw seafood, contaminated water, raw milk
Clostridium botulinum	12–72 h	Bulbar palsy, descending paralysis, lack of fever	Home-canned low-acid food, fermented fish
Clostridium perfringens	8–16 h	Abdominal pain, watery diarrhea	Undercooked foods, meat, poultry, gravy sauces, soups
E. coli O157:h7	24–72 h	Severe abdominal pain, diarrhea (bloody), nausea, vomiting, HUS	Soft unpasteurized cheese, contaminated water, undercooked foods
E. coli (traveler's diarrhea)	1–3 days	Abdominal cramps, vomiting, watery diarrhea	Food or water contaminated with human feces
Listeria monocytogenes	9–48 h for gastrointestinal symptoms, 2–6 weeks for invasive disease	Nausea, vomiting, stomach cramps, diarrhea, bacteremia, meningitis constipation, fever	Raw milk or milk products, undercooked poultry, unwashed raw vegetables
Salmonella spp.	12–36 h (up to 72 h)	Abdominal pain, diarrhea, chills, fever, nausea, vomiting, bacteremia	Poultry, meat products, eggs and eggs products, fecal-contaminated food
Shigella spp.	4–7 days	Abdominal pain, diarrhea (sometimes bloody), chills, fever	Moist prepared foods, salads, raw fruits and vegetables, raw milk, poultry
Staphylococcus aureus	2–4 h	Nausea, vomiting, abdominal pain, diarrhea	Ham, meat, poultry, cream-filled pastry, food mixtures, leftover foods
Vibrio parahaemolyticus	4–96 h	Abdominal cramps, fever, nausea, vomiting, watery diarrhea	Undercooked or raw seafood
Vibrio vulnificus	1–7 days	Abdominal pain, bleeding, diarrhea, ulcers, vomiting, death	Undercooked or raw seafood
Yersinia spp.	24–48 h	Watery diarrhea, vomiting, abdominal pain, fever, sore throat	Meats, oysters, tofu, fish, unpasteurized milk, soy products

(continued)

Table 5.1 (continued)

Etiology	Incubation period	Symptoms	Food sources
Hepatitis A	15–50 days	Abdominal pain, diarrhea, fever, headache, jaundice, nausea	Shellfish, fecal-contaminated water or food
Norovirus	12–48 h	Abdominal cramps, diarrhea, fever, headache, nausea, vomiting, chronic diarrhea	Contaminated water, food or food contact surfaces
Anisakis simplex	12 h-days	Abdominal pain, vomiting, coughing	Saltwater fish
Giardiasis	1 week	Abdominal pain, diarrhea, fever, cramps	Water, raw vegetables and fruits
Cryptosporidium	1–12 days	Abdominal cramps, watery diarrhea, mild fever	Contaminated food or water
Cyclospora cayetanensis	1–14 days	Abdominal cramps, watery diarrhea, fatigue, loss of appetite, nausea, weight loss, vomiting	Contaminated raw products (berries, basil, lettuce)

The most common clinical symptoms of *Campylobacter* infections include diarrhea (frequently bloody), abdominal pain, fever, headache, nausea, and/or vomiting. In transplant recipients, bacteremia is more frequent in the general population, with a mortality rate >20% [9, 10].

The symptoms of *Salmonella enteritidis* infection usually appear 12–72 h after infection and include fever, abdominal pain, diarrhea, nausea, and sometimes vomiting. In SOT recipients, bacteremia is common (20–30% of cases vs. 3–4% in non-transplant recipients) [3].

Escherichia coli foodborne disease is generally self-limiting, but it may lead to a life-threatening disease including hemolytic uremic syndrome (HUS). Symptoms of disease include abdominal cramps and diarrhea, which may be bloody. Fever and vomiting may also occur.

Symptoms of staphylococcal food poisoning usually develop within 30 min to 6 h of ingestion. Commonly patients suffer from vomiting, nausea, stomach cramps, and diarrhea. The illness cannot be transmitted to other persons and usually lasts for only 1 day.

Clostridium perfringens infection usually begins suddenly 6–24 h after ingestion and lasts for less than 24 h. Patients have diarrhea and abdominal cramps but usually no fever or vomiting.

Cryptosporidiosis is usually self-limited but in SOT recipients can be chronic with weight loss, electrolyte imbalances, and extraintestinal complications. It causes up to 20% of diarrhea episodes in SOT recipients in developing countries [11].

5.1.3 Microbiological Studies

In SOT recipient, microbiological studies should be performed, especially in cases where the illness persists [12]. In SOT patients with diarrhea, testing for *C. difficile*, norovirus by PCR, bacteria by stool culture, and *Giardia* and *Cryptosporidium* by EIA are recommended as first-line testing; supplemental testing with ova and parasites if at risk for parasite exposures, such as modified acid-fast stain, is useful for the identification of oocysts of the coccidian species (*Cryptosporidium*, *Cystoisospora*, and *Cyclospora*), which may be difficult to detect with routine stains such as trichrome. Multiplex PCR for viral, bacterial, and parasitic pathogens are now available and may have increased sensitivity with respect to the standard tests. Fresh stool samples for culture and analysis provide the highest yield. Stool examination for parasites generally is indicated for patients with suggestive travel histories, chronic diarrhea, and unresponsiveness to antimicrobials.

5.1.4 General Approach

Oral rehydration and symptomatic treatment are the cornerstone of the treatment of foodborne diseases. Unlike immunocompetent patients, transplant recipients frequently need antimicrobials. This is the case for *Salmonella* and *Campylobacter* infections. The empiric antimicrobial therapy in adults should be either a fluoroquinolone such as ciprofloxacin, or azithromycin, depending on the local susceptibility patterns and travel history. Giardiasis can be treated either with tinidazole or nitazoxanide; this last one is the first choice to treat cryptosporidiosis. Cyclosporiasis and yersiniosis are treated with trimethoprim-sulfamethoxazole. Antibiotics should be avoided in cases of STEC, as they may increase the risk of HUS. Antibiotics are also not indicated in toxin-mediated disease. Caution should be made to possible interactions of antimicrobial agents and immunosuppressants. There is no specific therapy for norovirus infection beyond hydration and antimotility; variable success has been seen with the use of immunoglobulin, breast milk, and nitazoxanide [13]. Immunosuppression therapy should be reduced as much as it is safe. However, there is no evidence of beneficial effects of immunosuppression reduction for norovirus infection. Antimotility agents may delay clearance of toxins; therefore, they should be used with caution in SOT recipients. Bismuth subsalicylate should be avoided for decreased renal function.

5.1.5 Prevention of Foodborne Diseases

Prevention is essential in reducing the cases of foodborne illness [14]. Some foods are more associated with illnesses than others (see Table 5.1). Transplant recipients and caregivers should pay particular attention to local recommendations when outbreaks occur to avoid exposure to contaminated foods.

According to the World Health Organization, there are five key rules for food safety [15]:

1. Hands should be washed before and often during food preparation and after going to the toilet. Surfaces and equipment used for food preparation should be washed and sanitized and protected from insects, pests, and other animals.
2. Raw and cooked food and the equipment and utensils used to prepare them need to be separated.
3. Food should be cooked thoroughly, especially meat, poultry, eggs, and seafood. Soups and stews should come to a boil, making sure that they have reached 70 °C. Cooking meat and poultry with a thermometer is advisable.
4. Food needs to be kept at safe temperatures (<5 °C or >60 °C). Cooked food should not be left at room temperature >2 h. Frozen food should not be thawed at room temperature.
5. Only safe water and raw materials should be eaten. Milk must be always pasteurized or boiled, and fruits and vegetables need to be washed if eaten raw and if possible peeled.

5.2 Travel Advice

Travel to tropical or developing countries poses substantial risk to transplant recipients, particularly during periods of maximal immunosuppression [16]. Plans to travel should be discussed at least 2 months before the travel, ideally in a Travel Medicine Clinic with specific transplant protocols. In this visit several issues need to be addressed:

1. Net State of Immunosuppression

Time since transplantation is the first issue to consider. Most authorities recommend avoid traveling to high-risk destinations during the first year of the transplant [17]. The net state of immunosuppression needs also to be considered. Recent episodes of rejection, changes in the immunosuppressive regime, and comorbidities increase the risk and severity of travel-related infections.

2. Graft Function and Medication

It is important that a SOT recipient who is planning to travel is in a stable situation. Patients should take a summary of his/her medical history, a signed copy of their medication list, and sufficient supply of medication as hand luggage. It is advisable to investigate healthcare facilities abroad in the event of an emergency in the area visited.

3. Travel Itinerary

Updated travel advisories should be obtained, as disease risks are not stable over time. The travel itinerary and specific travel plans need to be assessed, considering the specific areas of travel within the country, the activities planned (business vs. leisure), travel's length, and the type of accommodation [18]. Patients should be counseled about cancelation and travel insurance as well.

4. Advice on Minimizing the Risk of Illness

Insect-transmitted infections can be life-threatening in SOT recipients. The application several times a day of an insect repellent containing diethyltoluamide (DEET) is advised. It is also recommended clothing to cover the arms, ankles, and legs despite temperature conditions and the use of mosquito netting [19].

Walking barefoot and swimming in freshwater should be avoided, to reduce the risk of some parasitic infections such as strongyloidiasis, schistosomiasis, or hookworm infection. Leptospirosis may be transmitted through contact with water contaminated with rodent's urine.

Sunscreen lotions and avoidance measures are advised as SOT recipients are at increased risk of skin cancer and photosensitivity [20].

Patients should practice strict hand hygiene and maintain good food safety practices to avoid infections transmission (see foodborne diseases prevention).

To decrease the risks of endemic fungi, the SOT recipients traveler should minimize exposure to outdoor dust, travel in enclosed air-conditioned vehicles, and avoid buildings with active construction. Activities with high risk of aerosolization of spores such as caving or dirt biking must also be avoided.

Travelers to malarial areas should take malaria chemoprophylaxis based on antimalarial drug resistance at the destination and the potential drug interactions [17]. Mefloquine and chloroquine may increase calcineurin inhibitor levels and the risk of arrhythmias when given with TMP/SMX or tacrolimus. Atovaquone-proguanil has less interactions [19]. It must be noted that no antimalarial drug is 100% protective and must be combined with the use of personal protective measures.

Evidence supporting prophylaxis against leptospirosis is ambiguous; however, the CDC recommends doxycycline if high-risk exposures (i.e., floods, heavy rainfall, and recreational water activities [17]).

Traveler's diarrhea in a SOT recipient may lead to renal failure, drug toxicity, and graft dysfunction. Although prophylactic antibiotics can be employed, especially in short travels, the potential of breakthrough diarrhea and side effects usually outweigh the potential benefits. SOT recipients should travel with azithromycin or a fluoroquinolone to be used in cases of traveler's diarrhea.

5.3 Posttransplant Vaccines

Vaccine-preventable diseases are important causes of morbidity and mortality after SOT. Vaccines should generally be given pretransplant where possible [21]. Posttransplant patients can receive inactivated vaccines (Table 5.2). Live-attenuated vaccines are generally avoided with some exception.

Table 5.2 Routine and travel vaccination (highlighted) for the posttransplant patient

Inactivated vaccine	Risk/condition	Dosing schedule
TdaP (tetanus, diphtheria, acellular pertussis)	All	One dose—if not received in the last 10 years
Pneumococcal vaccines:Prevnar13 (PCV13)Pneumovax (PPV23)	All	*Persons who have never had pneumococcal vaccine*: Give one dose of Prevnar13 and Pneumovax at least 8 weeks later *Persons who have previously had Pneumovax*: Wait a minimum of 1 year from the last Pneumovax and give Prevnar13. Then give one dose of Pneumovax 5 years from previous dose and a minimum of 8 weeks from Prevnar13 dose. No further Pneumovax boosters are recommended
Hepatitis B	All (if anti-HBs negative)	Check anti-HBs, and if negative, start three-dose series 0, 1, 6 months Use high-dose hepatitis B vaccine (40 μg Recombivax)
Influenza	All	Annually—use injectable vaccine High-dose vaccines or two standard doses 5 weeks apart may have greater immunogenicity
HPV	Men ≤26 years and MSM of any age,Women ≤45 years of age	Three doses at 0, 2, 6 months
HiB (*Hemophilus influenzae*)	Asplenia or hyposplenia;lung transplantation	One dose
Hepatitis A	All	Two doses at 0, 6 months
Shingles (inactivated)	Age ≥50 years and VZV IgG positive	Two doses at 0, 2–6 months
Meningococcal A, C, Y, W-135	Asplenia or hyposplenia, travel to meningitis-endemic area,complement deficiencyEculizumab use	Two doses of quadrivalent vaccine 8 weeks apart (Menactra or Menveo)
Meningococcal B	Eculizumab use	Two doses of vaccine 8 weeks apart
Rabies	Extensive ongoing close contact with animals	Three doses intramuscular at 1, 7, 21–28 days

Table 5.2 (continued)

Inactivated vaccine	Risk/condition	Dosing schedule
Typhoid (*Salmonella typhi*)	Travel to areas of typhoid transmission	One dose Use inactivated parenteral vaccine
Dukoral	For prevention of traveler's diarrhea	Two oral doses 6 weeks apart Available in some countries only
Live vaccine		
Varicella	VZV IgG negative	Two doses 6 weeks apart Select posttransplant patients on minimal immunosuppression, normal lymphocyte count, close follow-up
MMR	Contraindicated	
Shingles (live-attenuated)	Contraindicated	
Yellow fever	Contraindicated	Small series post-SOT suggests it is safe although data are limited

Vaccine responses are generally reduced compared to healthy controls especially early posttransplant or rejection treatment, particularly if lymphocyte-depleting therapies or rituximab is utilized. In general, vaccination can be started any time after 1 month posttransplant; however, immunogenicity may be diminished with higher doses of immunosuppression. Vaccinations may be routine (e.g., pneumococcal, influenza, hepatitis B) or given in specific circumstances (e.g., meningococcal, rabies). Pneumococcal conjugate vaccine contains protein-conjugated polysaccharides from 13 common serotypes of pneumococcus and is immunogenic in SOT recipients [22, 23] polysaccharide pneumococcal vaccine covers an additional 10 serotypes and is also recommended for SOT recipients. Appropriate intervals are required between the vaccines (Table 5.2). Posttransplant, high-dose hepatitis B vaccine containing 40 μg antigen per dose should be used for optimal seroconversion. Anti-HBs should be determined after 2–4 weeks after vaccination. Combined hepatitis A and hepatitis B vaccines could be used but generally contain <40 μg of hepatitis B antigen and may be less effective. If response is inadequate, an additional three-dose series can be attempted. Influenza vaccine should be provided annually; recent studies have shown that either high-dose vaccine or two doses of standard doses of inactivated influenza vaccine 5 weeks apart may have greater immunogenicity in SOT recipients compared to standard regime [24, 25]. Recently a new inactivated shingles vaccine has been authorized for persons ≥50 years of age who have immunity to varicella. There are currently no published data in SOT recipients with this vaccine.

Meningococcal vaccines should be given to those with risk factors only. In transplantation, specific situations warranting meningococcal vaccine include splenectomy and the use of eculizumab. In patients who undergo planned splenectomy, two doses of meningococcal quadrivalent vaccine should be given with the last one being at least 2 weeks prior to surgery. For unplanned splenectomy, vaccination can be started after postoperative recovery. Response rates may be better if vaccines are given prior to splenectomy. In some parts of the world, there is an increased incidence of meningococcal B disease [26]. A separate vaccine for the B strain is

available and can also be given in cases of splenectomy. Meningococcal vaccine has an approximately 50% seroresponse rate in transplant recipients although data in this population post-splenectomy are lacking [27, 28].

Use of the terminal complement inhibitor eculizumab is shown to predispose to fatal meningococcal sepsis. Therefore, two doses of meningococcal quadrivalent vaccine should be given prior to initiating eculizumab. Similar to splenectomy, meningococcal B vaccine can also be given. Meningococcal disease has occurred despite vaccination, and therefore for additional protection, antibiotic prophylaxis is recommended. Agents for chemoprophylaxis include amoxicillin or ciprofloxacin given for the duration of eculizumab and continuing for 3 months after the last dose of eculizumab.

Inactivated travel vaccines include injectable typhoid and oral cholera vaccine. Live vaccines should be avoided in the posttransplant period although published literature in pediatric patients suggests that select posttransplant patients could safely receive live varicella vaccine [29]. Not enough data are available to recommend other live vaccines. A yellow fever vaccine waiver is generally required for SOT recipients traveling to yellow fever-endemic areas. Serology is only routinely available for certain vaccine-preventable diseases and includes hepatitis A and B, rabies, varicella, measles, mumps, and rubella.

Close contacts of transplant patients can receive the most necessary vaccines including live vaccines. Live vaccines contraindicated in close contacts are oral polio and smallpox vaccines due to the risk of transmission. For other live vaccines, the risk of transmission of attenuated pathogens is minimal. Frequent handwashing should be practiced after contact with infants and children who have received live vaccines including rotavirus, varicella, and MMR vaccines. Healthcare workers who work with SOT patients should be up-to-date on all vaccines.

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Part II

Specific Pathogens

Prevention and Treatment of CMV Infection (and Other Herpes Viruses)

6

Julian Torre-Cisneros and Atul Humar

6.1 Prevention and Treatment of Cytomegalovirus (CMV) Infection

6.1.1 Description of the Pathogen

CMV is a double-stranded DNA virus of the *Herpesviridae* family that has the capacity to produce primary infection or reactivation in SOT recipients.

6.1.2 Definitions

- *Infection or replication*: Isolation of the virus or the detection of viral proteins (antigenemia) or CMV DNA/mRNA in any body liquid or tissue. In SOT recipients, latent infection (i.e., seropositivity for CMV) is generally considered to be a separate entity.
- *Antigenemia*: Direct detection of the CMV pp65 antigen in peripheral blood leukocytes, mainly neutrophils.
- *DNAemia*: Detection of CMV DNA in plasma or whole blood.
- *CMV disease*: Evidence of symptoms or signs together with the detection of CMV infection in blood or tissue. CMV disease can be classified as a viral syndrome (see below) or tissue-invasive disease (in case of end organ disease such as CMV gastrointestinal disease or pneumonitis). Proven CMV disease requires

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the presence of CMV in tissue. A new category of probable CMV disease has been proposed in case of compatible symptoms of end-organ disease, but without confirmation by biopsy.

- *Viral syndrome*: Presence of fever and/or malaise associated with the presence of leukopenia and thrombocytopenia or an increase in transaminases. This is considered a type of CMV disease.
- *Universal prophylaxis*: Administration of an effective antiviral drug to prevent the development of CMV replication and/or disease in at-risk patients.
- *Preemptive therapy*: Regular monitoring for CMV replication followed by initiation of antiviral treatment in patients displaying asymptomatic CMV replication in order to prevent progression to CMV disease.

6.1.3 Diagnosis

Although antigenemia is still used, a quantitative real-time nucleic acid amplification-based assay or polymerase chain reaction (PCR) is recommended for the diagnosis and monitoring of CMV infection after transplantation. Viral loads can be determined in both plasma and whole blood samples, but the same type of sample should be used when comparing viral loads or following a given patient. There are also differences between viral loads obtained in different centers, thus making an international standard reference necessary. Of note, an improvement on the agreement between viral load values has been obtained with the calibration of tests using the World Health Organization (WHO) international standard. There is a direct association between viral load values and the likelihood that an individual will develop active disease. Moreover, the rate of increase of viral loads is also a predictor of developing disease. Due to the variability of the results among laboratories, a single test should be used for monitoring patients over time. Laboratories should establish their own cutoffs and audit clinical outcomes to verify the trigger points used for treatment.

Viral resistance depends on the existence of mutations in the CMV genome. Plasma or whole blood is the sample of choice. Genotypic assays (PCR amplification) are available for clinical use. Two genomic regions must be studied: UL97 kinase gene involved in the initial phosphorylation of ganciclovir (codons 400–670) and the UL54 polymerase gene (codons 300–1000). Common UL97 and UL54 mutations are shown in Table 6.1. A web-based search tool, www.informatik.

Table 6.1 Levels of ganciclovir resistance with the most common UL97 mutations

Mutations or deletions	Ganciclovir IC_{50} mutant strain/ wild type	Interpretation
M460V/I/T, H520Q, A594V/G, L595S/W, C603W	5–15	High-grade resistance
C592G	2–5	Low-grade resistance

For other less frequent mutations, search the web-based tool, www.informatik.uni-ulm.de/ni/staff/HKestler/hcmv/

uni-ulm.de/ni/staff/HKestler/hcmv/, has been developed that links the sequence to a database containing all published UL97 and UL54 mutations and corresponding antiviral drug susceptibility phenotypes. If mutations only appear in the UL97 gene, viruses are resistant only to ganciclovir. UL54 mutations typically added to pre-existing UL97 mutations, increasing the level of ganciclovir resistance and commonly conferring different levels of cross-resistance to other CMV antivirals such as foscarnet or cidofovir. In the future, next-generation sequencing (NGS) technologies may enable the detection of far smaller viral subpopulations and may therefore improve the detection of drug resistance emergence.

6.1.4 Immunological Monitoring

Testing for anti-CMV IgG antibodies should be performed before transplantation in donors and recipients for the purposes of risk stratification. In recipient CMV negative (R−) patients, testing should be repeated at the time of transplantation. Donor serostatus should also be performed to stratify the subsequent risk of CMV infection and disease.

The use of CMV specific cell-mediated assays may also be clinically useful. The characteristics of different technics available for immunological monitoring are reviewed in Table 6.2. If available, pretransplant CMV-specific cell-mediated

Table 6.2 Available methods for monitoring of CMV-specific T-cell-mediated immune response

Characteristic	Intracellular cytokine staining	ELISpot	QuantiFERON-CMV	MHC-tetramer staining
Turnaround time	8–10 h	24–48 h	24 h	1–2 h
Functional analysis	Yes	Yes	Yes	No (unless associated to intracellular cytokine staining)
Differentiation between $CD8^+$ and $CD4^+$ T cells	Yes	No	No (detects mostly $CD8^+$ T cells)	Yes
Commercially available test	No	Yes	Yes	Yes
Advantages	Gold standard. Potential for freezing PBMCs	Potential for freezing PBMCs, can be used in presence of lymphopenia	Standardized	Specificity
Limitations	Lack of technical standardization. Expert laboratory is needed	Lack of technical standardization. Expert laboratory is needed	Limitations in patients with lymphopenia	Lack of technical standardization. Expert laboratory is needed

CMV cytomegalovirus, *ELISpot* enzyme-linked immunosorbent spot assay, *PBMCs* peripheral blood mononuclear cells

immunity may better stratify the risk of CMV infection after transplantation as compared to serology, particularly in R+ recipients. After transplantation, the potential utility of monitoring CMV-specific cell-mediated immunity has been investigated in various clinical scenarios. Overall, a reactive test has a high negative predictive value for detecting risk of CMV replication, supporting the safety of discontinuing prophylaxis in high-risk patients above the protective threshold. Alternatively, patients with no evidence of protective response at the end of the prophylaxis period could benefit from the so-called hybrid approach (in which preemptive monitoring is initiated after completing prophylaxis). On the other hand, immune monitoring in intermediate-risk patients managed preemptively may be useful in guiding the frequency for surveillance of CMV infection and the thresholds for initiating antiviral therapy, or in case of treatment failure after appropriate antiviral therapy. However, interventional clinical trials are required to evaluate protocolized interventions based on the posttransplant kinetics of CMV-specific responses before including these assays in the routine clinical practice.

6.1.5 Prevention

Two major strategies have been used to prevent CMV infection: universal prophylaxis and preemptive therapy. Both are effective in the prevention of CMV disease.

Universal prophylaxis may be preferable in scenarios of rapid viral dynamics (lymphocyte-depleting therapy, potent immunosuppression, D+/R− setting). Oral valganciclovir is currently the preferred antiviral drug for the prevention of CMV infection, although intravenous ganciclovir can be used early after transplant if oral absorption is compromised. High-dose valacyclovir is an alternative option in renal transplantation. Letermovir is a promise drug that is currently under clinical development.

Late-onset CMV disease, defined as disease occurring after discontinuation of prophylaxis, is a common finding when using universal prophylaxis in D+/R− transplant recipients, developing in 20–36% of patients, depending on the type of organ transplant. A 200-day prophylaxis regimen has been shown to reduce the incidence of late-onset CMV disease, and it is recommended in D+/R− kidney transplant patients and, by extension, in other high-risk transplant recipients (e.g., heart, pancreas). In R+ patients, 3-month regimens are preferred. In lung and intestinal transplant recipients, the majority of the clinicians extend prophylaxis over 6 to 12 months after transplantation for both D+/R− and R+ patients. In recipients receiving alemtuzumab as induction therapy, monitoring of $CD4^+$ T lymphocytes has been used to continue prophylaxis (for at least 6 months) until CD4 T lymphocytes are over 200 cell/mm^3, although the efficacy of this strategy has not been tested on clinical trials.

In a preemptive strategy, viral load is typically monitored weekly for the first 12–14 weeks posttransplant. There are no evidence-based recommendations regarding the viral load cutoff for initiating antivirals and the optimal duration of preemptive therapy. It may be preferable to initiate preemptive therapy in any high-risk

patients with a positive viral load at any level. In lower-risk patients, it is possible to establish local cutoff points and eventually delay therapy, consider reducing the levels of immunosuppressive therapy, and repeat a second viral load after a short interval, since small blips may resolve spontaneously. Treatment should be administered for a minimum of 2 weeks. Monitoring of CMV viral load should direct the duration of treatment. At least one negative viral load determination (or viral load below a specific threshold) in plasma specimens is required in order to withdraw treatment. Relapse of CMV infection is frequent after a therapy course, although it is generally resolved after a new course of treatment or even spontaneously.

There is no available data supporting the use of a combined preemptive therapy strategy after prophylaxis in low-risk transplant recipients. Nevertheless, this strategy, which is known as a "hybrid strategy," is commonly used in certain high-risk transplant recipients (D+/R−, lung, pancreas, and small bowel recipients and/or those receiving lymphocyte-depleting treatments). The duration of a preemptive approach post-prophylaxis has not been determined.

Taking into account the low risk of CMV disease reported in the subgroup of D−/R− recipients, the use of prophylaxis or preemptive therapy have not been recommended. Other measures, such as the use of leuko-depleted or CMV-seronegative blood products, directed at preventing CMV infection acquisition, are recommended.

Hypogammaglobulinemia (IgG <500 mg/dL) has been proposed as being a risk factor for CMV disease after SOT transplantation. In heart transplant recipients, the administration of non-specific intravenous immunoglobulins (IVIGs) with the goal of maintaining normal IgG levels was associated with a lower risk of CMV infection. In heart, lung, and intestinal transplant recipients at high risk for CMV disease (D+R−), some centers add specific anti-CMV IVIG to prevent CMV infection. The best dosing regimen has not been established.

A recommendation regarding the use of CMV vaccine in SOT recipients cannot be made as no vaccine has been approved for use in a clinical setting.

6.1.6 Treatment

Intravenous ganciclovir and oral valganciclovir are the antiviral drugs of choice for treating CMV infection and disease. Intravenous ganciclovir (5 mg/kg/12 h) should be used in patients with severe CMV disease or when valganciclovir is poorly tolerated or not well absorbed. It is important to administer the appropriate doses of intravenous ganciclovir or oral valganciclovir adjusted for renal function, as inadequate dosing can cause clinical failure or viral resistance. Oral valganciclovir (900 mg/12 h) is effective in patients with mild to moderate CMV disease. It can also be used in sequential therapy in patients treated with intravenous ganciclovir, once clinical improvement is documented.

The optimal duration of treatment should be guided by weekly virological monitoring (treat until viral load negative or below a certain threshold) and clinical response. The minimum duration of treatment is 2 weeks. Following initial treatment secondary prophylaxis is commonly used for a period of 1–3 months although

evidence for this is lacking and it is currently not recommended. The treatment of a recurrence should generally be the same used during the first episode.

The evidence to support the use of specific anti-CMV immunoglobulins in cases of life-threatening CMV disease, particularly severe pneumonitis, is lacking, although it is often used.

Resistance to antiviral drugs should be suspected in the presence of progressive or stable viral loads or if clinical symptoms persist despite adequate antiviral treatment for 2 weeks, particularly in case of risk factors (D+/R− serostatus, lung transplantation, serious invasive disease and/or high viral load, intermittent low-level viral replication during therapy or suboptimal drug levels, and prolonged antiviral drug exposure). If genotypic tests demonstrate the existence of a high-level resistance mutation in the UL97 gene or the UL54 gene (Table 6.1), foscarnet is indicated. Increasing the dose of ganciclovir up to 10 mg/kg/12 h might be useful for other mutations in the UL97 gene and can be considered for patients with non-severe CMV disease or in those whom the use of foscarnet should be avoided (nephrotoxicity).

Maribavir has been successfully used in salvage therapy in patients with refractory/resistant CMV infection and is currently in phase 3 trial for this indication. Brincidofovir and letermovir are also promising drugs that need clinical development in this indication. Switching immunosuppression from calcineurin inhibitors to an mTOR inhibitor-based regimen has been proposed as an adjunctive therapy, although most data on the effect of mTOR inhibitors on resistant CMV are provided from uncontrolled studies. There is no enough evidence to recommend leflunomide as a therapeutic agent for treating antiviral-resistant CMV infection.

Adoptive immunotherapy can be useful for the rescue of case refractory to conventional treatment and who do not develop a satisfactory immune response. However, clinical experience in the solid organ transplant setting is very limited.

General Approach The key recommendations for the management of CMV infection are provided in Table 6.3.

6.2 Prevention and Treatment of Other Herpes Viruses

6.2.1 Description of the Pathogens

Herpes simplex virus (HSV), varicella-zoster virus (VZV), and human herpesvirus 6 (HHV-6) and human herpesvirus 8 (HHV-8) belong to the *Herpesviridae* family and have the capacity to produce primary infection or reactivation in the recipients of a solid organ transplant. Clinical manifestations of VZV and HSV include mucocutaneous disease, although a higher rate of disseminated disease (gastrointestinal disease, CNS infection, respiratory tract infection) is seen in SOT recipients. Epstein-Barr virus is reviewed in a specific chapter. Human herpesvirus 7 is generally not of significant clinical impact. HHV-8 is associated with Kaposi's sarcoma (with cutaneous and disseminated manifestations), multicentric Castleman disease, and primary effusion lymphoma.

Table 6.3 Key recommendations for the management of cytomegalovirus infection after solid organ transplantation

Area of interest	Recommendations
Diagnosis	Methods based on quantitative CMV DNA amplification are the methods of choice Genotypic testing has become the usual means for detecting drug resistance
Immunological monitoring	Testing for anti-CMV IgG antibodies should be performed before transplantation in donors and recipients Pretransplant CMV-specific cell-mediated immunity may be used together with serological testing to stratify the risk of CMV infection after transplantation Posttransplant monitoring of CMV-specific cell-mediated immunity can be useful in: – High-risk patients (D+/R−, prior use of T-cell-depleting antibodies) on antiviral prophylaxis can be used to predict the risk of late CMV infection – R+ patients under preemptive therapy to predict the occurrence of CMV infection or the spontaneous clearance of viremia without the need of antiviral prophylaxis – Lack of response to antiviral therapy
Prevention (strategy)	For D+/R− kidney and liver recipients, universal prophylaxis is preferable to preemptive therapy For D+/R− heart and lung recipients, the use of prophylaxis is preferable to preemptive therapy Prophylaxis is preferable to preemptive therapy in lung, pancreas, and intestinal transplantation until more data are available For seropositive recipients after kidney, liver, and heart transplantation, either strategy is acceptable Prophylaxis is preferred in other high-risk patients (lymphocyte-depleting therapy, potent immunosuppression, and HIV infection)
Prevention (drug of choice)	Oral valganciclovir is the preferred antiviral In patients with severe leukopenia, oral acyclovir or valacyclovir is an alternative to valganciclovir in kidney transplant recipients
Prevention (duration)	Six months is recommended for D+/R− kidney, heart, and pancreas transplant recipients For D+/R− liver transplant recipients, the duration of prophylaxis should generally be between 3 and 6 months When a prophylaxis strategy is used for the prevention of CMV in R+ patients (with either D+ or D−), 3 months of antiviral medication should be used for kidney, pancreas, liver, and heart transplant recipients Between 6 and 12 months of prophylaxis is recommended for lung and intestinal transplant recipients
Prevention (preemptive therapy)	Preemptive therapy must be initiated with any viral replication in high-risk patients (D+/R−, lymphocyte-depleting treatments) Preemptive therapy in R+ recipients must be initiated in base of a cutoff viral load established in each center or increasing kinetics Maintain therapy for at least 2 weeks and/or at least one negative viral load determination
Prevention (hybrid strategy)	Preemptive therapy after finishing CMV prophylaxis can be recommended in high-risk transplant recipients, including D+/R−, lung, pancreas, and small bowel recipients, and/or those receiving lymphocyte-depleting treatments (the duration has not been determined)

(continued)

Table 6.3 (continued)

Area of interest	Recommendations
Prevention (D−/R− patients)	The routine use of prophylaxis or preemptive therapy against CMV is not recommended Use leuko-depleted or CMV-seronegative blood products
Prevention (IgG deficit)	Non-specific or anti-CMV-specific IVIG is indicated in heart transplant recipients with IgG level <500 mg/dL
Treatment	CMV disease should be treated with oral valganciclovir (900 mg/12 h, for mild-moderate disease) or intravenous ganciclovir (5 mg/kg/12 h, for severe disease) corrected by renal function Intravenous ganciclovir can be followed by oral valganciclovir when clinical and virological improvement has been achieved (sequential therapy) Maintain treatment until resolution of symptoms and viral replication in plasma Combined use of immunoglobulins can be considered in patients with hypogammaglobulinemia of life-threatening CMV disease (pneumonitis)
Treatment (resistance)	This is a complicated situation that should be managed by an expert transplant ID CMV resistance must be suspected in cases of progressive or stable viral replication or persistence of symptoms despite adequate antiviral treatment for 2 weeks A genotypic analysis of the UL97 and UL54 genes must be performed Foscarnet is the alternative treatment of choice High-dose ganciclovir (up to 10 mg/kg/12 h with normal renal function) can be used in non-severe patients without neutropenia, for whom the use of foscarnet should be avoided An mTOR inhibitor-based regimen of immunosuppression should be used The experience of salvage therapy with alternative regimens is limited (maribavir, leflunomide, artesunate, letermovir, or brincidofovir)

6.2.2 Herpes Simplex Virus

6.2.2.1 Diagnosis

Although pretransplant IgG serostatus of recipients may be helpful for post-transplant risk stratification, serology is not useful for diagnosing acute disease. Transplant patients can have atypical mucocutaneous lesions and visceral or disseminated disease; therefore laboratory confirmation may be necessary. PCR testing of mucocutaneous lesions, and other clinical samples (plasma, cerebrospinal fluid, bronchoalveolar lavage), is the diagnostic test of choice. The clinical significance of finding HSV DNA in the blood of patients without disseminated disease has not been well established and therefore is not recommended to be tested routinely. Also, a positive PCR in the BAL may be either due to mucocutaneous contamination during sampling or due to HSV pneumonitis. Tissue histopathology with immunohistochemistry for HSV can be helpful in diagnosing invasive HSV disease.

6.2.2.2 Prevention

HSV prophylaxis is generally indicated for HSV-1- or HSV-2-seropositive recipients not receiving CMV prophylaxis ((val)ganciclovir prevents HSV replication). Some experts also recommend prophylaxis in HSV seronegative to prevent the infection transmitted from organs or blood transfusions; however, this is a rare occurrence. A low-dose acyclovir regimen (< 1gr/day) is effective (200 mg three or four times a day, 400 mg two times a day) for prophylaxis. Valacyclovir (two times a day) or famciclovir can also be used.

Antiviral prophylaxis should continue for at least 1 month. Resumption of prophylaxis may be considered for CMV-seronegative patients being treated with T-cell-depleting agents. In patients with severe clinical recurrences (≥2), suppressive antiviral therapy may be indicated and may occasionally be required for very prolonged durations.

All recipients (not only seronegative) should avoid contact with persons with active lesions. Condoms do not completely protect against HSV transmission. HSV-2-seronegative transplant recipients should consider having their partner tested for HSV-2. In serodiscordant couples, daily antiviral therapy taken by the seropositive partner can prevent HSV-2 transmission to the seronegative partner. The efficacy of postexposure prophylaxis is unknown.

6.2.2.3 Treatment

Disseminated, visceral, or extensive mucocutaneous HSV disease should be treated with intravenous acyclovir at a dose of 5–10 mg/kg every 8 h for a minimum of 2 weeks (3 weeks in case of encephalitis). Non-severe mucocutaneous disease can be treated with oral acyclovir, valacyclovir, or famciclovir for a minimum of 1 week. Overall treatment durations are determined by clinical response. HSV keratitis can be treated with systemic or topical agents (trifluridine solution, vidarabine ointment, or topical ganciclovir gel).

Resistance must be considered in patients whose lesions are not responding clinically to appropriate doses of systemic therapy. Genotypic testing for known resistance mutations is available in some settings. Intravenous foscarnet or cidofovir are recommended, but both are associated with significant renal toxicity. Topical agents (imiquimod, cidofovir, trifluridine) can be used for resistant anogenital disease.

General Approach The main recommendations for the management of HSV infection are provided in Table 6.4.

6.2.3 Varicella-Zoster Virus

6.2.3.1 Diagnosis

All transplant candidates should undergo serologic testing for VZV to determine the need for vaccination in case of seronegativity and to assess posttransplant risk. In general, both primary varicella and herpes zoster have typical clinical presentations

Table 6.4 Key recommendations for the management of herpes simplex virus infection after solid organ transplantation

Area of interest	Recommendations
Diagnosis	Pretransplant IgG serostatus of donor and recipient is necessary to determine preventive strategies Polymerase chain reaction is the diagnostic test of choice Tissue histopathology with immunocytochemistry can be helpful
Prevention	Prophylaxis is indicated only for seropositive recipients not receiving CMV prophylaxis Low-dose acyclovir (< 1gr/day) is indicated (200 mg three or four times a day, 400 mg two times a day) Valacyclovir (500 mg two times a day) or famciclovir can also be used Antiviral prophylaxis should continue for at least a month Suppressive antiviral therapy can be indicated even during years or lifelong in cases of frequent severe recurrences Avoid contact with persons with active lesions Condoms do not completely protect against HSV transmission Seronegative HSV-2 recipients: consider having their partner tested for HSV-2 Serodiscordant couples: daily antiviral therapy taken by the seropositive partner can be considered in individual basis
Treatment	Disseminated, visceral, or extensive mucocutaneous disease: intravenous acyclovir (5–10 mg/kg every 8 h during a minimum of 2–3 weeks) Not severe mucocutaneous disease: oral treatment during a minimum of 1 week (acyclovir, valacyclovir, or famciclovir) Keratitis: systemic or topical agents (trifluridine solution, vidarabine ointment, or topical ganciclovir gel)
Resistance	Genotypic testing can be available Intravenous foscarnet or cidofovir (renal toxicity) is indicated Topical agents (imiquimod, cidofovir, trifluridine) can be used for resistant anogenital disease

that allow for a presumptive clinical diagnosis. Nevertheless, transplant recipients can have atypical presentations or multi-organ involvement with delayed or absent rash. Also, in some instances, VZV Infection may be difficult to differentiate from HSV infection. Therefore a definitive laboratory testing is indicated for atypical cases and visceral disease. PCR is the method of choice (vesicle fluid, serum, spinal fluid, and other tissues).

6.2.3.2 Prevention

Antiviral Therapy Antiviral prophylaxis for VZV is not needed during periods of CMV prophylaxis with valganciclovir. In CMV-seronegative patients followed by a preemptive approach, (val)acyclovir is efficacious for preventing both HSV and VZV during the early posttransplant period.

Pretransplant Vaccination Seronegative potential transplant patients should receive varicella vaccination with the live attenuated vaccine at least 4 weeks before transplant.

Posttransplant Vaccination The live vaccine poses a risk of disseminated infection in immunosuppressed patients and therefore is contraindicated for posttransplant recipients. Recently, an inactivated zoster vaccine has become available for prevention of singles, but there are limited published data on its use in transplant patients.

Postexposure Prophylaxis Options for postexposure prophylaxis include passive immunoprophylaxis and/or antiviral therapy. VZV immunoglobulins are recommended in susceptible (seronegative) patients exposed to VZV and should be given as soon as possible but within at least 10 days of exposure. Antiviral therapy should be considered as adjunctive therapy or in patients who were unable to receive immunoprophylaxis before 10 days after their exposure. Acyclovir or valacyclovir or famciclovir can be used for a 7–14-day course.

6.2.3.3 Treatment

Varicella Patients should be treated with acyclovir, initiated early, especially within 24 h of rash onset.

Herpes Zoster Patients with disseminated or organ invasive disease should be treated with IV acyclovir. Localized non-severe HZ can be treated with oral valacyclovir or famciclovir, with the exception of herpes zoster ophthalmicus or herpes zoster oticus, for which intravenous administration is recommended.

General Approach The main recommendations for the management of HZV infection are provided in Table 6.5.

Table 6.5 Key recommendations for the management of herpes zoster virus infection after solid organ transplantation

Area of interest	Recommendations
Diagnosis	Pretransplant IgG serostatus of donor and recipient is necessary Polymerase chain reaction is the diagnostic test of choice
Prevention	Prophylaxis is not indicated for seropositive recipients receiving CMV or HSV prophylaxis Transplant candidates should receive varicella vaccination at least 4 weeks before transplant Posttransplant vaccination with the live VZV vaccine (Zostavax®) is contraindicated. Experience with the new inactivated vaccine (Shingrix®) is lacking but can be a very effective strategy to prevent zoster in transplant recipients Options for postexposure prophylaxis include passive immunoprophylaxis and/or antiviral therapy (as soon as possible but within at least 10 days of exposure)
Treatment	Patients with varicella or invasive disease should be treated with intravenous acyclovir Localized non-severe herpes zoster can be treated with oral drugs (with exception for herpes zoster ophthalmicus or oticus)

6.2.4 Human Herpesvirus 6

6.2.4.1 Diagnosis

Routine monitoring for HHV-6 is not recommended based on the current evidence or low rate of disease and subclinical infections. Diagnostic testing should be limited to symptomatic HHV-6 disease, in order to guide treatment.

Quantitative real-time PCR is preferred for the detection of HHV-6 viremia. It can distinguish between HHV-6A and HHV-6B, but they may not always differentiate active from latent infection depending on the sample type or assay used. HHV-6 has the characteristic of being capable of integrating into the human genome (ciHHV-6), specifically in the telomeric area of all chromosomes. ciHHV-6 is characterized by persistent HHV-6 viral loads typically of over a million copies per mL of whole blood, which may be misinterpreted as active infection leading to unnecessary treatment. It is not known whether patients with ciHHV-6 may develop active infection. Qualitative or quantitative HHV-6 PCR of the cerebrospinal fluid is useful to diagnose HHV-6 encephalitis in patients with the appropriate clinical signs. Immunohistochemistry to detect viral antigens in biopsy specimens is appropriate in cases of organ disease, although it can be detected in the absence of symptoms.

6.2.4.2 Prevention

Specific antiviral prophylaxis or preemptive therapy for HHV-6 infection is not recommended. Antiviral prophylaxis for CMV does appear to reduce the incidence of HHV-6 viremia.

6.2.4.3 Treatment

Treatment of asymptomatic viral reactivation is not recommended. Ganciclovir, foscarnet, and cidofovir can be active against HHV-6. Ganciclovir is the drug of choice although some experts prefer to give foscarnet in case of CNS infection. HHV6-A can be resistant to ganciclovir though mutations in U69 and U28 genes. Foscarnet can be used in resistant HHV-6. Reduction in immunosuppression is important for severe disease.

General Approach The main recommendations for the management of HHV-6 infection are provided in Table 6.6.

6.2.5 Human Herpesvirus 8

6.2.5.1 Diagnosis

Pretransplant serological screening is not routinely indicated due to a low specificity for screening, although it may be considered in geographic regions with high rates of infection. Quantitative PCR is the method of choice to detect viremia, which is associated with the development of Kaposi's sarcoma. PCR may be an option

Table 6.6 Key recommendations for the management of human herpesvirus 6 infection after solid organ transplantation

Area of interest	Recommendations
Diagnosis	Pretransplant IgG serostatus of donor and recipient is not recommended Polymerase chain reaction is the diagnostic test of choice. In case of persistent high viral loads (>10^6), chromosomal integrated HHV-6 should be suspected Routine monitoring for HHV-6 is not recommended Diagnostic testing should be limited to symptomatic HHV-6 disease, in order to indicate treatment PCR of the cerebrospinal fluid is useful to diagnose HHV-6 encephalitis
Prevention	Specific antiviral prophylaxis or preemptive therapy for HHV-6 infection is not recommended
Treatment	Treatment of asymptomatic viral reactivation is not recommended Ganciclovir is the drug of choice HHV6-A can be resistant to ganciclovir Foscarnet can be used in resistant HHV-6

to monitor for risk of disease as a part of a preemptive strategy in selected high-risk individuals. In addition, HHV-8 viral load measurements can be used to assess response to therapy. Testing for the presence of HHV-8 in biopsy or fluid samples using immunohistochemistry, in situ hybridization, or PCR is also valuable.

6.2.5.2 Prevention

The efficacy of antiviral prophylaxis in HHV-8-seropositive recipients or in patients receiving an organ from a seropositive donor is unknown. Avoidance of over-immunosuppression in high-risk individuals and in those with detectable HHV-8 viremia is advisable. Use of immunosuppression regimens containing sirolimus rather than calcineurin inhibitors may be indicated.

In high-risk patients, monitoring of HHV-8 viral load after transplantation may be a useful to determine the risk of disease. However, the frequency and duration of monitoring or the level of clinically relevant HHV-8 replication has yet to be determined. Moreover, once HHV-8 is detected, current data are insufficient to define a beneficial preemptive strategy with antivirals (ganciclovir, foscarnet, cidofovir),

6.2.5.3 Treatment

An individualized reduction or cessation of immunosuppression (kidney transplant) is the first-line therapy for the treatment of Kaposi's sarcoma. Patients receiving a calcineurin inhibitor-based regimen should be switched to an mTOR inhibitor-based regimen. Sirolimus has antitumor properties and can block HHV-8 replication. Patients whose tumor lesions do not regress may require intralesional chemotherapy, surgical excision or radiation therapy or other local treatment for isolated lesions, or systemic chemotherapy for visceral or severe disease, using liposomal doxorubicin, paclitaxel, or other agents. The benefits of antiviral therapy with (ganciclovir, foscarnet, cidofovir) have been suggested but are unproven.

Table 6.7 Key recommendations for the management of human herpesvirus 8 infection after solid organ transplantation

Area of interest	Recommendations
Diagnosis	Pretransplant IgG serostatus of donor and recipient can be necessary in geographic areas with high rate of infection Polymerase chain reaction is the diagnostic test of choice Routine monitoring for HHV-8 is recommended in high-risk patients (seropositive donor or recipient)
Prevention	Antiviral prophylaxis with ganciclovir can be indicated in high-risk patient with an undetermined duration Preemptive therapy can be indicated in high-risk patients
Treatment	First line: – Reduction or cessation of immunosuppression (kidney transplant) – Conversion to an mTOR inhibitor-based regimen of immunosuppression Second line: – Intralesional chemotherapy – Surgical excision – Radiation therapy or other local treatment for isolated lesions – Systemic chemotherapy for visceral or severe disease (liposomal doxorubicin, paclitaxel, or other agents) The benefits of antiviral therapy with ganciclovir, foscarnet, and cidofovir have been suggested

General Approach The main recommendations for the management of HHV-8 infection are provided in Table 6.7.

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Prevention and Treatment of EBV-Related Complications

7

Sophie Caillard and Michael Green

7.1 Description of Pathogen

Epstein–Barr Virus (EBV) is a ubiquitous human γ-herpesvirus (HHV4) notable for its tropism for B-cell lymphocytes and its ability to establish lifelong infection through latency. Infection typically spreads via saliva, with the virus initially targeting oropharyngeal epithelial cells and subsequently mucosal B lymphocytes leading to dissemination throughout the body. Of note, EBV can also be transmitted from organ donors, serving as perhaps the most important source of EBV infection in individuals undergoing solid organ transplantation (SOT).

7.2 Definitions and Epidemiology

EBV infection occurs worldwide, with seropositivity rates exceeding 90% of the adult population. Data identifies an EBV seroprevalence rate of 83% by the age of 19 in the United States [1] and 95% by the age of 20 in a French population [2]. In seronegative transplant recipients, primary EBV infection is frequently acquired from the donor via passenger leucocytes accompanying the transplant organ. EBV infection can lead to various outcomes after SOT ranging from asymptomatic infection to severe lymphoproliferative disorders including true malignancies. Primary infections are typically associated with more significant clinical syndromes, while

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reactivation of the recipient strain present prior to transplant or reinfection with a new strain of EBV from the donor tends to be mild or even asymptomatic in SOT recipients. Since most adults are already EBV seropositive prior to transplant, primary infection and its associated more prominent disease states occur much more frequently in the pediatric SOT population [3].

Definitions developed to describe the range of EBV infection and diseases are shown in Table 7.1 [4]. Unfortunately, only limited data quantifying the relative frequencies of the full range of EBV disease has been published. Smets and colleagues reported that only 15% of pediatric liver transplant recipients presented with a symptomatic primary EBV infection [5]. Observed symptoms varied from isolated fever or a non-specific viral syndrome to presentation with classical infectious mononucleosis. Not uncommonly, transplant recipients manifest organ-specific symptoms associated with hepatitis, enteritis, pneumonitis, and, rarely, meningoencephalitis. On exceptional occasions, a primary infection can progress toward a life-threatening disease with acidosis, intravascular disseminated coagulopathy, and multi-organ failure.

Symptomatic EBV infection was defined as either seroconversion, development of a positive viral load ≥200 genome copies per 100,000 PBL [12], or histologic evidence of EBV infection (by EBER) in the presence of typical symptoms or laboratory findings (e.g., fever, leukopenia, atypical lymphocytosis, exudative tonsillitis, and/or adenopathy). EBV disease was further characterized as either "proven," "probable," or "possible." "Proven" EBV disease required histologic confirmation using the EBER stain. "Probable" symptomatic EBV infection was diagnosed if there was evidence of EBV infection in the presence of typical symptoms and in the absence of alternate explanation. "Possible" symptomatic EBV infection was made if there was evidence of EBV, the presence of typical symptoms, and an inability to exclude the diagnosis despite the presence of alternate explanation. Episodes of "probable" and "possible"

Table 7.1 EBV infection and disease definitions

EBV infections and diseases	Characteristics
Symptomatic infection	Seroconversion, or more likely the presence of a positive viral load in the range that EBV disease is seen on the assay used to perform the measurement, histological evidence of EBV infection (by EBER) in the presence of typical symptoms or laboratory findings. For probable or possible cases, this could be further classified as viral syndrome, mononucleosis, adenopathy, or adenitis. For proven disease, where biopsy identifies the presence of EBV but does not demonstrate the presence of PTLD, this could be classified by affected organ (e.g., EBV hepatitis, enteritis, adenitis, etc.)
Proven EBV disease	Histological evidence of EBV staining using EBER probe in the presence of signs and symptoms of disease
Probable EBV disease	Presence of typical symptoms, in the absence of alternate explanation
Possible EBV disease	Presence of typical symptoms and inability to exclude alternate explanation

EBV disease were further classified as viral syndrome, mononucleosis, or adenitis/adenopathy.

Patients experiencing primary EBV infection may experience neoplastic transformation of B lymphocytes leading to the development of posttransplant lymphoproliferative disorders (PTLD). PTLD represent a continuous spectrum of abnormal lymphoid proliferations, ranging from lymphoid hyperplasia to polyclonal proliferations to frank malignant monoclonal proliferations, including Hodgkin lymphomas and myelomas [6] (see Table 7.2). Rarely, EBV has also been associated with T- or NK-cell lymphomas, hemophagocytic lymphohistiocytosis, gastric carcinoma, and smooth cells tumors.

7.2.1 PTLD Incidence After SOT

PTLD incidence varies according to the transplanted organ, recipient's age at the time of transplantation, and EBV serostatus [7]. Data from the 2010 OPTN/SRTR annual report revealing the cumulative 1- and 5-year incidence of PTLD in pediatric and adult SOT recipients by transplanted organ is shown in Table 7.3. Results from additional published studies are consistent with these data (reviewed in [8]). For all organ types, PTLD incidence is higher in pediatric compared to adult transplant recipients due to the differential risk of being EBV seronegative at the time of transplantation.

Table 7.2 PTLD histological classification, World Health Organization 2016 (Ref. [5])

Posttransplant lymphoproliferative disorders (PTLD)
Plasmacytic hyperplasia PTLD
Infectious mononucleosis PTLD
Florid follicular hyperplasia PTLD[a]
Polymorphic PTLD
Monomorphic PTLD (B and T/NK cell types)
Classical Hodgkin lymphoma PTLD

[a]Changes from the 2008 classification

Table 7.3 Cumulative 1- and 5-year incidence of PTLD in pediatric and adult SOT recipients by transplanted organ as reported in the 2010 OPTN/SRTR annual report [7][a]

Organ	Pediatric 1 year (%)	Pediatric 5 year(%)	Adult 1 year(%)	Adult 5 year(%)
Lung/heart-lung	4.0	16	1.0	1.5
Liver	2.1	4.7	0.25	1.1
Pancreas (isolated)	N/A	N/A	2.3	2.3
Heart	1.6	5.7	0.3	0.7
Kidney	1.3	2.4	<0.2	0.6

[a]Data for intestinal transplant recipients not broken down by pediatric versus adult and therefore not included

7.2.2 Risk Factors for PTLD

EBV seronegativity and the development of primary infection after transplant are the most important risk factors for PTLD [9, 10]. While primary infection usually occurs in the setting of an EBV-seronegative recipient receiving an organ from an EBV-seropositive donor, viral acquisition via usual transmission routes also occurs. Immunosuppression is another important risk factor impacting the development of EBV/PTLD. The impact of immunosuppression likely is dependent both on the "net state of immunosuppression" and exposure to specific agents. T-cell-depleting agents like OKT3 and polyclonal antithymocyte globulins have been associated with PTLD after SOT in most studies [11, 12]. An association between tacrolimus and PTLD was reported in adults and pediatric populations [12]. To date, MMF has not been found to impact PTLD [12]. Effects of mTOR inhibitors are unclear with experimental data suggesting inhibition of the lymphoblastoid cell proliferation, whereas clinical registry data showed an increased risk of PTLD in patients receiving these agents [13]. Finally, recent studies indicate that EBV-seronegative patients treated with belatacept, a drug inhibiting the costimulation pathway, are at higher risk of PTLD, especially CNS PTLD.

7.3 Diagnosis of EBV

The ability to quantify the EBV viral load (VL) in the peripheral blood using nucleic acid amplification testing (NAT) (e.g., PCR) has markedly enhanced the ability to monitor for and diagnose EBV infection and disease including PTLD (EBV/PTLD). EBV VL monitoring is routinely used to both identify those at risk of progression to and to diagnose patients presenting with EBV/PTLD. Data derived from multiple studies support the use of EBV VL to predict progression to EBV/PTLD, and published guidelines support the routine use of the viral load to guide therapeutic choices for EBV infection and disease [8]. Despite its widespread use, several areas of controversy around EBV load testing deserve discussion. The optimal component of peripheral blood to test is not fully defined with conflicting results for assays using peripheral blood lymphocytes, whole blood, or plasma [8, 14]. In fact, it is not completely clear exactly what is being measured within these different compartments. While is it presumed that one is measuring EBV-infected B lymphocytes when one measures the EBV load in peripheral blood lymphocytes, less is known about measurement of whole blood or plasma. For these compartments one may be amplifying EBV DNA fragments or lytic virions though at least some evidence argues against the latter. Another major limitation has been the fact that EBV load monitoring is not standardized between laboratories. While individual centers demonstrate a high level of internal reproducibility, substantial variability has been demonstrated between laboratories. This poor interlaboratory reproducibility contributes to a lack of consensus on threshold EBV VL which should trigger diagnostic and therapeutic interventions. It is hoped that the recently released WHO International Standard for EBV for Nucleic Acid Amplification Techniques will help to overcome these issues.

Viral load testing alone cannot be used to diagnose EBV/PTLD as the test can lack sensitivity and frequently lacks specificity. Rarely, the viral load will remain low in patients with EBV/PTLD, while patients with elevated EBV VL do not always have or develop EBV disease. Accordingly, aggressive use of imaging and performance of biopsies should be used when the diagnosis of EBV/PTLD is suspected. CT scanning of the neck, chest, and abdomen may identify lesions not apparent from symptoms or examination. Many if not most experts will now also use 18-FDG PET/CT in this scenario. Imaging of the brain is paramount if central nervous system symptoms are present. Biopsy of lesions or sites of disease is needed to definitively diagnose PTLD and rule out other opportunistic infections. Because the bowel can frequently be involved in PTLD, early endoscopic evaluation should be considered in patients with unexplained abdominal pain and diarrhea. Biopsy specimens should be evaluated by pathologists familiar with PTLD, and specific assays should be performed to characterize the involved cell including evaluating cell markers such as CD20 which may influence therapeutic options and in situ hybridization for EBER, a marker of EBV-infected cells.

7.4 Prevention of EBV Disease and PTLD

Increasing interest has focused on the prevention of EBV/PTLD in SOT recipients. Potential prevention strategies can be further categorized as immunoprophylaxis, chemoprophylaxis, and preemptive therapy.

Immunoprophylaxis Immunoprophylaxis can be categorized as active or passive. Active immunoprophylaxis would be accomplished through the use of an EBV vaccine. Unfortunately, no vaccine is currently available. Passive immunoprophylaxis is accomplished by providing anti-EBV antibody through the infusion of intravenous immune globulin (IVIG). Opelz showed in a retrospective analysis that SOT recipients receiving anti-CMV immunoglobulins for CMV prophylaxis did not develop PTLD during the first year (during the time of prophylaxis) [15]. These data were not confirmed in a randomized controlled trial using anti-CMV immunoglobulin prophylaxis vs. placebo in pediatric liver transplant recipients although a trend toward less EBV disease and PTLD was observed in patients receiving immunoglobulins [4]. Finally, the use of EBV-specific cytotoxic T lymphocytes (CTLs) as adoptive immunotherapy could serve as a third potential immunoprophylactic strategy. Unfortunately, although this approach has been proven to be efficacious in stem cell transplant recipients, efforts to translate these benefits to the prevention of EBV/PTLD in SOT recipients have not succeeded as of this time (reviewed in [6]).

Chemoprophylaxis Chemoprophylaxis using antiviral agents, such as acyclovir and ganciclovir, represents another possible approach to preventing EBV/PTLD. Ganciclovir or its prodrug valganciclovir may be the preferred drug for EBV prophylaxis because of its higher in vitro antiviral activity. Nevertheless, these drugs are only effective against the lytic forms of EBV which explains their

inefficiency when the virus is in latent phase. Despite a US case-controlled study suggesting a potential role of ganciclovir given for CMV prophylaxis to reduce the PTLD incidence in kidney transplant recipients [16], other studies have not confirmed the efficacy of ganciclovir, valganciclovir, or acyclovir against EBV/PTLD in SOT recipients. A randomized prospective trial of 2 weeks of ganciclovir compared to 2 weeks of ganciclovir followed by 50 weeks of oral acyclovir in EBV-seronegative pediatric liver transplant patients did not establish any benefit to the extended use of antiviral therapy to prevent EBV disease [17]. A 2016 meta-analysis showed that the use of antiviral drugs (ganciclovir, valganciclovir, acyclovir, and valacyclovir) in mismatched EBV transplant recipients (D+/R) had no effect on PTLD incidence [18]. No significant differences were seen across all types of solid organ transplants, age groups, or antiviral use as prophylaxis or preemptive strategy.

Viral Load Monitoring and Preemptive Strategies of Prevention Surveillance monitoring of EBV loads to inform preemptive reductions in immunosuppression has resulted in a decreased incidence of EBV/PTLD compared to historical controls. McDiarmid reported a decreased incidence of PTLD from 10 to 5% using EBV viral load monitoring to guide the combined use of reduced immunosuppression and intravenous ganciclovir in pediatric liver transplant recipients with rising EBV loads [19]. Two other studies demonstrated decreased incidences of PTLD using decreased immunosuppression alone without ganciclovir in response to elevated EBV loads [20, 21]. Some centers have considered the preemptive use of the anti-CD20 monoclonal antibody rituximab for those with elevated EBV load though little published data is available. Martin reported encouraging results using EBV load monitoring to inform the preemptive use of rituximab in EBV D+/R− adult kidney transplant recipients [22]. However, the majority of treated patients actually had clinical evidence of EBV disease at the time of treatment. Accordingly, these data speak more to use rituximab for early treatment and not prevention of EBV disease. Additional experience is needed to confirm efficacy and long-term safety of rituximab in a prevention/preemption model against EBV.

Based upon available data, it appears that the strategy of using EBV load monitoring to inform preemptive reduction in immunosuppression to prevent EBV/PTLD is the optimal currently available preventive strategy, while more data evaluating the comparative safety and efficacy of rituximab with reduced immunosuppression alone in response to rising or elevated EBV loads are needed.

7.5 Treatment of EBV Disease and PTLD

The optimal treatment of the spectrum of EBV disease has not been well established. While reduction of immunosuppression is widely accepted, the role of additional therapies remains controversial. Therapeutic interventions encompass

different tools depending on histological features, disease stages, localization of the tumor, and comorbid conditions.

7.5.1 Immunosuppression (IS) Reduction

IS reduction is the first and most important treatment strategy since it allows for the development of EBV-specific cytotoxic immunity. IS reduction should be considered in patients, particularly in children, at the time of diagnosis of EBV/PTLD. In many cases, including those with polymorphic lymphoproliferations, restoration of cytotoxicity is sufficient to control the transformed B-cell population [23]. IS reduction is more effective if the tumor expresses LMP1 and EBNA2, two viral proteins which facilitate the interaction between transformed B cells and recipient cytotoxic T cells. Nevertheless, the precise IS drug blood concentrations which allow a sufficient antiviral activity while still protecting against graft rejection are not known. In practice, calcineurin inhibitors (CNI) are reduced or withdrawn; steroids may be reintroduced or increased. The role of reduction of other classes of immunosuppression is less well established and may vary by organ. Using this approach, alone or in combination with other strategies, successful regression of both polyclonal and monoclonal EBV/PTLD lesions was reported to occur in 45% of patients [23]. Response rates of IS reduction among adults are highly variable, with excellent results reported in some series and very poor results in others. A progressive stepwise reduction schedule, maintaining the lower therapeutic ranges of immunosuppressive drugs and adjusting dosage depending upon blood level monitoring, may avoid onset of acute rejection. While reduction of IS clearly carries the risk of rejection, graft function is preserved without development of rejection in some patients despite completely stopping IS suggesting the presence of acquired graft tolerance.

7.5.2 Antiviral Therapy

There is no evidence that antiviral inhibition of lytic EBV replication by intravenous ganciclovir or oral valganciclovir is beneficial to SOT recipients with high EBV loads in the presence or absence of EBV disease. The vast majority of EBV-infected cells within PTLD lesions have been shown to be transformed B cells that are not undergoing lytic infection. Nevertheless, some experts use these antivirals as an adjunct to the reduction of immunosuppression in order to lower de novo infection and recruitment of B cells into lymphoproliferation.

7.5.3 AntiCD20: Rituximab

Rituximab targets CD20-positive B lymphocytes including those infected with and transformed by EBV. Rituximab has become a standard element in the treatment of CD20-positive EBV/PTLD, alone or in combination with chemotherapy.

While some centers opt for the early use of rituximab even before a trial of reduced immunosuppression, most experts consider this to be a second-line treatment for patients who fail to respond to, or develop rejection during periods of, reduced immunosuppression. Despite its widespread use, published data defining the optimal timing and use of rituximab remains limited. The use of rituximab alone (without additional chemotherapeutic agents) appears to be effective for non-specific EBV disease and polyclonal proliferations. In aggressive PTLD forms, response rate after rituximab therapy alone was only 45%, and patient survival fell to 30% at 2 years [24]. Accordingly, the use of rituximab in combination with additional chemotherapy should be considered for patients with monomorphic PTLD, especially those with late-onset disease. Unfortunately, the optimal combination of chemotherapy and rituximab has not been established. In the randomized multicenter phase 2 prospective trial PTLD-1, patients who received four infusions of rituximab followed by four cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone had a 67% rate of complete remission [25].

7.5.4 Chemotherapy

Chemotherapy represents the preferred strategy in the cases of monomorphic proliferations, myeloma, and Hodgkin diseases. Current protocols combine cyclophosphamide, adriamycine, vincristine, and steroids ("CHOP" or "ACVPB") with overall response rates of 60–75%, though the use of chemotherapy is associated with important toxicities in SOT recipients. Indeed, 15–30% of patient deaths were related to a toxic complication in the French Registry and PTLD-1 series. The use of dose-adjusted regimen, the systematic use of G-CSF, and the cures spacing are strongly recommended. Stopping IS during chemotherapy is also strongly encouraged [26]. In children, adapted protocols with low doses of cyclophosphamide and rituximab have been proposed in cases of malignant tumors [27]. Of note, none of the chemotherapy regimens have been directly compared to each other in controlled trials in the setting of PTLD.

7.5.5 Adoptive Cellular Therapy

Since the presence of EBV-specific CD8 CTL effectively controls EBV transformed B-cell proliferation in immunocompetent patients, the use of adoptive cellular therapy has been considered as a potential strategy in PTLD management in SOT. While the generation and use of EBV-specific CTL therapy have been well established for stem cell transplant recipients, this strategy has not translated easily to the SOT arena, where most PTLD are of host origin

requiring the presence of host EBV-specific CTLs to control the EBV-driven proliferation. Unfortunately, strategies using recipient cells have been tried, but the highest-risk recipients are EBV naïve prior to SOT and have dysfunctional T cells after transplantation due to iatrogenic immunosuppression. Of interest, the use of third party class 1 matched generated allogenic T cells coming from a donor bank for treatment of PTLD in SOT demonstrated a response rate greater than 50% in patients with refractory PTLD [28]. These procedures demonstrated an excellent safety profile but are currently restricted to few specialized teams.

In conclusion, treatment of PTLD remains challenging, and randomized controlled trials are still lacking. Immunosuppression lowering, rituximab, and chemotherapy are the cornerstones of transplant recipient's management, but the precise administration of these therapies should be adapted to each patient depending on its particular tumor and graft conditions.

General Approach Figure 7.1 provides an algorithmic approach to the diagnosis of EBV disease including PTLD. Figure 7.2 provides an algorithmic approach to the treatment of EBV disease including PTLD.

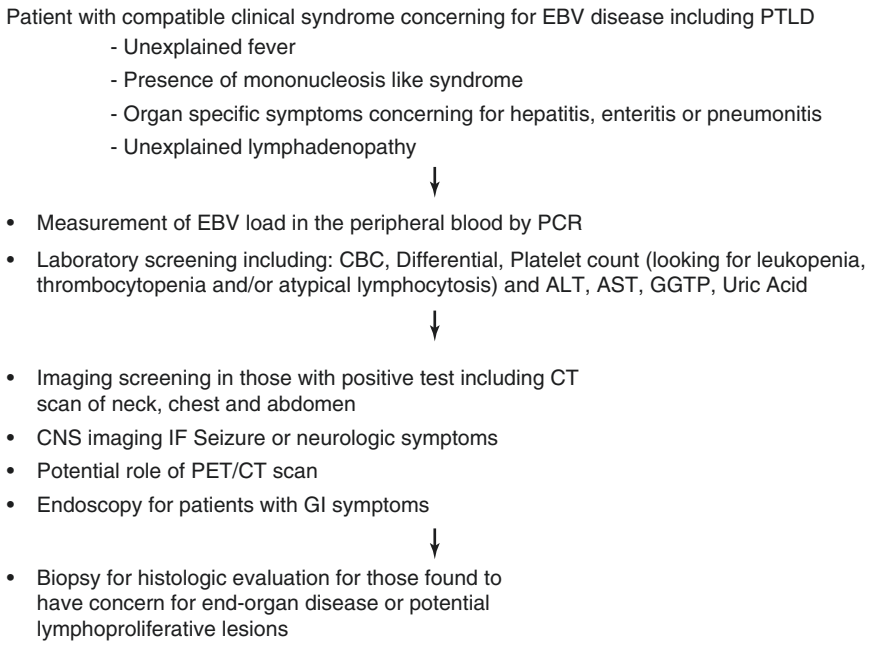

Fig. 7.1 Algorithmic approach to the diagnosis of EBV disease including PTLD

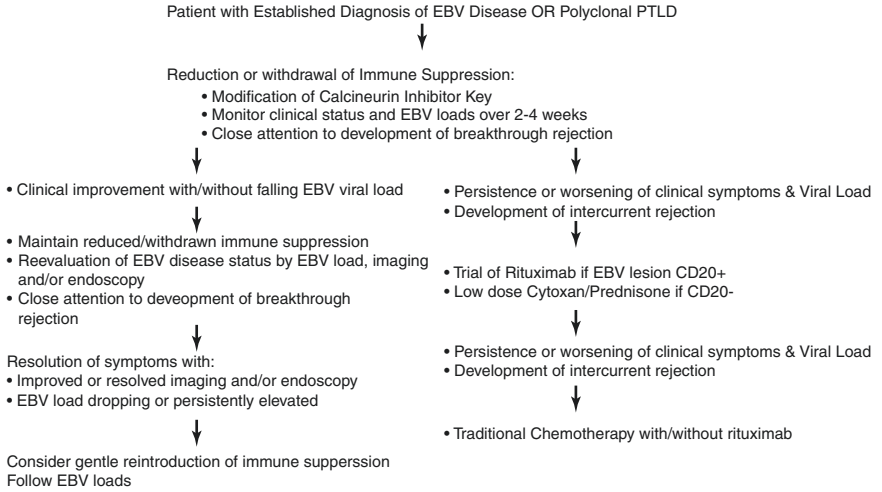

Fig. 7.2 Algorithm for the treatment of EBV disease including PTLD

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Prevention and Treatment of Polyomavirus-Associated Diseases

8

Joanna Schaenman and Chen Sabrina Tan

8.1 Description of Pathogens

The human polyomaviruses are ubiquitous non-enveloped DNA viruses in the *Orthopolyomavirus* genus and the *Polyomaviridae* family [1]. BKV was first isolated from the urine of a kidney transplant recipient with the initials of "BK," who presented with ureteric stenosis and obstruction [2]. JCV was initially isolated from the brain of the lymphoma patient with the initials of "JC," who had multiple areas of demyelination in the brain.

BKV and JCV are small non-enveloped double-stranded DNA virus with approximately 5 Kb of genome, which encodes the capsid proteins—VP1, 2, and 3, large T antigen, small T antigen, and agnoprotein. The genome also contains a ~200 bp noncoding region which serves as binding sites for transcriptional factors. Due to lack of viral DNA polymerase, BKV and JCV use the host machinery for viral replication. Multiple genotypes of each virus have been identified based on nucleotide differences in VP1; the distributions of specific genotypes are used as markers to trace human migrations throughout the world [3].

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8.2 BKV

8.2.1 Definitions and Epidemiology

Asymptomatic primary infection with BKV most likely occurs in childhood. Seroprevalence worldwide is 65–90% and increases with age [4]. After primary infection, BKV resides in the kidney tubular epithelial cells. Occasional viral replication occurs as BKV is detected in the urine of up to 10% of healthy individuals. BKV viuria is not associated with any disease in healthy individuals. Active BKV replication is associated with diseases in immunosuppressed individuals, specifically, those with kidney transplants and those with hematopoietic stem cell transplant. After kidney transplant, BKV can be detected in urine (~30%) and blood (10–20%) of the recipients. Patients with viremia are at risk of developing BKV-associated nephropathy (BKVN), which occurs in 1–10% of kidney transplant recipients [5] (Table 8.1). Up to about half of those with diagnosed

Table 8.1 BKV definitions

Term	Definition	Clinical implication/action suggested
BK viuria	Detectable BKV from urine by PCR testing	Predictive of BK viremia, suggest check BKV in plasma
BK viremia	Detectable BKV from plasma	• High viral load is predictive of development of BKVAN • Threshold for clinical response not well defined • Monitor renal function • Consider reduction in immunosuppression and/or biopsy
BKV-associated nephropathy (BKN)	Kidney dysfunction in association with detection of BKV by PCR in blood in (presumptive) or detected by biopsy (proven). Grading by Banff criteria [16]	Reduce immunosuppression (see Fig. 8.1)
BKN: Class 1	• ≤1% of all tubules/ducts with viral replication • Interstitial fibrosis in up to 25% of cortical area (mild interstitial fibrosis)	As above
BKN: Class 2	Either • ≤1% of all tubules/ducts with viral replication with interstitial fibrosis in ≤25% of cortical area (moderate to severe interstitial fibrosis) • or >1% to ≤10% of all tubules/ducts with viral replication with any level of interstitial fibrosis • or >10% of all tubules/ducts with viral replication with mild interstitial fibrosis	As above
BKN: Class 3	• >10% of all tubules/ducts with viral replication with mild interstitial fibrosis with moderate to severe interstitial fibrosis	As above

nephropathy will sustain graft loss. The majority of the BKVN cases occurs during the first year post transplant [6]; risks of developing BKVN include male sex, age, ureteric stents, donor seropositivity, increased levels of immunosuppression, and use of tacrolimus [7, 8]. Evidences show that most viral strains are from the donor [9, 10]. BKV viuria and viremia can occur in transplant recipients of other solid organs, such as the heart, liver, and lung, but at low incidences of 20% and 3%, respectively. These patients rarely progress to nephropathy absent a transplanted kidney [11]. Persistent viremia may also increase the risk of developing de novo donor-specific antibodies [12].

The detection of BKV in the urine has also been associated with genitourinary tumors [13].

8.2.2 Screening

BKV screening is performed post kidney transplant to reduce nephropathy and prevent graft loss. AST and KDIGO recommended systematic screening for BKV by PCR detection in kidney transplant recipients: monthly for the first 6 months after transplant and then every 3 months thereafter until 2 years [14, 15] (Fig. 8.1). Some centers screen urine for decoy cells, although this approach is less sensitive compared with PCR detection. Detection of the virus in urine is in of itself not associated with nephropathy. In those patients who go on to develop BK viremia, detection of virus in the urine usually precedes viremia by 4–12 weeks. Although specific virus quantity thresholds have not been prospectively developed, a blood viral load >10,000 copies/ml is highly associated with nephropathy.

8.2.3 Diagnosis

While detection of BKV in blood greater than $4\log_{10}$ copies/ml is presumptive of nephropathy in the kidney, pathological findings in kidney tissues obtained from biopsy are the gold standard in diagnosing BKV-associated nephropathy (BKN, also termed polyomavirus nephropathy (PVN) (Fig. 8.2). Histologically, BKN is categorized into three groups based on the latest Banff Working Group classifications, correlating to both increased creatinine and increased risk of graft loss from 16% to 31% to 50% [16]. Class 1, defined as involvement of ≤1% of all tubules/ducts with viral replication with minimal interstitial fibrosis, represents early-stage disease with favorable outcomes. Class 2 is defined as either minimal viral replication with more severe interstitial fibrosis or >1% to ≤10% of all tubules/ducts with viral replication. Class 3 carries the most severe prognosis and is defined as >10% of all tubules/ducts with viral replication. These classifications provide prognostic information at the time of kidney biopsy [16]. Of note, due to nonuniform involvement of the kidney, kidney biopsy may fail to detect BKN resulting in a false-negative biopsy [14].

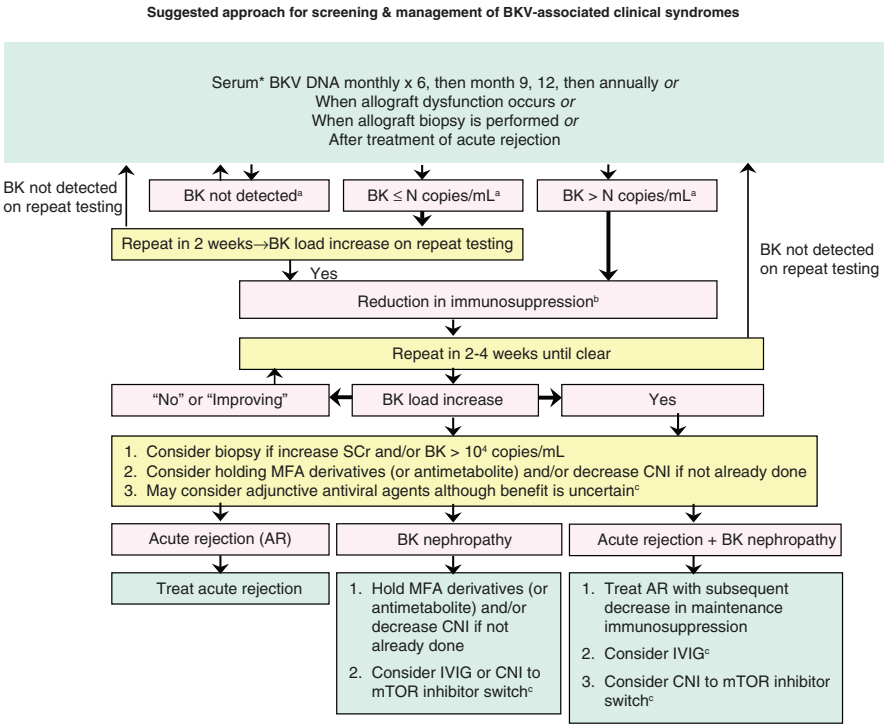

Fig. 8.1 BKV screening and management after kidney transplantation. *Alternatively screen with urine BKV PCR; perform serum testing if positive. [a]No standardized PCR assays for BKV are currently available. Cutoff levels for viral detection should be based on PCR assays used at individual institutions. N signifies the threshold established at each institution for BKV serum PCR positivity in copies/ml. [b]Common practice: (1) decrease or hold MFA derivatives (or antimetabolite), (2) decrease (MFA + CNI) by 25–50%, (3) decrease CNI. [c]Evidence-based recommendations are lacking (ongoing clinical trials). May avoid long-term nephrotoxic effect of CNI therapy. Not recommended in patients with baseline significant proteinuria (arbitrarily defined as >500 mg/24 h or at the discretion of the clinician). *SCr* serum creatinine, *MFA* mycophenolate acid, *CNI* calcineurin inhibitor, *AR* acute rejection, *BKN* BK nephropathy, *mTOR* mammalian target of rapamycin, *IVIG* intravenous immunoglobulins, *CSA* cyclosporine. Adapted from Pham PT, Schaenman J, Pham PC. Medical management of the renal transplant recipient: Infections and malignancies. In: Johnson RJ, Feehally J. Comprehensive Clinical Nephrology. Sixth Edition. Elsevier Saunders, Philadelphia, PA

8.2.4 Prevention

Systematic screening for evidence of BKV replication is effective in preventing disease when followed with reduction of immunosuppressants to promote adaptive anti-BKV immune responses [17] (Fig. 8.1). A general approach is to either reduce calcineurin inhibitors 25–50% and mycophenolate by 50% at onset of viremia [14, 15]. Further reduction may be needed with persistent viremia. Switching immunosuppressants to an mTOR inhibitor has been hypothesized and tried, based on the evidence that BKV uses the mTOR pathway for viral replication [18, 19].

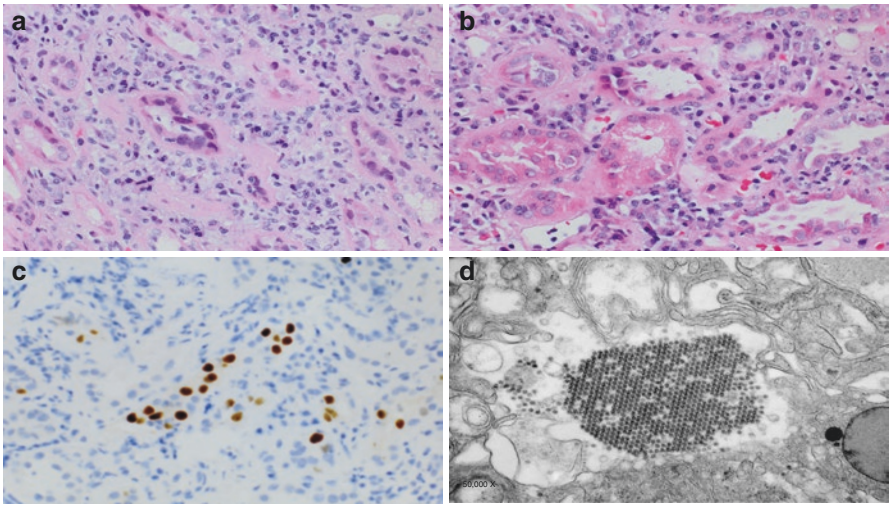

Fig. 8.2 BKN histology. Hematoxylin and eosin stain demonstrating tubular epithelial cells with viral inclusions and interstitial inflammation in (**a**, **b**). SV-40 antibody stain showing BKV-infected cells in (**c**), and electron microscopy image captured the BK virus (**d**). Images **a–c** courtesy of Dr. Fernando Palma-Diaz. (**a**) Hematoxylin and eosin stain, showing tubular epithelial cells some with viral inclusions along with interstitial inflammation. (**b**) Hematoxylin and eosin stain; tubular atrophy and surrounding interstitial inflammation. (**c**) Immunohistochemistry staining for the SV40 antigen demonstrates nuclear staining in infected cells. (**d**) Ultrastructure of BKV-associated nephropathy. Virions are arranged in a paracrystalloid structure within a tubular epithelial cell nucleus.

8.2.5 Treatment

There is no effective antiviral against BKV [20]. The mainstay of treatment is to reduce immunosuppression as discussed above [17, 21]. This is balanced with risk of rejection. The goal of reduction of immunosuppression is to restore adaptive immune responses against BKV. Specifically, BKV-specific T cell with polyfunctionality is crucial in control of viremia [22, 23]. Therefore, there is potential for harnessing adoptive T cells as treatment for BKV [24, 25].

While most patients have prior exposure to BKV and detectable antibodies against the virus, genotype-specific neutralizing antibodies may be required for control of viremia [26]. The BKV-neutralizing antibodies are specific to genotypes and do not cross react. This knowledge supports a potential role for developing broadly neutralizing antibodies against BKV and the use of intravenous infusion of pooled immunoglobulins (IVIG) [27]. Although case reports indicated control of viremia with IVIG [28], a randomized double-blinded clinical trial is underway to determine efficacy of this treatment.

Several potential medications have been studied in treatment of BKV viremia. Leflunomide, a pyrimidine synthesis inhibitor, has been given to kidney transplant recipients with BKV viremia with mixed effect [17, 29–32]. The drug was given in conjunction with reduction in immunosuppression in all cases, and a

meta-analysis comparing drug effect to immunosuppression alone did not show a difference [33]. Based on in vitro demonstration of viral inhibition by DNA gyrase inhibitors, fluoroquinolones have been also tried in the prevention and treatment of BKV infections. Two randomized studies failed to find clinical efficacy of fluoroquinolones in prevention and treatment of BKV viremia [34, 35]. Cidofovir, a nucleotide analogue, showed mixed effect in a non-randomized cohort study and in several case reports [36] but all in conjunction with reduction of immunosuppressants. There was no difference in a meta-analysis of reduction of immunosuppression with cidofovir compared to reduction alone [17]. Brincidofovir, a cidofovir with a lipid tail to enhance transport across the cellular membrane, is an antiviral drug in development that has shown promise as an anti-BK virus agent in cell culture and in case reports [37, 38]. However, efficacy of this drug in treatment of BK virus infection remains to be determined. Switch to mTOR inhibitors may also be of benefit, as suggested by the observed lower incidence of BKV and BKAN in patients receiving sirolimus, and a current randomized controlled trial is underway. T cell transfer of immunity is another promising avenue for treatment currently under development.

8.3 JCV

8.3.1 Definition and Epidemiology

JCV infects 30–90% of the general adult population worldwide, depending on the assay and region [39]. Specific strains of JCV can be used to trace human geographic migrations over time. Primary infection is believed to be asymptomatic and transmitted via urine or fecal to oral route. Although JCV is thought to be latent in the kidney tubular epithelium after primary infection, virus is detected in the urine of up to 30% of healthy individuals, indicating active replication. While viral shedding in the urine by healthy individuals is not associated with any symptom or indicative of any disease, active viral replication in immunocompromised individuals is associated with disease. JCV-associated nephropathy and encephalopathy are rare but have been reported in transplant recipients [40–42]. More prevalent is the JCV replication in the brain, which causes the devastating disease progressive multifocal leukoencephalopathy (PML) in patients with immunosuppression such as HIV, patients with lymphoma, and patients treated with natalizumab—a monoclonal antibody against alpha 4 integrin for multiple sclerosis and Crohn's disease

Table 8.2 Diagnosing PML without histopathology

PML diagnosis	CSF JCV PCR	Clinical characteristics	Radiographic images
Definite	+	+	+
Probable	+	+	–
	+	–	+
Possible	–	+	+

(Table 8.2). PML is a rare disease in transplant recipients, as only 11 cases have been reported in recipients of liver transplant [43, 44]. However, the incidence of PML in heart and/or lung recipients in one center was 1.24 per 1000 post-transplantation person-year, indicating potentially more cases than those reported in literature. In patients with solid organ transplantation, the mean time to detection of first symptom is 27 months, with mean survival of 6.4 months.

8.3.2 Screening

There are no recommended screening tests for transplant patients. Screening for JCV serology has been extensively studied in patients with multiple sclerosis using the STRATIFY JCV index assay. A rise in the antibody index, defined as the ratio between quantities of antibodies in the patient serum to the positive control, can be seen in some patients after prolonged treatment with natalizumab and is associated with increased risk of developing PML [45]. The STRATIFY JCV index has a false-negative rate of up to 2.4% and a poor specificity rate of 40% in patients with high index value. However, this test has not been validated in transplant patients and other immunosuppressed patients. Given the rare incidence of PML in solid organ recipients, screening for JCV by serology titers or PCR detection is currently not recommended.

8.3.3 Diagnosis

The gold standard diagnostic test for PML is brain biopsy demonstrating demyelination, large bizarre astrocytes, and positive immunohistochemical staining with SV40 antibody. Electron microscopy will also show virion-filled cells.

When brain biopsy is contraindicated, presumptive diagnosis is made in clinically appropriate context with CSF analysis, including JCV PCR, and radiographic images [46] (Fig. 8.3). CSF often demonstrates mild protein elevation and some lymphocytic pleocytosis. Glucose is usually within the normal range. PCR for JCV is positive in most cases. Magnetic resonance neuroimaging shows multiple and single areas of demyelination in white matter, irrespective of vascular boundaries. Involvement of gray matters can also be present in some cases. These lesions are T1 hypointense and T2/fluid-attenuating inversion recovery hyperintense. Without PML–IRIS (immune reconstitution inflammatory syndrome), there is no edema or mass effect (Fig. 8.4).

8.3.4 Prevention

Minimize immunosuppression. While risk of developing PML decreases with increased months post transplant, this risk is lifelong, as there are reported cases of patients developing PML years after transplantation.

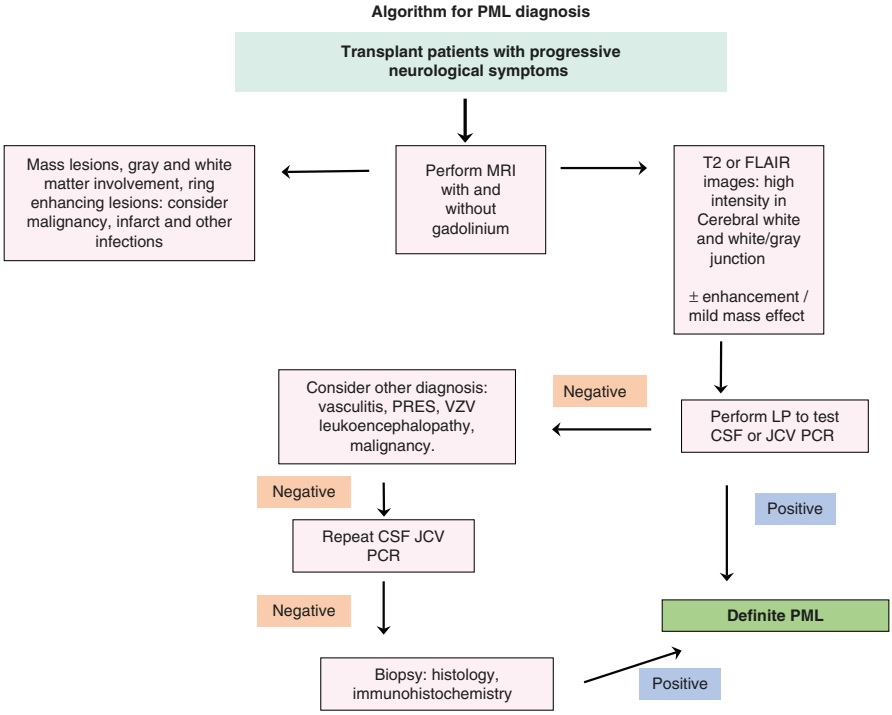

Fig. 8.3 PML diagnosis algorithm. *FLAIR* fluid-attenuated inversion recovery, *PRES* posterior reversible encephalopathy syndrome

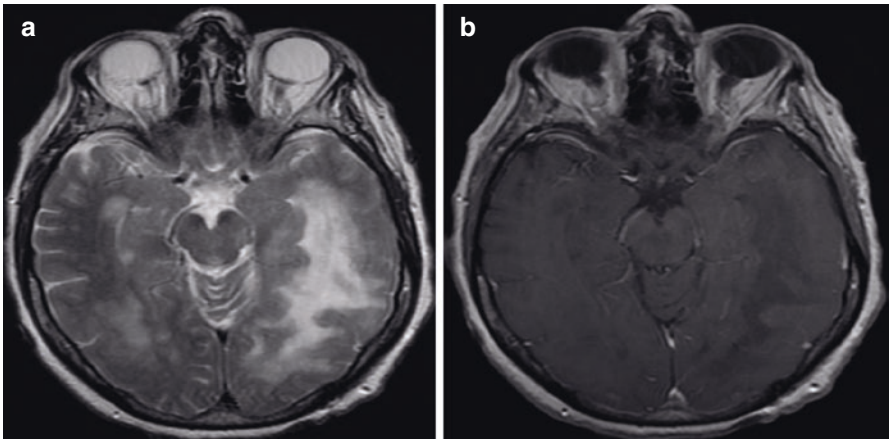

Fig. 8.4 MRI image of PM: brain magnetic resonance images of a 57-year-old woman with progressive multifocal leukoencephalopathy. High-intensity signals were present in the subcortical white matters in the left temporal lobe in T2-weighted image (**a**). These areas are hypointense in T1-weighted image (**b**) and do not enhance with gadolinium

8.3.5 Treatment

There is no effective treatment against JCV. The first step in treatment is to assess the balance of immunosuppression and infection risk of the patient. Reactivation of polyomaviruses is often an indication of overt immunosuppression. Multiple antivirals and even some antibiotics have been tried, including cidofovir, mefloquine, ganciclovir, and leflunomide [47]. Based on the discovery of JCV's use of serotonin receptors to enter cells, mirtazapine, a serotonin receptor antagonist, has also been used as treatment [48]. However, there is no data from clinical studies to support this use. Lastly, there is potential for use of ex vivo stimulated JCV-specific T cells to boost immune response and control viral replication [49]. In PML patients on monoclonal antibody treatments, plasmapheresis can remove the immune-restricting antibody in attempt to revive immune response. However, an IRIS response may follow removal.

Case fatality for PML after transplantation is high at 84% [44]. But the 1-year survival is 56%, comparable to HIV patients on HAART [50].

8.4 Other Human Polyomaviruses

Since 2007, the human polyomavirus family has now expanded to include newly discovered viruses [1]. They are names after places of discovery, KIPyV (Karolinska Institute), WUPyV (Washington University), MWPyV (Malawi), and STLPyV (St. Louis); associated diseases, MCPyV (Merkel Cell) and TSPyV (trichodysplasia spinulosa); and lastly in chronological order of discovery, HPyV6 (human polyomavirus), HPyV7, HPyV9, HPyV12, and HPyV13. Known diseases associated with these viruses are Merkel cell carcinoma caused by MCPyV in immunocompromised patients, trichodysplasia spinulosa—a rare follicular disease caused by TSPyV in pediatric heart transplant recipients—and pruritic rash in lung transplant recipient caused by HPyV7 [51]. While KI and WU have been detected in the respiratory secretions in non-immunocompromised children, there are new reports of KIPyV association with respiratory symptoms in transplant recipients [52, 53].

General Approach General algorithmic approach to identifying and diagnosing focus of topic (introduced above) (Figs. 8.1 and 8.3).

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Prevention and Treatment of Respiratory Virus Infection

9

Maddalena Peghin and Lara Danziger-Isakov

Abbreviations

AdV	Adenovirus
CoV	Coronavirus
FLU	Influenza
hMPV	Human metapneumovirus
HSV1–2	Herpes simplex 1–2
IVIG	Intravenous immunoglobulin
LRTI	Lower respiratory tract infection
MERS-CoV	Middle East respiratory syndrome coronavirus
PIV	Parainfluenza
PPE	Postexposure prophylaxis
PrEP	Pre-exposure prophylaxis
RBV	Ribavirin
RhVs	Rhinovirus
RSV	Respiratory syncytial virus
RVs	Respiratory virus
SARS-CoV	Severe acute respiratory syndrome coronavirus
SOT	Solid organ transplant
URTI	Upper respiratory tract infection

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9.1 Introduction

Respiratory viruses (RVs) are increasingly recognized as a major cause of morbidity and mortality in solid organ transplant recipients, especially within the lung transplant population. Respiratory viral infections are typically caused by rhinovirus (RhVs), coronavirus (CoV), respiratory syncytial virus (RSV), influenza (FLU), parainfluenza (PIV), human metapneumovirus (hMPV), and adenovirus (AdV) (Table 9.1). Respiratory infections can also be caused by viruses less commonly associated with the respiratory tract such as cytomegalovirus (CMV), human herpesviruses (HSV1, HSV2), and varicella zoster virus (VZV) that will be discussed in another chapter (Chap. 6). A detailed discussion of other newer respiratory viruses (Table 9.1) is beyond the scope of this chapter, since they have not been widely studied in immunocompromised patients and their clinical impact is not fully understood. However, these viruses should be considered in the differential diagnosis of patients presenting with severe lower tract disease, especially if clinical history indicates potential exposure. The newer RVs are more challenging to diagnose since they are not included in the routinely available diagnostic tests and optimal management has not been defined.

Table 9.1 Classification and distribution of major and minor respiratory viral infections in SOT

Major RVs	Distribution (%) in SOT
• Rhinovirus (RhVs)	21–62
• Coronavirus (CoV)	13–29
• Influenza virus (FLU)	2–16
• Respiratory syncytial virus (RSV)	6–20
• Parainfluenza virus (PIV)	3–18
• Metapneumovirus (hMPV)	4–7
• Adenovirus (AdV)	1–25
Minor RVs	
• Cytomegalovirus (CMV)	
• Herpes simplex virus 1–2 (HSV1–2)	
• Varicella zoster virus (VZV)	
• Measles	
• *Enterovirus* + *Enterovirus* D68	
• *Parechovirus*	
• Parvovirus B19	
• Bocavirus	
• CoV HKU1 and NL63	
• Middle East respiratory syndrome CoV (MERS-CoV)	
• Severe acute respiratory syndrome CoV (SARS-CoV)	
• Polyomaviruses KI and WU	

RVs respiratory viruses, *SOT* solid organ transplant

9.2 Clinical Manifestations

The definition of RV disease includes (1) a new onset of symptoms and (2) at least one respiratory symptom and (3) the clinician's judgment that the illness is due to an infection [1]. An upper respiratory tract infection (URTI) is defined with the onset of sore throat, rhinorrhea, or hoarseness. A lower respiratory tract infection (LRTI) is defined as new onset of shortness of breath, cough, sputum, rales, hypoxemia, and/or wheezing. When symptoms of LRTI are associated with a new pulmonary infiltrate (on chest radiograph or chest computed tomography), pneumonia is distinguished from tracheobronchitis.

Many common respiratory viral infections in SOT patients are mild, self-limiting upper respiratory tract infection (URTI) and do not require hospitalization. However, compared to immunocompetent hosts and due to alterations in cellular and humoral immunity, infections can cause protracted symptoms with greater risk of progression to LRTI, prolonged periods of viral shedding, and increased mortality. In SOT, LRTIs have been associated with increased risk of adverse complications and subsequent development of fungal, viral, and bacterial superinfections [2]. Although these complications may appear in the context of any type of transplantation, pediatric, lung, and heart-lung transplantation recipients appear to have the greatest risk of respiratory viral infections with more severe courses and complications [2–4].

In addition to their direct, cytopathic, and tissue-invasive effects, RVs can create an inflammatory environment that leads to local and systemic microbially determined immune modulation (MDIM) [5]. MDIM may increase the alloimmune and autoimmune responses that increase susceptibility to other opportunistic infections and are associated with the development of acute and chronic rejection. The greatest risk appears from data in lung transplant recipients, although data on this topic in the literature are conflicting [2, 5, 6].

In transplantation overall, RhV and CoV are the most common etiological agents, causing mostly mild URTI, with LRTI less frequently described. In contrast, FLU and other paramyxovirus (RSV, PIV, and hMPV) have a greater association with LRTI and particularly acute and chronic rejection in adult lung transplant recipients [2, 5] (Tables 9.1 and 9.2). Outcomes of infection are associated strongly with site of involvement, net state of immune suppression, and availability and use of antiviral agents.

9.3 Diagnosis

The clinical diagnosis of RVs can be difficult, since SOT recipients often present with mild or atypical symptoms and signs, which are often overlapping and not always specific for any one viral agent. Fever can be absent in SOT with pneumonia or can be the sole presenting sign. In addition bacterial and fungal coinfections may occur.

The distribution of RV infections throughout the year suggests that seasonal patterns of RV circulation in SOT are similar to those circulating in the general

Table 9.2 Seasonality, diagnostic tools, clinical presentation, treatment regimens, prevention, and isolation precaution for major RVs

Virus	Family and type	Seasonality	Diagnostic test	Clinical presentation	Treatment regimens	Prevention	Isolation recommendation
RhVs	Picornavirus RNA	All year-round with higher peaks in fall and spring	RT-PCR Cell culture Serology	Mostly URTI, LRTI	Primary: none Alternative: none	Prophylaxis: none Vaccine: none	Standard, contact and droplet
CoV	*Coronaviridae* RNA	Winter and spring	RT-PCR Serology	Mostly URTI, LRTI	Primary: none Alternative: none	Prophylaxis: none Vaccine: none	Standard precautions but SARS and MERS require contact, droplet, and airborne precautions
FLU	*Orthomyxoviridae* RNA	Winter between December and February	RT-PCR IF IA Cell culture Serology Susceptibility test	URTI, LRTI (pneumonia, ARDS, obliterative bronchiolitis) ± encephalitis, myocarditis, and myositis	Primary: oseltamivir or zanamivir Alternative: peramivir or DAS181 For oseltamivir resistant strains: zanamivir (active), peramivir (reduced susceptibility), or DAS181 (research/ compassionate use currently) M2 Inhibitors (amantadine and rimantadine): no longer recommended (not useful for influenza B, H1N1, H3N2) for high resistance rates (>95%)	Prophylaxis: oseltamivir 75 mg or zanamivir 2 puffs OD PrEP: OD for influenza season (12 weeks) PPE: OD prophylaxis or therapeutic regimen for 7–10 days very early after exposure Vaccine: yearly trivalent or quadrivalent inactivated influenza vaccination	Standard, contact, and droplet
RSV	*Paramyxoviridae* RNA	Fall and winter	RT-PCR IF IA Cell culture Serology	URTI, LRTI	Primary: oral, intravenous, or inhaled ribavirin ± IVIG[b] ± palivizumab[c] ± steroids[d] Alternative: intravenous ribavirin	Prophylaxis: palivizumab or IVIG PrEP: once a month during RSV season in pediatric transplant	Standard and contact

PIV	*Paramyxoviridae* RNA	PIV 1: fall and winter PIV 2: fall and winter PIV 3: spring and summer PIV 4: not well established	RT-PCR IF Cell culture Serology	PIV 1: croup, URTI PIV 2: croup, URTI PIV 3: URTI, LRTI PIV 4: rarely cause disease	Primary: none Alternative: oral, intravenous, or inhaled ribavirin ± IVIG[b]	Prophylaxis: none Vaccine: none	Standard and contact
hMPV	*Paramyxoviridae* RNA	Winter and spring	RT-PCR IF Serology	URTI, LRTI	Primary: none Alternative: oral, intravenous or inhaled ribavirin ± IVIG[b]	Prophylaxis: none Vaccine: none	Standard and contact
AdV	*Adenoviridae* DNA	All year-round	RT-PCR[a] IF Cell culture Serology	URTI, LRTI, gastroenteritis, nephritis, hepatitis, hemorrhagic cystitis, encephalitis disseminated infection	Primary: cidofovir ± IVIG[b] Alternative: brincidofovir (research/compassionate use currently), ribavirin, ganciclovir	Prophylaxis: none Vaccine: none	Standard, contact and droplet

[a]Adenovirus is unique in that, although PCR is the preferred diagnostic test, negative testing from the upper or lower airway may not exclude infections. RT-PCR should be applied on respiratory specimen, blood (quantitative viral load testing) and other compartments depending on clinical presentation (urine, cerebrospinal fluid)

[b]Intravenous immunoglobulin therapy at a dose of 500 mg/Kg the first day, followed by a repeated dose after 48 h

[c]Palivizumab 15 mg/kg once a month; maximum of 5 doses per season

[d]Methylprednisolone is increased at a dose of 1 mg/kg/day, followed by gradually tapering over 2 weeks to reach a maintenance dose of approximately 0.1–0.2 mg/kg/day

AdV adenovirus, *CoV* coronavirus, *FLU* influenza, *hMPV* human metapneumovirus, *HSV1–2* herpes simplex virus 1–2, *IA* immunoassay, *IF* Immunofluorescence, *IVIG* intravenous immunoglobulin, *LRTI* lower respiratory tract infection, *MERS-CoV* Middle East respiratory syndrome coronavirus, *OD* once daily, *PIV* parainfluenza, *PrEP* pre-exposure prophylaxis, *PPE* postexposure prophylaxis, *RhVs* rhinovirus, *RSV* respiratory syncytial virus, *RT-PCR* real time PCR, *SARS-CoV* severe acute respiratory syndrome coronavirus, *URTI* upper respiratory tract infection

population [2, 3]. Consequently, vigilance regarding circulating community RV infections is required while caring for SOT recipients.

Rapid and reliable laboratory diagnosis is required in SOT with respiratory syndrome to significantly impact on patient care and management. The ideal method of sampling has also come into question, as the yield of viral specimen may differ depending on the specimen source. All SOTs with suspected RV infection should have a nasopharyngeal sample tested by PCR, including nasopharyngeal swab (NPS), wash, or aspirate. Between common respiratory specimens collected from the upper respiratory tract, NPS are preferred, since they are practical for widespread use and comparable in sensitivity to nasopharyngeal aspirates or bronchoalveolar lavage (BAL) for the detection of all major RVs [1, 7, 8]. NPS should be collected diligently by trained staff, using the standardized procedures of the Centers for Disease Control and Prevention (CDC) (https://www.cdc.gov/urdo/downloads/speccollectionguidelines.pdf; https://www.youtube.com/watch?v=DVJNWefmHjE) [9]. If upper tract samples fail to document the RV cause of the respiratory illness and clinical or radiologic evidence of lower tract involvement exists, BAL should be performed for RV testing [7].

The array of diagnostic tools for RVs in immunocompromised patients has greatly increased over the last few years, and diagnosis can be performed using real-time PCR (RT-PCR) techniques, antigen detection, and serology (Table 9.3) [9].

The sensitivities of contemporary molecular diagnostic techniques have been substantially improved, allowing for the rapid simultaneous detection of a wide variety of conventional and emerging RVs in respiratory samples. At present, real-time multiplex nucleic acid amplification testing (multiplex NAT) based on the RT-PCR technology is the preferred diagnostic tool for studying RVs in immunocompromised patients and is incorporated into many of the current guidelines [1, 7]. Both laboratory-developed and commercial RT-PCR assays are currently available, differing in specificity and sensitivity (ranges from 72% to 100%, with best sensitivity seen for FLU and lower sensitivities for ADV and PIV). With the aim of overcoming technical complexity of PCR-based testing, fully automated RT-PCR instrument for rapid detection of RV has been tested in immunocompromised patients with promising results with a turnaround time of approximately 1–2 h [10]. Therefore, clinicians should be aware of the performance characteristics of the assay performed (https://www.cdc.gov/urdo/downloads/speccollectionguidelines.pdf). Of note that regarding ADV, negative testing from the upper or lower airway may not exclude infections particularly for SOT with disseminated disease if there is limited to no involvement of the respiratory tract. RT-PCR should be applied on respiratory specimen, blood (quantitative viral load testing), and other compartments depending on clinical presentation (urine, cerebrospinal fluid).

It is important to remember, however, that despite the excellent sensitivity, poorly collected samples may yield false-negative results, and results may greatly vary depending on the quality of the swab. The high sensitivity of these methods also has drawbacks, such as frequent detection of viruses in asymptomatic individuals and prolonged detection of viruses in patients who have already clinically recovered [2, 3].

Table 9.3 Laboratory methods for diagnosis of the major human respiratory viruses. From Hodinka (https://www.youtube.com/watch?v=DVJNWefmHjE) modified

Clinical methods	Specimen	RVs tested	Sensitivity	Specificity	Test time	Comments
Multiplex nucleic acid amplification tests—real-time PCR (RT-PCR)	NPS, BAL	RSV, FLU, PIV, AdV, hMPV, RhVs, CoVs	High	High	15 min–8 h	(+): new reference standard; superior performance characteristic (−): frequent detection of viruses in asymptomatic individuals; negative testing for AdV from the upper or lower airway may not exclude infection
Direct antigen detection tests						
– Immunofluorescence (IF)	NPS, BAL	RSV, PIV 1, PIV 2, PIV 3, AdV, hMPV Not RhVs or CoVs	Moderate	Moderate-high	1–2 h	(+): rapid, multianalyte detection (−): not available for RhVs or CoVs ; moderately complex and subjective reading
– Immunoassay (IA)	NPS, BAL	RSV, FLU (mostly) adenovirus	Low-moderate	Moderate-high	≤15 min	(+): fast and simple to use (−): amenable to point-of-care testing; suboptimal in SOT; some commercial kits do not distinguish between FLU A and B

(continued)

Table 9.3 (continued)

Clinical methods	Specimen	RVs tested	Sensitivity	Specificity	Test time	Comments
Virus culture systems						
– Shell vial or microwell plate	NPS, BAL NPS, BAL	RSV, FLU, PIV 1, PIV 2, PIV 3, AdV, hMPV	Low-moderate	High	1–3 days	(+): rapid centrifugation-assisted cultures for select viruses (−): less sensitive than tube cultures; not available for the growth of all viruses
– Conventional tube		RSV, FLU, PIV, AdV, RhVs (A and B)	Low-moderate	High	3–14 days	(+): capable of growing any virus; allows confirmation of virus viability and test of antiviral susceptibility (−): involves considerable time, labor, and resources; Group C RhVs, MPV, and CoVs do not routinely grow in standard cell culture
Serology	Blood	RSV, FLU, PIV, AdV, hMPV, RhVs, CoVs	NA	NA	NA	(+): used for research, epidemiologic studies and analyze the immune response to vaccination (−): not useful for diagnosis; need collection of blood samples at acute illness and 4–6 weeks after

(+) positive, (−) negative, *AdV* adenovirus, *BAL* bronchoalveolar lavage, *CoV* coronavirus, *FLU* influenza, *hMPV* human metapneumovirus, *NA* not applicable, *NPS* nasopharyngeal swab, *PIV* parainfluenza virus, *RhVs* rhinovirus, *RSV* respiratory syncytial virus, *RVs* respiratory virus, *SOT* solid organ transplant, *URTID* upper respiratory tract infectious disease

The major challenge is to determine association between the presence of microbial nucleic acids and a clinical syndrome in individual patients. Quantification of the virus may be a helpful result interpretation, since high viral loads are associated with the presence of symptoms and may be related to the severity of the clinical symptoms [9].

Antigen detection techniques, which include immunofluorescence (IF) and immunoassay (IA), are fast and have high specificity but are only available for specific viruses and their sensitivity less than molecular methods. This technique is not available for viral respiratory infections caused by RhV or CoV and is moderately complex, and interpretation of results is subjective [9]. A number of commercial IA are available for RSV and FLU (A and B) and require little technical expertise. However, false-negative and false-positive results can be generated. A low prevalence of circulating virus within the community decreases the positive predictive value of the test. For FLU, rapid IA has shown high specificity but low sensitivity (20–70%) as compared to other assays, making them suboptimal for SOT recipient, particularly in clinical decision-making for antiviral therapy [11].

Antiviral susceptibility testing for RVs is primarily focused on influenza, and both phenotypic and genotypic assays can be tested, although such testing is not widely available in local or commercial labs.

Antiviral resistance is of considerable concern among immunocompromised patients infected with influenza virus, and testing should be strongly considered in SOT undergoing treatment who fails to have an appropriate clinical response within 3–5 days of initiating antiviral therapy or who has a relapsing course despite ongoing therapy.

9.4 Treatment Options, General Considerations

In the absence of available treatment options and of strong evidence of effectiveness for any particular therapy, treatment strategies differ widely among centers [12]. Limited understanding of (1) risk factors for progression to severe LRTI and poor outcomes and (2) indirect inflammatory effects of viral infection impact opinions on appropriate interventions for respiratory viral infections. RV infections, particularly cause by influenza virus, are a risk factor for subsequent bacterial and fungal superinfections. In cases of LRTI, secondary infections must be ruled out and appropriately treated, and initiation of oral or nebulized antifungal prophylaxis to prevent invasive fungal infections should be evaluated in high-risk patients [1, 2, 12].

Management in transplant patients is generally focused on reduction of immunosuppression feasible to speed resolution of viral infection. Treatment options for RVs are limited (Tables 9.2 and 9.4). Resistance patterns may change and affect recommended antiviral strategies. Consequently, clinicians should consult national health authority regularly for updated recommendations, especially for influenza.

Table 9.4 Antiviral agents

Drug	Mechanism of action	Spectrum	Standard dose and duration of treatment	Hepatic and renal adjustment	Pediatric dose	Drug interactions[a] and toxicity
Ribavirin	Broad-spectrum nucleoside analog activity against DNA and RNA viruses	RSV hMPV PIV 1–4 CoV FLU AdV	Inhaled (SPAG, negative pressure room): 6 gm daily aerosolized continuously over 12–18 h or 2 gm every 8 h over 1–4 h each for 7–10 days Intravenous: 15–25 mg/kg/day in three divided doses for 7–10 days. Some authors use loading dose 35 mg/kg in three divided doses the first day Oral: 15–25 mg/kg/day in three divided dose for 7–10 days	No hepatic adjustment No renal adjustment but use with caution if CrCl <50 mL/min	Inhaled: 20 mg/mL as the starting solution in the drug reservoir Oral: Children ≥2 years and adolescents: 15 mg/kg/day in two divided doses	No drug interactions Inhaled RBV: teratogenic potential, bronchospasm, cough, nausea, rash, decreased pulmonary function, conjunctival irritation; can potentially be deposited in the ventilator delivery system Oral/intravenous: hemolysis, insomnia, lactic acidosis, rash hyperbilirubinemia and leukopenia

Oseltamivir	Neuraminidase inhibitor (NAI)	FLU A and B	Oral: 75 mg every 12 h for 5–10 days Some authors suggest double dose (150 mg every 12 h) in severe cases or in case of insufficient response to therapy or/and extended duration of treatment to 10 days in case of in critically ill patients and persistent viral shedding Intravenous: compassionate use	No hepatic adjustment Renal adjustment: CrCl ≥30 mL/min: 75 mg every 12 h (for treatment), 75 mg every 24 h (for prophylaxis) CrCl <30 mL/min: 75 mg every 24 h (for treatment), 75 mg every 48 h (for prophylaxis) HD/CAPD: 30–75 mg after dialysis CRRT: 75 mg every 12 h	For child of any weight >2 weeks <1 year old: 3 mg/kg/dose every 12 h For child ≥1 year old: ≤15 kg: 30 mg every 12 h 16–23 kg: 45 mg every 12 h 24–40 kg: 60 mg every 12 h >40 kg: 75 mg every 12 h Indicated for prevention in child ≥1 year old; for the treatment in child > 2 weeks	No drug interactions Gastrointestinal upset, hypersensitivity reactions, hepatotoxicity, neurotoxicity, rashes In children oseltamivir has been associated with neuropsychiatric adverse events
Zanamivir	Neuraminidase inhibitor (NAI)	FLU A and B	Nasal: 10 mg 2 puffs every 12 h for 5–10 days. Rare reports of inhaled zanamivir failure Intravenous: compassionate use	Approximately 4–17% of inhaled dose absorbed into plasma No hepatic adjustment No renal adjustment	Indicated for prophylaxis in children ≥5 years old and for treatment in children ≥7 years old: same dose than adults	No drug interactions Bronchospasm: cannot be used in patients on ventilators because obstruction of filters

(continued)

Table 9.4 (continued)

Drug	Mechanism of action	Spectrum	Standard dose and duration of treatment	Hepatic and renal adjustment	Pediatric dose	Drug interactions[a] and toxicity
Peramivir	Neuraminidase inhibitor (NAI)	FLU A and B	Intravenous: 600 mg every 24 h for 5–10 days Approved in China, Japan, South Korea, and the United States	No hepatic adjustment Renal adjustment: CrCl ≥50 mL/min: 600 mg IV every 24 hCrCl 30–49 mL/min: 200 mg IV every 24 hCrCl 10–29 mL/min: 100 mg IV every 24 h CrCl <10 mL/min: 100 mg single dose, than 15 mg every 24 h HD: administer post dialysis based on renal function: 100 mg on day 1 then 100 mg 2 h after HD CAPD/CRRT: no recommendations	Children 181 days to 5 years: 12 mg/kg OD Children 6–17 years: 10 mg/kg every 24 h for 5 days (maximum of 600 mg every 24 h) CrCl ≥50 mL/min: 600 mg IV every 24 hCrCl 30–49 mL/min: age 6–17 years: 2.5 mg/kg every 24 h; age 180 days to 5 years: 3 mg/kg every 24 hCrCl 10–29 mL/min: age 6–17 years: 1.6 mg/kg every 24 h; age 180 days to 5 years: 1.9 mg/kg every 24 h CrCl <10 mL/min: age 6–17 years: 1.6 mg/kg on day 1 then 0.25 mg/kg every 24 h age 180 days to 5 years: 1.9 mg/kg on day 1 then 0.3 mg/kg Hemodialysis: age 6–17 years: 1.6 mg/kg on day 1 then 1.6 mg/kg 2 h after HD Age 181 days to 6 years: 1.9 mg/kg on day 1 then 1.9 mg/kg 2 h after HD	No drug interactions Gastrointestinal intolerance, neutropenia, neuropsychiatric disturbances, rash, hyperglycemia

Laninamivir	Neuraminidase inhibitor (NAI)	FLU A and B	Inhaled: 40 mg every 24 h 20 mg daily for 2 days is recommended for prophylaxis Approved in Japan	No hepatic adjustment No renal adjustment Approximately 15% of inhaled dose absorbed into plasma	Age <10 years: 20 mg every 24 h	No drug interactions
Cidofovir	Nucleotide analog activity against DNA viruses	AdV Herpesvirus JC virus	Intravenous: induction of 5 mg/kg IV once weekly × 2 weeks Maintenance: 5 mg/kg IV once every 2 weeks (minimum two doses) or 1 mg/kg IV three times per week for 2 weeks + probenecid + hydration[b] Intravescical: 5 mg/Kg in 100 mL of NS (for hemorrhagic cystitis)	No data on hepatic adjustment No renal adjustment but if CrCl <55 mL/min or urine protein ≥100 mg/dL: avoid use Changes in renal function during therapy: If serum creatinine increases by 0.3–0.4 mg/dL: reduce dose to 3 mg/kg; If serum creatinine increases ≥0.5 mg/dL or development of ≥3 + proteinuria: discontinue therapy No data on dialysis	Infants ≥6 months <3 years IV: 1 mg/kg/dose every other day or three times weekly for 4 consecutive weeks	Cidofovir: dose dependent nephrotoxicity, proteinuria, glycosuria, metabolic acidosis Fanconi syndrome, bone marrow toxicity Probenecid: fever, gastrointestinal symptoms, rash, asthenia, ocular diseases Caution: the use of tacrolimus or cyclosporine with cidofovir may enhance the risk of nephrotoxicity

[a]Drug interactions are focused on interactions with immunosuppressive therapy: steroids, cyclosporine, tacrolimus, sirolimus, everolimus, mycophenolate mofetil
[b]Probenecid: 2 g 3 h prior to cidofovir dose, then 1 g at 2 h and 8 h after completion of the infusion. Hydration: patients should also receive 1 L of normal saline intravenously infused over 1–2 h immediately prior to each cidofovir infusion. If tolerated, a second liter may be administered over 1–3 h at the start of cidofovir infusion or immediately following infusion

AdV adenovirus, *CAPD* continuous ambulatory *peritoneal dialysis*, *CoV* coronavirus, *CrCl creatinine clearance*, *CRRT* continuous renal replacement therapy, *FLU* influenza, *HD* hemodialysis, *hMPV* human metapneumovirus, *NS* normal saline, *PIV* parainfluenza, *RSV* respiratory syncytial virus, *SPAG* small particle aerosol generator

In our opinion treatment efforts should be always performed in any SOT with LRTI or in lung transplant and heart-lung transplantation recipients both with URTI and with LRTI, due to increased morbidity and mortality [12].

Reconstitution of the immune system appears to be important in overcoming RV infections. Clearly, the currently available treatment option is a clinical dilemma [6, 7, 13]. There are numerous reports in the literature citing the use of intravenous immunoglobulin (IVIG) as part of therapy for viral infections in immunocompromised patients. Hypogammaglobulinemia has been associated with an increased risk of opportunistic infections in SOT, but not to community-acquired RVI. However, some experts recommend considering the addition of IVIG for severe RV infection in SOT [13].

The use of monoclonal antibodies is limited to the treatment of RSV. Immunotherapy including transfer of RV-specific T lymphocytes from healthy donors is under investigation and has been reported to be safe and effective when performed early in the course of the infection for hMPV, adenovirus, RSV, and PIV. At the same time, virus-associated immune modulation may sometimes be deleterious in RVs due to local inflammatory responses. Adjunctive therapy with corticosteroids has been purposed for SOT with influenza and RSV and for lung transplant recipients with any RVs with LRTI because of the risk of both acute and chronic rejection [13].

9.5 Prevention, General Considerations

Treatment options for RVs are limited, and maximizing prevention measures against viral infections in SOT is mandatory.

RVs are potential community and nosocomial pathogens that can be spread by staff or visitors with mild upper respiratory illness. Overall awareness among SOT, healthcare personnel, family members, and caregivers about the potential deleterious outcomes of RV infections in SOT and the importance of early detection of infection may have a significant impact on the incidence of RV infections and risk of transmission [1].

Strict adherence to hand hygiene, contact precautions, and respiratory droplet isolation are required to reduce RV nosocomial spread and outbreaks during hospitalization (Table 9.2) (https://www.cdc.gov/infectioncontrol/guidelines/isolation/). The appropriate length of isolation for patients with laboratory proven RVs is debated, as prolonged shedding is a common finding in SOT patients, but viral load thresholds for infectivity are unknown. Infection control measures should be maintained until the patient is discharged home or until PCR is negative. Stringent hygiene precautions should be also applied in community settings, where SOT recipients should avoid close contact with individuals with respiratory tract infections [1]. The influenza virus is currently the only CARV that can be prevented with vaccination [14].

9.6 Prevention and Treatment of Specific RVs

9.6.1 Influenza

Three main viral strains have been recently associated with human infection, namely, influenza A/H1N1, influenza A/H3N2, and influenza B. Influenza infection in SOT causes significant morbidity and mortality compared to general population [15]. In studies performed in 2009 H1N1 pandemic, the proportion of patients who required hospitalization varied between 73% and 96%, and one of every five patients suffered severe complications with 7–8% mortality [15].

Treatment The mainstay of treatment for influenza A and B are the neuraminidase inhibitors (NAI), mainly oseltamivir (Tables 9.2 and 9.4) [16]. Doubling the treatment dose of oseltamivir in hospitalized patients with influenza does not seem to increase virologic efficacy, except perhaps for influenza B infections or in case of oral absorption concerns, with no evidence of emergence of oseltamivir resistance [17, 18]. Zanamivir is used less frequently than oral oseltamivir, likely due to the inhaled delivery route, although it has shown better activity against influenza B and few cross-resistance with oseltamivir.

Regarding intravenous formulations, if available, intravenous zanamivir or peramivir can be considered in SOT recipients who are severely ill despite oral oseltamivir, in case of concerns with oral absorption, although experience with these drugs in SOT recipients is lacking [1]. Parenteral zanamivir is currently available in Europe, and a single dose intravenous peramivir has been approved in the United States for treatment of uncomplicated influenza infections. However, peramivir use in SOT likely would require repeated dosing or switching to oral oseltamivir to complete therapy.

NAI resistance is currently uncommon (0.09–1.9% of isolates), especially for influenza A/H3N2 and influenza B viruses, but remains an area of growing concern. In case of high-level oseltamivir resistance (such as H1N1 viruses strains with H275Y substitution), peramivir usually preserves reduced susceptibility, but zanamivir is usually active. Another common resistance mutation (H274Y in H3N2) confers resistance to both oseltamivir and peramivir, but not zanamivir. Therefore, peramivir should not be used in patients with oseltamivir resistance unless the isolate is proven to be susceptible [16] (Tables 9.2 and 9.4). DAS181, an inhaled sialidase potentially inhibiting influenza and parainfluenza infection, has shown promising in vitro results of activity against oseltamivir-resistant influenza strains but failed to show superiority compared to placebo in previous studies in healthy subjects with influenza infection [17].

Treatment should be initiated as soon as possible since antiviral therapy is most likely to provide benefit when initiated within the first 48 h of illness in SOT, with a reduced rate of influenza-associated complications (admission to ICU, use of invasive ventilation, and death) [15]. However, benefit has been demonstrated even with

delayed treatment, and most experts endorse influenza-specific antiviral treatment at any point in the illness. Further, treatment should not be delayed while awaiting diagnostic testing results or if a rapid antigen IA test is negative when clinical symptoms are suggestive of infection due to the poor sensitivity of rapid antigen tests (Table 9.3) [19].

In general, duration of antiviral therapy should be at least 5 days for SOT patients although some data suggest that longer duration (≥10 days) may be required, particularly in critically ill patients, those with pneumonia and persistent viral shedding.

Aside from advances in supportive care, no specific adjunctive therapies are routinely recommended. Corticosteroids have been shown to decrease the need for mechanical ventilation and progression to LRTI but at the cost of prolonged viral shedding and risk for invasive fungal coinfection. Corticosteroids are not routinely recommended but should be used if indicated for another reason such as concurrent acute rejection [17].

Prevention The main preventive strategy against influenza in SOT recipients remains the administration of yearly inactivated influenza vaccine. All transplant recipients and candidates, as well as family members, close contacts, and healthcare workers, should receive the influenza vaccine to provide herd immunity [14, 20] (Table 9.2). Influenza vaccines are available in inactivated (intramuscular or intradermal administration) and live-attenuated (intranasal) formulations. The live-attenuated vaccine is not recommended for immunocompromised recipients and close contacts, due to a potential risk of dissemination of the vaccine [14, 21].

Current guidelines recommend the standard injected inactivated influenza for SOT starting 2–6 month posttransplantation with option for administration as early as 1 month posttransplantation in an outbreak setting. If influenza vaccine was administered earlier than 2 months posttransplantation, when it is likely to be less effective, consideration may be given to administering a second dose of vaccine later in the influenza season [14, 20]. An association between vaccination and the development of the de novo antibodies and graft rejection is unproven.

A higher-dose vaccine in pediatric SOT and a booster strategy 5 weeks after standard influenza vaccination in adult SOT have shown to induce an increased antibody response compared with standard single dose. Whether or not protection is increased by use of higher-dose vaccine, adjuvants, booster doses, or quadrivalent versus trivalent vaccines constitutes an area of active research [21].

Clinical failure of influenza vaccination in SOT recipients has not been extensively studied, but most of the studies clearly suggest a reduced immune response in SOT, with a seroconversion rate that varies between 15% and 90%, although this is also dependent on the match between the vaccine and the circulating strains [20]. Vaccination has shown to attenuate adverse outcomes among SOT recipients with a lower incidence of pneumonia and shorter length of hospital stay [19, 22].

Beyond influenza vaccination, pre-exposure or postexposure chemoprophylaxis with either oseltamivir or zanamivir is approved (Tables 9.2 and 9.4) and may be

considered [7]. Caution should be used with prescribing oseltamivir for prophylaxis in patients exposed to an index case because prophylaxis has been associated with emergence of resistant mutants; therefore, monitoring and empiric therapy are generally recommended in these cases [17].

9.6.2 Respiratory Syncytial Virus

Respiratory syncytial virus has long been recognized as a concerning pathogen in immunocompromised hosts. In SOT, RSV infection typically manifests as an URTI with progression to LRTI in 27–67%. Risk factors for more severe disease after organ transplantation include infection in children under a year of age or lung transplantation [2, 4].

Treatment The use of ribavirin (RBV) for the treatment of RSV infection is controversial. In immunocompromised patients (mainly hematopoietic stem cell transplant recipients), RBV has been shown to decrease progression to LRTI when given to patients with URTI. Among SOT, the greatest experience with RBV is with lung transplant recipients. Based on published reports as well as self-reported treatment strategies in surveys from SOT centers, lung and heart-lung recipients often receive RBV for both RSV-related URTI and LRTI [12]. Due to lack of clear evidence of efficacy, wide variation in the management of RSV exists including variability often dependent on availability of the inhaled, intravenous, and oral RBV formulations [23]. Intravenous and inhaled RBV are not available in most European countries. Oral ribavirin appears to be an effective, well-tolerated alternative to intravenous or inhaled ribavirin, providing potential cost savings and reducing length of hospital stay [24] (Tables 9.2 and 9.4). ALN-RSV01, a small interfering RNA that targets the RSV nucleocapsid messenger RNA, has shown some early promise in potentially preventing chronic rejection in lung transplant recipients with RSV; this agent is no longer being developed clinically. In addition, there are a number of other small molecule therapies in various stages of development including early clinical trials [13].

Immunomodulators have also been investigated. Experts recommend considering the addition of an antibody preparation (palivizumab) and IVIG with or without corticosteroids for severe RSV infection in SOT, although data are limited to support this recommendation [12, 23]. A systematic review reported that any form of RBV, alone or in combination with an immunomodulatory agent, was effective in preventing progression from URTI to LRTI, with a trend toward better outcomes with inhaled RBV plus an immunomodulatory with monoclonal (palivizumab) or polyclonal antibody preparations (IVIG) (Table 9.2).

Prevention In addition to the general preventive measures, the only FDA-approved agent for the prevention of severe RSV infection in high-risk patients under the age of 2 years is palivizumab [23, 25]. Survey data suggest that antibody-based prophy-

laxis is used among pediatric transplant centers in young candidates and recipients. However, guidelines regarding the use of this agent in older children and adults do not exist, and the high combined with a lack of clear evidence of efficacy in SOT recipients precludes its wide-scale use (Table 9.2).

9.6.3 Parainfluenza Virus

In SOT patients PIV, most commonly PIV 3, is able to cause more serious and even fatal infections, which mostly occur in patients after lung transplantation [26]. An outbreak of PIV 3 infections in a kidney transplant unit demonstrated that all infections were mild and symptoms resolved spontaneously without associated mortality [27].

Treatment There are no currently approved antiviral treatments for parainfluenza disease. Treatment is supportive and includes reduction in immunosuppression. Oral, aerosolized, and intravenous RBV and/or IVIG and corticosteroids have been used off-label in PIV with variable results and no impact on mortality [28]. DAS181 has been used to treat PIV infections in immunocompromised patients and has shown encouraging results including reduction in PIV quantitative viral load and overall outcomes [28]. Clinical trial results are pending.

Prevention Outbreaks caused by PIV have been reported previously [27], and patients with known or suspected PIV should be isolated with standard contact precautions. There are no approved vaccines or prophylactic antiviral agents.

9.6.4 Human Metapneumovirus

Human metapneumovirus has a clinical pattern similar to RSV and is a significant cause of disease in transplant recipients [3]. hMPV Has been associated with LRTI (pneumonia) and high hospitalization rates [2].

Treatment There is no approved drug for the treatment for hMPV respiratory infection. Supportive therapy is the main treatment although RBV alone or with IVIG could be considered for the management of LRTI and severe cases of hMPV in SOT [29].

Prevention There are no approved vaccines or prophylactic antiviral agents.

9.6.5 Rhinovirus

Rhinovirus has more than 100 serotypes in 3 different species: A, B, and the more recently characterized C. Rhinoviruses are the leading cause of community-acquired

RV infections, and that finding is in agreement with the knowledge that this RV is the primary cause of acute viral respiratory illnesses [2, 3]. Infections with rhinovirus are usually mild and self-limiting URTI, although significant LRTI has been described in lung transplant recipients [2, 3]. Prolonged shedding for over 6 months with minimal symptoms has been reported in lung transplant recipients.

Treatment No specific treatment is approved for rhinovirus infection.

Prevention There are no approved vaccines or prophylactic antiviral agents.

9.6.6 Coronavirus

Coronavirus generally results in self-limited disease but may progress to LRTI. The most common types of HCoV are OC43, 229E, HKU1, and 25 NL63. Severe acute respiratory syndrome coronavirus (SARS-CoV) and

Middle East respiratory syndrome coronavirus (MERS-CoV) are novel coronavirus that have been responsible for recent acute respiratory syndrome epidemics.

Treatment There are no antivirals licensed for the treatment of HCoV infections, and therapy consists of supportive care. RBV has been used for the treatment of LRTI caused by coronavirus during the outbreak of SARS, and the use of RBV in combination with interferon-α-2a on MERS-CoV has been reported. However, this combination has not been reported in SOT, and there are no specific data to recommend RBV for the treatment of CoV infection in SOT recipients [13].

Prevention There are no approved vaccines or prophylactic antiviral agents.

9.6.7 Adenovirus

Adenovirus is a double-stranded DNA virus of the family *Adenoviridae*, with 7 subgroups (A–G) and 52 serotypes.

In contrast to many of the other community-acquired RVs, adenoviral infection can occur from primary acquisition or through reactivation. The transplanted organ is typically the site of infection, and pneumonia is most frequent in lung transplant recipients [30]. Of note, commercial RT-PCR assays differ in sensitivity and specificity for adenovirus (AdV), and quantitative AdV PCR from blood may also be obtained to aid in diagnosis (Tables 9.2 and 9.3).

Treatment Treatment is supportive and includes reduction in immunosuppression. The optimal timing for therapeutic intervention during the course of illness is unclear. Existing data suggests that cidofovir and brincidofovir, an orally bioavailable lipid conjugate of cidofovir, may provide the highest likelihood of antiviral efficacy. Brincidofovir appears to have increased in vitro and in vivo efficacy

against AdV for treatment of serious infections with less renal and bone marrow toxicity than cidofovir (Table 9.4). RBV does not appear to have significant anti-AdV activity in humans and is generally not recommended to treat serious AdV infections. The use of IVIG remains controversial because it does not appear to have a clear benefit at this time. Adoptive T-cell transfer has generally been limited to a few centers (predominantly in hematopoietic stem cell transplantation) and has been reported to be safe and effective when performed early in the course of the infection [30].

Prevention There are no approved vaccines or prophylactic antiviral agents.

9.7 Conclusions

Longitudinal prospective surveillance using molecular diagnostics is needed to understand the true epidemiology and clinical spectrum of respiratory viral diseases in SOT, particularly in non-lung population. Optimal timing, duration, and treatment indication for RVs are a dilemma that needs to be clarified in clinical practice. The efficacy of adjuvant immunogenic therapies remains controversial. Maximizing prevention and infection control measures against RVs in SOT is essential (Table 9.5).

Table 9.5 Key points for RV infections in SOT

Epidemiology and clinical presentation
• There is increasing recognition of infections caused by RVs as a major cause of morbidity and mortality in SOT • In addition to their direct, cytopathic, and tissue-invasive effects, RVs can create a microbially determined immune modulation The impact of RVs in acute and chronic rejection remains controversial, with the greatest risk in lung transplant recipients • Pediatric solid organ, lung transplant, and heart-lung transplantation recipients appear to have the greatest risk of both RVs infections and more severe complications • Rhinovirus and coronaviruses are the most common etiological agents • Influenza and other paramyxovirus (RSV, PIV, and hMPV) have a greater propensity to produce LRTID
Diagnosis
• Diligent collection of respiratory specimens and knowledge of the limitations of the assay used by your laboratory are essential for interpreting the results • Nasopharyngeal swabs (NPS) are preferred for the detection of all major RVs • Bronchoalveolar lavage is the preferred specimen for diagnostic testing in LRTID with negative NPS • Laboratory diagnostic methods include virus culture, rapid antigen detection tests, the reverse-transcriptase polymerase chain reaction (RT-PCR) and other nucleic acid amplification assays, and serology • Nucleic acid amplification tests, mainly RT-PCR, are the best diagnostic tools for studying RVs in SOT

Table 9.5 (continued)

Treatment
• Treatment options remain limited and consist of supportive care, reduction of immunosuppression and, if available, antiviral therapy • The use of immunomodulatory agents (intravenous immunoglobulin, monoclonal antibodies, RV-specific T lymphocytes or augmented corticosteroid therapy) is a clinical dilemma • SOT should receive antiviral therapy with a neuraminidase inhibitor (NAI, either oseltamivir or zanamivir) when influenza is suspected, before laboratory confirmation • Treatment of influenza with M2 inhibitors (amantadine and rimantadine) is not recommended for high resistance rates • Treatment for influenza with NAI should be initiated as soon as possible (<48 h) for optimal benefit, however and all symptomatic patients should receive antiviral therapy, irrespective of symptom onset • Duration of therapy should be minimum of 5 days, but longer duration of therapy (≥10 days) may be required in critically ill patients • Double dosing of oseltamivir is not recommended but may be considered in severe cases or in case of insufficient response to therapy • The use of intravenous zanamivir or peramivir can be considered in patients not responding to oseltamivir therapy or for whom oral absorption is a concern • In case of high-level oseltamivir resistance, zanamivir is usually active • The efficacy of ribavirin (aerosolized, intravenous, or oral) for the treatment of RSV infection in SOT recipients has not been determined • In severe cases of LRTIs with RSV, PIV, and hMPV infections in SOT recipients, therapy with ribavirin (aerosolized, intravenous, or oral) may be used, alone or in combination with an immunomodulatory agents
Prevention
• Maximizing prevention infection control measures against RVs in SOT is mandatory • SOT recipients should avoid close contact with individuals with respiratory tract infections • The main preventive strategy against influenza remains the administration of yearly trivalent inactivated influenza vaccine in all SOT recipients and their relatives • Influenza vaccination is safe in SOT recipients, even in the early posttransplant period • Oseltamivir may be used as pre-exposure and postexposure prophylaxis in selected patients • The use of palivizumab for prevention of RSV infection is not recommended in adult SOT recipients

FLU influenza, *hMPV* human metapneumovirus, *LRTID* lower respiratory tract infectious disease, *NPS* nasopharyngeal swab, *PIV* parainfluenza, *RBV* ribavirin, *RSV* respiratory syncytial virus, *RVs* respiratory viruses, *SOT* solid organ transplant

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Prevention and Treatment of Viral Hepatitis

10

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This chapter focuses on the prevention and management of the primary hepatotropic viruses, hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatitis E virus (HEV), which may result in chronic infection in organ transplant candidates and recipients.

10.1 Hepatitis C

Prior to the recent development of direct-acting antiviral therapy for HCV, it was the leading indication for liver transplantation in much of the world, resulted in almost universal reinfection in the transplanted liver, had low cure rates both before and after transplantation, and was associated with decreased patient and graft survival in liver and kidney transplantation [1, 2].

10.1.1 Liver Transplantation (LT)

The direct-acting antiviral agents (DAAs) used for the treatment of chronic hepatitis C virus (HCV) infection have led to a reduction in the proportion of patients waitlisted for LT for decompensated HCV cirrhosis and reduction in waitlist mortality and progression of disease in those who are listed [3, 4]. Globally, however, 21% of hepatocellular carcinomas (HCC) are attributable to HCV [5], and HCV-related HCC continues to increase as an indication for LT [6].

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Although DAA therapy reduces the risk of progressive liver disease, hepatic decompensation, HCC, and liver-related and all-cause mortality, when to treat HCV-infected patients awaiting LT remains controversial. Achieving sustained virological response (SVR) in some patients with cirrhosis may improve the model for end-stage liver disease (MELD) score, therefore lowering the likelihood of LT, without improving the poor quality of life associated with complications of end-stage liver disease, a situation termed "MELD limbo" or "MELD purgatory" [7, 8]. A recent analysis by Foster et al. included 467 patients with Child-Turcotte-Pugh (CTP) class B or C cirrhosis that received clinician-selected treatment for HCV demonstrated a disappointing overall SVR rate of 83.5%. In addition, treatment led to stabilization or improvement in hepatic function in up to 60% of the patients; however 17% had no change and 23% had an increase in MELD score [9]. This highlights the uncertainty with regard to improvement and degree of change in liver function with SVR as well as the lower rate of SVR in those with decompensated liver disease compared to that achievable post LT [10]. Another concern about treatment of HCV before LT is that it also might decrease the ability to be considered for an HCV-positive donor. This may be of particular concern in areas of higher HCV prevalence in the donor population, including that related to the opioid crisis in the United States [11].

In 2016, the International Liver Transplantation Society convened a working group to develop a guideline focused on the use of DAA therapy in LT candidates. Table 10.1 summarizes the recommendations from this guidance document [12]. These recommendations aim to balance the risks of progressive liver failure and complications of untreated HCV with the higher cure rate achievable post LT compared to those with advanced hepatic decompensation. In addition to the severity of liver disease as measured by MELD score and the presence of complications such as portal hypertension and HCC, there are a number of center-specific factors to consider in deciding the optimal timing of HCV therapy, including:

- Anticipated time to LT
- Access to living donor LT
- Availability of anti-HCV-positive donors
- Waitlist drop-off rates for HCC progression
- Access to and costs of antiviral therapy

Table 10.1 Summary of timing of treatment of HCV in LT candidates (adapted from [12])

Treat on waitlist	Do not treat
• Decompensated cirrhosis with CTP B and/or MELD <20 *without* refractory portal HTN • MELD 20–29 *OR* MELD <20 *with* refractory portal HTN (selectively) • Decompensated cirrhosis and HCC; expected to wait ≥3–6 months • HIV/HCV coinfected • Compensated cirrhosis and HCC	• Those with MELD ≥30 OR expected to undergo LT within 3 months • MELD 20–29 OR MELD <20 with refractory pHTN (selectively) • Decompensated cirrhosis and HCC; expected to wait <3–6 months

In LT recipients, the outcome of DAA therapy is similar to the general population with overall SVR 96.6% in a recent analysis of 347 LT recipients enrolled in the HCV-TARGET cohort study [10]. Treatment regimens included sofosbuvir/ledipasvir, ombitasvir/paritaprevir/ritonavir plus dasabuvir, and sofosbuvir plus daclatasvir. Overall therapy was well tolerated, and episodes of acute rejection associated with therapy were rare, occurring in only four patients. Ribavirin use did not influence SVR, and the only factors associated with SVR were female gender, baseline albumin >3.5 g/dL, baseline total bilirubin <1.2 mg/dL, absence of cirrhosis, and absence of hepatic decompensation. The MAGELLAN-2 trial evaluated a 12-week course of the daily fixed-dose combination of glecaprevir/pibrentasvir in 80 treatment-naïve and treatment-experienced liver transplant recipients, as well as 20 kidney transplant recipients, with all genotypes except 5 represented [13]. This resulted in SVR in 98% of patients. High cure rates and good long-term outcomes are achievable even in those with advanced HCV recurrence post LT and fibrosing cholestatic hepatitis C, a previously universally fatal complication [14, 15]. As such there are now several well-tolerated, highly effective regimens to treat HCV post LT. There are also few drug interactions with immunosuppressive agents [16]. Cyclosporine is contraindicated in combination with HCV protease inhibitors including grazoprevir, simeprevir and voxilaprevir.

The use of HCV viremic donors for HCV viremic liver recipients is safe with appropriate selection of donors who generally have no more than moderate hepatic fibrosis [17]. This has become a well-accepted practice in most centers. More recently, there have been a few of cases of intentional LT from a viremic donor to uninfected recipient with post LT DAA therapy and cure [18, 19]. A recently published American Society of Transplantation Consensus suggests that transplantation from HCV viremic donors to negative recipients can only be considered in the setting of clinical research at this time [20]. However as HCV can now be cured in almost all posttransplantation, the benefits of accepting an HCV viremic donor, who, at least in the United States, is likely to be a younger donor with better quality organs [11], likely outweigh this risk of HCV infection in the era of DAA therapy.

10.1.2 Kidney Transplant Patients

Screening blood products for hepatitis C virus (HCV) and the use of recombinant erythropoietin have reduced the prevalence of HCV infection during dialysis and in kidney transplant patients [21]. HCV-positive RNA-positive dialysis patients and HCV-positive RNA-positive kidney transplant patients have significantly decreased survival compared to those that are HCV-negative dialysis patients and HCV-negative kidney transplant patients, respectively. However, survival of HCV-positive RNA-positive kidney transplant patients is significantly higher than that of HCV-positive RNA-positive dialysis patients. The main causes of death of HCV-positive kidney transplant patients are cardiovascular disease, posttransplant diabetes mellitus, and liver disease. Survival of the kidney allograft is also significantly decreased

in kidney transplant patients infected by HCV. The main causes of graft loss are de novo or relapse of HCV-associated glomerulonephritis [21].

10.2 Management of HCV Infection Before and After Kidney Transplantation

Until very recently and before the era of direct-acting agents (DAAs) against HCV, the treatment of dialysis patients relied on interferon, with or without very low doses of ribavirin, which led to a sustained virological response (SVR) in ~40% of cases [22]. The drop-out rate from side effects was very high. No anti-HCV therapy was offered to HCV-positive RNA-positive kidney transplant patients as interferon is contraindicated in this setting because of its immunostimulatory properties, which can lead to an increased risk of acute rejection.

The number of cases of HCV has dramatically reduced within the last couple of years because of the emergence of DAAs. In the large, randomized C-surfer study, the combination of grazoprevir and elbasvir, given for 12 weeks to patients that had stage 4 and 5 genotype-1 HCV-positive RNA-positive chronic kidney disease (CKD), resulted in a SVR rate of 94–99% [23]. A lower SVR rate (85%) was found in patients with genotype-1a with NS5A-resistance-associated variants (RAVs); thus, it is now suggested that duration of this therapy is increased to 16 weeks for these patients. This combination was not assessed in genotype-4-infected CKD patients. However, because it is highly efficient in genotype-4 patients with normal kidney function, the results can be extrapolated to CKD patients.

The Ruby 1 study, which included 20 genotype-1 patients with CKD, found that the combination of ombitasvir, paritaprevir, ritonavir, and dasabuvir (with or without ribavirin) was associated with a SVR of 90% [24]. Genotype-1 hemodialysis patients receiving daclatasvir plus asunaprevir also had highly efficacious outcomes, with SVRs ranging between 90 and 100% [25]. A pan-genotype therapy that combined glecaprevir and pibrentasvir, given to genotype-1 to genotype-6 patients with impaired kidney function (including dialysis patients), resulted in a SVR rate of 98% [26]. In all these studies, the tolerance was excellent.

Although sofosbuvir is not approved for use in patients with a glomerular-filtration rate <30 mL/min because it is renally cleared, sofosbuvir-based therapies have been given to CKD-4 and CKD-5 patients (including dialysis patients). The SVR rate was reported at ~90%, with no safety issues, and the accumulation of its metabolite (GS007) was mild [27, 28]. Sofosbuvir did not have a harmful effect on kidney function in most patients; when it did occur, it was reversible in most cases [29].

Sofosbuvir-based therapy was also highly efficient and cured most kidney transplant patients [30, 31]. The combination of sofosbuvir plus ledipasvir has been the most commonly used combination. A phase II randomized prospective study showed that the efficacy of the combination of sofosbuvir and ledipasvir was equivalent when given for 12 or for 24 weeks [32]. The tolerance to anti-HCV therapies

was excellent after transplantation. There was no increased risk of acute rejection or impaired kidney function. However, no reports on the effects of sofosbuvir and velpatasvir in the setting of kidney transplantation have been published yet. Thus, because several very efficient therapies are available to treat HCV, both before and after kidney transplantation, the main focus is to determine the optimal timing of treatments, i.e., before or after transplantation.

Treating CKD patients before transplantation can avoid the harmful effects of HCV and will decrease the risk of nosocomial transmission. However, it can delay transplantation. Conversely, having HCV replication at transplantation can allow the use of kidneys from HCV-positive donors.

Before the era of using DAAs after transplantation, it was shown that patient and graft survival rates of HCV-positive RNA-positive recipients did not differ if the donors were HCV-positive or HCV-negative [33]. More recently, it has been shown that using HCV-positive kidneys from HCV-positive recipients, followed by the early introduction of DAAs (median of 125 days posttransplantation), was successful and obtained a SVR in 96% of cases [34]. In addition, it significantly reduced the waiting times to receive a graft [34]. Very recently, a preliminary report showed that HCV-positive donors could also be given to HCV-negative recipients pending starting anti-HCV therapy and as soon as day 3 posttransplant [35]. These very interesting data need to be confirmed.

Hence, if kidney transplantation is expected within a 24-week period (12 weeks of therapy and 12 weeks of follow-up to evaluate SVR) or if there is the possibility of obtaining a kidney from a HCV-positive donor, it is preferable to treat HCV infection after kidney transplantation. In other cases, candidates for kidney transplantation can be treated before transplantation (Fig. 10.1).

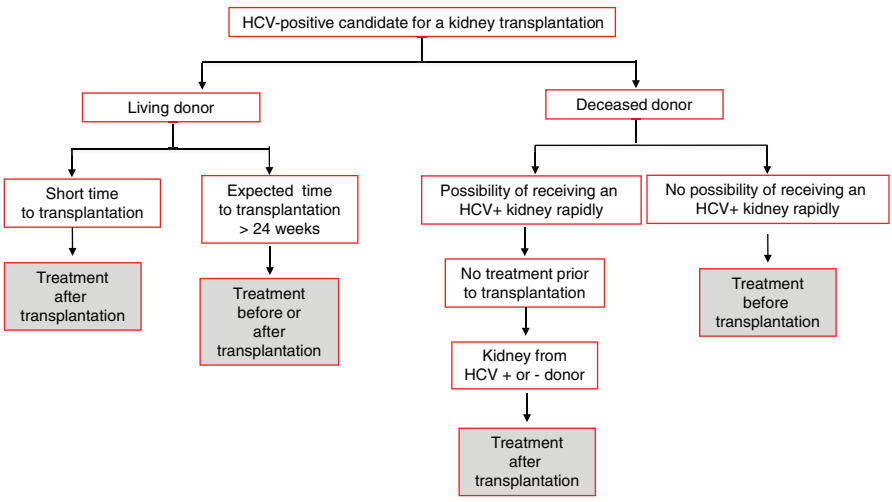

Fig. 10.1 Management of HCV infection in candidates for a kidney transplantation

10.2.1 Other Organ Groups

There here are limited data regarding the management of HCV in thoracic (heart, lung, heart-lung), small bowel, or pancreas recipients. Even the prevalence of chronic HCV infection in thoracic transplant recipients is uncertain with most of the data available being seroprevalence without documentation of HCV RNA. UNOS/SRTR data suggest the seroprevalence to be less than 2%, approximating the population prevalence. As in liver and kidney transplant, survival of HCV-positive recipients is inferior to HCV-negative recipients in heart and lung transplant [36, 37]. There are also limited data regarding the safety and efficacy of DAA therapy in those with end-stage heart and lung disease or following thoracic transplantation, although case reports and small case series to date show favorable outcomes [38–40]. There is no reason to believe the principles of HCV DAA therapy in liver and kidney transplantation would not apply in thoracic transplantation. There are no data to address the optimal timing of HCV therapy in thoracic transplantation, but as in kidney transplantation, factors to consider include the severity of hepatic fibrosis, expected wait time, and likelihood of an HCV viremic donor becoming available based on local prevalence. As in other organ groups, there are emerging reports of transplanting thoracic organs from HCV viremic donors to HCV-negative recipients with subsequent DAA therapy [40, 41]. This has the potential to expand the donor pool in this population as well, and there are trials enrolling in heart and lung transplantation (https://clinicaltrials.gov/ NCT03146741, NCT03146741, NCT03112044, NCT03222531).

10.3 Hepatitis B

10.3.1 Liver Transplantation

Because of the efficacy of nucleos(t)ide analogue (NA) therapy, hepatitis B virus (HBV)-related severe liver disease has become an uncommon indication for liver transplantation in the United States and many other Western countries, although remains a common indication in many Asian countries. Hepatocellular carcinoma is the most common indication for liver transplant in HBV patients with HBV accounting for about one-third of HCC globally [5]. Prior to the use of hepatitis B immunoglobulin (HBIg) and NAs, recurrent HBV infection after liver transplantation resulted in high rates of morbidity, mortality, and early graft loss [42]; this is now very rare.

As in all patients with HBV-related liver disease or HCC, all liver transplant candidates should be treated with NA therapy. Potent NAs are preferred [entecavir (ETV), tenofovir disoproxil fumarate (TDF), or tenofovir alafenamide (TAF)] due to their high barrier to resistance and rapid drop in HBV viral load induced. Pre LT, the goal is to achieve an undetectable HBV-DNA, as this is associated with the lowest risk of post-LT recurrence.

Post LT, the standard of care for prevention of HBV reinfection is the combination of HBIg and NA which prevents reinfection in over 95% of cases [43]. With the

advent of potent NAs, along with the challenge of HBIg administration, including the cost and need for parenteral or intramuscular injection, several studies have looked at the use of short-course HBIg [44, 45]. Studies using prophylaxis with potent NAs alone also suggest that this is feasible with a low rate of HBsAg recurrence in selected low-risk patients [46, 47]. Currently the route of administration, dosing, and duration of treatment with HBIG still varies from one transplant center to the other. In selected patients with a low risk of HBV recurrence (i.e., undetectable HBV-DNA at transplant, HBeAg negative, no hepatocellular carcinoma, no HIV or HDV coinfection, good adherence to potent NA therapy), evidence supports that HBIG can be safely discontinued 6–12 months after transplant.

Use of donors with evidence of past HBV infection (HBsAg-negative and anti-HBc-positive with or without anti-HBs) is safe with prophylaxis in the recipient. Where possible, allocation is preferred to HBsAg-positive recipients, followed by anti-HBc-positive recipients. In all cases, patients receiving a liver from an anti-HBc-positive donor have a risk of 50–80% of HBV reactivation because of immunosuppression and should receive prophylaxis with NAs [48, 49]. The majority of the available data support the use of lamivudine (LAM), with low risk of HBV recurrence [49]; however many centers prefer to use potent NAs such as ETV or TDF. In addition, following a year of antiviral prophylaxis, the risk of recurrence in recipients who are anti-HBc positive with protective anti-HBs titres (>10 IU/mL) is low, and guidelines suggest discontinuing NA may be considered, although many centers continue indefinite prophylaxis in all. There are small series reporting the use of HBsAg-positive donors with NA and HBIg prophylaxis post LT suggesting this may be safe. Currently however this is generally only recommended in urgent clinical settings, when there are likely to be no other better donor options, and following informed consent [49].

10.4 Hepatitis B Virus Infection in Kidney Transplant Patients

The prevalence of hepatitis B virus (HBV) infection in dialysis patients is low [50]. In this setting, HBV infection [i.e., HBs antigen (Ag)(+) patients] may have a mutated virus, i.e., a pre-core mutant that results in a HBe(−) antigen and a HBe(+) antibody [51].

After transplantation, the implementation of immunosuppression results in viral replication if it was absent during dialysis or in a flare-up of the virus infection if it was present at pretransplant. This can increase HBV viral load and flare-up of liver enzymes (to worsen HBV-related liver lesions [52]) and, in a few cases, increase the occurrence of cholestatic fibrosing hepatitis.

HBs Ag(+) dialysis and kidney transplant patients have worse survival rates compared to HBs Ag(−) dialysis and kidney transplant patients, respectively [50]. However, it has been shown that obtaining HBV clearance using antiviral therapy can significantly improve the survival of kidney transplant patients [53]. Survival of kidney transplant grafts was also significantly decreased in patients with positive HBs Ag [50]. Therefore, as soon as a HBV(+) patient receives a kidney transplant,

prophylactic antiviral medication should be provided. Lamivudine has been used in this setting. However, under this therapy, many patients develop DNA polymerase (YMDD) mutations, which render lamivudine therapy inefficient [54, 55]. Adefovir dipivoxil, a prodrug of adefovir and a nucleotidic analogue of adenosine monophosphate, has been used in kidney transplant patients [56]. However, because of its nephrotoxicity [57] and the availability of new anti-HBV treatments, adefovir dipivoxil is no longer used in this setting.

Although few publications have reported on kidney transplantation in this setting, two drugs are being successfully used to treat HBV infections after kidney transplantation: entecavir and tenofovir [58, 59]. No side effects have been reported with entecavir. However, because of cross reactivity, it cannot be given to patients that are already resistant to lamivudine. Tenofovir can be nephrotoxic when its dose is not adapted to kidney function. Hence, when used, strict monitoring of kidney function is required, and the dose of tenofovir should be adapted accordingly. Thus, entecavir is usually used in the early period posttransplantation when kidney function is still unstable; afterward, both entecavir and tenofovir can be used. In addition, although vaccine responsiveness is impaired, HBV-seronegative patients should be vaccinated against HBV.

10.4.1 Other Organ Groups

As in HCV, there are limited data regarding the management of HBV in thoracic (heart, lung, heart-lung), small bowel, or pancreas recipients. As in historical kidney transplant cohorts, those undergoing thoracic transplant in the era prior to effective NA therapy had high rates of progressive liver disease, cirrhosis, and liver-related death [60, 61]. Lamivudine has also been shown to be effective for treatment of HBV infection after heart and lung transplantation [61]. Although the data are fewer, it is reasonable to apply the principles of management from the available data in kidney transplant. As such, those with indications for treatment in the general population should be initiated on antiviral therapy prior to transplant. In those not on therapy, NA should be initiated as soon as possible following transplantation with a potent NA such as ETV, TDF, or TAF preferred. In those with renal dysfunction, ETV or TAF is preferred.

10.5 Hepatitis E Virus Infection in Solid Organ Transplant Patients

Hepatitis E virus (HEV) is the most common cause of viral hepatitis worldwide [62]. There is one serotype plus four main genotypes. Genotypes 1 and 2 (GT1 and GT2) are mainly prevalent in developed countries. Humans are the virus' reservoir and transmission is waterborne. GT3 and GT4 are prevalent in high-income countries and zoonoses. The main animal reservoirs are pigs, wild boar, rabbits, and

other animals. HEV usually spreads to humans through the food chain via fecal contamination of drinking water or consumption of meat from infected animals, but iatrogenic transmission through blood products is also possible [63].

HEV infection is often a self-limiting infection. However, all genotypes can cause fulminant hepatitis, so-called acute-on-chronic hepatitis, in patients with an underlying liver disease, which leads to death in up to 70% of patients. Only genotypes 1 and 2 have caused fulminant hepatitis in pregnant women, which has led to death of the mothers and newborns in up to 30% of cases [63].

Genotype-3 (and few cases of genotype-4) can cause chronic hepatitis and cirrhosis in immunosuppressed patients, especially solid organ transplant (SOT) patients [64]. No case of chronic hepatitis has been reported in genotype-1- or genotype-2-infected patients. In SOT patients, HEV evolves to chronicity in nearly 60% of infected patients and, without treatment, can cause cirrhosis in nearly 10% of these [65]. The main risk factor for chronic hepatitis in this setting is deep immunosuppression, e.g., a decreased HEV-specific T-cell response and decreased CD4 and CD8 lymphocyte subset counts. Reducing immunosuppression, especially those that target T cells (i.e., calcineurin inhibitors), is considered to be the first therapeutic option for SOT patients with chronic HEV infection [65]. Indeed, in vitro experiments show that calcineurin inhibitors and sirolimus increase HEV replication. In vivo, tacrolimus trough levels were significantly lower in SOT patients with chronic hepatitis and that had been cleared of HEV compared to those that remained viremic. In a retrospective multicenter study, ribavirin as a monotherapy can be highly efficient at treating chronic HEV infection in SOT patients and has achieved a sustained virological rate of ~90% [66]. The median duration of ribavirin therapy was 3 months. Patients without detectable HEV RNA in the serum, but with persistent HEV RNA detected in the feces at the end of therapy, had a significantly higher risk of relapse [67]. An algorithm for treating HEV infection in SOT patients is presented in Fig. 10.2.

A rapid decrease in HEV RNA in the serum within the first week after starting ribavirin has been identified as a predictive factor for SVR [68]. Conversely, ribavirin trough level on day 7 and at month 2 after initiating ribavirin has been associated with a SVR [68]. Hence, the optimal duration and dose of ribavirin still need to be determined.

Mutations in HEV RNA polymerase have been detected in some patients before therapy, under therapy, or in those with treatment failure. However, their effect on virological response is still unknown [63]. In relapsers after ribavirin therapy, retreatment for a longer period has enabled a SVR to be achieved [66]. Actually, there is no alternative therapy if there is treatment failure, except for liver transplant patients where pegylated interferon has been shown to efficiently treat HEV infection [69]. Because of the increased risk of acute rejection, interferon cannot be used in other SOT patients.

In immunosuppressed patients, prevention relies on avoiding eating raw meat. Up to 20 min of heating to an internal temperatures of 70°C is necessary to inactivate HEV [70]. An anti-HEV vaccine is also available and seems to be highly efficient [71]; however, it is only licensed in China.

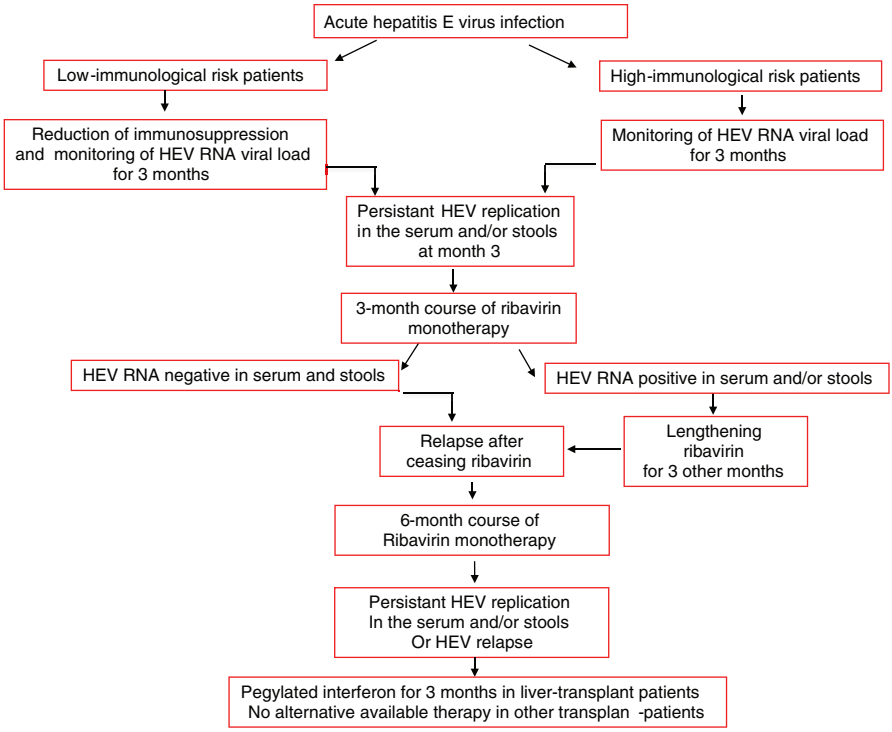

Fig. 10.2 Management of Hepatitis E virus infection

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Multidrug-Resistant Organisms in Solid Organ Transplantation

11

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11.1 Introduction

Multidrug-resistant (MDR) bacterial infections are responsible for significant morbidity and mortality in solid organ transplant (SOT) recipients worldwide. Although there has been an increasing recognition of the threat of antimicrobial resistance over the last decade, SOT recipients remain vulnerable to infections with MDROs (multidrug-resistant organisms). Most commonly, these infections are seen early after transplantation when healthcare-associated risk factors, surgical complications, and donor-derived factors predominate.

MDR bacteria are defined as bacteria that are resistant to at least one agent in three different antibiotic classes [1]. These organisms can be further classified as extremely drug-resistant (XDR) or pan-drug-resistant (PDR). In XDR infections, bacteria are only susceptible to two classes of antimicrobials. In PDR infections, bacteria are resistant to all active antimicrobials. The most common organisms that "escape" the effects of antimicrobials and become MDROs are *Enterococcus faecium*, *Staphylococcus aureus*, *Clostridium difficile*, *Acinetobacter* species, *Pseudomonas aeruginosa*, and *Enterobacteriaceae*, commonly known as the ESCAPE organisms [2].

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Infections with MDROs often result in increased hospital length of stay, higher costs, exposure to medications with adverse effects and decreased graft, and patient survival. Mortality rates are higher in these patients, often compounded by inappropriate empiric antimicrobial therapy. Lastly, insufficient clinical data in how to treat SOT recipients with MDR infections, specifically in the setting of resistant Gram-negative infections, frequently contribute to higher mortality rates.

11.2 Gram-Positive Bacteria

Multidrug-resistant infections with Gram-positive organisms typically include methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE). MRSA infections appear to be decreasing, likely in the setting of infection prevention and control strategies [3]. Newer antimicrobials have provided improved treatment options for the management of MRSA and VRE infections.

11.3 Methicillin-Resistant *Staphylococcus aureus* (MRSA)

Staphylococcus aureus colonizes the nares and skin, causing infection in the setting of a breach of mucosal barriers or skin such as in the setting of an intravascular catheter. The Centers for Disease Control and Prevention (CDC) reported that 47.9% of all Hospital acquired infections caused by *Staphylococcus aureus* were methicillin-resistant in 2014 [4]. MRSA bloodstream infections (BSIs) and surgical site infections (SSIs) have been associated with longer median duration of hospital stay, increased hospital costs, and higher mortality rates as compared to patients with methicillin-susceptible *Staphylococcus aureus* (MSSA) infection [5, 6]. Despite this, overall rates of HAIs secondary to MRSA appear to be declining in both the United States and Europe, perhaps due to improved infection control measures [3].

MRSA infections in SOT recipients typically present in the first 3 months after transplant. They most commonly cause bloodstream infections in the setting of intravenous catheters, surgical site infections, and respiratory tract infections [7]. Donor-derived infections have also been described, specifically in recipients of donors with MRSA bacteremia and endocarditis. Despite appropriate use of antimicrobials active against MRSA in the recipient and negative blood cultures in the donor at the time of procurement, transmission still occurred as evidenced by whole genome sequencing [8, 9].

Risk factors for MRSA infections in SOT recipients have previously been reported, largely in liver transplant (LT) recipients. These include nasal colonization with MRSA, recent surgical intervention, CMV seronegativity, primary CMV infection, prior antibiotic exposure, and increased ICU length of stay [10–13]. In lung transplant recipients, mechanical ventilation greater than 5 days was a significant risk factor for MRSA infection [14].

Among these risk factors, MRSA colonization seems to confer a significantly increased risk for infection with MRSA after transplant. In a large single center study, liver transplant candidates and recipients with MRSA colonization had an increased risk of MRSA infection but not of death [15]. These findings were confirmed in a meta-analysis in which patients with pre- and posttransplant MRSA colonization had a sixfold and 11-fold increase in MRSA infections posttransplant, respectively. About 8.5% of SOT candidates were colonized with MRSA, similar to other high-risk populations such as those on hemodialysis [16].

The management of patients with MRSA infection involves appropriate antimicrobial therapy (Table 11.1) along with source control [17–19]. Vancomycin remains the most commonly used antimicrobial to treat patients with MRSA infection and is still recommended as a first-line therapy when the vancomycin MIC is less than 2 [20, 21]. The phenomenon of "MIC creep" seen with vancomycin is controversial and has been associated with increased treatment failure and mortality in some studies. However, a recent meta-analysis showed no significant difference in the risk of death when comparing patients with a vancomycin MIC ≥1.5 to MIC <1.5 [22].

Table 11.1 Treatment options for methicillin-resistant *Staphylococcus aureus* (MRSA) infections

Treatment	Recommended adult dosing (nl CrCl)	Adverse effects	Comments
Vancomycin	15–20 mg/kg IV q12	Nephrotoxicity	• First-line therapy when the vancomycin MIC is less than 2 • Requires PK/PD monitoring to achieve an AUC/MIC ratio of 400 or a trough of 15–20 for bacteremia, endocarditis, osteomyelitis, meningitis
Daptomycin	6 mg/kg IV daily for bacteremia, endocarditis; some reports of using higher doses (8–10 mg/kg) in severe infections	Myopathy, rhabdomyolysis, weekly CPK should be monitored; eosinophilic pneumonia	• Bactericidal • Cannot be used for pulmonary infections because inactivated by surfactant
Linezolid	600 mg IV or PO q12	Myelosuppression Peripheral neuropathy Optic neuritis Lactic acidosis Serotonin syndrome (with other SSRIs)	• Approved for HAP, CAP, and SSTIs • Orally bioavailable

(continued)

Table 11.1 (continued)

Treatment	Recommended adult dosing (nl CrCl)	Adverse effects	Comments
Ceftaroline	600 mg IV q12	Similar to other cephalosporins (rash, diarrhea)	• Fifth-generation cephalosporin with activity against MRSA, VISA, and GNRs • Approved for SSTIs, CAP but has been used for bacteremia and in some case reports in combination with daptomycin for salvage therapy
Telavancin	10 mg/kg IV q24	Nephrotoxicity, QT prolongation, dysgeusia	• Approved for HAP and SSTIs but black box warning of increased mortality observed in patients with renal impairment • Combination with tacrolimus may prolong QT • Woman should have a pregnancy test prior to use
Dalbavancin	Two-dose regimen, 1000 mg IV followed by 500 mg IV 1 week later	Nausea/HA/ diarrhea	• Approved for SSTIs • Long half-life which allows for two doses 1 week apart
Tigecycline	100 mg IV × 1 followed by 50 mg IV q12	Nausea/vomiting	• Bacteriostatic • Achieves low plasma drug concentrations and thereby controversial in use for severe infections and bacteremia • Approved for SSTIs, IAB, or HAP
Clindamycin	600–1200 mg IV q6–8 h	Gastrointestinal, *C. difficile* infection	• Bacteriostatic with good tissue penetrations • Appropriate for SSTIs, not bacteremia or severe infections
Sulfamethoxazole-trimethoprim	8–10 mg/kg daily based on trimethoprim component in two divided doses (orally or IV)	Hematologic effects, hepatotoxicity, severe dermatologic reactions	• Avoid use in bacteremia • Can be used for SSTIs

Mg/kg milligrams/kilogram, *IV* intravenous, *MIC* minimum inhibitory concentration, *PK/PD* pharmacokinetic/pharmacodynamics, *AUC/MIC* area under the curve/minimum inhibitory concentration, *HAP* healthcare-associated pneumonia, *CAP* community-associated pneumonia, *SSTI* skin and soft tissue infection, *VISA* vancomycin-intermediate *Staphylococcus aureus*, *GNRs* Gram-negative rods, *IAB* intra-abdominal infection

Commonly used alternatives for treatment of MRSA infection include daptomycin and linezolid. Daptomycin, most commonly used for the treatment of bacteremia and right-sided endocarditis, is inactivated by surfactant and cannot be used for the treatment of pneumonia. MRSA isolates with higher vancomycin MICs may also exhibit higher MICs to daptomycin, and some recommend higher doses of daptomycin (8–10 mg/kg). Combination therapy, particularly the use of daptomycin with beta-lactams such as ceftaroline, may be used as salvage therapy to minimize the emergence of resistance with daptomycin alone [23, 24]. Linezolid is most commonly used in the treatment of pneumonia where it may have superior efficacy when compared to vancomycin [25].

Duration of treatment is typically 4–6 weeks of therapy in patients with complicated MRSA bacteremia. In patients with uncomplicated bacteremia (exclusion of endocarditis, no prosthesis, clearance of bacteremia in 2–4 days, defervescence within 72 h of initiating therapy, no evidence of metastatic sites of infection), 2 weeks of therapy may be considered [20]. MRSA abscess and complicated skin and soft tissue infections should be debrided, and intravascular catheters should be removed in the setting of bacteremia.

The emergence of heteroresistant populations of vancomycin intermediate strains (hVISA) and VISA (vancomycin intermediate *Staphylococcus aureus*) infections have also been documented, although uncommon. Heart transplantation in a patient with hVISA left ventricular assist device infection, mediastinitis, and bacteremia has previously been described as has the clonal spread of an hVISA strain in a cohort of liver transplant recipients [26, 27].

Aggressive infection prevention and control measures, such as active surveillance, have previously been shown to help curtail MRSA infections in SOT recipients [28]. Infection prevention and control measures such as hand hygiene, chlorhexidine bathing for ICU patients, and implementation of contact precautions for patients infected with MRSA have also been shown to reduce hospital-acquired MRSA infections [29]. Larger, multicenter studies are needed to evaluate the benefit of such practices as decolonization in SOT recipients [30].

11.4 Vancomycin-Resistant *Enterococcus* (VRE)

Enterococcus is a Gram-positive organism that commonly colonizes the gastrointestinal tract and frequently causes infections in abdominal organ transplant recipients. Vancomycin resistance, specifically in *Enterococcus faecium*, became increasingly recognized in liver transplant recipients in the 1990s. Although typically known as a less virulent organism, infection with VRE has been associated with increased morbidity and mortality in SOT recipients, especially prior to the widespread availability of newer antimicrobials [31, 32].

Risk factors for VRE infection in liver transplant recipients include prior antibiotic use, intra-abdominal surgical procedures, biliary complications, and previous colonization [33–35]. Compared to non-colonized patients, liver transplant candidates and recipients colonized with VRE have an increased risk of VRE infection and death [15]. A meta-analysis documented an increase in VRE infection in patients with pre- and posttransplant VRE colonization [16].

Treatment for VRE infections should include source control and implementation of an active antimicrobial agent against VRE (Table 11.2). The most commonly used agents in the treatment of VRE infection are linezolid and daptomycin. Linezolid, an oxazolidone, has been used with good success in SOT recipients [36, 37]. Prolonged

Table 11.2 Treatment options for vancomycin-resistant *Enterococcus* (VRE) infections

Treatment	Recommended adult dosing (nl CrCl)	Adverse effects	Comments
Linezolid	600 mg IV or PO q12	Myelosuppression Peripheral neuropathy Optic neuritis Lactic acidosis Serotonin syndrome (with other SSRIs)	• Approved for VRE infection/ bacteremia • Orally bioavailable
Daptomycin	6 mg/kg IV daily but can be used in higher doses (see text)	Myopathy, rhabdomyolysis, weekly CPK should be monitored; eosinophilic pneumonia	• Frequently used for VRE infection/bacteremia • Bactericidal • Cannot be used for pulmonary infections because inactivated by surfactant
Quinupristin-dalfopristin	7.5 mg/kg IV q8	Phlebitis Myalgias/arthralgias Elevation in transaminases/bilirubin	• Approved for VRE in the late 1990s, largely a second-line drug given treatment-related adverse events and likely decreased efficacy compared to newer agents
Tigecycline	100 mg IV × 1 followed by 50 mg IV q12	Nausea/vomiting	• Bacteriostatic • Achieves low plasma drug concentrations and thereby controversial in use for severe infections and bacteremia • Approved for SSTIs, IAB, or HAP
Tedizolid	200 mg IV or PO once daily	Fewer reported AEs when compared to linezolid—specifically hematologic and gastrointestinal- and lacks drug interactions with other SSRIs	• Activity against MRSA in addition to VRE • Orally bioavailable
Oritavancin	1200 mg as a one-time infusion	Nausea, vomiting, headache	• Long half-life enables single dose administration • Activity against MRSA in addition to VRE • Approved for SSTIs

Mg/kg milligrams/kilogram, *IV* intravenous, *MIC* minimum inhibitory concentration, *MRSA* methicillin-resistant *Staphylococcus aureus*, *HAP* healthcare-associated pneumonia, *SSTI* skin and soft tissue infection, *IAB* intra-abdominal infection, *AEs* adverse events, *SSRIs* selective serotonin reuptake inhibitor

therapy can be associated with thrombocytopenia and leukopenia. Other adverse effects include peripheral neuropathy, serotonin syndrome in patients receiving concomitant SSRIs and lactic acidosis. Earlier meta-analyses suggested linezolid may be associated with improved clinical outcomes when compared to daptomycin although the outcome of these studies may have been affected by suboptimal daptomycin dosing [38].

Daptomycin, a bactericidal agent, is frequently used off-label as treatment for VRE infections and has been successfully used in SOT recipients [39]. However, the optimal dosing strategy of daptomycin for VRE infections still remains unclear. A recent retrospective cohort study of patients with VRE bloodstream infections (BSI) found that patients treated with daptomycin doses greater than 8 mg/kg had significantly improved microbiological clearance of infection; patients treated with even higher doses of daptomycin (≥10 mg/kg) had improved survival. There was no significant increase in CPK in the patients treated with higher-dose daptomycin [40]. Another prospective study from Taiwan found all-cause 14-day mortality was improved in patients receiving either high-dose daptomycin (9 mg/kg) or linezolid as compared to those receiving low-dose daptomycin (6–9 mg/kg) [41]. Higher doses of daptomycin may therefore be safely used to treat VRE infections although larger studies in SOT recipients are lacking. Combination therapy with beta-lactams has also been used in treatment of VRE infections, specifically in endocarditis [42–44].

Single-center studies have documented both daptomycin and linezolid resistance in patients with VRE infections. In a single center study of 14 liver transplant recipients with daptomycin non-susceptible *Enterococcus faecium* infections, all except one had previous exposure to daptomycin, and there was a 71% overall mortality rate [45]. Other studies have also described liver transplant recipients with linezolid-resistant VRE infections [46].

A comprehensive prevention strategy against VRE includes judicious use of antimicrobial agents and implementation of infection prevention and control measures such as hand hygiene and chlorhexidine bathing in the ICU. Routine surveillance is not indicated; however, in units with high prevalence rates or outbreak settings, active surveillance and use of contact precautions may be helpful to prevent cross-transmission and guide perioperative prophylaxis at the time of transplant [31, 32, 47]. Limited data exists regarding the use of decolonization strategies for rectal carriage of VRE, and larger studies are needed [48].

11.5 Gram-Negative Bacteria

Increasing resistance among Gram-negative bacteria in the last decade has accounted for a significant rise in antimicrobial resistant infections worldwide and presents a serious public health threat. The three most common Gram-negative organisms to "escape" the effects of antimicrobials are *Acinetobacter* species, *Pseudomonas aeruginosa*, and *Enterobacteriaceae*.

11.6 Carbapenem-Resistant *Enterobacteriaceae* (CRE)

Infections with carbapenem-resistant *Enterobacteriaceae* (CRE) have been increasingly described in SOT recipients. ß-lactamases which hydrolyze carbapenems are responsible for CRE infections. These are largely classified by molecular structure as described in the Ambler classification (Table 11.3). Types of carbapenemases among *Enterobacteriaceae* include Ambler class A (KPC), class B (zinc-dependent metallo-B-lactamases, VIM, IMP, NDM), and class D (OXA type). The most commonly described carbapenemase is KPC (Ambler class A), which accounts for a large proportion of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infections. KPC-producing isolates account for most CRE infections seen in the United States, Israel, Europe, China, and South America [49]. They hydrolyze all ß-lactams and are usually resistant to other classes of drugs such as fluoroquinolones and aminoglycosides. More recently in 2009, infections with the New Delhi metallo-beta-lactamase 1 (NDM-1) were described in South Asia and the United Kingdom. These have subsequently been described worldwide, largely in immigrants from South Asia. Lastly, infections with oxa-48 carbapenemase have been described in Europe, Turkey, North Africa, and India [49–52].

In the United States, CRE accounts for about 9300 infections annually and 600 deaths a year [53]. The incidence of CRKP varies by center and type of transplant. Various studies have reported rates between less than 1 and as high as 20% although the incidence of CRKP infection in LT recipients is likely around 5% in endemic areas [49, 50, 54]. LT recipients typically present with primarily intra-abdominal infections or bacteremia, whereas kidney transplant (KT) recipients present with urinary tract infections. Respiratory tract infections are more commonly seen in heart and lung recipients [50]. Necrotizing skin and soft tissue infections has also been described in transplant recipients [55]. Mortality rates in SOT recipients with CRKP vary by report but are usually between 30 and 50% with some studies describing mortality rates as high as 70% [49, 50, 56–58].

SOT recipients with CRE infection often have multiple risk factors that predispose them to infection including prolonged hospital and ICU stay, antimicrobial use, and mechanical ventilation [49, 59]. Transplantation itself has been an independent risk factor for CRKP [59]. In LT recipients, risk factors for CRKP have included MELD score at LT, re-transplantation, biliary leak, renal replacement therapy, and mechanical ventilation [60–62]. In KT recipients, risk factors have also included receipt of antimicrobials (other than sulfamethoxazole-trimethoprim) and increased transplant admission length of stay and use of ureteral stent [63, 64].

Table 11.3 Ambler classification of ß-lactamases

Ambler classification	ß-lactamases	Examples
A	Penicillinases	KPC, TEM, SHV, CTX-M
B	Metallo-ß-lactamases	IMP, VIM, NDM
C	Cephalosporinases	Amp-C
D	Oxacillinases	OXA

Pretransplant and posttransplant colonization has also been shown to be associated with posttransplant infection [56, 62, 65]. However, in a recent multicenter study, patients who were colonized with CRKP had 1-year survival rates approaching 80% posttransplant. Colonization with CRE may therefore not be considered an absolute contraindication to transplant [66].

Donor-derived infections with CRKP have also been reported. In one report, four recipients received tissue from a donor with CRKP, but there was evidence of transmission to only one recipient. In this case, timely communication and early involvement of transplant infectious disease specialists resulted in all four recipients receiving perioperative prophylaxis with antimicrobial agents directed toward the donor's KPC isolate resulting in only one transmission [67].

Treatment of CRE infections is largely based on observational clinical studies and should include source control and susceptibility-directed antimicrobial therapy (Table 11.4) [2, 68–70]. Source control is essential to improved clinical outcomes and mortality [59]. Tigecycline can be used for the treatment of intra-abdominal, skin and soft tissue and pulmonary infections but may be less effective in treating bloodstream or urinary tract infections because it does not achieve good serum or urinary levels. The polymyxins are some of the most active agents against CRE and require complex dosing schemes that have only recently been elucidated [2]. Polymyxin B, which differs from colistin or polymyxin E by amino acid structure, appears to be associated with less nephrotoxicity than colistin [71]. Neurotoxicity is also less common with more recent formulations. Fosfomycin has been used in combination therapy successfully but is only available in IV formulation in Europe [72].

Other data has suggested that combination therapy may have more efficacy in the treatment of CRE infections when compared to monotherapy. In one multicenter retrospective cohort study in Italy, triple combination therapy was associated with lower mortality; specifically, the use of a carbapenem was associated with improved survival [73]. Other studies have reported on combination therapies involving the use of colistin and a carbapenem, colistin and tigecycline, or even dual carbapenem therapy [74]. In vitro synergy studies have confirmed activity of dual carbapenem therapy against carbapenemase-producing strains as well as polymyxin and rifampin; rifampin however should be used with caution in transplant recipients as it decreases the levels of calcineurin inhibitors, mTOR inhibitors and triazole antifungals [49]. However, in a large, international retrospective cohort study that included 480 patients with CRE BSI, there was no difference between monotherapy and combination therapy except in patients who had severe infections and were considered to have a high mortality score [75]. Larger clinical trials are still needed to understand why and which combination therapy may be effective for severely ill patients and elucidate optimal treatments for CRE infection [74].

Ceftazidime-avibactam is a recently approved beta-lactam/beta-lactamase inhibitor combination with activity against CRE [68]. Recent observational data suggests that ceftazidime-avibactam may be superior to alternative treatments such as colistin [76–78]. However, resistance to ceftazidime-avibactam has already been reported [79]. Of note, ceftazidime-avibactam cannot be used for NDM-1 infections as avibactam does not inhibit metallo-B-lactamases.

Table 11.4 Treatment of multidrug-resistant (MDR) Gram-negative infections

Treatment	Recommended adult dosing (nl CrCl)	Adverse effects	Comments
Commercially available			
Tigecycline	100 mg IV × 1 followed by 50 mg IV q12	Nausea/vomiting	• Bacteriostatic • Achieves low plasma drug concentrations and thereby controversial in use for severe infections and bacteremia • Approved for SSTIs, IAB, or HAP • Does not have activity against *Proteus*, *Providencia*, or *Pseudomonas*
Polymyxins	Colistin 5 mg/kg/day IV or polymyxin B 1.25 mg/kg IV q12	Nephrotoxicity Neurotoxicity	• Approved for GNR infections including *Pseudomonas* • Requires complex PK/PD dosing with a loading dose
Ceftazidime-avibactam	2.5 gm IV q8	Nausea/vomiting	• Approved for complicated IAB and UTIs • Inhibits the activity of class A, B, and D enzymes, but not against B
Ceftolozane-tazobactam	1.5 gm IV q8	Nausea/vomiting, headache	• Approved for complicated IAB and UTIs • Has activity against MDR/XDR *Pseudomonas* and ESBL organisms
Fosfomycin	3 gm orally × 1; IV formulation available outside of the United States		• Oral formulation should only be used for uncomplicated cystitis • Rapid development of resistance if IV formulation used as monotherapy
Aminoglycosides	5–7 mg/kg/day IV of tobramycin or gentamicin; 15 mg/kg/day IV of amikacin	Nephrotoxicity, ototoxicity, vestibular toxicity	• Needs peak and trough monitoring
Meropenem/vaborbactam	4 gm IV q8	Headache, infusion site reaction, diarrhea	• Recently approved for UTI/pyelonephritis • Inhibitor of class A and class C ß-lactamases
Drugs in the pipeline			
Imipenem/relebactam			• Inhibitor of class A and class C ß-lactamases with additional activity against *Pseudomonas*

Table 11.4 (continued)

Treatment	Recommended adult dosing (nl CrCl)	Adverse effects	Comments
Plazomicin			• Aminoglycoside with activity against KPC- and OXA-producing organisms and MDR *Pseudomonas*
Eravacycline			• Fluorocycline tetracycline with activity against NDM- and KPC-producing organisms and CRAB

Mg/kg milligrams/kilogram, *IV* intravenous, *MIC* minimum inhibitory concentration, *PK/PD* pharmacokinetic/pharmacodynamics, *HAP* healthcare-associated pneumonia, *SSTI* skin and soft tissue infection, *GNRs* Gram-negative rods, *IAB* intra-abdominal infection, *UTI* urinary tract infection, *MDR* multidrug-resistant, *XDR* extremely drug-resistant, *ESBL* extended-spectrum beta-lactamase, *KPC Klebsiella*-producing carbapenamase, *NDM* New Delhi metallo-beta-lactamase, *CRAB* carbapenem-resistant *Acinetobacter baumannii*

Prevention of CRE in the healthcare setting often requires a combination of several infection control and prevention strategies. These include hand hygiene, cohorting of patients or staff, contact isolation precautions for patients infected or colonized with CRE, environmental cleaning, and focus on implementation of an effective antimicrobial stewardship program [80].

11.7 MDR *Pseudomonas aeruginosa*

Resistance mechanisms in *Pseudomonas aeruginosa* can be complex and often involve loss of outer membrane porins and upregulation of efflux pumps resulting in few therapeutic options [81]. *Pseudomonas aeruginosa* is a common cause of pneumonia and/or bacteremia early posttransplant [82, 83]. In one study, SOT recipients were 3.47 times more likely to have an MDR strain of *Pseudomonas* as compared to a non-SOT recipient [84]. Frequently, MDR *Pseudomonas* colonizes the lungs of CF patients pre- and posttransplant with colonization in 75% of lung transplant recipients in some reports [54, 83]. It is also the most common cause of bacterial pneumonia in lung transplant recipients, responsible for 25% of infections [54]. However, colonization with MDR *Pseudomonas* is not an absolute contraindication to lung transplant as overall rates of survival are similar in patients with or without colonization [54, 82, 85, 86].

The most significant risk factor for colonization or infection with MDR *Pseudomonas* remains prolonged exposure to antimicrobial therapies [54]. Other risk factors include ICU stay, previous transplantation, hospital-acquired BSI and septic shock [84, 87].

Treatment should utilize prolonged infusion of beta-lactam antimicrobials or increased doses of concentration-dependent therapy (i.e., fluoroquinolones) when susceptible. The polymyxins can also be utilized, and inhaled colistin or

aminoglycosides can be used in the treatment of pneumonia as adjunctive therapy [88]. The role of combination therapy especially in the management of XDR isolates remains controversial and can be used initially in severely ill patients prior to obtaining susceptibilities [31].

Both new B-lactam/b-lactamase inhibitors, ceftazidime-avibactam and ceftolozane-tazobactam, have activity against MDR *Pseudomonas* isolates [31]. However, ceftolozane-tazobactam shows particular promise against MDR and XDR isolates of *Pseudomonas* due to stability against multiple resistance mechanisms [89]. Successful use of ceftolozane-tazobactam has been described in several case reports of SOT recipients with MDR and XDR *Pseudomonas* infections including one lung transplant recipient and another LVAD patient undergoing HT [90, 91]. It is also a promising treatment option for pneumonia due to good penetration into the epithelial lining.

11.8 Carbapenem-Resistant *Acinetobacter baumannii* (CRAB)

Prevalence data for carbapenem-resistant *Acinetobacter baumannii* (CRAB) in SOT recipients varies by transplant center and region [54]. *Acinetobacter* is a particularly resilient pathogen, and many carbapenem-resistant isolates are resistant to other available antimicrobials [92]. A recent prospective cohort study at a single center in Brazil found that 46% of their LT recipients were colonized with CRAB and CRAB was the most common MDR Gram-negative isolated on surveillance [65]. MDR and XDR *Acinetobacter* are frequently seen in ventilator-associated pneumonia in cardiothoracic patients; however, respiratory infections in LT recipients are also described [65, 92, 93]. Treatment of MDR and XDR *Acinetobacter* infections remains challenging. Sulbactam, a B-lactamase inhibitor, has intrinsic activity against *Acinetobacter* and should be used if susceptible. Other therapeutic options include tigecycline, minocycline, aminoglycosides, and polymyxins if susceptible. A single center demonstrated that combination therapy with colistin and carbapenems was effective in SOT recipients [92]. Cefiderocol (formerly S-649266), an investigational siderophore cephalosporin, demonstrated potent in vitro activity against a 2014–2016 worldwide collection of clinical isolates of MDR *A. baumannii* and other carbapenem non-susceptible Gram-negatives [94].

11.9 *Burkholderia cepacia*

The *Burkholderia cepacia (B. cepacia)* complex comprises multiple different subspecies and is most known for its significance in patients with cystic fibrosis (CF) and lung transplantation, where it has been associated with increased morbidity and mortality. Infection with *B. cepacia* can lead to a progressive necrotizing pneumonia, resulting in a decline in pulmonary function [95]. The subspecies, *B. cenocepacia*, in particular, has been associated with poor outcomes [54]. In one single center study, patients infected with *B. cenocepacia* before transplant were six times more likely to

die within 1 year of lung transplant compared to those infected with other *Burkholderia* species and eight times more likely to die than compared to patients who were not infected [96]. In addition, transplant recipients infected with *B. gladioli* had significantly higher mortality compared to patients who were not infected [97]. Other studies have shown that infection with other *B. cepacia* species, such as *B. multivorans*, may not be associated with increased mortality after lung transplant [98].

Guidelines from the International Society for Heart and Lung Transplantation (ISHLT) suggest that *B. cenocepacia* and *B. gladioli* may be considered a relative contraindication to lung transplant and that these patients should be referred to a transplant center with significant experience in managing these infections [99]. *B. cepacia* complex strains are intrinsically resistant to multiple antimicrobials and can acquire resistance through efflux pumps or beta lactamases. Effective antimicrobials include trimethoprim-sulfamethoxazole, ceftazidime, meropenem, levofloxacin, and minocycline, and oftentimes combination drug therapy is utilized in patients with MDR or XDR infections [100]. Ceftazidime-avibactam has also been shown to have potent activity against *B. cepacia* [101]. Transmission of *B. cepacia* in healthcare and non-healthcare settings has been described, including through poor adherence to handwashing and contaminated respiratory equipment. Infection control interventions such as education, use of contact precautions, segregation of patients with *B. cepacia* in single-patient rooms with showers, and environmental decontamination have been shown to reduce transmission among CF patients [102, 103].

11.10 Conclusion

SOT recipients are at risk for MDR infections in the early posttransplant setting due to an interplay of complex risk factors that include exposure to broad-spectrum antimicrobials, healthcare-associated exposures, and surgical risk factors. Of particular concern are increasing reports of resistant Gram-negative infections and their association with high mortality rates in SOT recipients. Infection prevention and control measures are important, but more data is needed specifically in SOT recipients. Source control is essential in the management of SOT recipients with MDR infections. Lastly, while newer antimicrobials are being developed, more randomized controlled trials are needed to determine the optimal therapeutic regimens for these patients.

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Prevention and Treatment of Mold Infections

12

Claire Aguilar, Benoit Pilmis, Olivier Lortholary, and Shahid Husain

12.1 Description of Pathogen

Molds are filamentous fungi present in the environment including different species such as *Aspergillus* spp., hyalohyphomycetes (*Fusarium* spp., *Scedosporium* spp.), *Mucorales* spp., phaeohyphomycetes, and dermatophytes. The primary route of transmission is inhalation of spores. Dermatophytophytosis and phaeohyphomycosis, however, are usually transmitted through the skin.

12.2 Definitions

It is very important to differentiate between *colonization* with a fungal organism, defined by the presence of mold without clinical or radiological evidence of disease, which does not necessarily require a specific treatment, and *invasive disease* [1, 2]. In particular, molds, most of which are ubiquitous in environment, can be found in the airways, and all necessary diagnostic tests need to be performed in assessing, if the presence of the fungus is associated with invasive disease.

In this chapter we will discuss different prophylactic strategies used to decrease the rate of invasive mold infections in SOT recipients. *Universal prophylaxis* refers to an antifungal medication administered systematically to all patients in a group, whereas *targeted prophylaxis* is the use of antifungal drugs in patients identified as

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high risk within the group. *Preemptive treatment* is given in patients with direct or indirect microbiological tests suggesting the presence of fungus but without evidence of invasive disease [1].

12.3 Epidemiology of Mold Infections in SOT

In the large multicenter TRANSET study, conducted in the USA between 2001 and 2006, invasive aspergillosis (IA) represented the second most frequent fungal infection among SOT recipients, after invasive candidiasis [3]. Mucormycosis was rare (2.3% of invasive fungal infections in this cohort), as well as other mold infections (8.5% of all invasive fungal infection). However, the epidemiology of mold infections strongly varies between the different organ groups.

12.3.1 Aspergillosis

Lung transplant recipients have the highest risk of invasive mold infections, owing to the continuous exposure to the environment and decreased mucociliary clearance in addition to a higher net state of immunosuppression. Seventy percent of mold infections in lung transplant recipients are due to invasive aspergillosis (IA) [4].

Colonization with *Aspergillus* sp., mainly *Aspergillus fumigatus*, is frequent in lung transplant recipients, with varying rates according to the underlying disease. The highest rates (up to 59%) were reported in cystic fibrosis patients. IA is more rare, with reported incidence rates ranging from 3 to 14% [1]. In a recent multicenter international study about 900 patients, the cumulative incidence of IA at 4 years posttransplantation was 8.8% [5]. The risk factors identified in previous studies were pretransplant colonization with *Aspergillus* sp., cystic fibrosis, single lung transplant, use of anti-thymocyte globulins, and cytomegalovirus infection. In the recent multicenter study, at the era of wide use of antifungal prophylaxis, the main risk factors were single lung transplant and colonization with *Aspergillus* sp. within the first year posttransplantation.

In heart transplant recipients, incidence of IA varies among centers and often occurs as outbreaks. Isolation of *Aspergillus* sp. in airways, reoperation, CMV disease, posttransplant hemodialysis, and episode of IA in the program in the 2 months before or after the transplantation are risk factors for IA in heart transplant recipients [6]. In liver transplant recipients, the most frequent invasive fungal infection is candidiasis, but incidence of IA is significant and also associated with some unique features. In a large study comparing characteristics of invasive fungal infections in transplant recipients, it was noted that in liver transplant recipients IA tended to occur early posttransplantation and was disseminated in half of the patients, whereas disseminated IA was very rare lung transplant recipients [7]. Moreover, mortality of IA in liver transplant recipients was much higher than in other SOT recipients.

In kidney transplant recipients, incidence of IA is low. An international multicenter retrospective study highlighted the high mortality of IA in this group,

especially in cases of IA occurring before 6 months from transplant. Significant risk factors were chronic obstructive disease before transplant, delayed graft function, occurrence of other infections, and rejection [8].

12.3.2 Hyalohyphomycosis: Fusariosis and Scedosporiosis

Among *Fusarium* species, *F. solani* species complex is most frequently involved in invasive disease, followed by *F. oxysporum* species complex and more rarely other species. *Fusarium* spp. can induce superficial skin infections, nail infections, and keratitis in immunocompetent patients. Disseminated disease can occur in immunocompromised patients, mainly patients with hematological malignancies and bone marrow transplant recipients [9]. The incidence of fusariosis is very low in SOT patients and represents <1% of all invasive fungal infection in SOT recipients. The main routes of infection are skin inoculation, consequently cutaneous symptoms, and inhalation, accounting for pulmonary fusariosis affecting mainly lung transplant recipients [10].

While overall incidence of *Scedosporium* spp. infections is low in SOT recipients, its mortality is high [11]. Moreover, *Scedosporium* sp. can cause a significant problem in cystic fibrosis patients colonized with *Scedosporium apiospermum* or *Scedosporium prolificans*. *S. prolificans* in particular can be resistant to all known antifungals, and extreme caution should be exercised in transplanting these individuals.

12.3.3 Mucormycosis in SOT

The incidence of mucormycosis is low in SOT recipients. In TRANSNET registry, mucormycosis accounted for 2% of all invasive fungal infections. Incidence of mucormycosis among all transplant groups was 0.07% [3]. The most prevalent species was *Rhizopus*, followed by *Mucor* and *Cunninghamella*. In a case control study, the median time of mucormycosis was 5 months from transplant; however, it occurred earlier in liver transplant recipients [12]. The risk factors noted were diabetes, renal failure, and prior use of voriconazole or caspofungin.

In SOT patients, mucormycosis is usually localized to the lungs or sinuses. Dissemination is more frequent in liver transplant recipients compared to other organ groups [13].

12.3.4 Phaeohyphomycosis

In the TRANSNET registry, 2.5% of invasive fungal infections in SOT patients were phaeohyphomycoses, which occurred as late event with a median delay from transplant of 685 days. Half of the patients were lung transplant recipients. The most common clinical localizations of infection were the skin, lungs, and sinuses.

Infection was disseminated in more than half of cases. *Alternaria* was found in almost one third of cases, followed by *Exophiala*; the other species were found in <10% of cases [14].

12.3.5 Dermatophytes

Dermatophytes are ubiquitous filamentous fungi responsible for skin and nail infections, mostly benign in immunocompetent patients. Severe dermatophytosis usually presenting with skin nodules can rarely occur in immunocompromised patients, including SOT patients. In a recent retrospective study of 16 SOT patients with severe dermatophytosis defined by the presence of the fungus in the derma or involving two parts of the body, the diagnosis was done at a median time from transplant of 16 months [15]. Interestingly, in two thirds of the patients, clinical symptoms of superficial dermatophytosis were present before the occurrence of severe form, highlighting the need for careful skin monitoring in SOT patients.

12.4 Diagnosis: Discussion of Screening and Diagnostic Strategies to Detect or Mitigate Infection

In immunocompromised hosts, early diagnosis of invasive fungal infections is essential as delayed treatment results in increased mortality rates. However, diagnosis of invasive mold infections is difficult because of limitations of diagnostic tools currently available. Indeed, for these infections the standard microbiological techniques with direct examination and culture have a low sensitivity and specificity. In addition, the contribution of nonconventional tests, such as galactomannan antigen and beta-D-glucan assay, is lower than that observed among neutropenic patients [16]. The performance of diagnostics tests used to detect invasive mold infection (IMI) is summarized in Table 12.1. Finally, radiological abnormalities are progressive over time and most often non-specific.

12.4.1 Conventional Assays

12.4.1.1 Microscopy Techniques

Microscopy techniques include fresh and stained examination of microbiological samples, as well as histopathological studies. Microscopy techniques are useful to distinguish hyaline molds (septate hyalohyphomycetes and nonseptate *Mucorales*) from pigmented phaeohyphomycetes. However, those methods have important limitations, one being their low sensitivity, especially if systemic antifungal therapy has already been initiated. Furthermore, all hyaline *Hyphomycetes*, including *Aspergillus*, *Scedosporium*, *Fusarium*, *Acremonium*, and *Paecilomyces*, exhibit similar appearance in clinical specimens under microscopic examination, and correlation with culture results is needed for definitive identification.

Table 12.1 Diagnosis of the main invasive mold infection among solid organ transplant recipients

	Aspergillosis	*Scedosporium*	Fusariosis	Mucormycosis	Phaeohyphomycosis
Pathogen detection					
Microscopy techniques					
Color	Hyaline	Hyaline	Hyaline	Hyaline	Brown
Size	3–8 µm wide	3–8 µm wide	3–8 µm wide	5–15 µm wide	Variable
Septation	Yes	Yes	Yes	No	Yes
Branching	Acute angle (45°)	Acute angle (45°)	Acute angle	Right angle	Variable
Culture	Among SOT All samples: Sens (91.4%) Sputum and BAL: PVP (58%) Blood culture: no utility	No positive blood culture	Blood culture Sens (41–60%)	Blood culture: limited utility Culture of the CNS often negative for CNS infection	Blood culture: limited utility
PCR	Among lung SOT BAL: Sens (100%) Spe (88%)	Insufficient data	Insufficient data	Serum Sens (90%) Positive before the diagnosis up 68 to 3 days before diagnosis Serum negativation is associated with better outcome	Insufficient data
Beta-D-glucan assay	Sens (66%) Spe (44%)	NA	Few data but some positive results	Negative	Few data but some positive results
Galactomannan Ag	Serum Sens (22%), Spe (84%) BAL Sens (81.8%), Spe (95.8%)	NA	Serum Sens (73.3%) Positive before the diagnosis in 73% at a median of 10 days	Negative	Cross reactivity in some cases Not recommended

12.4.1.2 Culture

Cultures are usually positive after 1–3 days of incubation except for slow-sporulating species (e.g., *Aspergillus lentulus*, *Neosartorya udagawae*). Once isolated in culture, molds are primarily identified based on their macroscopic morphology on culture media and type of reproductive structures observed microscopically. If possible, EORTC/MSG recommends appending the identification at the genus or species level from the culture results. It is important to note that the previous systemic antifungal therapy and aggressive processing of the specimens before plating are associated with false-negative cultures. It must also be emphasized that culture isolation of mold species from the airways does not necessarily indicate invasive disease. Indeed, respiratory tracts of up to 59% of lung transplant recipients become colonized with *Aspergillus* spp. Although contamination of clinical specimens by *Mucorales* is possible, positive culture results, especially when repetitive and associated with positive smear results, strongly suggest mucormycosis in SOT patients.

12.4.2 Nonconventional Assays

Because of the limitations of conventional methods, alternatives to culture techniques for the diagnosis of mold infections have been developed such as detection of fungal cell components (galactomannan, 1,3-β-d-glucan) and molecular tools.

12.4.2.1 Galactomannan Antigen Detection Assay

Galactomannan (GM) is a cell wall component of several filamentous fungi including *Aspergillus* sp. and *Fusarium*, but not *Mucorales*. GM can be detected in serum and BAL by an ELISA assay. However, performance of the test for the diagnosis of IA depends on the population studied. In serum, while the specificity of the test was good (84%), the sensitivity of the test among SOT was significantly lower compared to bone marrow transplant (22% and 82%, respectively) in a meta-analysis of 27 studies [17].

In BAL, in a study of 116 lung transplant recipients, an index cutoff value to ≥1.0 yielded a sensitivity of 60%, a specificity of 98%, and positive and negative likelihood ratios of 28 and 0.40, respectively [18]. In a recent Brazilian study, Nucci et al. assessed the performance of galactomannan in 18 patients with invasive fusariosis. The sensitivity and specificity of galactomannan were 83% and 67%, respectively. Galactomannan was positive before the diagnosis of invasive fusariosis in 73% of the cases at a median of 10 days [19].

12.4.2.2 1,3-β-D-Glucan

The 1,3-β-D-glucan (BG), a cell wall component of most fungal species, can be detected in serum during invasive fungal infections. The BG test is used as a diagnostic tool for the detection of a broad spectrum of fungal pathogens, with the exception of *Mucorales*. It was included in the updated consensus definition of probable invasive fungal disease by the EORTC/MSG consensus in combination with classical clinical, radiological, and microbiological findings. However, the test

has low sensitivity, and its best performance is in the hematological population. A study assessing performance of β-D-glucan assay in BAL samples of lung transplant recipients showed moderate sensitivity and specificity for the diagnosis of IA [20]. The low specificity could be due to potential colonization of lung airways by *Candida* sp.

12.4.2.3 Molecular Assays

A range of different PCR assays (conventional, nested, and real time) have been developed, targeting different gene regions (mainly 18S, 28S, internal transcribed spacer, and D1/D2 of the rRNA or β-tubulin), including a variety of amplicon detection methods. According to recent recommendations from the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and European Confederation of Medical Mycology (ECMM), regarding diagnosis of IMIs, molecular methods are recommended for accurate identification of mucormycosis and phaeohyphomycosis, especially in case of outbreak and to a less extent for hyalohyphomycosis identification [21]. In the TRANSNET study, over 10% of the isolates associated with IA in transplant recipients were found to be cryptic species, and molecular identification methods were essential in distinguishing them. However, the level of evidence for fungal detection by the use of PCR methods is still lower and not supported by current recommendations. Harmonization of PCR-based techniques is necessary before any clear recommendations can be made regarding their clinical utility. However, results are promising, especially for *Aspergillus* and *Mucorales*.

12.4.3 Diagnostic Strategy

As soon as a clinical scenario is consistent with invasive mold infections, imaging of the suspected site of infection should be performed, most often with computed tomography of the chest, as well as CT of the brain and sinuses depending on the clinical symptoms. If lung infiltrates are identified, a bronchoscopy with bronchoalveolar lavage is indicated, in order to perform fungal cultures and GM testing in BAL. Detection of serum GM should not be used for routine diagnosis of invasive fungal infections in SOT recipients. Blood cultures should also be drawn. If a lesion easily accessible to a biopsy is identified (skin lesion, sinusitis), the tissue should be sent for histopathology as well as fungal culture and molecular testing if needed.

A proven diagnosis of IMI can be based on positive blood cultures that yield particular filamentous fungi (*Scedosporium* spp., *Fusarium* spp.), observation of the tissue with invasive fungal structure, or isolation of fungus from sterile tissue or fluid. A diagnosis of probable IMI is based on direct or indirect microbiologic test of fungal infection associated with suggestive radiological features. Nodules, air crescent sign, cavity, and halo sign are suggestive of IA, but not specific, and are less frequently seen in SOT patients compared to neutropenic patients. One study about radiological features of IA in lung transplant recipients showed that the most common findings were bilateral bronchial wall thickening and centrilobular opacities with tree-in-bud pattern [22].

12.5 Prevention: Discussion of Approaches to Prevent Onset of Disease

Different approaches can be used in order to avoid occurrence of invasive mold infections in SOT patients, including environmental measures and chemoprophylaxis with antifungal drugs.

12.5.1 Environmental Measures

Filamentous fungi are present in the environment. The main routes of infections are inhalation and skin inoculation. Although it is impossible to prevent any exposure to fungi, as, for instance, each individual is daily exposed to hundreds of *Aspergillus* spores, SOT patients should be aware of the increased risk of fungal infection and try to avoid construction sites and excavations with a possible high concentration of spores. Wearing a surgical mask in situations with exposure to dust or moisture or during home remodeling is probably useful too [23]. However, the data remains thin, unlike hematopoietic stem cell transplant recipients where positive pressure rooms are suggested; no such recommendations are enacted for SOT recipients. Antifungal chemoprophylaxis remains the mainstay of prevention.

12.5.2 Antifungal Chemoprophylaxis

Antifungal medications can be used as universal prophylaxis, applied to all individuals in a group, targeted prophylaxis, given to patients with defined risk factors, and preemptive therapy, which aims to treat evidence of early disease. The indication of a prophylaxis depends on the incidence of the disease in the group.

12.5.2.1 Lung Transplant Recipients

Lung transplant recipients have the highest risk of IA, and this prompted most of the lung transplant teams to administer antifungal prophylaxis, as universal or targeted prophylaxis, especially in patients with cystic fibrosis and/or pretransplant colonization with *Aspergillus* sp. However, the efficacy and modalities of prophylactic strategies are debated, and protocols vary among centers. A meta-analysis did not find a clear benefit of antifungal prophylaxis in lung transplant recipients [24]. Currently, the most frequent medication used for prophylaxis is voriconazole. However, side effects of this medication in SOT patients should be considered when making decisions about prophylaxis. Liver toxicity of voriconazole is reported in as much as 50% of lung transplant recipients [25]. Moreover, the use of voriconazole has been associated with an increase on the incidence of skin cancer [26]. Another approach is to use preemptive treatment with voriconazole if *Aspergillus* colonization is identified after lung transplantation, which seems to be effective, but does not prevent all cases of IA, as the disease occurs frequently in patients without previous known colonization [27]. However, recent data shows

that the use of preemptive strategy combining culture and galactomannan may be more effective than culture alone [28]. AST guidelines recommend the use of antifungal prophylaxis with activity against mold in lung transplant recipients with *Aspergillus* sp. colonization before transplant or within 1 year posttransplant or if more than one of the following risk factors: induction with alemtuzumab or thymoglobulin; single lung transplant; *Aspergillus* sp. colonization following cytomegalovirus infection, rejection, and augmented immunosuppression; and acquired hypogammaglobulinemia. The drugs that can be used in this context are voriconazole, itraconazole, and inhaled lipid formulations of amphotericin B [6]. The duration is not standardized, usually 12 weeks.

12.5.2.2 Heart Transplant Recipients

In heart transplant recipients, the incidence varies among centers. The existence of an episode of IA in program 2 months before or after heart transplant is considered as a risk factor that should lead to initiate an antifungal prophylaxis with mold activity in this population [6].

12.5.2.3 Liver Transplant Recipients

In liver transplant recipients, incidence is low, but the disease tends to be more severe and disseminated. Data from observational studies suggest a benefit of antimold prophylaxis in high-risk liver transplant recipients (retransplantation, renal failure, reoperation involving thoracic or abdominal cavity) [29]. In this population, the use of lipid formulations of amphotericin B or echinocandin is usually favored [6].

12.5.2.4 Kidney Transplant Recipients

In kidney transplant recipients, the incidence is low so antifungal prophylaxis is usually not indicated. Because of the potential progression of these infections, empiric antifungal therapy should be introduced early in kidney transplant patients with high suspicion of invasive mold infections [30].

12.6 Treatment: Discussion of Approaches to Treat Disease

12.6.1 General Considerations

The cornerstones of treatment of invasive mold infections rely on early systemic antifungal therapy, assessment of the need for surgical debridement, and reduction of immunosuppression if possible. When amphotericin B is considered, a lipid-based preparation should be favored over amphotericin B deoxycholate because of lower toxicity. It should be noted that azoles interact with most of immunosuppressive therapies, as shown in Table 12.2. Interaction with other drugs, especially anticonvulsant medications which are sometimes needed in cases with central nervous system involvement, warrants caution. Therapeutic drug monitoring is recommended when azoles are used.

Table 12.2 Drug interaction between antifungal and immunosuppressive agents

	Immunosuppressive drugs (ID)		
Antifungal drugs (AD)	Cyclosporin	Tacrolimus	Sirolimus
Amphotericin B	Renal toxicity	Renal toxicity	No interaction
Fluconazole	↗ Plasma concentration of ID	↗ Plasma concentration of ID	↗ Plasma concentration of ID
Itraconazole	↗ Plasma concentration of ID	↗ Plasma concentration of ID	↗ Plasma concentration of ID
Posaconazole	↗ Plasma concentration of ID	↗ Plasma concentration of ID	↗↗ Plasma concentration of ID
Voriconazole	↗ Plasma concentration of ID	↗ Plasma concentration of ID	↗↗ Plasma concentration of ID
Caspofungin	Possible interaction (↗ plasma concentration of AD)	Possible interaction (↘ plasma concentration of ID)	
Micafungin	Possible interaction (↘ plasma concentration of ID)	No interaction	↗ Plasma concentration of ID
Flucytosine	No interaction	No interaction	No interaction
Terbinafine	No interaction	No interaction	No interaction

Table 12.3 Antifungal treatment of invasive mold infections in solid organ transplant recipients

	First-line treatment recommendations	Alternatives
Aspergillus	IV or oral voriconazole (6 mg/kg q12 h day 1 and then 4 mg/kg q12 h)	L-Amb 3 mg/kg daily IV Caspofungin 70 mg day 1 and then 50 mg daily IV
Scedosporium	*S. apiospermum*: voriconazole *S. prolificans*: voriconazole[a]	Voriconazole + terbinafine
Fusarium	Voriconazole or L-Amb	Posaconazole
Mucormycosis	L-Amb 5 mg/kg/day	Isavuconazole Posaconazole

L-Amb liposomal amphotericin B
[a]Can be resistant

12.6.2 Antifungal Therapy

The antifungal treatment of invasive mold infections is most often based on the use of azoles or polyenes. Voriconazole is the first-line treatment for IA. The duration of therapy is not standardized, usually at least 6–12 weeks, and then reassessed depending on clinical and radiological response. Treatment of *Scedosporium* spp. infections can be particularly difficult given the resistance pattern [31]. The main therapeutic recommendations are presented in Table 12.3.

12.6.3 Other Approaches

12.6.3.1 Surgery

During non-*Aspergillus* mold infection, extensive early surgical debridement is generally recommended in combination with antifungal therapy. For invasive mold infections, the highest level of evidence for the need of surgery has been provided in mucormycosis. In this setting, surgery was reported to be an independent predictor of successful therapy and survival in SOT recipients with pulmonary or rhino-orbital-cerebral mucormycosis [13].

12.6.3.2 Improvement of Immune and Metabolic Factors

Improvement of immune and metabolic factors can contribute to successful treatment of invasive mold infections in SOT recipients. Reducing immunosuppression, when feasible, should be considered. Management of hyperglycemia is very important, especially in the case of mucormycosis.

12.7 General Approach: General Algorithmic Approach to Identifying and Diagnosing Focus of Topic (Fig. 12.1)

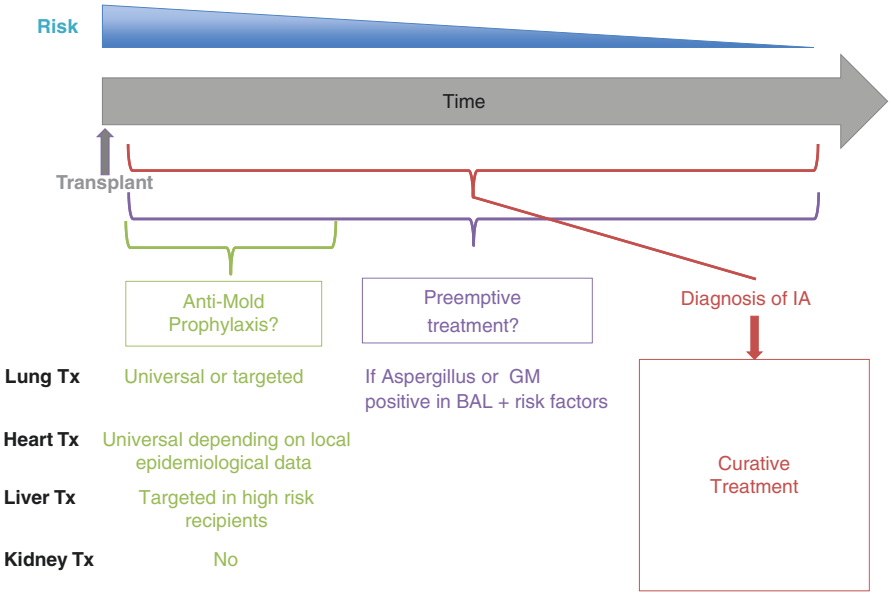

Fig. 12.1 Overview of prophylactic and curative strategies for invasive aspergillosis in SOT recipients

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Prevention and Treatment of Yeast and Endemic Fungal Infections

13

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Abbreviations

5-FC	Flucytosine
ABLC	Amphotericin B lipid complex
AmB	Liposomal amphotericin B
AmB-d	AmB deoxycholate
ARDS	Acute respiratory distress syndrome
ATG	Antithymocyte globulin
BAL	Bronchoalveolar lavage
CMV	Cytomegalovirus
CNI	Calcineurin inhibitor
CNS	Central nervous system
CrAg	Cryptococcal antigen
CSF	Cerebrospinal fluid
CVC	Central venous catheter
EIA	Enzyme immune assay
G-CSF	Granulocyte colony-stimulating factor
HD	Hemodialysis
HHV-6	Human herpesvirus 6
HIV	Human immunodeficiency virus
HLH	Hemophagocytic lymphohistiocytosis
IC	Invasive candidiasis
ICP	Intracranial pressure

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IDSA	Infectious Diseases Society of America
IFI	Invasive fungal infection
IFN-γ	Recombinant interferon-gamma
IRIS	Immune reconstitution inflammatory syndrome
KOH	Potassium hydroxide
L-AmB	Liposomal amphotericin B
LFAmB	Lipid formulation of amphotericin B
MALDI-TOF	Matrix-assisted laser desorption ionization-time-of-flight mass spectrometry assay
MELD	Model of end-stage liver disease
MIC	Minimal inhibitory concentration
MSK	Musculoskeletal system
PCR	Polymerase chain reaction
PNA-FISH	In situ hybridization assay
SOT	Solid organ transplantation
TRANSNET	Transplant-Associated Infection Surveillance Network
VAD	Ventricular assisted devices
βDG	1,3-β-D-glucan

13.1 Introduction

Solid organ transplantation (SOT) for the treatment of end-organ disease has increased over the last three decades. While novel immunosuppressive regimens have improved allograft survival and function, combined with surgical complications, these predispose transplant recipients to infectious complications [1, 2]. Invasive fungal infections (IFIs) are particularly concerning in this population due to the associated high morbidity and mortality [1]. The most common IFIs in SOT recipients are candidiasis, aspergillosis, cryptococcosis, and those caused by endemic fungi such as *Blastomyces*, *Coccidioides*, and *Histoplasma* [3]. The incidence of IFIs varies according to type of organ transplant, and the risk of infection changes over time based on host state of immunosuppression and many fungal factors (e.g., virulence and resistance of fungi) [2, 4]. In this chapter, we review epidemiology, clinical presentation, diagnosis, and treatment of fungal infections due to yeast and endemic fungi in SOT recipients.

13.2 Epidemiology

The data from the US Transplant-Associated Infection Surveillance Network (TRANSNET) estimated that invasive candidiasis (IC) was the most common (53%) IFI, followed by invasive aspergillosis (19%) in most organ transplants. The exception was for lung transplants where aspergillosis was more common than IC. Cryptococcosis (8%) was the third most common IFI, and endemic fungi

Table 13.1 Frequency of yeast and endemic fungal infections by type of transplant from the TRANSNET study [3]

IFI type	Liver (n = 378)	Kidney (n = 332)	Lung (n = 248)	Pancreas (n = 128)	Heart (n = 99)	Small bowel (n = 22)
Candidiasis	255 (68)	164 (49)	56 (23)	97 (76)	48 (49)	19 (85)
Cryptococcosis	24 (6)	49 (15)	6 (2)	6 (5)	10 (10)	1 (5)
Endemic mycoses	17 (5)	33 (10)	3 (1)	8 (6)	3 (1)	0 (0.0)
Other yeast	9 (2.4)	6 (1.8)	0 (0.0)	5 (3.9)	0 (0.0)	1 (5)
Unspecified yeast	5 (1.3)	3 (0.9)	6 (2.4)	1 (0.8)	0 (0.0)	1 (5)

No. (%)

accounted for 5.3% of IFIs, whereas other yeasts accounted for less than 3% of the IFIs (Table 13.1) [3].

Candida is a normal commensal of humans and becomes pathogenic when the host immune system is compromised. *Candida* colonization and biofilm formation on human tissues, intravascular catheters, implants, and prosthetic material support IC [5, 6]. Donor-derived infections by *Candida* have been reported [7]. Among infections caused by *Candida* species in SOT recipients, *C. albicans* was the most common isolate (46.3%), followed by *C. glabrata* (24.4%) and *C. parapsilosis* (8.1%) [8]. Resistance to azoles and echinocandins is increasing, and previous data suggested that prior exposures to azole or echinocandins lead to the development resistance and increased incidence of infections due to non-*albicans Candida* in SOT recipients [9–12]. *C. auris* is an emerging multidrug-resistant yeast in the healthcare settings in the USA and other parts of the world (Spain, South America, and Asia) [13].

Cryptococcal infections occur due to the inhalation of the aerosolized basidiospores from soil or avian excreta, although rarely it can be transmitted from donor organs and tissue grafts [14]. Most infections are caused by *C. neoformans* although infections due to *C. gattii* have emerged in North America since 1999 where it was in the past more typical of tropical and subtropical areas [15]. Cryptococcosis causes approximately 8% of IFIs in SOT recipients [3] and has an overall mortality of 14% at 90 days after diagnosis in this population [16]. The median time to cryptococcosis ranges between 16 and 21 months posttransplantation, although time to onset was earlier (<12 months) in liver and lung transplant recipients possibly related to the more intense immunosuppression they receive compared to other types of transplants [16, 17]. A recent multicenter study suggested that lung transplant recipients are at highest risk of cryptococcosis [18]. When infection occurs in the first 30 days posttransplantation, donor-derived cryptococcosis should be considered [14].

Endemic fungal infections can occur in patients who reside or have resided in endemic areas and occur posttransplantation with a median time of 343 days. Histoplasmosis is caused by *H. capsulatum* and is endemic to the Ohio and the Mississippi River valleys in the USA and has been isolated in many parts of the world particularly around river valleys. Blastomycosis, caused by *B. dermatitidis*, is

also seen in the Ohio-Mississippi River Valley. Histoplasmosis or blastomycosis occurs only in about 0.5% of transplant patients in endemic areas [19]. Coccidioidomycosis is endemic in the Southwestern United States, New Mexico, western Texas, and some parts of Central and South America [20] and is caused by two species: *C. immitis* and *C. posadasii*. The disease may be primary or secondary to reactivation of a latent infection [20] and may occur in up to 8% of transplant patients in endemic areas [21]. Other yeasts or endemic fungi that have been rarely reported in SOT recipients include *Trichosporon*, *Rhodotorula*, *Malassezia*, *Hansenula*, and paracoccidioidomycosis [22].

13.3 Timing and Risk Factors for Fungal Infections

The timing of IFIs posttransplantation is typically divided into three intervals based on the risk and type of IFIs: early (0–1 month), intermediate (1–6 months), and late (>6 months). Infections in the early interval are similar to that in non-immunocompromised patients postoperatively, usually due to surgical complications, nosocomial, or donor-derived infections [3]. *Candida* species are the common cause of IFIs in the early period. The intermediate interval has the most frequent IFIs as immunosuppression plays a major role, while the effects of surgical and nosocomial factors decrease. IC is less common, while mold infections due to aspergillosis, mucormycosis, scedosporiosis, or other molds predominate [3]. By late stage when 80% of SOT recipients are maintained on minimal chronic immunosuppression, the risk of IFIs declines [2]. The predominant fungal pathogens in this interval are *Cryptococcus* and endemic fungi, but mold infections such as aspergillosis and mucormycosis are possible and may occur at any time posttransplantation [3, 17].

The net state of immunosuppression is an important determinant of the overall risk of infection and involves a number of host and environmental factors. Host factors include underlying immune defects; extrinsic factors such as loss of integrity of mucocutaneous barriers and surgical complications; dose, duration, and sequence of immunosuppressive therapy; and environmental exposures to specific pathogens (Table 13.2) [23, 24]. Other risk factors that are specific to the type of organ transplant include the type of anastomosis or drainage, intensity of immunosuppression especially in the immediate posttransplantation period, and postoperative complications (anastomotic leak, ischemia, thrombosis, fluid collection, and the presence of foreign bodies) (Table 13.3) [2, 23–36].

Several immunosuppressive agents are used in SOT recipients including cyclosporine, tacrolimus, mycophenolate mofetil, azathioprine, as well as antithymocyte globulin (ATG) or monoclonal antibodies such as alemtuzumab, basiliximab, or rituximab in order to avoid or minimize the use of glucocorticoids [36, 37]. Calcineurin inhibitors (CNIs) (such as cyclosporine and tacrolimus) have synergistic antifungal activity against *C. neoformans* isolates, and thus, cryptococcal disease in SOT recipients manifests with skin and soft tissue disease rather than CNS disease owing to the antifungal activity of tacrolimus at 37–39 °C and the lower skin

Table 13.2 Risk factors of yeast and endemic fungal infections in SOT recipients and "net state of immunosuppression" [23, 24]

Immunosuppression and immunosuppressive therapy	
– Dose and duration of current and past immunosuppressive agents	
– Previous use of chemotherapy	
– Antibody or complement deficiency and other immune disorders	
Healthcare related	
– Prolonged use of empiric antibiotics	
– Prolonged intensive care unit stay and mechanical ventilation	
– Use of prophylactic agents with myelosuppressive side effects (e.g., trimethoprim-sulfamethoxazole, valganciclovir, ganciclovir, dapsone)	
– Acquired myelosuppression, neutropenia, and/or lymphopenia	
– Total parental nutrition, renal replacement therapy	
Underlying immune disorders	
– Autoimmune disorders (e.g., systemic lupus erythematosus)	
Loss of mucocutaneous barriers/integrity	
– Drains, lines, catheters	
– Ischemic tissue, fluid, or blood collections	
Metabolic conditions (cirrhosis, diabetes mellitus, malnutrition, uremia)	
Chronic viral infections	
– CMV, herpes simplex virus, human herpesvirus 6 (HHV-6)	
Environmental and new technologies	
– Travel to endemic areas or transplantation in endemic areas	
– Occupational or recreational exposures, marijuana use	
New technologies	
– Use of ventricular assisted devices (VAD) (heart transplants)	
– Reperfusion injury and bronchiolitis obliterans (lung transplants)	
Risk assessment	
Greater risk of infection • Active/latent donor/recipient infection • Early graft rejection • Graft dysfunction • High-dose corticosteroids • High rejection risk • Induction therapy – lymphocyte depletion • Plasmapheresis • Technical complications – Anastomotic leak, bleeding, prolonged intubation/intensive unit care. Drains and catheters, wound infection/poor wound healing	*Lower risk of infection* • Appropriate surgical prophylaxis • Appropriate vaccination • Effective antiviral prophylaxis • Good graft function Good HLA match • Immunologic tolerance • PCP prophylaxis • Technically successful surgery

temperatures [38]. Episodes of rejection pose a particular risk for IFIs as patients receive pulse doses of glucocorticoids, intensified immunosuppressive therapy, ATG, and monoclonal antibodies as well as they experience high rates of cytomegalovirus (CMV) reactivation which can contribute to IFIs and immunosuppression [37].

Table 13.3 Specific risk factors of yeast and endemic fungal infections per type of solid organ transplant [3, 23, 26–36]

Transplant type	Specific factors
Heart	Active CMV infection Antilymphocyte globulins Central venous catheters Colonization of VAD Extracorporeal membrane oxygenation Hemodialysis (HD) Prolonged use of broad-spectrum antibiotics Reoperation Treatment for rejection
Kidney	Alemtuzumab Chronic allograft rejection and intense immunosuppression therapy Corticosteroids Diabetes mellitus Indwelling venous catheters Prolonged dialysis before transplant Requirement for HD posttransplant
Liver	Active CMV infection Allograft failure Baseline creatinine >3.0 mg/dL Choledochojejunostomy anastomosis (Roux-en-Y) Early colonization Hepatic dysfunction HHV-6 Intraoperative requirement of >40 blood products Model of end-stage liver disease (MELD) score > 20, major if >30 Operative time ≥ 11 h Renal dysfunction requiring HD Retransplantation
Lung or lung-heart	Antibody deficiency (hypogammaglobulinemia) Damage of local pulmonary defenses by transplant Intense immunosuppression Ischemia of anastomosis
Pancreas or pancreas-kidney	Enteric drainage Preoperative peritoneal dialysis Postreperfusion pancreatitis Retransplantation or laparotomy after transplantation Vascular graft thrombosis
Small bowel	Abdominal reoperation Graft rejection or dysfunction Intense immunosuppression Multivisceral transplantation Small bowel anastomotic leaks

Donor-derived yeast infections have been reported due to *Candida* and *Cryptococcus* among other fungi. Also, *Candida* contamination of preservation fluid has been associated with posttransplantation infections in renal and liver transplant recipients [39, 40]. In a study of graft-site infections in renal transplant recipients, the incidence was 1 case per 1000 grafts [41]. A recent case of *C. auris* was

transmitted during lung transplantation [42]. Of note, early cases of cryptococcosis were reported posttransplantation especially in liver transplant recipients that were attributed to unrecognized pretransplant or donor-derived infections [14]. Donor-derived infections due to *Histoplasma* and *Coccidioides* but not *Blastomyces* have been reported [43].

13.4 Clinical Manifestations

13.4.1 Infections Due to *Candida*

Candida colonizes skin, respiratory, gastrointestinal, and genitourinary tracts. Colonization usually precedes IC, and the infection depends on the breach of integrity of mucocutaneous barriers, the virulence of infecting strain, and the intensity of immunosuppression [4]. Candidemia is the most common form of IC in SOT recipients (64%), followed by urinary tract infections (11%) and peritonitis (9%) [3, 11]. Candidemia may occur due to translocation across damaged intestinal barriers or from central venous catheters (CVC) [2, 44]. Intra-abdominal infections are particularly common among liver, pancreas, and small bowel transplant recipients [3]. Intra-abdominal manifestations include biliary, perirenal, and peritoneal infections. Bilomas, in liver transplant recipients, may result from *Candida* and can lead to the loss of liver transplant function [4, 45].

Candida may cause anastomotic tracheobronchitis in lung transplant recipients and sternal wound infections in heart and lung transplant recipients [46]. Asymptomatic *Candida* colonization is common in renal transplant recipients; however, the need for indwelling catheters can result in ascending renal parenchymal infection or ureteral fungal balls due to *Candida* species [26]. Of note, infections of allograft vascular anastomosis have been reported in renal [41], pancreatic [47], heart, and lung transplants [48].

13.4.2 Infections Due to *Cryptococcus*

The two major sites of cryptococcosis in SOT recipients are the lungs and the central nervous system (CNS). Other sites that can be involved include the skin and soft tissues, bones, joints, liver, kidney, and prostate [49]. Isolated pulmonary infection is seen in 33% of SOT recipients [16]. Lung disease ranges from asymptomatic colonization to pneumonia leading to respiratory failure [49]. Endobronchial disease is an increasingly recognized disease [50]. Extrapulmonary dissemination was seen in 61% of SOT recipients, and liver transplant recipients have a sixfold higher risk for dissemination [16]. Cryptococcal meningitis was seen in 44% of SOT recipients with cryptococcosis and had a mortality of 26% [18]. Predictors of CNS involvement in SOT recipients include late-onset disease >24 months posttransplantation, altered mental status, and serum cryptococcal antigen (CrAg) titer >1:64 [51].

Skin manifestations are diverse and may include nodules, papules, pustules, abscess, and necrotizing cellulitis commonly in the lower extremities [52]. The use

of calcineurin inhibitors is associated with fewer CNS infections and more cutaneous manifestations [17]. Immune reconstitution inflammatory syndrome (IRIS) is an uncommon manifestation and results from rapid reduction of immunosuppressive therapy when initiating antifungal therapy in SOT recipients and mimics worsening cryptococcosis or antifungal failure [53]. It may present as lung nodules, hydrocephalus, cerebral mass lesions, aseptic meningitis, lymphadenitis, or cellulitis [52, 53].

13.4.3 Infections Due to Endemic Fungi

Infections due to endemic fungi result from environmental exposures and enter into the body through the lungs. Pneumonia is common, and fulminant multilobar pneumonia, acute respiratory distress syndrome (ARDS), and respiratory failure are feared complications [20]. The most common presentation of blastomycosis in SOT is pneumonia, but extrapulmonary dissemination of the skin, musculoskeletal system (MSK), genitourinary, or CNS disease is seen in almost 50% of SOT recipients [3, 19, 54]. Clinical manifestations of coccidioidomycosis range from pneumonia to disseminated disease. Extrapulmonary disseminated disease in SOT recipients involves the skin, MSK, and CNS and occurs in about 1–5% [55]. Those of African, Filipino, or Native American descent, males, pregnant women, and immunosuppressed are at increased risk [55]. Histoplasmosis can involve any organ but most commonly presents with disseminated disease in SOT patients. Clinical findings usually underestimate the severity and burden of disease [19].

13.4.4 Infections Due to Other Yeasts

Other yeasts that are rare in SOT recipients include *Trichosporon*, *Rhodotorula*, and *Malassezia*. *T. asahii* is associated with intravenous catheter-related infections [56]. *Rhodotorula* and *Malassezia* have been associated with fungemia and disseminated disease [22]. Table 13.4 outlines the clinical manifestations of yeast infections in SOT recipients [3, 14, 17–20, 52, 53, 57–62].

13.5 Diagnosis and Monitoring

Diagnosis of IFIs in SOT recipients is challenging due to their nonspecific signs and symptoms owing to impaired inflammatory responses as a result of immunosuppression and the lack of highly sensitive and specific diagnostic modalities. Early diagnosis is key to successful outcomes, and physicians should have a high index of suspicion based on risk factors and epidemiology of these pathogens [23]. IFIs are categorized into proven, probable, and possible based on specific cytologic/histopathologic findings and host, clinical, radiographic, and microbiological criteria [63].

Table 13.4 Clinical manifestations of yeast and endemic fungal infections in SOT recipients [3, 14, 17–20, 52, 53, 57–62]

IFI type	Clinical manifestation
Candida	Candidemia Intra-abdominal and hepatobiliary infections Sternal wound infections (heart transplants) Bronchial anastomotic infections (lung transplants) Urinary tract infections Ureteral fungal ball Vascular anastomotic infections Less common: septic arthritis, chronic meningitis, endocarditis, mediastinitis Cutaneous infections
Cryptococcus	Asymptomatic pulmonary infection to severe pneumonia with ARDS, respiratory failure Meningitis Skin infections (necrotizing cellulitis) Disseminated disease Fungemia Osteoarticular disease Immune reconstitution inflammatory syndrome
Blastomyces	Pneumonia, including fulminant multilobar pneumonia, ARDS, respiratory failure Disseminated disease: cutaneous, osteoarticular, genitourinary, or CNS disease Fungemia is rare
Coccidioides	Pneumonia, ranging from mild to severe, with ARDS, respiratory failure Disseminated disease: meningitis, fungemia, erythema nodosum, erythema multiforme, musculoskeletal disease
Histoplasma	Pneumonia, ranging from mild to severe with respiratory failure Disseminated disease: hepatosplenomegaly, gastrointestinal disease such as ileocecal ulceration and perforation, pancytopenia, weight loss, transaminitis, mucocutaneous disease, increased lactate dehydrogenase levels Unusual: thrombotic microangiopathy and hemophagocytic lymphohistiocytosis (HLH)
Trichosporon *Rhodotorula* *Malassezia*	Catheter-related intravenous infections Peritonitis, fungemia Folliculitis, groin abscess

Histopathological demonstration of tissue invasion by fungal elements helps to establish proven disease, and special stains may be utilized. Isolation of *Candida* from blood cultures (which has a sensitivity of 50–70% [35]) or sterile sites is indicative of true infection, while *Candida* isolated from nonsterile sites usually represents colonization which could indicate infection in the right context but also is a risk factor for future invasive candidiasis [41]. Diagnosis of anastomotic tracheobronchitis in lung transplant recipients is to be based on direct visual examination, histopathological confirmation, and positive cultures [64]. Otherwise, the recovery of *Candida* species in sputum rarely indicates disease in the lungs [35, 64]. Isolation of other yeasts such as *C. neoformans*, *H. capsulatum*, *B. dermatitidis*, *and C.*

immitis even without clinical findings suggests disease and calls for additional testing. SOT recipients suspected to have cryptococcosis should undergo evaluation with a lumbar puncture (LP), blood and urine cultures, and bronchoalveolar lavage (BAL) with or without biopsy [58]. Species identification and drug susceptibilities help to decide on antifungal therapy and to predict clinical outcomes.

Sensitivity of *Histoplasma* urine and serum antigen exceeds 90% in immunocompromised patients with disseminated disease and is at least 59% in pulmonary disease [65]. Similarly, *Blastomyces* Ag detection assays in urine, blood, or BAL have a sensitivity of >90%. Ag detection assays for *Histoplasma* and *Blastomyces* in BAL may cross-react with each other [66]. IgM (detected by tube precipitin method, immunodiffusion, latex agglutination, and enzyme immune assay (EIA)) and IgG complement-fixing antibody serology tests for *Coccidioides* are very sensitive and specific to diagnose coccidioidomycosis and to define the severity of disease [55]. Diagnosis and management of suspected meningeal coccidioidomycosis require an LP and cerebrospinal fluid (CSF) analysis for CSF complement-fixing IgG antibodies [20]. Table 13.5 shows the different laboratory and radiographic diagnostic modalities for yeast infections [20, 35, 49, 58, 64, 67–69].

Table 13.5 Diagnosis of yeast and endemic fungal infections in SOT recipients [20, 35, 49, 58, 64, 67–69]

IFI type	Diagnostic tests
Candida	*Commonly used* Blood cultures (sensitivity 50–70%) or smear (yeast, hyphae, pseudohyphae) and cultures of sterile sites 1,3-β-D-glucan (βDG) detection assays Matrix-assisted laser desorption Ionization-time-of-flight mass spectrometry assay (MALDI-TOF) *Not commonly used* Polymerase chain reaction (PCR) T2 magnetic resonance Species identification: peptide nucleic acid fluorescent In situ hybridization assay (PNA-FISH)
Cryptococcus	Blood cultures Serum cryptococcal antigen testing BAL with or without biopsy (stains for yeast, culture) Lumbar puncture (opening pressure, Gram's stain, CSF cultures, cell count, protein, glucose, and cryptococcal antigen testing) Tissue biopsy and cultures Brain imaging: basal ganglia and midbrain lesions, hydrocephalus, single or multiple nodules with or without enhancement, dilated Virchow-Robin spaces, pseudocysts, masses, gyral enhancement, cryptococcomas, lacunar and cortical infarcts
Blastomyces	Direct microscopy (Gram, Giemsa, and potassium hydroxide (KOH)/calcofluor stains) Tissue cultures Antigen testing (urine, serum, BAL)

Table 13.5 (continued)

IFI type	Diagnostic tests
Coccidioides	Direct microscopy (Gram, Giemsa, and KOH/calcofluor stains): visualization of spherules containing endospores Tissue culture PCR of respiratory specimens or CSF Antigen enzyme immunoassay (EIA) test (urine, serum, BAL) Serum IgM detection (tube precipitin method, immunodiffusion, latex agglutination, and EIA Complement-fixing IgG antibodies (helps to quantify severity and monitor infection) Lumbar puncture (opening pressure, Gram's stain, CSF cultures cell count, protein, glucose, and complement-fixing IgG antibodies)
Histoplasma	Direct microscopy (Gram, Giemsa, hematoxylin, and eosin, Wright-Giemsa and KOH/calcofluor stains) in tissue, blood, or bone marrow Tissue culture Histoplasma antigen test (urine, serum, BAL)
Trichosporon *Rhodotorula* *Malassezia*	Blood cultures; smear shows hyaline septate fungal hyphae and pseudohyphae Budding yeast in tissue KOH preparation or culture

13.6 Treatment and Prevention

13.6.1 Prophylaxis and Prevention

Preventive strategies have been developed in SOT patients at high risk of opportunistic IFIs [70]. There is no current recommendation to start universal prophylaxis to prevent IC in SOT recipients, and a targeted approach is based on type of transplant and other risk factors [35]. Similarly, there is no recommendation to start primary antifungal prophylaxis for cryptococcosis. However, secondary prophylaxis is recommended in some cases [49]. Primary or secondary antifungal prophylaxis for blastomycosis in SOT recipients is not currently recommended [20]. Table 13.6 shows different antifungal prophylaxis recommendations in SOT recipients [20, 35, 71–77].

13.6.2 Treatment of Yeast and Endemic Fungal Infections in SOT Recipients

The choice of antifungal therapy in the treatment of candidemia should be based on the *Candida* species in cultures and their susceptibilities, azole exposure in the last 90 days, and history of intolerance to antifungal agents [78]. Early antifungal therapy for suspected candidemia has been associated with better outcomes in patients with candidemia [79, 80]. Fluconazole can be used as first-line in patients with

Table 13.6 Antifungal prophylaxis of yeast and endemic fungi recommendations in SOT recipients [20, 35, 71–77]

Organism/transplant type	Antifungal drug	Alternatives	Duration	Note
Candida				
Kidney	No prophylaxis			
Liver	Fluconazole 400 mg daily	LFAmB[a] 3–5 mg/kg/day[b]	Up to 4 weeks or until risk factors resolve	Possible role of anidulafungin or caspofungin
Pancreas or pancreas-kidney	Fluconazole 400 mg daily	LFAmB[a] 3–5 mg/kg/day[b]	At least 4 weeks	
Small bowel	Fluconazole 400 mg daily	LFAmB[a] 3–5 mg/kg/day[b]	Until healing of anastomosis and absence of rejection	
Lung or lung-heart	No specific prophylaxis for yeast or endemic fungi			
Heart	No prophylaxis			
Secondary cryptococcal prophylaxis after initial 12 months treatment • In patients needing increased immunosuppression (e.g., treatment of rejection) • Renal transplant patients who can have a hemodialysis bridge may be considered for transplantation if received a year of antifungal therapy, have no signs of active cryptococcosis, and have negative cultures from the site of infection • For renal transplant patients with graft failure where hemodialysis bridging cannot be done, at least 1 year of secondary prophylaxis with fluconazole is considered • Retransplantation can be considered after receiving induction therapy, clearance of positive cultures, and decline of CrAg				
Blastomycosis Primary or secondary prophylaxis is not recommended				
Coccidioidomycosis • All patients undergoing SOT in endemic areas without active disease should receive an oral azole (e.g., fluconazole 200 mg daily) for at least 6–12 months • Secondary lifelong prophylaxis after controlling active infection to prevent relapse				
Histoplasmosis • SOT patients who recovered from active disease with or without treatment during the 2 years before transplantation should receive itraconazole 200 mg daily (duration unknown). Monitoring for relapse during immunosuppression with serial urinary antigen is recommended • Detection of *H. capsulatum* in explanted organs or donor tissue especially lung transplants should be considered for antifungal prophylaxis				

[a]LFAmB (lipid formulation of amphotericin B includes liposomal amphotericin B (L-AmB) and amphotericin B lipid complex (ABLC))

[b]If high rates of non-*albicans Candida* species or risk of *Aspergillus*

mild-moderate disease and who are unlikely to have infections with fluconazole-resistance *Candida* species [64]. The use of an echinocandin is now strongly recommended in the treatment of candidemia [64], especially in SOT patients with hemodynamic instability or with previous exposures to azoles or colonized with Candida species resistant to azoles [81]. Liposomal amphotericin B (AmB) or an azole should be used when other IFIs are suspected due to the limited activity of echinocandins, but the use of AmB is limited but its toxicities. Monitoring drug levels is important as azoles are potent inhibitors of liver cytochrome P-450 CYP3A4 and can increase the levels of CNIs, everolimus, and sirolimus [35, 82]. Patients with candidemia should have repeated blood cultures every 48–72 h until it is cleared, and central venous catheters should be removed as soon as possible. It is also strongly recommended to do a dilated fundoscopic exam in these patients [64]. Management of anastomotic tracheobronchitis should include using inhaled or systemic AmB. Treatment of other manifestations of IC is outlined in Table 13.7.

Table 13.7 Recommendations for the treatment of yeast and endemic fungal infections in SOT recipients [20, 35, 49, 58, 64, 75–77, 83]

Condition	Primary therapy	Alternative therapy	Comments
Candidemia			
Nonneutropenic	Echinocandin or fluconazole 800 mg (12 mg/kg) load and then 400 mg (6 mg/kg) daily	LFAmB 3–5 mg/kg/day for intolerant patients or non-susceptible *Candida* species. Fluconazole initially if not critically ill and low risk of azole resistance	Step-down to fluconazole. Voriconazole step-down recommended for *C. krusei.* Remove all CVC and obtain a dilated eye examination for all patients. Treat for at least 2 weeks after clearance of candidemia and resolution of symptoms
Neutropenic	Echinocandins or LFAmB 3–5 mg/kg/day. Voriconazole 400 mg (6 mg/kg) twice daily for 2 doses and then 200–300 mg (3–4 mg/kg) twice daily for additional mold coverage or for *C. krusei*	Fluconazole 800 mg (12 mg/kg) load and then 400 mg (6 mg/kg) daily for less critically ill patients and no azole exposure	Step-down to fluconazole 400 mg daily or voriconazole. Remove all CVC and obtain a dilated eye examination for all patients. Treat for at least 2 weeks after clearance of candidemia and resolution of symptoms. Granulocyte colony-stimulating factor (G-CSF) can be used in persistent candidemia with protracted neutropenia

(continued)

Table 13.7 (continued)

Condition	Primary therapy	Alternative therapy	Comments
Intra-abdominal infections	Treat as candidemia		Duration determined by source control and clinical response
Urinary tract infections			
Asymptomatic candiduria	Not necessary unless high risk for dissemination. Fluconazole 400 mg (6 mg/kg) daily, for several days before and after urological procedures	AmB deoxycholate (AmB-d) 0.3–0.6 mg/kg daily for several days before and after urological procedures	Remove indwelling bladder catheters
Symptomatic cystitis	Fluconazole 200 mg (3 mg/kg) daily for 2 weeks	AmB-d 0.3–0.6 mg/kg daily for 1–7 days or flucytosine (5-FC) 25 mg/kg four times daily for 1–7 days	AmB-d IV or bladder irrigation indicated for fluconazole-resistant *C. glabrata* or *C. krusei*. Remove indwelling bladder catheters
Pyelonephritis	Fluconazole 200–400 mg (3–6 mg/kg) daily for 2 weeks	AmB-d 0.3–0.6 mg/kg daily for 1–7 days with or without 5-FC 25 mg/kg four times daily or 5-FC alone for 2 weeks	AmB-d with or without 5-FC or 5-FC alone for 2 weeks in *C. glabrata* and AmB-d alone for 1–7 days for *C. krusei*. Eliminate urinary obstruction, and consider removing or replacing nephrostomy tubes and stents. Treat for candidemia if suspected
Urinary fungus balls	Surgical removal strongly recommended. Antifungal therapy as for cystitis or pyelonephritis		Local irrigation with AmB-d through nephrostomy tube, if present, is recommended

Table 13.7 (continued)

Condition	Primary therapy	Alternative therapy	Comments
Cryptococcal meningoencephalitis			
Induction	L-AmB 3–4 mg/kg daily or ABLC 5 mg/kg daily plus 5-FC 25 mg/kg four times daily for 2 weeks	L-AmB 6 mg/kg daily, ABLC 5 mg/kg daily, or AmB-d 0.7 mg/kg daily all for 4–6 weeks	Give induction for 4–10 weeks if persistent infection. Can increase induction dose of L-AmB to 6 mg/kg daily or AmB-d to 1 mg/kg daily. If intolerant to polyene, consider fluconazole ≥800 mg daily plus 5-FC 25 mg/kg four times daily. If intolerant to 5-FC, consider AmB-d 0.7 mg/kg daily plus fluconazole 800 mg (12 mg/kg) daily. Intrathecal or intraventricular AmB-d use is discouraged and is rarely necessary. Check minimal inhibitory concentrations (MIC) for fluconazole in persistent or relapsed infections
Consolidation	Fluconazole 400–800 mg daily for 8–12 weeks	Consider salvage consolidation in relapses for 10–12 weeks with fluconazole 800–1200 mg daily, voriconazole 200–400 mg twice daily, or posaconazole 200 mg four times daily or 400 mg twice daily	
Maintenance	Fluconazole 200–400 mg daily for 6–12 months		
Mild-moderate non-CNS disease	Fluconazole 400 mg (6 mg/kg) daily for 6–12 months		Also applies to mild-moderate isolated pulmonary disease

(continued)

Table 13.7 (continued)

Condition	Primary therapy	Alternative therapy	Comments
Moderately severe-severe non-CNS or disseminated disease without CNS involvement	Treat the same as CNS disease		Also applies to isolated severe pulmonary disease
Management of cryptococcal complications – Elevated CSF pressure: If CSF opening pressure ≥25 cm of CSF, with symptoms of ICP, do LP to relieve pressure to opening pressure ≤20 cm of CSF. Repeat LP daily until CSF pressure and clinical symptoms have stabilized for >2 days, or consider temporary percutaneous lumbar drains or ventriculostomy if daily LP is required. Permanent ventriculoperitoneal (VP) shunt only if other measures failed to control elevated ICP. Continue concomitant antifungal therapy – IRIS: Minor IRIS resolves spontaneously in days to weeks. For major cases with CNS inflammation and increased ICP, consider prednisone 0.5–1.0 mg/kg daily and possibly dexamethasone for severe CNS signs and symptoms. Taper over 2–6 weeks. Continue concomitant antifungal therapy			
Blastomycosis			
Mild-moderate disease	Itraconazole 200 mg three times daily for 3 days and then twice daily		Give at least for 6–12 months
Moderately severe-severe disease	LFAmB 3–5 mg/kg/day or AmB-d 0.7–1 mg/kg/day		Give at least for 2 weeks or until clinical improvement is noted
Coccidioidomycosis			
Mild-moderate disease	Fluconazole 400–800 mg daily or itraconazole 200 mg twice daily		For at least 6–12 months, followed by chronic suppressive therapy
Moderately severe- severe disease	AmB-d 0.5–1.5 mg/kg/day or LFAmB 2–5 mg/kg/day		For at least 2 weeks or until clinical improvement is noted and then step-down to oral azoles
Meningeal disease	Fluconazole 800–1000 mg daily and itraconazole 400–600 mg daily	Itraconazole 400–600 mg daily, intrathecal amphotericin B	Lifelong suppression for meningeal disease
Pretransplant or donor infection	Fluconazole 200–400 mg daily		For at least 6–12 months
Histoplasmosis			
Mild-moderate disease	Itraconazole 200 mg three times daily for 3 days and then twice daily		For at least 12 months

Table 13.7 (continued)

Condition	Primary therapy	Alternative therapy	Comments
Moderately severe- severe disease	L-AmB 3 mg/kg daily for 1–2 weeks and then itraconazole 200 mg three times daily for 3 days and then twice daily	AmB-d 0.7–1 mg/kg daily	For at least 12 months
Trichosporon	Azoles	Amphotericin B	
Rhodotorula	Amphotericin B	Posaconazole	
Malassezia	Topical preparation of clotrimazole 1% and selenium sulfide lotion	Oral fluconazole for superficial infections	Catheter removal and fluconazole for disseminated infections

Guidelines for the treatment of cryptococcosis in SOT patients are mostly based on clinical trial data among HIV patients [49, 58]. In order to choose the right antifungal therapy, it is essential to define the extent and severity of disease as well as the net state of immunosuppression. Identifying localized pulmonary from disseminated disease and sites of involvement including CNS helps to define the extent of disease. When meningeal disease is suspected, an LP should be done for CSF analysis, CSF CrAg, and opening pressure. This can also have therapeutic implications to relieve elevated intracranial pressure (ICP) to $\leq$20 cm.

Patients with localized pulmonary cryptococcal disease, even if asymptomatic, should be treated with fluconazole for 6–12 months. Treatment of severe, diffuse pulmonary disease or disseminated disease should follow the treatment of cryptococcal meningoencephalitis [49]. Similar to cryptococcosis, treatment for blastomycosis [75], coccidioidomycosis [77], and histoplasmosis [76] is based on IDSA guidelines and is based on the site of involvement and severity of disease. Table 13.7 shows the treatment recommendations of IFIs in SOT recipients [20, 35, 49, 58, 64, 75–77, 83].

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Prevention and Treatment of Mycobacterial Infections

14

Yolanda Meije, Eun J. Kwak, and José M. Aguado

14.1 Tuberculosis

14.1.1 Epidemiology

The epidemiology of TB in a country determines the risk of developing TB disease after transplantation, compounded by the increased risk among SOT recipients compared with the general population in a given area. The incidence of TB ranges from <20 to >125 per 100,000 people according to country and multidrug-resistant rates [1]. The incidence of TB in SOT ranges from 0.45% in low-endemic countries to 15.2% in high-endemic countries [2, 3]. The highest incidence (6.4–10%) is observed in lung transplant recipients [4].

Although mortality rate in SOT recipients may have decreased due to better diagnostic techniques, it remains high (9.5–17%) [2, 3]. In addition, there are scarce reports of the mortality rate in countries with high prevalence of TB. Most patients develop TB infection in the first year posttransplantation [2], but a bimodal distribution has also been observed, with the incidence of TB at a peak 2 years after SOT [5].

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14.1.2 Diagnosis

14.1.2.1 Latent Tuberculosis Infection

Documenting a positive tuberculin skin test (TST) in a person who has no signs, symptoms, or chest radiograph evidence of active TB disease usually makes the diagnosis of LTBI, but this diagnosis is usually hampered by the lack of a reference standard test [6]. Unfortunately, TST often gives false-negative results in anergic patients, such as those receiving immunosuppressive therapies and/or affected by chronic kidney and liver disease. It may also give false-positive results in areas in which BCG vaccination is prevalent or when there is accidental exposure to environmental non-tuberculous mycobacteria (NTM).

Novel blood tests have become available which detect gamma interferon production in response to antigens encoded by the RD-1 region of the MTC genome. These tests, now known as IGRAs (interferon gamma release assays), seem to be more specific (presenting no cross-reactivity with BCG and NTM) and less affected by immunosuppressive therapies, despite undergoing the same inhibition of immune mechanisms that is responsible for the impaired performance of TST [7]. Two commercially produced IGRAs are available, the QuantiFERON-TB Gold In-Tube or Gold Plus (QFT; Qiagen, Germantown, USA) and the T-SPOT.TB (T-SPOT; Oxford Immunotec, Abingdon, UK). Both tests employ a mitogen-induced positive control able to differentiate between an anergic and a true negative response.

Both tests, TST and IGRAs, may have false-positive and false-negative results; their concurrent use would be the ideal approach for increasing diagnostic sensitivity [8, 9]. However, this is not always feasible, either for financial reasons or due to

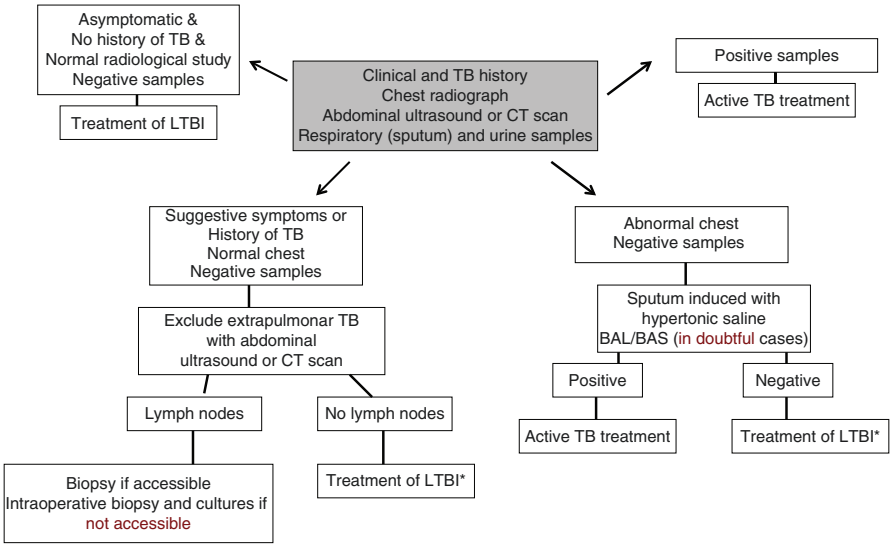

Fig. 14.1 Diagram to rule out active TB. *If urgent transplant, perform treatment of LTBI after transplantation

the characteristics of specific centers. In everyday practice, many patients undergo transplantation without a prior TST [10].

All living donors should also undergo TST and/or IGRA [11–14]. If the result of one of the assays is positive, active TB should be ruled out (see Fig. 14.1) [12, 14]. Treatment of latent TB infection must be administered to recipients of an organ whose donor has a history of, or data suggesting, untreated TB or recent exposure to active TB [14], particularly in lung transplants recipients.

14.1.2.2 Active Tuberculosis

Diagnosis of tuberculosis is challenging due to the non-specific clinical manifestations, the lack of specific radiological findings, and the presence of frequent extrapulmonary involvement [13]. The presence of fever, night sweats, weight loss, lymphadenopathy, or radiographic abnormalities should raise suspicion of TB, especially in patients with a history of contact with *M. tuberculosis* [13].

The first step in diagnosing TB is to obtain specimens for acid-fast bacilli (AFB) stains and mycobacterial culture. If pulmonary disease is suspected, three induced sputums should be collected, and/or invasive techniques, including bronchoalveolar lavage, transbronchial biopsy, and/or mediastinoscopy, should be performed. For extrapulmonary TB, a diagnostic approach aiming to obtain direct sampling from the involved site is recommended. If an unexplained fever raises the suspicion of disseminated disease, mycobacterial blood cultures should be obtained. Definitive diagnosis requires AFB cultures or the use of PCR to identify specific nucleic acid sequences in a clinical specimen collected. In addition to their sensitivity, AFB cultures allow for definitive species identification and full drug susceptibility testing. Although TST and IGRAs are the cornerstone of the evaluation of latent infection, they are not typically helpful in ruling out active TB, and positive testing may not indicate active infection [8].

14.1.3 Prevention

14.1.3.1 Pretransplant

The treatment of LTBI should start before transplantation. If it cannot be completed before the procedure, it should be continued afterward. It should be provided to all patients on the waiting list for SOT who has ≥1 of the following conditions [11, 12]:

- A TST (initial or after a booster effect, with a second TST performed 1–2 weeks later) with an induration ≥5 mm and/or a positive IGRA
- A history of untreated TB or chest radiograph findings compatible with untreated TB (apical fibronodular lesions, calcified solitary nodule, calcified lymph nodes, or pleural thickening), especially in geographical areas such as Europe where endemic mycoses mimicking TB lesions do not occur
- A history of contact with a patient with active TB

The drug of choice for LTBI in the transplant recipient is isoniazid, supplemented with vitamin B6, for 9 months [15, 16] (See Table 14.1). Other prophylactic alternatives for which only limited data [17, 18] are available in the SOT population are shown in Table 14.1. Isoniazid is generally well tolerated, although

Table 14.1 Suggested regimens for the treatment of LTBI

Drug	Duration	Recommendations
INH (5 mg/kg) (maximum of 300 mg)	Daily, 9 months	Combine with pyridoxine, 25–50 mg/day
INH (15 mg/kg) (maximum of 900 mg)	Twice weekly, 9 months DOT	Combine with pyridoxine, 25–50 mg/day
Rifampin (10 mg/kg) (maximum of 600 mg)	Daily, 4 months	Used preferably before transplantation due to interaction with immunosuppressive drugs
INH (15 mg/kg); (maximum of 900 mg) plus RFP (<50 kg, 750 mg; >50 kg, 900 mg)	Once weekly, 3 months, DOT or WR	Combine with pyridoxine, 25–50 mg/day Used preferably before transplantation due to interaction with immunosuppressive drugs

NH isoniazid, *RFP* rifapentine, *DOT* direct observed therapy, *WR* weekly reminders

isoniazid-induced hepatotoxicity may occur, especially in pre-liver candidates. Recent data showed that rifampicin has similar efficacy and reduced toxicity as compared to isoniazid [19], although data on the use of rifampicin in SOT candidates is scarce. Aminotransferases should be monitored closely [14]. Treatment of LTBI should be suspended if AST or ALT values increase threefold in patients with symptoms or fivefold in patients without accompanying symptoms.

In case of discontinuation of LTBI treatment, patients should be closely monitored, and treatment should be completed with drugs other than isoniazid in high-risk patients or could be deferred to posttransplant in lower-risk patients. Alternative regimens include rifampin or fluoroquinolones [12].

When active TB cannot be ruled out in an SOT recipient, it is recommended to start treatment with three drugs (INH, ethambutol, and pyrazinamide) [11]. A fourth drug, e.g., a fluoroquinolone, should be added if the disease is severe or until susceptibilities are known. Treatment can be completed with only INH if, after 8 weeks, cultures are negative for *M. tuberculosis* and the chest radiograph is considered normal [11].

Liver transplant recipients may present a high risk of hepatotoxicity with isoniazid prophylaxis. Some authors consider that this risk outweighs any potential benefits in relation to the fairly low frequency of TB reactivation compared with the possibility of liver dysfunction and the need for emergency transplant [15]. Other authors did not report increased toxicity associated with isoniazid in the liver transplant population [20].

There is widespread agreement regarding the treatment of LTBI in liver recipients when risk factors such as a recent change in TST results, a history of incorrectly treated TB, direct contact with a smear-positive TB patient, residual TB lesions, and immunosuppression factors are present [11, 20]. It also seems reasonable to consider treatment only in patients with compensated cirrhosis and in whom hepatotoxicity is closely monitored [12]. For the remaining cases, we consider that the decision should be individualized. Other drugs such as fluoroquinolones may also be considered for LTBI treatment, although adverse effects associated with long treatment duration have been described [21].

14.1.3.2 Posttransplant

If the treatment of LTBI has not been conducted before transplant, it should be performed afterward. The indication for and duration of isoniazid prophylaxis is the same as in the pretransplantation period. The interaction of isoniazid with calcineurin inhibitors is small [69]. Isoniazid may increase corticosteroid levels and, consequently, corticosteroid-mediated side effects [58]. Regimens that include rifamycins are not generally recommended in the posttransplantation period because of drug interactions.

14.1.4 Treatment

14.1.4.1 Pretransplant

When active TB cannot be ruled out, we recommend initiation of TB treatment with the standard three/four drugs. Treatment may be completed with isoniazid alone if cultures for MTC are negative after 8 weeks of incubation [12]. In general, patients with active TB should not undergo transplantation. Possible exceptions are patients with well-controlled infections and non-pulmonary SOT [11, 12].

14.1.4.2 Posttransplant

Recommendations for treating active TB in transplant recipients also differ from those applied to the general population, because of the interactions between rifamycins and immunosuppressive drugs, and the potential for hepatotoxicity associated with first-line TB therapy [11]. Additionally, many first-line anti-TB drugs (isoniazid, streptomycin, and ethambutol) warrant dose adjustment in renal transplant patients.

The use of rifamycins remains controversial. The interaction between rifampicin and calcineurin inhibitors, inhibitors of the mammalian target of rapamycin (mTOR), and corticosteroids is known to increase the risk of acute rejection [22, 23]. However, studies in populations other than SOT recipients have shown an increased risk of TB recurrence and high TB resistance rates when rifamycin-sparing regimens are used [24].

Some authors have reported difficulties adjusting immunosuppressive drug serum levels and a high graft failure rate with rifampicin usage [25]. Other authors have demonstrated that these drugs may be safe with rigorous control of immunosuppressive drug levels [26]. Favorable experiences with rifabutin have been described in small series of kidney and lung transplant patients [27]. However, other authors have reported a similar need to increase immunosuppressive drug doses for rifabutin in liver transplant patients [20].

The benefits of rifamycins must be balanced against the risk of rejection. Their recommendation for patients with severe or disseminated forms of tuberculosis or with suspicion of resistance to isoniazid seems reasonable. On the other hand, for localized, non-severe forms of tuberculosis and transplantation periods with a high rejection rate, physicians may weigh up the risks and benefits before including rifamycins in the anti-TB regimen [11–13]. See Table 14.2.

Table 14.2 Tuberculosis treatment options

Situation	Initial treatment	Maintenance treatment
Patients with localized and no severe TB and non-suspicion or evidence of resistance to isoniazid	• Avoid the use of rifamycins • INH, ethambutol, and pyrazinamide (or levofloxacin)	• Isoniazid and ethambutol (or pyrazinamide) are recommended for 12–18 months • The incorporation of a third drug, such as pyrazinamide or levofloxacin, could reduce this period to 12 months[a]
Severe forms or disseminated forms of TB or suspicion or evidence of resistance to isoniazid[b]	• Consider adding rifampicin or rifabutin to the regimen[c] • Levels of immunosuppressors should be closely monitored	• Complete treatment with isoniazid and rifampicin or rifabutin for at least 9 months
Multidrug-resistant TB or when there is some limitation for the use of the aforementioned drugs	• If isoniazid and rifamycins cannot be used, induction treatment should include 4–6 drugs • Possible drugs: injectable antimicrobials (e.g., streptomycin[d] amikacin, kanamycin, or capreomycin), linezolid, or other second-line drugs[e]	• The duration of treatment and the types of drugs should be individualized

[a]Prolonged use of fluoroquinolones can be associated with arthralgias; it may enhance the risk of tendon-related side effects of corticosteroids, may decrease mycophenolate levels, and may increase cyclosporine levels, and the combination with pyrazinamide is poorly tolerated by the digestive system

[b]If isoniazid cannot be used, induction and maintenance treatment that includes four drugs for at least 18 months is recommended

[c]A standard treatment based on a three-drug regimen may be considered (isoniazid, rifampicin or rifabutin, and pyrazinamide). Monitoring of the liver enzyme is mandatory and of particular concern for liver transplant patients. Alternatively, pyrazinamide could be replaced with a fluoroquinolone. The dose of calcineurin inhibitors and mTOR should be increased between three- and fivefold (increasing the frequency of administration from twice to three times daily), and the corticosteroid dose should be doubled. Levels of immunosuppressants should be closely monitored for both kinds of rifamycins, and their dose may need to be increased even in the case of rifabutin. Resistance to rifampin is almost systematically associated with cross-resistance to rifabutin and rifapentine; therefore, these drugs are not suitable alternatives

[d]In cases of resistance to streptomycin, there is no cross-resistance with other injectable drugs (e.g., amikacin, kanamycin, and capreomycin); however, cross-resistance between amikacin and kanamycin is universal. The combination of injectable drugs is not recommended because of their intolerance and the association of adverse effects

[e]There is no experience with the use of intermittent regimens, which, in any case, are not recommended for the management of multidrug-resistant TB, with the injectable drugs after a period of at least 2–3 months of daily therapy

14.1.4.3 Regimens Including Rifamycins

If the anti-TB regimen chosen includes rifampicin or rifabutin, a standard treatment based on a three-drug regimen (with the exception of high rates of isoniazid-resistant TB countries) may be considered. Complete treatment with isoniazid and rifampicin or rifabutin in the maintenance phase for at least 9 months is recommended [11, 12]. Some authors suggest that extrapulmonary TB presentations and patients with cavitary pulmonary TB who remain culture-positive after 2 months require 12–18 months of treatment [11, 14, 20].

14.1.4.4 Regimens That Do Not Include Rifamycins

If rifampicin therapy is not used, prolonged treatment has been considered for SOT patients due to the experience gained in the general population. Regimens should be continued for at least 12–18 months [24]. In rifamycin-free treatment regimens, the combination therapy with isoniazid and ethambutol for 12–18 months with the addition of pyrazinamide for the first 2 months is an option [28]. Maintenance agents may include isoniazid and pyrazinamide or ethambutol, and the possible addition of levofloxacin/moxifloxacin should be considered; a three-drug regimen may reduce the treatment length [12].

In the general population, isoniazid, pyrazinamide, and streptomycin have proven to be effective when the regimen is administered for 9 months [24], although it is difficult to maintain injected therapy for long periods because of the risk of ototoxicity and renal toxicity. Little information in the transplant setting is available.

Fluoroquinolones (FQs) are an alternative for transplant patients because of the disadvantages associated with rifamycins and aminoglycosides. In the transplant setting, good outcomes with FQs in the initial four-drug regimen for kidney and lung transplant recipients have been described [4]. In addition, the possibility that the widespread use of FQs for other infections could lead to a high prevalence of FQ-resistant TB is a matter for concern.

Linezolid has proven to be effective for patients with TB [29]. However, prolonged use of this drug has been associated with thrombopenia, anemia, and polyneuropathy, especially in patients with diabetes or kidney disease.

14.1.5 General Approach

Because active tuberculosis (TB) is associated with high mortality in solid organ transplant (SOT) recipients, all transplant candidates should undergo evaluation for latent TB infection (LTBI). The tuberculin skin test (TST) and/or an IGRA test are currently the standard methods for identifying subjects at risk. Before initiation of treatment for LTBI, patients with positive immunological test results (TST and/or IGRA) should be evaluated to rule out active TB. A diagnosis of TB can only be

confirmed by culturing MTC or by identifying specific nucleic acid sequences in a clinical specimen collected from the suspected site of disease. Treatment for LTBI should be administered to patients on transplant waiting lists or to recipients after transplantation who have ≥1 of the following conditions: (1) a TST with a 5-mm induration or positive IGRA result, (2) a history of untreated TB, or (3) a history of contact with a patient with active TB. The drug of choice for LTBI is isoniazid (300 mg/day) supplemented with vitamin B6 for 9 months or rifampicin for 4 months. For localized, non-severe forms of TB and periods with high rejection rates, it may be advisable to avoid the use of rifamycins. Maintenance therapy with isoniazid and ethambutol (or pyrazinamide) is recommended for 12–18 months. For severe forms or disseminated TB, the use of a TB regimen that includes rifampicin or rifabutin should be considered. Maintenance therapy with isoniazid and rifampicin or rifabutin is recommended for at least 9 months.

14.2 Non-tuberculous Mycobacteria

Introductory Abstract
Non-tuberculous mycobacteria (NTM) are uncommon causes of human disease despite their ubiquity in the environment including soil and water [30] but are increasingly recognized as significant pathogens in solid organ transplant (SOT) recipients as opportunistic agents. NTM disease progression is facilitated by impaired cell-mediated immunity in this population and, in the case of lung transplant candidates and recipients, by structural disease promoting airway colonization [31]. High index of suspicion is required for timely diagnosis and treatment. On the other hand, a subset of NTM isolated from the lungs may represent colonization or early subclinical infection, for which watchful observation without therapy is reasonable. Given the complicated and prolonged treatment regimens for the majority of NTM, which can adversely interact with immunosuppressive medications, true therapeutic need should be established before initiation of treatment for pulmonary NTM. Treatment is usually given for 12–18 months or longer, with regimen tailored to speciation and sensitivity testing results [32]. In recent years, *M. abscessus* infection in lung transplant candidates has emerged as a major therapeutic challenge due to its propensity to cause early surgical site infection posttransplant.

14.2.1 Epidemiology

NTM are a heterogeneous group of organisms numbering >125 species and growing, over half of which have the potential to cause human infections. However, majority of NTM infections are caused by approximately 20 common pathogens [33]. NTM are broadly classified as rapidly growing mycobacteria (RGM) vs. the rest, based on the speed of growth of the organism on the culture media once incubated. RGM typically grow within 7 days of incubation and include *Mycobacterium abscessus*, *M. fortuitum*, and *M. chelonae*. The rest of NTM such as *Mycobacterium*

avium complex (MAC) or *M. kansasii* take longer to grow, although time to culture positivity is also impacted by the inoculum size. While the source of most NTM infections is believed to be environmental, possibility of person-to-person transmissions has been raised recently with *M. abscessus*, with the conjectured route of spread via fomite or aerosol [34]. True incidence of NTM in SOT recipients is difficult to determine due to its lack of reporting requirement, but literature suggests relatively low incidence of <1% in abdominal transplant recipients and up to 2.8% in heart transplant recipients. The incidence is by far the highest in lung transplant recipients, varying widely and ranging from 0.5% up to 18% [35], with higher rates seen in centers that perform routine surveillance bronchoscopies.

As with their presentation in immunocompetent hosts, pulmonary disease is by far the most frequent site of NTM infection in SOT recipients, followed by skin and soft tissue infections (SSTI). While MAC causes the majority of NTM disease overall, RGM are mostly frequent etiological agent for SSTI, which typically presents as erythematous to violaceous subcutaneous nodules or ulcerative lesions that occur at a surgical site or in extremities, often in clusters or along a lymphangitic spread [33]. Other less common manifestations include osteoarticular infections such as vertebral osteomyelitis, catheter-associated mycobacteremia, lymphadenitis, and disseminated disease involving two or more organ systems.

SOT recipients are at increased risks for more severe infections by NTM due to their compromised cell-mediated immunity. Specific risk factors for different NTM species have been elucidated for certain subsets of patients: Pulmonary infections with MAC are increased in subjects with impaired lung architectures and function, such as emphysema and bronchiectasis. *M. abscessus* has emerged as a major pathogen in patients with cystic fibrosis (CF) and other immunodeficiencies associated with recurrent pulmonary infections and bronchiectasis [36]. All three RGM species have been linked to foreign body/prosthetic infections. Certain species have specific risk factors, such as *M. marinum* and its close association with injuries from marine life or contact with contaminated seawater or fish tank.

NTM infection can occur at varying times from transplant, from early postoperative period to years after the transplant. A recent single-center study suggested a bimodal distribution, with the first peak at median of 2.2 months and second at 7.5 years. Early NTM infections occurring <1 year posttransplant was significantly associated with increased mortality compared to matched control [37]. A specific subset of early posttransplant NTM infection of note is *M. abscessus* surgical site infection that occurs in lung transplant recipients colonized with the organism pretransplant, usually within the first few weeks to months during wound healing. Management of *M. abscessus* infection in this scenario has posed significant therapeutic challenges.

14.2.2 Diagnosis

Diagnosis of NTM in SOT patient requires a high index of suspicion and prompt submission of appropriate specimen for mycobacterial cultures. NTM should be

high on the list of differential diagnosis in any SOT recipients with unexplained febrile illness, atypical pulmonary radiological abnormalities, subacute SSTI with nodular or ulcerative components, surgical site infections, or foreign body-associated infections. For extrapulmonary infections, delay in diagnosis is common due to frequently omitted request for mycobacterial cultures during the processing of clinical samples. Once an NTM is isolated in mycobacterial blood or tissue cultures, the diagnosis is relatively unambiguous, although sampling error or low bacterial inoculum may lead to falsely negative culture results, necessitating repeated attempts at fluid or tissue cultures.

For pulmonary infection, diagnosis of NTM is a more layered topic. Isolation of NTM from a respiratory sample might represent colonization of the airways or environmental contamination rather than an invasive disease. Lung transplant recipients have a particularly high rate of isolation of NTM from respiratory samples, due to their abnormal airway anatomy and impaired ciliary function facilitating NTM colonization, as well as frequent submission of respiratory samples. The American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) guideline for diagnosis of pulmonary disease by NTM [32] attempts to distinguish symptomatic infections from asymptomatic colonization or early subclinical disease, by considering clinical, radiological, and microbiological criteria as a whole (Table 14.3). While this provides a useful reference, clinicians should be advised that these diagnostic criteria were devised with largely immunocompetent hosts in mind. Early invasive NTM infections that do not meet the criteria may progress more rapidly than expected in SOT recipients. Close follow-up with repeated respiratory cultures and serial imaging is warranted for patients at high risk for invasive NTM disease.

Once an NTM was isolated, precise speciation is needed for the clinicians to choose optimal combination therapy. DNA probes and other molecular-based assays are frequently employed for rapid diagnosis of common mycobacteria such as *M. tuberculosis* and MAC. Speciation of less common NTM species may require DNA sequencing or for the isolates to be sent to a reference testing laboratory. Identification down to the subspecies level is of particular importance for *M. abscessus*, as

Table 14.3 ATS/IDSA diagnostic criteria of NTM lung diseases

Clinical
1. Pulmonary symptoms, nodular or cavitary opacities on chest radiographs, or a high-resolution scan that shows multifocal bronchiectasis with multiple small nodules
2. Appropriate exclusion of other diagnoses
Microbiological
1. Positive culture results from at least two separate expectorated sputum samples
2. Positive culture results from at least one bronchial wash or bronchoalveolar lavage
3. Transbronchial or other lung biopsy with mycobacterial histopathological features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histopathological features and one or more sputum or bronchial washings that are culture-positive for NTM

Adapted from ATS/IDSA guideline [32]

subspecies *M. massiliense* is associated with better sensitivity profile and a more favorable response to therapy [38]. In case of positive AFB stain seen in histopathologic examination without corresponding positive cultures, direct detection of AFB DNA from tissue may be attempted using broad-range, multi-locus PCR [39].

14.2.3 Prevention

Many NTMs are ubiquitous in the environment and difficult to avoid. Transplant recipients are advised to refrain from cleaning aquariums or, if unavoidable, to use gloves during the cleaning to minimize the exposure to *M. marinum* [40]. Gloves should also be used during gardening. Insufficiently heating in household water systems has been associated with increased number of NTM [41]; thus at-risk patients such as transplant candidates or recipients should ensure adequate water heater temperatures. In contrast to *M. tuberculosis*, pharmacological prophylaxis has not been well established in NTM prevention in SOT recipients. The closest analog would be rifabutin or azithromycin chemoprophylaxis against MAC, reserved for patients with advanced AIDS [32]. However, the rate of MAC infection across SOT populations is not consistent or high enough to warrant therapy with agents that carry significant GI side effects or interact with immunosuppressive medications.

14.2.4 Treatment

14.2.4.1 General Considerations

In-depth discussion of various regimen used for NTM is beyond the scope of this review, but Table 14.4 lists first-line therapy for several medically significant NTMs, the majority of which requires multidrug combinations for ≥12 months. In general, susceptibility testing is recommended for RGM to guide therapy, whereas its utility is more debated for slower-growing NTM species. MAC isolates should be tested for macrolide sensitivity; testing of MAC sensitivities for other agents such as rifabutin, ethambutol, amikacin, and quinolones may be requested, but correlation with clinical response is more questionable. Rifampin sensitivity testing should be performed on *M. kansasii*, with further testing for secondary agents to be considered for rifampin-resistant isolates [32].

If feasible, reduction in immunosuppression is recommended for severe or disseminated disease. Rifamycins are strong inducers of CYP3A4 enzymes through which calcineurin inhibitors and mTor inhibitors are metabolized, and coadministration results in reduction of exposure for these immunosuppressive agents. Rifabutin is a weaker inducer compared to rifampin and is the preferred agent in NTM therapy among transplant patients, although dose adjustment in CNI and mTor inhibitors is still necessary in most cases. Similarly, while the ATS/IDSA guideline lists clarithromycin as the major macrolide backbone in most NTM

Table 14.4 First-line therapy for several medically significant NTMs

Organism	Susceptibility testing	Recommended regimen	Comments
MAC	Clarithromycin; correlation between susceptibility and clinical response not well established for other agents	Azithromycin + rifabutin + ethambutol for at least 12 months after microbiological clearance	Induction with amikacin may be considered for severe or disseminated infection
M. kansasii	Rifampin; if resistant, consider testing for additional agents	Isoniazid with pyridoxine + rifabutin + ethambutol for 18 months (≥12 months after microbiological clearance)	Isoniazid may be active even if in vitro resistance is reported
M. haemophilum	No standardized susceptibility testing available	Azithromycin + ciprofloxacin + ethambutol	Resistant to ethambutol
M. marinum	Routine susceptibility testing not recommended	Azithromycin + ethambutol ± rifabutin	Shorter course of therapy, e.g., 6 months, might be adequate
M. abscessus	Amikacin, cefoxitin, imipenem and/or meropenem, quinolones, clarithromycin, doxycycline, minocycline, sulfonamide, linezolid	Based on susceptibility data, ≥3 active drug combination preferred including macrolide backbone if susceptible	Induction with parenteral antibiotics recommended; for MDR pathogens, test for tigecycline and clofazimine sensitivities
M. chelonae	Amikacin, cefoxitin, ciprofloxacin, clarithromycin, doxycycline, sulfonamides, linezolid	Based on susceptibility data, two active drugs including a macrolide recommended	For localized infection, consider surgical debridement
M. fortuitum	Same as *M. chelonae*	Based on susceptibility data, two active drugs recommended	Contains inducible macrolide resistance via methylase gene; use macrolides with caution

treatment regimen, substitution with azithromycin is recommended in SOT recipients due to its minimal interaction with transplant medications compared to clarithromycin, which inhibits CYP3A4 [42].

The ATS/IDSA guideline recommends minimum of 12 months of therapy for NTM after microbiological clearance. Longer therapy of ≥18 months may be needed for osteoarticular or disseminated infections. For disease limited to the skin and soft tissue, a shorter duration of therapy such as 3–6 months may be acceptable provided there is clinical resolution.

14.2.4.2 Special Consideration: Lung Transplant and NTM

Patients with structural lung disease awaiting lung transplant, especially those with CF, are one of the highest risk groups for NTM infection. While severe MAC infection may contribute to respiratory insufficiency in rare instances, in majority of cases, isolation of MAC pretransplant represents colonization, and MAC colonization pretransplant has not been associated with increased posttransplant morbidity or mortality [43]. That said, once listed, most clinicians would opt to treat MAC until transplant with combination therapy [44], although treatment is not usually extended posttransplant once colonized lungs have been explanted. On the other hand, infection with *M. abscessus* has posed a major clinical challenge in this population, especially in cystic fibrosis patients. Since the early 2000s, multiple published case reports and case series brought attention to the tendency of *M. abscessus* to cause aggressive early recurrent infections in the surgical sites associated with poor outcome [45–48], prompting the majority of lung transplant centers to consider *M. abscessus* infection a relative, if not absolute, contraindication for transplant listing. In contrast, a cohort study from a large US lung transplant center showed *M. abscessus*-colonized CF patients may still be transplanted with comparable survival to CF patients without the infection [49]. Further reports suggest that, while surgical site infection remained a major issue, *M. abscessus* infection needs not be an absolute contraindication for lung transplant [50–52]. However, these reports come with several caveats: (1) eradication attempts should be made prior to transplant; (2) aggressive treatment for *M. abscessus* is needed pre- and posttransplant; (3) consider further methods to minimize contamination of the surgical space during transplant surgery, including antibiotic irrigation, lymphadenectomy, and changing of surgical gloves prior to handling donor organs. The optimal duration of *M abscessus* therapy posttransplant has not been well established.

For lung transplant recipients developing NTM infection past early postoperative period, the decision to treat depends on a variety of clinical factors, such as extent of symptoms and radiological abnormalities, number/persistence of positive cultures, concomitant rejection, and anticipated medication toxicities. Moreover, NTM isolation in this population is often transient and may not require therapy and has not been associated with increased posttransplant mortality [53]. Even for difficult pathogens such as *M. abscessus*, the ATS guideline appears useful in determining significant infection warranting therapy [54].

14.2.5 General Approach

NTM should be considered for subacute respiratory infections associated with atypical pulmonary radiological presentation in SOT patients. Nodular or ulcerative SSTI, indolent osteoarticular infections, chronic wasting illness, and persistent or recurrent foreign body-associated infections should also raise a suspicion of NTM. Repeated sampling may be needed to establish the diagnosis. Once NTM has been isolated, extensive susceptibility testing should be performed on all clinically significant RGM, whereas more limited testing is recommended for MAC and *M. kansasii*. With frequent respiratory sampling, NTM may be isolated incidentally. As treatment is usually complex and prolonged, therapeutic necessity should be established in each individual case based on clinical signs and symptoms and radiological progression. Reduction in immunosuppression is recommended for severe and/or disseminated disease. Lastly, *M. abscessus* infection in lung transplant candidates is a complex topic that requires a multidisciplinary approach. Every attempt should be made to eradicate the organism pretransplant, although final decision whether to list these patients remains up to the practice of individual institution, given the high risk of aggressive early recurrence.

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15 Prevention and Treatment of Other Opportunistic Infections: Nocardiosis, Toxoplasmosis, Chagas and Pneumocystis Disease

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15.1 Nocardiosis

15.1.1 Introduction

Nocardiosis is an uncommon opportunistic infection that primarily affects immunocompromised hosts with defects in cell-mediated immunity such as solid organ transplant recipients [1]. There are several species that can cause disease depending on geography. These include *N. nova*, *N. brasiliensis*, and *N. farcinica* [2]. Two of the key features that are characteristic of *Nocardia* spp. include (1) the ability to cause disseminated disease (the lung, central nervous system, and skin are common sites) and (2) a high probability of relapse or recurrent disease once treated. Among solid organ transplant recipients, the risk of infection is highest in the first year following transplantation. Particular risk groups include those who have received glucocorticoid therapy, have high calcineurin inhibitor concentrations, and have had antecedent cytomegalovirus infection. Heart and lung transplant recipients are disproportionally represented among solid organ transplant recipients, but all solid organ transplant patients are at risk.

15.1.2 Clinical Presentation

Transplant patients often present non-specifically. A common presentation is the patient who gets evaluated for pulmonary nodules and other findings seen on chest imaging as

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part of a workup for fevers or can be incidentally found [3]. However as the "great imitator," *Nocardia* commonly affects other organ systems as well such as the central nervous system (brain abscess, meningitis) and skin (subcutaneous abscesses) [4]. One clinical pearl is that central nervous system disease is often asymptomatic. All transplant patients presenting with pulmonary or cutaneous disease should be evaluated clinically and/or radiologically for central nervous system disease.

15.1.3 Diagnosis

Nocardia is a gram-positive bacterium that is quite unusual in appearance. It is distinguished by its delicate filamentous gram-positive branching rods that appear almost fungal in morphology. It is weakly acid-fast in contrast to *Actinomyces* species which can have a similar appearance otherwise. It can be easily missed by non-experienced microbiologists. Clinicians with a high pretest probability should alert laboratory staff accordingly and order a modified acid-fast stain for BAL samples, abscess, and biopsy specimens. Newer diagnostic methods such as 16S ribosomal sequencing and other molecular methods are increasingly being used given the poor sensitivity of current methods. Given the wide variation in susceptibilities based on the specific species, we always recommend identification at the species level with susceptibility testing once empiric treatment has been started [5].

15.1.4 Treatment

The principles of treatment for infection with *Nocardia* in solid organ transplant recipients are as follows: (1) treat for a prolonged period in the order of 6–12 months given the tendency for *Nocardia* to relapse (a shorter course may be adequate if no CNS disease or if localized cutaneous disease but most treat for 12 months) [6]; (2) treat with dual therapy while awaiting susceptibilities, including one IV agent at least, while the patient is critically ill; (3) use TMP-SMX in the regimen if that option is available [7]; and (4) surgically drain if necessary. Given the multiple species and unpredictable susceptibilities, we request identification and susceptibility testing for all our isolates. For sick patients, we typically use a carbapenem and TMP-SMX empirically (Table 15.1). Other options before final susceptibilities are known include linezolid, minocycline, and amikacin.

15.1.5 Prevention

We do not currently recommend prophylaxis for *Nocardia* in at-risk patients such as solid organ transplant recipients. Interestingly, most of these patients are on

Table 15.1 Prevention and treatment regimens for nocardiosis, toxoplasmosis, Chagas disease, and *Pneumocystis*

	Prevention	Treatment[a]
Nocardiosis	None	Non-severe: TMP-SMX 15 mg/kg orally of the trimethoprim component in 3–4 divided doses Severe: TMP-SMX 15 mg/kg IV of the trimethoprim component in 3–4 divided doses *and* Amikacin 7.5 mg/kg IV every 12 h *or* Imipenem 500 mg IV every 6 h *or* Linezolid 600 mg IV/orally every 12 h
Toxoplasmosis	Primary prophylaxis First line: TMP-SMX 1 DS tablet (800 mg/160 mg) orally per day *or* TMP-SMX 1 DS tablet orally three times per week *or* TMP-SMX 1 SS tablet orally per day Second line: Dapsone 50 mg orally per day *and* Pyrimethamine 50 mg orally per week *and* Leucovorin 25 mg orally per week Third line: Atovaquone 1500 mg orally per day (with or without pyrimethamine 50 mg orally per week *and* Leucovorin 25 mg orally per week)	First line: Sulfadiazine 1000 mg orally four times per day (if ≥60 kg, 1500 mg four times per day) *and* Pyrimethamine 50 mg orally per day (if ≥60 kg, 75 mg per day), after a 200 mg loading dose *and* Leucovorin 10–25 mg orally per day Second line: Clindamycin 600 mg IV/orally four times per day *and* Pyrimethamine 50 mg orally per day (if ≥60 kg, 75 mg per day), after a 200 mg loading dose *and* Leucovorin 10–25 mg orally per day *or* TMP-SMX 5 mg/kg IV/orally of the trimethoprim component two times per day
Chagas disease		First line: Benznidazole 10 mg/kg orally per day in two divided doses for 60 days Second line: Nifurtimox 8–10 mg/kg orally per day in 3–4 divided doses for 90–120 days

(continued)

Table 15.1 (continued)

	Prevention	Treatment[a]
Pneumocystis	Primary prophylaxis First line: TMP-SMX 1 DS tablet (800 mg/160 mg) orally per day *or* TMP-SMX 1 DS tablet orally three times per week *or* TMP-SMX 1 SS tablet orally per day Second line: Dapsone 100 mg orally per day in 1–2 divided doses *or* Atovaquone 1500 mg orally per day *or* Dapsone 50 mg orally per day *and* Pyrimethamine 50 mg orally per week *and* Leucovorin 25 mg orally per week *or* Pentamidine 300 mg inhaled monthly	First line: TMP-SMX 15–20 mg/kg IV/orally of the trimethoprim component in 3–4 divided doses Second line: Clindamycin 900 mg IV three times per day (or 600 mg IV four times per day or 600 mg orally three times per day) *or* Primaquine 30 mg (base) orally per day *or* Pentamidine 4 mg/kg IV once daily Adjunctive glucocorticoids (if PaO2 < 70 mmHg) Prednisone 40 mg orally two times per day for 5 days, followed by 40 mg orally once daily for 5 days, followed by 20 mg orally once daily for 11 days

TMP-SMX trimethoprim-sulfamethoxazole, *DS* double-strength oral tablet, *SS* single-strength oral tablet
Amikacin not preferred in renal transplant recipients
[a]Adjust dose in renal impairment

TMP-SMX prophylaxis for *P. jirovecii* which should theoretically prevent *Nocardia* as well. However, this does not appear to provide complete benefit with several instances of breakthrough infection reported.

15.2 Toxoplasmosis

15.2.1 Introduction

Toxoplasmosis is a rare disease caused by *Toxoplasma gondii*, an intracellular parasite with a worldwide distribution. There are classic risks for infection such as eating raw or undercooked meat and cat exposure. However, because more than half of patients do not have identifiable risk factors, using epidemiologic features to stratify transplant donors at risk is not useful. Serology is used to define risk of disease transmission in transplant recipients. The highest risk of transmission is in the scenario where the organ of an exposed donor (D+) is placed in an unexposed (R−)

recipient. Among solid organ transplant recipients, the highest risk of disease is among heart transplant patients, as the *Toxoplasma* cysts are commonly found in muscle when infection occurs [8]. However, there is increasing recognition that D+ donors can also cause disease in non-heart R− recipients [9]. It is important for transplant professionals to know these risks and institute prophylaxis accordingly.

15.2.2 Clinical Presentation

Solid organ transplant recipients may develop disease in two scenarios: either as reactivation of old disease or in the setting of donor-derived infection. In most individuals, primary infection is asymptomatic or may be seen as patients presenting with lymphadenopathy, chorioretinitis, hepatitis, or flu-like symptoms (fever, headache, myalgias, malaise). In solid organ transplant recipients, reactivation may be seen as some of the symptoms in primary infection but in many cases with brain abscesses, encephalitis, myocarditis, rash, and widely disseminated disease [10].

15.2.3 Diagnosis

In the general population, *T. gondii* acute infection is diagnosed indirectly with serology. Following acute infection, *Toxoplasma*-specific IgM antibodies appear first, followed by IgG antibodies 2 weeks later. The *Toxoplasma*-specific IgG antibodies persist for life. Transplant and other immunocompromised patients may not be able to mount an antibody response rendering the serology test insensitive [11]. Although there are no standardized polymerase chain reaction (PCR) assays, commercially available PCR tests may be helpful for diagnosis of organ-specific disease (e.g., pneumonia, central nervous system, eye) in immunocompromised patients. Pathology on biopsy may be diagnostic if characteristic tachyzoites or cysts are seen.

15.2.4 Treatment

We usually treat up front with sulfadiazine and pyrimethamine (Table 15.1). Clindamycin and pyrimethamine is an alternative combination. In any pyrimethamine-based regimen, leucovorin is added to prevent bone marrow toxicity. The initial regimen is usually given for 6 weeks, followed by maintenance therapy which is usually the same drugs used for initial therapy but at lower doses.

15.2.5 Prevention

In general, heart transplant patients who are seronegative recipients of seropositive donors receive from 6 months to lifelong prophylaxis. There is limited data, but many centers opt to provide lifelong prophylaxis in this setting. Prophylaxis in

seronegative recipients from positive donors has now been expanded to non-heart solid organ recipients given several reports of donor-derived infections involving these organs [12]. Trimethoprim-sulfamethoxazole (TMP-SMX) is usually already given for the prevention of *Pneumocystis* pneumonia but is also highly effective for toxoplasmosis primary prophylaxis for the targeted high-risk D+R− population (Table 15.1). Most patients receive TMP-SMX. An alternative for primary prophylaxis is dapsone-pyrimethamine. There is less data for atovaquone, but this is also a potential option for patients intolerant to TMP-SMX or dapsone-pyrimethamine.

15.3 Chagas Disease (American Trypanosomiasis)

15.3.1 Introduction

Chagas disease is a vector-borne infection caused by *Trypanosoma cruzi* (a protozoan parasite) and is transmitted by the reduviid bug. These insects naturally occur only on the American continent. Outside the Americas, infected immigrants may transmit the infection acting as blood or organs donors. Infected mothers may vertically transmit the infection to their offspring, explaining infection occurring in people born from non-endemic areas. International travel (with extended stays in rural areas) is another way to acquire infection among people from non-endemic areas. Among transplant recipients, there are three ways we consider infection risk: (1) in patients who have end-stage cardiac disease due to Chagas disease and who need heart transplantation, (2) in those who have chronic Chagas infection who need a solid organ transplant for a non-Chagas reason, and (3) in those with donor-derived infection from a donor with chronic Chagas infection. Patients with chronic Chagasic cardiomyopathy with heart transplantation have survival rates better than patients who were transplanted because of other heart conditions. Heart, kidney, kidney-pancreas, and liver transplantation have been successfully performed in patients with chronic Chagas infection. Reactivation has been reported in 20–50% of kidney transplant recipients and in less than 20% of liver transplant recipients with Chagas disease [13]. Finally, with the proper molecular monitoring protocol in place, it is safe to accept non-heart organs from donors with chronic *T. cruzi* infection [14].

15.3.2 Clinical Presentation

In humans, the disease has an acute and a chronic phase. The acute stage may be asymptomatic, or it may present only mild clinical symptoms such as a malaise, fever, anorexia, and lymphadenopathy, which usually resolve spontaneously in 8–12 weeks. In most cases, the immune response controls the parasitic infection, but (in the absence of specific anti-parasitic drug treatment) is ineffective to clear it. The infection results in clinical latency (chronic or indeterminate phase), which may last 10–30 years or lifelong. The infection is evident only by positive serology, with extremely low and intermittent parasitemia. After several years of

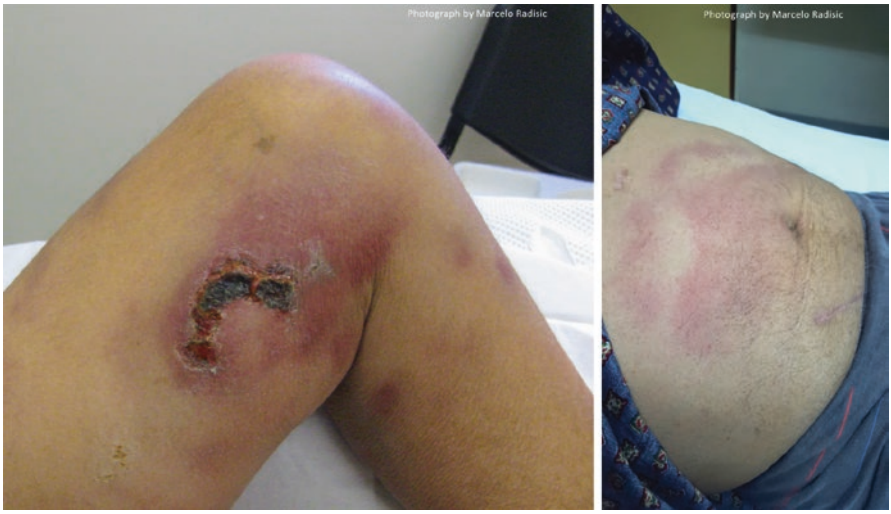

Fig. 15.1 Skin lesions caused by Chagas reactivation in kidney transplant patients

asymptomatic disease, progression to symptomatic Chagas may be observed in 20–30% of infected patients who may develop Chagasic cardiomyopathy (90%) and, less frequently, gastrointestinal (15–20%) and peripheral nervous system disease (10%) [13].

In SOT recipients, most reactivated cases have parasitemia with positive PCR or/and Strout tests (see below) but with no clinical manifestations of disease. Less frequently, the patient may present with fever and skin lesions (usually very painful solitary or multiple subcutaneous nodules and rarely panniculitis and ulcers) (Fig. 15.1). Skin lesions are predominantly located in the limbs. Severe disease may sporadically occur (usually with a high level of parasitemia), presenting as Chagasic meningoencephalitis, tumorlike brain lesions (Chagomas), and acute myocarditis. In heart transplant recipients, Chagasic myocarditis is more frequent than in non-heart transplant recipients and must be differentiated from rejection. The risk of Chagas reactivation seems to be related to the amount of immunosuppression. Possible risk factors for reactivation are mycophenolate mofetil use for maintenance immunosuppression, rejection episodes, and neoplasias.

Patients with donor-derived infection with *T. cruzi* may present asymptomatically if detected on molecular monitoring (see below). However, they may also present with disseminated disease as above typically in cases where donor screening and recipient PCR monitoring have not occurred.

15.3.3 Screening and Diagnosis

Pretransplant serological screening for Chagas should be part of routine evaluation in transplantation donors and recipients in endemic areas. In non-endemic areas,

screening should be performed in people who were born or who lived in endemic areas and in people who received blood transfusions or whose mothers were born in endemic areas [14]. Serological screening may be done with enzyme-linked immunosorbent assay (ELISA), indirect hemagglutination (HA), and indirect fluorescent antibody (IFA) tests. Health agencies from endemic areas recommend obtaining positive results from at least two of three different methods to diagnose Chagas. Radioimmunoprecipitation (RIPA), Western blot, immunoblot, and IFA have the highest specificity and sensitivity and are considered confirmatory tests [13].

FDA-licensed screening tests for blood or organ donors include Ortho *T. cruzi* ELISA Test System and ABBOTT PRISM Chagas chemiluminescent immunoassay (ChLIA) with sensitivity and specificity close to 100%. Depending on the country and setting, there may be additional tests available.

Reactivation of chronic Chagas disease may occur with immunosuppression therapy, especially in the first months after transplantation, or with intensification of the immunosuppressive regimen. Therefore, sequential monitoring for early detection of parasitemia (reactivation) and implementation of preemptive treatment are recommended. Monitoring is done weekly or every 2 weeks for the first 6 months after transplantation and monthly thereafter until 1 year. Weekly monitoring for 2 months after intensification of immunosuppression is also recommended.

Parasitemia may be detected by direct observation of motile trypanosomes using microscopic examination of the buffy coat, thin or thick blood films stained with Giemsa, or by a concentration method (Strout test) or microhematocrit. Real-time PCR for *T. cruzi* has a higher sensitivity for low-grade parasitemia, preceding a positive Strout test or clinical signs of disease [15, 16].

PCR sensitivity may differ regarding whether they amplify nuclear (nPCR) or kinetoplast (kPCR) *T. cruzi* DNA. The best performing PCR methods for detection of *T. cruzi* in human blood samples have a high sensitivity (83–94%) and specificity (85–95%).

Pathology can be also used to diagnose active disease. On pathological examination, skin nodules show nests of intracytoplasmic *T. cruzi* amastigotes. Both rejection and Chagas reactivation in the heart can present with lymphocytic infiltrates with edema and areas of necrosis in endomyocardial biopsies. However, Chagas disease is diagnosed by identification of *T. cruzi* (either by immunohistochemistry and/or tissue-based PCRs).

15.3.4 Treatment

Patients with reactivated Chagas disease usually respond very well to benznidazole treatment (Table 15.1) (10 mg/kg/day in two divided doses for 60 days). Nifurtimox (8–10 mg/kg/day orally in three or four divided doses for 90–120 days) could also be effective, but its side effects are considerable. The adverse side effects of these drugs include dermatitis, peripheral polyneuropathy, weight loss, gastrointestinal disease, hematologic disorders, and an increased incidence of lymphoma. Posaconazole has activity against *T. cruzi*, but clinical results when treating chronic

indeterminate Chagas disease demonstrate inferiority to benznidazole [17]. Allopurinol also has good in vitro activity against *T. cruzi*. There is anecdotal experience of successful use (dose 600–900 mg/day for 2–3 months) for the treatment of reactivation following heart transplantation.

Parasitemia clearance and remission of clinical manifestations are usually obtained in the first week of treatment. In the heart transplant patients, relapses may occur. They may be multiple and may be observed many years after the first reactivation episode, with parasitemia or clinical manifestations; however, these individuals have had good responses to subsequent treatment courses. Mortality related to Chagas disease reactivation in heart transplantation has been reported to be 0.3% [13].

15.3.5 Prevention

Prevention strategies include identification of donors and recipients at risk of *T. cruzi* infection. In endemic countries, up to 5% of all deceased donors are patients chronically infected with Chagas disease [13]. In non-endemic countries, transmission by unscreened deceased organ donors and unscreened blood transfusions has been reported. Donor screening should be considered in when risk factors for Chagas are present (Fig. 15.2). The decision to accept Chagasic organ donors should be made balancing the risk of expected mortality in the waiting list against expected morbidity from eventual Chagas transmission. The likelihood of transmission appears to vary by organ type [14]. Transmission by infected donors to negative kidney recipients was reported to be from 0 to 18%. In liver transplant recipients,

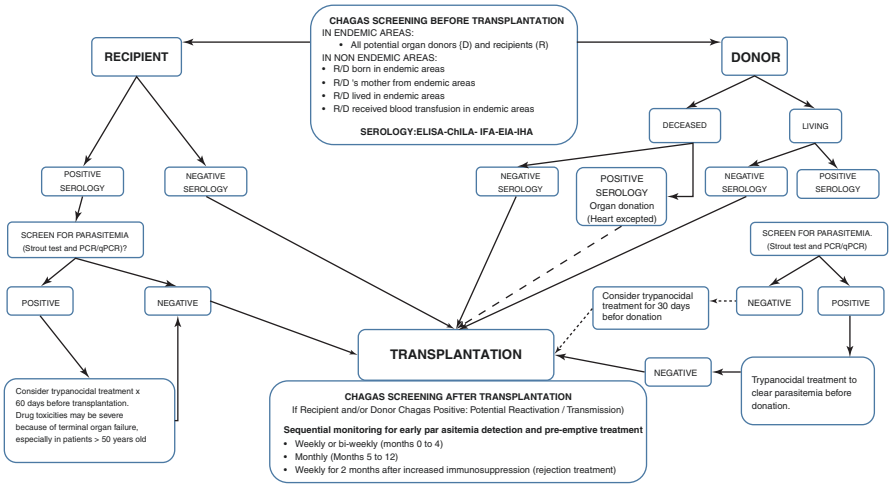

Fig. 15.2 Screening of transplant donors and recipients at risk for *T. cruzi* infection. Key: *R/D* recipient/donor, *ELISA* enzyme-linked immunosorbent assay, *ChILA* Chagas chemiluminescent immunoassay, *IFA* indirect fluorescent antibody, *EIA* enzyme immunoassay, *IHA* indirect hemagglutination

infection from positive donors was 0% (with prophylactic treatment with benznidazole) and 0–22% without prophylaxis [13, 15]. When transplant recipients are monitored for *T. cruzi* transmission from infected donors, treatment with benznidazole is highly effective, with no mortality attributable to Chagas disease. Therefore, in endemic countries (with appropriate informed consent), organs from infected deceased donors are considered acceptable (with exception of the heart) for infected recipients and for uninfected kidney recipients and for uninfected lung and liver recipients in emergency situations. It is recommended that infected living donors receive trypanocidal treatment for 30 days prior to donation to decrease the risk of transmission, and donation should take place immediately after treatment completion [13]. When transplantation is performed on a non-infected patient who resides in or who moves to an endemic area, the patient may be exposed to vector transmission, as has been reported in a few cases.

15.4 Pneumocystis

15.4.1 Introduction

Pneumocystis jirovecii is an important fungal etiologic agent of pneumonia in transplant recipients. The risk is highest in heart and heart-lung recipients (with incidence of up to 40% in the absence of prophylaxis) and lowest in kidney transplant recipients [18]. Infection in humans is likely transmitted by the airborne route and is usually acquired in childhood. Reactivation of dormant infection may occur with acquired immunosuppression. *Pneumocystis* outbreak reports in transplantation units suggest person-to-person transmission or a common environmental source of *Pneumocystis* [19]. The risk of *Pneumocystis* pneumonia (PCP) is related to the net state of immunosuppression of the patient and seems to be highest during the first 6–12 months after transplantation, but rejection, cytomegalovirus, and other immunomodulating infections may allow late infections to appear [20].

15.4.2 Clinical Presentation

Pneumocystis should be considered in the differential diagnosis of pneumonia in solid organ transplant recipients. In this setting, symptomatic progression often is acute or subacute and develops in few days, though progression over 1–2 weeks may also be observed. Dry cough, fever, and dyspnea out of proportion to physical findings are common, but co-infection may be present, changing the clinical presentation.

15.4.3 Diagnosis

Chest X-ray may be normal or reveal diffuse bilateral interstitial pulmonary infiltrates. Chest computed tomography may demonstrate disease not observed on plain

chest X-ray [18]. The etiological diagnosis of pneumonia in transplanted patients usually requires sampling from deep airways by bronchoalveolar lavage (BAL), although *P. jirovecii* may be detected in sputum and oral wash samples. The most sensitive staining method is with specific immunofluorescent (IF) monoclonal antibodies. When IF is not available, calcofluor white and Gomori methenamine silver are the most sensitive methods, although the microorganism can be observed with other stains (Gram-Weigert, Wright-Giemsa, modified Papanicolaou stains, or toluidine blue). PCR techniques of BAL fluid, induced sputum, or oral wash increase the diagnostic yield over conventional staining alone [18]. Quantitative assays may increase specificity, as false positives (asymptomatic carrying) may be observed with qualitative PCR. *P. jirovecii* may also be observed in transbronchial biopsies, which should be considered when performing bronchoscopy for diagnosis of pulmonary infiltrates. Measurement of plasma (1 → 3) β-D-glucan levels may aid in the diagnosis of PCP. However, this assay may be positive in other invasive fungal infections and lacks specificity for PCP.

15.4.4 Treatment

Trimethoprim-sulfamethoxazole (TMP-SMX) is the treatment of choice (Table 15.1). When treatment with TMP-SMX is not feasible (due to allergy or toxicities), intravenous pentamidine is an effective second-line agent. Pentamidine pancreatic toxicity is a potential concern when treating pancreas or islet cell transplant recipients. In severe disease (patients with hypoxemia, i.e., pAO2 < 70 mmHg on room air), adjunctive treatment with 40–60 mg of prednisone (or equivalent) is recommended along with antimicrobial therapy, ideally starting within the first 72 h of antimicrobial treatment. Steroids should be given for 5–7 days and tapered over the following 2–3 weeks. The recommended antimicrobial therapy duration is generally 21 days, particularly in those with severe disease. Echinocandins in combination with TMP-SMX or clindamycin have also been reported as salvage therapy in case reports.

15.4.5 Prevention

The risk of PCP is highest within the first 6 months after transplant. In most transplant centers, prophylaxis is routinely used during the first 6–12 months after transplantation. In patients with risk factors (heavy immunosuppression, cytomegalovirus infection, prior PCP), prophylaxis extension (even lifelong as in the case of HIV-infected transplant recipients) may be considered, as PCP has been described at any time after transplantation. TMP-SMX is the drug of choice for PCP prophylaxis [18]. Side effects of TMS-SMX that may occur are bone marrow toxicity (more common when other myelotoxic drugs are administered along) and cutaneous allergic manifestations, which can be severe (Stevens-Johnson syndrome, toxic epidermic necrolysis, and, less commonly, hepatitis, aseptic meningitis, interstitial nephritis, and hyperkalemia). In patients with glucose 6 phosphate dehydrogenase

(G6PD) deficiency, TMX-SMX may produce hemolysis [18]. Dapsone may be used as a second-line agent for PCP prophylaxis, whenever TMP-SMX use is not feasible. However, patients with severe allergy to TMP-SMX may present similar reactions to dapsone. Hemolytic anemia and methemoglobinemia may also occur with the use of dapsone, especially when there is G6PD deficiency [18]. Other alternatives for PCP prophylaxis are atovaquone [21] and inhaled or intravenous pentamidine [22, 23]. Prophylaxis failures have been described [18, 20]. There is a potential for airborne transmission from infected patients, suggested from reports of PCP outbreaks in transplantation units. Formal infection control policies could be considered for PCP patients [19].

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Part III

Management of Specific Syndromes

Pneumonia in Solid Organ Transplant Recipients

16

John-David Aubert and Jordi Carratalà

16.1 Definition and Epidemiology

The clinical definition of the pneumonia relies on the presence of a new chest infiltrate on a chest X-ray or a computed tomography (CT) scan, usually accompanied by acute symptoms such as cough, fever, sputum production, or chest pain [1]. The influx of inflammatory cells in the lung parenchyma is responsible for the alveolar or interstitial infiltrate on chest imaging. Pneumonia should be distinguished from bronchitis, in which the alveolar space is preserved and therefore is not associated with a radiological infiltrate. In some occasions, such as severe neutropenia or dehydration, radiological changes are minimal, particularly on CXR.

With the recent venue of metagenomic techniques, the concept of lung dysbiosis has emerged. Dysbiosis is defined as the overrepresentation of one bacterial phylum over the others, with a concomitant decrease in biodiversity. It should be noted that if pneumonia is usually associated with a lung dysbiosis, the reverse is not always true, with many dysbiotic states not corresponding to overt clinical pneumonia [2].

Pneumonia is one of the most common infections in solid organ transplant (SOT) recipients. Thoracic organ recipients are more frequently affected than abdominal organ recipients. The lung being in direct contact to the environment is particularly susceptible to pathogens carried in the atmosphere. Lung transplant recipients are especially prone to pneumonia, as the alveolar epithelium is damaged, the mucociliary clearance is impaired, and lymphatic clearance is limited [3]. Moreover, certain

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Table 16.1 Differential diagnosis

Diagnosis	Hint	Useful diagnosis test
Acute bronchitis	Absence of lung infiltrate	CRP, Pro-CT
Drug-induced pneumonitis	Medication history	(Blood eosinophilia)
Left heart failure	Patient's medical history Nocturnal dyspnea	BNP, echocardiography
Allergic pneumonitis	Exposure history	BAL cellular profile, allergen specific precipitin
Cancer	Recurrent "pneumonia" at the same location	–
Cryptogenic organizing pneumonia (COP)	Migrating lung infiltrate	BAL cellular profile
Inhalation of toxic	Patient's history	–

CRP C-reactive protein, *Pro-CT* pro-calcitonin, *BNP* brain natriuretic peptide, *BAL* bronchoalveolar lavage

diseases such as cystic fibrosis are characterized by high microorganism's load in the upper airways and the sinuses that lead to infection in the lower airways.

As immunosuppressive drugs predominantly inhibit T lymphocyte immune responses, opportunistic infections, including cytomegalovirus (CMV) and *Pneumocystis jirovecii* pneumonia, can occur. The broad use of prophylactic antimicrobials has reduced the frequency of these infections (with valganciclovir and trimethoprim-sulfamethoxazole (TMP-SMX), respectively). Other microorganisms under the control of cellular immunity are *Mycobacterium tuberculosis*, *Nocardia*, the herpes group viruses, and *Toxoplasma*. Humoral immunity may also be affected, particularly with the current use of drugs such as rituximab, and increase the risk of bacterial pneumonia. Finally, neutropenia is a common complication of both immunosuppressive drugs and anti-infectious agents (e.g., mycophenolate mofetil and valganciclovir) and may lead to bacterial and, less commonly, fungal infections such as aspergillosis or mucormycosis.

Extrapulmonary symptoms and clinical signs should be systematically looked for and may be suggestive of a specific diagnosis. In addition, the transplant physician should be aware of (1) the past 6 months' history of the patient's microbiological studies, (2) the patient's travel and occupational history, and (3) any additional immunosuppressive drugs administered in addition to the standard regimen. As not all chest infiltrates are caused by pneumonia, alternate diagnosis should be considered, especially in the case of unsatisfactory response to therapy (Table 16.1).

Diagnostic studies are essential for determining the cause of pneumonia in transplant patients. Such diagnostic studies may require specialized testing and invasive procedures (see Table 16.2).

16.2 Role of Chest Imaging in the Diagnosis

Chest imaging is central to the clinical diagnosis of pneumonia. The increasing availability of low-dose, thin-slice chest CT makes it an essential part of the initial diagnosis (Table 16.3). The chest CT is superior to plain chest X-ray for detecting

Table 16.2 Diagnostic strategies

Diagnostic procedure	Test types	Clinical examples
Sputum (a) Spontaneous (b) Induced (NaCl 3%)	Gram stain and culture Direct fluorescent antibody PCR	Bacterial pneumonia, Gram-positive or Gram-negative *Legionella* *Nocardia* *Mycobacterium tuberculosis*
Nasopharyngeal swab	PCR (single or multiplex)	Community-acquired respiratory virus
Bronchoscopy: bronchial aspirates	Ziehl-Neelsen stain PCR	*Mycobacterium tuberculosis* Community-acquired respiratory virus
Bronchoscopy: bronchoalveolar lavage	Gram/specific stains and culture Direct fluorescent antibody PCR	*Pneumocystis jirovecii*, bacterial pneumonia, *Aspergillus,* cytomegalovirus, community-acquired respiratory virus
Bronchoscopy: transbronchial biopsy	Culture PCR	Miliary tuberculosis
Blood sample	Culture	*Streptococcus pneumoniae*
Urine	Soluble antigen testing	*Streptococcus pneumoniae* *Legionella pneumophila* serogroup 1
Fungal serum markers	(1-3)-β-D-glucan, galactomannan, cryptococcal antigen	*Aspergillus*, *Cryptococcus*

Yield of (1-3)-β-D-glucan and galactomannan is reduced in SOT recipients compared to other populations, particularly if mold-active antifungal therapy or prophylaxis is being used for the patient

Table 16.3 Suggestive CT imaging patterns

Radiological pattern	Possible etiology
Alveolar consolidation. Air bronchogram	Bacterial pneumonia
Diffuse ground-glass opacities	Viral pneumonia. *Pneumocystis jirovecii*
Abscesses, cavitation	Anaerobic bacteria. *Staphylococcus aureus*. *Pseudomonas* spp.
Miliary pattern	Miliary tuberculosis, *herpes zoster*, fungi
Nodules with peripheral ground glass (halo sign)	Filamentous fungi

less dense infiltrates such as ground-glass opacities, for the localization of the lesions and for the detections of complications (pleural effusion, abscesses, cavitation). While specific radiologic patterns may suggest certain pathogens [4, 5], imaging is not a surrogate for microbiological diagnosis: classical patterns are frequent in radiological reviews and in textbooks, but atypical presentations are frequent in the real life. Pathogen-directed treatment should never be based on imaging alone. A proposed diagnostic strategy for evaluation on a patient with suspected pneumonia is outlined in Fig. 16.1; new clinical or laboratory testing should be considered as they may not be captured in this figure.

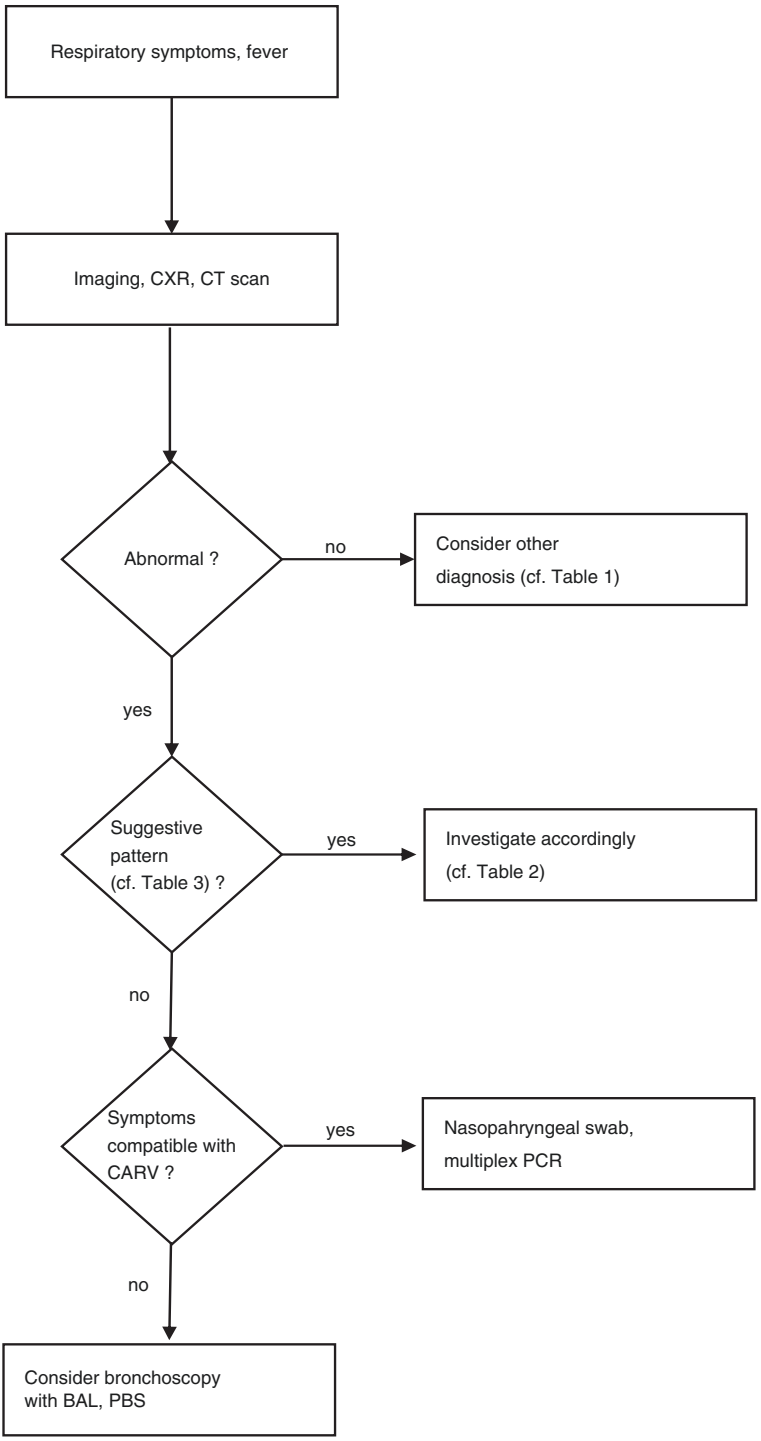

Fig. 16.1 Diagnostic algorithm for a suspected pneumonia in SOT. *CARV* community-acquired respiratory virus, *BAL* bronchoalveolar lavage, *PBS* protected brush sampling

16.3 Prevention

Ventilation-associated pneumonia (VAP) and hospital-acquired pneumonia (HAP) in non-ventilated patients are significant perioperative complications of SOT. Strategies to prevent VAP should include avoiding intubation whenever possible, minimize sedation, maintain and improve physical conditioning, minimize pooling of secretions above the endotracheal tube cuff, elevate the head of the bed (30–45°), and maintain ventilation circuits [6]. Oral care has been associated with a decrease in HAP rate [7].

Streptococcus pneumoniae is a leading cause of community-acquired pneumonia (CAP) in SOT recipients and is associated with significant morbidity and mortality. Current guidelines recommend the use of pneumococcal vaccine in SOT candidates and recipients. Priority should be given to the use of the 13-valent pneumococcal conjugate vaccine (PCV13). For non-vaccinated patients, the PCV13 should be given followed by a dose of PPSV23 at least 8 weeks later; for patients who have previously received one or more doses of PPSV23, a single dose of PCV13 should be given 1 or more years after the last PPSV23 dose was given. It should be noted, however, that these recommendations are not based on clinical evidence of superiority of one strategy vs. other. Some countries, like Switzerland, recommend two doses of PCV13, because of the theoretical risk of reduced response with PPSV23 [8].

SOT recipients are at greater risk than the general population for complications and mortality due to influenza infection. Pulmonary complications of influenza are most common and include primary influenza and secondary bacterial infection [9]. Less often influenza infection can be complicated by the development of invasive aspergillosis [10]. Infection with influenza virus can occur at any time after transplantation, and it appears to be more severe in the early posttransplant period (<3 months). Seasonal inactivated influenza vaccination is strongly recommended every year in SOT recipients, their close contacts, and healthcare workers caring for transplant recipients [10]. Influenza vaccine can be given after the first month after transplant. The live attenuated vaccine is not recommended for transplant recipients. Pre-exposure and postexposure antiviral chemoprophylaxis should not routinely be used in SOT recipients and might be only reserved for selected cases such as patients who are severely immunosuppressed and at high risk for influenza-related complications [11]. Postexposure chemoprophylaxis should be given for 10 days after the influenza contact, although for most patients monitoring for development of symptoms and expedited treatment is preferred.

Tuberculosis (TB) remains a significant opportunistic infection in SOT recipients. Transplant candidates should routinely be screened for TB [12]. Those with positive screening tests, radiologic evidence of current or past disease, or significant exposure histories should be evaluated and treated; more detail is available in the chapter on TB.

The incidence of CMV pneumonia has been reduced by routine antiviral prophylaxis. Comprehensive and specific recommendations for prevention of CMV infection according to serostatus and type of transplant have recently been published elsewhere and in the CMV chapter of this book [13].

The risk of developing *Pneumocystis jirovecii* pneumonia (PCP) is particularly high in the first 6 months after transplantation and during periods of increased immunosuppression; more recent studies have documented that most cases of PCP are now occurring late posttransplant and should remain in the differential diagnosis [14]. Routine anti-*Pneumocystis* prophylaxis should be used in centers with an incidence of at least 3–5% among SOT recipients. In general, prophylaxis should be administered for all SOT patients for at least 6–12 months posttransplant. Nevertheless, longer durations should be considered for lung and small bowel transplant patients, as well as any recipient with a history of previous PCP or chronic CMV disease, in which lifelong prophylaxis may be indicated [14]. Prophylaxis should be given to patients with increasing immunosuppression in the setting of graft rejection, recurrent CMV infection, prolonged courses of corticosteroid therapy (e.g., >20 mg daily of prednisone for at least 2 weeks), or prolonged neutropenia. TMP-SMX remains the drug of choice for PCP prophylaxis and can be given at 80 mg TMP/400 mg SMX or 160 mg TMP/800 mg SMX po (single or double strength) daily or three times a week. TMP-SMX can offer also some protection against *Toxoplasma* and *Nocardia*. Alternative prophylaxis regimens for sulfa-allergic patients include dapsone (50–100 mg po qd), atovaquone (1500 mg po qd, as single dose), aerosolized pentamidine (300 mg q 3–4 weeks), or clindamycin and pyrimethamine (up to 300 mg clindamycin po qd with 15 mg of pyrimethamine po qd).

Invasive aspergillosis is a life-threatening infection in SOT recipients. Invasive pulmonary aspergillosis is the most common clinical form. Aspergillosis can also cause invasive tracheobronchitis in single, ulcerative, and nodular forms in lung transplant recipients and may affect the bronchial anastomosis. Lung transplant patients with pretransplant *Aspergillus* colonization or posttransplant *Aspergillus* colonization within a year of transplant should receive prophylaxis [15]. Lung recipients with more than one risk factor for IA including induction with alemtuzumab or thymoglobulin, single lung transplant *Aspergillus* colonization, rejection and augmented immunosuppression, and acquired hypogammaglobulinemia (IgG <400 mg/dl) should be given antifungal prophylaxis. Recommended regimens are inhaled Abelcet (50 mg every 2 days for 2 weeks and then once per week for at least 13 weeks) or inhaled AmBisome (25 mg 3 times per week for 2 months, followed by weekly administration for 6 months and twice per month afterward) and/or an oral regimen (voriconazole (200 mg bid), itraconazole (200 mg bid), posaconazole (300 mg qd), or isavuconazonium (372 mg qd) for 4 months or longer). Liver recipients with retransplantation, renal failure, or reoperation should be given prophylaxis with fluconazole 400 mg daily (adjusted to renal function), an echinocandin, or a lipid formulation of amphotericin B (3–5 mg/kg/day) for 4 weeks posttransplant. Finally, heart recipients with isolation of *Aspergillus* spp. in respiratory tract

culture, reoperation, CMV disease, or posttransplant hemodialysis should receive itraconazole (200 mg bid) or voriconazole (200 mg bid) during 50–150 days. While there is less published data, some centers are utilizing new azoles (posaconazole or isavuconazole) for prophylaxis with coverage of *Aspergillus*.

16.4 Treatment

SOT recipients with suspected VAP/HAP should receive a prompt empirical antibiotic therapy. Whenever possible it is important to accurately target antibiotic therapy and then de-escalate antibiotics based upon respiratory and blood culture results. Empiric treatment regimens should be selected according to the local epidemiology of pathogens associated with VAP/HAP and their antimicrobial susceptibilities. In general, in SOT recipients with suspected VAP/HAP, it is recommended to include coverage for *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and other Gram-negative bacilli in all empiric regimens. An agent active against methicillin-resistant *S. aureus* (MRSA) such as vancomycin or linezolid should be included in the empiric treatment for recipients treated in units where >10 to 20% of *S. aureus* isolates are methicillin-resistant [16]. For SOT recipients with VAP due to Gram-negative bacilli that are susceptible to only aminoglycosides or polymyxins, both inhaled and systemic antibiotics may be used.

SOT recipients presenting with CAP should receive antibiotic coverage against *S. pneumoniae* and *H. influenzae*; during period when influenza circulation in the community is ongoing, influenza should be considered and empirically treated. Empirical treatment should include a ß-lactam (ceftriaxone or amoxicillin-clavulanate) with or without a macrolide or a respiratory fluoroquinolone (levofloxacin or moxifloxacin). In those patients with risk factors for *Pseudomonas* and/or presenting with shock, the ß-lactam component of the empirical treatment should be an antipseudomonal antibiotic (i.e., cefepime or meropenem). Levofloxacin should be given for SOT recipients with pneumonia and a urine test result positive for *Legionella* [17].

Influenza should be considered in the differential diagnosis of every case of pneumonia occurring in SOT recipients during the influenza season, especially in patients with flu-like symptoms and bilateral pulmonary infiltrates. Early treatment with oral oseltamivir (75 mg bid) should be given to SOT recipients with pneumonia, as the presence of this complication is an important factor for poor outcome [10]. Therapy should be started while waiting for confirmation of influenza to avoid delays in therapy which have been shown to result in worse outcomes [18].

Antimicrobial treatment of the most frequent opportunistic infections that can cause pneumonia in SOT recipients is detailed in Table 16.4.

Table 16.4 Antimicrobial treatments of the main opportunistic organisms causing pneumonia in SOT recipients

Organism	Treatment
Mycobacterium tuberculosis	Regimens including rifamycins A three-drug standard regimen, including rifampicin or rifabutin for at least 9 months Regimens that do not include rifamycins Isoniazid and ethambutol for 18 months with the addition of pyrazinamide for the first 2 months. Fluoroquinolones can be used for rifampin sparing or as a part of four-drug regimen for severe disease
Cytomegalovirus	Intravenous ganciclovir (5 mg/kg/12 h)
Nocardia	Trimethoprim-sulfamethoxazole (TMP-SMX) at a dose of 15 mg/kg in 3–4 divided doses, either iv or oral, during 6–12 months Imipenem plus amikacin or TMP-SMX can be considered for serious pulmonary infections
Pneumocystis jirovecii	TMP-SMX is the drug of choice: 15–20 mg/kg/day of the component given in divided doses every 6–8 h; for milder disease, two double-strength tablets can be given po bid or tid Main second-line alternative options include pentamidine isethionate, atovaquone, and primaquine plus clindamycin
Aspergillus	The drug of choice for invasive pulmonary aspergillosis is voriconazole[a] 6 mg/kg/iv every 12 h for 1 day, followed by 4 mg/kg/iv every 12 h; oral dosage is 200 mg/every 12 h Alternative agents include lipid formulations of amphotericin B, caspofungin, micafungin, posaconazole, and itraconazole

[a]Monitoring of plasma levels of voriconazole, hepatic aminotransferase levels, and calcineurin agent levels is recommended

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Management of CNS Infections

17

Patricia Muñoz and Tina Stosor

17.1 Definitions and Epidemiology

Neurologic events are common after solid organ transplantation (SOT), occurring in 40% of transplant recipients, with variable presentations including encephalopathy, delirium, focal deficits, headaches, and seizures [1–5]. Among the myriad metabolic, cerebrovascular, and systemic processes that lead to neurologic dysfunction, infections account for 20–25% of such events [2, 3, 5]. Central nervous system (CNS) infections occur in 5–10% of SOT recipients, but the overall incidence is influenced by patient population, organ transplanted, and transplant center-specific practices [2, 4].

The timing of infection after SOT provides important context for diagnosing CNS infections. Following SOT, risk intervals for infections are categorized into three time periods, although this timeline is influenced and altered by anti-infective prophylaxis practices, intensity of immunosuppression, and development of allograft rejection [6]. In the first month following transplantation, CNS infections are rare and most often attributed to herpes simplex virus (HSV) and *Aspergillus* or infection transmitted by the organ donor [1, 3, 5, 6]. Notable donor-transmitted CNS pathogens include West Nile virus (WNV) [7], lymphocytic choriomeningitis virus (LCMV) [8], rabies virus [9, 10], *Cryptococcus* [11], and *Balamuthia* [12–14]. The classic opportunistic infections (OI), occurring between 2 and 6 months posttransplant and coinciding with the maximal effects of immunosuppression, result from reactivation of latent infections harbored by the recipient, donor

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transmission events, or community acquisition. Typical pathogens during this period include cytomegalovirus (CMV), *Toxoplasma*, and *Mycobacterium tuberculosis* (MTb). In the late posttransplant period, OI risk diminishes, but infections with *Listeria*, *Nocardia*, and the endemic mycoses may still occur.

Patients with CNS infections have typical syndromic presentations, including meningitis, encephalitis, and brain abscess/parenchymal disease, although considerable overlap exists. Meningitis is characterized by meningeal inflammation with CSF pleocytosis and manifests with altered sensorium, fever, headache, and neck stiffness. However, these symptoms may be blunted or absent in immunocompromised patients. Encephalitis is an inflammatory process involving brain tissue and presents with fever, seizure, confusion, encephalopathy, and bizarre behavior. Patients with parenchymal processes, including brain abscesses, cerebritis, and leukoencephalopathy, present with fever, headache, seizures, and focal neurologic deficits [15].

17.2 Pathogens of Significance in Transplant Patients

17.2.1 Viral Pathogens

The central or peripheral nervous system can be affected by various viral pathogens that will cause infections of very different severity, prevalence, and timing.

17.2.1.1 Herpesviruses

Herpes simplex virus may be responsible for encephalitis and meningitis after SOT, but the incidence is low and like that of the non-transplanted population [5]. The diagnosis of CNS involvement by HSV is usually based on the detection of the viral genome by PCR in a CSF with white blood cell count (WBC) of at least 5 cells/mm^3 [16]. The treatment of choice is intravenous acyclovir.

Varicella zoster virus (VZV) causing herpes zoster is a common cause of neurological problems in the transplant population. In cardiac transplantation, peripheral herpes zoster accounted for 17/78 infectious complications (median, 268 days after heart transplantation) [3]. It is estimated that 8–11% of SOT recipients will experience a zoster outbreak during the first 4 years following transplant [17]. Primary VZV infection, however, is rare in transplanted adults but can have serious consequences as a result of disseminated infection. Some risk factors include older age and heart and lung transplantation. Diagnosis is easily identified clinically by its cutaneous manifestations and can be confirmed with polymerase chain reaction (PCR), direct fluorescent assays (DFA), and viral culture. Treatment includes acyclovir, valacyclovir, or famciclovir.

More rarely, VZV can cause meningitis, encephalitis, or myelitis, even in the absence of skin lesions [18]. In this case, it is necessary to perform VZV PCR on CSF to achieve a diagnosis, and the chosen treatment is intravenous acyclovir.

Epstein-Barr virus (EBV) is a major pathogen in SOT recipients, and clinical manifestations range from asymptomatic viremia to aggressive forms of

posttransplant lymphoproliferative disorders (PTLD). EBV infection rarely causes neurological complications, though cases of encephalitis and myelitis without PTLD have been reported, mainly due to EBV reactivation and, more rarely, primary infection [19, 20]. Time from transplant to infection onset ranged from months to 10 years. Manifestations are usually subacute and include the typical findings in patients with encephalitis such as fever, headache, altered consciousness, visual symptoms, ataxia, and seizures. Other manifestations of EBV include meningitis, polyradiculomyelitis, and cranial and peripheral neuropathies.

Magnetic resonance (MR) imaging may show high intensity lesions and edema or also be unremarkable. Diagnosis is based on CSF findings and viral detection by plasma PCR. Electroencephalogram (EEG) may show diffuse encephalopathy. Treatment includes reduction of the immunosuppression along with IV ganciclovir and immunoglobulins. Monoclonal antibody therapies, directed toward infected B lymphocytes, have also been used. Immunosuppression is reduced if severe EBV infection is diagnosed.

17.2.1.2 JC Virus

JC polyomavirus (JC PyV) causes progressive multifocal leukoencephalopathy (PML) which is characterized by multiple lesions in the CNS white matter and usually late appearance after transplantation (median time 27 months) [21]. The incidence of PML among heart and/or lung transplant recipients at a single institution was 1.24 per 1000 posttransplantation person-years, comparable to that reported in patients who are treated with natalizumab. Clinical manifestations are varied and may include behavior alterations, clumsiness, progressive weakness, and visual, speech, and personality changes. Cases following rituximab-treated acute antibody-mediated rejection have been reported [22]. This disease can be difficult to recognize, with vascular disease often clinically suspected initially. The diagnosis is established by detecting white matter lesions on brain MR and JC PyV PCR in the CSF or tissue. The mortality rate is 30–84%, and most survivors have very significant sequela [21]. Reduction of immunosuppression may lead to immune reconstitution inflammatory syndrome (IRIS), with further neurological deterioration.

17.2.1.3 Other Viruses

Other viruses that may affect the CNS of SOT recipients include human herpesvirus-6 (HHV-6), WNV, and, less commonly, rabies virus and LCMV.

Human herpes virus-6 may cause encephalitis and myelitis, but the incidence of these complications in SOT recipients is very low [23, 24]. The diagnosis is established with PCR detection of the virus, and management includes antiviral therapy with ganciclovir, foscarnet, or cidofovir and reduction in immunosuppression [23, 25].

Several clusters of rabies virus infection after SOT have been described [9, 10, 26]. The disease was not recognized in the donor premortem, resulting in viral transmission to various recipients of organs and tissues. In cases of donor infection caused by bat or dog bite, the onset of symptoms occurred within the first 6 weeks following transplant, and mortality was almost uniform, except for one patient who was previously vaccinated against rabies. However, in a case of donor-transmitted

raccoon-variant rabies, the onset of clinically apparent disease in the recipient was much later in the posttransplant course, and, other than the index case, the other organ recipients from the same donor survived after administration of postexposure prophylaxis. Clinical manifestations usually start with a nonspecific prodrome followed by confusion, paresthesias, insomnia, agitation, paresis, spasm of swallowing muscles, and coma.

Lymphocytic choriomeningitis virus is an *Arenaviridae* that has been described primarily in people with rodent contact. After SOT, LCMV may cause aseptic meningitis and severe meningoencephalitis, several of which have occurred in donor-derived clusters [8]. Donors often died from neurological conditions without suspicion of infection (subdural hemorrhage, hemorrhagic stroke) and without known exposure to rodents [26]. The diagnosis could be reached by means of pathologic investigation and immunohistochemical staining in recipient samples or after cell culture and electron microscopy examination of the donor specimens.

West Nile virus is a flavivirus responsible for the largest epidemics of arboviral encephalitis in the Western Hemisphere. It is acquired through the bite of infected mosquitoes and birds, acting as amplifying hosts. Posttransplant, the infection can also be transmitted through a donor with naturally acquired infection or infected blood products [12].

Infections can occur either in isolation or as clusters in several recipients of organs from a single donor, making its recognition easier [7]. The clinical presentation is particularly severe in SOT recipients, with a high frequency of neuroinvasive disease and associated mortality. Symptoms include febrile illness, meningitis, encephalitis, and poliomyelitis-like limb paralysis. Blood screening through pooled donation nucleic acid testing (NAT) or with triggered individual testing was put into place in some countries to avoid donor transmissions. However, outbreaks from donors with negative viremia but with WNV-specific IgM and IgG have been described [26]. These cases suggest that transmission may be due to persistence of the virus in the transplanted organ even after clearance of viremia in the donor. The diagnosis of WNV infection is made by the determination of viral load in blood and CSF. Care of WNV-infected recipients is largely supportive; there are no approved antiviral therapies for this infection.

17.2.2 Bacterial Pathogens

The most common causative pathogens of bacterial meningitis in SOT recipients are *Streptococcus pneumoniae* and *Listeria monocytogenes*.

17.2.2.1 *Listeria monocytogenes*

L. monocytogenes is a gram-positive, catalase-positive bacillus, which is mainly acquired from contaminated foods, such as fresh cheeses, undercooked meat, or prepared foods that are kept cold. In a recent series in which all cases of listeriosis detected in an institution with important transplanting activity during 22 years were analyzed, the incidence increased significantly in the second period of the study,

especially in elderly patients (from 4.8 ± 2.92/106 inhabitants to 10.7 ± 4.3/106 inhabitants; $P = 0.001$) [27]. However, a reduction in listeriosis was observed in SOT recipients (21.9% vs 6.3%; $P = 0.037$).

Listeriosis in SOT recipients is a late infection (mean of 29 months after transplantation in one series), when patients are no longer receiving cotrimoxazole prophylaxis, although earlier cases have been reported [28]. The most common clinical presentations in this population are primary bacteremia, disseminated infection, and meningitis [28].

The diagnostic evaluation includes CSF and blood cultures and CNS imaging. It is recommended to exclude CNS involvement in all patients with listeriosis. In cases of posttransplant listeriosis, empirical anti-infective regimens frequently are inappropriate (41.7% in one series). Ampicillin is the preferred drug, and there is controversy regarding the need of combination therapy (with gentamicin or cotrimoxazole) since this increases toxicity with no clear impact on the outcome. Therapy is usually maintained for 3 weeks. Mortality of *Listeria* meningitis in SOT may reach 50% [27, 28].

17.2.2.2 *Nocardia* Species

Nocardia is a gram-positive, branched bacillus that is acquired either by inhalation or by percutaneous inoculation after blunt trauma during outdoor activities, e.g., with branches. The incidence of nocardiosis is low in SOT recipients, ranging from 0.1% to 3.5% [29]. In a recent series, SOT accounted for 18.9% of nocardiosis in a general hospital [30]. Incidence is higher after lung and cardiac transplantation than in other organ transplant groups [29].

Nocardiosis is usually a late infection, with the median presentation being 120 days (range, 28–1497 days) posttransplant. However, the infection must be suspected at any time, especially after increased immunosuppression, including high-dose steroids, alemtuzumab, or antilymphocyte globulin.

The most frequent form of presentation is subacute pulmonary involvement (>85%), appearing as nodules or even masses in a paucisymptomatic patient. Skin and subcutaneous tissues are frequently involved, and nodules or even lymphocutaneous syndromes may occur. Neurological involvement is described in approximately 5% of the cases, and the most frequent form is appearance of parenchymal abscesses with neurological focality. CNS involvement should be excluded in all patients with nocardiosis.

If there is no simultaneous pulmonary involvement, an invasive maneuver is usually necessary to obtain a sample of the CNS lesions, since blood cultures are usually negative and there are no serological techniques. The isolation of *Nocardia* from a respiratory sample does not establish the diagnosis itself, as there are colonized patients, but it must be investigated very thoroughly when recovered from a transplant patient. The visualization of fine, highly branched gram-positive bacilli that are stained with Gram or modified acid-fast (Kinyoun) stain is very suggestive. The culture should be incubated longer than usual, as the average growing time is 3–5 days. Identification at the species level is currently carried out by molecular biology, and the species most involved in human pathology are *Nocardia*

cyriacigeorgica, *Nocardia farcinica*, and *Nocardia otitidiscaviarum* [30]. Some of these species show resistance to cotrimoxazole and even to carbapenems, so species-level identification is warranted. Antimicrobial susceptibility testing is particularly important in patients with disseminated disease, with poor response to treatment, or with species with a higher level of resistance (*N. farcinica*, *N. otitidiscaviarum*).

Treatment of CNS nocardiosis involves an initial phase of parenteral treatment with a carbapenem (particularly imipenem), alone or in combination with cotrimoxazole and even with amikacin. Other drugs that may be used as second line include linezolid, ceftriaxone or cefotaxime, or minocycline. Surgical drainage of the CNS lesions is usually not necessary. Length of treatment is usually prolonged (9–12 months for CNS nocardiosis) but must be adapted to the radiological evolution. Oral maintenance drug is usually cotrimoxazole. Cures have also been described with shorter treatment cycles, so this must be individualized. One-year mortality, in a recent series including 30 cases of CNS nocardiosis, was 16%, and risk factors for poor outcome included history of tumor, invasive fungal infection, donor age, and absence of acute organ rejection in the year before nocardiosis [31]. Cotrimoxazole prophylaxis is effective in a significant percentage of cases, but, in our series, 42.9% of SOT recipients with nocardiosis were receiving low-dose cotrimoxazole prophylaxis at the time of diagnosis [30]. The role of secondary prophylaxis is not well established.

17.2.2.3 *Mycobacterium tuberculosis*

The incidence of tuberculosis in SOT patients is at least 20 times more frequent than in the general population, and approximately 25% of patients present with disseminated tuberculosis. Nevertheless, CNS involvement is very rare and may appear with or without simultaneous involvement in other parenchyma [3, 32–35]. It may present in the form of subacute meningitis, tuberculoma, CNS abscess, or other manifestation [35]. Although most cases are due to reactivation of latent disease, donor-transmitted cases and even nosocomial infections have been reported.

Clinical manifestations may be subtle and include subacute lymphocytic meningitis, paralysis of the cranial (ocular) nerves, and focal ischemia. Imaging methods may show meningitis, tuberculomas, basilar arachnoiditis, cerebral infarction, or hydrocephalus. A lumbar puncture should be performed in all SOT patients with MTb if there is any neurological manifestation. Laboratory tests in the CSF must include cytology, glucose, protein, adenosine deaminase, culture, and PCR.

Empirical therapy should be considered in unstable patients or in patients with suspected MTb (compatible signs or symptoms plus risk factors such as residence or recent travel to a country with high endemic rates, contact with tuberculosis patients, history of alcoholism or intravenous drug use, HIV positive, etc.) [3, 34]. In these situations, antituberculous treatment should be initiated and withdrawn later if TB is excluded. In patients with proven CNS involvement, a 4-drug regimen (isoniazid, pyrazinamide, ethambutol, and rifabutin or quinolone) is recommended. Treatment is normally maintained for 7–10 months. If rifampin or rifabutin is used,

immunosuppressive levels should be checked and the dose of cyclosporine A or tacrolimus increased 3–5 times. Hepatotoxicity is also a risk, especially in liver transplant recipients. Finally, it is important to note that the risk of inflammatory reconstitution syndrome (IRIS), characterized by a paradoxical reaction or worsening of fever, cough, shortness of breath, or other tuberculosis-related symptoms, may occur after treatment initiation with concomitant reduction of immunosuppression.

17.2.3 Fungal Pathogens

Aspergillus and *Cryptococcus* are the most important causes of brain abscess and meningoencephalitis, respectively, after SOT [3, 5, 36]. *Candida* species are now infrequent CNS pathogens [36]. In the highly immunosuppressed, emerging pathogens, including *Scedosporium* spp./*Lomentospora prolificans* and *Cladophialophora bantiana*, are occasional causes of brain abscess [36–38]. Recently, the microsporidian species, *Encephalitozoon cuniculi*, was implicated in a cluster of donor-transmitted encephalitis [39].

17.2.3.1 *Candida* Species

Although candidiasis is the leading cause of invasive fungal infections after SOT, *Candida* rarely causes CNS infection in the most recent era. *Candida* species disseminate to the CNS in the setting of (central line-associated) candidemia and, thus, are most often an early complication of transplant. Infection manifests as brain microabscesses, abscesses, mycotic aneurysms, or meningitis [2, 40]. The treatment of choice is liposomal amphotericin B (L-AmB) with or without flucytosine, followed by step-down therapy with fluconazole [41]. Central line removal is essential for control of infection.

17.2.3.2 *Cryptococcus* Species

Cryptococci are leading fungal pathogens after SOT. These ubiquitous yeasts are acquired by inhalation, result in respiratory tract infection, and have a notorious predilection for dissemination to the CNS. In point of fact, CNS disease complicates up to 60% of posttransplant cryptococcal infections. Cryptococcosis is most often a late complication of SOT, with a mean onset of 28 months posttransplantation [42], with cases occurring in the first month following SOT representing either reactivation of latent host disease or donor transmission events [11, 12]. The most common CNS manifestation is subacute or chronic meningitis with elevated intracranial pressure; intracerebral cryptococcomas may also occur. Presenting symptoms include fevers, night sweats, weight loss, headaches, cranial neuropathies, impaired sensorium, nausea, and vomiting [42].

Diagnostic evaluation includes brain imaging for leptomeningeal enhancement, mass lesions, hydrocephalus, leptomeningeal enhancement, and cerebral edema, although immunosuppression may have attenuating effects on the latter findings [43]. Lumbar puncture and CSF analysis demonstrate elevated opening pressure,

variable CSF mononuclear pleocytosis, elevated protein, and low glucose [42]. Rapid antigen detection in CSF and serum and isolation of the pathogen in CSF culture establish the diagnosis.

Cryptococcal meningitis therapy includes an induction phase with L-AmB plus flucytosine followed by consolidation and maintenance therapy with fluconazole [44]. To optimize outcomes, it is critically important for clinicians to recognize and aggressively manage elevated intracranial pressure with serial lumbar punctures and drainage of CSF and lumbar drains or ventriculoperitoneal shunts in more refractory cases [44]. Judicious reduction of immunosuppression is desirable to control infection, with corticosteroids reduced in preference to calcineurin inhibitors which have known anti-cryptococcal activity [42, 44]. Drastic reductions in immunosuppressive therapy can precipitate an immune reconstitution inflammatory syndrome with exacerbation or recrudescence of symptoms [44, 45]. The post-SOT mortality ranges from 30% to 50% [42].

If cryptococcomas are present, longer durations of therapy are required, and corticosteroids are administered for the surrounding edema. Surgical intervention is reserved for cryptococcomas >3 cm and those causing mass effect [44].

17.2.3.3 *Aspergillus* Species

Aspergillus species are the most common cause of fungal brain abscess in organ recipients; less common CNS presentations include meningitis, rhinocerebral infection, and mycotic aneurysm [36]. Presenting features include fever, alterations in mental status, seizures, and focal deficits. Other symptoms and signs, such as headache and meningismus, are less common [36, 46, 47]. MRI may demonstrate ring-enhancing lesions, cerebral infarction, hemorrhage, or mycotic aneurysms [43]. Definitive diagnosis requires histopathologic evidence and culture isolation of *Aspergillus*, although this approach is not without risk and may not be feasible in patients with coagulopathy or thrombocytopenia. Because CNS disease occurs most often in the setting of disseminated infection, an established diagnosis of invasive pulmonary aspergillosis in combination with typical CNS imaging findings supports diagnosis of cerebral involvement. Serologic testing methods for measuring galactomannan antigen or 1,3-beta-d-glucan further support the [48]. CSF examination may show an elevated protein level but is not diagnostic; however, galactomannan antigen or molecular detection assays of CSF may have some utility. In recent studies, the sensitivity and specificity of PCR-based detection methods range from 75% to 100% and 93%, respectively [48–50].

First-line pharmacologic therapy for aspergillosis is voriconazole, with lipid formulations of amphotericin B (LF-AmB) reserved for salvage therapy [48, 51]. Data supporting the use of combination antifungal therapy are limited [48]. Clinicians must navigate clinically significant drug interactions between voriconazole and calcineurin inhibitors and also some anti-epileptic medications via inhibition of cytochrome P450 enzymes. Surgical resection of aspergillomas is associated with improved outcomes [47, 52]. Reduction or withdrawal of immunosuppression for control of infection is also strongly recommended. Mortality from posttransplant

CNS aspergillosis approaches 100% [46], although improved outcomes, with survival rates of up to 27%, have been achieved with voriconazole [52].

17.2.3.4 Mucorales Species

The incidence of mucormycosis after SOT has increased, and this infectious syndrome now accounts for 2% of invasive fungal infections following SOT [53, 54]. The most commonly implicated pathogens are *Rhizopus*, *Mucor*, *Rhizomucor*, *Cunninghamella*, and *Lichtheimia* species [53, 54]. Re-transplantation, treatment of allograft rejection, corticosteroid therapy, diabetes mellitus, renal failure, and iron overload increase the risk of mucormycosis after SOT, while tacrolimus appears protective over other immunosuppressive agents. The highest frequency of infections is observed in kidney and liver recipients [53–55]. The mean onset of infection occurs 312 days posttransplant.

Once acquired through inhalation of fungal spores, mucormycosis is a rapidly progressive, angioinvasive process that results in extensive tissue necrosis and thrombosis. Infection of the CNS occurs primarily through direct extension of rhinosinusitis. Hallmark features include fever, headaches, unilateral facial pain, nasal and sinus congestion, impaired vision, periorbital swelling, proptosis, and ophthalmoplegia. Necrotic palatal, nasal, or facial ulcer is present in up to 50% of patients. With extension into the brain, patients exhibit lethargy, cranial nerve palsies, internal carotid artery thrombosis with stroke, and seizures. Alternatively, mucormycosis can occur as isolated CNS disease or arise after dissemination from the lung [56].

The diagnosis of mucormycosis is based on clinical, imaging, histopathologic, and microbiologic findings. MR imaging may show cavernous sinus invasion or thrombosis, internal carotid artery thrombosis, intracerebral abscesses, or cavernous or sagittal sinus thrombosis [43]. The histopathologic diagnosis is established by identification of necrosis with tissue, vascular and perineural, invasion by thin-walled, non-septated, irregularly branching hyphae. Fungal isolation in culture and identification with antifungal susceptibility testing can inform salvage and long-term azole treatment choice. Suspected mucormycosis requires emergent intervention with repeated surgical debridement, antifungal therapy, reversal of immunosuppression, and correction of hyperglycemia. L-AmB is the treatment of choice, sometimes in combination with an echinocandin. Posaconazole and isavuconazole are salvage options, although many isolates exhibit high isavuconazole MICs [54]. Overall prognosis of CNS mucormycosis is dismal, and mortality approaches 100%.

17.2.3.5 Dimorphic Fungi

Endemic mycoses such as *Histoplasma capsulatum* and *Blastomyces dermatidis* are occasionally implicated as CNS pathogens after SOT, but CNS involvement is more common with disseminated coccidioidomycosis [57]. Infection onset occurs throughout the posttransplant period depending on the specific pathogen and whether the infection represents a donor transmission event, reactivation of latent

disease, or new exposure. Chronic basilar meningitis is the most common presentation, although focal cerebritis/brain abscesses and granulomatous vasculitis with subarachnoid hemorrhage have been described [43]. Initial treatment for CNS histoplasmosis and blastomycosis is L-AmB and, for *Coccidioides immitis* meningitis, high-dose fluconazole with repeat lumbar punctures or ventriculoperitoneal shunting for elevated intracranial pressure. For *Coccidioides* meningitis, lifelong therapy is required [57, 58].

17.2.4 Protozoal Pathogens

Protozoal infections in SOT recipients occur in restricted geographic distributions with *Toxoplasma gondii* being the most important CNS pathogen [59]. Granulomatous amoebic meningoencephalitis related to donor-transmitted *Balamuthia mandrillaris* infection has been reported in two distinct clusters in the USA [14, 26, 59]. *Acanthamoeba* and *Naegleria* are additional causes of amoebic meningoencephalitis in transplant patients [26, 59].

17.2.4.1 *Toxoplasma gondii*

Toxoplasmosis is most prevalent in Europe, Africa, and Central and South America and less so in the USA and Asia. Disease occurs by reactivation of latent infection, primary infection following ingestion of contaminated foods, or transmission of parasites from blood or donor tissue, most notably, the heart [59, 60].

Toxoplasmic meningoencephalitis typically manifests in the first 3 months following SOT [59, 60]. In a Spanish multicenter study, SOT recipient seronegative status was the only risk factor identified [61]. Affected patients present with fevers, headache, seizures, confusion, and focal deficits [61]. *Toxoplasma* has a propensity for infecting the basal ganglia and cerebrum, and important MR findings include ring-enhancing lesions, edema, or hemorrhage [43].

Empiric and initial therapy for toxoplasmosis is sulfadiazine, pyrimethamine, and leucovorin, and long-term suppressive therapy is required. The presumptive diagnosis is based on *Toxoplasma* seropositivity, clinical presentation, characteristic imaging, and response to anti-*Toxoplasma* therapy. While CSF may show elevated *Toxoplasma*-specific IgG index or detectable *Toxoplasma* DNA, no diagnostic finding is specific other than histopathology [59, 60].

17.3 Differential Diagnosis

The differential diagnosis of infectious and noninfectious CNS syndromes is summarized in Table 17.1. Acute meningitis is usually caused by *L. monocytogenes* and subacute or chronic meningitis by *C. neoformans*. However other pathogens may present in a similar way (*M. tuberculosis*, *L. monocytogenes*, *H. capsulatum*, *N. asteroides*, *S. stercoralis*). Therapy with OKT3 monoclonal antibody has been

Table 17.1 Differential diagnosis of suspected central nervous system infections in solid organ transplant recipients

Time to presentation	(First month after Tx) Early	>1 month to <6 months after Tx	(>6 months after Tx) Late
Noninfectious	PRES DRESS Calcineurin-inhibitor toxicity Other drug toxicity Metabolic encephalopathy Vascular CNS events	PRES PTLD Lymphoma	Neoplasm PTLD
Infectious	Donor-derived infection (WNV, LCMV, rabies, *Balamuthia*) Nosocomial bacterial infection Herpes simplex virus CMV *Aspergillus* spp.	Opportunistic infections Herpes virus, CMV, VZV, EBV, Influenza, WNV, JC virus *Mycobacteria* spp Nocardiosis *Cryptococcus neoformans* *Aspergillus* spp. Endemic fungi (*Histoplasma*, *Coccidioides*, *Blastomyces)* *Leishmania* *Toxoplasma gondii* Microsporidium	Community-acquired infections Opportunistic infections CMV, VZV, WNV, JC virus Bacterial meningitis (*Streptococcus pneumoniae*, *Listeria monocytogenes)* *Mycobacteria* spp. *Cryptococcus neoformans* *Aspergillus* spp. Mucorales *Toxoplasma gondii*

CMV cytomegalovirus, *CNS* central nervous system, *DRESS* drug reaction with eosinophilia and systemic symptoms, *EBV* Epstein-Barr virus, *LCMV* lymphocytic chorioretinitis virus, *PRES* posterior reversible encephalopathy syndrome, *PTLD* post-transplant lymphoproliferative disorder, *RSV* respiratory syncytial virus, *Tx* transplant, *VZV* varicella zoster virus, *WNV* West Nile virus

related to the production of acute aseptic meningitis, characterized by CSF pleocytosis with negative cultures, fever, and transient cognitive dysfunction.

Focal brain infection (seizures or focal neurologic abnormalities) may be caused by *Listeria*, *T. gondii* (3 months posttransplant), fungi (*Aspergillus*, *Mucorales*), posttransplantation lymphoproliferative disease, or *Nocardia* (5 months posttransplant). Finally, infectious progressive dementia has been related to JC virus, HSV, CMV, and EBV. Pyogenic bacterial brain abscess is quite uncommon in this population. *Aspergillus* spp. is the principal causative organism, followed by *T. gondii* and *Nocardia*.

Among noninfectious central and peripheral nervous system adverse events, toxicity from tacrolimus and cyclosporine and posterior reversible encephalopathy syndrome should be considered. These complications are not related to drug levels and may cause protean manifestations such as altered sensorium, seizures, myelitis, blindness, and hydrocephalus. Vascular problems or pretransplant encephalopathy may also be common causes of CNS early events.

17.4 Diagnosis

Recognition of CNS infection after transplantation is challenging because multiple metabolic and systemic infectious processes often coexist and may obscure the presence of CNS infection. The effects of immunosuppression introduce additional complexity as transplant recipients often have subtle or atypical presentations and blunted CSF inflammatory changes.

Table 17.2 summarizes the basic diagnostic approach to CNS infections after transplantation, and Table 17.3 outlines the salient clinical features of important CNS pathogens. A timely diagnosis requires rapid integration of epidemiologic and

Table 17.2 Diagnostic evaluation of suspected central nervous system infection in solid organ transplant recipients

Complete medical and social history
• Type of transplant
• Donor history
• Immunosuppressive therapy
• Allograft rejection and treatment
• Travel and immigration
• Neurologic presentation
Physical examination
• Neurologic findings
• Systemic (extraneural) findings focusing on cutaneous and pulmonary abnormalities
Blood studies
• Complete blood count with differential
• Comprehensive chemistry panel
Radiographic studies
• Brain imaging (MR)
• Chest imaging (radiography or CT imaging)
EEG (if altered mental status or suspected seizures present)
Initial cerebrospinal fluid analysis
• Opening pressure measurement
• Cell count with differential
• Glucose
• Protein
• VDRL
• Cytology
Additional studies for viral infection
• Blood studies – PCR detection of herpesviruses (HSV, VZV, EBV, CMV, HHV-6) – PCR detection of polyomaviruses (JC virus, BK virus)
• CSF studies – PCR detection of herpesviruses (HSV, VZV, EBV, CMV, HHV-6) – PCR detection of polyomaviruses (JC virus)
• Direct fluorescent-antibody staining or PCR of skin samples for HSV, VZV (if exanthem present)

Table 17.2 (continued)

Additional studies for bacterial infection
• Blood cultures
• CSF studies – Bacterial gram stain and culture – Mycobacterial smear and culture – PCR detection of *Mycobacterium tuberculosis*
• Brain tissue (for parenchymal lesions) – Bacterial gram stain and culture – Histopathology
• Respiratory tract (sputum, bronchoalveolar lavage, or lung biopsy), gram stain, and culture – Bronchoalveolar lavage cytopathology – Lung histopathology
Additional studies for fungal infection
• Blood studies – Standard blood cultures (for detection of *Candida*, *Cryptococcus*) – Fungal blood culture (for detection of endemic mycoses) – Serum cryptococcal antigen – Serum *Aspergillu*s galactomannan – Serum 1,3-beta-d-glucan
• Cerebrospinal fluid – CSF cryptococcal antigen – CSF *Aspergillus* PCR – CSF *Aspergillus* galactomannan
• Brain tissue (for parenchymal lesions)
– Fungal smear and culture
– Histopathology
• Respiratory – Sputum, bronchoalveolar lavage, and/or lung tissue for fungal smear and culture – Bronchoalveolar lavage *Aspergillus* galactomannan – Bronchoalveolar lavage cytopathology – Lung histopathology
• Urine – Urine *Histoplasma* antigen – Urine *Blastomyces* antigen – Urine *Coccidioides* antigen
Additional studies for protozoal infection
• Blood – *Toxoplasma* IgG and IgM antibodies – PCR detection of *Toxoplasma gondii*
• Cerebrospinal fluid – *Toxoplasma* IgG and IgM antibodies – PCR detection of *Toxoplasma gondii*
• Brain tissue histopathology (for parenchymal lesions)
• Respiratory tract – *Toxoplasma* IgG and IgM antibodies – PCR detection of *Toxoplasma gondii* – Bronchoalveolar lavage cytopathology – Lung histopathology

GVHD graft versus host disease, *MR* magnetic resonance, *CT* computed tomography, *EEG* electroencephalogram, *PCR* polymerase chain reaction, *HSV* herpes simplex virus, *VZV* varicella zoster virus, *EBV* Epstein-Barr virus, *CMV Cytomegalovirus*, *HHV-6* human herpesvirus-6, *HHV-7* human herpesvirus-7

Table 17.3 Central nervous system pathogens of special significance in solid organ transplantation

Pathogen	Syndromic presentation(s)	Salient clinical features	Predisposing conditions and risk factors	Key diagnostic findings	Initial therapy of choice
Viruses					
Varicella zoster virus [17, 68]	Meningitis Encephalitis Myelitis Vasculopathy	Skin lesions may be absent	African American race, mycophenolate mofetil, intense immunosuppression	MRI abnormalities: infarcts, arteritis, demyelination CSF VZV DNA VZV DFA or PCR of skin lesions	Acyclovir
Epstein-Barr virus [19, 68]	Encephalitis Myelitis	Subacute presentation Systemic features distinguish from PTLD	EBV D+/R− serostatus	CSF EBV DNA	Supportive care Antivirals are unproven
Human herpesvirus-6 [68–70]	Limbic encephalitis Myelitis	Antecedent rash Confusion Involuntary movements Seizures	Lymphocyte depletion	MRI abnormalities involving frontal and parietal lobes, temporal lobes, hippocampus, and amygdala Blood and CSF HHV-6 DNA	Ganciclovir or foscarnet
West Nile virus [7, 68, 71]	Meningitis Encephalitis	Flaccid ascending paralysis	Donor-derived infection	MRI with lesions in basal ganglia, thalamus, substantia nigra, and spinal cord CSF WNV IgM antibody Serum WNV IgM	Supportive care

JC virus [21, 22, 68]	Progressive multifocal leukoencephalopathy	Prolonged T cell depletion		CSF or tissue JCV DNA	Supportive care Withdrawal or reduction of immunosuppression
Bacteria					
Nocardia spp. [29, 72–75]	Brain abscess Meningoencephalitis Myelitis Parkinsonism	Concomitant lung disease	High calcineurin inhibitor level, tacrolimus, corticosteroid dose, lymphocyte-depleting antibodies, CMV disease, older age, length of ICU stay before transplant	Brain biopsy with histopathology, gram stain, and bacterial culture	TMP-SMX + imipenem or third-generation cephalosporin + amikacin
Listeria monocytogenes [76–78]	Meningoencephalitis Brain abscess Rhombencephalitis	SIADH Cranial neuropathy	Corticosteroid, lymphocyte-depleting antibodies rejection	Blood culture, CSF gram stain and bacterial culture, brain biopsy with gram stain and bacterial culture	Ampicillin or penicillin G + gentamicin
Mycobacterium tuberculosis [35, 62, 79]	Meningitis Brain abscess Tuberculoma	Donor-derived infection Disseminated disease IRIS	Endemicity of *M. tuberculosis*, lung > other organs, lymphocyte-depleting antibodies, treatment for allograft rejection, HCV infection, DM, chronic liver disease, older age, renal insufficiency, or dialysis in kidney recipients	CSF/tissue AFB smear/culture; CSF MTb DNA	Isoniazid + rifabutin + pyridoxine + pyrazinamide + ethambutol

(continued)

Table 17.3 (continued)

Pathogen	Syndromic presentation(s)	Salient clinical features	Predisposing conditions and risk factors	Key diagnostic findings	Initial therapy of choice
Fungi					
Cryptococcus spp. [11, 42, 44, 45]	Meningitis Cryptococcoma(s)	Donor-derived infections, elevated ICP, IRIS	Heart and pancreas-kidney transplants	CSF cryptococcal antigen, CSF fungal smear/culture	L-AmB + flucytosine
Aspergillus spp. [46–48, 52]	Brain abscess(es) Infarction Mycotic aneurysm Rhinocerebral infection Meningitis	Concomitant lung disease	*Aspergillus* airway colonization (lung), hypogammaglobulinemia (lung), re-transplantation (liver), re-operation (liver, heart), CMV (lung, heart), corticosteroids (kidney) treatment of rejection (all)	Brain biopsy with histopathology and fungal smear and culture	Voriconazole
Mucorales [54–56]	Rhinocerebral infection Brain abscess(es)	Mucosal black eschar	Re-transplant, DM, renal failure, iron overload, voriconazole and/or echinocandin treatment	Histopathology Tissue fungal smear and culture	L-AmB ± echinocandin

Protozoa					
Toxoplasma gondii [59–61]	Cerebritis/brain abscess Meningoencephalitis Spinal cord abscesses	Donor-derived infections occur; disseminated infections are common	Heart recipients; D+/R− serostatus	Histopathology, PCR detection of *Toxoplasma* DNA in tissue	Sulfadiazine + pyrimethamine + leucovorin
Balamuthia mandrillaris [13, 14]	Granulomatous amoebic meningoencephalitis	Donor-derived infections Facial and extremity lesions described in naturally occurring infections	–	MRI with multiple (ring)-enhancing lesions CSF pleocytosis and elevated protein Histopathology PCR detection of *Balamuthia* DNA in tissue	Regimens including combinations of pentamidine, flucytosine, sulfadiazine, L-AmB, azithromycin or clarithromycin, fluconazole, and miltefosine

CNS central nervous system, *SOT* solid organ transplantation, *SCT* stem cell transplantation, *CMV Cytomegalovirus*, *TMP-SMX* trimethoprim-sulfamethoxazole, *SIADH* syndrome of inappropriate antidiuretic hormone secretion, *GVHD* graft versus host disease, *HLA* human leukocyte antigen, *IRIS* immune reconstitution inflammatory syndrome, *PCR* polymerase chain reaction, *DM* diabetes mellitus, *MTb Mycobacterium tuberculosis*, *DNA* deoxyribonucleic acid, *L-AmB* lipid formulations of amphotericin B, *ICP* intracranial pressure, *D/R* donor/recipient
Adapted from reference [80]

clinical information to formulate a differential diagnosis. Geographic and environmental exposures of both recipient and donor provide potential clues, especially for tuberculosis, the endemic mycoses, and toxoplasmosis. In addition to the neurologic findings, the physical examination may identify concomitant lung disease, viral exanthem, or other skin lesions.

Brain imaging, with MR as the preferred modality, is essential for identification of focal lesions and noninfectious processes including primary and metastatic malignancies, hemorrhage, stroke, thromboemboli, and hydrocephalus. Advantages of MR versus CT scanning include better distinction of gray versus white matter involvement, as well as superior visualization of the posterior fossa and cerebellum, the leptomeninges, and the venous sinuses [1]. In those with suspected encephalitis, MR is the most sensitive imaging technique, and certain patterns of findings may assist in determination of the etiologic agent [13]. As an initial study, computed tomography (CT) imaging is recommended prior to lumbar puncture to detect those at risk for brain herniation.

An electroencephalogram is indicated if the presentation includes altered sensorium or suspected seizure activity; however, findings are generally nonspecific with the exception of HSV encephalitis, in which up to 80% will have periodic lateralizing epileptiform discharges.

The CSF analysis remains an essential evaluation for suspected CNS infection. Opening pressure is measured, and initial studies include white blood cell count with differential, red blood cell count, glucose, protein, gram stain, bacterial and fungal cultures, and cryptococcal antigen. Further CSF analysis is based upon the individual clinical scenario. The diagnostic tests of choice for individual infections are outlined in discussions of relevant pathogens and summarized in Table 17.3.

17.5 Prevention

Prevention of CNS infections in the transplant recipient begins in the pretransplant evaluation stage and continues throughout all phases of transplant. Screening for latent infections such as *M. tuberculosis* in transplant candidates followed by preventive therapy is highly effective in prevention of posttransplant reactivation disease [62]. Transplant recipients should receive routine immunization against *S. pneumoniae* as well as those indicated for those who travel to endemic areas (*N. meningitidis*, poliovirus, rabies virus, and Japanese encephalitis virus). Additionally, transplant recipients require education regarding strategies to avoid exposure to pathogens that cause CNS infections. Important safe living and travel precautions that directly pertain to CNS pathogens include food safety (*Listeria*, *Toxoplasma*), mosquito avoidance (WNV), animal exposure (rabies virus), and refraining from spelunking, excavating, or masking when performing such activities (*Cryptococcus*) [63].

During the organ donor evaluation process, standard screening procedures for pathogens such as *Toxoplasma*, CMV, and EBV define risk for donor-acquired infection, allowing for posttransplant prophylactic therapies [59, 60, 64]. Unrecognized CNS infection of organ donors poses great risk to recipients due to

Table 17.4 UNOS/OPTN Disease Transmission Advisory Committee "warning signs" for unrecognized CNS infection in organ donors [65]

• Cerebrovascular accident in a donor without traditional risk factors or comorbidities
• Unexplained fever in a donor at time of presentation of illness or hospital admission
• Altered mental status and/or seizure in a donor at time of presentation of illness or hospital admission
• Central nervous system imaging findings such as hydrocephalus or infarcts
• Cerebrospinal fluid abnormalities such as pleocytosis, low glucose, and/or elevated protein
• Environmental or geographic exposures (including homelessness)
• Immunosuppressed host

high rates of disease transmission resulting in high mortality rates [7, 9, 12]. For geographically restricted or seasonal pathogens such as West Nile virus, organs from donors with virus detected by nucleic acid testing will be excluded from donation. The Disease Transmission Advisory Committee of the United Network for Organ Sharing/Organ Procurement Transplant Network, based on review of donors implicated in unrecognized CNS pathogen transmission, has developed a set of "warning" criteria intended to identify donors that may have meningoencephalitis. These criteria are outlined in Table 17.4 and, when present, suggest that the donor requires further evaluation (such as lumbar puncture) for infection. In the presence of suspected or confirmed infection, the risks and benefits of organ utilization require careful consideration [65]. Organs from donors with known bacterial meningitis, especially if pre-donation treatment of the donor and prophylactic antimicrobial therapy in the recipient are employed, can be utilized safely [66, 67].

17.6 Treatment

Specific therapy of documented infections is presented in Table 17.3. In SOT recipients, it is usually possible to obtain suitable samples for diagnosis before starting antimicrobials. However, sometimes empirical therapy will have to be initiated before the results are available. Treatment of meningitis should be based on the clinical setting (patient characteristics, clinical presentation, skin lesions, etc.) and microscopy of CSF sediment, which helps to predict the most likely pathogen. If meningeal involvement is suspected and the patient is not receiving cotrimoxazole prophylaxis, therapy should include ampicillin to cover *Listeria* which will be administered usually with high doses of a third-generation cephalosporin and vancomycin. The co-administration of corticosteroids in acute purulent bacterial meningitis remains controversial. Dexamethasone (1.2 mg/m^2 every 6 h for 4 days) appears to be safe in children, although sufficient data is missing in adults. It might be reasonable to consider the use of dexamethasone if a high number of organisms are present in CSF on microscopy or in adults with poor prognostic factors such as coma or stupor.

In the presence of cerebral abscesses in a SOT patient, fungus should always be considered, so, after obtaining appropriate samples for microbiology, L-AMB, voriconazole, or isavuconazole may be initiated. CT-guided stereotactic aspiration or an

open craniotomy and drainage are recognized as adjunctive to medical therapy for diagnosis and therapeutic purposes.

Sulfonamides are effective if rapidly administered for patients with a nonfungal brain abscess and should be initiated empirically until a specific etiology is established in cases not suspected of being caused by fungi.

17.7 Summary

CNS infections, although not very prevalent in SOT recipients, may result in very severe morbidity. The etiologic considerations are different from those in the general population, with a higher importance of viral and fungal pathogens. Noninfectious etiologies should be always considered. Management should always include consultation with a multidisciplinary team including a neurologist and an infectious diseases/clinical microbiologist expert.

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Management of Urinary Tract Infection

18

Carlos Cervera and Francisco López-Medrano

18.1 Introduction

Urinary tract infections (UTI) are the most frequent infectious complication of kidney transplant recipients (KTR). UTI increase morbidity and mortality of KTR, with additional impacts on graft's outcome, patient's quality of life, hospitalization rates, and cost of transplantation. Other solid organ transplant (SOT) recipients are also at increased risk of UTI, usually early posttransplant and acquired in the hospital.

Prevention of UTI in KTR involves a precise and individualized evaluation of the risk factors, as well as balancing the benefits and disadvantages of antibiotic therapy. The use of antibiotics in clinically irrelevant positive urine cultures may lead to side effects and development of antibiotic resistance. On the other hand, the development of ascending upper UTI may lead permanent damage to the kidney allograft in KTR or even fatal outcomes in all SOT patients.

18.2 Epidemiology

18.2.1 Kidney Transplantation

Drawing from a several studies with significant vast heterogeneity in inclusion criteria, immunosuppression, and definition of UTI used, the prevalence of UTI post renal

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transplantation ranges from 23 to 85%. In KTR, UTI is responsible for 42–75% of infections with an incidence rate of 0.45 episodes/1000 transplantation days [1, 2].

The first month posttransplantation is the period at highest risk of UTI for different reasons [3, 4]. KTR usually carry indwelling urine catheters early posttransplant, and the presence of ureteric stent, placed after surgery to prevent ureteric stenosis, may alter the urine flow increasing the risk of UTI. Usually, 6 months after transplantation, the risk decreases considerably, but a small subgroup of KTR may develop recurrent UTI.

A variety of risk factors associated with increased risk of UTI in KTR have been described (Table 18.1) [2]. Most series describe female gender and advanced age as the most important risk factors associated with UTI posttransplant. Posttransplant urinary obstruction not only increases the risk of UTI, but it is also associated with higher rates of antibiotic-resistant bacteria. Patients with end-stage kidney disease secondary to urine reflux are also at increased risk of posttransplant UTI. Other risk factors include the intensity of immunosuppression, diabetes mellitus pre- or posttransplant, the duration of indwelling urinary catheterization, and acute rejection.

18.2.2 Non-kidney Solid Organ Transplant Patients

The incidence of UTI in solid organ transplantation other than kidney is less known. The incidence rate by type of transplant in one study was, in kidney-pancreas, 0.22 episodes/1000 transplantation days; heart, 0.07 episodes/1000 transplantation days; liver, 0.06/1000 transplantation days; and lung, 0.02 episodes/1000 transplantation days [4]. In this group of patients, the main risk factors for UTI are pretransplant predisposing conditions and nosocomial acquisition early posttransplant usually related to the use of indwelling urinary catheters (Table 18.1).

The most frequent bacterial genre causing UTI in all SOT patients is *Enterobacteriaceae* and more specifically *Escherichia coli*. Other bacteria include *Klebsiella* spp., *Pseudomonas aeruginosa*, and *Enterococcus* spp. [4–6].

Table 18.1 Risk factors for UTI in solid organ transplant patients

Common for all SOT
Female gender
Advanced age
Intensity of immunosuppression
Need of posttransplant hemodialysis
Repeated episodes of acute rejection
Length of hospitalization
Diabetes mellitus
Length of urinary catheterization
Specific for kidney transplant recipients
Ureteral stents in place
Ureteral stent placement for more than 30 days
Deceased donor kidneys
Reflux kidney disease prior to transplantation
Posttransplant urinary obstruction

Current data indicate a rising incidence of multidrug-resistant (MDR) strains of urinary pathogens worldwide, including SOT recipients. In order to optimize the management of these patients, it is very important to have detailed and updated information on the local antimicrobial resistance epidemiology.

18.3 Clinical Manifestations

Urinary tract infection is classified into lower (cystitis) and upper (pyelonephritis) tract infections. Cystitis is characterized by the combination of some of the following symptoms: frequency, urgency, dysuria (pain with micturition), hematuria, and suprapubic pain. Concurrent prostate disease should be ruled out in males with lower UTI symptoms (perineal or low back pain may be the only manifestation). Fever should be considered as a sign that indicates upper UTI. Fever may be the most reliable clinical finding to differentiate upper from lower UTI. Asymptomatic bacteriuria is defined by the combination of the absence of symptoms with the isolation of 10^5 CFU/mL in a single specimen for men and in two consecutive specimens for women [2].

The clinical picture of pyelonephritis includes the presence of rigors and pyrexia, hematuria, and pain over the affected kidney. Occasionally, symptoms of cystitis are also present, but their absence does not exclude the possibility of pyelonephritis. Renal transplant recipients are at the highest risk of pyelonephritis, and pain is common over the graft instead of the flank [7, 8]. Sometimes the initial clinical manifestations of pyelonephritis include nausea, vomiting, and diarrhea or constipation. Appendicitis, diverticulitis, and other abdominal conditions should be considered in the differential diagnosis. Ectopic pregnancy, pelvic inflammatory disease, and ovarian cyst torsion should also to be considered in the differential diagnosis of the female transplant recipient. Graft rejection is another clinical situation that can rarely produce fever and pain over the transplanted kidney.

After pathogen-directed therapy is initiated, fevers may persist for several days despite clinical improvement. If fever persists beyond 48 to 72 h with adequate antimicrobial therapy, imaging to evaluate for an abscess or other space-occupying lesion should be performed (Table 18.2).

18.4 Diagnosis

A urinary tract infection should be considered in patients with clinical symptoms in addition to urine analysis testing consistent with infection (see below) and positive culture. Urine analysis typically demonstrates leukocyte esterase, nitrites, and bacteria. Microscopic examination demonstrates $\geq$10 white blood cells/mm^3 of unspun urine (by a chamber method); absences of pyuria may be suggestive of an alternative diagnosis, such as urethritis or vaginitis. Gram stain of urine is diagnostic if one or more bacterium per oil-immersion field is present as this correlates with at least 10^5 colony-forming units (CFU)/mL. Gram stain may also help guide initial

Table 18.2 Clinical picture

Lower urinary tract infection (cystitis)	Upper urinary tract infection (pyelonephritis of a native kidney)
– Frequency – Urgency – Dysuria – Hematuria – Suprapubic pain – Perineal or low back pain (males with prostatitis)	– Fever – Loin pain (+/− irradiation to the genital area) –+/− hematuria –+/− symptoms of cystitis – May begin with digestive tract symptoms!
Pyelonephritis of the graft in kidney transplant recipients – Fever – Pain over the graft (usually right or left iliac fossa) – Dysuria +/− hematuria – Consider in the differential diagnosis: appendicitis, diverticulitis, ectopic pregnancy, pelvic inflammatory disease, ovarian cyst torsion, graft rejection	
Consider the possibility of an abscess if fever persists for more than 48–72 h despite adequate antimicrobial treatment	

therapy; the presence of Gram-positive bacteria suggests the need to cover for *Enterococcus*.

Urine culture is mandatory for any suspected UTI of SOT recipients [2]. A careful clean-catch urine specimen must be collected for culture. Both female and male recipients have to be instructed for the correct collection of the urine sample. In women with dysuria and confirmed pyuria, the threshold for significant bacteriuria is 10^2 CFU/mL or more of a single or predominant pathogen. When suprapubic bladder aspirates are compared with voided midstream urine in acutely dysuric women, 10^2 or more CFU/mL in midstream urine have a sensitivity and specificity of 95% and 85%, respectively, for UTI [9]. In dysuric men a growth of 10^3 CFU/mL or more should be considered significant. For asymptomatic bacteriuria, the isolation of 10^5 CFU/mL in a single specimen for men and in two consecutive specimens for women is considered the standard for diagnosis. Colony counts are considered to be significant if greater than 10^2 CFU/mL for straight catheter or suprapubic aspiration specimens and for samples collected during nephrostomy tube insertion. If fever is present, drawing blood cultures is mandatory for this population.

There is lack of consensus about when to perform a urologic evaluation in KTR with recurrent infections. The goal of imaging studies is to rule out anatomical abnormalities (mainly obstruction) that may predispose to reoccurrence. They are indicated to evaluate persistent hematuria and when urinary stones are suspected or proven. Most experts recommend imaging studies for every SOT recipient developing pyelonephritis, especially for KTR and for those with recurrent infections. Renal ultrasound is useful to assess noninvasively for obstructive uropathy, but computerized tomography (CT) is more sensitive for the detection of stones and abscesses [2].

Some alternative diagnosis should be considered for patients presenting with pyuria but with sterile simultaneous urine culture (“sterile pyuria”). Depending on epidemiological characteristics, tuberculosis, schistosomiasis, infection by

Table 18.3 Key points for the diagnosis of UTI in SOT recipients

– The absence of pyuria essentially excludes UTI
– A Gram stain of urine could be a useful tool
– Urine culture is mandatory for diagnosis in this population
– Draw blood cultures if fever is present
– Consider renal ultrasound or CT in severe recurrent infection in order to rule out stones and obstruction abscesses
– "Sterile pyuria": rule out tuberculosis, schistosomiasis, *Corynebacterium urealyticum*, *Ureaplasma urealyticum*, *Mycoplasma hominis*, adenovirus, or tumor

CT computerized tomography

adenovirus, infection by difficult-to-diagnose organisms (*Corynebacterium urealyticum* [10], *Ureaplasma urealyticum*, or *Mycoplasma hominis*), or tumor should be ruled out [8] (Table 18.3).

18.5 Treatment of Urinary Tract Infections

18.5.1 Treatment of Lower Urinary Tract Infection

Cystitis is almost always treated with oral antibiotics [2]. Empiric treatment must be immediately started, pending results of urine culture. Antibiotics useful in this clinical situation are listed in Table 18.4. When selecting empirical treatment, local pattern of resistance of the most frequent urinary pathogens must be taken into consideration. Trimethoprim-sulfamethoxazole is not an appropriate option for SOT recipients who are currently under or who have received prophylaxis with this antibiotic. Review of prior isolates to determine prior colonization or infection with resistant bacteria should be used to inform empiric therapy. Patients reporting a previous allergic reaction to a β-lactam antibiotic should receive appropriate alternative therapies. Quinolones, cephalosporins, and fosfomycin do not interact with immunosuppressive drugs. Short-course or single-course regimens are not recommended for SOT recipients, especially for KTR. Generally patients are treated for 7 days for uncomplicated cystitis. The US Food and Drug Administration (FDA) advised that the serious side effects associated with fluoroquinolones generally outweigh the benefits for patients with uncomplicated urinary tract infections who have other treatment options (these side effects can involve the tendons, muscles, joints, nerves, and central nervous system). For uncomplicated urinary tract infections, the FDA recommended to reserve fluoroquinolones for those who do not have alternative treatment options.

High fluid intake and frequent voiding are complementary maneuvers to antibiotic treatment. Urinary analgesics such as phenazopyridine hydrochloride (200 mg orally three times a day after meals) may be useful to relieve symptoms of dysuria and urethra irritation. It should be stressed to the patient that this drug is not a substitute for an antibiotic and that it should not be used in pregnancy. A follow-up culture of an after-treatment urine sample is recommended in this population to confirm eradication.

Table 18.4 Empiric oral antibiotic treatment for SOT recipients with lower UTI infection (cystitis)[a,b,c]

Antibiotic	Dose (mg)	Interval
Trimethoprim-sulfamethoxazole[d,e]	160/800	q12h
Fosfomycin	3000	q24h
Cefixime	400	q24h
Nitrofurantoin	100	q8h
Amoxicillin plus clavulanate	500/125	q8h
Norfloxacin[f, g]	400	q12h
Ciprofloxacin[f, g]	500	q12h
Levofloxacin[f,g]	500	q24h

[a]Dose modification may be necessary in renal failure
[b]Regimens 7 days long are preferred for SOT recipients
[c]Take into consideration previous microbiological results of the patients. Susceptibility of pathogen to selected antibiotic must be confirmed with in vitro susceptibility testing of the urine sample
[d]Not appropriate as empirical treatment for SOT under prophylaxis with this antibiotic
[e]Empiric use limited to those geographical areas where frequency of resistance is less than 20%
[f]Fluoroquinolones should be avoided in pregnancy, nursing mothers, and adolescents younger than 17 years old for lower UTI if an alternative is available
[g]See text for FDA warning

18.5.2 Treatment of Upper Urinary Tract Infection

Inappropriate empiric antibiotic treatment is associated with worse outcomes and increased mortality. Selection of the optimal empiric treatment of upper urinary tract infection requires review of prior infections and colonization in the patient as well as review of local resistance patterns in common uropathogens.

For most centers with low rates of MDR bacteria UTI, β-lactams are the preferred empiric treatment as resistance to quinolones for *Enterobacteriaceae* is >20% in most centers. Preferred β-lactams include IV third-generation cephalosporins (such as ceftriaxone) or amoxicillin-clavulanate. In areas of high-level resistance to these agents, carbapenem or piperacillin-tazobactam should be considered. If *Enterococcus* spp. is suspected, based on history of urine gram stain, coverage with an active penicillin, vancomycin, or daptomycin should be used. In general, nephrotoxic drugs, such as aminoglycosides, should be avoided unless the patient has septic shock and local resistance patterns favor the use of these agents over alternative drugs, including carbapenems.

In most cases, the duration of antibiotic treatment should be prolonged to 14–21 days depending on the evolution of the patient (Table 18.5).

18.6 Approach to Asymptomatic Bacteriuria

The treatment of asymptomatic bacteriuria is only recommended for pregnant women and for those whose urinary tract is going to be surgically manipulated (e.g., for transurethral prostatectomy). The same recommendations apply to SOT with the exception of kidney transplant recipients [2].

Table 18.5 Empiric intravenous β-lactams for SOT recipients with upper UTI infection (pyelone phritis)[a,b,c]

Antibiotic	Dose (mg)	Interval
Ceftriaxone	1–2 g	Q24h
Amoxicillin plus clavulanate	1000 mg/200 mg	Q8h
Piperacillin-tazobactam	3.375 g	Q6h
Meropenem	1 g	Q8h
Imipenem	500 mg	Q6h
Ertapenem	1 g	Q24h

[a]The choice of empiric treatment should be guided by the local epidemiology of antibiotic resistance and by previous patients' bacterial isolations
[b]Dose modification may be necessary in renal failure
[c]Regimens 14–21 days long are preferred for SOT recipients

Table 18.6 Key messages about asymptomatic bacteriuria in SOT recipients

- Excluding kidney transplantation, asymptomatic bacteriuria should not be systematically screened or treated in SOT recipients except when indicated for the general population (pregnancy and surgical urinary tract manipulation)
- Asymptomatic bacteriuria may be systematically screened and treated in kidney transplant recipients within the first 1–2 months after transplantation (very low level of evidence)
- In a clinical trial, no benefit has been demonstrated for the systematic screening and treatment of asymptomatic bacteriuria in kidney transplant recipients beyond the first 1–2 months after transplantation (other studies ongoing)

Despite a very low level of evidence, systematic treatment of asymptomatic bacteriuria is suggested for kidney transplant recipients within the first 1–2 months after transplantation [2].

There are controversies about the necessity of monitoring and treatment of asymptomatic bacteriuria in renal transplant recipients beyond the immediate post-transplantation period. The association between repeated episodes of asymptomatic bacteriuria and the development of pyelonephritis has been reported [11]. Nevertheless, a prospective randomized controlled clinical trial did not show any benefit of the systematic screening and treatment of asymptomatic bacteriuria in terms of reduction in the development of subsequent pyelonephritis [12]. Other prospective comparative studies are ongoing (Table 18.6).

18.7 Approach to Recurrent Urinary Tract Infection

Recurrent UTI is one of the complications that worsen the quality of life of KTR. Recurrent UTI are defined as at least three episodes of symptomatic UTI in a 12-month period or two episodes within 6 months documented by culture [2]. The incidence of this complication varies from 3 to 30% of all KTR depending on the definition of recurrence [13–15]. The incidence of recurrent UTI in non-kidney SOT is less known but probably much lower than for KTR. For this reason, we will refer to the management of recurrent UTI in KTR.

Recurrent UTI in KTR may be secondary to anatomical abnormalities of the urinary tract. Urinary obstruction or reflux should be always ruled out in the management of recurrent UTI in KTR. Usually, these complications are associated with worsened kidney function and in most cases are easily diagnosed by ultrasound. It is important to emphasize that it is not uncommon to see recurrent UTI in KTR without urinary abnormalities and excellent kidney function.

Another significant issue regarding recurrent UTI is the association with multidrug-resistant bacteria [14]. Whether antibiotic resistance is a cause or a consequence of recurrent UTI has not been well established, although it seems reasonable to think that the overuse of antibiotics in this scenario may lead to the development of resistance.

The association between recurrent UTI and deterioration of the kidney function is controversial [3, 5, 16]. Although it is common to see recurrent UTI in KTR with allograft dysfunction in the clinical practice, causality has been less established. As previously stated, it is not uncommon to see recurrent UTI in KTR with excellent graft functioning.

As there are no clinical trials evaluating the optimal strategy to prevent recurrent UTI in KTR, the strategies should be extrapolated from the general population. The five strategies to prevent recurrent UTI in women with published clinical trials comprise daily antibiotic prophylaxis with nitrofurantoin, daily estrogen prophylaxis, daily cranberry prophylaxis, acupuncture prophylaxis, and symptomatic self-treatment. Daily antibiotic prophylaxis is the most effective strategy to prevent UTI [17]. Chronic prophylaxis with nitrofurantoin in KTR is contraindicated in many centers because of potential pulmonary interstitial disease. Fosfomycin and sulfamethoxazole-trimethoprim (if the patient is not on active prophylaxis with this drug) are good options for prophylaxis. Chronic use of quinolones could lead to side effects and should be used with caution. In the case of antibiotic resistance or in situations in which daily antibiotic treatment is contraindicated (e.g., recurrent *Clostridium difficile*-associated diarrhea or Norovirus infection), symptomatic self-treatment may be considered.

Other strategies for the management of recurrent UTI with variable success include urine acidification with L-methionine [18], topical estrogens in postmenopausal female transplant patients [19], and daily cranberry juice [18] (Table 18.7).

Table 18.7 Key messages about recurrent UTI in SOT recipients

- The first approach for the management of recurrent UTI in KTR is to exclude anatomical or functional abnormalities of the urinary tract
- To decide antibiotic prophylaxis for recurrent UTI in KTR, we should take into account the clinical impact of previous UTI, the kidney allograft function, antibiotic sensitivities of previous isolated uropathogens, and colonization with multidrug-resistant bacteria. Chronic nitrofurantoin use is contraindicated for KTR in many countries, and chronic quinolones use should be used with caution
- Symptomatic self-treatment may be considered for patients with previous hospitalizations for UTI and chronic allograft dysfunction or when antibiotic prophylaxis is contraindicated (e.g., recurrent *C. difficile*-associated or Norovirus diarrhea)

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19 Management of Infections of Devices: Catheter-Related Infections, Pretransplant VAD Infections, Infections of ECMO Devices

Cameron R. Wolfe and Martha L. Mooney

19.1 Definitions and Epidemiology

19.1.1 Central Venous Catheter (CVC) and Extracorporeal Mambrane Oxygenation (ECMO)

The definitions of CVC or ECMO infection are the same in the pre- and posttransplant recipient, though clinical and radiographic signs may be subdued in the posttransplant period, especially when if the patient is still in an intensive care setting (Table 19.1). Firstly, CVC infections can be categorized as either bloodstream infections (BSI) or entry site infections. BSI can be usefully defined as either primary or secondary: primary infections arise from the central catheter itself, which is either a tunneled or non-tunneled device, whereas secondary BSI is a term reserved for when there is a proven or probable distant source, for example, urine or GI tract, yet a culture may have been drawn through the catheter. CVC infections may also be associated with the skin and soft tissue around the entry site.

The definition of an infected ECMO device is variable across the literature, but can be thought of in the same way as CVC infections, with an infection being classified as a primary or secondary ECMO BSI or a skin and soft tissue infection related to the insertion site. Additionally, however, some institutions collect data on infections that arise during an admission where ECMO is deployed, for example, hospital or ventilator-associated pneumonia (HAP, VAP). These are termed ECMO-associated infections.

Critical illness leads to more frequent nosocomial infections in general, but especially when CVC or ECMO support is required, including hospital- or ventilator-associated pneumonia and catheter-associated urinary tract infections (CAUTI) [1].

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Table 19.1 Signs and symptoms of infection

Routine signs and symptoms of infection	*Challenges to routine evaluation for Mechanical Circulatory Support (MCS)*
Altered mental status	Sedation, stroke, posterior reversible encephalopathy syndrome (PRES) with transplant medication
Tachypnea, dyspnea	Neuromuscular blockade in ICU, medication side effects
Fever or hypothermia	Core temperature artificially maintained by ECMO, or swings blunted by dialysis
Leucopenia, leukocytosis	SIRS generated not by infection, but by continuous blood flow and blood product consumption from circuit
Thrombocytopenia	Consumption, bleeding, heparin-induced thrombocytopenia
Hemodynamic support level	Circuit flow dynamics and support
ID biomarker evaluation (e.g., CRP, procalcitonin)	Unclear influence of ECMO or VAD circuit—discrimination possible but less sensitive
Alternative signs and symptoms used to consider infection	
Signs of increasing metabolism (e.g., CO2 climbing, failing "sweep" trials)	Falling SvO2
Unexplained lactic acidosis	Change in hemodynamic support
Change from baseline in WBC, Plts	Signs of unexplained hypovolemia

Regarding bloodstream infections, the rates likely vary depending on patient age (adults more frequently infected than children) and type of ECMO support required (venoarterial ECMO more frequently associated with infection than Veno-Venous) and are proportional to the duration of cannulation [2]. Infection also appears more common in urgently deployed extracorporeal cardiopulmonary resuscitation (ECPR), compared to ECMO used for cardiac or respiratory support.

Given the high mortality and morbidity associated with sepsis or tissue-invasive device infections, predicting what microbial flora will predominate is important. Skin and soft tissue colonizers such as coagulase-negative staphylococci and *Staphylococcus aureus* are the most common bacteria affecting both CVCs and ECMO. The types of pathogens affecting ECMO circuits may be slightly different, with a high proportion of candida and pseudomonas isolates likely, 12.7% and 10.5%, respectively, in one study [2]. Aspergillus species have also been seen to occur with greater frequency in a number of retrospective ECMO cohorts, and although it can be difficult to differentiate invasive disease from more indolent airway colonization, the identification still appears to portend a high morbidity [3, 4]. Ultimately, understanding the local flora and antibiogram in a patient hospital and/or ICU remains vital.

19.1.2 Ventricular Assist Devices (VAD) Infections

The definitions of VAD infections have been described in the International Society of Heart and Lung Transplantation (ISHLT), in a multidisciplinary consensus

document. Infections can be defined as VAD-specific and VAD-related [5]. VAD-specific infections include infection of the pump and/or cannula, the pocket (if present), or the percutaneous driveline (superficial or deep). The ISHLT expert panel suggests driveline infection should be classified into "proven," "probable," and "possible," on the basis of clinical and microbiologic findings. Contrastingly, VAD-related infections involve adjacent tissues and include infective endocarditis of the native valve, bloodstream infections, and mediastinitis.

It is worth remembering that infections resulting from VAD can present in the post-heart transplant period, post device removal. In these circumstances, typically infection arises either because infection was only partially treated when transplant occurred, or infection resisted treatment due to retained material from the partially removed infected VAD, or from other retained foreign bodies present when infected VAD was present (ICD, Pacer, etc.).

Bloodstream infections are not uncommon in VAD patients. Although the rates vary significantly between studies and are dependent on the type of VAD, rates are quoted as 20–27% (0.35–0.42 events per year of LVAD support) [6]. The risk for BSI is highest in the first month after implantation, and when a BSI occurs, there is an increased mortality in LVAD recipients presenting with sepsis syndrome. The majority of BSI in LVAD patients are thought to originate from the driveline.

Prevention of infection remains key to the longevity of any VAD. VAD recipients who have pre-transplant septic episodes are less likely to be successfully bridged to transplantation. Furthermore, VAD implantation itself has been associated with an increased posttransplant rate of infection. Once transplanted, however, several studies have shown that a prior history of VAD infection does not affect posttransplant survival, with 3-year survival rates of up to 80%.

The most common causative organisms in VAD infections are Staphylococcal species (>50%) with *S. aureus* and *S. epidermidis* predominating, followed by gram-negative bacteria with *Pseudomonas* species predominating (up to 28%), but *Serratia* (9%), *Enterobacter* (2%), and *Klebsiella* (2%) also seen. Fungal infections account for <10%, and candida species account for the majority of these [7]. *Aspergillosis* is rare but has been published in case reports, with very significant mortality [8]. Atypical mycobacterial infections have also been reported with significant morbidity, particularly rapidly growing mycobacteria such as *M. abscessus*, although they are fortunately rare [9, 10]. It is likely that the microbial flora seen in VAD infections, as well as their resistance profiles, will vary depending on hospital and community flora. It is also likely dependent on how the VAD was exposed to microbes, with, for example, anecdotally waterborne and environmental organisms more commonly seen in patients with inadequately sterile driveline cleaning practices.

The etiologic pathogens of infections in the posttransplant period from retained material from a partially removed infected VAD or other retained devices (i.e., ICD, pacers) are not well characterized, as few case reports are published. It is tempting to assume that the pathogens in the retained foreign material are the same as the data reveals from infected VADs; however prolonged antibiotic exposure in the perioperative

period, a risk factor for the development of resistant organisms, and the impact of immunosuppression may affect potential pathogens found after heart transplantation (HT).

There are a number of factors that contribute to the development of intravascular infection within VADs and that are similar to risks seen in ECMO and CVC infections. The presence of thrombus is important and increases depending on the virulence of the offending pathogen, as well as device surface characteristics, dynamics of blood flow, internal surface area of the device, and coagulopathy. Older VAD devices have been associated with higher rates of intravascular thrombosis and consequently higher rates of endocarditis. Newer continuous-flow VAD devices are both smaller and possess continuous-flow dynamics, hence may end up with lower incidence of infections. More studies are needed to bear this out.

19.2 Description of Differential Diagnosis

The signs and symptoms of infection in a SOT are variable, so for the transplanted patient presenting with a change in clinical status, infection should always be considered in the differential. That is particularly true in the presence of support devices. Transplanted patients with device-associated infections usually present with fever, leukocytosis, and, in more severe cases, septic shock. Occasionally, patients may present with septic embolization to distant sites or new incompetence of pump inflow or outflow valves.

In the posttransplant period, a patient with a CVC, ECMO, or VAD may have clinical signs and symptoms consistent with SIRS that are blunted due to immunosuppression or even enhanced due to concomitant issues. For example, in the early posttransplant period, the patient's temperature, blood pressure, and wbc and plt count may be increased or decreased due to infection although perhaps more commonly fluctuates due to numerous noninfectious causes such as surgical stress, steroids and other medication, bleeding, hemodynamic instability, etc. Similarly the increased utilization of heating and cooling devices in ICU, not to mention the frequent use of renal replacement therapies in the postoperative period can all mask temperature fluctuations.

Wound dehiscence may mimic infection and be due to infection or non-ID causes such as tissue ischemia, nutritional deficiencies, steroids, or other medications, for example, mTOR inhibitors like sirolimus.

19.2.1 Diagnostic Approach

Given the propensity for clinical signs to be blunted, especially posttransplant, we believe a number of standard investigations are paramount when evaluating

infection. For all patients suspected of having a CVC-, ECMO-, or VAD-associated infection, the following testing should be strongly considered:

All patients:

- White blood cell count.
- Sterile aspirate of driveline at the exit site, if pus present, initially for Gram stain (looking for bacteria) and K-OH stain (for fungal forms), and then for bacterial, fungal, and mycobacterial culture.
- Blood cultures: At least three sets of cultures taken at different times over 24 h; two sets from peripheral sites preferably. At least one central and one peripheral set of blood cultures should be taken at the same time if there is a CVC in situ. Each set including aerobic and anaerobic bottles with at least 10 ml of blood per bottle in adult cases or 1 ml/kg of blood per bottle for pediatric patients (up to a max of 10 kg).
- Chest X-ray

Sputum culture and urine for microscopy and culture (to rule out all other possible causes of the septic episode)

If blood cultures positive, or if further investigations unrevealing but infection still suspected:

- Echocardiogram (optimally a TEE, if a TTE is negative)

If blood cultures positive, or if a fluid collection is suspected, especially related to a pocked infection or retained fragment of previous VAD:

- Abdominal US, CT abdomen/thorax, nuclear imaging study (e.g., Indium WBC scan, or positron emission tomography (PET) scan [11])

Additional: Some centers prefer serial C-reactive protein, erythrocyte sedimentation rate, and procalcitonin to infer the likelihood of bacterial infection, when it cannot be proven through other means, although these are not universally performed nor routinely recommended. In particular, the use of procalcitonin, despite being helpful in other infections, may not be as usefully discriminatory in patients undergoing evaluation for infected VAD [12, 13].

For CVC infections with bacteremia, ECMO infection or suspected residual VAD-associated infection post HT with hematologic or soft tissue component, careful physical exam for inflammatory changes or disseminated embolic phenomenon can be vitally important.

Refer to Table 19.2 for the diagnosis of MCS Associated Residual Infection post HT with a history of an infected VAD pre HT.

Table 19.2 Diagnostic strategies to detect VAD infections, pre- and posttransplant

	Pump/cannula	VAD pocket	Superficial DL	Deep DL	Infective endocarditis	BSI	Mediastinitis
Microbiology							
Blood culture	Usually +	Rarely +	–	Rarely +	Usually +	+	+/–
Sterile site fluid	+/–	+/–	–	+/–	–	–	+/–
Exit DL drainage	–	–	+/–	+	–	–	–
CXR valuable	+	+	No	Rarely	+	+	+
Extended radiology necessary?	Yes, define extent of infection, plan surgical intervention	Yes, define extent of infection, plan surgical intervention	Only if concern for deep tunnel involvement	Only if concern for deep tunnel involvement	+ Embolic/–	Rarely	Yes, define extent of infection, plan surgical intervention
CT chest/abdo	– Fluid collection, esp. adjacent to inflow/outflow cannulae – Gas locules – End organ – Emboli	– VAD pocket fluid collection +/– Gas locules	Normal	– Fluid in anterior abdominal wall, surrounds DL – Stranding around DL	+/– End organ emboli (common sites, spine, iliopsoas, spleen, sternoclavicular joint)	–	– Anterior and/or posterior mediastinal fluid collection – Gas locules – Thoracic adenopathy
Indium nuclear scan	+/–	+/–	–	No	No	Unhelpful	+/–
PET scan	+ Can be helpful to differentiate blood from infection	+	Usually unnecessary	Usually unnecessary	Usually unnecessary	–	+
ECHO	Important to define severity and rule out cardiac abscess	Only if bacteremic	–	Only if bacteremic	Important to define severity and rule out valvular abscess	Needed to rule out I/E	Should be done if bacteremia suspected to rule out I/E

BSI bloodstream infection, *CT* computerize topography, *CVC* central venous catheter, *DL* driveline, *ECMO* extracorporeal membranous oxygenation, *WBC* white blood count, *I/E* infective endocarditis

19.3 Prevention: Discussion of Approaches to Prevent Onset of Disease

For CVC and ECMO circuits: strict adherence to infection control measures is recommended, both for the placement of such lines and devices, but also for their maintenance. Routine catheter exchange is not recommended.

A bundle of interventions should be introduced and enforced by all hospitals that includes hand hygiene, a maximal sterile barrier at the point of insertion, chlorhexidine skin antisepsis, optimal site selection (with avoidance of the femoral vein in adults where possible), and daily review of the site necessity of the central line [14]. No agreed standard for preventing infection in ECMO circuits exists, over and above that for CVCs. Many centers will perform daily antiseptic cleaning and dressing of cannula sites, as is recommended by the Extracorporeal Life Support Organization, ESLO [15].

For the patient with an infected VAD progressing to heart transplant, removal of the entire VAD at the time of heart transplantation is paramount to a successful course post HT. Antibiotics should be employed in the posttransplant period as directed by ID consultation with considerations of the specific pathogen and type of MCS infection pre-transplantation [7]. Post-HT removal or replacement of other devices that were present at the time the infected VAD was intact, i.e., ICD, pacer, should be considered soon in the post-HT period.

19.4 Treatment of the Different Types of Device Infection

Treatment for recognized CVC or ECMO infection is indicated when an organism is cultured that is not only recognized as a pathogen, but not related to an infection at another site. Management of the CVC itself is the first priority, with removal being optimal and exchange or salvage less so. Indications for removal are severe sepsis, hemodynamic instability, suppurative thrombophlebitis in the affected vein, or evidence of resultant metastatic infection. Persistent bacteremia for more than 3 days should also mandate line removal.

The type of organism is also important—*Staphylococcus aureus*, *Pseudomonas aeruginosa*, non-tuberculous mycobacteria, and fungi should also require line removal, if at all possible, given their higher pathogenicity and, in some instances, propensity to form biofilm, thereby reducing successful retention of the device.

Salvaging a CVC, and continuing to use it, should only be attempted when alternative modes of access are impossible. Antibiotic lock therapy can be tried for certain low-pathogenicity organisms [16], but there is limited data for its use in the transplant setting. Vancomycin has most commonly been used, although other drugs have been used [17]. Ethanol locks have also been tried without conclusive evidence [18].

Infected ECMO devices pose a much greater challenge, as there is considerably more morbidity associated with exchanging or removing the catheters and circuit. Decisions about catheter and circuit exchange should be discussed with the thoracic

surgery and/or transplant team involved, weighing up both patient and pathogen factors. Once again, an ECMO device that can be removed optimally altogether presents the best chance of cure, with exchange next best, and retention least likely to be successful (Table 19.3).

Most VAD-specific infections occur at the exit site of the driveline, or along its tunneled track through the abdominal wall. Depending on the degree of clinical extent, these should be managed with escalating levels of intensity. Exit site infections without signs of bloodstream infection or abscess can be managed with directed antibiotics alone in some cases. We typically try and give IV therapy for at least 2–4 weeks. More extensive driveline infections will require driveline debridement, and optimally the driveline can be moved within the abdominal wall so as not to traverse the previously infected territory. In these instances, antibiotics targeting

Table 19.3 Management of heart transplant recipient after extraction of infected VAD

Pre heart transplant infection diagnosis	Post heart transplant treatment
VAD-specific infections:	
– Superficial (exit site) DLI	– Ideally treated to resolution pre transplant – If still infected at the time of transplant, provided all driveline material gone, close observation may be sufficient. 10–14 days if superficial infection remains
– Deep DLI/pocket	– Continue directed antibiotics until after HT. There is no available literature regarding this topic, authors typically use 2–4 weeks
– MCS pump and/or cannula	– Continue directed antibiotics until after HT. There is no available literature regarding this topic, authors typically use 4–6 weeks of therapy, akin to mediastinitis
VAD-associated infection:	
– Bacteremia	– Duration of antibiotics depends on source, organism, and time to clearance of bacteremia – CRBSI secondary to *Staphylococcus aureus* is treated for at least 4 weeks (akin to "complicated bacteremia" in any other clinical circumstance) and the catheter is removed – If not *S. aureus*, and source known, at least 2 weeks from first negative blood culture (e.g., urinary tract source) – If no source is identified, treatment may be considered as with MCS pump and cannula infection
– Bacterial mediastinitis	– Duration of antibacterial therapy is at least 6 weeks after last surgical debridement – ID consultation is recommended – Consider removal of any hardware in infected space, e.g., sternal wires
– Infective endocarditis	– Duration of antibacterial therapy is the same as for MCS pump and cannula infection – ID consultation is recommended

BSI bloodstream infection, *CRBSI* catheter-related bloodstream infection, *DLI* driveline infection, *HT* heart transplantation, *ID* infectious disease, *MCS* mechanical circulatory support, *VAD* ventricular assist device

operative tissue cultures should be administered for 4–6 weeks, and in some instances, continued long-term suppression follows after. There are no firm guidelines as to who should be suppressed, but it is a patient-specific decision based on pathogen, available antibiotics and their long-term tolerability, the risk of relapse, and the likelihood of a deleterious outcome should relapse occur.

If the pump pocket or the VAD device itself is infected, antibiotics alone will not be curative, and extraction is sometimes required. For an infected VAD that is being extracted, one should ideally send the device and/or surrounding tissue for culture. Removal of the infected VAD during transplantation accomplishes source control, but residual infection must be addressed in this now highly immunocompromised host. VAD-specific infections in the pump/cannula or VAD-related infections of IE or BSI have a hematogenous feature, whereas the driveline and mediastinitis infections are primarily soft tissue. Table 19.3 addresses the treatment of these infections. ID consultation should be obtained to direct the specific treatment and duration appropriate for the individual HT. This table was adapted (with permission) from the ISHLT MCS_ID consensus paper [7] and reflects the need for further research in this area.

In the posttransplant patient with VAD-associated infection due to retained fragments of MCS, source control with fragment removal should be accomplished, and empiric antibiotic therapy for drug-resistant gram-positive and gram-negative bacteria and candida species should be considered and then tailored based on subsequent microbiologic results. Microbiologic results will direct ultimate antibiotic selection. Empiric therapy with Vancomycin and a pseudomonal-active gram-negative agent is one preference, with an echinocandin or azole antifungal a suitable choice for the particularly sick individual. A good clinician should understand their local hospital antibiogram, as well as the patient's personal history of colonization and allergy list, in order to help guide any empiric decisions.

If an infection is associated with a retained device (ICD, pacer, etc.), the device should be removed, and antibiotics should continue as for endocarditis—a hematogenous infection of unknown duration. Duration of antibiotic treatment post-device removal is an individualized decision, but 6 weeks is usually given by the authors.

VAD infections that occur in patients waiting for transplant may be managed differently. Given it can take several months to find a suitable heart donor, chronic infection suppression of VAD infections is often tried, although it can be difficult depending on drug needed and route of administration. Some of the older VAD devices also had a soft tissue pocket created for the pump (Heartmate II, etc.), which may be a site for residual infection after any ultimate device removal.

For patients where the VAD cannot be removed (a "destination" device), the device is exchanged, we recommend continuing pathogen-directed chronic suppressive therapy because the new device is placed in a presumably contaminated operative field. Occasionally VAD exchange can be considered, when the infected VAD is replaced by a new device. This is typically only entertained when there is a long anticipated wait until transplant, when infection suppression proves difficult, and the considerable surgical morbidity is considered justifiable.

For those who start chronic suppressive antibiotics, therapy is usually stopped once the heart is transplant and the VAD is removed, as long as all intravascular foreign bodies (e.g., VAD fragments, pacemaker/automatic implantable cardioverter defibrillators, leads) are removed.

Summary of the Approach to an Infected Device

Infections can be difficult to manage in anyone who requires a CVC, an ECMO device, or a VAD. Not only are they more common, typically involve skin and soft tissue organisms, but frequently require complete device removal, or at least exchange in order to affect durable cure.

Keys to management are:

- Recognize many of the usual signs of device infection may be blunted, so be prepared to take more cultures, more frequently if suspicion exists.
- Strict hospital infection control policies, including the deployment of infection control bundles, are crucial to minimize infection risk.
- Understand the most common organisms are skin-colonizing bacteria, so at a minimum, broad gram-positive active agents are appropriate for empiric therapy.
- Ideally remove any device, because device exchange is less preferable. Device retention and suppressive antibiotic therapy are least preferred and often fail.
- Once heart transplant has occurred, if infection persists, consider retained foreign bodies.
- Close engagement with infection disease and thoracic surgery specialists is optimal in complex cases, especially when ECMO and/or VAD infections are involved.

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Management and Prevention of Skin Infections

20

Nicolas Barros and Ricardo M. La Hoz

20.1 Introduction

The cumulative incidence of skin and soft tissue infections in solid organ transplant (SOT) recipients is estimated at 50–80%; therefore it is crucial for transplant specialists to familiarize themselves with the most common etiologies of these infections [1–3]. The focus of this chapter is to review relevant viral, bacterial, and fungal infections affecting the skin in SOT recipients and to provide a concise practical approach to their evaluation, management, and prevention. The clinical clues that will allow clinicians to construct a differential diagnosis include type of SOT, pre-transplant serologies, time after transplantation (Fig. 20.1), acuity of the presentation, type of primary lesion (Table 20.1), distribution of the lesions (Fig. 20.2), associated symptoms, net state of immunosuppression, and epidemiological risk factors.

20.2 Viral Infections

20.2.1 Herpes Simplex Virus

The majority of herpes simplex virus type 1 and 2 (HSV-1, HSV-2) disease in adult SOT recipients represent reactivation [4]. Regardless of serostatus prior to transplantation, HSV infections should be considered in the differential diagnosis of compatible syndromes as the disease can occur in seronegative patients who recently acquired the infection. Initial studies describe a high incidence of HSV disease during the first 1–2 months post-transplantation [5]. The introduction of antiviral prophylaxis has delayed the onset of HSV disease and decreased the incidence during

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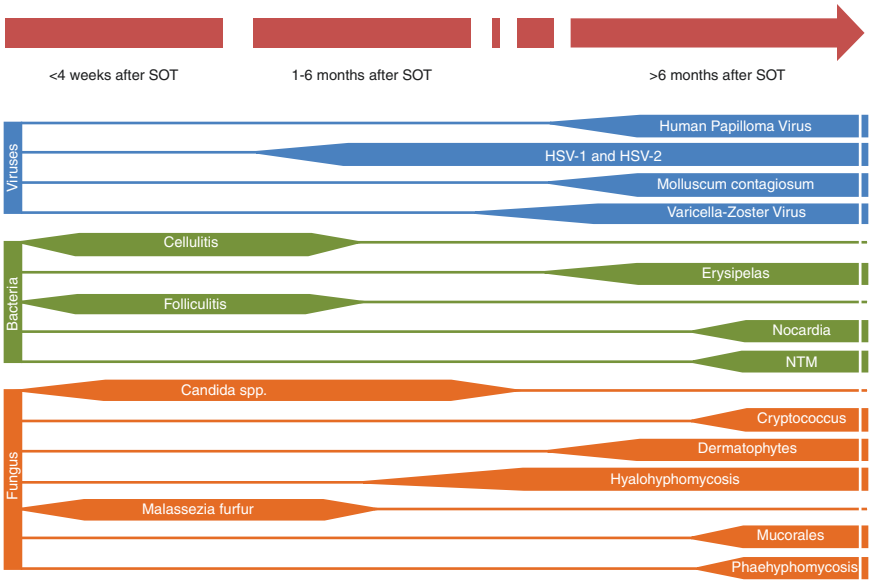

Fig. 20.1 The timeline of infections following organ transplantation. Infections occurring after solid organ transplantation are associated with the net state of immunosuppression and time from transplantation. Antiviral prophylaxis has delayed the presentation of viral infections including (HSV-1, HSV-2 and VZV). However, individual risks of infections vary according to epidemiological exposures

the first post-transplantation period. Currently, most events occur 3 or more months post-transplantation, and the cumulative incidence in the first year post-transplantation is 4% [6]. The most common manifestations of HSV infection are mucocutaneous lesions of the oropharynx and genital regions. Typically, they begin as a cluster of vesicles and pustules that, when ruptured, evolve to shallow ulcers with an erythematous base [7]. In some instances, the early lesions may coalesce leading to large ulcers.

Efforts to develop a vaccine for HSV have been unsuccessful. Therefore, strategies to prevent HSV infection focus on antivirals and behavioral interventions. Antivirals used for prophylaxis of CMV infection also prevent HSV replication. HSV-specific prophylaxis should be considered for all HSV-1 and HSV-2 seropositive SOT recipients who are not receiving antivirals for cytomegalovirus prevention. Mucocutaneous HSV disease is treated with oral acyclovir, valacyclovir, famciclovir, or intravenous acyclovir if unable to take PO [4].

20.2.2 Varicella Zoster Virus

The incidence of varicella zoster virus (VZV) reactivation is approximately 8–11% during the first 4 years post-transplantation [8]. Previous reports describe an earlier onset compared to contemporary studies (median 9 months), likely related to the widespread use of antiviral prophylaxis [9–11]. Older patients and thoracic

Table 20.1 Frequency of skin manifestations by disease

Organism/disease	Erysipelas	Desquamative	Folliculitis	Cellulitis	Macules, papules	Vesicular	Ulcers	Nodular	Exophytic lesions	Ecthyma-like
Viral										
HSV-1						+++	+			
HSV-2						+++	+			
HPV									+++	
MC virus	+++									
Trichodysplasia spinulosa									+++	
VZV						+++	+			
Bacterial										
Actinomyces					+			+++		
Nocardiosis				+	+			+++		
Non-Pseudomonal gram negatives			+	+			++			+
Non-tuberculous Mycobacteria			+		++		++	+++		
Staphylococcus aureus			++	+++	+					+
Streptococcus spp.	+++		+	+++						
Pseudomonas aeruginosa			++	+			++			+++
Fungal										
Aspergillus spp.					+		+	+		
Candida spp.		++		+	+					+
Cryptococcus spp.			++	++	+	++	++			
Dermatophytes		+++	+							
Dimorphic fungi							+	+++		
Fusarium spp.				+	+		+	+		+
Histoplasma spp.				+	+			+++		
Mucormycosis				+++	+		++			++
Phaeohyphomycosis				+	+		+	++	+	
Pseudallescheria/Scedosporium				++			+	+		

The frequency of presentations is represented by the sign "+". The presence of "+++" indicates the most common presentation while "++" denotes a less common presentation and "+" a rare presentation

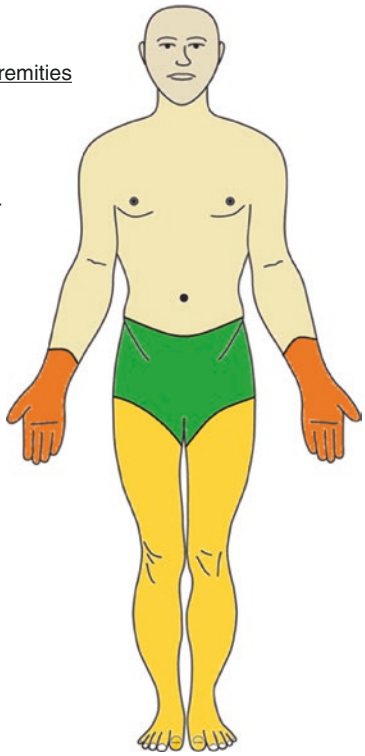

Fig. 20.2 Distribution of infections following solid organ transplantation. Although infections in immunocompromised patient can be atypical most presentations have patterns of distribution which are described on the figure. *HSV* Herpes virus simplex, *VZV* Varicella zoster virus, *NTM* Non-tuberculous mycobacteria, *HPV* Human papilloma virus

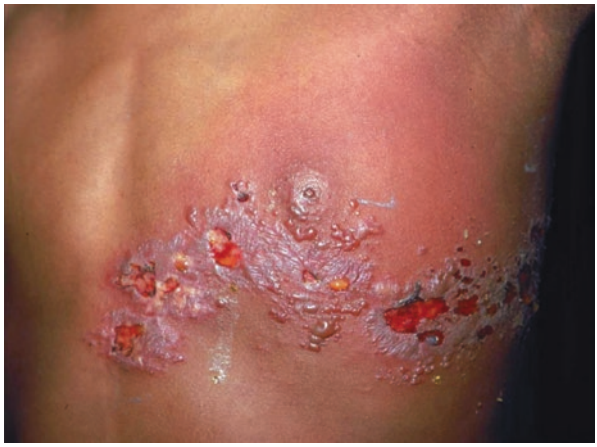

Fig. 20.3 Large coalescent vesicular rash on a T-5 dermatomal distribution in a patient with varicella zoster reactivation. Note that in SOT patients the vesicles may coalesce to form large ulcers. Image appears with permission of VisualDx

transplant recipients appear to be at increased risk [8]. VZV reactivation most commonly presents as a painful vesicular rash in a dermatomal distribution (herpes zoster) (Fig. 20.3). Herpes zoster ophthalmicus, herpes zoster oticus, and other uncommon presentations have also been described. Complications in SOT are common with about 50%, 20%, and 4% developing postherpetic neuralgia, cutaneous scarring, and recurrent disease, respectively. Disseminated VZV infections were an uncommon event in contemporary reports [9–11].

Prevention strategies for VZV include antiviral prophylaxis, pre-transplant vaccination and infection control measures. Antivirals used for prophylaxis of cytomegalovirus likely prevent VZV reactivation. VZV prophylaxis should be considered for VZV seropositive SOT recipients not receiving antivirals for cytomegalovirus (CMV) prevention [8]. Two doses of live attenuated Oka vaccine at least 2–4 weeks before transplant with a minimal interval of 4 weeks are recommended for VZV seronegative transplant candidates. The herpes zoster live attenuated and recombinant vaccine are recommended for adults >50 years of age, but the impact on reactivation post-transplantation is unknown [8, 12]. VZV live vaccines are not approved for post-transplantation use. The recombinant vaccine is not contraindicated in immunocompromised hosts albeit efficacy data are lacking for this population.

20.2.3 Human Papillomavirus

Cutaneous warts are common following SOT. Multiple reports indicate that by the fourth or fifth year post-transplantation up to 50–92% of SOT recipients will develop cutaneous warts [13, 14]. The different types of presentations include deep plantar warts, common warts, and plane warts. In SOT recipients they predominantly appear in sun-exposed areas and may be recalcitrant and difficult to control. In SOT recipients the lesions tend to be more numerous, extensive, and exuberant [15, 16]. Deep plantar warts (*verrucae plantaris*) characteristically present as painful, hyperkeratotic papules and plaques with disruption of normal dermatoglyphics. Common warts (*verruca vulgaris*) appear as well-demarcated exophytic, hyperkeratotic papules with a rough surface. They occur on the dorsum of the hands, fingers, periungual skin folds, palms, and soles. Plane warts (*verrucae planae*) present as sharply defined, papules in the face and neck.

The prevalence of anogenital warts, also known as condyloma acuminata, is about 2% in SOT recipients [17]. The lesions are flesh or gray colored, hyperkeratotic, and exophytic. They can range from smooth papules to rough acuminata growth. SOT recipients with anogenital warts are frequently infected with high-risk HPV types and thus will require screening for HPV-mediated malignancies [10].

A quadrivalent vaccine is available and has an efficacy above 90% to protect against types 16 and 18 (most commonly associated with cancer) and 6 and 11 (most commonly associated with warts). There are no specific recommendations for HPV vaccination in SOT recipients. Hence, clinicians are encouraged to follow the general population HPV vaccination schedule [14].

20.2.4 Molluscum Contagiosum

Molluscum contagiosum (MC) virus is reported worldwide and mainly affects children, sexually active adults, and immunocompromised hosts [7]. Immunocompetent patients typically present with fewer than 20 lesions. They are small (3–5 mm), firm, shiny, umbilicated papules and in immunocompetent hosts the lesions self-resolve in 3–12 months [16]. However, in SOT recipients the disease may be severe, spread widely, and lesions may coalesce to form a plaque. Giant nodular MC (>10 mm) are also seen in this population [18]. While in children the disease occurs on the face, chest, abdomen, and extremities; in adults, it usually involves the genitalia, lower portion of the abdomen, and upper thighs.

A systematic review of randomized trials that investigated the efficacy of treatments for non-genital MC in healthy individuals indicated that there is insufficient evidence to conclude that any treatment is definitively effective [19]. Nevertheless, intravenous and topical cidofovir has been used in immunocompromised hosts with severe refractory MC [20].

20.2.5 Trichodysplasia Spinulosa

Trichodysplasia spinulosa is a rare but disfiguring disease that appears to occur after primary infection by trichodysplasia spinulosa-associated polyomavirus. It is characterized by follicular papules with or without keratotic spines occurring in the face. However, cases involving the trunk and extremities have been reported. Reduction of immunosuppression, topical cidofovir, and systemic valganciclovir has been used to treat this infection [21].

20.3 Bacterial Infections

20.3.1 Folliculitis

Folliculitis is an infection of the hair follicle and is most frequently secondary to *S. aureus and P. aeruginosa* infections. Non-pseudomonal gram-negative bacteria and fungal etiologies are less common. Given the relatively minor nature of the infection, it is likely to be underdiagnosed. Reports indicate an incidence ranging from 2 to 27% [3, 22, 23]. The majority of episodes of folliculitis occur within the first 3 months following SOT and are characterized by papular or pustular lesions associated with a hair follicle. They appear more commonly on the buttocks and upper legs [5]. There are no effective methods to prevent the development of folliculitis. The management of folliculitis depends upon the etiology. No therapy is required for mild bacterial infections. However, patients with moderate presentations (or recurrent infections) may benefit from topical or systemic antimicrobials.

20.3.2 Erysipelas and Cellulitis

Erysipelas is the manifestation of an infection of the most superficial layers of the dermis and is characterized by dermal erythema with well-defined borders. The incidence of infection is unknown and usually occurs after the first year following SOT [5]. In contrast, cellulitis is an infection of deeper structures of the dermis and can present as purulent or non-purulent lesions. *Staphylococcus aureus* is the most common organism leading to purulent cellulitis, while streptococcal species are the most common microorganisms leading to non-purulent cellulitis. Less frequently gram-negative rods and several fungal infections can present as non-purulent cellulitis [24]. The frequency of cellulitis in SOT recipients is not well described. While recent reports indicate that it occurs in about 2% of SOT recipients, older reports indicated higher incidences of up to 33% [25, 26]. The reduction in the incidence during the recent years may be related to the use of cotrimoxazole prophylaxis and improved health care, though underreporting may be an important factor. Risk factors include skin disruption due to trauma, edema, obesity, skin inflammation (eczema), and preexisting skin infection (i.e., herpes zoster or tinea pedis). Prophylactic antibiotics, such as oral penicillin or erythromycin, should be considered in patients with recurrent cellulitis (3–4 episodes per year) despite attempts to control predisposing factors [24].

20.3.3 Ecthyma

Ecthyma gangrenosum (EG) is a rare skin lesion which was previously thought to be pathognomonic of systemic *Pseudomonas aeruginosa* infection. Lesions initially present as a hemorrhagic papule or plaque but progress into necrotic ulcers that can be surrounded by an erythematous halo (Fig. 20.4). In a recent report, EG was found to be secondary to *P. aeruginosa* in 74% of the cases, while other bacteria

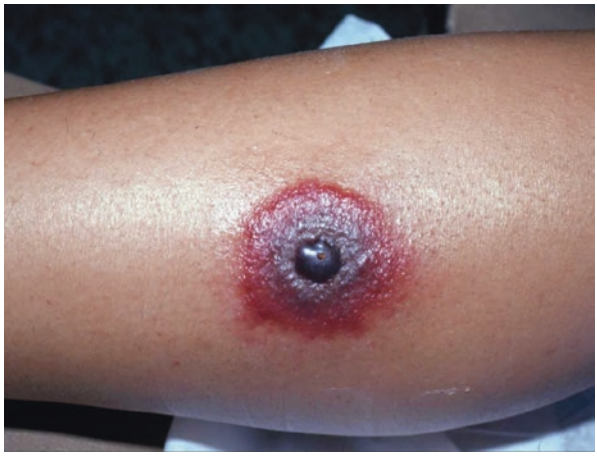

Fig. 20.4 Ecthyma gangrenosum secondary to *Pseudomonas aeruginosa* infection. The lesions present as a hemorrhagic papule or plaque and progress into necrotic ulcers that can be surrounded by an erythematous halo as noted in this patient. Image appears with permission of VisualDx

and fungi were involved in 17% and 9% of the cases, respectively. Septicemia was found in 58% of the patients with pseudomonal EG but only in 43% of those with non-pseudomonal EG. Up to 66% of the cases presented with lesions in the gluteal area or lower extremities with the rest affecting various parts of the body. Given the paucity of reports, the timing of presentation has not been well described. Diagnosis relies on clinical examination and microbiological confirmation of infection. Treatment includes antibiotic or antifungal therapy and often requires surgical debridement [27].

20.3.4 Opportunistic Bacterial Infections

The risk of developing nocardiosis after SOT varies depending on the type of transplanted organ and occurs in 0.04 to 3.5% of SOT recipients. Lung transplant recipients appear to be at a higher risk [28]. A retrospective European study described a median time of presentation of 17.5 months posttransplant and high calcineurin inhibitor levels in the prior month as the most important associated factor [29]. Skin manifestations may be the result of primary inoculation or secondary dissemination. Most skin lesions occur in the setting of nodular pneumonia and central nervous system (CNS) lesions [29]. As such, a SOT recipient with cutaneous nocardiosis, even if asymptomatic, should be evaluated for pulmonary and CNS involvement. Primary lesions present as mycetomas, sporotrichoid lesions, abscesses, ulcerated lesions, or nodules, while secondary lesions present as pustules, abscesses, or nodules [16]. The diagnosis is confirmed by culturing tissue specimens. *Nocardia farcinica* and *nova* complex are the most common species isolated from SOT recipients [29]. Although some reports have described a protective effect of TMP-SMX, more recent reports have not found such an association [28, 29]. Empiric therapy is recommended with 2–3 agents depending on the degree of severity and organ involvement [28]. Unfortunately, despite advancements in the diagnosis and treatment of this infection, the mortality remains high (~20%).

The incidence of non-tuberculous mycobacterial (NTM) infection varies according to the geography and type of transplant ranging from 0.04 to 8%. Liver transplant recipients appear to be at the lowest risk while lung transplant recipients at the highest. The median time for the presentation is variable and ranges from 8 to 48 months [30–32]. Cutaneous manifestations of NTM infection are the result of direct inoculation (usually in the extremities) or disseminated disease. More infrequently, patients that are colonized pre-transplantation may develop surgical site infections. Skin infections are currently the second most common clinical presentation of NTM infections after pleuropulmonary infection [32]. The skin lesions characteristically are erythematous or violaceous painful nodules that may ulcerate or form subcutaneous abscesses which spontaneously drain. Skin infections with NTM may be single lesions or multiple lesions associated with dissemination. NTM species associated with skin lesions are *M. fortuitum*, *M. abscessus*, *M. chelonae*, and *M. marinum*. The diagnosis is confirmed by isolating NTM species from the tissue of a compatible skin lesion. Treatment of NTM skin infections is

determined by the isolated species and susceptibility testing [33]. Beyond the recommended strategies for safe living after SOT, there are no proven interventions to prevent NTM infections [34].

20.4 Fungal Infections

20.4.1 Superficial Fungal Infections

Dermatophytes (e.g., *Trichophyton* spp., *Microsporum* spp. *Epidermophyton* spp.) and *Malassezia furfur* are the most common organisms leading to superficial fungal infections [35]. The incidence of dermatophytosis and *Malassezia furfur* are increased in patients with SOT and range from 24 to 30% and 9.5 to 14.3%, respectively [3, 25]. Some reports indicate that in tropical climates dermatophytosis may be present in up to 52% of SOT recipients [35]. Infections by dermatophytes usually occur in the late period following SOT with most cases occurring after the first year [5]. *Trichophyton* spp. (*T. rubrum, T. mentagrophytes*, and *T. tonsurans*) are the most commonly isolated dermatophytes. While *T. rubrum* is associated with tinea corporis and tinea cruris, *T. mentagrophytes* is associated with tinea unguium. *T. tonsurans* is associated with tinea capitis [35]. The presentation is similar to immunocompetent individuals. Majocchi's granuloma or trichophytic granuloma is an uncommon condition in which the dermatophyte invades the dermis or subcutaneous tissue. These lesions are described as perifollicular papules, pustules, or small nodules [36]. Pityriasis versicolor, caused by *Malassezia furfur,* presents as well-demarcated hypopigmented, hyperpigmented, or mildly erythematous macules or patches. The most common localization is the trunk. *Malassezia* folliculitis has also been described. Unlike dermatophytosis, both presentations of pityriasis are more common in the early post-transplantation period [35].

Candida skin infections occur in 3–10.8% and are predominantly during the first period. The most common presentations include primary superficial involvement (mucocutaneous). Given that most studies report mucosal and cutaneous involvement in aggregate (as mucocutaneous presentations), it is difficult to ascertain the incidence of cutaneous presentations without mucosal involvement [35].

20.4.2 Subcutaneous Fungal Infections

Subcutaneous fungal infections involve deeper layers of the dermis and are usually the result of direct inoculation of the fungal elements into the host tissue [37]. The lack of response to antimicrobials that target the common skin pathogens should prompt the evaluation for non-bacterial opportunistic infections [38].

Although multiple fungi have been implicated in the development of subcutaneous infections, *Sporothrix schenckii*, chromoblastomycosis, and mycetoma (eumycetoma) are the most prevalent [37]. Most of these infections are considered emerging fungal diseases, and their incidence in SOT is unknown. *Sporothrix*

schenckii can be found in the soil and thorny plants of endemic areas. It can produce fixed sporotrichosis or more commonly a lymphangitic or lymphocutaneous sporotrichosis. Cases of disseminated disease in immunocompromised hosts have been described [39]. Chromoblastomycosis is a disease caused by a variety of dematiaceous fungi including *Fonsecaea* spp., *Rhinocladiella aquaspersa*, *Phialophora verrucosa*, and *Cladosporium carrionii.* It usually presents as a verrucous plaques or nodules but can progress into large hyperkeratotic verrucous plaques [37, 39]. There are no effective prevention strategies, but given that subcutaneous fungal infections are the result of direct inoculation into deeper layers of the dermis, occupational exposures and gardening should be avoided or performed with barrier equipment [34].

20.4.3 Systemic Fungal Infections

A multicentric cohort study, including 16,808 SOT recipients, calculated a 12-month cumulative incidence of first invasive fungal disease of 1.3–11.6% depending on the organ type. Invasive candidiasis (candidemia and disseminated candidiasis) was the most common systemic mycosis among SOT recipients with a cumulative incidence of 1.9%. The risk of invasive candidiasis varies by transplanted organ, with the highest risk among small bowel transplant recipients, followed by pancreas, liver, kidney, heart, and lung [40]. In pancreas recipients, enteric drainage is associated with a higher risk compared to bladder drainage. In liver transplant recipients, factors associated with a higher risk include reoperation, re-transplantation, renal failure, high transfusion requirements, choledochojejunostomy, and *Candida* colonization at multiple sites [41]. The median time to presentation is 80 days (14–454) [42]. Embolic skin lesions can occur during invasive candidiasis. The lesions are described as erythematous macules, papules, pustules, and ecthyma-like lesions. They may be localized or disseminated, single or multiple, and usually involve the trunk and extremities (Fig. 20.5). The diagnosis is confirmed by histopathology and cultures of the lesions. Current guidelines favor empiric treatment with echinocandins, with de-escalation of therapy based on identification to the species level and susceptibility testing [43]. Interventions to ameliorate the risk of invasive candidiasis include infection control measures and prophylactic antifungals in the case of liver transplant recipients [41, 43].

Cryptococcosis is the third most common invasive fungal disease in SOT recipients with a 12-month cumulative incidence of Cryptococcosis post-transplantation of 0.2% [40]. T-cell depleting agents are associated with an increased risk of Cryptococcosis in SOT recipients [44]. Patients receiving a calcineurin inhibitor-based regimen were less likely to have disseminated disease and more likely to have disease limited to the lung [45]. Cutaneous cryptococcosis was the third most common presentation (17.8%) after meningoencephalitis and pulmonary disease and occurred at a median of 27.3 months. Most cutaneous cryptococcosis are the result of disseminated disease and should prompt an evaluation for meningoencephalitis, pulmonary disease, and fungemia. The lower extremities were the most commonly

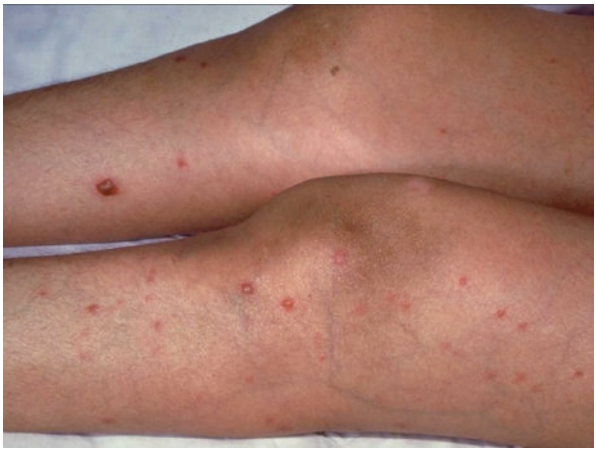

Fig. 20.5 Generalized pustular lesions characteristic of a patient with disseminated candidiasis. Image appears with permission of VisualDx

affected site (65%), followed by the trunk (26%) and upper extremities (21%). The lesions of cutaneous cryptococcosis are protean, and multiple lesions can present at the same time. The most common include nodule (35%), maculopapular (30%), ulcers/pustules or abscesses (30%), and cellulitis (30%) [37]. Primary cutaneous cryptococcosis can be treated with fluconazole, while cutaneous manifestations of disseminated disease should be treated with amphotericin B formulations as induction and fluconazole for consolidation and maintenance [46]. Routine prophylaxis is not recommended against cryptococcosis in SOT recipients [16].

Although aspergillosis is the second most common invasive fungal disease in SOT recipients with a 12-month cumulative incidence of 0.7%, cutaneous lesions are uncommon [40]. The lesions are described as tender erythematous or purpuric macules or papules that progress to violaceous plaques often with hemorrhagic bullae or may ulcerate or form necrotic lesions.

Mucormycosis and other molds (*Pseudallescheria*/*Scedosporium* and *Fusarium*) are uncommon invasive fungal diseases that tend to present around 12 months post-transplantation (312 and 465 days median time to presentation) [40]. The lesions are described as erythematous nodules, necrotic ulcers, erythematous-violaceous cellulitis, and ecthyma gangrenosum-like lesions. Mold skin disease is treated with reduction of immunosuppression if feasible, surgical debridement, and antifungals.

Histoplasma capsulatum is a dimorphic fungus which is highly prevalent in Ohio and the Mississippi river valleys. The incidence following transplantation is less than 1% and can be the result of primary infection, reactivation from a prior exposure, or as a donor-derived infection [40, 47]. Up to 25% of patients with disseminated histoplasmosis present with cutaneous involvement, and it portends a poor prognosis [48]. The lesions may present with heterogeneous morphologies including subcutaneous nodules, cellulitis, ulcers, or purpura. Infections usually occur during the late stage following SOT.

20.5 Conclusions

Cutaneous infections are common after SOT and are often the first manifestation of systemic infections associated with high morbidity and mortality. For this reason, it is imperative for transplant specialists to familiarize themselves with the most common manifestations and etiologies of skin and soft tissue infections in this population. The clinical clues that will allow clinicians to construct a differential diagnosis include type of SOT, pre-transplant serologies, time after transplantation, acuity of the presentation, type of primary lesion, distribution of the lesions, associated symptoms, the net state of immunosuppression, and epidemiological risk factors.

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