Preface
Management of Infections in Solid Organ Transplant Recipients

Sherif Beniameen Mossad, MD, FACP, FIDSA, FAST
Editor

It has been 5 years since the last update on infections in solid organ transplant (SOT) recipients was published in *Infectious Disease Clinics of North America* in 2013. There has been a 20% increase in the number of organ transplants over the last 5 years, largely driven by increase in the number of deceased donors, with more than 33,000 transplants performed annually in the United States. Our nation is facing an unprecedented opioid epidemic, which is currently accounting in several parts of the country for a quarter of organ donors who die of overdose. These donors are considered at increased risk for transmitting blood-borne pathogens, including hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV). However, data have accumulated, documenting the long-term survival benefit of accepting such organs. One recent article showed that only a third of kidney transplant candidates who were offered and declined an increased risk donor (IRD) later received non-IRD kidney transplants. The irony is that the kidney donor risk profile index (which predicts the likelihood of graft failure) of these non-IRD kidneys was more than double that of the IRD kidneys that had been declined. Although the mortality risk in the first 30 days following acceptance of IRD kidneys was higher compared with non-IRD kidneys, mortality risk was 33% lower 1 to 6 months, and 48% lower beyond 6 months after decision, respectively.

The transplant community has benefited greatly from the infectious diseases practice guidelines first published by the American Society of Transplantation Infectious Diseases Community of Practice in 2004 and then updated in 2009 and 2013. Authors of the current issue of *Infectious Disease Clinics of North America* have set out to provide the transplant community with an update in several pertinent topics in this field.

While the need for organs is ever increasing, more than 115,000 people are currently on the waiting list, identifying donors that are safe from the infectious diseases perspective remains of paramount importance. On average, 2 to 3 organs are procured...
from each donor; range is 1 to 8 organs. It thus befits to start the current issue with an
update of this topic. In addition, several other articles in this issue address specific
aspects of this topic, such organs from donors colonized or infected with multidrug-
resistant bacterial infections, and organs from HCV- or HIV-infected donors. Certain
infections, such cytomegalovirus (CMV), are “expected” to be transmitted from
donors to recipients; thus specific guidelines for surveillance and prevention have
been published. Most organ donor–derived infections present within the first 6 weeks
after transplantation. However, certain infections, particularly latent infections with
long incubation periods that are not readily recognized to be transmitted, may cause
disseminated disease in the immunosuppressed organ recipient. Donors with possible
meningoencephalitis are particularly associated with dire consequences.

Immunizations are considered the “seatbelts” of health care. While the majority of
immunizations are provided by primary care providers who are currently caring for a
large number of patients awaiting SOT, many of these patients are immunocompro-
mised due to their end-organ disease and its consequences, or due to immunosup-
pressive medications attempting to support organ function while awaiting
transplant. It is important to vaccinate transplant candidates as early as possible dur-
ing transplant evaluation. Barring the holy grail of tolerance, SOT recipients are ex-
pected to remain on immunosuppressive medications for life to prevent organ
rejection. While inactivated vaccinations are safe before or after transplantation,
live-attenuated vaccines usually cannot be safely administered to patients receiving
immunosuppressive medications. Thus, updating immunizations before transplantation
may represent the only opportunity to administer live-attenuated vaccines. As
importantly, certain vaccines may allow SOT recipients to accept organs they may
not have otherwise, as in the case of the hepatitis B core antibody positive donor or-
gans. To improve vaccine-induced immunogenicity posttransplant, most centers start
vaccinating SOT recipients 3 to 6 months after transplant.

We live in a microbial world, mostly in symbiosis. While this may be true for the ma-
jority of the population, immunosuppressed individuals, particularly SOT recipients,
view microbes surrounding them as their primary enemy, and rightly so. It’s true
that after transplantation they should return, as much as possible, to their normal ac-
tivities, and not “live in a bubble.” However, patients, their families, and health care
providers (HCP) hold many beliefs about safe living that may or may not be true.
The transplant community needs sound advice on a variety of issues ranging from
leisurely activities, food and water safety, safe sex, animal contact, and travel.
Precious lives extended by SOT should be protected by education before and after
transplantation, providing the knowledge and measures to mitigate exposures to
various infections in the community.

Almost all health care systems currently have an antimicrobial stewardship program
(ASP) in place. Judicious use of antibiotics is “expected” of all HCP, but implementing
programs to oversee such practice is actually in its infancy. The Infectious Diseases
Society of America and the Society of Healthcare Epidemiology of America published
its first edition of such guidelines in 2016.4 Perhaps no more important than in SOT
recipients, should ASP be implemented, given the rising rates of antimicrobial resis-
tance in this patient population. Such ASP should be specifically customized to the
SOT population, accounting for the multidisciplinary nature of the care for these pa-
tients, and the particularly important aspect of integrating the microbiology laboratory
in this process, also known as “diagnostic” stewardship.

Infections due to multidrug-resistant organisms (MDRO) disproportionately affect
SOT recipients and are associated with a 3-fold increase in mortality. In endemic
areas, the incidence of infections due to carbapenem-resistant enterobacteriaceae
(CRE) is 5%; most of which occur within 2 to 4 weeks of transplantation. Several new antibacterial agents have been developed to treat these infections, including ceftolozane-tazobactam, ceftazidime-avibactam, and meropenem-vaborbactam. Studies have shown a mortality advantage in using these agents, compared to older agents, such as polymyxin in treating infections due to CRE. It is important to use these agents judiciously, since resistance can develop. Outcomes of SOT in patients colonized with MDRO vary with the organ transplanted and type of organism. For example, pretransplant colonization of lung transplant candidates with MDR *Pseudomonas aeruginosa* strains does not affect short- or long-term survival following transplantation.

Morbidity and mortality associated with invasive fungal infections (IFI) in SOT recipients remain high. Candida infections remain the most common cause of IFI in these patients. Invasive mold infections (IMI) are associated with mortalities ranging from 20% to 60%, because they are difficult to diagnose; commonly requiring invasive procedures, and difficult to treat, possibly with combination antifungal medications. IMI most commonly affect the lungs, except for dematiaceous (pigmented) molds and paecilomycetes, which most commonly cause localized skin infections. Endemic mycoses are rare in SOT recipients, but are also difficult to diagnose, with progressive disseminated disease as the most common form of presentation, and therapy typically recommended for 12 months or more. In the last 5 years, no new classes of antifungal agents have come on the market, but new members of antifungal classes have been developed, such as isavuconazole. Better formulated antifungal agents, such the extended-release posaconazole, are now available. Combinations of antifungal agents have been studied in transplant recipients, with some success. While antifungal prophylaxis in SOT recipients has been relatively successful, it is clear that “one size does not fit all.” As expected, breakthrough fungal infections with both commonly and rarely encountered fungi continue to occur. In addition, newly described fungi, such as *Candida auris*, have been encountered in SOT recipients.

CMV is arguably the most important pathogen in SOT recipients. High CMV seroprevalence, unique viral biology, and “sicker” transplant recipients contribute to this fact. Adoption of the World Health Organization CMV standard based on international units per milliliter, rather than copies per milliliter, has allowed labs to standardize quantitative polymerase chain reaction results. One important caveat is that tissue-invasive CMV disease, particularly gastrointestinal disease, can occur in the absence of CMV viremia, particularly in CMV seropositive recipients. Prophylactic ganciclovir and valganciclovir have been very successful in preventing CMV-related events, but late infections after completing prophylaxis course and the emergence of ganciclovir resistance have been formidable problems facing the transplant community. Letermovir, the only new agent active against CMV that has been approved in the United States in the last 5 years, has a different mechanism of action than previously approved classes; it inhibits CMV deoxyribonuclease terminase complex, thus inhibiting viral packaging. It is currently approved only for prevention of CMV reactivation in CMV seropositive allogeneic hematopoietic stem cell transplant recipients, but studies in SOT recipients are underway. Newer diagnostic tests assessing the cell-mediated immune response to CMV are currently available and may soon be integrated in risk stratification for duration of primary or secondary prophylaxis.

Although BK polyomavirus is the most common opportunistic viral infection occurring in kidney and pancreas transplant recipients, there is currently no specific antiviral treatment for BK viremia and the associated nephropathy. Reduction of immunosuppression remains the mainstay of management. Systematic surveillance is currently standard of care, and early recognition is crucial for graft survival.
Infection prevention interventions have been successful in reducing several hospital-acquired infections, with the exception of *Clostridium difficile*–associated diarrhea (CDAD). Rates of CDAD have actually doubled in the last decade. Heavy use of antimicrobial agents in SOT recipients puts them at a particularly high risk for recurrent CDAD. The highest incidence is in lung transplant recipients. A 2-fold increased risk of graft loss has been observed, even with mild clinical presentation of CDAD. Diagnostic stewardship has become a cornerstone of preventing *C difficile* infection. Treatment in SOT recipients is similar to that in immunocompetent patients. Fecal microbiota transplantation has been safely used in SOT recipients, but randomized trials in this population are lacking. Fidaxomicin was approved in 2011, and a study is currently underway comparing its use to standard of care in SOT recipients. Bezlotoxumab, a human monoclonal antibody binding *C difficile* toxins A and B, decreases the rate of recurrent CDAD, but studies in SOT recipients are lacking.

Nucleoside or nucleotide analogues with or without hepatitis B immunoglobulin have resulted in excellent outcomes in all SOT recipients with HBV infection. All SOT candidates should receive the 40 μg/mL preparation 3-dose series of HBV vaccine. Donors who are positive for anti-HB core antibody can be safely used for recipients who are immune to HBV (anti-HB surface antibody >10 IU/mL), or with appropriate prophylaxis of the nonimmune recipients. Limited data exist regarding the use of HBsAg-positive donors. We are in the “golden age” for management of HCV infection. Directly acting antivirals, particularly with pangenotypic combinations, have significantly improved the outcomes in SOT candidates and recipients. Timing of whether to treat HCV infection before or after SOT remains controversial. There is growing interest in transplanting HCV viremic organs in HCV-negative recipients. Hepatitis E virus (HEV) infection is much less prevalent than HBV and HCV infections, but it becomes chronic in 60% of cases and results in cirrhosis in 10%. HEV antibodies may be absent in 20% of patients; thus, diagnosis relies on the detection of HEV ribonucleic acid in serum or stool. Most transplant recipients with HEV infection respond well to ribavirin.

Tuberculosis (TB) is not endemic in the United States, but screening of SOT candidates is recommended, as well as epidemiological assessment of SOT donors for TB. Treatment of active TB is much more complicated than treatment of latent tuberculosis infection (LTBI) in SOT candidates and recipients, given the myriad of drug interactions with immunosuppressive medications, and overlapping side effects. Isoniazid for 9 months is the preferred therapy for LTBI. Risk of TB following SOT is at least 4 times that of the general population, and about twice as common as the risk in patients with end-organ disease. Most cases of TB following SOT are due to reactivation of LTBI due to iatrogenic immunosuppression and occur months to years following SOT. Thus, diagnosis of TB in the early period following SOT should raise suspicion for a donor-derived infection. In general, treatment of active TB following SOT should follow the same guidelines as for the general population.

Mycobacteria other than tuberculosis (MOTT) are ubiquitous in the environment. Lung transplant candidates are particularly at higher risk for colonization and infection with MOTT, which may pose significant risks, particularly in the early period after transplantation. Explanting the infected lungs at the time of transplantation significantly reduces the burden of infection, but anastomotic sites remain at risk. Different MOTT organisms require specific combination of antimicrobials; many have significant drug interactions with immunosuppressive medications. Several antimicrobials have been added to the list of agents active against MOTT, including clofazimine, bedaquiline, tedizolid, tigecycline, and inhaled amikacin.
Strongyloidiasis remains endemic in the southern United States. Reactivation after SOT is rare, but should be eliminated by pretransplant surveillance and targeted treatment. Ideal screening method is yet to be determined, but treatment with ivermectin appears to be well tolerated in SOT candidates and recipients.

Life expectancy of patients infected with HIV is currently similar to the general population, thanks to effective antiretroviral agents. Progress of SOT in these patients has been slow. Efforts should be made to refer HIV-infected patients for assessment for SOT, before they become too ill for transplant. New hope came with the HIV Organ Policy Equity “HOPE” act, which was implemented in 2015. This will allow for standardized research into transplanting organs from HIV-positive donors into HIV-positive recipients.

I thank the authors of the 16 articles in this issue of *Infectious Diseases Clinics of North America*. I especially thank Dr Helen Boucher, who invited me as editor for this exciting issue.

Sherif Beniameen Mossad, MD, FACP, FIDSA, FAST  
Department of Infectious Diseases  
Respiratory Institute  
Cleveland Clinic  
Section of Transplant Infectious Diseases and Transplant Center  
Lerner College of Medicine of Case Western Reserve University  
9500 Euclid Avenue G21, Room 131  
Cleveland, OH 44195, USA  
E-mail address: mossads@ccf.org

REFERENCES