

## Special Article

# Introduction: Infections in Solid Organ Transplantation

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**Abbreviations:** BOS, bronchiolitis obliterans syndrome; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; PCP, *Pneumocystis jirovecii* pneumonia; PTLD, post-transplant lymphoproliferative disorder; RSV, respiratory syncytial virus; SOT, solid organ transplantation; WNV, West Nile virus.

The use of solid organ transplantation (SOT) has been established as accepted therapy for end-stage disease of the kidneys, liver, heart and lungs for nearly 30 years. Intestinal and pancreas transplantation are also generally available but are provided on a more limited basis. While surgical procedures are well established, the field of transplantation continues to explore and experience innovations in immunosuppressive therapy with goals of improving outcomes and in pursuit of tolerance. The potential for surgical and technical complications combined with the impact of immune suppression predisposes recipients of SOT to clinically important infectious sequelae. The diversity and consequences of infectious complications of SOT have led a growing numbers of infectious disease specialists to focus their career interests on the pursuit of clinical expertise with this population resulting in the acquisition of a growing body of clinical evidence in support of optimal management of these patients. The availability of this evidence (or in some cases the development of clinical consensus where definitive evidence is lacking) serves as the basis for this 3rd edition of the AST Guidelines for the Prevention and Treatment of Infectious Complications of Solid Organ Transplantation. While individual sections within the 3rd edition of the Guidelines focus on specific pathogens or disease categories, risk factors for and timing of presentation of infectious complications in this population tend to apply to recipients of all types of organs and to most pathogens and their associated clinical syndromes.

Accordingly, an understanding of these general principles provides a strong foundation for the care and prevention of infections in this population.

## Predisposing Factors for Infection After SOT

Risk factors that predispose to infections in recipients of organ transplantation can be categorized as being present before transplant within the recipient or donor and those secondary to intraoperative and posttransplant events.

### Pretransplant factors—recipients

For all recipients of SOT, the organ being transplanted is the critical determinant of the location of infection in these patients, especially during the first 3 postoperative months (1). The chest, abdomen and urinary tract are the most common sites of infection experienced by recipients of thoracic, liver and kidney transplantation, respectively. The likely explanation for predilection to these sites include the presence of local ischemic injury and bleeding, as well as potential contamination (2).

The underlying illnesses causing organ failure may also be associated with an increased risk for developing infection after organ transplantation. For example, patients with cystic fibrosis who undergo lung or less commonly liver transplantation are predisposed to pseudomonal and fungal infections. Similarly, adult liver recipients undergoing transplantation for HCV-associated cirrhosis are at an increased risk for recurrent infection in the new hepatic allograft although strategies to protect against recurrence are increasingly being evaluated. More generally, a history of palliative surgery before transplant as part of the management of the underlying illness increases the technical difficulty of the transplant procedure, enhancing the risk of developing a posttransplant infection (3). In general, the severity of the underlying disease leading to end organ failure and its impact on other organs systems at the time of transplantation correlates with risk of postoperative morbidity and mortality (4). Similarly, chronic malnutrition predisposes to infections before and after transplantation. Attempts to correct nutritional deficits with intravenous TPN increases the likelihood of catheter-associated blood stream infections. Finally, mechanical ventilation prior to SOT increases the likelihood of developing infection with multidrug-resistant nosocomial pathogens.

The age of the recipient at the time of transplant significantly impacts on susceptibility to and severity of infection in organ recipients. Transplantation at a young age has

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been associated with higher rates of infection during the first few years after transplantation (5). Infants and toddlers undergoing SOT experience greater morbidity and mortality with community-acquired viruses (e.g. respiratory syncytial virus [RSV], parainfluenza) compared to older children or adult recipients. They are more likely to develop primary infection with cytomegalovirus (CMV) and Epstein–Barr virus (EBV), predisposing them to worse outcomes compared to patients experiencing viral reactivation or reinfection with a new strain of these pathogens (6,7). By contrast, other pathogens, such as *Cryptococcus neoformans*, are rarely seen in children but are important opportunistic pathogen in adult organ recipients. Age also potentially impacts on risk of infection for older (>65 year old) organ transplant recipients. Preliminary evidence suggests that older organ recipients may experience exaggerated effects of immune senescence compared to age matched controls (8). Accordingly, they may be more prone to infectious risks after transplant than younger adult recipients. However, evidence confirming this risk is limited (9).

Finally, younger children frequently undergo SOT before they are fully immunized, increasing their risk for vaccine-preventable infections. When vaccines are given after transplant, they may not provide full protection. Accordingly, at least some younger recipients are at increased risk for infection with vaccine preventable diseases despite being immunized after transplant (10). Similarly, adult patients undergoing organ transplantation in their 60s may also be at increased risk for vaccine preventable disease. Although not carefully studied, booster immunizations of these older recipients may be missed due to the presence of end-stage organ disease or lack of attention to updating vaccinations by the transplant specialists who have often assumed primary responsibility for candidates care.

### **Pretransplant factors—donors**

Organ transplant recipients are at risk of acquiring pathogens from donors with active or latent infections at the time of procurement. While many potential infectious exposures from the donor can be anticipated or identified, some donor-derived infections occur unexpectedly, defying efforts to effectively recognize the presence of risk within a given donor. Examples of pathogens associated with expected donor-derived infections include CMV (11–13), EBV and *Toxoplasma*. Knowledge of the serologic status of the donor and recipient informs the use of preventive strategies mitigating infectious risk from these pathogens. Of greater concern is the development of unexpected donor-derived infection from a growing number of pathogens, including, *Mycobacterium tuberculosis*, *Histoplasma* spp., West Nile virus (WNV), hepatitis B (HBV) and C viruses (HCV) and human immunodeficiency virus (HIV) (14). The unexpected transmission of these agents can lead to infection in one or more recipients and cause significant morbidity and occasional mortality. Strategies have been developed in an effort to reduce the

incidence and impact of unexpected transmission of potential pathogens from the donor. In considering the use of any donor, there is clearly a potential risk to the recipient who experiences unexpected transmission of a pathogen but there is also a consequence to potential recipients on the waiting list when potentially viable donors are turned down. Issues related to donor-derived transmission of infectious pathogens are discussed in detail in chapter 3 of the guidelines.

Another donor-related concern is the presence of bacteria or fungi colonizing the respiratory tract of a lung donor or infecting organs or vessels from other allografts; such organisms can cause infection in the postoperative period (15). Similarly, unrecognized acute bacteremia or viremia at the time of organ recovery is an additional risk to the recipient. The presence of potential pathogens may be identified by culture or by histopathology. The true identity of pathogens identified by pathologic methods may never be known or proven. However, recognition of the presence of some marker of potential risk in the donor can allow for the recipient's transplant team to develop a rationale response. Early recognition of potential risk might allow the implementation of a serial monitoring of the recipients and in some circumstances may warrant the use of antimicrobial therapy as prophylaxis or treatment of subclinical infection. As increasing attention focuses on the problem of donor-derived infection, our recognition of specific risk factors for and the potential to screen for and implement prophylaxis against these infections will likely increase leading to improved clinical outcomes.

### **Intraoperative factors**

The choice of surgical reconstruction used for a given transplant recipient can predispose to infectious complications. For example, the risk of infection is different in liver transplant recipients undergoing duct-to-duct biliary anastomosis compared to those whose biliary drainage is accomplished via Roux-en-Y anastomosis (16). Unexpected events occurring during surgery also predispose to infection. Injury to the phrenic, vagal, or recurrent laryngeal nerves during surgery affect pulmonary toilet, predisposing a lung transplant recipient to pneumonia (17). Ischemic injury to the allograft during the transplant procedure reduces its viability and increases the risk of infection. Additional factors, including prolonged operative time, contamination of the operative field, and bleeding at or near surgical sites have been associated with an increased risk of postoperative infections in these patients.

### **Posttransplant factors**

Immunosuppression is the major risk factor for infection following transplantation. The immunosuppressive regimens used in SOT recipients continue to evolve with a goal of minimizing toxicity and side effects while optimizing organ function. Unfortunately, while the level of infectious risk may vary by individual agent or specific combination,

all such combinations appear to place organ recipients at some risk for opportunistic infections. However, it is difficult to quantify how immunosuppressed an individual organ recipient is. Although there are nonspecific assays that measure immunity, these are not always predictive of infection. Requirement for augmented immune suppression to treat rejection further increases the risk of infection after SOT. This risk associated with the use of immune suppression continues throughout the entire posttransplant course. The use of antilymphocyte preparations and many of an increasingly diverse list of biologic agents used in these patients have been associated with an enhanced risk of infection (13,16,18). As newer immunosuppressive agents are introduced, clinicians must be aware of and alert for changes in infectious manifestations and profiles seen in these patients (19).

Technical problems affecting the vascular supply and functional integrity of the allograft are major risk factors for infectious complications that manifest after the transplantation. Examples of specific technical problems associated with infection include thrombosis of the hepatic artery after liver transplantation (20); vesicoureteral reflux after renal transplantation (21) and mediastinal bleeding requiring re-exploration in thoracic transplantation. These complications have been associated with hepatic abscesses and blood stream infection (20), graft pyelonephritis (21) and mediastinitis, respectively (11). The ongoing presence of uncorrected technical problems can predispose to multiple episodes of recurrent infections until these issues are corrected. Efforts should be made to identify and potentially correct these technical problems in patients presenting with infectious syndromes associated with their presence.

The prolonged use of indwelling cannulas is another significant risk factor for infection after transplantation. The use of central venous catheters is associated with bloodstream infections; urethral catheters predispose to urinary tract infection; the use of a cannula in an obstructed biliary tract predisposes to cholangitis; and prolonged endotracheal intubation is associated with pneumonia. The risk for these catheter-associated infectious syndromes persists until the catheter is removed. Accordingly, active efforts should be undertaken to review the ongoing requirements for these cannulas with removal undertaken as soon as practical.

Nosocomial exposures constitute the final group of posttransplant risk factors. All transplant recipients are at risk for developing infection with transfusion-associated pathogens. Patients undergoing transplantation during the winter months are often exposed nosocomially to viruses associated with annual community based outbreaks (e.g. RSV, influenza, rotavirus). While this is particularly true in pediatric patients, adult recipients can also experience clinically significant infections secondary to these pathogens through exposure to affected hospital staff, family and other visitors. The presence in the hospital of areas of

heavy contamination with pathogenic fungi, such as *Aspergillus* spp. increases the risk of invasive fungal disease in these patients. And finally, there is increasing concern for nosocomial exposure to and development of infection with multiple-drug resistant bacteria after transplantation.

Finally, community exposure is an important potential source of later infection after organ recipients are discharged from hospital. These exposures may vary from common community-acquired viral infections to less commonly seen pathogens that might be related to occupational or travel exposures. These are discussed in more detail in Chapter 30, which focuses on 'safe living' after transplantation.

## Timing of Infections After SOT

The timing of specific infections developing after SOT is generally predictable regardless of which organ is transplanted. The majority of clinically important infections occur within the first 180 days; individual pathogens typically present at stereotypical times after transplantation. However, the time of onset for certain pathogens can be affected by the use of prophylactic strategies, alterations in immune suppression or need for additional surgery. In considering potential causes of infection in SOT recipients, it is useful to divide risk periods into three major intervals in order to consider which pathogens are most likely: (1) early (0–30 days after transplantation); (2) intermediate (30–180 days) and (3) late (beyond 180 days). However, this assessment by time is not absolute. Some infections can occur throughout the posttransplant course and others may occur outside of their usual risk period. Nevertheless, consideration of these time intervals provides a useful framework for the approach to a patient with fever after transplantation, guiding the initial differential diagnosis (Table 1).

### Early infections

Early infections (0–30 days after transplant) are usually associated with the presence of preexisting conditions or complications of surgery. Bacteria and yeast are the most frequent pathogens recovered during in the first 30 days after transplant (11,22). Fifty percent or more of all bacterial infections that develop after transplantation occur during the early posttransplant period (11,22). Superficial and deep surgical site infections are among the most common infectious complications seen during this period. Technical difficulties, particularly those resulting in anastomotic stenosis, leaks or other complications, are important risk factors for the development of invasive infection in the first month after most types of organ transplantation. Finally, donor-derived bacterial and/or fungal infections may present during this time period and when donor derivation is suspected, notification of the appropriate local and national organizations/agencies should be performed to minimize the risk to other recipients.

**Table 1:** Timing of infectious complications following transplantation<sup>1</sup>

Early period (0–1 months)	Middle period (1–6 months)	Late period (> 6 months)
Bacterial infections	Viral infections	Viral infections
Gram-negative enteric bacilli	Cytomegalovirus	Epstein–Barr virus
Small bowel, liver, neonatal heart	All transplant types	All transplant types, but less than middle period
<i>Pseudomonas/Burkholderia</i> spp.	Seronegative recipient of seropositive donor	Varicella-zoster virus
Cystic fibrosis: lung	Epstein–Barr virus	All transplant types
Gram-positive organisms	All transplant types	Community-acquired viral infections
All transplant types	Seronegative recipient	All transplant types
Fungal infections	Small bowel highest-risk group	Bacterial infections
All transplant types	Varicella-zoster virus	<i>Pseudomonas/Burkholderia</i> spp.
Viral infections	All transplant types	Cystic fibrosis: lung
Herpes simplex virus	Opportunistic infections	Lung recipients with chronic rejection
All transplant types	<i>Pneumocystis jirovecii</i>	Gram-negative bacillary bacteremia
Nosocomial respiratory viruses	All transplant types	Small bowel
All transplant types	<i>Toxoplasma gondii</i>	Fungal infections
	Seronegative recipient of a heart from a seropositive donor	<i>Aspergillus</i> spp.
	Bacterial infections	Lung transplants with chronic rejection
	<i>Pseudomonas/Burkholderia</i> spp.	
	Pneumonia	
	Cystic fibrosis: lung	
	Gram-negative enteric bacilli	
	Small bowel	

<sup>1</sup>Listed in decreasing order of relative importance.

### Intermediate period

The intermediate period (31–180 days after transplant) is the typical time of onset of infections attributable to latent pathogens transmitted from donor organs and blood products and those reactivated within the recipient. This is also the period where classical 'opportunistic infections' will present. In the absence of prophylaxis, CMV infection peaks during this time period (11–13). Similarly, in the absence of the use of preventive strategies, EBV-associated posttransplant lymphoproliferative disorders (PTLD) (6,23,24), *Pneumocystis jirovecii* pneumonia (PCP) (25–27) and toxoplasmosis (28), could also occur during this period. A review of autopsies found infections to be the most common cause of death during this period after lung or heart-lung transplantation; disseminated adenovirus and *Aspergillus* infection predominated, followed by CMV and EBV disease (29,30).

### Late infections

In the later period (beyond 180 days following transplantation), infection risks vary with immunosuppression and exposures. There are some differences in adults and children. In general, rates and severity of infection in children more than 6 months after transplantation are similar to those observed in otherwise healthy children (7). This is most likely attributable to the fact that pediatric transplant recipients are usually maintained on lower levels of immunosuppression at that time. This may not be the case for adults in whom underlying comorbidities, such as diabetes mellitus and malignancies, may increase the risk for infections during this later period. Those individuals who

require increased immunosuppression, either related to rejection or underlying disease, will be at greater risk for late opportunistic infections. CMV can manifest late, particularly in children and adults who receive prolonged prophylaxis (31) and PTLD continues to manifest in the late period (23,24). In addition, recurrent infections with stereotypical pathogens may occur late after transplant in certain recipients with specific conditions as demonstrated in recipients of lung transplantation with chronic lung rejection manifested as bronchiolitis obliterans syndrome (BOS). These patients frequently become infected with *Pseudomonas*, *Stenotrophomonas* and *Aspergillus* (15,29,30). In both pediatric and adult organ recipients, chronic or recurrent infections continue to occur in the subset who have uncorrected anatomic or functional abnormalities (e.g. vesicoureteral reflux, biliary stricture). During this period, children are more likely to be at risk for primary infection with certain community-acquired viral pathogens, such as the herpesviruses (Varicella, EBV and CMV) (32). Finally, both adult and pediatric patients continue to be at risk of being exposed to community-acquired respiratory and gastrointestinal viral pathogens. In general, in the absence of ongoing requirements for higher levels of immune suppression or graft dysfunction, these infections are fairly well tolerated by transplant recipients late after SOT.

### Infections occurring throughout the postoperative course

Some infections occur irrespective of time. These may reflect nosocomial acquisition which is seen more commonly in the presence of invasive devices (e.g.

intravenous catheters, urinary catheters, endotracheal intubation and surgical procedures). Community and nosocomial exposures to diverse bacteria, viruses, fungi and parasites/protozoa may also result in new infections in this population at any time. In some cases, these may be seasonal (e.g. influenza, RSV, rotavirus) or related to unique outbreak situations. Diagnostic studies should be modified to address these possibilities. Specific pathogens are addressed throughout these guidelines.

### **AST infectious disease guidelines: use and applications**

The third edition of the AST Infectious Disease Guidelines updates and expands the content and recommendations provided in the first two editions. As a comprehensive set of clinical practice guidelines, they were developed to assist in clinical decision making. They are based upon the highest level of scientific evidence available. The content of the guidelines includes salient background, clinical and pathophysiologic data as well as specific statements and recommendations relevant to the diagnosis, management and prevention of specific pathogens and disease entities. Given the unique circumstances associated with individual transplant candidates and recipients, these guidelines are not proscriptive; rather they provide preferred approaches for management of these very complex patients. It is hoped that through the application of the general principles outlined in this introduction and the more specific recommendations included throughout the guidelines, practitioners will acquire useful knowledge that will enhance the outcome and care of recipients of SOT.

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