

# Infection Prevention in Transplantation

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Published online: 28 January 2016  
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**Abstract** The number of patients undergoing hematopoietic cell and solid organ transplantation are increasing every year, as are the number of centers both transplanting and caring for these patients. Improvements in transplant procedures, immunosuppressive regimens, and prevention of transplant-associated complications have led to marked improvements in survival in both populations. Infections remain one of the most important sources of excess morbidity and mortality in transplant, and therefore, infection prevention strategies are a critical element for avoiding these complications in centers caring for high-risk patients. This manuscript aims to provide an update of recent data on prevention of major healthcare-associated infections unique to transplantation, reviews the emergence of antimicrobial resistant infections, and discusses updated strategies to both identify and prevent transmission of these pathogens in transplant recipients.

**Keywords** Infection prevention · Infection control · MRSA · VRE · Clostridium difficile · Respiratory viruses · Measles ·

This article is part of the Topical Collection on *Transplant and Oncology*

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Transplant · Screening · Hand hygiene · Vaccines · Fungus · Filamentous mold

## Introduction

Patients undergoing hematopoietic cell transplantation (HCT) or solid organ transplantation (SOT) are at high risk for development of infectious complications during the course of their care. Infections remain one of the most important sources of excess morbidity and mortality in both populations, not only in the early post-transplant phase, but for years following transplantation. Institution of standardized prophylactic strategies has helped to limit some major infections, but medication and disease-related deficits in both innate and cellular immunity, multiple invasive procedures and frequent antibiotic exposures, among other issues (Table 1), place transplant patients at high risk for the development of infections. These patients also have extensive contact with inpatient and outpatient healthcare environments, increasing the risk for many nosocomial or healthcare-associated infections (HAI).

Infection prevention (IP) programs at centers with high numbers of transplant recipients must develop and implement enhanced screening, organize isolation programs, and plan interventions tailored to curtail transmission and spread of these infections. IP teams must also recognize and prepare for infections, such as molds and respiratory viruses, which are not only uniquely challenging in this population, but which have been associated with center-specific outbreaks. Many of these infections occur with higher frequency in these patients and require specific prevention strategies targeted for transplant populations. Finally, IP teams must be prepared for major emerging (e.g., Middle East respiratory

**Table 1** Risk factors for infections in transplant populations

Hematopoietic cell transplantation	Solid organ transplantation
Underlying disease	Underlying disease
Hematologic	Organ dysfunction
Neutropenia	Renal failure
Lymphopenia	Liver failure
Pancytopenia	Respiratory dysfunction
Treatment-related issues	Treatment-related issues
Conditioning regimens	Immunosuppressive therapy
Chemotherapy	Calcineurin inhibitors
Radiation (e.g., total body irradiation)	(e.g., tacrolimus)
GVHD prophylaxis/treatment	Glucocorticoid use
ATG/biologic therapies (e.g., alemtuzumab)	mTOR inhibitors
Calcineurin inhibitors	Mycophenolate
Glucocorticoids	Induction therapy
Maintenance chemotherapy	ATG/biologic therapies
mTOR inhibitors	(e.g., alemtuzumab)
Mycophenolate	Integument breakdown
Integument breakdown	Central line
Central line	Port-a-catheter
Ommaya reservoir placement	Surgical site/drains
Port-a-catheter	Surgical issues
Skin GVHD	Intraluminal stenting
Mucosal barrier breakdown	Post-surgical drains
Mucositis	Surgical site
Oral/gut GVHD	Others
Others	Antibiotic use / microbiota disruption
Antibiotic use/microbiota disruption	CMV Reactivation
CMV reactivation	Drug side effects
Drug side effects (e.g. marrow toxicity)	(e.g., marrow toxicity)
Gastric acid suppression	Gastric acid suppression
(e.g., marrow toxicity)	TPN/PPN use
Iron overload	Transfusions
Organ dysfunction (e.g., renal)	Increased healthcare exposures
Splenectomy	Endoscopic procedures
TPN/PPN use	Inpatient admissions
(e.g., renal) Transfusions	Medical ICU admission
Increased healthcare exposures	Multiple outpatient visits
Endoscopic procedures	Surgical unit/ICU
Inpatient admissions	
Medical ICU admission	
Multiple outpatient visits	

virus coronavirus [MERS-CoV]) and reemerging (e.g., measles) pathogens in these highly susceptible patients.

This manuscript will review the most recent data on prevention of major HAI and pathogens unique to transplantation, discuss the emergence of antimicrobial resistant infections, and suggest strategies to prevent such infections in these populations. Although it is not possible to cover all areas, these data should provide updates that will be useful for a wide variety of institutions that care for these patients.

## Basics of Prevention in Transplant Patients

The basics of IP in transplant populations begin with policies and procedures that most centers utilize in their other inpatient and ambulatory care environments. At the same time, protracted carriage/shedding, prolonged hospitalization, and clustering of these highly susceptible patients can also increase the risk for transmission events, particularly in centers where co-accommodation is necessary [1, 2•]. In centers where transplant populations enter into the general hospital populations, these concerns can become even more challenging to control. Major efforts must focus on practices that are foundational to IP: infectious disease epidemiology, outbreak investigation, screening programs, hand hygiene, isolation practices, vaccination, and proper use personal protective equipment (PPE) (Table 2). Methods for disinfection and sterilization of equipment and environmental cleaning are well described in other publications [3, 4], but are also critically important aspects of infection prevention policies. Additional efforts to protect patients from airborne fungi, respiratory viruses, and highly resistant gram-negative rod (GNR) bacteria are critical. Organization of these high-risk populations on singular units can assure consistency with transplant-specific IP and that experienced staff monitor and care for these patients.

## Methicillin-Resistant *Staphylococcus aureus*

A large meta-analysis of screening studies estimated the overall rate of methicillin-resistant *Staphylococcus aureus* (MRSA) in the SOT population to be approximately 8 % pre-transplant; liver transplant recipients appear to have the highest rates of colonization [5•]. Although current guidelines do not recommend standard screening, studies show that patients with either pre- or post-transplant colonization are thought to have significantly increased rates of MRSA-related complications, suggesting the potential benefits of routine screening [6•, 7]. Studies evaluating the benefits of pre-transplant surveillance that focus on the prevention of transmission are limited, and data on specific location, number of sites, and laboratory studies (e.g., culture vs. polymerase chain reaction [PCR]) for such strategies have not been assessed in transplant patients. In addition, although few studies to date have

evaluated the benefit of decolonization efforts pre-transplant [8], recent simulation suggests such practices may be valuable and cost-effective in certain SOT populations [9•]. Large multi-center trials to assess the value of surveillance and decolonization are likely needed to address the value of these practices in SOT patients.

There are few studies that have assessed MRSA screening in HCT recipients, but one of the largest studies to date, demonstrated among over 1800 HCT recipients, less than 2 % in the population were positive on pre-transplant surveillance MRSA nasal cultures [10•]. Additionally, in contrast to SOT patients, pre-transplant colonization did not appear to be linked to post-transplant MRSA-related complications [10•]. Screening has been shown to contribute to the control of MRSA outbreaks in HCT units [11], but whether such efforts extend to non-outbreak settings is unclear.

### Vancomycin-Resistant Enterococcus

In many centers, vancomycin-resistant enterococcus (VRE) has become a dominant and challenging infection in transplant populations. The majority of HCT centers routinely screen inpatients for VRE rectal colonization [12], and while rates vary between centers, rates of colonization at admission have been reported to be approximately 25 % [12, 13]. In comparison, rates of VRE colonization in SOT patients are estimated to be 12 % pre-transplant and 16 % post-transplant [6•]. Although post-transplant bacteremia has been associated with pre-transplant colonization, the effectiveness of active surveillance for VRE colonization to prevent health care-associated transmission of VRE is unknown and currently not recommended in HCT recipients [14]. Recent data from a study that employed a novel molecular typing technique suggested that clustering consistent with nosocomial spread does occur in high-risk units, indicating an advantage to routine surveillance [15•]. Other groups, using different laboratory techniques, have not found molecular evidence of transmission clusters [16]. Screening may however have negative effects, such as increasing use of linezolid and or daptomycin, hampering antimicrobial stewardship efforts and promoting the emergence of additional resistance [17••]. The increasing reports of daptomycin-resistant [18] and linezolid-resistant [19] VRE strains continue to be an area of major concern in transplant.

### *Clostridium Difficile* Infection

*Clostridium difficile* infection (CDI) has become a leading HAI in transplantation, due in part to the frequent use of broad spectrum antibiotics in these populations. Isolation strategies, and hand-washing and antimicrobial stewardship programs are key components to prevention, but newer data on use of various forms of ultraviolet light for environmental

disinfection may provide a novel method for prevention [20]. A number of studies have shown benefit in other populations [21], but benefits in transplant units have not been completed to date.

CDI has been shown to be the most common cause of infectious diarrhea in these populations [22•, 23], where rates vary between 3–13 % in SOT [24••] and to 2–22 % in HCT recipients [25•]. Interestingly, emerging data suggest that a high number of HCT patients are colonized with *C. difficile* pre-transplant [26•, 27•]. Although, colonization when combined with frequent diarrhea and testing may lead to over-reporting of incident CDI [25•], patients with asymptomatic colonization can progress to symptomatic infection [26•, 27•]. Understanding colonization rates may be of major value to transplant centers, as these data may affect reporting to Centers for Medicare and Medicaid Services (CMS). Data that non-toxicogenic *C. difficile* strains may provide protection against colonization with toxigenic strains in these populations [28•] could be important in developing alternate prevention strategies. Finally, IPs will need to understand and monitor efforts to provide stool transplants, particularly as additional safety data are shown in these transplant populations [29•].

### Multi-Drug-Resistant Gram-Negative Rods

Extended-spectrum  $\beta$ -lactamase (ESBL)-producing GNRs are increasingly reported in transplant populations and, not surprisingly, are associated with both antibiotic use as treatment and prophylaxis [30, 31•, 32]. Carbapenemase-resistant enterobacteriaceae (CRE), which have been increasingly detected worldwide, are associated with mortality rates of 40–65 % in these high-risk populations [33•, 34]. Since some hospitals have noted that nearly 50 % of *Klebsiella* spp. isolated from transplant patients are now carbapenem-resistant [35], it is important for health care providers to know the epidemiology of these organisms in their hospitals and to develop systems for early reporting and isolation of patients with evidence of CRE. As immunosuppressed patients may be the highest risk for asymptomatic colonization [36, 37], stool screening programs for ESBLs [38•] and CRE [33•] should be considered in centers that are dealing with an outbreak or in those that have high baseline incidence. Contact isolation for patients with documented multi-drug resistant (MDR)-GNRs is recommended; however, guidelines, when one can remove such contact precautions, have not been established for many of these organisms and may be dependent on the species, resistance mechanism, site of infection, and immunosuppression level of the host. Antimicrobial stewardship efforts are needed in this population to prevent inappropriate antibiotic use linked to the selection of many of these high-risk pathogens [33•].

**Table 2** Major infection control efforts to prevent infections in transplant recipients standard infection prevention policies

	Hand hygiene policies
	Evaluation and assessment
	HAI screening
	MRSA, VRE, CRE
	Isolation
	Bacteria:
	C diff, MRSA, VRE, CRE, other MDR-GNRs, MTB
	Viral infections:
	Influenza, RSV, other respiratory viruses, VZV, measles, etc. <sup>a</sup>
	PPE training
	Environmental cleaning
	Environmental services
	Surface cleaning (e.g., bleach, quaternary ammonium)
	Disinfection/sterilization
	Disinfection and sterilization of medical equipment <sup>a</sup>
	Employee health/healthcare staff
	Vaccination
	Sick policies
Transplant	-specific infection prevention policies
	Fungal prevention
	Frequent air exchanges, HEPA filtration on inpatient units
	Construction and renovation environmental controls
	Avoidance of ornamental plants/fresh flowers
	Filter and airway duct policies
	Masking policies
	Respiratory virus prevention
	Patient screening and isolation
	Staff and visitor screening
	Masking policies
	Water prevention
	Water management plans
	Legionella screening policies for high-risk units

\*Examples of important screening programs, no inclusive to all pathogens

### *Norovirus and Other GI Viruses*

Noroviruses (NV) are increasingly being recognized as a major cause of diarrhea in transplant patients. Current data suggests that NV are the second most frequent cause of community-acquired and hospital-acquired infectious diarrhea in adult transplant patients [22•]; rates may be even higher in pediatric transplant recipients [39]. Outbreaks have occurred in transplant units and require close surveillance of diarrheal symptoms among patients and staff, tracking of diarrheal laboratory assessments, additional efforts to assure environmental disinfection, and isolation/furlough of symptomatic patients and staff [40•]. Strategies for addressing transplant patients who develop protracted shedding, common among transplant patients [41], and their role in the prolonging

outbreaks are currently not addressed by current Centers for Disease Control and Prevention (CDC) guidelines [40•]. Data that norovirus can be associated with significant morbidity and mortality in these patients [39, 42], and that pre-transplant detection may be linked to the development of graft-versus-host-disease [43•], suggest that enhanced strategies for screening and prevention may be important beyond outbreak situations. Furthermore, it has been hypothesized that transplant patients may serve as a reservoir for the emergence of new novel norovirus variants [44].

While there are a number of other gastrointestinal (GI) viruses, astroviruses are increasingly being reported as pathogens in transplant patients, presenting as diarrheal disease and rarely as disseminated or severe central nervous system infections [43•, 45, 46]. These infections appear to be the most

prominent in pediatric marrow transplant recipients to date, but as use of multiplex PCR-based screening tools expands, data on adults may become more readily available. Methods for prevention have not been well characterized, but should include a focus on contact isolation of patients with active diarrhea, aggressive promotion of hand hygiene, and environmental disinfection.

### Emerging and Reemerging Infections

Vaccine preventable diseases, such as measles [47] and *Bordetella pertussis* [48], have reemerged throughout the world, and are of major concern for transplant centers and IP staff. Minor symptoms that are similar to other infections and the ability of some to transmit prior to symptom presentation, suggest that these infections can enter into high-risk centers through patients, caregivers, and/or healthcare staff. Centers should focus efforts on providing vaccines to transplant patients as per international guidelines [49], since many can be given safely and effectively pre and post-transplant [50, 51].

Targeted education for caregivers and family to encourage vaccination is also important, particularly among siblings of those in pediatric transplant units. Household contacts should be up to date on standard vaccinations according to age-specific Advisory Committee on Immunization Practices (ACIP) guidelines [52, 53]. Immunocompetent individuals who live in households of transplant patients can receive live-virus vaccines (reviewed in reference [49]), except for oral polio vaccine, which is contraindicated [49]; these same individuals can safely receive all inactivated vaccines (e.g., inactivated influenza vaccine [IIV] or diphtheria-tetanus-acellular pertussis [dTAP]). Household members who qualify for varicella or herpes zoster vaccines can be vaccinated, but if they develop skin lesions after receiving these vaccines, then the transplant recipient should avoid contact with these persons until their skin lesions have cleared. Live attenuated influenza vaccine (LAIV) can be given to household members of transplant recipients eligible for this vaccine, except for those who are currently residing with HCT recipients <2-month post-transplant, where IIV is preferred. If LAIV is given, those who receive the intranasal vaccine should avoid contact with the transplant recipient for 7 days following vaccination [49]. In cases where the inactivated vaccine is unavailable, the risk of complications from acquiring influenza should be weighed against the theoretical risks of transmission from LAIV, and its use should strongly be considered [54].

Ebola virus [55], Middle East respiratory virus coronavirus (MERS-CoV) [56], enterovirus D68 (EV-D68) [57], influenza H7N9, and other emerging infections are new concerns for transplant patients and transplant centers. With the influx of patients seeking transplants from every region of the world, IP teams need to be prepared to address both rare and highly

contagious pathogens, and efforts to prepare centers to identify and isolate patients with possible exposures are needed.

### Fungal Prevention

Much of the effort regarding mold prevention in transplant patients relates to antifungal prophylaxis strategies and has been addressed by others [58]. However, outbreaks of filamentous mold infections in high-risk patient populations reflect the requirements for IPs to focus on fungal prevention. Efforts by centers to address air systems are key to protecting high-risk patients, including use of positive pressure, and high-efficiency particulate arresting (HEPA) filtration systems on high-risk inpatient units are important [14, 59]. Additional efforts to avoid fungal exposures from potted plants and fresh flowers, gardening, composting, woodworking, dusting, and other modes known to be associated with the production of airborne mold spores should be addressed through patient and caregiver education programs. While currently not a routine recommendation, data suggesting links to fungi from water sources may be important when addressing hospital-acquired invasive fungal infections [60].

A critical component for fungal prevention is to protect patients during active construction (reviewed in reference [61] in detail). Air sampling may be used to measure airborne fungal levels inside and outside of hospitals before, during, and after construction projects, but thresholds for safe versus unsafe levels of fungal spores are not well characterized in clinical studies [62]. Procedures for communication, risk assessment, and review of construction projects by IP and environmental health teams should be established prior to the project start dates, and should contain introductory education for contracted workers. Evaluating active barriers, portable air-handling units, and construction staff regularly is critical also to assure guidelines are being followed. Centers should carefully monitor fungal cases during construction projects and investigate all potentially linked events. Additional protective measures, such as masking for patients, have been used as an adjunctive for potential outbreaks [63], albeit without prospective clinical trials demonstrating their benefits. Environmental exposures to construction sites in the outpatient arena are much more difficult to prevent, but educating patients to avoid such exposures should be emphasized.

### Respiratory Viral Prevention

A major challenge to transplant centers is the control and prevention of respiratory viruses (RV) [64]. The multitude of viruses, including influenza A, respiratory syncytial virus, parainfluenza viruses, rhinoviruses, metapneumovirus, among others, of which some occur seasonally and others throughout the year, can be both challenging to prevent and difficult to control. Since transplant patients increasingly are exposed to

outpatient environments, frequent exposures outside of centers provide ample opportunities for patients to acquire RVs in the community. At the same time, there have been clinical outbreaks in high-risk immunocompromised patients that are clearly linked to healthcare [2•, 65, 66•]. Respiratory virus prevention is also critical in the pre-transplant period, as these viral infections can delay transplantation and are associated with significant post-transplant complications [67•].

Methods for prevention of respiratory viruses include isolating symptomatic patients, respiratory virus testing for patients with symptoms, and efforts to prevent active cohorting and interactions between patients (and staff) [2•, 64•, 66•]. Respiratory virus policies which include screening both visitors and healthcare workers can also help limit transmission events [66•]. Routine masking and isolation of all at-risk patients has not been prospectively evaluated, but may be effective in controlling outbreaks [2•]. Data that providing masks for caregivers, visitors, and healthcare staff that interact closely with patients during respiratory virus season have been described by one center to decrease respiratory viruses in HCT recipients [68]. Influenza vaccination remains an important component of prevention every year and should be addressed through multimodal healthcare vaccine programs for patients, caregivers/families and healthcare workers [69, 70]. The appropriate length of isolation for patients with laboratory proven RVs is debated, as prolonged shedding is a common finding in these patients but viral load thresholds for infectivity are unknown.

A critical component of prevention is also strict guidelines to prevent sick healthcare workers from entering high-risk units and outpatient facilities that care for transplant patients; such policies should extend to family and caregivers [66•]. Recent data suggesting that providers frequently come to work sick [71] indicate there is a need for sufficient back-up systems, proactive education, and surveillance of employees within these highly protected units. Centers should consider healthcare-transmitted respiratory viruses as “never events” and review all possible nosocomial respiratory viral infections to identify gaps in education and practice.

### **Central Line-Associated Blood Stream Infection Prevention**

Multiple other publications review standard guidelines for central line-associated blood stream infection (CLABSI), including the use of standardized line care bundles [72]. The use of chlorhexidine wipes and/or washes during the post-transplant period have become increasingly used at many centers, due to data supporting that such efforts decreased rates of CLABSIs in a large study that included transplant patients and other high-risk patients [73•]. Translating such practices to outpatient arenas during high-risk periods has not been assessed to date. Alcohol-impregnated disinfection caps have been shown to be a cost-effective method for

decreasing CLABSIs among immunosuppressed patients in a least one study [74•]. Although to date, no studies support ethanol, heparin, and other lock therapies for CLABSI prophylaxis, future studies addressing such approaches in these populations are needed [75].

### **Hand Hygiene**

While certainly not unique to these patient populations, hand hygiene policies are a critical but underappreciated aspect of IP efforts in all units engaged in caring for transplant patients. Hand hygiene should be actively encouraged in all clinical staff, with easy access to sinks and hand sanitizer stations, visual reminders, and comprehensive education programs that include the promotion of the five moments of hand hygiene in both hospital units and outpatient transplant clinics [76]. Although there are numerous methods for monitoring hand hygiene, including new electronic monitoring systems [77], evaluation itself, as well as direct feedback and coaching, is essential. Multimodal approaches to improve and sustain hand hygiene compliance in those working with transplant patients are needed, particularly since transplant specific units have been reported to have compliance rates that are no better than other parts of the hospital [78].

In addition, transplant centers should make efforts to educate and improve hand hygiene practices among patients and visitors. Transplant patients, for example, have been shown to infrequently use adequate hand hygiene after bathroom visits (29.7 %), prior to eating (39.1 %), and on entry (2.9 %) and exit (6.9 %) from their hospital rooms. [79•] Caregiver- and visitor-targeted education may be even more important. Many of these individuals are not only in close contact with patients and associated high touch areas [80], but have significantly more freedom to move around hospitals, clinics, and communal living areas. Targeted training programs for caregivers, families, and visitors are needed [81].

### **Conclusions**

Infectious diseases consultants, infection preventionists, and hospital epidemiologists are critical to protecting transplant patients from major pathogens. Dedicated efforts to address standard infection control practices are needed at all centers. Additional measures to protect against fungal infections, respiratory viruses, gastrointestinal viruses, and emerging infections, are critical components of all IP programs in transplant units and outpatient care centers. Multi-disciplinary IP teams are required to interpret and collect epidemiologic data, prepare guidelines, create screening programs, review implementation, and assure compliance, in order to provide the highest level of quality and safety for transplant patients. Such teams should partner with primary transplant teams, nursing administration, employee health,

environmental services, construction contractors, and hospital administrators, to assure the promotion of prevention efforts. Finally, IP teams must educate caregivers, families, and patients, to protect transplanted patients in ambulatory care units and exposures in the community.

**Acknowledgments** Dr. Pergam would like to thank Karen Chaddock, Julie Knight, Kim MacLeod, Sara Podczervinski, and Lois Helbert from the Seattle Cancer Care Alliance (SCCA) Infection Prevention team for their support.

### Compliance with Ethical Standards

**Conflict of Interest** Dr. Pergam has served as a consultant for Merck, Optimer/Cubist, and Chimerix, and participated in clinical trials with these three entities; all efforts have been outside the submitted work.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by the author.

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- Of major importance

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