

# Infection Prevention and Control Issues After Solid Organ Transplantation

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Transplantation has been accepted as a treatment modality for terminal organ failure. Therapies used to prevent rejection suppress the immune system and as a result, the transplant recipient is often at high risk of infection. Prolonged and frequent exposure to healthcare settings and multiple antibiotics may predispose the transplant recipient to colonization or infection with multidrug-resistant organisms. The use of good infection prevention and control practices is extremely important throughout the continuum of care for solid organ transplant (SOT) recipients. In the hospital setting, antimicrobial-resistant pathogens often cause the infections identified during admission or after discharge, resulting in increased morbidity and mortality.

This chapter reviews selected infection prevention and control practices that address common infections in transplant recipients. The U.S. Centers for Disease Control and Prevention (CDC) has issued guidelines for the prevention of infection for hematopoietic stem cell transplantation (HSCT) recipients, but not specifically for SOT recipients. Pertinent guidelines on infection prevention and control issues have been developed by the CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC) to provide specific recommendations that are pertinent to all patient populations. Guidelines referenced in this chapter include the Guideline for Hand Hygiene in Health-Care Settings—2002 [1], Guidelines for Preventing HealthCare-associated Pneumonia, 2003 [2], Guidelines for Environmental Infection Control in Health-Care Facilities, 2003 [3], Management of Multidrug-Resistant Organisms in Healthcare Settings, 2006 [4], Guidelines for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings, 2007 [5], and the Guideline for Disinfection and Sterilization in Healthcare Facilities, 2008 [6]. The American Transplant Society has published guidelines for the management and prevention of infections in organ transplant candidates and recipients which address specific aspects of infection control practices pertinent to transplantation [7]. The Society for Healthcare Epidemiology of America (SHEA) and the

Infectious Diseases Society of America (IDSA) have also published a compendium of strategies to prevent healthcare-associated infections (HAIs) in acute care hospitals [8]. These strategies, most recently revised in 2014, highlight basic prevention practices that are often referred to as “bundles,” guidance to infection control programs regarding implementation of these practices, as well as special approaches for infections that are not controlled using basic infection control practices. Despite the publication of expert guidance documents and guidelines some issues are still unresolved. The authors of this chapter describe some of the practices in their institutions, while acknowledging that different approaches to the same problem might exist.

## 46.1 Healthcare-Associated Infections

### 46.1.1 Prevention and Isolation Practices

Caregivers must maintain good infection prevention practices to minimize the transmission of infection in the healthcare setting. Invasive devices such as central venous catheters (CVCs), indwelling urinary catheters, and ventilators expose the patient to additional risks for infection. Most facilities have implemented infection prevention “bundles” designed to prevent these device-associated HAIs. Due to the success seen in reducing HAIs, the Centers for Medicare and Medicaid Services (CMS) issued new guidelines. After October 1, 2008, hospitals no longer receive additional payment for cases in which selected conditions were not present on admission, which include CVC-associated bloodstream infections and catheter-associated urinary tract infections [9]. What this means to hospitals is that claims are paid as though the secondary diagnosis was not present. These “Hospital-Acquired Conditions” (HACs) are considered “never events,” but may still be problematic in transplant recipients. Careful attention must be given to good hand hygiene practices and CVC care, as well as to practices that decrease the risk of catheter-associated urinary tract infection. As a protective

measure, patients may also be placed into protective precautions to heighten the awareness of the caregivers to the potential for serious infection.

Whereas the 1991 Occupational Safety and Health Administration (OSHA) Bloodborne Pathogens Standard focused primarily on employee protection [10], the CDC and HICPAC have published numerous patient-focused guidelines and recommendations for the prevention of HAIs. Revised in 2007, the Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings 2007 [5] updated and expanded the 1996 *Guideline for Isolation Precautions in Hospitals*. The transition of healthcare delivery from primarily acute care hospitals to other healthcare settings (e.g., home care, ambulatory care, freestanding specialty care sites, and long-term care) created a need for recommendations that could be applied in all healthcare settings using common principles of infection control practice, but could be modified to reflect setting-specific needs. In this revision, the term “nosocomial infections” was replaced by “healthcare-associated infections” to better reflect the changing patterns in healthcare delivery. It may be difficult to determine the exact site of exposure to an infectious agent and/or acquisition of infection as patients move through the healthcare delivery system. The SARS experience, and more recently, the experience with Ebola virus disease, highlighted the need to better prepare for new emerging pathogens and focused on the ways minor breaks in infection control technique resulted in infections being transmitted to healthcare professionals. Sections of this guideline were created as evidence mounted that environmental controls could decrease the risk of fungal infections in severely immunocompromised patients. While the Protective Environment (PE) has been found to be of greatest benefit for patients undergoing allogeneic hematopoietic stem cell transplants, there may be some lessons to be learned from successful implementation in this group of patients. Organizational characteristics (e.g., nurse staffing levels and composition, establishment of a safety culture) are also identified as key components to promote adherence to recommended infection control practices. Combining the universal precautions and body substance isolation precautions, contact with human blood, body fluids, secretions or excretions (except for sweat), nonintact skin, mucous membranes, and contaminated items requires the use of personal protective equipment, as part of standard precautions. Respiratory hygiene/cough etiquette, safe injection practices, and the use of masks during insertion of catheters or injection of material into spinal or epidural spaces via lumbar puncture procedures were added to standard precautions in 2007. Transmission-based precautions are used, in addition to standard precautions, to prevent infections spread by airborne, droplet, and direct contact routes. Certain infections that had required disease-specific isolation precautions are now included under standard precautions.

Airborne precautions are used if a patient has a known or suspected infection with an agent that can be transmitted by

evaporated droplets [droplet nuclei of <5 mm (micron)] that remain suspended in the air and that may be carried away from the infected patient. Measles, varicella, and tuberculosis are the primary infections included in this category; a patient infected with any of these must be housed in a room with controlled ventilation. Specialized air filters and negative pressure in the room prevent the infectious droplet nuclei from entering the general air supply and infecting others.

Certain diseases, such as influenza and adenovirus, generate droplets larger than 5 mm. These larger-sized particles are too big to remain suspended in the air; therefore, no special ventilation is required. Close contact with respiratory tract secretions is required for disease transmission, so masks should be worn by healthcare workers when they are working within 3 ft (0.9 m) of an infected patient to prevent the inhalation of infectious droplets.

Contact precautions are used to prevent the transmission of certain microorganisms that may be found on the patient’s skin or on inanimate objects in the patient’s environment. Included in this category are epidemiologically significant organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), *Clostridium difficile*, and respiratory syncytial virus (RSV). Private rooms are recommended, but patients colonized or infected with the same organism(s) may be cohorted together, if necessary. If neither of these options is achievable, the immunosuppressive state of potential roommates should be evaluated. For example, placing a VRE-colonized patient with an otherwise healthy 30-year-old who has a broken leg would be preferable to placing that patient with a postoperative transplant recipient who might become more easily colonized and infected. Contact precautions require gloves and gowns be worn for contact with the patient or potentially contaminated items and areas in the patient room. While the likelihood of transmission to other patients through contact with clothing is remote, caregivers are likely to touch their own clothing (e.g., lab coat pockets) and thus transmit the organism on their hands. The 2006 HICPAC/CDC guideline, *The Management of Multidrug-Resistant Organisms in Healthcare Settings*, recommends donning gowns and gloves upon room entry and discarding them before exiting the room of a patient with organisms that have been implicated in environmental transmission (e.g., VRE, *C. difficile*, noroviruses and other intestinal tract agents, and RSV) [4].

The 1975 CDC isolation techniques manual defined a protective isolation category to protect neutropenic or immunosuppressed patients. Whereas other isolation categories were designed to prevent the transmission of disease from an infected patient to others, the purpose of protective or “reverse” isolation is to protect the highly susceptible patient. Neutropenic precautions are practices designed to reduce microbial contamination in the patient’s environment. Because many infections in immunosuppressed patients are attributable to the patient’s endogenous flora, the use of special environmental precautions is not recommended, except for allogeneic stem cell transplant recipients, for whom a

TABLE 46-1. Centers for disease control and prevention isolation precautions for selected infections

Infection	Precautions	Comments
Abscess, draining (minor)	Standard	Contact for major draining abscess
Adenovirus	Droplet, contact	
Aspergillosis	Standard	
Candidiasis	Standard	
Cellulitis	Standard	
<i>Clostridium difficile</i>	Contact	Private room preferred
Cytomegalovirus	Standard	
Epstein–Barr virus	Standard	
Fungus, endemic	Standard	Blastomycosis, coccidioidomycosis, histoplasmosis
Hepatitis, viral (HBV and HCV)	Standard	
Herpes simplex virus	Standard Contact	Encephalitis, recurrent mucocutaneous—skin/oral/genital Disseminated or severe mucocutaneous
Influenza	Droplet	
Legionnaires' disease	Standard	
Listeriosis	Standard	
Multidrug-resistant organisms (MRSA, VRE, and MDR-GNB)	Contact	Gown and gloves recommended on entry into room Private room preferred
Mycobacteria, nontuberculous	Standard	
Nocardiosis	Standard	
Parainfluenza	Contact	Respiratory infection in infants and young children
Parvovirus B19	Droplet	
RSV	Contact	
Rotavirus	Contact	
Tuberculosis	Airborne Airborne, contact	Pulmonary and/or laryngeal Extrapulmonary, draining lesion
Varicella-Zoster virus	Airborne, contact	Varicella (chickenpox), disseminated herpes zoster (shingles)
Zygomycosis ( <i>Mucor</i> and <i>Rhizopus</i> )	Standard	

Abbreviations: HBV hepatitis B virus, HCV hepatitis C virus, MRSA methicillin-resistant *Staphylococcus aureus*, MDR-GNB multidrug-resistant gram-negative bacteria, RSV respiratory syncytial virus, VRE vancomycin-resistant enterococcus.

protective environment is necessary to minimize fungal spore counts in the environment and decrease the risk of invasive fungal infections [5]. To reduce the risk of infection, nursing care often focuses on skin integrity, indwelling intravenous devices, and good oral hygiene.

Isolation precautions for select organisms or disease syndromes are presented in Table 46-1. A complete list can be found in Appendix A of the CDC guideline on isolation precautions [5].

#### 46.1.2 Definition of Healthcare-Associated Infections

The National Nosocomial Infections Surveillance (NNIS) system, a cooperative effort of the CDC and participating hospitals, began in 1970 with the purpose of creating a database to track nosocomial infections in the USA. In 2005, the National Healthcare Safety Network (NHSN) was established to integrate and supersede three surveillance systems at the CDC: the NNIS, the Dialysis Safety Network (DSN), and the National Surveillance of Healthcare Workers (NaSH). Patient-specific event data are entered into this Web-based system by individual facilities but comparative results can be found on the NHSN Web site (<http://www.cdc.gov/nhsn>) and are published annually in the *American Journal of Infection Control*. Many states have mandated that HAIs be reported through NHSN to better evaluate the magnitude of HAIs. The public reporting of infection data is state specific, ranging from all infections being reported in Pennsylvania to more limited requirements, such as primary bloodstream infections only. CMS requires reporting of certain HAIs as part of pay for performance initiatives. Healthcare facilities use the standardized definitions created by the CDC, previously in the NNIS program and now in the NHSN [11], to classify HAIs, thereby enabling comparisons to national benchmarks. For device-associated infections, such as ventilator-associated pneumonia, central line-associated bloodstream infection (CLABSI), and catheter-associated urinary tract infections, rates should be calculated (the denominator is device-days and numerator is the number of infections recorded; result is multiplied by a factor of 1000). Rates are thus recorded as the number of infections per 1000 device-days. HAI data are stratified into types of patient care areas (e.g., medical ICU, medical/surgical ICU, and SOT specialty care area) to provide infection rates according to the risk factors of the patient population served [12]. Operative procedure codes available for identification of surgical site infection (SSI) rates include liver, kidney, and heart transplant surgeries. Healthcare facilities reporting

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HAIs to NHSN can get a standardized infection ratio (SIR) which is calculated by dividing the number of observed infections by the number of predicted (i.e., expected) infections. The number of predicted infections is calculated using infection probabilities estimated from multivariate logistic regression models constructed from NHSN data during a baseline period, which represents a standard population's infection experience. NHSN provides a p value and 95% confidence intervals to determine the statistical significance of the SIR for the healthcare facility's HAIs.

### 46.1.3 Central Line-Associated Bloodstream Infections

A general increase has occurred in the incidence of bloodstream infections caused by gram-positive bacteria, particularly *Staphylococcus* species. Many infections with coagulase-negative staphylococci are related to the increased use of various indwelling central lines. CLABSI is one of the primary infections seen in the immunosuppressed patient, because normal skin flora may colonize long-term access devices. In 2011, the CDC published Guidelines for the Prevention of Intravascular Catheter-Related Infections to help address this issue [13]. The incidence of infection varies with the type and intended use of intravascular devices. The two main device types are short term or temporary devices and those that are used for long-term access. Every device has some advantages and some risks. Attention should be focused on preventing site infections and on providing education for the patients and their caregivers if the catheter is not removed before hospital discharge.

The basic approaches to preventing CLABSI include the following [13]:

#### Before insertion

1. Educate healthcare personnel involved in the insertion, care, and maintenance of CVCs on CLABSI prevention.
2. Bathe ICU patients over 2 months of age with a chlorhexidine preparation on a daily basis.

#### At insertion

3. Use a catheter checklist to ensure adherence to insertion practices.
4. Perform hand hygiene before insertion or manipulation of a CVC.
5. Avoid the femoral vein for CVC access in adults, if possible.
6. Use maximal sterile barrier precautions during CVC insertion.
7. Use a chlorhexidine-based antiseptic for skin preparation in patients older than 2 months.
8. Use ultrasound guidance for internal jugular catheter insertion.

#### After insertion

9. Daily assessment of the need for the CVC and prompt removal of unnecessary CVCs.
10. Disinfect CVC hubs, connectors, and injection ports before accessing the CVC.
11. Change transparent dressings and perform catheter care with a chlorhexidine-based antiseptic every 5–7 days or immediately if the dressing is soiled, loose, or damp.
12. Use antimicrobial ointments for hemodialysis catheter insertion sites.

Several varieties of catheters and cuffs coated or impregnated with antimicrobial or antiseptic agents that reduce the risk of catheter-related bacteremia are available and have been shown to decrease the risk of CLABSI. Although catheters with chlorhexidine/silver sulfadiazine coatings, catheters impregnated with minocycline/rifampin or platinum/silver, and silver-coated cuffs may provide additional protection from skin flora [14, 15], they are more costly than the standard catheters and are recommended only if CLABSI rates could not be controlled using the basic approaches. The use of antimicrobial ointments for catheter insertion sites is no longer recommended, except for hemodialysis catheter insertion sites. Chlorhexidine-impregnated dressings may be beneficial in preventing CLABSI [16]. Daily chlorhexidine bathing may also reduce the rate of CLABSI in intensive care and bone marrow transplantation units [17, 18]. Although the routine replacement of catheters is unnecessary, the CVC site should be diligently monitored for evidence of infection. Guidewires should not be used for catheter exchange if any local redness, tenderness, or purulent material is present at the insertion site.

### 46.1.4 Prevention of Exposure from Healthcare Workers and Visitors

Employees and visitors may also transmit infections to the transplant recipient. Healthcare workers should undergo an evaluation of their health history and immunization status at the beginning of their employment [19]. Vaccination of healthcare workers who have no history of varicella infection or who are seronegative is strongly encouraged, because varicella can be life threatening in the SOT recipient. All staff members should receive the influenza vaccine annually, and, if they have not already been immunized for hepatitis B, they should receive hepatitis B vaccine at employment. Healthcare facilities should have well-defined policies to establish when potentially infectious personnel should not have patient contact. Employees should be encouraged to report any potential exposures or illnesses; human resource policies should permit temporary reassignment or furlough from duty to minimize the potential exposure of transplant recipients to

communicable infections. During the pretransplantation screening process, family members should be educated about infection prevention strategies and receive an annual influenza vaccination and ensure that their other vaccinations are up to date in order to better protect the transplant recipient [20]. Clinical personnel should monitor visitors for illnesses, such as colds, to prevent transmission. Posters may be displayed during flu season as additional reminders.

### 46.1.5 Fungal Infections

Despite the establishment of definition criteria, determining whether pneumonia is acquired in the hospital setting is one of the most difficult infections for the infection preventionist to classify. The CDC has three specific definitions of nosocomial pneumonia [11]. No defined incubation period exists when fungal pneumonia is suspected, so the traditional “onset of infection 48 hours after admission” standard that separates community-acquired infections from hospital-acquired infections is not valid. The isolation of fungal species from expectorated sputum may not be diagnostic, but clinicians often start antifungal therapy when they are encountered. These isolates could also represent transient colonization or a laboratory contaminant, not necessarily invasive disease [21]. Therefore, comparing fungal pneumonia rates among hospitals is difficult. Because of the ubiquitous nature of circulating fungal spores and of generally higher spore counts outdoors, determining whether a discharged patient who is readmitted with invasive fungal pneumonia acquired the infection while he or she was in the hospital is challenging. Comparative data on the incidence of nosocomial fungal pneumonia are unavailable, and many institutions have attempted to develop their own definitions of hospital-associated fungal pneumonia. Table 46-2 details the case definitions at some of the authors’ institutions; an arbitrary hospitalization of 7 days prior to onset of infection is used to distinguish between hospital- and community-acquired fungal infections. A recent review of construction and renovation-related healthcare-associated fungal infections showed a decrease in number of outbreaks between 2010 and 2014, which may be due to effectiveness of infection prevention measures, or because of the high number of previously reported outbreaks [22].

### 46.1.6 Aspergillosis

#### 46.1.6.1 Environmental Concerns

Healthcare-associated aspergillosis is associated with the following three main mechanisms: airborne acquisition, which is typically secondary to contaminated ventilation systems; direct contact, through contaminated objects such as wound dressings; and airborne and contact, in which both mechanisms may be implicated, as is seen in sternal fungal

TABLE 46-2. Case definitions

Term	Definition
Hospital-associated (nosocomial) infection	The patient has one or more positive cultures with the same pathogenic fungal species and clinical signs of infection and histopathologic or radiographic evidence of invasive fungal disease. OR Histopathologic or radiographic evidence of invasive disease with no microbiologic culture confirmation may be considered an infection if the patient is treated with an antifungal agent. Date of onset should be more than 7 days after admission with no evidence of active or incubating infection at the time of admission.
Colonization	Significant isolate(s) that cannot be classified as disseminated or locally invasive or if no systemic antifungal therapy is given.
Not significant	One isolate of a fungal species from a nonsterile site, no systemic antifungal therapy, or no correlation of routine microbiologic and fungal cultures.
Community-acquired infection	Signs or symptoms of infection are present at the time of admission and the patient was not hospitalized within the prior 2 weeks.

osteomyelitis after sternotomy [23]. The hospital water system may be a potential reservoir for *Aspergillus* and other molds, which are then aerosolized [24]. No “safe levels” for bioaerosols have been recognized, and standards for the frequency of air sampling are also lacking. Rural outdoor air concentrations of fungi may be as high as 10,000 colony-forming units per cubic meter of air (CFU/m<sup>3</sup>) without causing pulmonary infections in the general population. The establishment of a safe threshold limit in the indoor environment is problematic. Some studies have established a positive correlation between increased airborne spore counts and the incidence of invasive aspergillosis [25–27].

Researchers have collected air samples to quantify the number of airborne spores. Open agar plates, which are commonly referred to as “settle plates,” should not be used to estimate the airborne concentration of fungal spores. The number of spores that settle on the agar due to the effects of gravity are presumed to be proportional to the airborne concentration, but are not reliable enough for routine use in facilities that perform organ transplants. Settle plates, however, may detect fungi aerosolized during medical procedures (e.g., during wound dressing changes), as described in an outbreak of aspergillosis among liver transplant patients [28]. Air sampling methods using calibrated sieve impactors or centrifugal samplers are recommended to provide standardized counts, the results of which are expressed as CFU per cubic meter. Routine air sampling for fungi is not generally recommended. During construction or renovation or in

times when isolates of *Aspergillus* or other fungi are identified in patient cultures, air sampling may be performed to assess the relative level of spores in the environment. Outdoor samples may be collected as appropriate controls. Fungal colony types found in the indoor samples should be the same as those from outdoor samples, but with a tenfold (1 log) reduction in indoor counts due to air-handler filtration [29]. Indoor samples that have a predominance of a particular fungus that is not in proportion to the outdoor samples may reflect contamination of the indoor environment.

#### 46.1.6.2 Environmental Controls

The CDC guidelines for prevention of healthcare-associated pneumonia recommend protective environment units only for allogeneic HSCT recipient units; there are no specific recommendations for SOT recipients [2]. However, in 2003, the CDC published Guidelines for Environmental Infection Control in Healthcare Facilities which address specific controls applicable to all patients, and include recommendations specific to organ transplant recipients [3]. It is beyond the scope of this review to detail all recommendations in that guideline but several specific infection types are discussed. Facilities performing SOT surgeries should at minimum have contingency plans in case of disruption of HVAC services.

Specially designed isolation rooms that use laminar air flow (LAF) and/or high-efficiency particulate air (HEPA) filtration may provide the cleanest air possible. HEPA filtration, which provides a minimum of 12 air changes per hour, often reduces fungal spore counts. HEPA filters remove 99.97% of particles larger than 0.3  $\mu\text{m}$  (micron). HEPA filters may be installed within the room ventilation system to provide a highly filtered, positively pressurized room, or portable units may be placed in any patient room for additional air filtration. Patient rooms should be tightly sealed to prevent contamination from outdoor sources, and their doors should remain closed to ensure positive pressurization. Reportedly, areas that use HEPA filtration and positive pressurization of patient rooms (fungal spore control ventilation) have total spore counts of less than 15 CFU/m<sup>3</sup>, with *Aspergillus* counts of less than 0.1 CFU/m<sup>3</sup> [29].

Room design should focus on the use of easy-to-clean surfaces. The walls and horizontal surfaces should be smooth and nonporous to facilitate cleaning and to prevent entrapment of bacteria and spores. Porous ceiling tiles, carpeting, and fabric window treatments, such as shades and curtains, should be avoided as they may attract dust particles. Some new designs available are house curtains or shades within two glass panels which minimize dust collection while still providing privacy and controlling light. Vinyl or plastic blinds are safe if they are frequently cleaned.

Hospitalized SOT recipients should not travel through areas under construction or renovation. Severely immunocompromised patients requiring transport out of the protective environment should wear a high-efficiency respiratory protection mask, like N95, to prevent the inhalation of

particulates [2]. Transplant recipients should also avoid dusty construction or excavation and landscaping sites after discharge. Historically, studies reported an association between the use of other protective isolation strategies, such as the restriction of fresh fruit and flowers with a decrease in the incidence of infection. The length of hospital stay is declining dramatically, so the benefits of a protective environment are being reevaluated. The most important risk factor for invasive aspergillosis remains the patient's underlying immunosuppressive condition. High-risk patients may develop invasive aspergillosis even with low fungal spore counts [25].

#### 46.1.6.3 Construction Guidelines

Construction and renovation in the hospital are often associated with an increase in the number of cases of aspergillosis. At the beginning of renovation, airborne particulates and fungal spore counts may be exceptionally high because spores are dispersed into the environment during the demolition process. The Facility Guidelines Institute publishes guidelines for the design and construction of hospital and healthcare facilities [30]. Infection control personnel should be involved from the planning stages through project commissioning. Building owners are required to provide an infection control risk assessment (ICRA) to determine the potential risks of transmission of various infectious agents during the project. The ICRA is conducted by a panel with expertise in infection control and epidemiology, risk management, facility design, construction ventilation, and safety. An ICRA should be conducted during the early planning phase of the project, before construction begins, and continue through project construction and commissioning. Specific construction-related requirements mandated by the ICRA should be included in the contract documents. Many state health departments now require the ICRA submission before they will issue permits for hospital construction and renovation projects. When construction or renovation activities are planned in or near facilities that handle high-risk transplant recipients, even more strict protective guidelines and monitoring requirements may be established during the planning process [31]. Such guidelines help to define the appropriate barriers and techniques for preventing the spread of dust and debris into other areas of the facility. Construction and housekeeping personnel should be trained in the dangers of aspergillosis, with an emphasis on control measures. Strategies for the prevention of nosocomial aspergillosis will control any other fungi that are transmissible by dust, such as the zygomycetes (e.g., *Mucor* and *Rhizopus* species). Infection control interventions to prevent nosocomial aspergillosis were well illustrated during one construction-associated outbreak, in which the incidence of invasive aspergillosis rose from 3.18 to 9.88 cases per 1000 patient-days during the construction period [32]. The control measures that were used included portable HEPA filtration units, the installation of sealed windows and easy-to-clean tiles and shades, and the increased maintenance of the ventilation sys-

tem. The introduction of portable HEPA filter units was the most important step in this undertaking. After the institution of control measures, the infection rate decreased to 2.91 cases per 1000 patient-days.

When the construction activities are outdoors, the air intakes for the ventilation system may become heavily loaded with construction dust, potentially leading to an increased contamination of the indoor environment. An increased focus on filter maintenance is important, and successful containment may be possible, as a bone marrow transplantation unit reported during construction in its vicinity [31]. Maintaining the construction area at negative pressure, establishing plastic sheeting or drywall barriers, and controlling access to construction zones prevented dust from contaminating patient areas.

#### 46.1.6.4 Surveillance for Fungal Healthcare-Associated Infection

If a case of nosocomial aspergillosis is suspected, it is crucial to look at the facility history of aspergillosis cases to assess background rates. An investigation of any ventilation deficiency is very important [2]. If there is a good chance that the case is healthcare-associated, then an epidemiologic investigation should be initiated in an effort to find and eliminate the source. *Aspergillus flavus* has frequently been identified in reports of construction-related contamination of the indoor environment [33]. Arnov et al. [34] reported an increase in spore counts of *Aspergillus fumigatus* and *A. flavus*, with a mean of more than 1 CFU/m<sup>3</sup> associated with the opening of a new hospital. An environmental assessment identified fungal contamination of the carpet, fireproofing material, and ventilation filters. Fungi may contaminate damp areas, discolored ceiling tiles, and peeling wallpaper. Most studies documented decreased indoor spore counts after the institution of appropriate control measures [31, 33]. Sometimes, air sampling is recommended for the assessment of air contamination after construction or HEPA filter changes and as part of an outbreak investigation. Repeat air samples may be collected after an identified source is decontaminated or removed. An environmental audit may also include periodic sampling. The role of fungal typing in the investigation of outbreaks is unclear; multiple fungal strains can cause healthcare-associated infections in one outbreak given the ubiquitous presence of fungi in the environment and the identification of different serial *Aspergillus* strains by whole genome sequencing within a single patient [35] may limit the application of this epidemiological tool.

*Aspergillus* species are certainly not the only significant fungal pathogen found in the environment. *Fusarium* and *Trichosporon* species, the dematiaceous molds, zygomycetes, and normally innocuous soil and plant fungi may cause infections in the immunocompromised patient. Good housekeeping practices are vital in high-risk patient areas. These areas should be visually monitored to ensure that all dust is contained and removed from the patient environment. If nosoco-

mial infections occur within an institution, the renovation of ventilation systems to provide highly filtered air for high-risk patient areas may be considered. Although antifungal prophylaxis of patients may be useful, cases may still occur, necessitating the temporary closure of contaminated patient units or a suspension of transplant activities during hospital construction projects.

#### 46.1.7 Waterborne Infections

Researchers at the University of Arkansas for Medical Sciences reported the results of a MEDLINE search of medical literature published from 1966 through 2001 to determine the number of HAIs caused by waterborne pathogens. Forty-three outbreaks had been reported, including many nosocomial outbreaks caused by *Pseudomonas aeruginosa* [36]. HAIs attributed to the use of contaminated water include those caused by *Legionella pneumophila P. aeruginosa*; *Aeromonas*, *Acinetobacter*, *Burkholderia*, *Enterobacter*, *Flavobacterium*, and other *Pseudomonas species*; *T. gondii*; and *Serratia*, Mycobacteria, and *Aspergillus* species. In 2006, the Environmental Protection Agency (EPA) published the Long Term 2 Surface Water Treatment Rule (LT2 rule), which addresses strategies to reduce disease incidence associated with *Cryptosporidium* and other disease-causing microorganisms in drinking water [37]. Individual state regulations or codes may identify requirements for maintaining hot water temperatures to protect patients from being scalded. Temperatures at the return should ideally be  $\geq 124$  °F ( $\geq 51$  °C), and cold water temperature at  $< 68$  °F ( $< 20$  °C) in healthcare facilities [3].

#### 46.1.8 Legionellosis

Transplant recipients are considered to be at increased risk of developing *Legionella* pneumonia, commonly known as Legionnaires' disease. Even after processing at water treatment plants, small quantities of these aquatic bacteria may enter homes and buildings and may live in the biofilm that lines the pipes. *Legionella* species multiply in warm water, with an ideal temperature range of 35–46 °C [38, 39]. Regulations concerning maximum water temperature, which are designed to prevent scalding accidents, often fall into this range, increasing the possibility that a facility will become contaminated with *Legionella* species and several other species of nontuberculous mycobacteria, including *Mycobacterium xenopi* [40]. Traditionally, it was believed that infection was caused by the inhalation of contaminated aerosols generated by humidifiers, air-conditioning units, cooling towers, and showers into the respiratory tract. The aspiration of contaminated water is an additional mechanism of transmission [41, 42]. Laboratory-confirmed Legionellosis in a patient who has spent  $\geq 10$  days continuously in a healthcare facility prior to the onset of illness is considered a definite case of healthcare-associated *Legionella*

pneumonia; that which occurs in a patient who has spent 2–9 days in a healthcare facility prior to the onset of illness is considered possible healthcare-associated Legionellosis [2, 3]. The 2003 CDC guidelines for the prevention of nosocomial pneumonia discuss issues of environmental monitoring and control. The recommendations state that facilities provide routine maintenance of their potable water systems and should consider the use of sterile water in immunocompromised patients if *Legionella* is isolated from the water to reduce the incidence of legionellosis [2].

*L. pneumophila* strains may be more virulent than the non-pneumophila strains. Advances in molecular fingerprinting techniques have been instrumental in associating patient isolates with *Legionella* species cultured from a facility's potable water supply. Furthermore, lawsuits have successfully linked nosocomial infection to perceived facility negligence [38].

#### 46.1.8.1 Environmental Monitoring

Culturing plumbing fixtures, such as sink spouts, showerheads, ice machines, and drinking fountains, for *Legionella* species can identify potential sources of the bacteria in high-risk patient areas. The degree of contamination (percent of positive fixtures and quantity of bacteria present) varies significantly from building to building. The type of hot water system, the water temperature, location, and building age all play a role in the colonization of pipes within a facility [43]. The monitoring and control of *Legionella* species in a healthcare facility require a team effort, in which the microbiology laboratory, infection prevention and control, and maintenance departments must work together to provide a safe environment for high-risk patients. The CDC does not recommend routine environmental culturing for *Legionella*, but guidelines state that (1) this could be a component of *Legionella* prevention in healthcare facilities that provide care to transplant recipients, (2) may be appropriate to identify the source of infection as part of an outbreak investigation, and (3) to assess the effectiveness of water treatment or decontamination protocols [2, 3]. No guidelines regarding culturing frequency or acceptable levels of positivity are available. Generally, each facility will establish a policy on environmental monitoring that is dependent on the patient population. Environmental investigation to identify the source of *Legionella* is recommended when there is an outbreak, defined as one case of definite or two cases of possible healthcare-associated Legionnaires' disease within a 6-month period [3].

#### 46.1.8.2 Legionella Control Measures in the Hospital

As a rule, if significant quantities of *Legionella* species are isolated in a facility, control measures to reduce the level of colonization should be instituted. Systems that use holding tanks or heaters that allow water to stagnate in the bottom of the tank provide a reservoir for the multiplication of

*Legionella* species. For immediate control of *Legionella* in the setting of an outbreak, thermal eradication (superheat and flush) or hyperchlorination of the water supply is recommended [3]. Ongoing control of *Legionella* could be done with the use of copper/silver ionization systems, which release low concentrations of metal ions into the water distribution system, ultraviolet light sterilization, or maintenance of an elevated water temperature or chlorine content [44, 45]. Point-of-use filters have been found to be effective in eliminating *Legionella* and could be used without modification or disinfection of the potable water system [46], though are not on the current guidelines. In transplant units, shower heads and tap aerators should be removed, cleaned, and disinfected monthly using a chlorine-based, EPA-registered product; a 1:100 dilution of bleach may be used if no EPA-registered chlorine disinfectant is available [3]. In addition, large-volume room air humidifiers that generate aerosols should not be used unless they are subjected to high-level disinfection and only sterile water is used.

Even when control mechanisms are in place, healthcare-associated legionellosis may occur. Disruptions in the water distribution system, such as water main breaks, the use of fire hydrants, floods, and internal maintenance and construction disruptions, may cause changes in water pressure that disrupt the biofilm within the potable water system [38]. When pieces of the biofilm break free and enter the water supply, the water may appear cloudy or dirty. Local water authorities may issue water restrictions in the event of major contamination of the drinking water supply. Establishing water service disruption policies can be helpful for protecting immunosuppressed patients. Substitution of the appropriate bottled water is encouraged for drinking and for mouth care. Ice machine filters may become contaminated, so filters should be changed after restoration of water service [47]. Suspending showering until the water is determined to be safe may be necessary. When service is restored, all fixtures should be flushed until the water appears clear. Tub bathing may be acceptable because little aerosolization of the water occurs during the bathing process. Bed baths or other systems that do not generate aerosols are recommended.

The American Society of Heating, Refrigerating, and Air-Conditioning Engineers (ASHRAE) Standard 188p [48] establishes minimum risk management requirements to control legionellosis in water building systems, including inpatient healthcare facilities. An interdisciplinary designated team with the authority and responsibility to establish and implement a legionellosis risk management program, including but not limited to facilities staff familiar with the building water system and infection prevention and control staff should be formed. Components of the program include (1) description of the potable and nonpotable water systems in the building in water flow diagrams, including all water sources, water treatment systems and control measures, water processing, and end use points such as sinks, showers, water features, and ice machines, (2) identification of areas with higher probabil-



ity of infection based on the intended water use and the vulnerability to infection of patients in these areas, (3) identification of the control points where Legionella control measures can and should be put into place, (4) establishment of critical limits at the control points (e.g., temperature or chlorine level), (5) establishment of a monitoring system that includes the means, methods, and frequency for monitoring physical and chemical characteristics of the control measures to ensure they are within critical limits, (8) verification that the program is being implemented and validation that the control measures are effective in controlling Legionella, including a determination of if, when, where and how environmental cultures for Legionella are to be performed, and (9) documentation and communication of the plan.

#### 46.1.8.3 Recommendations for the Discharged Patient

In areas where *Legionella* species have been identified in the water supply, patients who rely on well or spring water should be encouraged to have their own water supply checked [43]. One mistaken assumption is that all bottled water is safer or healthier than tap water; however, many water products are not processed to reduce bacterial contamination. Products such as spring water that emphasize natural properties may actually contain more bacteria than do other water products.

#### 46.1.9 Antibiotic-Resistant Organisms: Vancomycin-Resistant Enterococcus, Methicillin-Resistant Staphylococcus, and Multidrug-Resistant Gram-Negative Bacteria

Infections caused by resistant organisms have emerged as a serious problem in hospitals all over the world. This is due in part to an increase in the nonselective use of broad-spectrum antibiotic agents for prophylaxis and treatment. The indiscriminate use of antibiotics reduces the normal host flora, predisposing the patient to colonization with endemic multidrug-resistant organisms and *C. difficile*. The emergence of *Streptococcus viridans* that is highly resistant to penicillin has been associated with the use of  $\beta$ -lactam antibiotics in neutropenic cancer patients [49]. Centers that routinely use quinolone prophylaxis for neutropenic patients have reported coagulase-negative *Staphylococcus* and gram-negative blood isolates that are resistant to these agents [50, 51]. HAIs with resistant gram-negative organisms (*Klebsiella species*, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia*) are on the rise, a trend that may be related to the use of broad-spectrum antibiotics [52–54]. Gram-negative bacteria that produce extended-spectrum  $\beta$ -lactamases are becoming increasingly prevalent. Pretransplant broad-spectrum antibiotic use has been associated with post-transplant infections caused by multidrug-

resistant organisms [55]. Antimicrobial stewardship programs and the use of local data to select appropriate treatments reduce the reservoir of multidrug-resistant pathogens within a medical facility. Reducing inappropriate antibiotic use by only prescribing an antibiotic when it is likely to be beneficial to the patient, minimizing the treatment of colonization, using broad-spectrum antibiotics judiciously, and discontinuing unnecessary and lengthy treatment with antimicrobials are the essence of antimicrobial stewardship. The CDC launched the “Get Smart for Healthcare” initiative to guide and support antimicrobial stewardship programs in different settings in order to improve antibiotic prescribing practices [56].

Patients who have longer inpatient stays before transplantation surgery may become colonized with multidrug-resistant organisms. Changes in the United Network for Organ Sharing (UNOS) allocation algorithm have resulted in an increased duration of preoperative hospitalization in some institutions. Data has demonstrated an increased number of cases of mediastinitis after heart transplantation caused by multidrug-resistant pathogens associated with an increased length of pretransplantation inpatient hospitalization prior to transplant [57].

Active surveillance identifies more patients colonized with resistant bacteria than clinical cultures alone, and this strategy can be used to control rates of colonization and infection due to resistant bacteria. The use of active surveillance for MRSA and subsequent decolonization with mupirocin has shown some effectiveness in reducing infections post liver transplantation [58] though some data have not demonstrated effectiveness [59]. Whereas the CDC guideline on the control of multidrug-resistant organisms recommends active surveillance for MRSA and VRE if other approaches have failed to control transmission adequately [4], the SHEA guideline recommends the use of active surveillance to identify patients colonized with MRSA and VRE among all high-risk patients [60]. Some states have mandated screening patients for MRSA. Active surveillance for MDR gram-negative organisms, including carbapenem-resistant enterobacteriaceae (CRE), is recommended in certain high-risk situations in order to prevent spread of these highly resistant and potentially virulent organisms [61]. Although active surveillance is not done routinely in most centers, the role of active surveillance for CRE in solid organ transplant candidates and recipients is unclear, and is an area worthy of future study.

##### 46.1.9.1 Vancomycin-Resistant Enterococcus

Enterococci have become a significant infection control problem for decades, which is evidenced by the 20-fold increase in nosocomial infections reported to the NNIS from 1989 through 1993 [62]. Comparative data from the 1998 reports showed an additional 55% increase in VRE infections compared with that from 1993 through 1997. Between January 2006 and October 2007, 33% of enterococcal

device-related healthcare-acquired infections reported to the NHSN were caused by VRE [63]. The enterococci differ from other streptococci in their relative resistance to penicillins and cephalosporins and in their intrinsic low-level resistance to aminoglycosides and lincosamide antibiotics [64]. They are also resistant to bile, they are considered normal enteric flora in adults, and they generally exhibit low virulence. They may be isolated from the mouth, vagina, groin, and anterior urethra. The target of vancomycin in the cell wall is D-alanyl-D-alanyl, but, in VRE, this target is altered so that it has low affinity to vancomycin [65]. Using molecular typing techniques, VRE strains have been identified as comprising mainly three resistance phenotypes—van A, van B, and van C [64]. The van A phenotype is plasmid mediated, and, by definition, it is resistant to high levels of vancomycin and teicoplanin. The van B strains exhibit high-level resistance to vancomycin, but they are susceptible to teicoplanin. Class C shows constitutive low-level resistance to vancomycin; this is encountered in *Enterococcus gallinarum* and *Enterococcus casseliflavus*.

### Risk Factors

Epidemiologic analysis has shown that enterococcal infection often originates from the patient's colonizing flora. Intraabdominal and cardiothoracic surgery and manipulation of the urinary tract are the risk factors for enterococcal infection. Reportedly, the severity of illness is one of the main risk factors for the development of VRE bacteremia [66–70]. Critically ill patients in the intensive care unit or those with underlying medical conditions, including immunocompromised patients residing on oncology and transplant units, are also at increased risk of colonization and infection with VRE strains. An increased length of hospitalization and antibiotic use contribute to the patient's risk [70]. Although vancomycin use is a predisposing factor for the acquisition of the organism, any antimicrobial agent that alters the normal gram-positive and anaerobic gut flora may allow VRE to flourish [66, 67]. In Europe, a glycopeptide (avoparcin) that is used in animal feeds has been associated with VRE in animals and humans. Antibiotics with antianaerobic activity have been shown to promote VRE high-density colonization both in animal models and in humans [70]. Both vancomycin and third-generation cephalosporins reportedly are independently associated with VRE prevalence in 126 intensive care units in the USA [71]. Reports have demonstrated the contact spread of the bacteria from patient to patient, both directly and indirectly via the hands of healthcare workers [72, 73]. Contaminated equipment and environmental surfaces are also sources for disease transmission [74].

In the setting of solid organ transplantation, most VRE infections occur in the early post-transplant period, with a strong association with antimicrobial use and surgical, specifically biliary, complications. Liver transplant recipients who developed VRE bacteremia were compared retrospectively

with transplant recipients who developed bacteremia with vancomycin-sensitive enterococci (VSE) [75]. VRE infection was associated with increased episodes of recurrent bacteremia and persistent isolation of the bacteria from the original site of infection. Whether VRE strains are more virulent than VSE is still a controversial issue, but, in that study, few cases of endovascular infection were encountered among the VRE patients and none among the VSE control patients.

The VRE colonization rate of patients awaiting liver transplantation was reported to be 13% [76]. Another 18% became colonized after transplantation. Infection with VRE occurred in 23% of these patients. A recent meta-analysis demonstrated that post-transplant MRSA and VRE colonization was significantly associated with post-transplant MRSA and VRE infection [77]. Patients who were colonized with VRE either before or after transplantation had longer hospital and ICU stays. Those that acquired VRE after transplantation also had higher 90-day mortality.

The fecal carriage of VRE has also been studied in an outbreak on a renal unit. The authors used restriction enzyme analysis and ribotyping to show that the outbreak isolate was clonally related [70]. VRE was isolated from the stool of 15% of renal patients (i.e., those with end-stage renal disease), 5% of other patients in the hospital, and 2% of sampled patients in the community with no history of hospitalization or antibiotic use. Many studies have used DNA analysis to show that nosocomial transmission is the primary route of VRE colonization among patients.

### Infection Prevention and Control Measures

The CDC Hospital Infection Control Practices Advisory Committee developed guidelines for preventing the spread of VRE [78]. The following four main points are crucial for prevention: (1) prudent vancomycin use, (2) an education program, (3) an effective microbiology laboratory, and (4) a multidisciplinary effort to control the organism.

The microbiology laboratory initiates the process of VRE control by promptly and accurately identifying the organism. Vancomycin resistance can be identified through routine bacterial susceptibility testing or through polymerase chain reaction (PCR) testing using primers to detect the vanA and vanB genes. When a vancomycin-resistant strain is identified, the infection control department, the patient's physician, and unit personnel should be notified. Those patients who are colonized or infected should be placed in single rooms, or they may be cohorted with other VRE-positive patients. Because the bacteria may colonize the intestinal tract, patients with poor personal hygiene or fecal incontinence may contaminate the environment with the bacteria. Patients may also contaminate their immediate environment by touching surfaces, such as bed rails, nurse call buttons, and television controls. This type of equipment may not be adequately disinfected after the patient leaves, increasing the risk of transmission for the next patient. The recommendation is that gloves and gowns should

be worn when one is entering the room of colonized patients, especially in endemic settings. Some groups report significant decreases in VRE infection and VRE colonization after the institution of enhanced infection control measures in conjunction with judicious restriction of certain antibiotics, such as vancomycin and third-generation cephalosporins [79, 80].

Various reports have documented the isolation of VRE strains from environmental surfaces [72, 73, 81]. Noncritical items, such as stethoscopes or thermometers, should not be used with other patients unless they are thoroughly disinfected after use for a VRE patient. Dedicated equipment is preferred, but it may be shared among cohorted patients. Patients may be screened for VRE carriage by the collection of rectal swabs or stool for cultures or PCR testing to identify additional cases. This information is useful for determining transmission between roommates or to others on a unit where infected patients have been identified. Despite the institution of contact precautions for carriers, the incidence of carriage may remain about the same [69]. VRE colonization may persist for long periods [82]; therefore, colonized or infected patients may require continuous isolation until their discharge. If a patient is being transferred to another facility, notifying the receiving institution about the patient's VRE status so that the appropriate precautions are taken is imperative. VRE-positive patients who are readmitted should be placed in contact isolation until surveillance cultures have been completed.

Concerns that a plasmid that carries the vancomycin resistance gene could transmit this resistance to other gram-positive bacteria, particularly *S. aureus*, do exist. Because of the multiple virulence factors associated with this pathogen, these infections would potentially be life threatening because the organism is already resistant to multiple antimicrobial agents. Vancomycin-resistant *S. aureus* (VRSA) has been isolated. Seven cases of VRSA were identified in the USA from 2002 to 2006. All isolates were vanA positive. All patients had a prior history of MRSA and enterococcal infection or colonization. They all had severe underlying conditions and most had received vancomycin prior to VRSA infection. Proper isolation precautions were in place and prevented person-to-person transmission in all seven cases [83]. As of 2014, 13 cases of VRSA have been identified [84].

#### 46.1.9.2 Methicillin-Resistant *S. aureus*

MRSA is a well-recognized nosocomial pathogen causing significant infections in all patient populations. Contact precautions are used to isolate patients with MRSA infection or colonization. Some controversy exists over the use of masks to enter MRSA patient rooms. Because patients with nasal colonization may spread the organism into the surrounding air, some advocate that caregivers don masks to prevent their acquisition of the organism, thus minimizing spread to other patients. Transmission on the hands of colonized staff members may be increased if they touch their noses during patient care activities.

#### Risk Factors

As the Temple University experience illustrates [85], MRSA colonized patients are more likely to infect their surgical wounds. Researchers in a French study collected surveillance cultures from liver transplant recipients. The analysis of the infection data found that MRSA infection occurred more frequently in the MRSA carriers (7 of 8 patients, 87.5%) than in the MRSA noncarriers (8 of 79 patients, 10.1%) ( $P < 0.001$ ) [86]. Among liver transplant recipients, patients who underwent surgery within the prior 2 weeks were at markedly higher risk for MRSA infection [87]. A review of infections occurring from 1990 to 1998 in another liver transplant center in the USA showed that 23% of organ recipients became infected with MRSA, with significant increases in the incidence and prevalence of patients infected with MRSA over time [88]. The primary sites of infection were the vascular catheter (39%), the wound (18%), the abdomen (18%), and the lung (13%). CMV seronegativity ( $P = 0.01$ ) and primary CMV infection were significantly associated with MRSA infections ( $P = 0.005$ ). Although relatively uncommon, donor-derived MRSA transmission has been described following liver transplantation [89].

#### Infection Prevention and Control Measures

Quality improvement programs should be aimed at reducing HA-MRSA acquisition and infection rates and a multifactorial approach towards decreasing MRSA transmission has been described [90]. The collection of surveillance cultures may be cost-effective in all patient populations, and the high-risk transplant recipient group may be an ideal starting point for the process. An MRSA control program involving liver transplant patients consisting of active surveillance, use of contact precautions and cohorting of colonized patients, treatment with intranasal mupirocin at the time of transplantation, and education of patients and visitors on the importance of hand hygiene resulted in a decrease in the incidence of new MRSA colonization, MRSA bacteremias, and MRSA infections at other sites [58].

#### 46.1.9.3 Multidrug-Resistant Gram-Negative Bacteria

There is no standard definition for multidrug-resistant gram-negative bacteria (MDR-GNB). Included in this category are bacteria resistant to multiple classes of antibiotics, such as *P. aeruginosa* and *Acinetobacter baumannii*, as well as Enterobacteriaceae (e.g., *Escherichia coli* and *Klebsiella pneumoniae*) with extended-spectrum  $\beta$ -lactamases (ESBLs) that hydrolyze  $\beta$ -lactam antibiotics including extended-spectrum cephalosporins [4]. There has been a substantial increase in MDR-GNB, defined as being resistant to three or more antimicrobial classes [91, 92]. *A. baumannii*, which is frequently resistant to multiple antibiotics including  $\beta$ -lactams, fluoroquinolones, and aminoglycosides, is becoming increasingly resistant to carbapenems, and isolates resistant to all

tested antibiotics have been reported [93]. Patients with infections due to MDR-GNB are more likely to experience delay in institution of effective antimicrobial therapy, have a higher mortality, and increased cost of care [94, 95].

Extended-spectrum  $\beta$ -lactamases are usually found in *K. pneumoniae*, *K. oxytoca*, and *E. coli*, but have also been reported in *Citrobacter*, *Enterobacter*, *Proteus*, *Salmonella*, *Serratia*, and other gram-negative bacteria [96]. Gram-negative bacteria with ESBLs are typically sensitive to the carbapenems, which are recommended as treatment for infections due to these organisms. Recently, *K. pneumoniae* with a carbapenem hydrolyzing enzyme, which confers resistance to all carbapenems, have been reported, and this organism caused 8% of device and surgery-associated HAIs [63, 97]. Though named KPC (*K. pneumoniae* carbapenemase) as this was initially found in *K. pneumoniae*, KPC has been reported in other enterobacteriaceae, including *E. coli*, *Enterobacter* species, and *Serratia* [94, 98]. There is variation in the geographic distribution of ESBL-containing organisms. While it occurs sporadically in various states, *K. pneumoniae* with KPC has become endemic in the eastern United States and spread throughout the USA is increasing [99]. Infections caused by carbapenem-resistant enterobacteriaceae are associated with high mortality rates among liver transplant recipients [100].

Resistance genes in gram-negative bacteria could be chromosomal, or could be located in mobile genetic elements, such as plasmids and transposons, which can be transferred between different species [101]. Some of these gene elements may contain multiple genes encoding resistance to penicillins, cephalosporins, carbapenems, and aminoglycosides conferring multidrug resistance [102]. Quinolone resistance is usually due to chromosomal mutations and not usually transferable, but transferable quinolones resistance genes encoded on plasmids have been identified, and recently, MDR-*K. pneumoniae* with a plasmid containing resistance determinants for carbapenems, aminoglycosides, and fluoroquinolones was reported [103].

### Risk Factors

Risk factors for colonization or infection with MDR-GNB are similar to those for MRSA and VRE and include advanced age, underlying diseases and severity of illness, transfer of patients from another institution particularly from a nursing home, prolonged hospitalization, gastrointestinal surgery or transplantation, presence of invasive devices such as CVCs, and exposure to antimicrobial drugs [104]. Prior solid organ or hematopoietic stem cell transplantation has been identified as a risk factor for infections caused by carbapenem-resistant *K. pneumoniae* [105]. Bacteremia due to a KPC-2-producing *Enterobacter cloacae* and *Pseudomonas putida* has been reported in a liver transplant recipient [106].

Automated susceptibility testing systems have limitations in detecting drug resistance in these organisms [97, 107].

Providers and clinical microbiology laboratories should be familiar with these organisms and ensure that organisms are tested using methods that will provide reliable susceptibility results.

Hospital outbreaks due to MDR-GNB have been reported [97, 108]. Similar to MRSA and VRE, many more patients may be colonized than infected, providing an unrecognized reservoir, and active surveillance screening may be necessary to prevent cross-transmission.

### Infection Prevention and Control Measures

Measures to control the spread of MDR-gram-negative bacteria are similar to other drug-resistant organisms which include (1) administrative support such as instituting automatic alerts and provision for adequate hand hygiene facilities, (2) education of personnel regarding MDROs and prevention methods, (3) judicious antimicrobial use, (4) surveillance, (5) contact precautions, and (6) enhanced environmental cleaning. Published guidelines have specifically addressed infection control guidance for the prevention of infections caused by carbapenem-resistant organisms which addresses active surveillance of high-risk units and contacts with infected patients [61].

#### 46.1.9.4 *C. difficile* Infection

Numerous factors may cause diarrhea in transplant recipients, including immunosuppressants, antibiotics, enteral nutrition, and other agents that affect bowel motility. The extended use of antimicrobials alters the bacterial flora of the gut, providing a niche for the multiplication of *C. difficile*, an anaerobic, spore-forming, gram-positive rod that is resistant to many antimicrobial agents. Although the organism occurs as normal enteric flora in approximately 4% of adults, it may also cause severe gastroenteritis that manifests as either diarrhea or colitis. *C. difficile* produces the following two toxins: toxin A, or enterotoxin, and toxin B, or cytotoxin. These toxins act synergistically, resulting in cellular damage, hemorrhage, and the accumulation of fluid in the colon. Most patients have a history of antibiotic usage before the onset of diarrhea. *C. difficile* is the most common cause of healthcare-associated diarrhea, with higher rates of carriage, ranging from 15% to 30%, reported in hospitalized patients [109]. *C. difficile*-associated diarrhea occurs in 1–31% of SOT recipients [110].

In 2011, there were an estimated 453,000 cases of *C. difficile* disease (CDD) in the USA resulting in over 29,000 deaths [111]. One specific strain (NAP1/BI/027) has emerged that is more virulent and more resistant to antibiotics, particularly fluoroquinolones. It produces more toxin A and toxin B, and produces a third toxin, binary toxin. The disease is more severe and has affected patients with no underlying risk factors for CDD [112]. Outbreaks have been associated with fluoroquinolone use, though other antimicrobials have also been implicated [113, 114].

### Risk Factors

Although any antibiotic agent can affect the normal balance of the intestinal flora, clindamycin, penicillins, fluoroquinolones, and the third generation cephalosporins have been particularly associated with the development of infection [115, 116]. Other factors that alter the gut flora also increase the risks of carriage of the organism in the bowel and of disease. The use of stool softeners and antacids has been associated with increased carriage [117]. Diarrhea has also been associated with older age, underlying disease, and enemas. Symptomatic patients usually have more risk factors, and certain intrinsic patient factors influence the relative risk of developing symptomatic infection [118]. In solid organ transplantation, most cases of CDD occur in the first 3 months of transplant, likely attributable to the increased rates of hospitalization and use of antibiotics during this time period [119].

#### 46.1.9.5 Healthcare-Associated Transmission

Documented clusters of cases due to healthcare-associated transmission have frequently been associated with environmental contamination with bacterial spores. In one study, 21% of patients who were initially culture-negative admitted to a general ward acquired *C. difficile* while in the hospital; of these, 37% developed diarrhea [120]. The authors were able to prove transmission between patients with the use of an immunoblot technique, and they documented clustering in patient rooms with two occupants. Other authors have suggested other patterns of acquisition in situations in which no evidence of transmission to roommates exists [121]. One cluster investigation identified two case strains of bacteria by restriction endonuclease testing, in which most of the strains were associated with abdominal surgeries performed by one surgical team [122].

Because of spore production, this organism can survive well in the environment. *C. difficile* has been cultured from inanimate objects, such as medical instruments, toilets, bathroom floors, and furniture [123]. Bacteria have been cultured from the hands of medical personnel, and strains isolated from medical staff caring for patients with *C. difficile* were confirmed to be the same as those of the patient isolates [120].

Patients may become colonized with *C. difficile* via transmission through contact with other patients, contaminated rooms or equipment, or medical personnel carrying these bacteria on their hands. More environmental contamination with spores occurs in the room of a patient who has CDD, than with those with asymptomatic carriage. Nosocomial attack rates vary from facility to facility. Clinicians caring for transplant recipients should therefore be aware that nosocomial transmission of *C. difficile* is a real possibility and that the early implementation of infection control measures may prevent the occurrence of other cases.

Detailed strategies for the prevention of *C. difficile* in hospital settings have been published [124]. Patients should be placed in private rooms or cohorted with other infected patients. Symptomatic patients should be placed on contact precautions. Healthcare personnel should wear gloves and gowns when they enter the patient's room. Patient transport outside the unit should be minimized if the patient has diarrhea to avoid contaminating other areas with the bacterial spores. Good hand hygiene is essential. Soap and water or alcohol hand sanitizer may be used in routine or endemic settings; soap and water is preferred for outbreak or hyperendemic settings. Staff members must observe proper procedures, and visitors should be encouraged to wash their hands thoroughly before leaving the patient's room. A dilute (1:10) hypochlorite solution or a product with an EPA-approved claim for *C. difficile* activity should be considered in units with high *C. difficile* rates [6]. During outbreaks, environmental decontamination, isolation or cohorting of infected patients, and the limitation of clindamycin have significantly reduced CDD [125]. The use of dedicated patient equipment or of disposables, such as rectal thermometers, may significantly reduce the incidence of CDD in both acute and chronic care facilities and should be used whenever possible [126].

#### 46.1.9.6 Antimicrobial Therapy Issues

Although the initial step in the treatment of *C. difficile* is the discontinuation of the antibiotic agent(s) to allow the recolonization of the gut with normal flora, oral metronidazole or oral vancomycin is often used to treat the infection [127]. A randomized double-blinded placebo-controlled study shows that patients with mild to moderate disease respond comparatively with either metronidazole or oral vancomycin. Patients with severe disease, however, had better clinical cures with vancomycin [128], and so vancomycin should be considered as the first-line agent for patients with severe disease. Fecal microbiota transplantation has emerged as a promising treatment for patients with frequent relapses of CDAD [129], however, its safety and efficacy in the setting of organ transplantation is unknown. Guidelines recommend against antimicrobial prophylaxis for patients at risk for CDD, treatment of asymptomatic carriage, and test of cure [124].

#### 46.1.9.7 Outcomes

CDD has been reported to follow a more fulminant course in transplant recipients. A retrospective study of severe CDD showed that 13% of lung transplant patients had fulminant symptoms compared to 1.6% of all patients with CDD. Of those who required colectomy, 27% were transplant recipients, mostly lung transplants, though they actually had a better survival than nontransplant recipients [130]. The authors stated that improved awareness, lower threshold for surgery,

and closer follow-up may have paradoxically improved the outcome in transplant recipients. A review of cystic fibrosis patients showed that those who had lung transplants tended to have a more complicated disease course [131]. Other studies did not show more complicated disease, relapse rates, or mortality from CDD in SOT recipients [132, 133].

## 46.2 Community-Acquired Infections

### 46.2.1 Tuberculosis

Overall TB incidence rate in the USA has been declining, but TB in foreign-born and racial/ethnic minorities has been much higher compared to US-born Caucasians [134]. The proportion of cases in foreign-born persons has been increasing and accounted for 66% of cases reported in 2014, with Mexico, the Philippines, India, Vietnam, and China as the top 5 countries of origin [135]. Most cases of TB in foreign-born patients represented the reactivation of TB that had been acquired in the country of origin [136]. Between 1983 and 1994, the authors treated 14 liver transplant recipients (0.5%) for active TB; the most important risk factor was birth in a foreign country with endemic TB [137].

Multidrug-resistant (MDR) TB, defined as resistant to at least isoniazid and rifampin, appeared in the USA and worldwide in the 1990s, and required treatment with second-line anti-TB medications [138]. In the USA, the proportion of patients with MDR TB in those without previous TB has remained stable at 1% from 2009 to 2013. The percentage of MDR TB has remained below 1% in US-born cases, but of the total number of reported primary MDR TB, the proportion occurring in foreign-born cases increased from 30.8% in 1993 to 89.5% in 2013, accounting for 92% of primary MDR TB US cases in 2013 [135]. The CDC and World Health Organization (WHO) surveyed laboratories across the world and found that between 2000 and 2004, 20% of TB isolates were MDR and 2% were extensively drug-resistant (XDR) TB. The provisional definition of XDR-TB was an isolate resistant to isoniazid and rifampin and at least three or more of the six main classes of second-line drugs [138]. The definition was revised in October 2006 and XDR-TB is that which is resistant to isoniazid and rifampin, and resistant to any fluoroquinolone and at least one of three injectable second-line drugs (amikacin, kanamycin, and capreomycin) [139]. From 1993 to 2011, 63 such cases were reported in the USA, 17 of which occurred in 2000–2006 [140].

TB prevalence in the community and the presence of MDR- and XDR-TB [141] heighten the possibility that an immunosuppressed individual will be exposed to a case of active TB. Transplant recipients are susceptible to infection with *M. tuberculosis* species, and the progression to active disease can be quite rapid, similar to the experiences of patients infected with HIV [142]. In April 2007, three patients received organs from a 46-year-old US-born man

with history of seizure disorder, alcoholism, homelessness, and incarceration, who was initially hospitalized for presumed aspiration pneumonia [143]. The two kidney recipients developed fever 6–7 weeks after transplant and cultures grew *M. tuberculosis* which matched the donor's *M. tuberculosis* isolate which grew from CSF postmortem.

#### 46.2.1.1 Isolation

In the transplant unit, instituting appropriate isolation as quickly as possible when active TB is a possibility is essential. Patients who have an increased potential for TB should be placed in isolation rooms if active disease is even a remote possibility. In a 1990 nosocomial outbreak of TB that occurred among renal transplant recipients, the disease was transmitted from the source patient to five other patients on the same unit. The institution of airborne precautions was delayed because the TB infection had an atypical presentation in this patient [144]. Restriction fragment length polymorphism analysis confirmed the strain. Mortality in this patient group was 50%, with the shortest incubation time between exposure and active infection being approximately 5 weeks.

It is important to have a high index of suspicion for TB disease, in order to prevent transmission by prompt placement of suspect patients in an airborne infection isolation (AII) room until active TB is ruled out [145]. Airborne precautions can be discontinued when infectious TB is considered unlikely and either (1) another diagnosis is made that explains the patient's illness, or (2) 3 sputum specimens collected at 8-hour intervals, at least one of which is collected in the early morning, are AFB smear-negative. The Xpert MTB/RIF assay is an FDA-approved nucleic acid assay (NAA) that detects the presence of TB and rifampin resistance in sputum specimens; the negative predictive value for the presence of AFB smear positive TB is 99.7% after 1 negative assay and 100% after 2 negative assays [146]. CDC recommendations of 3 negative sputum specimens prior to discontinuation of airborne precautions in patients with suspected TB allow for the use of AFB smear, or NAA, or a combination of the two [147]. For patients with TB, decisions regarding discontinuation of AII require 3 negative sputum smears and clinical criteria.

The CDC guidelines describe ventilation system requirements for TB isolation rooms [145]. These include engineering controls to contain any droplet nuclei to prevent dissemination outside the patient's room. The AII room must be at negative pressure to the corridor, and exhaust air must be vented to the outside of the building or filtered through HEPA filters before it is recirculated. The AII room should have a permanently installed visual mechanism to monitor the pressure differential between the room and the corridor when occupied by patients with suspected or confirmed TB [30]. An ultraviolet germicidal irradiation device can be installed to irradiate the air in the conduit so bacteria are inactivated. There should be more than or equal to six air

changes per hour. New or renovated healthcare facilities should construct the AII room with more than or equal to 12 air changes per hour. Facilities may have to replace or retrofit their ventilation system to fulfill the safety criteria. This ventilation design is also required for varicella isolation. All employees must use a National Institute for Occupational Safety and Health (NIOSH)-approved fit-tested N95 respirator or powered air-purifying respirator when they enter the room of a patient with active or suspected TB.

#### 46.2.1.2 *Diagnosis*

Active infection in the transplant recipient may not present with the traditional symptoms found in the general population [85]. Pulmonary infiltrates or pleural effusion may constitute TB infection without the other typical symptoms. Many transplant candidates with terminal organ failure are anergic, and after transplantation, most recipients remain or become anergic secondary to immunosuppressive agents that are administered to prevent organ rejection. Therefore, the use of the tuberculin skin test (TST) to monitor transplant recipients rarely provides useful information. Important information is provided when conversion from negative to positive tuberculin skin testing occurs, but negative results do not rule out infection. Furthermore, the value of the anergy testing is in question and is no longer recommended to be done routinely [145, 148]. Even when the patient reacts to one of the other antigens and his or her TST test is negative, the patient may still have latent infection or even active TB. Disseminated TB occurs more frequently in transplant recipients because the major host defense against TB is cell-mediated immunity [85].

TST testing of close family members may provide additional information on the patient's potential to spread this infection. In recent years, *in vitro* interferon gamma release assays (IGRAs) became available for diagnosis of latent TB (QuantiFERON TB test (Qiagen, Germany) and T-SPOT.TB test (Oxford Immunotec, UK)). These tests measure  $\gamma$ -interferon production when lymphocytes are incubated with synthetic peptides that simulate some proteins present in MTB [149, 150]. These tests are more specific than TST for detection of MTB infection, with much less false positive results related to previous BCG administration and previous exposure to atypical mycobacteria. Both tests are approved by the U.S. Food and Drug Administration. The CDC recommends using these tests for the same indications as the TST [145].

Fluorescent microscopy for the evaluation of acid-fast bacillus (AFB) smears and radiometric culture methods provide important diagnostic information, which may lead to the earlier initiation or discontinuation of patient isolation. Many microbiology laboratories now use rapid testing methods to detect and confirm TB, including nucleic acid amplification tests for detection of MTB in smear-positive and smear-negative respiratory specimens and DNA probes for species identification [151].

#### 46.2.1.3 *Post-exposure Follow-Up*

If transplant recipients are exposed to a person with active TB, a contact investigation should be initiated. Recent TST or IGRA results and chest radiographs taken before the exposure may be used for baseline data. Additional TST testing should be performed 8–10 weeks after the exposure to evaluate for skin test conversion. Prophylactic isoniazid (INH) therapy should be considered for the prevention of the disease if the exposure is considered significant. If the source patient has a strain of TB that is either documented or suspected to be drug resistant, the use of alternative prophylactic regimens should be considered [152]. Prophylactic regimens for multidrug-resistant TB are not well established. In the past, the authors have used pyrazinamide with levofloxacin after such an exposure occurred among organ transplant recipients [153]. This regimen was associated with a high rate of discontinuation of the medication due to the adverse drug effects.

An international debate regarding the use of BCG vaccine for the prevention of TB spread has been ongoing. In the USA, indication for its use rarely exists [154]. Disseminated BCG disease is a risk in immunocompromised patients, including transplant recipients.

In June 2000, the CDC and the American Thoracic Society (ATS) formulated some new recommendations regarding TB prophylaxis and introduced two terms [155]. The first term is “targeted tuberculin testing” (i.e., TB testing by TST placement of patients at high risk for the development of TB). The second term is “latent TB infection” (i.e., patients who have been infected with TB but who have not developed TB disease). Chemoprophylaxis or preventive therapy is termed the “treatment of latent TB infection.”

A skin induration of 5 mm or more after TST testing is considered positive for the following patient categories: patients infected with HIV, patients receiving immunosuppressive agents including transplant recipients, patients with recent contact with active TB, and patients who have an abnormal chest radiograph that is consistent with old TB. These patients are at high risk and are candidates for treatment of latent TB [145].

Three regimens for the treatment of latent TB infection exist. These are as follows:

1. INH for 9 months
2. Rifampin for 4 months
3. INH and rifapentine for 12 weeks

INH and rifapentine are convenient as the long half-life of rifapentine allows for once weekly dosing; the CDC recommends directly observed treatment with this regimen [156]. The clinician should note, however, that these regimens could have risks when used in SOT recipients. Cases of severe INH hepatitis have been reported [157]. Severe liver injuries, resulting in the death of five patients, occurred as a result of the rifampin–pyrazinamide combination [158] and it is no

longer recommended. Rifampin has also been associated with the severe rejection of solid organs, due to its interactions with cyclosporine and tacrolimus [159].

## 46.2.2 Varicella-Zoster Virus

Varicella is a highly infectious virus and up to 90% of seronegative household contacts may become infected after infection in the family.

### 46.2.2.1 Isolation

The infection control management of VZV in the immunosuppressed population involves some difficult issues. Varicella is transmitted via the airborne route during the primary infection (chickenpox) as virus particles are released from the airways of the patient into the environment. Transmission may also occur after direct contact with moist vesicles. Transmission of the virus usually starts 1–2 days prior to rash onset and lasts until the skin lesions are crusted. CDC guidelines require both airborne and contact precautions for patients with varicella and disseminated zoster [5]. One of the most difficult tasks for infection control is to define “disseminated” zoster for instituting room isolation. In localized dermatomal zoster, transmission occurs primarily through direct contact with the skin lesions, and only standard precautions are necessary.

In the immunosuppressed host, even small number of moist lesions and possibly respiratory secretions may contain enough viral particles to transmit the infection to other susceptible individuals through airborne routes or the shedding of the viral particles from skin lesions into the surrounding air. An adult cadaveric renal transplant recipient who occupied a private room adjacent to a patient with zoster developed fatal hepatitis after the nosocomial transmission of primary varicella infection [160]. Using PCR, Sawyer et al. confirmed VZV DNA in 82% of air samples collected in varicella patient rooms and in 70% of air samples collected in zoster patient rooms [161]. In a few samples, the virus was detected outside the door of negatively pressurized isolation rooms. Although this may represent a failure of the ventilation system to maintain negative pressurization of the room or of staff members leaving the door to the room open, obviously aerosolization of the viral particles does occur. The virus was also detectable up to 6 days after the onset of rash with the use of the same technique.

### 46.2.2.2 Patient Screening

Varicella infection in susceptible immunosuppressed patients may result in visceral disease, and it is associated with high mortality. In a series of three adult liver transplant recipients who developed varicella hepatitis, one patient died after developing adult respiratory distress syndrome and disseminated

intravascular coagulation [162]. The introduction of a vaccine has significantly reduced varicella-zoster morbidity and mortality. Its use has been expanded since 1999 to include HIV-infected children with CD4 percentage of 15–24% and adults with CD4 count of at least 200 cells/ $\mu$ L [163]. There are two vaccines currently available: Varivax, a single-antigen varicella vaccine, and ProQuad, a combination of varicella and MMR vaccines. The latter contains more virus than the former vaccine [164]. Varicella vaccine is contraindicated in the transplant recipients, because it is made from a live, attenuated virus. However, the experience with leukemic children has shown that the vaccine is safe and effective [163]. Some reports have also demonstrated that the live, attenuated vaccine is safe and efficacious in susceptible pediatric kidney transplant recipients [165]. Researchers in that study administered the vaccine at candidacy; the results showed a reduced incidence of varicella after transplantation. There are also some reports of vaccination after transplantation. In one of these, seroconversion occurred in 20 of 31 (64.5%) children; 7 required multiple doses and only minor local skin reactions were observed [166]. The risk that healthy individuals will develop a rash after vaccination and transmit it to an immunosuppressed patient is low, and, therefore, vaccinating susceptible individuals, including healthcare workers, living in the same household with transplant recipients is not contraindicated [164]. The vaccine manufacturer does recommend that healthcare workers who develop vesicles should not care for susceptible individuals. Although some have hypothesized that the vaccine strain of virus may not be capable of causing secondary infections, a few such cases have been documented [167, 168]. The general consensus is that the benefits of vaccination of household contacts of immunocompromised individuals outweigh the very low risk of transmission of the vaccine virus to the transplant recipient. Varicella vaccine is also used in healthy persons as a post-exposure preventive measure, mostly in unvaccinated children, ideally within 3–5 days after exposure [169].

### 46.2.2.3 Post-exposure Management

Transplant coordinators must frequently evaluate the exposure of a transplant recipient to an individual with “possible” chickenpox. Most commonly, the exposure occurs after contact with a family member, usually a child. Defining the nature of the exposure by duration, proximity, and disease progression is an important step in the assessment process. Direct exposure is one that occurred face-to-face indoors. The duration of significant exposure is not clear; some experts say exposure for more than 5 min is significant, though others state that more than an hour is needed [163].

Documentation concerning each patient’s varicella-zoster immune status must be easily accessible. Most adult patients are seropositive for VZV even if they do not recall having had chickenpox. After exposure to a patient with VZV infection the CDC’s Advisory Committee on Immunization Practices



(ACIP) currently recommends VariZIG administration be considered for seronegative immunocompromised patients and certain other groups such as pregnant women and their newborns, for whom complications of disease could be life threatening [170].

VariZIG is expected to provide maximum benefit when administered as soon as possible after exposure, although it can be effective if administered within 10 days after exposure [170]. Although breakthrough infection after varicella-zoster immunoglobulin (VZIG) administration was common, its use ameliorated the severity of the disease. In one study in a SOT pediatric population receiving VZIG (median age of 8 years), 55% developed varicella, but only 4% developed severe disease [171]. The usual dosage is 125 units for each 10 kg of weight, up to a maximum of 625 units. If another exposure occurs more than 3 weeks after the administration of the VZIG dose, an additional dose of VZIG should be administered to provide continued passive immunity [169]. Patients who get monthly high-dose IVIG (>400 mg/kg) are protected if the last dose was given less than 3 weeks before exposure [161]. Because varicella immune globulin could prolong the incubation period by  $\geq 1$  week, patients given VariZIG should be monitored for signs or symptoms of varicella for 28 days after exposure. Antiviral therapy should be started as soon as signs or symptoms of varicella occur. Acyclovir may also prevent or attenuate infection after VZV exposure and may constitute a valid alternative, especially in those cases that come to medical attention more than 10 days after exposure. Some authors have advocated using it with VZIG in cases where life-threatening VZV infection is possible, such as in children with renal disease who are receiving steroids [172]. Acyclovir is FDA approved for the treatment of varicella in healthy children. The American Academy of Pediatrics (AAP) recommends consideration of acyclovir treatment of individuals at risk of moderate or severe varicella [173]. The value of acyclovir as a prophylactic agent in the immunocompromised host is unclear; VariZIG is recommended after exposure of these individuals to VZV. There is limited data to support the use of acyclovir for post-exposure prophylaxis in healthy children [174] though some experts support this approach in immunocompromised patients, particularly if VariZIG is unavailable.

#### 46.2.2.4 Staff Considerations

Not all susceptible healthcare workers who report exposure to VZV develop chickenpox. In one report, the incidence of varicella after exposure approached 10% [175]. Susceptible healthcare workers who report such exposures should be furloughed from work from the 8th to the 21st day after exposure. This is based on the average incubation period of 14 days and the knowledge that transmission may occur up to 5 days before and 6 days after the onset of the rash [176]. Susceptible healthcare workers who are exposed to VZV put their transplant recipients at risk, but their furloughed

absences also have cost implications and cause disruptions of patient care [177]. Therefore, CDC recommends the vaccination of susceptible healthcare workers if no contraindications are identified [178]. Healthcare workers who receive acyclovir prophylaxis may exhibit a longer incubation period before the development of a rash. Maintaining accurate records of employee data concerning vaccination or a previous history of chickenpox is important. Susceptible employees should be actively encouraged to receive varicella vaccine.

### 46.2.3 Respiratory Viruses

Most respiratory tract viral infections are seasonal, are more prevalent in children than in adults, and are transmitted by droplets rather than aerosols. Coughing, sneezing, or talking may generate droplets that are not usually projected farther than 3 ft (0.9 m) from the source patient. Special ventilation is not required for inpatient isolation. In the hospital setting, suctioning respiratory secretions and performing bronchoscopy may also generate droplets. The most common respiratory viral infections include RSV, influenza, parainfluenza, and adenovirus. The infection control aspects of respiratory viral infections are similar, and RSV is described here as an example. In recent years, the importance of these viruses in SOT recipients has received more recognition, as has the realization that these viruses cause significant morbidity [179]. These viral infections could be followed by superinfection with bacterial pathogens, leading to bacterial pneumonia, and they have also been associated with acute and chronic rejection, particularly in lung transplantation [180, 181]. In recent years the introduction of sensitive molecular techniques for clinical diagnosis of respiratory viruses has allowed not only early detection of these viruses [182], but also puts emphasis on other viruses like rhinovirus and metapneumovirus [183].

#### 46.2.3.1 Respiratory Syncytial Virus

##### Overview

Respiratory syncytial virus (RSV) is an RNA virus that causes upper and lower respiratory tract infections, usually before 3 years of age. Reinfection is common, but, in the healthy host, it is self-limited and generally mild. Outbreaks in the community usually occur seasonally, with peaks in the late spring and autumn that last until winter [184]. There is variability of onset of infection from year to year as well as between various regions in the USA [185]. For example, in Florida, the RSV season comes earlier and lasts longer [186]. The virus may be spread in nurseries, causing severe respiratory infection in infants who have underlying medical conditions, such as bronchopulmonary dysplasia, congenital heart disease, or prematurity [187]. Viral shedding usually lasts for a week, but this period may be longer in infants who are younger than 1 month of age or in those with pneumonia [188]. Nosocomial infections often parallel outbreaks in the community.

RSV can survive drying, and it can stay viable for 6 hours on surfaces and fomites, including gloves [189]. Transmission occurs by direct contact with a person who sheds the virus in the form of droplets or from contact with contaminated hands, handkerchiefs, eating utensils, or other articles. Viral particles may be inoculated into the eyes and nasal mucosa by touching these areas with contaminated hands [189]. Therefore, nosocomial outbreaks may occur not only from patient to patient but also from caregivers or visitors having a “cold” [190, 191].

Immunocompromised patients may develop lower tract lung infection with pneumonia. RSV may infect SOT recipients [192, 193]. In recent years, cases have been reported not only in pediatric SOT populations [194] but also in adults presenting with respiratory symptoms [195]. Two liver transplant recipients younger than 15 months of age were intubated when symptoms began soon after transplantation, but they later died from RSV pneumonia [193]. This may suggest the direct inoculation of the virus in the lower respiratory tract, bypassing the upper airways. Ribavirin, administered orally or intravenously, may reduce the morbidity and mortality due to RSV, influenza B, and parainfluenza [196]. Nevertheless, its routine use has not been recommended because of possible toxicity to exposed healthcare providers (the inhalation form) and because of ongoing debate regarding its definitive beneficial effects.

There is no vaccine available for RSV prevention. Palivizumab, a humanized murine anti-RSV monoclonal antibody, can be given as a monthly IM injection beginning prior to and continuing through the RSV season (typically November to April in the northern hemisphere) for prophylaxis in infants and children at risk for severe RSV infection [197]. In a survey of pediatric solid organ transplant centers in the USA, almost 50% of responding centers use palivizumab prophylaxis [198].

### Infection Prevention and Control Measures

Infection control measures should be promptly instituted to prevent nosocomial transmission. Contact precautions should be used for infants, young children, and immunosuppressed individuals. Gloves and gowns should be used when entering the room of patients with RSV, parainfluenza, or adenovirus to prevent contact with respiratory secretions. Mask and eye protection is necessary if procedures that generate vaporization of respiratory secretions are expected [2]. In outbreaks, cohorting of symptomatic patients while emphasizing hand hygiene may reduce transmission to others. Successful cohorting requires the early diagnosis of RSV when the epidemic is starting in the community. Shell vial cultures and rapid antigen detection by immunofluorescent assay (IFA) or enzyme-linked immunosorbent assay (ELISA) have greatly accelerated the diagnosis, compared with viral isolation techniques [199, 200]. More recently, more institutions have used PCR for the diagnosis of respiratory viruses, a molecular technique which is more sensitive [182, 201].

### 46.2.3.2 Other Respiratory Viruses: Influenza, Parainfluenza, and Adenovirus

Other respiratory viral infections that usually manifest as self-limited upper respiratory tract illness may result in potentially life-threatening lower respiratory infections in immunocompromised patients. At the University of Pittsburgh Medical Center, influenza was more prevalent among lung transplant recipients than it was among other organ recipients [202]. Secondary bacterial pneumonia occurred in 17% of the patients with influenza. Other complications occurred in three patients, including myocarditis, myositis, and bronchiolitis obliterans. Reports of transplant recipients who received the influenza vaccine but who developed influenza despite vaccination have been published [203]. This is due to the suboptimal response of transplant recipients to protein vaccines, and it raises the question of the use of antiviral chemoprophylaxis in the future. During the H1N1 April 2009 influenza A pandemic, of the reported 237 solid organ transplant recipients with H1N1, 32% developed pneumonia, 16% were admitted to ICU, and 4% died [204]. Organ recipients, their families, and the healthcare providers must realize the importance of receiving the annual inactivated influenza vaccine to reduce the risk of disease transmission. CDC, the Advisory Committee on Immunization Practices (ACIP), and the HICPAC recommended that all US healthcare workers get annual influenza vaccine [205]. The live, attenuated influenza vaccine (LAIV) administered as a nasal spray is not recommended for immunocompromised patients but may be given to close contacts of immunosuppressed individuals, though persons caring for patients in a protective environment should avoid contact with such patients for at least 7 days after receipt of LAIV [206].

Parainfluenza and adenoviruses may also cause life-threatening infection, and they may also be spread nosocomially [207, 208]. Rapid identification of these respiratory viruses, especially in pediatric wards, will help in cohorting staff and patients when an epidemic is recognized in the community [209]

## 46.2.4 Rotavirus and Viral Gastroenteritis

### 46.2.4.1 Overview

Viral gastroenteritis is usually a self-limited syndrome in the healthy host. Several viruses are associated with gastroenteritis, including rotavirus, norovirus, enteric adenovirus, caliciviruses, enteric coronavirus, and astrovirus [210]. Rotaviruses and noroviruses are the most epidemiologically significant agents of the gastroenteritis viruses, causing endemic and epidemic disease throughout the world. In particular, the rotaviruses have been associated with outbreaks in children and in developing countries where they have been associated with high mortality rates [211]. The symptoms often include vomiting, diarrhea, and dehydration. Fever may be present. Dehydration may be severe enough to

require hospitalization for intravenous fluid replacement. The incubation period ranges from 1 to 3 days, with symptoms usually lasting less than 1 week. The transmission of rotavirus occurs through the fecal–oral route, with maximum viral shedding in the stool occurring 2–5 days after the onset of diarrhea. Nosocomial infections have been associated with the insufficient use of appropriate infection control measures. Rotavirus infections represent between 20% and 40% of the cases of nosocomial diarrhea in children [212, 213]. There has been an association between rotavirus gastroenteritis and rejection of small bowel allograft but this may have been related to decrease in immunosuppressive agents due to diarrhea [214, 215]. In the USA, most infections occur in children between the ages of 6 and 24 months after maternal antibody protection wanes [216]. Infections occur more frequently between October and April. Usually, the virus produces a self-limited diarrhea; however, premature infants and transplant recipients may develop severe disease [210]. Although rotaviruses do not generally cause bloody stool, fecal occult blood loss has been reported in pediatric liver transplant recipients [217].

#### 46.2.4.2 Healthcare-Associated Transmission

Rotaviruses can remain viable in water and on dry inanimate objects and hands for many days. An investigation in day care centers with rotavirus outbreaks demonstrated the virus by PCR on toys (39%) and environmental surfaces (21%) [217]. Rotavirus may be transmitted to the patients by aerosols. Contamination of inanimate objects occurs not only by feces but also by aerosols generated by bedpan cleaning [211]. Patient-to-patient transmission may result in mini-epidemics within the hospital [210]. Adult contacts of patients with rotavirus may exhibit subclinical illness [213]. Infection control measures should be instituted promptly whenever patients are incontinent or develop diarrhea. Standard precautions are adequate unless the patient is incontinent or diapered; contact precautions should be added in such cases. Good hand hygiene is essential, with glove and gown usage for patient contact if fecal contamination is likely. Cleaning of room surfaces with an EPA-registered hospital disinfectant is adequate for cleaning of surfaces in the patient's room [5]. The institution of infection control measures interrupted an outbreak in a pediatric oncology ward that was presumed to have occurred through contaminated toys [218]. These included contact precautions, and the daily cleaning of playroom with a dilute bleach solution.

#### 46.2.4.3 Vaccination

The first rotavirus vaccine approved in 1998 in the USA was the Rotashield (Wyeth–Lederle Vaccines and Pediatrics), which was taken off the market 1 year later because of its association with intussusception [219]. In February 2006, a new vaccine, RotaTeq (Merck and Co.), was licensed in the USA.

This is an oral live vaccine which was developed from human and bovine virus and has not been associated with intussusception [220]. It is given in three doses at 2, 4, and 6 months with completed administration by 32 weeks of age. A second vaccine Rotarix (GlaxoSmithKline) was licensed in April 2008. It is live attenuated oral vaccine and is given to infants in two doses at 2 and 4 months infants. The two vaccines are equivalent. Although the original studies have not shown an association, post-licensure studies did demonstrate low risk of intussusception in certain populations [221], and support for use of the vaccine is universal. Between November 2007 and May 2008, delayed onset and reduced rate of rotavirus infection was observed [222], attributed to the introduction of the rotavirus vaccine. There are no data available regarding the safety and efficacy of this vaccine in immunosuppressed infants. It is believed that infants who live in the same household with immunosuppressed patients can still be vaccinated despite the small risk of transmission of the vaccine rotavirus [219].

### 46.3 Summary

Good infection prevention and control practices are essential for protecting highly susceptible transplant recipients. Quality management and patient safety initiatives have become driving forces in providing better patient outcomes. Insurers are interested in infection data to identify programs that have superior patient results. All of these process improvement initiatives are balanced by the evaluations of cost-effectiveness. Although some preventive measures, such as LAF, are highly effective, they may be too costly for routine use if they provide no additional benefit to the patient. While scientists are validating the use of new strategies, a renewed focus on best practices, including such basic concepts as hand hygiene, cleaning, disinfection, and preventing infections, is essential.

**Acknowledgement.** We would like to acknowledge the help of Sharon Krystofiak MS, MT (ASCP), CIC, from University of Pittsburgh Medical Center who assisted in writing the previous edition of this chapter.

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