Infection Control and Prevention Considerations

Titus L. Daniels and Thomas R. Talbot

Abstract

Due to the nature of their underlying illness and treatment regimens, cancer patients are at increased risk of infection. Though the advent and widespread use of anti-infective agents has allowed for the application of ever-greater immune-suppressing therapies with successful treatment of infectious complications, prevention of infection remains the primary goal. The evolutionary changes of microorganisms, whereby resistance to anti-infective therapy is increasingly common, have facilitated a paradigm shift in the field of healthcare epidemiology. No longer is the focus on "control" of infection once established in a healthcare environment. Rather, the emphasis is on prevention of infection before it occurs. The most basic tenet of infection prevention, and the cornerstone of all well-designed infection prevention and control programs, is hand hygiene. The hands of healthcare workers provide a common potential source for transmission of infectious agents, and effective decontamination of the hands reduces the risk of transmission of infectious material to other patients. Once infection is suspected or established; however, implementation of effective control strategies is important to limit the spread of infection within

T. L. Daniels (✉)
Vanderbilt University School of Medicine, Vanderbilt University Medical Center, A2200 MCN, 1161 21 AVE S, Nashville, TN 37232, USA
e-mail: titus.daniels@vanderbilt.edu

T. R. Talbot
Vanderbilt University School of Medicine, Vanderbilt University Medical Center, A2200 MCN, 1161 21 AVE S, Nashville, TN 37232, USA
e-mail: tom.talbot@vanderbilt.edu

V. Stosor and T. R. Zembower (eds.), *Infectious Complications in Cancer Patients*,
Cancer Treatment and Research 161, DOI: 10.1007/978-3-319-04220-6_15,

a healthcare environment. This chapter outlines the basic tenets of infection prevention, principles of isolation precautions and control measures, and elements for a successful infection control and prevention program.

Keywords

Infection control and prevention · Hand hygiene · Healthcare-associated infections (HAIs) · Transmission-based precautions · Contact precautions · Droplet precautions · Airborne precautions · Standard precautions · Protective environment · Multidrug-resistant organisms (MDROs) · *Clostridium difficile*

Contents

1 Introduction

The area of infection control has undergone substantial changes in the past decade. The most substantive change has been a shift in emphasis from "control" of healthcare-associated infections (HAIs) to developing and implementing strategies for preventing HAIs. This effort has been led by the Centers for Disease Control and Prevention (CDC), who adopted the addition of "and Prevention" in 1992 to their name [1]. A variety of published reports support the notion that most HAIs are preventable. These data challenge the concept of HAIs as a simply the "cost of doing business" in an increasingly complex healthcare environment. Thus, developing effective strategies to prevent HAIs is the foundation of any infection "control" program.

Healthcare-associated infections not only impart substantial morbidity and mortality upon patients; they are associated with enormous costs to the healthcare system. As an effort to provide better safer care and to assist in containing costs associated with HAI, the Centers for Medicare and Medicaid Services (CMS) no longer provides reimbursement for many hospital-acquired conditions. Several of these conditions are related to infection including catheter-associated blood stream infections, catheter-associated urinary tract infections, and selected surgical site infections.

The increased interest in HAIs has highlighted many important challenges that institutions must overcome. These include the development of systematic processes to ensure hand hygiene compliance and provide acceptable rates of healthcare-worker (HCW) influenza vaccination rates, develop methods for tracking and reporting infection rates, and designing and/or implementing evidence-based practice "bundles" associated with reductions in several HAIs (i.e., ventilator-associated pneumonia, catheter-associated blood stream infections, and surgical site infections). Developing effective infection prevention programs involves unique challenges under the best of circumstances. Many of these challenges are exemplified when considering the immune-compromised host. However, the majority of infection prevention and control initiatives apply to all patients equally regardless of the immune status of the host. Ensuring adherence to the basic tenets of infection prevention and control will serve all patient populations well, especially those already at increased risk of infectious complications.

2 Hand Hygiene

Ignaz Semmelweis demonstrated in 1847 that disinfecting the hands resulted in a marked reduction in puerperal fever. More than 150 years have passed since learning of the fundamental role that contaminated hands play in the transmission of HAIs [2]. Unfortunately, hand hygiene rates remain unacceptably low at around 40 % in most U.S. healthcare institutions. It is accepted by most experts that high rates of hand hygiene compliance are associated with reductions in HAIs. Emphasis thus is on improving the rate of hand hygiene compliance in healthcare institutions rather than continued study into the effectiveness of hand hygiene.

A comprehensive approach is necessary to sustain high rates of hand hygiene compliance. While education must be conducted and maintained, the majority of healthcare professionals accept the value and importance of hand hygiene. Therefore, directed efforts aimed at ensuring hand hygiene are performed and are the most beneficial. Such efforts are best focused on modeling of behavior by key institutional leaders [4, 5] and ensuring wide availability of hand hygiene products [3]. The selection of hand hygiene products often involves an extensive process that includes many representatives of the healthcare team (e.g., physicians, nurses, technicians, phlebotomists, etc.). The CDC recommends the use of alcohol-based hand-rubs preferentially over the use of soap and water in most situations. Reasons for such recommendations are severalfold. Because these products do not require the use of water, can be distributed in a variety of locations, are rubbed onto the hands until dry, and can be applied while walking to the location of the next task, hand hygiene is more likely to be performed appropriately and can be done quickly when using alcohol-based hand-rubs. On the contrary, use of soap and water requires remaining in a specified location, staying in this location while washing, and using soap and water for at least 15–20 s. Because of the frequent time-constraints placed on busy healthcare professionals, it is less likely that use of soap and water for hand hygiene is performed appropriately. Therefore, preference is given to the use of hand-rubs.

However, there are instances when the use of soap and water is preferred over that of an alcohol-based hand-rub. When hands are visibly soiled, hand-rubs are not effective in removing debris, and the use of soap and water is necessary to clean the hands. Another common situation where soap and water is preferred is when caring for patients infected or colonized with organisms that are not effectively killed or inactivated by hand-rubs. Organisms capable of forming spores are not inactivated with the use of hand-rubs. Therefore, use of a hand-rub does not eliminate the organisms from the hands allowing for possible transmission to another patient. *Clostridium difficile* is a commonly encountered pathogen that has the ability to form spores. While soap and water does not kill or inactivate the spores, the mechanical action of rubbing the hands under running water removes the spores from the hands. Soap is still necessary in order inactivate other organisms on the hands and to provide a surfactant for effective removal of spores from the hands [6].

3 Standard Precautions

Standard precautions encompass a set of infection prevention practices that are used for all patient encounters [5]. Standard precautions are based on the premise that all blood, body fluids, secretions, non-intact skin, and mucous membranes contain potentially infectious material. Therefore, handling of blood or body fluids demands the use of precautions to protect the HCW from exposure to a potentially infectious agent and to minimize the risk of transmission of such pathogens to others. Standard precautions include the practice of hand hygiene, the use of personal protective equipment (gowns, gloves, masks, and eye protection) depending on the anticipated procedure, and the performance of safe injection practices. Hand hygiene is a universal action practiced in all healthcare settings and with all patient interactions. The use of personal protective equipment (PPE), however, is designed only when exposure to potentially infectious material (blood and bodily fluids) may occur.

The 2007 CDC Guidelines for Isolation Precautions include *respiratory hygiene/cough etiquette*, a new practice recommendation incorporated as part of standard precautions [6]. Respiratory hygiene and cough etiquette refer to practices that minimize transmission of respiratory pathogens (i.e., influenza, common cold viruses, etc.) and includes covering of coughs/sneezes, use of a surgical mask for those with respiratory symptoms, and performing hand hygiene after coughing and/or sneezing. Further, use of signage to provide instruction on the performance of respiratory hygiene and cough etiquette is suggested. While these practices are congruent with the notion of standard precautions, they differ in that respiratory hygiene and cough etiquette applies to all individuals within the healthcare institution, including visitors and patients in addition to HCWs. Standard precautions, on the other hand, generally apply only to HCWs.

4 Transmission-Based Precautions

Transmission-based precautions are utilized to prevent the spread of specific pathogens and are based on the mode of transmission of the organism in question. Such precautions generally are of three types: airborne, droplet, and contact. Each of these sets of precautions has specific environmental components and recommendations for the use of PPE by HCWs. For all circumstances, the implementation of transmission-based precautions should occur whenever infection or colonization with a pathogen is suspected or confirmed to be present. Implementation of precautions early in the course when infection or colonization is suspected, even before being confirmed, minimizes the risk of disease transmission to other patients and HCWs. Minimizing the exposure risk is expected to minimize the risk of transmission to subsequent patients.

Airborne precautions are designed to minimize the transmission of infectious pathogens spread by the airborne route. Pathogens spread by the airborne route are highly infectious particles that have the ability to spread via air currents, thus allowing for easy spread over relatively long distances. These include tuberculosis, measles, and varicella zoster virus. The spread of novel respiratory viruses (i.e., avian influenza H5N1) is often unknown. Recommendations for control of these viruses includes using airborne precautions as a component of protection until further data demonstrating other precautions are sufficient for interruption of transmission [6, 7].

Use of an airborne infection isolation room (AIIR) is necessary for patients requiring airborne precautions. An AIIR is a room in which the pressure in the room (where the infected patient is located) is negative relative to the pressure in the areas adjacent to the room. This design allows for air outside of the room to flow into the room, pass through a high-efficiency filter, and then be exhausted. The other major component of caring for patients with suspected or confirmed pathogens requiring airborne precautions is that all HCWs entering into the room wear a respirator capable of filtering the potentially infectious material (i.e., fit-tested N-95 particulate respirator). The design to minimize the risk of transmission of infectious organisms to patients in adjacent areas and rooms poses unique challenges to patients with compromised immune systems where the general goal is to move environmental air from the patient's environment into adjacent areas, hence using positive pressure ventilation rather than negative pressure ventilation. However, positive pressure ventilation allows for the dispersion of airborne infectious material to potentially be spread to other, often immune-compromised, patients in adjacent areas or rooms. Because of the risk of disease transmission to others from patients with infections such as tuberculosis and measles, it is recommended that all patients requiring airborne precautions, regardless of immune status, be cared for in negative pressure rooms.

A not uncommon situation, though, occurs when immune-compromised patients present with cutaneous or disseminated varicella zoster virus (VZV) infections. Due to impaired immunity, these patients are likely to shed virus from lesions for prolonged periods. Daily culturing of lesions from immune-compromised patients with cutaneous VZV demonstrated that virus may be viable and able to be cultured from lesions for up to 8 days (mean 4.7 days) [8]. Immune-compromised patients are also more likely to develop disseminated disease, and in this same series of patients, 61 % (11/18) developed disseminated disease after the third day of rash onset. Because airborne transmission of VZV has been demonstrated to occur in hospital settings [9], patients with either primary varicella or disseminated zoster infections are recommended to be cared for using airborne precautions. The propensity for dissemination, and therefore potential airborne transmission, after the first day of rash onset in immune-compromised patients suggests that the use of airborne isolation precautions early in the course of illness is a prudent strategy for mitigating the nosocomial spread of VZV infections. The CDC recommends the use of airborne precautions for patients with disseminated disease, regardless of immune status and any disease severity, including localized skin eruptions, due to VZV in immune-compromised patients. Discontinuing the use of airborne precautions is dependent primarily on the pathogen of concern. For VZV (shingles), for example, it is recommended that patients remain in an AIIR with airborne precaution use until all lesions have fully crusted.

The next type of transmission-based precautions is droplet precautions. Droplet transmission occurs when infectious material is expelled from the respiratory tract of an individual when the person coughs, sneezes, or talks [10]. The droplet particles are of larger size than particles associated with pathogens that are spread by the airborne route. The larger size of the droplet particles, therefore, does not allow the infectious material to be dispersed over long distances via air currents as occurs with airborne transmission. The specific distance for which droplet particles remain infectious is largely unknown. Limited data suggest that the risk of transmission is limited to a distance within three feet of the patient [11, 12]. Personal protective equipment for droplet precautions includes the use of a surgical mask by healthcare personnel. The masks should be donned when within about six feet of the patient, a distance considered to be safe and recommended as an additional modicum of caution [6]. Pathogens transmitted via respiratory droplets include influenza virus, adenovirus, rhinovirus, *Bordetella pertussis, Streptococcus pyogenes,* and *Neisseria meningitides*. Respiratory syncytial virus may be transmitted by the droplet route, though the primary mode of transmission is via direct contact with infected material.

Transmission of pathogens within the healthcare environment most commonly occurs by the contact route. Contact transmission is divided into direct and indirect contact transmissions. Direct contact transmission is that which occurs when pathogens are transmitted from one person to another without an intermediary, be it a person or object. Transmission of hepatitis B virus from an infected patient to an HCW from a contaminated needle stick and transmission of scabies from a patient to a HCW are two examples of direct transmission. More commonly, however, indirect contact transmission of pathogens occurs in the healthcare environment.

Indirect contact transmission occurs when a microorganism is transmitted from one person to another via a contaminated person or object. The contaminated hands of HCWs are the most important vector responsible for the indirect contact transmission of microorganisms. Other potential transmission sources include equipment used in the care of patients (i.e., thermometers, blood pressure measurement devices, stethoscopes, etc.). These objects have the opportunity to transmit infectious material if not appropriately disinfected between patients.

Equipment necessary for interrupting transmission of organisms spread by the contact route includes the use of gloves and gowns by HCWs. Ideally, patients should be cared for in a private room. Cohorting of patients colonized or infected with the same type of infectious agent is acceptable [6, 13]. Guidelines for discontinuation of contact precautions have not been well defined.

5 Environmental Issues

One aspect of infection control and prevention unique to the immune suppressed population is the use of the protective environment. The protective environment has been specifically designed for patients who have undergone hematopoietic stem cell transplantation (HSCT). A primary goal of the protective environment is to reduce fungal spore counts in the air and, therefore, the risk of invasive fungal disease. Though many types of fungal spores are likely affected by the environmental controls of the protective environment, control of *Aspergillus* spores and mitigation of invasive aspergillosis have been the primary goal.

High-efficiency particulate air (HEPA) filtration of incoming air, directed room airflow, positive room air pressure relative to the corridor, and well-sealed rooms to prevent flow of air from the outside are all part of the protective environment concept. The neutropenic diet is an additional component of the protective environment. The neutropenic diet consists of foods low in bacterial counts with the goal of limiting the introduction of bacteria into the gastrointestinal tract of patients and, thereby, potentially reducing infection by reducing the occurrence of colonization. Many institutions employ the use of the neutropenic diet in an effort to diminish the risk of infection in patients during periods of neutropenia (neutrophil counts $< 500 \times 10^9$/L). Prior to the introduction of the neutropenic diet, food was autoclaved and irradiated prior to serving to patients. This left the food unpalatable by many. The National Cancer Institute performed a randomized trial demonstrating little advantage to the sterile diet over a "cooked food" diet designed by the National Institutes of Health, Department of Dietary and Environmental Sanitation. The cooked food diet was more palatable than the sterile diet. However, it reportedly left patients dissatisfied after prolonged use [14]. Use of commercially available foods was desirable. Culturing of commercially available food [15] found that 66 % grew less than 500 colony-forming units of bacteria per gram of food. Therefore, this became the upper limit of bacterial counts determined to be acceptable for neutropenic patients. However, only 20 % of processed meats and 30 % of fresh fruits and vegetables had colony counts of bacteria below this threshold. However, data evaluating the specific impact of the neutropenic diet are lacking. A systematic review and meta-analysis performed by Schlesinger et al. [16] evaluated the effect on the protective environment. Components of the protective environment varied across studies, though primarily included air quality control, barrier isolation, and the use of nonabsorbable antibiotics. The protective environment was associated with a 40 % reduction in all-cause mortality at 30 days (RR 0.6 [95 % CI: 0.50–0.72]). When evaluated for the longest period of follow-up (range, 100 days–3 years), mortality reduction was less substantial for patients when care was provided in a protective environment with a relative risk for mortality of 0.86 (95 % CI: 0.81–0.91). Examination of the individual components of the protective environment demonstrates that control of air quality alone was associated with a 19 % reduction in mortality at 100 days (RR 0.81 [95 % CI: 0.73–0.91]). Neither barrier isolation (RR 1.25 [95 % CI: 0.66–2.38]) nor suppression of endogenous flora alone (RR 0.88 [CI: 0.63–1.21]) resulted in a statistically significant effect on mortality. Significant reductions in mortality were also demonstrated among recipients of allogeneic hematopoietic stem cell transplantation (HSCT) (RR0.81, [95 % CI: 0.73–0.89]) and autologous HSCT (RR 0.72, [95 % CI: 0.58–0.88]) when cared for in a protective environment.

These data support the recommendation that patients undergoing HSCT should be cared for in a protective environment [17]. Because of the intensity of chemotherapy and associated prolonged periods of neutropenia associated with treatment for acute leukemia, it is reasonable to extend the use of a protective environment to this population, as well. The lack of available data coupled with dissatisfaction and potential for adverse events associated with isolation of the patient should temper the widespread use of the protective environment for all cancer patients. Strict adherence to routine infection prevention practices should be sufficient to protect non-HSCT patients.

6 Multidrug-Resistant Organisms

A number of bacterial pathogens have emerged demonstrating increased resistance to common, or more worrisome, many classes of antibiotics. The emergence of resistance complicates treatment of infections due to these pathogens, made all the more difficult in patients with underlying immune-compromising conditions. With the dwindling availability of effective antibiotic therapy, prevention of infection is paramount. Reducing the transmission of antibiotic-resistant bacteria is not necessarily different from that of other bacterial pathogens. Attention is focused on these antibiotic-resistant organisms because of their propensity to cause infection, their associated morbidity and mortality, and limited therapeutic options should infection be established.

Staphylococci remain the most common single bacterial cause of HAIs. The past two decades have seen an emergence of resistant staphylococci, namely methicillin-resistant *Staphylococcus aureus* (MRSA) [18–27]. A report by the CDC estimated that nearly 100,000 persons annually experience infections caused by MRSA. Infections due to MRSA vary from superficial carbuncles to life-threatening bloodstream infections, device-associated infections, and necrotizing pneumonia. Data have emerged demonstrating that infection with MRSA is associated with an increased mortality compared with an infection with a non-MRSA strain of *S. aureus*. Cosgrove et al. [28] conducted a meta-analysis demonstrating an increased odds of death (Odds Ratio OR 1.93, 95 % CI: 1.54–2.42) among patients with bloodstream infections from MRSA compared with patients with bloodstream infections due to methicillin-susceptible *S. aureus*.

Developing effective strategies to reduce transmission of MRSA remains a challenge. Much attention has focused on efforts to screen patients who may be harboring (i.e., colonized with) MRSA. This strategy, known as active surveillance culturing (ASC), has been reported to be beneficial in reducing infections from MRSA in selected populations [26]. However, other data have demonstrated that ASC is not useful in combination with several other infection control-based interventions in reducing infections due to MRSA or MRSA transmission [27].

Unless future data demonstrate conclusively that screening all patients for MRSA is associated with reduced transmission of and reduced infections due to MRSA, an approach targeted at a variety of pathogens seems most reasonable. For institutions that do well with other infection prevention and control activities (i.e., hand hygiene, adherence to isolation practices), yet still have high rates of infection due to MRSA, implementation of a screening program targeted at patient populations with the greatest risk and/or burden of infection may prove beneficial in assisting in the control of infections caused by MRSA.

Enterococcus species [29–38] are gram-positive bacteria related to the *Streptococcus* species. These bacteria have plagued healthcare institutions for years and have generated much interest among clinicians caring for immune-compromised patients due to the frequency of infections caused by these organisms as well as the associated morbidity and mortality. The basic tenets of infection prevention, an emphasis on hand hygiene, early isolation, and antimicrobial stewardship apply to this organism just as they do for other antibiotic-resistant pathogens.

Whereas MRSA is associated with increased mortality when compared with methicillin-susceptible *S. aureus* infection, data are less clear that VRE is associated with increased mortality when compared with vancomycin-susceptible enterococci. Risk factors for VRE [29, 34, 39–50] have been well described and most notably include an underlying hematologic malignancy, neutropenia, invasive device use, and prior antimicrobial therapy, of which vancomycin is the most consistently identified antibiotic associated with an independent risk for either colonization or infection.

Once either colonized or infected, however, whether VRE is an independent risk factor for death is less clear. Experience with VRE bloodstream infections (BSI) in an HSCT unit [51] found that 13 % of patients colonized with VRE subsequently developed VRE BSI. The majority of these patients had acute leukemia. On multivariate analysis, the authors found that VRE BSI was not an independent risk factor for death and suggested the presence of VRE BSI is more a marker for severity of underlying illness. Similar findings were noted in another study of VRE BSI by Han et al. [52]. In contrast, a meta-analysis [53] demonstrated that vancomycin resistance is associated with increased mortality when compared with vancomycin-susceptible enterococci causing BSI (OR 2.52, 95 % CI: 1.9–3.4). In neutropenic patients, prolonged bacteremia may be a possible explanation [54].

Prevention of infection, then, becomes ever more important. Screening of patients is a strategy employed by many institutions to determine whether colonization is present. Patients with positive screening cultures are subsequently isolated in an effort to reduce transmission of bacteria to other patients. Culturing the perirectal region of patients for the presence of VRE is a strategy performed by many institutions. The goal of screening patients is twofold: first, to initiate isolation precautions to minimize the risk of transmission of bacteria to other patients and second, to identify carriage in the event, empirical antimicrobial therapy must be used for subsequent infection—a common occurrence among immune-suppressed patients. Weinstock et al. [55] followed 92 patients who were screened for VRE stool colonization at the time of admission for allogeneic HSCT (alloHSCT). Colonization with VRE was common (40.2 % of patients) and 34.2 % of patients with positive VRE screens on admission later developed BSI, whereas 1.8 % without initial VRE positive screens subsequently developed VRE BSI. Thus, for patients where stool culture is obtained for VRE and it is positive, subsequent empirical therapy for BSI should include adequate activity against VRE. Though screening for VRE in high-risk populations has also been associated with an overall decreased incidence of VRE-related infection in medical and surgical intensive care units [56], routinely screening all patients is not recommended [13]. If, however, standard infection prevention methods are not associated with control of healthcare-associated VRE infections, the addition of active screening programs targeted to the appropriate population should be considered. Such screening programs, though, must not supplant ongoing and more well-established infection prevention and control initiatives. Though much interest has been directed toward the gram-positive organisms, MRSA and VRE, many experts believe a more concerning situation exists with multidrug-resistant gram-negative pathogens. A variety of difficulty to treat gram-negative bacteria has emerged over the past decade. Currently, *Klebsiella pneumoniae, Eshershicia coli, Pseudomonas aeruginosa,* and *Acinetobacter baumannii* appear to be the primary gram-negative organisms exhibiting the most troublesome resistance trends. These range from the previously known extended-spectrum beta-lactamase (ESBL)-producing pathogens to the newly emerged carbapenem-resistant *Enterobacteriacae* (CRE). Several recent reviews detail the changing epidemiology of these antibiotic-resistant bacteria [57–61]. Perhaps most disturbing is the emergence of CRE, which exhibit resistance to the carbapenem class of antibiotics, long considered the agents of choice for resistant gram-negative bacteria. More concerning is that these bacteria are frequently accompanied by resistance to many, if not all, other classes of antibiotics.

Outcomes associated with infections due to the resistant gram-negative organisms are difficult to ascertain. Several studies have reported increased attributable mortality [62–68]. However, other studies have not been able to demonstrate a specific impact of the multidrug resistance on mortality [69–71]. The difficulty in ascertaining outcomes associated with gram-negative resistance is likely due to several factors. First, unlike the gram-positive organisms, where resistance is typically manifested against one class of antibiotic (e.g., methicillin or vancomycin for MRSA and VRE, respectively), the gram-negative organisms demonstrate complex and variable resistance profiles. Second, these pathogens appear to be more common among severely ill patients who are often hospitalized for prolonged periods of time and discerning the impact of one variable (resistance) from potentially hundreds of factors that may contribute to death is extraordinarily difficult. Next, related to the first, there is not an accepted standard definition for what comprises "multidrug resistance," and the heterogeneity of definitions has made interpretation and investigation of the effect of multidrug resistance elusive. Finally, it has been demonstrated that initial antimicrobial therapy ineffective against the causative pathogen is associated with poorer outcomes, even if appropriate therapy is initiated once susceptibilities are known [72–74]. With complex resistance patterns often demonstrated by these multidrug-resistant gram-negative pathogens, there is a greater risk of not choosing an effective empirical antimicrobial agent, and the poor outcomes observed in these patients may be more reflective of inappropriate antimicrobial choice rather than the a specific effect of resistance.

From an infection control and prevention perspective, there is no difference in the management of the patients infected or colonized with these pathogens. Patients harboring ESBL-producing organisms have long been recommended to have contact precautions used [6, 13]. The same principles apply to these pathogens as they do for others (i.e., MRSA, VRE). The use of active screening cultures to identify patients that may be colonized with multidrug-resistant gram-negative bacteria has not proven to be beneficial [75–77]. Emphasis on hand hygiene along with initiation of contact precautions for patients who are either colonized or infected is recommended. No specific guidance has been offered as to when patients can have contact precautions discontinued, though most experts suggest maintaining contact precautions at least until hospital discharge [13].

7 Other Organisms of Epidemiological Importance

C. difficile is a gram-positive, spore-forming organism that has been well described to be a common cause of intestinal infection among hospitalized patients [78, 79]. *C. difficile* is spread by direct or indirect contact with a patient or the environment of a patient who is either colonized or infected [80–89]. A variety of risk factors for disease have been described and include prior use of antibiotics, advanced age, prolonged hospital stay, and severe underlying disease [90–92]. Persons with underlying malignancy may be especially at risk given their compromised immune status. Receipt of chemotherapy has been associated with an increased risk of developing diarrhea with a toxigenic *C. difficile* strain (OR 6, [95 % CI: 1.51–23.8] [93]. The use of interleukin-2, either during the index hospitalization or within 30 days of admission, has also been demonstrated to be associated with a greater risk of *C. difficile* infection [94]. The past decade has seen the emergence of a new strain of *C. difficile* [95–97]. When considering previously described strains of *C. difficile*, this newly described strain has increased virulence, increased toxin production, increased spore formation, and resistance to the fluoroquinolone antibiotics. While these factors may cause more severe clinical presentations, there are no data to suggest that control of infections due this new *C. difficile* strain requires an approach different from that of traditional control mechanisms for *C. difficile*.

Patients with suspected or confirmed infection with *C. difficile* should be placed in contact precautions. The use of gowns and gloves serves as a barrier to minimize the HCWs hands and clothing contamination. Empiric isolation of patients with diarrhea is a strategy that may help mitigate the transmission of *C. difficile* within an institution. A more targeted approach may be to empirically isolate those patients with a prior known history of *C. difficile* infection given that, as Boone et al. [98] described, 15 % of patients readmitted within 6 months of being diagnosed with *C. difficile* infection continued to test positive for toxigenic strains of *C. difficile*. The use of infection control measures (empiric isolation of patients with diarrhea, gowns, gloves, hand hygiene with soap/water) has been demonstrated to be effective in terminating transmission of *C. difficile* [64] infections, including among patients with leukemia [99, 100]. As described before, the spores of *C. difficile* are not inactivated by alcohol-based hand-rubs. Therefore, the use of soap and water is recommended for hand hygiene after contact in order to remove the spores from the hands, particularly in outbreak settings.

Aspergillosis is caused by a variety of *Aspergillus* species. The typical person inhales *Aspergillus* spores regularly, yet invasive aspergillosis is rare and typically seen only among those with severe immune suppression. Thus, control of *Aspergillus* is of primary concern among patients with severely impaired immune function, such as HSCT patients. Other patients, namely solid-organ transplant patients and those with acute leukemia undergoing induction chemotherapy, also appear to have increased risk for invasive aspergillosis. The control of *Aspergillus* spores begins with healthcare facility construction. To minimize the risk of mold exposure to patients, rooms with false ceilings should be avoided since these areas may serve as a reservoir for dust and various molds to accumulate. If false ceilings are present, ensuring a mechanism for routine cleaning and vacuuming is necessary to minimize the exposure risk. Rooms for patients undergoing HSCT should have HEPA filtration of the incoming air, and the air pressure in the room should be positive in relation to the corridor. The positive pressure allows air to be moved from within the room to outside the room, minimizing the risk of drawing in airborne infectious material, such as *Aspergillus* spores [6, 17, 101].

However, as healthcare facilities continue to experience construction and renovation, it becomes essential to ensure that before any construction begins, an infection control risk assessment (ICRA) is completed. The ICRA is designed to evaluate the type of construction that is planned and to determine whether there may be a potential risk for exposing patients to infectious agents, namely *Aspergillus* spores [17, 102]. While aspergillosis is commonly cited to be associated with hospital construction [103–105], one matched case–control study among renal transplant recipients found that an average daily dose of corticosteroid use equivalent to 1.25 mg/kg per day of prednisone was predictive of subsequent invasive aspergillosis [106]. Control of dust during construction or renovation generally involves erecting airtight barriers between the construction area(s) and patient care area(s). Ensuring a facility-wide systematic approach to evaluate construction projects, no matter how minor or trivial they may seem, is critically important to minimize the dissemination of *Aspergillus* spores, especially in areas where immune-suppressed patients are housed. Should a patient develop invasive aspergillosis while hospitalized full epidemiologic evaluation should be undertaken in an effort to evaluate for an environmental source.

Legionellosis, caused by *Legionella* species of bacteria, most commonly presents as pneumonia and has been well described to occur within healthcare institutions, including among immune-suppressed patients [107]. Outbreaks are typically associated with a contaminated water source such as a decorative fountain [107], common water supply [108–111], and cooling towers [112]. Therefore, the finding of even one healthcare-associated *Legionella* infection should prompt an investigation into a potentially contaminated water source [102]. Control measures for *Legionella* are many and varied and most have achieved inconsistent results [113]. For patients in protective environments or transplant units, the CDC recommends that heated water temperatures be maintained >123 °F (>50 °C) and cold water <68 °F (<20 °C). Alternately, heated water may be chlorinated to achieve 1–2 mg/L of free residual chlorine measured at the tap. Periodic culturing for *Legionellae* may also be performed though is not specifically recommended, as there is little guidance for the optimal culturing methodology. Showerheads in patient rooms or in inpatient care areas should be disinfected monthly using a chlorine-based cleaning solution. Use of humidifiers should be avoided as these may create aerosols increasing the risk of legionellosis. If the use of a humidifier is unavoidable, high-level disinfection should occur and only sterile water should be used.

Because of the epidemiologic importance of healthcare-associated legionellosis, an epidemiologic investigation should occur if even a single case of nosocomial *Legionella* is identified. Reporting to the local or state health department may be required in some jurisdictions. Investigation of healthcare-associated legionellosis will necessarily involve some form of environmental culturing. Sampling methods for obtaining reliable environmental cultures present unique challenges, and the resources, especially when attempting to identify fastidious pathogens such as *Legionella*, may not be readily available. Molecular typing of identified isolates from suspected patients, and also the environment is useful to identify a water source responsible for patient infection.

Finally, various respiratory viral pathogens, such as respiratory syncytial virus (RSV) and influenza, can cause HAIs in the immune-compromised patient. While transmission of these pathogens may differ (i.e., RSV is spread primarily via direct contact, while influenza is spread mainly by respiratory droplets), control of febrile respiratory infections (FRI) due to these pathogens occurs through several core infection control practices. Patients with FRI should be identified upon entry to a healthcare facility. Such patients can then be cohorted from other noninfected patients and placed into appropriate isolation precautions. Strict adherence to hand hygiene, use of PPE, restriction of ill visitors and healthcare workers, and source control of the infected patient (such as having the patient wear a surgical mask when in public areas) are all important infection control measures [6].

For some respiratory pathogens, particularly influenza, vaccination remains a cornerstone of efforts to prevent nosocomial FRI. Healthcare workers are recommended as a target group for influenza vaccination due to their close contact with patients at high risk for complications of influenza [114]. Many healthy healthcare workers may become infected with influenza yet have no or minimal symptoms. These persons can still shed and spread influenza virus to their patients. In addition, in the 24 h prior to development of classic influenza symptoms (i.e., myalgias, high fevers, cough, fatigue), infected persons can shed virus. Studies have shown that influenza vaccination of healthcare workers reduces laboratory-confirmed influenza, sick days due to respiratory illness, and days lost from work [115]. Perhaps most striking are findings in several studies in long-term care facilities that demonstrate that vaccination of healthcare workers significantly reduced the mortality of their patients [116–119]. Despite the benefits of healthcare worker influenza vaccination, coverage rates of healthcare workers remain unacceptably low at approximately 65 %. Because of these low rates, several medical centers and hospitals have moved to requiring influenza vaccination as a condition of employment for healthcare workers [120]. Whatever the strategy utilized, increasing healthcare worker influenza vaccination rates is important to protect patients from healthcare-associated infections.

8 Essential Elements of a Successful Infection Control and Prevention Program

Essential for discovery of HAIs and developing processes to prevent infection is a strong infection prevention, control, and epidemiology program. Critical to the success of any program are highly trained nurses specially trained in infection prevention, control, and hospital epidemiology—infection preventionists (IP). The CDC recommends a staffing ratio of 1 full-time equivalent (FTE) IP for the first 100 beds of a hospital to 1 FTE IP for every additional 250 beds [121, 122]. The basis for this recommendation is the Study on the Efficacy of Nosocomial Infection

Control (SENIC) Project [123], sponsored by the CDC in the 1970s and the Delphi project [124] which recommended a staffing ratio 0.8–1 IP for every 100 occupied beds. The investigators of the SENIC Project, for the first time, provided evidence supporting the link between an established infection control and prevention program and fewer HAIs. The role of the IP has undergone substantial changes since the original SENIC Project, from initially gathering data and reporting infection rates to now requiring an understanding of process improvement, data analysis, transmission of infectious diseases, and epidemiology, to name a few. With the complexities of infection prevention and control along with the specialized knowledge necessary to implement and maintain a successful prevention program, formal certification in the specialty is available. All institutions, though especially those where care for severely immune-compromised patients is delivered, should have at least one certified IP leading the program of infection prevention.

Another important element of successful infection prevention and control programs is the use of standardized definitions, such as those provided by the CDC [125], for determining HAIs. The universal application of validated, standardized definitions for surveillance of HAIs provides several advantages. First, there is less variability in what is deemed an infection, and second, the use of standardized definitions allows for tracking trends over time. Institutional data on infection rates are most helpful for that specific institution in order to determine how successful a program is at reducing HAIs. Next, the use of standard definitions allows for data to be aggregated from multiple institutions to develop mean and median rates of specific types of infections. Only if definitions are applied in a consistent manner throughout multiple institutions is the development of such statistical "benchmarks" possible. Such benchmarks, then, allow institutions to develop an understanding of their specific HAIs and which types may be either significantly above or below that of other institutions, thus serving to direct resources where most appropriate. The CDC publishes aggregated infection rate data by infection type and care location annually [126]. These data are helpful to help understand how hospitals compare to one another and where there may be opportunities for improvement.

By directing appropriate resources to infection prevention programs and ensuring that these programs are staffed with specially trained infection preventionists and epidemiologists, healthcare institutions can substantially mitigate HAIs. Though achieving a rate of zero infections may not be possible, especially among severely immune-suppressed patients, the goal of having zero *preventable* infections is possible and is recommended to be the goal of all healthcare institutions. Focusing on effective prevention initiatives such as active surveillance for HAIs, minimizing exposure hazards (i.e., mold from construction, poorly maintained water sources), ensuring appropriate isolation of patients, and hand hygiene adherence will serve to provide a safe environment for the care of the immune-suppressed patient, as well as all other patients.

References

1. CDC (1992) The nation's prevention agency. MMWR Morb Mortal Wkly Rep 41(44):833
2. Hugonnet S, Pittet D (2000) Hand hygiene-beliefs or science? Clin Microbiol Infect 6(7):350–356
3. Talbot TR et al (2013) Sustained improvement in hand hygiene adherence: utilizing shared accountability and financial incentives. Infect Control Hosp Epidemiol 34(11):1129–1136
4. Schneider J et al (2009) Hand hygiene adherence is influenced by the behavior of role models. Pediatr Crit Care Med 10(3):360–363
5. Lankford MG et al (2003) Influence of role models and hospital design on hand hygiene of healthcare workers. Emerg Infect Dis 9(2):217–223
6. Siegel JD et al (2007) Guideline for isolation precautions: preventing transmission of infectious agents in health care settings. Am J Infect Control 35(10(2)):S65–S164
7. Use of Surgical Masks and Respirators in Health Care Settings (2010) Oct 2006 (cited 26 Apr 2010). Available from www.pandemicflu.gov/professional/hospital/maskguidancehc.html
8. Bean B, Braun C, Balfour HH Jr (1982) Acyclovir therapy for acute herpes zoster. Lancet 2(8290):118–121
9. Leclair JM et al (1980) Airborne transmission of chickenpox in a hospital. N Engl J Med 302(8):450–453
10. Papineni RS, Rosenthal FS (1997) The size distribution of droplets in the exhaled breath of healthy human subjects. J Aerosol Med 10(2):105–116
11. Feigin RD et al (1982) Epidemic meningococcal disease in an elementary-school classroom. N Engl J Med 307(20):1255–1257
12. Dick EC et al (1987) Aerosol transmission of rhinovirus colds. J Infect Dis 156(3):442–448
13. Siegel JD et al (2007) Management of multidrug-resistant organisms in health care settings, 2006. Am J Infect Control 35(10(2)):S165–S193
14. Moody K, Charlson ME, Finlay J (2002) The neutropenic diet: what's the evidence? J Pediatr Hematol Oncol 24(9):717–721
15. Pizzo PA, Purvis DS, Waters C (1982) Microbiological evaluation of food items. For patients undergoing gastrointestinal decontamination and protected isolation. J Am Diet Assoc 81(3):272–279
16. Schlesinger A et al (2009) Infection-control interventions for cancer patients after chemotherapy: a systematic review and meta-analysis. Lancet Infect Dis 9(2):97–107
17. Dykewicz CA, Jaffe HW, Kaplan JE (2000) Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. MMWR Recomm Rep 49(RR-10):1–125, CE 1–7
18. Supriya M et al (2009) Controlling MRSA in head and neck cancer patients: what works? Otolaryngol Head Neck Surg 140(2):224–227
19. Reitzel RA et al (2009) Efficacy of novel antimicrobial gloves impregnated with antiseptic dyes in preventing the adherence of multidrug-resistant nosocomial pathogens. Am J Infect Control 37(4):294–300 (Epub 19 Jan 2009)
20. Wenzel RP, Bearman G, Edmond MB (2008) Screening for MRSA: a flawed hospital infection control intervention. Infect Control Hosp Epidemiol 29(11):1012–1018

22. Wang FD et al (2008) Risk factors and mortality in patients with nosocomial *Staphylococcus aureus* bacteremia. Am J Infect Control 36(2):118–122

22. Rogers SN et al (2008) Which patients are most at risk of methicillin resistant *Staphylococcus aureus*: a review of admissions to a regional maxillofacial ward between 2001 and 2005. Br J Oral Maxillofac Surg 46(6):439–444

23. Hidron AI et al (2008) NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006–2007. Infect Control Hosp Epidemiol 29(11):996–1011

24. Miyake M et al (2007) Risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) and use of a nasal mupirocin ointment in oral cancer inpatients. J Oral Maxillofac Surg 65(11):2159–2163
25. Scudeller L et al (2000) MRSA carriage: the relationship between community and healthcare setting. A study in an Italian hospital. J Hosp Infect 46(3):222–229
26. Robicsek A et al (2008) Universal surveillance for methicillin-resistant *Staphylococcus aureus* in 3 affiliated hospitals. Ann Intern Med 148(6):409–418
27. Harbarth S et al (2008) Universal screening for methicillin-resistant *Staphylococcus aureus* at hospital admission and nosocomial infection in surgical patients. JAMA 299(10):1149–1157
28. Cosgrove SE et al (2003) Comparison of mortality associated with methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* bacteremia: a meta-analysis. Clin Infect Dis 36(1):53–59
29. Worth LJ et al (2007) Vancomycin-resistant Enterococcus faecium infection in patients with hematologic malignancy: patients with acute myeloid leukemia are at high-risk. Eur J Haematol 79(3):226–233
30. Huang SS et al (2007) Improving the assessment of vancomycin-resistant enterococci by routine screening. J Infect Dis 195(3):339–346
31. Matar MJ et al (2006) Colonization and infection with vancomycin-resistant Enterococcus among patients with cancer. Am J Infect Control 34(8):534–536
32. Knoll M et al (2005) Outbreak of vancomycin-resistant enterococci (VRE) in a hematological oncology ward and hygienic preventive measures. A long-term study. Onkologie 28(4):187–192
33. Oh HS et al (2004) Outbreak of vancomycin resistant Enterococcus in a hematology/oncology unit in a Korean University Hospital, and risk factors related to patients, staff, hospital care and facilities. Scand J Infect Dis 36(11–12):790–794
34. Husni R et al (2002) Risk factors for vancomycin-resistant *Enterococcus* (VRE) infection in colonized patients with cancer. Infect Control Hosp Epidemiol 23(2):102–103
35. Hanna H et al (2001) Management of an outbreak of vancomycin-resistant *Enterococci* in the medical intensive care unit of a cancer center. Infect Control Hosp Epidemiol 22(4):217–219
36. McCarthy KM et al (2000) Control of an outbreak of vancomycin-resistant *Enterococcus faecium* in an oncology ward in South Africa: effective use of limited resources. J Hosp Infect 44(4):294–300
37. Kuehnert MJ et al (1999) Association between mucositis severity and vancomycin-resistant enterococcal bloodstream infection in hospitalized cancer patients. Infect Control Hosp Epidemiol 20(10):660–663
38. Roord JJ et al (1986) Infection prevention during induction of remission in children with newly diagnosed acute leukemia. Ann Ist Super Sanita 22(3):973–977
39. Olivier CN et al (2008) Risk of vancomycin-resistant *Enterococcus* (VRE) bloodstream infection among patients colonized with VRE. Infect Control Hosp Epidemiol 29(5):404–409
40. Fuller RE et al (1998) Vancomycin-resistant enterococci: risk related to the use of intravenous vancomycin in a university hospital. Infect Control Hosp Epidemiol 19(11):821–823
41. Sakka V et al (2008) Risk-factors and predictors of mortality in patients colonised with vancomycin-resistant enterococci. Clin Microbiol Infect 14(1):14–21
42. Dan M et al (1999) Rectal colonization with vancomycin-resistant enterococci among high-risk patients in an Israeli hospital. J Hosp Infect 43(3):231–238
43. Beltrami EM et al (2000) Risk factors for acquisition of vancomycin-resistant enterococci among patients on a renal ward during a community hospital outbreak. Am J Infect Control 28(4):282–285

44. MacIntyre CR et al (2001) Risk factors for colonization with vancomycin-resistant enterococci in a Melbourne hospital. Infect Control Hosp Epidemiol 22(10):624–629
45. Zaas AK et al (2002) Risk factors for development of vancomycin-resistant enterococcal bloodstream infection in patients with cancer who are colonized with vancomycin-resistant enterococci. Clin Infect Dis 35(10):1139–1146
46. Martinez JA et al (2003) Role of environmental contamination as a risk factor for acquisition of vancomycin-resistant enterococci in patients treated in a medical intensive care unit. Arch Intern Med 163(16):1905–1912
47. Padiglione AA et al (2003) Risk factors for new detection of vancomycin-resistant enterococci in acute-care hospitals that employ strict infection control procedures. Antimicrob Agents Chemother 47(8):2492–2498
48. McEvoy SP et al (2006) Risk factors for the acquisition of vancomycin-resistant enterococci during a single-strain outbreak at a major Australian teaching hospital. J Hosp Infect 62(2):256–258
49. Assadian O et al (2007) Prevalence of vancomycin-resistant enterococci colonization and its risk factors in chronic hemodialysis patients in Shiraz. Iran BMC Infect Dis 7:52
50. Askarian M et al (2008) Risk factors for rectal colonization with vancomycin-resistant enterococci in Shiraz. Iran Int J Infect Dis 12(2):171–175
51. Dubberke ER et al (2006) Vancomycin-resistant enterococcal bloodstream infections on a hematopoietic stem cell transplant unit: are the sick getting sicker? Bone Marrow Transplant 38(12):813–819
52. Han SH et al (2009) Vancomycin-resistant enterococci bacteremia: risk factors for mortality and influence of antimicrobial therapy on clinical outcome. J Infect 58(3):182–190
53. DiazGranados CA et al (2005) Comparison of mortality associated with vancomycin-resistant and vancomycin-susceptible enterococcal bloodstream infections: a meta-analysis. Clin Infect Dis 41(3):327–333
54. DiazGranados CA, Jernigan JA (2005) Impact of vancomycin resistance on mortality among patients with neutropenia and enterococcal bloodstream infection. J Infect Dis 191(4):588–595
55. Weinstock DM et al (2007) Colonization, bloodstream infection, and mortality caused by vancomycin-resistant enterococcus early after allogeneic hematopoietic stem cell transplant. Biol Blood Marrow Transplant 13(5):615–621
56. Siddiqui AH et al (2002) The effect of active surveillance for vancomycin-resistant enterococci in high-risk units on vancomycin-resistant enterococci incidence hospital-wide. Am J Infect Control 30(1):40–43
57. Livermore DM (2009) Has the era of untreatable infections arrived? J Antimicrob Chemother 64(1):i29–i36
58. Hawkey PM, Jones AM (2009) The changing epidemiology of resistance. J Antimicrob Chemother 64(1):i3–i10
59. Gould IM (2008) The epidemiology of antibiotic resistance. Int J Antimicrob Agents 32(1):S2–S9
60. Septimus EJ, Kuper KM (2009) Clinical challenges in addressing resistance to antimicrobial drugs in the twenty-first century. Clin Pharmacol Ther 86(3):336–339
61. Walsh TR (2008) Clinically significant carbapenemases: an update. Curr Opin Infect Dis 21(4):367–371
62. Falagas ME, Bliziotis IA (2006) Attributable mortality of *Acinetobacter baumannii* infections in critically ill patients: a systematic review of matched cohort and case-control studies. Crit Care 10(2):R48
63. Falagas ME et al (2009) Attributable mortality of *Stenotrophomonas maltophilia* infections: a systematic review of the literature. Future Microbiol 4:1103–1109
64. Falagas ME, Kopterides P, Siempos II (2006) Attributable mortality of *Acinetobacter baumannii* infection among critically ill patients. Clin Infect Dis 43(3):389; author reply 389–390

65. Furtado GH et al (2009) Imipenem-resistant *Pseudomonas aeruginosa* infection at a medical-surgical intensive care unit: Risk factors and mortality. J Crit Care 24(4):625 (epub 9 Jul 2009, e9–e14)
66. Hakki M et al (2007) Invasive *Pseudomonas aeruginosa* infections: high rate of recurrence and mortality after hematopoietic cell transplantation. Bone Marrow Transplant 39(11):687–693
67. Krcmery V Jr et al (1998) Bacteremia due to multiresistant gram-negative bacilli in neutropenic cancer patients: a case controlled study. J Chemother 10(4):320–325
68. Zavascki AP et al (2006) The influence of metallo-beta-lactamase production on mortality in nosocomial *Pseudomonas aeruginosa* infections. J Antimicrob Chemother 58(2):387–392
69. Zavascki AP et al (2006) Reappraisal of *Pseudomonas aeruginosa* hospital-acquired pneumonia mortality in the era of metallo-beta-lactamase-mediated multidrug resistance: a prospective observational study. Crit Care 10(4):R114
70. Daniels TL et al (2008) Mortality rates associated with multidrug-resistant *Acinetobacter baumannii* infection in surgical intensive care units. Infect Control Hosp Epidemiol 29(11):1080–1083
71. Sunenshine RH et al (2007) Multidrug-resistant Acinetobacter infection mortality rate and length of hospitalization. Emerg Infect Dis 13(1):97–103
72. Morrell M, Fraser VJ, Kollef MH (2005) Delaying the empiric treatment of candida bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality. Antimicrob Agents Chemother 49(9):3640–3645
73. Lodise TP Jr et al (2007) Predictors of 30-day mortality among patients with *Pseudomonas aeruginosa* bloodstream infections: impact of delayed appropriate antibiotic selection. Antimicrob Agents Chemother 51(10):3510–3515
74. Kollef MH et al (1999) Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest 115(2):462–474
75. Reddy P et al (2007) Screening for extended-spectrum beta-lactamase-producing Enterobacteriaceae among high-risk patients and rates of subsequent bacteremia. Clin Infect Dis 45(7):846–852
76. Santos RP, Mayo TW, Siegel JD (2008) Healthcare epidemiology: active surveillance cultures and contact precautions for control of multidrug-resistant organisms: ethical considerations. Clin Infect Dis 47(1):110–116
77. Maragakis LL et al (2008) Incidence and prevalence of multidrug-resistant acinetobacter using targeted active surveillance cultures. JAMA 299(21):2513–2514
78. Bartlett JG et al (1978) Antibiotic-associated pseudomembranous colitis due to toxin-producing clostridia. N Engl J Med 298(10):531–534
79. Johnson S et al (1990) Nosocomial *Clostridium difficile* colonisation and disease. Lancet 336(8707):97–100
80. Kuijper EJ et al (2001) Nosocomial outbreak of *Clostridium difficile*-associated diarrhoea due to a clindamycin-resistant enterotoxin A-negative strain. Eur J Clin Microbiol Infect Dis 20(8):528–534
81. Muto CA et al (2005) A large outbreak of *Clostridium difficile*-associated disease with an unexpected proportion of deaths and colectomies at a teaching hospital following increased fluoroquinolone use. Infect Control Hosp Epidemiol 26(3):273–280
82. Mekonen ET et al (2002) Predominance of a single restriction endonuclease analysis group with intrahospital subgroup diversity among *Clostridium difficile* isolates at two Chicago hospitals. Infect Control Hosp Epidemiol 23(11):648–652
83. Manian FA, Meyer L, Jenne J (1996) Clostridium difficile contamination of blood pressure cuffs: a call for a closer look at gloving practices in the era of universal precautions. Infect Control Hosp Epidemiol 17(3):180–182
84. Kaatz GW et al (1988) Acquisition of *Clostridium difficile* from the hospital environment. Am J Epidemiol 127(6):1289–1294

85. Brooks S et al (1998) Reduction in vancomycin-resistant *Enterococcus* and *Clostridium difficile* infections following change to tympanic thermometers. Infect Control Hosp Epidemiol 19(5):333–336
86. Gaynes R et al (2004) Outbreak of *Clostridium difficile* infection in a long-term care facility: association with gatifloxacin use. Clin Infect Dis 38(5):640–645
87. Komatsu M et al (2003) High frequency of antibiotic-associated diarrhea due to toxin A-negative, toxin B-positive *Clostridium difficile* in a hospital in Japan and risk factors for infection. Eur J Clin Microbiol Infect Dis 22(9):525–529
88. Pulvirenti JJ et al (2002) Difference in the incidence of *Clostridium difficile* among patients infected with human immunodeficiency virus admitted to a public hospital and a private hospital. Infect Control Hosp Epidemiol 23(11):641–647
89. Talon D et al (1995) Use of pulsed-field gel electrophoresis for investigation of an outbreak of *Clostridium difficile* infection among geriatric patients. Eur J Clin Microbiol Infect Dis 14(11):987–993
90. McFarland LV, Surawicz CM, Stamm WE (1990) Risk factors for Clostridium difficile carriage and *C. difficile*-associated diarrhea in a cohort of hospitalized patients. J Infect Dis 162(3):678–684
91. Brown E et al (1990) Risk factors for *Clostridium difficile* toxin-associated diarrhea. Infect Control Hosp Epidemiol 11(6):283–290
92. Safdar N, Maki DG (2002) The commonality of risk factors for nosocomial colonization and infection with antimicrobial-resistant *Staphylococcus aureus*, *Enterococcus*, gram-negative bacilli, *Clostridium difficile*, and *Candida*. Ann Intern Med 136(11):834–844
93. Blot E et al (2003) Outbreak of *Clostridium difficile*-related diarrhoea in an adult oncology unit: risk factors and microbiological characteristics. J Hosp Infect 53(3):187–192
94. Gifford AH, Kirkland KB (2006) Risk factors for *Clostridium difficile*-associated diarrhea on an adult hematology-oncology ward. Eur J Clin Microbiol Infect Dis 25(12):751–755
95. McDonald LC et al (2005) An epidemic, toxin gene-variant strain of *Clostridium difficile*. N Engl J Med 353(23):2433–2441
96. Warny M et al (2005) Toxin production by an emerging strain of *Clostridium difficile* associated with outbreaks of severe disease in North America and Europe. Lancet 366(9491):1079–1084
97. Kuijper EJ et al (2008) Update of *Clostridium difficile* infection due to PCR ribotype 027 in Europe. Euro Surveill 13(31)
98. Boone N et al (1998) Evaluation of an interdisciplinary re-isolation policy for patients with previous *Clostridium difficile* diarrhea. Am J Infect Control 26(6):584–587
99. Hanna H et al (2000) Control of nosocomial *Clostridium difficile* transmission in bone marrow transplant patients. Infect Control Hosp Epidemiol 21(3):226–228
100. Delmee M et al (1987) Epidemiology and prevention of *Clostridium difficile* infections in a leukemia unit. Eur J Clin Microbiol 6(6):623–627
101. Sherertz RJ et al (1987) Impact of air filtration on nosocomial *Aspergillus* infections. Unique risk of bone marrow transplant recipients. Am J Med 83(4):709–718
102. Sehulster L, Chinn RY (2003) Guidelines for environmental infection control in health-care facilities. Recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC). MMWR Recomm Rep 52(RR-10):1–42
103. Haiduven D (2009) Nosocomial aspergillosis and building construction. Med Mycol 47(1):S210–S216
104. Maschmeyer G, Haas A, Cornely OA (2007) Invasive aspergillosis: epidemiology, diagnosis and management in immunocompromised patients. Drugs 67(11):1567–1601
105. Carter CD, Barr BA (1997) Infection control issues in construction and renovation. Infect Control Hosp Epidemiol 18(8):587–596
106. Gustafson TL et al (1983) Invasive aspergillosis in renal transplant recipients: correlation with corticosteroid therapy. J Infect Dis 148(2):230–238

107. Palmore TN et al (2009) A cluster of cases of nosocomial legionnaires disease linked to a contaminated hospital decorative water fountain. Infect Control Hosp Epidemiol 30(8):764–768
108. Meletis J et al (1987) Legionnaires' disease after bone marrow transplantation. Bone Marrow Transplant 2(3):307–313
109. Parry MF et al (1985) Waterborne *Legionella bozemanii* and nosocomial pneumonia in immunosuppressed patients. Ann Intern Med 103(2):205–210
110. Neill MA et al (1985) Nosocomial legionellosis, Paris, France. Evidence for transmission by potable water. Am J Med 78(4):581–588
111. Arnow PM et al (1982) Nosocomial Legionnaires' disease caused by aerosolized tap water from respiratory devices. J Infect Dis 146(4):460–467
112. Garbe PL et al (1985) Nosocomial Legionnaires' disease. Epidemiologic demonstration of cooling towers as a source. JAMA 254(4):521–524
113. Levin AS (2009) Nosocomial legionellosis: prevention and management. Expert Rev Anti Infect Ther 7(1):57–68
114. Fiore AE et al (2009) Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 58(RR-8):1–52
115. Talbot TR et al (2005) Influenza vaccination of healthcare workers and vaccine allocation for healthcare workers during vaccine shortages. Infect Control Hosp Epidemiol 26(11):882–890
116. Lemaitre M et al (2009) Effect of influenza vaccination of nursing home staff on mortality of residents: a cluster-randomized trial. J Am Geriatr Soc 57(9):1580–1586
117. Hayward AC et al (2006) Effectiveness of an influenza vaccine programme for care home staff to prevent death, morbidity, and health service use among residents: cluster randomised controlled trial. BMJ 333(7581):1241
118. Carman WF et al (2000) Effects of influenza vaccination of health-care workers on mortality of elderly people in long-term care: a randomised controlled trial. Lancet 355(9198):93–97
119. Potter J et al (1997) Influenza vaccination of health care workers in long-term-care hospitals reduces the mortality of elderly patients. J Infect Dis 175(1):1–6
120. Babcock HM et al (2009) Mandatory influenza vaccination: translating policy to practice, in Society for Healthcare Epidemiology of America 19th annual scientific meeting. San Diego, CA
121. Stone PW et al (2009) Staffing and structure of infection prevention and control programs. Am J Infect Control 37(5):351–357
122. Richards C et al (2001) Characteristics of hospitals and infection control professionals participating in the National Nosocomial Infections Surveillance System 1999. Am J Infect Control 29(6):400–403
123. Haley RW et al (1980) The SENIC Project. Study on the efficacy of nosocomial infection control (SENIC Project). Summary of study design. Am J Epidemiol 111(5):472–485
124. O'Boyle C, Jackson M, Henly SJ (2002) Staffing requirements for infection control programs in US health care facilities: Delphi project. Am J Infect Control 30(6):321–333
125. Horan TC, Andrus M, Dudeck MA (2008) CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control 36(5):309–332
126. Edwards JR et al (2008) National Healthcare Safety Network (NHSN) Report, data summary for 2006 through 2007, issued November 2008. Am J Infect Control 36(9):609–626