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### Nosocomial Fungal Infections: Epidemiology, Infection Control, and Prevention

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#### Recommended Citation

Suleyman G, and Alangaden GJ. Nosocomial Fungal Infections: Epidemiology, Infection Control, and Prevention. *Infect Dis Clin North Am* 2021; 35(4):1027-1053.

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# Nosocomial Fungal Infections

## Epidemiology, Infection Control, and Prevention



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### KEYWORDS

• Nosocomial • Fungal infection • *Candida* • *Aspergillus*

### KEY POINTS

- Invasive candidiasis and mold infections are a common cause of hospital-acquired infections often related to the use of invasive lines, immunosuppression, and a contaminated environment.
- Traditional culture methodologies may be insensitive for the diagnosis of fungal infections and may require the use of more sensitive nonculture-based testing.
- The control and prevention of invasive fungal infections require a combination of traditional infection control practices, as well as the use of antifungal prophylaxis in high-risk individuals.
- There has been an increase in the rates of invasive fungal infection during the COVID-19 pandemic as a result of gaps in infection control practices and use of immunosuppression for treatment of COVID-19 infection.

### IMPACT OF NOSOCOMIAL FUNGAL INFECTIONS

There has been an overall increase in fungal health care–associated infections (HAIs). The increase is partly due to the increased population of immunocompromised patients at risk for invasive fungal infection as a consequence of the wider use of treatment modalities, such as hematopoietic stem cell transplantation (HSCT), solid organ transplantation (SOT), and newer immunomodulatory agents (**Table 1**).<sup>1–3</sup> Moreover, the increasing use of invasive devices, especially central venous catheters (CVCs), has resulted in an increase in nosocomial central line-associated bloodstream infections (CLABSIs) due to *Candida* spp.<sup>1,3,4</sup> Exposure to airborne molds such as *Aspergillus* spp. within the hospital environment has caused outbreaks of nosocomial aspergillosis in severely immunocompromised patients such as allogeneic HSCT recipients and neutropenic patients with hematologic malignancies.<sup>5</sup>

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Infect Dis Clin N Am 35 (2021) 1027–1053

<https://doi.org/10.1016/j.idc.2021.08.002>

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**Table 1**  
**Risk factors associated with invasive fungal infections**

<b>Candida</b>	<b>Aspergillus</b>	<b>Mucorales</b>	<b>Fusarium</b>	<b>Scedosporium</b>
<ul style="list-style-type: none"> <li>• Acute necrotizing pancreatitis</li> <li>• Abdominal surgery; anastomotic leak; or repeat laparotomies</li> <li>• Broad-spectrum antibiotics</li> <li>• Central venous catheters</li> <li>• Hemodialysis</li> <li>• HSCT</li> <li>• Immunosuppression including corticosteroids, chemotherapy</li> <li>• Malignancy</li> <li>• Mechanical ventilation &gt;3 d</li> <li>• Multifocal candida colonization</li> <li>• Neutropenia</li> <li>• Prolonged ICU stay</li> <li>• Prolonged hospitalization</li> <li>• SOT (kidney and liver)</li> <li>• Total parenteral nutrition</li> </ul>	<ul style="list-style-type: none"> <li>• Alemtuzumab</li> <li>• Allogeneic HSCT</li> <li>• Anastomotic complications in lung transplantation</li> <li>• <i>Aspergillus</i> colonization</li> <li>• CMV disease</li> <li>• Corticosteroids</li> <li>• Infliximab</li> <li>• Neutropenia</li> <li>• Older age</li> <li>• Prolonged ICU stay</li> <li>• Renal failure requiring dialysis</li> <li>• Retransplantation</li> <li>• Severe GVHD</li> <li>• T-cell depleting agents</li> </ul>	<ul style="list-style-type: none"> <li>• CMV disease</li> <li>• Corticosteroids</li> <li>• Diabetes mellitus</li> <li>• Echinocandin use</li> <li>• Iron overload</li> <li>• Malnutrition</li> <li>• Myelodysplasia</li> <li>• Neutropenia</li> <li>• Older age</li> <li>• Renal failure</li> <li>• Severe GVHD</li> <li>• Voriconazole use</li> </ul>	<ul style="list-style-type: none"> <li>• Corticosteroid</li> <li>• Myeloma</li> <li>• Severe GVHD</li> </ul>	<ul style="list-style-type: none"> <li>• Corticosteroid</li> <li>• Neutropenia</li> <li>• Severe GVHD</li> </ul>

*Abbreviations:* CMV, cytomegalovirus; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; IA, intraabdominal; ICU, intensive care unit; SOT, solid organ transplantation.

*Candida* spp. are associated with serious HAIs, especially in patients in intensive care units (ICUs)<sup>1,3,4,6</sup> and are one of the most common causes of nosocomial bloodstream infections (BSIs) in US hospitals.<sup>3,4</sup> It is estimated that approximately 25,000 cases of invasive candidiasis (IC) occur in the United States each year.<sup>7,8</sup> The true incidence of candidemia is likely higher because of the poor sensitivity (approximately 50%) of blood cultures (BCs) for detection of *Candida* spp. Newer automated rapid nonculture-based test (NCT) molecular platforms have improved the diagnostic yield in patients with IC.<sup>3</sup> *Candida auris*, an emerging multidrug-resistant species that is difficult to identify, has been associated with nosocomial outbreaks and IC globally and in the United States.<sup>7</sup> The attributable mortality for IC, including candidemia, is significant, and the excess health care cost ranges from \$35,000 to \$68,000 for each episode of candidemia in the United States.<sup>3,9</sup>

The incidence rate of invasive aspergillosis (IA) per million persons rose from 32.8 in 2000 to 46.0 in 2013, especially in SOT recipients.<sup>10</sup> Aspergillosis accounted for 59% of all invasive fungal infections and was associated with a 6-week mortality rate of 22% in severely immunocompromised patients.<sup>11,12</sup>

Thus, the overall burden of disease caused by nosocomial fungal infections is substantial. Limitations of the current diagnostic tests, the emergence of resistant fungal pathogens, and significant mortality make the prevention of fungal HAIs increasingly important. The epidemiology, risk factors associated with nosocomial fungal infections, and control and prevention strategies are discussed in the following paragraphs.<sup>13–15</sup>

## COMMON NOSOCOMIAL INFECTIONS CAUSED BY YEASTS

### *Candida* spp.

*Candida* spp., especially *Candida albicans*, are part of the human microbial flora; hence, most candidal infections are endogenous in origin. IC, namely, candidemia, disseminated hematogenous infections, or deep-seated infections can occur in immunocompromised patients, such as those with neutropenia, and in critically ill patients. In patients with chemotherapy-induced neutropenia and mucositis, candidemia may originate from the gastrointestinal tract. However, in critically ill patients, the source of candidemia is most likely a CVC colonized by *Candida* spp. from the patient's endogenous microflora or acquired from the health care environment.<sup>1,3</sup> *Candida* spp. have been isolated from environmental cultures of the floor, countertops, and other inanimate surfaces in the hospital.<sup>16,17</sup> Patient acquisition and colonization with *Candida* spp. found in the hospital environment and food has been demonstrated.<sup>8,16</sup> The propensity of *Candida* spp., especially *Candida parapsilosis*, to cause CLABSIs is likely related to this pathogen's ability to form biofilms on catheters.<sup>18</sup>

Overall, *Candida* spp. accounted for 6.4% of 356,633 HAIs reported to the National Healthcare Safety Network (NHSN) at the Centers for Disease Control and Prevention (CDC) between 2015 and 2017.<sup>4</sup> Approximately, 11% of infections in North American ICUs were due to *Candida* spp.<sup>19</sup> Notably, *Candida* spp. were the most common cause of CLABSIs in the ICU and hospital wards, accounting for 25% and 16.7% of CLABSIs, respectively.<sup>4</sup> The increasing proportion of patients with candidemia in non-ICU settings is possibly due to the presence of long-term CVCs.<sup>3</sup> Additional risk factors for nosocomial candidemia are listed in **Table 1**. Candidemia-related hospitalization per 100,000 population rose by 52%, from 3.65 to 5.56 cases between 2000 and 2005.<sup>20</sup> However, from 2009 to 2017, the change in incidence of IC-related hospitalizations remained low at 1.3%.<sup>21</sup>

A study of IC from 203 centers in the United States between 2009 and 2017 identified *C albicans* (48%), *Candida glabrata* (24%), *C parapsilosis* (11%), and *C tropicalis* (7%) as the most common *Candida* pathogens.<sup>21,22</sup> The overall 90-day crude mortality rate associated with candidemia was 39%. Overall, there has been an increase in the proportion of infections caused by nonalbicans *Candida* spp.<sup>22,23</sup> In the United States, nonalbicans *Candida* spp. were reported to cause most candidemias.<sup>22</sup> Most of the nonalbicans species, particularly *C glabrata*, are reported from cancer centers in the United States.<sup>22</sup> In contrast, higher rates of *C parapsilosis* and *C tropicalis* are reported from Latin America.<sup>24</sup> Nonalbicans *Candida* spp. have an increased likelihood of resistance to fluconazole: 16% of *C glabrata*, 78% of *Candida krusei*, and 11% of *C guilliermondii*.<sup>24</sup>

Although most cases of IC are endogenous, exogenous transmission of *Candida* spp. may occur. Characteristics of specific *Candida* spp. may influence the risk for exogenous transmission and nosocomial infections in certain patient populations.

In molecular epidemiologic studies, *C albicans* has been implicated in nosocomial transmission among patients in burn units.<sup>25</sup> Person-to-person transmission has also been reported from geriatric short-stay units.<sup>26</sup>

*C parapsilosis* candidemia is common in the neonatal population<sup>18,22</sup> and transplant recipients.<sup>18</sup> *C parapsilosis* is commonly isolated from the hands of health care workers (HCWs), and a review of molecular epidemiologic studies of outbreaks suggests horizontal transmission from HCWs to neonates.<sup>18</sup> The ability of *C parapsilosis* to produce biofilms and its selective growth advantage in glucose-rich hyperalimentation solutions in total parenteral nutrition (TPN) may explain its propensity to cause outbreaks associated with CVCs.<sup>18</sup> Hence, the frequent isolation of *C parapsilosis* should prompt measures to enhance hand hygiene and appropriate care of CVCs.

Emerging *Candida* spp. that are relatively resistant to fluconazole such as *C auris*,<sup>8</sup> *C guilliermondii*,<sup>27</sup> and *Candida rugosa*<sup>28</sup> have also been associated with nosocomial outbreaks, some involving CVCs. *C auris* first isolated from the external ear canal of a hospitalized patient in Japan in 2009 has since been associated with nosocomial outbreaks in health care facilities globally.<sup>8,29</sup> Its ability to persistently colonize patients and survive on surfaces for months has contributed to outbreaks.<sup>8,29–32</sup>

The first *C auris* case in the United States was identified in New York in 2013.<sup>30</sup> As of March 19, 2021, there have been 1708 confirmed clinical cases in the United States, most of which have occurred in New York City, New Jersey, and Chicago, Illinois.<sup>8</sup> More recently, an outbreak was reported in patients with coronavirus disease 2019 (COVID-19) who received care in a dedicated COVID-19 unit.<sup>31</sup> Infection and colonization have been detected mainly in critically ill patients with comorbidities and exposure to healthcare facility (HCF). Risk factors for *C auris* are similar as those for other *Candida* infections and include prolonged ICU stay, recent surgery, antibiotic and antifungal use, CVCs or indwelling urinary catheters, TPN, hematological malignancies, SOT, HSCT, and immunosuppression.<sup>30,32</sup>

*C auris* has been misidentified as *C haemulonii* when using conventional diagnostic methods.<sup>8,29,30,32</sup> It has been cultured from blood, urine, bile, wounds, and rectum.<sup>8,30,32</sup> Most of the reported *C auris* cases are BSIs, but pericarditis, otitis, and wound infections can occur.<sup>30,32</sup> *C auris* is often resistant to one or more classes of antifungal agents.<sup>31–33</sup> Of 35 isolates in the United States, 86% were resistant to fluconazole, 43% to amphotericin B, and 3% to echinocandins,<sup>29</sup> which is the drug of choice in clinical infections.<sup>8,29</sup> Despite geographic variability, overall mortality rates range from 35% to 72%.<sup>32</sup>

### Other Yeasts

*Malassezia* spp. are lipophilic yeasts that are frequent skin colonizers and the cause of pityriasis. Outbreaks of *Malassezia* fungemia have been reported in premature

neonates and immunocompromised patients.<sup>34,35</sup> Prolonged use of CVCs and TPN were important predisposing conditions.<sup>34,35</sup>

*Trichosporon* spp. fungemia has been reported in patients with hematologic malignancies and HSCT and SOT recipients.<sup>36</sup> Systemic disease has also been reported in premature neonates, diabetics, nonneutropenic ICU, and burn patients.<sup>36,37</sup> Common risk factors in cases of nosocomial trichosporonosis are the presence of a CVC and exposure to prior antibiotics.<sup>37</sup> Waterborne outbreaks have also been reported.<sup>38</sup> The reported mortality rate ranges from 42% to 83%.<sup>36,37</sup>

Most outbreaks of nosocomial IC and invasive infections with other yeasts have been associated with CVCs. Hence, infection control strategies targeted to improve adherence to hand hygiene recommendations, including avoidance of long nails and artificial nails, adherence to guidelines for insertion and care of CVCs, and prompt removal of unnecessary catheters are important in the prevention of these infections.<sup>39</sup>

### NOSOCOMIAL INFECTIONS CAUSED BY MOLDS

Unlike IC, which can affect relatively immunocompetent patients, invasive disease caused by *Aspergillus* spp. and other molds generally involves severely immunocompromised patients. *Aspergillus* spp. account for most mold infections: 76% among HSCT recipients and 81% among SOT recipients.<sup>1</sup> Although several outbreaks of environmental airborne fungal infection within hospital settings have been reported,<sup>5</sup> most cases of IA are sporadic. At present, there is no uniform definition of what constitutes nosocomial aspergillosis. One of the primary reasons for the difficulty in defining hospital-acquired aspergillosis is that the incubation period of IA is unknown.<sup>2</sup> Moreover, the prolonged period of immunosuppression in high-risk patients such as HSCT recipients and frequent hospital admissions and discharges make it difficult to determine if exposure to *Aspergillus* spores occurred during hospitalization or within the community. Generally, invasive disease that occurs after 1 week of hospitalization is considered nosocomial.<sup>2</sup> Although most hospital outbreaks have been caused by *Aspergillus* spp.,<sup>5</sup> other airborne molds have also been implicated, including *Zygomycetes* spp.,<sup>5,40</sup> *Fusarium* spp.,<sup>5</sup> and *Scedosporium* spp.<sup>5,41</sup> The risks factors for mold infections and vehicles of transmission are summarized in [Table 1](#) and [Table 2](#).

Table 2 Reported vehicles of transmission in invasive mold infections and associated types of infections		
Mold	Reservoir or Source	Type of Infection
<i>Aspergillus</i>	Contaminated air, ventilation system, air filters, false ceilings and insulation material, water supply, plumbing, showers, food, ornamental plants, arm boards, dressing package	Invasive pulmonary and disseminated aspergillosis, cutaneous disease
Mucorales	Contaminated air, Elastoplast adhesive dressing, karaya ostomy bag, wooden tongue depressor, ventilation systems, water-damaged plaster, cornstarch, linens	Cutaneous infections, sinopulmonary disease, gastrointestinal mucormycosis
<i>Fusarium</i>	Contaminated air, contact lens solution, showers, sink drains and faucets, water tanks	Keratitis, disseminated fusariosis
<i>Scedosporium</i>	Contaminated air	Pulmonary and disseminated disease, cutaneous lesions

### ***Aspergillus spp.***

*Aspergillus* spp. are ubiquitous molds found widely in the environment. Exposure to airborne spores of *Aspergillus* occurs frequently in the environment, especially near decaying organic matter. Although these conidia (2.5–3.0 μm in diameter) are frequently inhaled, invasive pulmonary disease is rare in immunocompetent persons. Opportunistic IA occurs primarily in high-risk severely immunocompromised patients namely allogeneic HSCT and neutropenic patients with hematologic malignancies. *Aspergillus fumigatus* is most often associated with invasive disease, although *Aspergillus flavus*, *Aspergillus niger*, and *Aspergillus terreus* have also been isolated from patients.<sup>1,42</sup> Aspergillosis is an important cause of morbidity and mortality ranging from 65% to 92% in this high-risk population.<sup>2,43</sup>

SOT recipients,<sup>2,44</sup> patients with acquired immunodeficiency syndrome (AIDS), and those with chronic granulomatous disease are also at risk for IA.<sup>2</sup> There are increasing reports of IA in critically ill patients in the ICU, including patients with chronic obstructive pulmonary disease, severe influenza, COVID-19, liver cirrhosis, and those receiving corticosteroids.<sup>2,45–47</sup>

### ***Aspergillus outbreaks***

The information on the environmental exposures and the association with infection has been derived from investigations of outbreaks of aspergillosis in hospital settings. An extensive review of nosocomial aspergillosis identified 53 reported outbreaks involving 458 patients.<sup>48</sup> Of these, 33 outbreaks involving 299 patients (65%) occurred in HSCT recipients or patients with hematologic malignancies. Other patient populations involved in these outbreaks were SOT recipients (10%), predominantly renal transplant recipients; patients without severe immunodeficiency (8%); and patients on high-dose steroids (3%).<sup>48</sup> Aspergillosis was associated with mortality greater than 50% in patients with hematologic malignancies, HSCT and SOT recipients, and patients with severe immunodeficiency. The lung was the most common site of infection, with 5% involving the surgical site or skin. *A. fumigatus* and *A. flavus* were the most identified species. Volumetric air sampling performed during epidemiologic investigations in 24 of the outbreaks noted spore counts ranging from 0 to 100 spores per cubic meter. Outbreaks were primarily attributed to airborne infections related to construction or renovation activities in about 50% of cases and to compromised air quality in 17%.<sup>48</sup> The various environmental vehicles implicated in the transmission of *Aspergillus* spp. and other molds have also been detailed in the CDC guidelines for environmental infection control in HCFs (see [Table 2](#)).<sup>14</sup>

The most frequent nosocomial source of *Aspergillus* infection is contaminated air, but *Aspergillus* has also been recovered from the hospital water supply and plumbing systems.<sup>2,38</sup> The highest airborne *Aspergillus* spore counts were detected in patient's bathrooms, suggesting possible aerosolization of *Aspergillus* spores from the shower facilities.<sup>2</sup> The clinical implications of this finding remain to be defined.

Although the association between construction and IA has often been reported, there is poor correlation of the *Aspergillus* spp. recovered from the hospital environment and species isolated from patients with aspergillosis.<sup>2</sup> One explanation for this discordance between hospital and patient strains of *Aspergillus* might relate to the lack of a clearly defined incubation period for aspergillosis and the relationship to exposure within the hospital environment and subsequent infection.<sup>2</sup> Other factors include the methods of air sampling used, the broad diversity of *Aspergillus* spp. in the environment, and the various methods used for typing of *Aspergillus* and other pathogenic molds.<sup>49,50</sup>

## Zygomycetes

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Zygomycetes are ubiquitous molds found in the soil and decaying organic matter in the environment. Infection often occurs via inhalation of fungal spores, resulting in sinopulmonary disease, but systemic infection can result from inoculation of the skin or gastrointestinal mucosa.<sup>51</sup> Although infection caused by Zygomycetes is uncommon, it is often a fatal disease. In a review of 929 patients with zygomycosis, mortality was 76% with pulmonary zygomycosis and 100% with disseminated and central nervous system diseases.<sup>52</sup>

Nosocomial infections caused by Zygomycetes have been recently reviewed.<sup>40</sup> Clusters of cutaneous infections have occurred in orthopedic and cardiothoracic patients, children with leukemia, and burn patients. These infections were associated with Elastoplast adhesive dressings possibly contaminated with *Rhizopus* and *Absidia* spp.<sup>40</sup> Outbreaks in patients with hematologic malignancies have resulted from airborne transmission associated with contamination of hospital ventilation systems.<sup>5</sup> Use of negative pressure rooms during construction has also been implicated in a cluster of invasive mucormycosis infection among SOT recipients during a 12-month period.<sup>53</sup> Water-damaged plaster has been associated with *Rhizomucor pusillus* outbreak in patients with leukemia.<sup>40</sup> Unusual routes of transmission have been traced to the use of contaminated wooden tongue depressors, nonsterile karaya (plant-derived adhesive) for securing ostomy bags, and wooden tongue depressors.<sup>40</sup> An outbreak of gastrointestinal zygomycosis caused by *Rhizopus* in 12 patients with hematologic malignancies was traced to contaminated cornstarch used as an excipient in the manufacture of allopurinol and ready-to-eat foods.<sup>54</sup> Additionally, hospital linens have also been implicated in outbreaks.<sup>55</sup>

## Fusarium spp.

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*Fusarium* is a soil saprophyte and causes keratitis and onychomycosis in humans.<sup>56</sup> Outbreaks of keratitis caused by possible contamination of contact lens solutions have been described.<sup>56,57</sup> Invasive disease has been reported in patients with prolonged neutropenia, especially in HSCT recipients<sup>56,58</sup> and to a lesser extent in SOT recipients.<sup>56</sup> The incidence of fusariosis is estimated to be 4 to 5 cases per 1000 matched allogeneic HSCT recipients to as high as 20 cases per 1000 mismatched recipients.<sup>59</sup> Fusariosis in HSCT recipients has a bimodal distribution, with a peak before engraftment and later during the period of graft-versus-host disease (GVHD), and is associated with an actuarial survival of 13%.<sup>58</sup> Most infections are believed to be caused by airborne transmission; however, contamination of the water system in the hospital has been reported to result in dispersal of airborne conidia.<sup>38</sup>

## Other Molds

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Several other pathogenic molds have been associated with HAIs. Nosocomial outbreaks caused by *Scedosporium* spp. during hospital reconstruction have been reported.<sup>60</sup> *Phialemonium* spp. have been linked to outbreaks of intravascular infections in patients undergoing hemodialysis (HD), resulting from contamination of water distribution systems.<sup>61</sup> A multistate outbreak of fungal meningitis, parameningeal, and joint infections occurred in 753 patients who received injections of contaminated methylprednisone acetate solutions, resulting in 64 (8.5%) deaths across 20 states. The predominant pathogen detected in this outbreak was *Exserophilum*.<sup>62</sup>



### ***Pneumocystis jirovecii***

Opportunistic pneumonia caused by *Pneumocystis jirovecii* has been traditionally attributed to reactivation of latent infection during periods of severe T-cell-mediated immunosuppression, particularly in transplant recipients and patients with AIDS. However, recent data suggest possible person-to-person transmission or common environmental source as a potential mode of transmission.<sup>63</sup> Molecular evidence has also identified nosocomial person-to-person transmission of *Pneumocystis jirovecii* to be the likely cause of outbreaks of *Pneumocystis* pneumonia, particularly among renal transplant recipients.<sup>63</sup> In a meta-analysis of 30 outbreaks, more than 80% occurred among renal transplant recipients. None of the patients received appropriate antipneumocystis prophylaxis.

## **STRATEGIES FOR PREVENTION OF NOSOCOMIAL CANDIDIASIS**

### ***Prevention of Intravascular Catheter-Related Candidemia***

Guidelines for the prevention of CLABSI have been published.<sup>13</sup> Although randomized clinical trials have shown that daily 2% chlorhexidine gluconate (CHG) bathing of patients in the ICU decreases the incidence of nosocomial multidrug-resistant bacterial BSIs, few studies have evaluated the impact on candidemia.<sup>64,65</sup> A meta-analysis of five randomized controlled trials evaluating the efficacy of CHG bathing in reducing BSIs showed that CHG had no effect on fungal BSIs.<sup>65</sup> However, a more recent meta-analysis of 26 randomized and nonrandomized studies demonstrated that CHG bathing was associated with a significant reduction in BSIs, including those due to *Candida* spp.<sup>64</sup> A multicenter, randomized, crossover study also found that the incidence of fungal CLABSIs was 90% lower during the CHG intervention period compared with the control period.<sup>66</sup> Despite the conflicting results, use of daily CHG bathing in patients in the ICU is a simple and effective strategy to decrease the overall rate of primary BSIs.

Additionally, the use of disinfection caps, which include alcohol or alcohol/CHG combinations, placed on needleless connectors or access ports has demonstrated decreased CLABSI rates.<sup>67,68</sup>

Unlike other *Candida* spp., *C auris* can spread rapidly in HCFs and lead to nosocomial outbreaks that can be difficult to contain. Patients can remain colonized even after a year, leading to environmental shedding where it can survive and persist on a wide range of surfaces.<sup>32</sup> A single case of *C auris* requires rapid implementation of infection control measures and investigation. When *C auris* is suspected or confirmed, the patient should be placed in a single room under contact precautions with reinforcement of hand hygiene practices. Additional infection prevention and control measures include daily and terminal cleaning and disinfection of patient care areas using an Environmental Protection Agency-registered hospital-grade disinfectant effective against *Clostridioides difficile* spores, contact tracing and testing, prospective laboratory surveillance to identify other potential cases for at least 1 month until there is no evidence of ongoing transmission, and interfacility communication during patient transfer.<sup>8,29</sup>

## **STRATEGIES FOR PREVENTION OF NOSOCOMIAL ASPERGILLOSIS AND MOLD INFECTIONS**

Aspergillosis is primarily acquired by inhalation of fungal spores and subsequent invasive disease in immunocompromised patients. Hence, the primary infection control strategy is to minimize exposure to airborne environmental fungal spores within HCFs during the high-risk period. Exposure to fungal spores of *Aspergillus* spp. and

other pathogenic molds after hospital discharge may occur in high-risk patients, such as allogeneic HSCT recipients with chronic GVHD who are administered corticosteroids. Patient education to minimize exposures to fungal spores and chemoprophylaxis with antifungal agents may be necessary. Guidelines for the use of antifungal agents for prophylaxis against IA have been previously published<sup>15</sup> and updated.<sup>2</sup>

The CDC and Healthcare Infection Control Practices Advisory Committee have published recommendations regarding environmental infection control measures to prevent nosocomial mold infections in HCFs.<sup>14</sup> These recommendations include infection control strategies and engineering controls directed primarily for the prevention of exposure of immunocompromised patients to environmental airborne fungal spores of *Aspergillus* and other molds.<sup>14</sup>

Because opportunistic *Aspergillus* and airborne mold infections occur primarily in severely immunocompromised patients such as HSCT recipients; one of the main components of these prevention strategies is the provision of a protected environment (PE) for these patients within the HCF.

### **Protected Environment**

A PE is a specialized patient care environment in acute care hospitals for the care of allogeneic HSCT recipients.<sup>13,14</sup> The benefit of a PE for other immunocompromised patients such as autologous HSCT or SOT recipients remains undefined.<sup>14,60</sup> A PE is designed to minimize HSCT patient exposure to airborne environmental *Aspergillus* and other fungal spores. The essential features of a PE are shown in **Box 1**. Additional infection control measures for patients housed in a PE include (1) daily monitoring and maintenance of a positive pressure in PE areas, (2) minimizing exposures to activities that can cause aerosolization of fungal spores (eg, vacuuming), (3) minimizing the length of time that the patients are outside the PE for procedures, and (4) provision of high-efficiency respiratory protection (eg, N95 respirators) when outside the PE if there is ongoing construction activity in the HCF.<sup>14</sup> The effectiveness of respirators in the absence of construction or the use of surgical masks to prevent fungal infection has not been evaluated.

The other infection control strategies and engineering control recommendations that reduce exposure to environmental airborne *Aspergillus* and other fungal spores emphasize the provision of safe air during routine care and importantly during hospital construction.<sup>14</sup> These strategies are outlined in **Table 3**.

#### **Box 1**

##### **Protective environment**

Requirements of protective environment rooms

- Central or point-of-use high-efficiency particulate air (HEPA) filters with 99.97% efficiency for removing particles 0.3  $\mu$ m or larger
- Directed airflow, air intake occurs at 1 side and air exhaust occurs at the opposite side of the room
- Positive air pressure differential between the room and corridor ( $\geq 2.5$  Pa)
- Maintenance of 12 or more air changes per hour
- Well-sealed patient rooms

*Data from* Sehulster L, Chinn RY. Guidelines for environmental infection control in health-care facilities. Recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC). MMWR Recomm Rep 2003;52(RR-10):1–42.

<b>Table 3</b>	
<b>Environmental infection control measures in healthcare facilities to minimize exposure to fungal spores</b>	
<b>Recommendations</b>	<b>Rating Category</b>
<b>Air handling systems</b>	
Use the American Institute of Architects (AIA) guidelines or state regulations for design and construction of ventilations systems <sup>164</sup>	1C
Conduct ICRA and provide adequate number of PE rooms for the HSCT population	1A, 1C
Monitor ventilation systems for removal of particulates and excess moisture Proper location and maintenance of air intake and exhaust outlets, for example, removal of bird roosts from near air intake outlets to prevent entry of fungal spores Appropriate installation, maintenance, and disposal of HVAC filters Monitor PE areas for ACH, filtration, and pressure differentials	1B, 1C
Develop a contingency plan for backup capacity in case of a power failure	1C
Coordinate HVAC system shutdowns with infection control staff to allow for safe air handling to PE areas and to relocate immunocompromised patients if necessary	1C
<b>Infection control measures during construction projects</b>	
Set up a multidisciplinary team that includes infection control staff to coordinate proactive preventive measures to reduce exposure to fungal spores and monitor adherence	1B, 1C
Provide education to HCWs and the construction crew in immunocompromised patient care areas regarding airborne infections	1C
Perform an ICRA to assess potential exposure of high-risk patients to high ambient air fungal spore count	1B, 1C
Develop and implement measures to keep airborne spores from construction areas away from patient care units Dust control measures (eg, dust barriers, safe air handling, negative pressure in construction work zones)	1B, 1C
<b>Water damage response plan to prevent fungal growth</b>	
Maintain surveillance for cases of HCF-associated aspergillosis and mold infections in immunocompromised patients	1B
Undertake an epidemiologic investigation if a case of nosocomial <i>Aspergillus</i> or other mold infection is detected Surveillance for additional cases Determine appropriate air handling in the PE and in construction areas. Conduct environmental assessment to identify the source Take corrective action to improve deficiencies identified and to eliminate the source of fungal spores	1B
<b>Environmental service recommendations to minimize exposure to fungal spores</b>	
Avoid carpeting and upholstered furniture and furnishings in areas housing immunocompromised patients	1B

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**Table 3**  
(continued)

Recommendations	Rating Category
Avoid cleaning methods that disperse dust	1B
Wet dust horizontal surfaces using EPA-registered hospital disinfectant	
Equip vacuums with HEPA filters	
Close the doors of rooms of immunocompromised patients when cleaning	
Dry carpeting immediately if wet to prevent growth of fungi, replace if wet after 72 h	
Avoid fresh flowers and potted plants in areas housing immunocompromised patients	II

*Abbreviations:* ACH, air changes per hour; EPA, Environmental Protection Agency; HCW, health care worker; HSCT, hematopoietic stem cell transplantation; HVAC, heating ventilation air conditioning; 1A, strongly recommended for all hospitals and supported by well-designed experimental or epidemiologic evidence; 1B, strongly recommended for all hospitals and viewed as effective by experts because of strong rationale and suggestive evidence; 1C, required by state or federal regulation or representing an established association standard; ICRA, infection control risk assessment; II, suggested for implementation in many hospitals, supported by suggestive clinical or epidemiologic studies with a strong theoretical rationale or definitive studies applicable to some but not all hospitals; PE, protected environment.

*Data from* Sehulster L, Chinn RY. Guidelines for environmental infection control in health-care facilities. Recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC). *MMWR Recomm Rep* 2003;52(RR-10):1-42; and Tablan OC, Anderson LJ, Besser R, et al. Guidelines for preventing health-care-associated pneumonia, 2003: recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee. *MMWR Recomm Rep* 2004;53(RR-3):1-36.

### **Infection Control Risk Assessment**

Infection control risk assessment is a multistep process that determines the potential effect of construction within an HCF on the environment and exposure of at-risk patients to infectious agents, particularly fungal spores.<sup>69</sup> Implementation of recommended infection control strategies during hospital construction has been successful in the prevention of fungal contamination of air in patient care areas in prospective environmental surveillance studies using cultures and polymerase chain reaction (PCR) assays for detection of airborne fungi.<sup>70,71</sup> Newer mobile nonfiltration-based air treatment systems that use exposure to electric fields and electrostatic nanofiltration to destroy airborne organisms have also been effective in preventing fungal contamination during construction.<sup>72,73</sup> Additional recommendations for the prevention and control of nosocomial aspergillosis are included in [Table 4](#).

### **STRATEGIES FOR PREVENTION OF FUNGAL INFECTION IN HEMATOPOIETIC STEM CELL TRANSPLANTATION RECIPIENTS**

To implement strategies to prevent fungal infections in the severely immunocompromised population, it is important to define the high-risk periods. In the allogeneic HSCT recipient, the risk of infections is related to the time from transplant.<sup>15</sup> The post-HSCT period is generally divided into 3 phases:

- Phase I: the preengraftment period (<30 days after HSCT). Risk of infection is related to prolonged neutropenia and disruption of the mucocutaneous barriers

<b>Table 4</b>	
<b>Recommendations for prevention and control of healthcare-associated pulmonary aspergillosis</b>	
<b>Recommendations</b>	<b>Rating Category</b>
<b>Staff education</b>	
Educate HCWs about infection control procedures to reduce HCA-PA	II
<b>Surveillance</b>	
Conduct surveillance for HCA-PA in severely immunocompromised patients <sup>a</sup>	1A
Monitor for HCA-PA by surveillance and periodic review of microbiologic and histopathologic data	II
Do not perform routine surveillance cultures of patients or devices	1B
Monitor ventilation status of PE and maintain appropriate standards	1B
<b>Specialized care units for high-risk patients</b>	
Provide a PE for care of allogeneic HSCT recipients	1B
Do not routinely use LAF in the PE	1B
No recommendation for a PE for autologous HSCT and SOT recipients	UR
Minimize the time high-risk patients are outside the PE for procedures	II
High-risk patients to wear N95 respirators outside the PE during ongoing construction.	
No recommendation for type of mask outside the PE when no construction	
<b>When case of aspergillosis occurs</b>	
Assess if health care related or community acquired	
Determine if there is an increase in the number of cases of HCA-PA and IB length of hospital stay	1B
Determine if there is ventilation deficiency in the PE	1B
If not health care related, continue routine maintenance as mentioned earlier	
If health care related, conduct epidemiologic investigation to identify and eliminate source	1B
Use EPA-registered antifungal biocide for decontamination of structural materials	

**Abbreviations:** EPA, Environmental Protection Agency; HCA-PA, health care-associated pulmonary aspergillosis; HCW, health care worker; HSCT, hematopoietic stem cell transplantation; 1B, strongly recommended for all hospitals and supported by well-designed experimental or epidemiologic evidence; 1b, strongly recommended for all hospitals and viewed as effective by experts because of strong rationale and suggestive evidence; II, suggested for implementation in many hospitals, supported by suggestive clinical or epidemiologic studies with a strong theoretical rationale or definitive studies applicable to some but not all hospitals; LAF, laminar airflow; PE, protective environment; SOT, solid organ transplantation; UR, unresolved, practices for which insufficient evidence or consensus regarding efficacy exists.

<sup>a</sup> Severely immunocompromised patients, those with absolute neutrophil counts less than  $500/\text{mm}^3 \times 2 \text{ wk}$  or less than  $100/\text{mm}^3 \times 1 \text{ wk}$ , for example, HSCT and SOT recipients and patients on prolonged high-dose steroids.

*Data from* Sehulster L, Chinn RY. Guidelines for environmental infection control in health-care facilities. Recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC). *MMWR Recomm Rep* 2003;52(RR-10):1–42; and Tablan OC, Anderson LJ, Besser R, et al. Guidelines for preventing health-care-associated pneumonia, 2003: recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee. *MMWR Recomm Rep* 2004;53(RR-3):1–36.

because of cytotoxic chemotherapy. Infections during this period are generally caused by bacteria, *Herpes simplex virus*, *Candida*, and *Aspergillus* spp.

- Phase II: the postengraftment phase (30–100 days after HSCT). Risk of infection is related to impaired cell-mediated immunity based on the severity of GVHD and the intensity of immunosuppressive therapy used for treatment. Infections during this period are caused by cytomegalovirus (CMV), *Aspergillus* spp, and *P jiroveci*.
- Phase III: the late phase (>100 days after HSCT). Risk of infection is dictated by chronic GVHD and its treatment. Pathogens are primarily CMV, varicella-zoster virus, encapsulated bacteria, and *Aspergillus* spp.

As a general measure, avoidance of certain foods has been recommended to reduce exposure to fungi, primarily during the high-risk period of neutropenia (such as during receipt of conditioning therapy).<sup>15</sup> These foods include unpasteurized dairy products, cheeses made from mold cultures, uncooked eggs, meat, fish, tofu, unwashed vegetables, and fruits.<sup>15</sup>

IA displays a bimodal distribution, with increasing number of cases of late-onset disease (>40 days after HSCT) that is associated with immunosuppression for chronic GVHD.<sup>12</sup> A similar pattern of late-onset disease has also been noted with invasive infection with *Zygomycetes* and *Fusarium*<sup>58</sup> spp. in HSCT recipients. Educating the patient in minimizing exposure to *Aspergillus* spp. and pathogenic molds outside the hospital is important. However, because the risk of exposure within the hospital and community settings cannot be eliminated, strategies such as the use of antifungal prophylaxis may be necessary.

### Prevention of Invasive Candidiasis

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Antifungal chemoprophylaxis during the preengraftment period of neutropenia and mucositis can prevent the dissemination of endogenous *Candida* spp. from the gastrointestinal tract of patients. The antifungals are outlined in **Table 5**.

### Diagnosis of Invasive Candidiasis

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Although BCs are positive in about 50% of patients with IC, they are considered the gold standard for the diagnosis of candidiasis.<sup>3,74</sup> Thus, the true incidence of nosocomial candidemia is often underestimated. This has resulted in the increasing use of fungal biomarkers for the detection of candidemia and IC. These assays are used in the clinical management of patients with suspected IC in situations where BCs may be negative. However, the use of these assays for routine surveillance of nosocomial IC is yet to be defined. 1,3  $\beta$ -D-Glucan (BG) assays and PCR-based assays are some of these tests used to aid in the diagnosis of IC (**Table 6**).<sup>3</sup> Although  $\beta$ -D glucan has high false-positive rates and is not specific, it has been shown to have a high negative predictive value in the ICU setting.<sup>3,75</sup> In-house PCR assays are not validated or standardized.<sup>3,74</sup>

NCT molecular platforms, including fully automated multiplex T2 Magnetic Resonance (T2MR) and T2Candida Panel (T2 Biosystems, Lexington, Massachusetts),<sup>74,75</sup> have the potential to improve early diagnosis and management of IC in high-risk patients and outbreak settings. The Food and Drug Administration (FDA)-approved T2Candida Panel detects the five most common *Candida* spp. from whole blood by category: *C albicans* and/or *C tropicalis* (A/T); *C parapsilosis* (P); *C krusei*, and/or *C glabrata* (K/G).<sup>75,76</sup>

*C auris*, a nationally reportable pathogen, is difficult to identify and has been often misidentified as *C haemulonii*, *C famata*, *C sake*, *Rhodotorula glutinis*, *Rhodotorula mucilaginosa*, and *Saccharomyces* or less commonly as *C catenulate*, *Candida lusitanae*, *C guilliermondii*, or *C parapsilosis* or only to the *Candida* spp. level when using

**Table 5**  
**List of antifungal agents used for the prevention and treatment of invasive fungal infections**

Antifungal Agent	Spectrum of Activity	Expected Resistance	Adverse Events	Drug Interactions	Clinical Considerations
<b>Polyenes</b>					
Conventional and lipid-based formulations of amphotericin B	Most yeast Dimorphic fungi Molds: <i>Aspergillus fumigatus</i> , <i>Aspergillus lentulus</i> , <i>Mucor</i> spp., <i>Rhizopus</i> spp., <i>Fusarium</i> spp.	<i>Candida lusitanae</i> , <i>C guilliermondii</i> , <i>C rugosa</i> , non- <i>fumigatus</i> <i>Aspergillus</i> ( <i>Aspergillus terreus</i> , <i>A. ustus</i> ), <i>Trichosporon</i> spp., <i>Scedosporium apiospermum</i> , <i>Scedosporium prolificans</i>	Infusion reactions (hypoxia, fever, chills), phlebitis, nausea, vomiting, anemia, nephrotoxicity, elevated liver enzymes, hypersensitivity reaction	Increased risk of nephrotoxicity with other nephrotoxic agents and hypotension with blood pressure lowering agents	Lipid formulations are associated with less nephrotoxicity and infusion reactions
<b>Triazoles</b>					
Fluconazole <sup>a</sup>	Most yeast, including most <i>Candida</i> spp. Dimorphic fungi	<i>Candida krusei</i> Increasing resistance in <i>C glabrata</i> Molds Dematiaceous fungi	Nausea, vomiting, diarrhea, headaches, hepatitis, cholestasis and fulminant hepatitis, allergic reactions	Inhibits CYP1A2, CYP2C19 CYP2C9, and CYP3A4 and may increase the concentration of several classes of drugs, including, anticonvulsants, antiarrhythmics, steroids, QT-prolonging agents, immunosuppressant and antineoplastic agents, anticoagulants, ergot alkaloids, HMG-CoA reductase inhibitors (statins)	Dose adjustment required if GFR is < 50 mL/min Excellent oral bioavailability Highest penetration in CSF and vitreous among azoles High urine concentration and preferred for cystitis Step-down therapy in a critically ill patient who becomes stable Alternative initial therapy in noncritically ill patients

Isavuconazole	Yeast, including all <i>Candida</i> spp. Mold: most <i>Aspergillus</i> spp. and <i>Mucor</i> spp. Dimorphic fungi	<i>Fusarium</i> spp. <i>Scedosporium prolificans</i>	Nausea, vomiting, diarrhea, abdominal pain, constipation, headache, rash, peripheral edema, dyspnea, cough, hepatotoxicity, hypokalemia Dose-dependent QT shortening	Moderate inhibitor of CYP3A4 and inhibits the metabolism of sirolimus, tacrolimus, cyclosporine, mycophenolate mofetil, and other drugs metabolized by CYP3A4	Excellent oral bioavailability Large volume of distribution with long half-life Newly approved extended spectrum triazole for invasive aspergillosis and mucormycosis Use with caution in patients with severe hepatic impairment
Itraconazole <sup>b</sup>	Most yeast Dimorphic fungi Molds: most <i>Aspergillus</i> spp. Dematiaceous fungi	<i>Candida krusei</i> , <i>Aspergillus lentulus</i> , <i>Aspergillus terreus</i> , <i>Fusarium solani</i> , <i>Rhizopus</i> spp., <i>Mucor</i> spp., <i>S apiospermum</i> , <i>S prolificans</i>	Nausea, vomiting, diarrhea, abdominal discomfort, peripheral and pulmonary edema, CHF, hypertension, hypokalemia, hepatotoxicity	Potent CYP3A4 and P-glycoprotein inhibitor that increases the concentration of several classes of drugs, including calcium channel blockers, antiarrhythmics, immunosuppressant agents, anticoagulants, ergot alkaloids, HMG-CoA reductase inhibitors Contraindicated in patients with ventricular failure	No IV formulation available Not well studied for invasive candidiasis Primarily used in dimorphic fungi infections Therapeutic drug monitoring required Use with caution in patients with liver and renal failure
Posaconazole <sup>a,b</sup>	Yeast Dimorphic fungi Molds: <i>Aspergillus</i> spp., <i>F solani</i> , <i>Mucor</i> spp., <i>Rhizopus</i> spp. Dematiaceous fungi	<i>Scedosporium prolificans</i> , <i>S apiospermum</i>	Nausea, vomiting, diarrhea, fever, headache, coughing, hypokalemia, and liver enzyme elevation	Potent CYP3A4 inhibitor Concomitant use of drugs that are metabolized through CYP3A4 (sirolimus, ergot alkaloids, HMG-CoA reductase inhibitors) or CYP3A4 substrates that prolong the QT interval (pimozide, quinidine) is contraindicated	Indicated for oropharyngeal but not primary candidiasis Primarily used for invasive <i>Aspergillus</i> and <i>Candida</i> prophylaxis in high-risk patients Oral suspension has unpredictable bioavailability

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**Table 5**  
(continued)

Antifungal Agent	Spectrum of Activity	Expected Resistance	Adverse Events	Drug Interactions	Clinical Considerations
					IV formulation should be avoided if GFR <50 mL/min
Voriconazole	Yeast Dimorphic fungi molds: most <i>Aspergillus</i> spp. Dematiaceous fungi	<i>Aspergillus lentulus</i> , <i>Rhizopus</i> spp., <i>Mucor</i> spp.	Skin rash, photosensitivity, hepatic toxicity, transient visual disturbances, hallucinations, periostitis,	Inhibits CYP2C19, CYP2C9, and CYP3A4 and increases the concentration of several classes of drugs, including steroids, anticonvulsants, antiarrhythmics, QT- prolonging agents, immunosuppressant and antineoplastic agents, anticoagulants, ergot alkaloids, HMG-CoA reductase inhibitors	IV formulation: cyclodextrin vehicle can accumulate if GFR <50 mL/min Dose adjustment required in hepatic impairment Good CSF and vitreous penetration Therapeutic drug monitoring required First-line therapy for <i>Aspergillus</i> infections Step-down oral therapy for patients with fluconazole-resistant <i>Candida</i> spp.
<b>Echinocandins</b>					
Anidulafungin	<i>Candida</i> spp. <i>Aspergillus</i> spp. Dimorphic fungi	<i>Cryptococcus</i> spp. <i>Trichosporon</i> spp. <i>Aspergillus lentulus</i> <i>Fusarium</i> spp. <i>S. prolificans</i> <i>Mucor</i> spp. Dematiaceous fungi	Nausea, vomiting, diarrhea, fever, rash, insomnia, infusion reaction, edema, elevated liver enzymes, hypokalemia, hypomagnesemia	No major drug interactions	Only available in IV formulation Does not penetrate the eye, CNS, or urine Fist-line therapy in invasive candidiasis

Caspofungin	<i>Candida</i> spp. <i>Aspergillus</i> spp. Dimorphic fungi	<i>Cryptococcus</i> spp. <i>Trichosporon</i> spp. <i>Aspergillus lentulus</i> <i>Fusarium</i> spp. <i>S prolificans</i> <i>Mucor</i> spp. Dematiaceous fungi	Nausea, vomiting, diarrhea, headache edema, chills, rash, phlebitis, hypotension, hypokalemia, anemia, elevated liver enzymes	May decrease the serum concentration of tacrolimus Cyclosporine may increase and rifampin may decrease the concentration of caspofungin	Only available in IV formulation Does not penetrate the eye, CNS, or urine Dose adjustment in patients with moderate hepatic impairment Fist-line therapy in invasive candidiasis
Micafungin <sup>a</sup>	<i>Candida</i> spp. <i>Aspergillus</i> spp. <i>Dimorphic fungi</i>	<i>Cryptococcus</i> spp. <i>Trichosporon</i> spp. <i>Aspergillus lentulus</i> <i>Fusarium</i> spp. <i>S prolificans</i> <i>Mucor</i> spp. Dematiaceous fungi	Nausea, vomiting, diarrhea, abdominal pain, headache, insomnia, phlebitis, skin reactions, hepatotoxicity, hemolytic anemia, renal failure	Micafungin may increase the serum concentration of sirolimus	Only available in IV formulation Does not penetrate the eye, CNS, or urine Fist-line therapy in invasive candidiasis

<sup>a</sup> FDA-approved for candidiasis prophylaxis.

<sup>b</sup> FDA-approved for aspergillosis prophylaxis.

<b>Table 6</b>			
<b>Nonculture-based microbiologic tests for detection of invasive fungal infections</b>			
<b>Assay</b>	<b>1,3 <math>\beta</math>-D-Glucan (BG)</b>	<b>Galactomannan (GM)</b>	<b>T2MR Assay</b>
Method	Protease zymogen-based colorimetric assay	Anti-GM monoclonal antibody	Amplification and detection of Candida DNA by PCR and T2 magnetic resonance
Clinical application	Early detection of IFI	Early detection of invasive aspergillosis	Early detection of candidemia ( <i>C albicans</i> , <i>C glabrata</i> , <i>C krusei</i> , <i>C parapsilosis</i> , <i>C tropicalis</i> )
Specimen type	Serum	Serum, BAL	Whole blood
Result Interpretation	Negative < 60 pg/mL Intermediate 60–79 pg/mL Positive >80 pg/mL	Negative <0.50 Positive >0.50	Negative Positive Indeterminate
Sensitivity	67%–84%	BAL: 72%–92% Serum: 59%–83%	91.1%
Specificity	80%–90%	BAL: 78%–92% Serum: 92%–94%	99.4%
Cross-reactivity	<i>Pneumocystis jiroveci</i> , <i>Coccidioides immitis</i> , <i>Histoplasma encapsulatum</i> , <i>Candida spp.</i> , <i>Acremonium</i> , <i>Fusarium spp.</i> , <i>Trichosporon spp.</i> , <i>Aspergillus spp.</i>	<i>Aspergillus spp.</i> , <i>Fusarium spp.</i> , <i>Paecilomyces</i> , <i>Penicillium spp.</i> , <i>Alternaria spp.</i> , <i>Histoplasma encapsulatum</i> , <i>Blastomyces dermatitidis</i> , <i>Cryptococcus neoformans</i>	<i>Candida bracarensis</i> , <i>C metapsilosis</i> , <i>C orthopsilosis</i> , <i>Saccharomyces cerevisiae</i>
False positives	Semisynthetic $\beta$ -lactam antibiotics Hemodialysis with cellulose membranes, Bacteremia Transfusion given through cellulose membranes Gauze Intravenous immunoglobulins and albumin	Semisynthetic $\beta$ -lactam antibiotics Mucositis or GI tract GVHD Multiple myeloma Plasmalyte used in BAL Cotton swabs	Cross-contamination

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Table 6 (continued)			
Assay	1,3 $\beta$ -D-Glucan (BG)	Galactomannan (GM)	T2MR Assay
False negatives	Concomitant use of antifungals	Concomitant use of antifungals	Insufficient blood volume, clotted blood sample, specimen not at room temperature, presence of inhibitors, technical error, infection caused by an organism not detected by the panel

standard laboratory methods.<sup>8,29,32</sup> If the aforementioned species are identified or species identity cannot be determined, the CDC recommends further characterization using alternative methodology, including matrix-assisted laser desorption/ionization time-of-flight or molecular-based methods. The GenMark ePlex BC Identification Fungal Pathogen Panel is the first FDA-approved multiplex molecular panel that detects 16 fungal targets, including *C auris*, from positive BC with a high sensitivity and specificity.<sup>77</sup> The T2Cauris Panel, available for research use, is able to directly detect several *Candida* spp. from skin, blood, and environmental samples.<sup>78</sup> Various other PCR methods have been developed for the detection of *C auris*.

The use of newer NCTs such as T2Candida could impact the reporting of CLABSIs to NHSN. A positive NCT result may meet the laboratory-confirmed BSI (LCBI) criteria regardless of the BC result. In response to concerns from reporting health care institutions, NHSN revised reporting criteria starting January 1, 2020: If an NCT is positive but the BC is negative 2 days before, the day of, or 1 day after for the same organism, the NCT result is disregarded. However, if no BC is collected within this timeframe, the NCT result is used for LCBI surveillance determination and will be reported as a CLABSI if criteria are met.<sup>79</sup>

### Prevention of Aspergillosis

Given the prolonged duration of the risk for aspergillosis in HSCT recipients with chronic GVHD, guidelines recommend the use of an antimold prophylaxis (see [Table 5](#)).<sup>2</sup> The duration of prophylaxis is not clearly defined but is generally dictated by the severity of GVHD and the intensity of immunosuppression used to treat GVHD. Antimold prophylaxis has also been recommended for patients with acute myelogenous leukemia and myelodysplastic syndromes during periods of prolonged neutropenia.<sup>2</sup> Among patients receiving SOT, lung transplant recipients are at the greatest risk for IA. Current guidelines recommend prophylaxis with an antimold azole agent or inhaled amphotericin B product for 3 to 4 months after lung transplantation.<sup>2</sup> Reinitiation of prophylaxis is also recommended after intensification of immunosuppression for episodes of rejection.<sup>2</sup> Antimold prophylaxis may be considered in high-risk patients during institutional outbreaks of mold infection.<sup>2</sup>

### Diagnosis of Invasive Aspergillosis

The true incidence of community-associated or nosocomial IA may be underestimated as BCs are almost always negative. Diagnosis of invasive pulmonary aspergillosis

(IPA) has traditionally relied on the isolation of fungi in culture in combination with compatible histopathologic or radiographic findings. Moreover, it is often difficult to perform invasive testing in the severely immunocompromised patients to obtain specimens for microbiological testing. This has led to the increasing use of fungal biomarkers for the detection of IA, including the BG and the galactomannan (GM) assay (see **Table 6**). These assays are increasingly used in the clinical management of patients with suspected IA. Serum and bronchoalveolar lavage (BAL) GM and BG are recommended for the diagnosis of IA in patients with hematologic malignancies and HSCT recipients. However, GM is not recommended in nonneutropenic patients given its low sensitivity, and BG is not specific for *Aspergillus* spp.<sup>2</sup> Historically, molecular assays such as PCR were excluded due to lack of standardization and validation. However, recent efforts have been directed at addressing these limitations and optimizing assay performance using various specimens.<sup>80–82</sup> The use of these NCTs for routine surveillance of nosocomial IA is undefined.

### **Prevention of *Pneumocystis Pneumonia***

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*Pneumocystis pneumonia* prophylaxis is recommended for HSCT and SOT recipients during high-risk periods of immunosuppression, especially the first 100 days after transplantation.<sup>15</sup> Although there is potential for person-to-person transmission of *P jirovecii* leading to nosocomial outbreaks, current guidelines do not recommend specific isolation measures for the care of these hospitalized patients.<sup>14</sup> However, they do recommend avoiding cohorting infected patients with those who are immunocompromised.<sup>14</sup>

### **Diagnosis of *Pneumocystis Pneumonia***

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*P jirovecii* cannot be cultured, and microscopic visualization of cysts and/or trophozoites in lower respiratory samples (LRSs) such as induced sputum and BAL fluids is the gold standard for diagnosis, despite the low sensitivity and specificity.<sup>82</sup> In recent decades, molecular diagnostics such as PCR are increasingly being used for detection of *P jirovecii* in clinical respiratory samples; although the sensitivity (91%–100%) is high, specificity is much lower (86%) and false-negative results can occur in LRSs.<sup>81</sup> Conversely, PCR of oropharyngeal wash fluid has a higher specificity (93%) compared with LRSs.<sup>82</sup> As such, quantitative PCR is preferred to qualitative PCR to establish probable disease. However, threshold for positivity has not been determined.<sup>80</sup>

### **Coronavirus Disease 2019–Associated Candidiasis**

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Candidemia is increasing reported in critically ill patients with COVID-19, a condition termed COVID-19–associated candidiasis (CAC).<sup>83–86</sup> No specific underlying COVID-19–associated immunologic defects that predispose to IC have been identified. The incidence of CAC ranges from 0.7% to 24% in case series reported from various geographic regions.<sup>83–86</sup> The median time from the hospital or ICU admission to diagnosis of CAC was 10 to 15 days, indicating that CAC is likely an HAI. The overall 30-day mortality in patients with CAC was 50% or higher.<sup>83,85,86</sup> Non-*C albicans* species including *C auris* were frequently isolated, and infection with non-*C albicans* spp. was associated with worse outcomes.<sup>83</sup> Potential risk factors included extended ICU stay, cardiovascular disease (CVD), diabetes mellitus (DM), mechanical ventilation (MV), HD and prolonged CVC dwell time, and use of tocilizumab.<sup>83–86</sup> Traditional risk factors such as cancer chemotherapy, neutropenia, or transplantation were uncommon.

These reports suggest that CAC predominately results from CVC infection, and the increased incidence may reflect the unique challenges of caring for critically ill patients in the ICU during a pandemic. It also highlights the importance of strict adherence to

infection control measures in ICUs to prevent CLABSIs in critically ill patients with COVID-19.

### CORONAVIRUS DISEASE 2019–ASSOCIATED PULMONARY ASPERGILLOSIS

Critically ill patients with influenza can develop secondary influenza-associated pulmonary aspergillosis.<sup>46</sup> Similarly, there have been increasing reports of pulmonary aspergillosis among critically ill patients with COVID-19, a condition termed COVID-19–associated pulmonary aspergillosis (CAPA).<sup>47,87–92</sup> It is believed that CAPA occurs as a consequence of direct damage to the airway epithelium, impaired immune function caused by Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and increased susceptibility to aspergillosis as a result of the use of immune modulatory therapies such as corticosteroids and IL-6 blockers.<sup>92</sup> The incidence of CAPA ranges from 4.8% to 33% in reports from various geographic locations, among ICU and non-ICU settings.<sup>87–91</sup> The wide range in incidence may be primarily due to the varying definitions used and the difficulty in establishing the diagnosis as sampling of the lower respiratory tract was limited due to the risk of aerosolization during bronchoscopy.<sup>92</sup> A recent study from 17 countries, done between March and August 2020, described 186 patients with CAPA defined using established standard criteria.<sup>47</sup> The incidence of CAPA among these patients with COVID-19 ranged from 0.1% to 9.7%, with increasing incidence of 1.0%–39.1% in patients in the ICU and 1.1%–47.4% in patients requiring MV.<sup>47</sup> In this study, the median time to diagnosis of CAPA was 10 days from diagnosis of COVID-19 (Interquartile range, IQR: 5–16 days) and 8 days from ICU admission (IQR: 3–14 days). The time to diagnosis of 7 or more days suggests that most of these cases of CAPA might be HAIs. CAPA was significantly associated with worse outcomes compared with patients with COVID-19 without CAPA.<sup>88</sup> The overall mortality has been in excess of 50% with worse outcomes in intubated patients,<sup>47,88,89</sup> with CAPA attributable mortality of 33%.<sup>47</sup> Treatment with voriconazole was associated with improved outcomes.<sup>47,89</sup> *A fumigatus* was the most commonly isolated species, followed by *A flavus*.<sup>47,87–89</sup> Unlike the traditional risk factors of prolonged neutropenia or transplantation reported with IPA, the underlying comorbidities associated with CAPA include COVID-19–associated acute respiratory distress syndrome, CVD, renal failure, DM, chronic lung disease and obesity, and use of corticosteroids.<sup>47,89</sup> Similarly, the clinical and radiographic features differ from those previously described for IPA. The diagnosis was established using fungal cultures and NCTs, including BG, GM, aspergillus PCR, and lateral flow assays.<sup>91</sup> In order to standardize reporting, consensus criteria have been proposed for CAPA.<sup>91</sup> The diagnosis of CAPA requires entry criteria of laboratory-confirmed diagnosis of COVID-19 pneumonia in an ICU patient and then stratifies CAPA as proven, probable, or possible using a combination of histopathology, clinical features, imaging, and microbiology.

From an infection prevention perspective, the increasing incidence of CAPA in critically ill patients with COVID-19 emphasizes the need for surveillance for nosocomial aspergillosis in this population and strict adherence to standard measures for mitigating risk for nosocomial aspergillosis as previously described.

### SUMMARY

Nosocomial fungal infections, especially IC, including candidemia and IA, can result in significant morbidity and mortality in critically ill and severely immunocompromised patients. Implementation of recommended infection control strategies can prevent catheter-related candidemia and minimize exposure of severely immunocompromised patients to airborne *Aspergillus* spores within the hospital environment. In select

patient populations at high risk for invasive fungal infections, antifungal prophylaxis should be considered during the periods of intense immunosuppression. Newer nonculture-based methods have the potential to improve the diagnosis of nosocomial fungal infections.

### CLINICS CARE POINTS

- Surveillance for new entities of COVID-19–associated invasive candidiasis and aspergillosis and emerging fungal pathogen *C auris* is important.
- Thoughtful application of newer nonculture-based fungal diagnostics can improve identification of nosocomial infections.
- Adherence to established infection prevention and control practices is essential to minimize risk of nosocomial fungal infections.

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