Invasive Fungal Infections in the Intensive Care Unit

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KEYWORDS

• ICU • Fungal infection • Antifungal • Candidiasis • Aspergillosis

KEY POINTS

- The 2 major fungal pathogens in immunocompetent intensive care unit (ICU) patients are *Candida* spp and *Aspergillus* spp.
- Invasive candidiasis develops in patients with specific risk factors, and most of those risk factors occur in critically ill patients.
- Invasive aspergillosis is encountered in ICU settings in patients with certain risk factors, such as chronic obstructive pulmonary disease, liver cirrhosis, and diabetes.
- Microbiological cultures have been the main diagnostic method for invasive fungal infections for many years; however, new rapid tests can help achieve a faster diagnosis.
- Antifungals have different spectra of activity. Knowledge of the mechanism of action, efficacy, and adverse effects is crucial in managing ICU patients.

INVASIVE CANDIDIASIS

Candida are ubiquitous yeasts and part of the human microbiome; they are also linked to multiple nosocomial infections. Invasive candidiasis (IC) is a spectrum of syndromes, including blood stream infection (BSI) or candidemia, deep-seated candida infections in the presence of BSI, and deep-seated infections without BSI, each contributing of almost a third of intensive care unit (ICU) IC.[1] The incidence of infections by non-*albicans Candida* species has increased in recent years. *Candida* is currently one of the most frequent causes of BSI in US hospitals.[2] Attributable mortality can be up to 40%.[2,3] The main species of *Candida* that are found to cause IC are *Candida albicans*, *Candida glabrata*, *Candida parapsilosis*, *Candida krusei*, and *Candida tropicalis*. *Candida parapsilosis* has the tendency to cause device and central catheters infections.

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RISK FACTORS

IC pathophysiology is thought to be related to the translocation of *Candida* spp from their colonization sites (gastrointestinal tract or skin) to achieve hematogenous or contiguous spread. Up to 80% of ICU patients can be colonized with *Candida* spp; however, it has been shown that only 10% of them develop IC.[4] Bronchial *Candida* isolates are generally considered nonpathogenic and reflect colonization. Pulmonary IC is very rare and, even in the rare reported cases, the source of infection can be traced back to hematogenous spread.[4,5]

Efforts have been made to recognize ICU patients at risk of developing IC. In one study, Candida score, which uses risk factors of surgery on ICU admission, multifocal *Candida* colonization, severe sepsis or septic shock, and total parenteral nutrition, was used to predict invasive candida infection.[6] Although it had been a topic of research, *Candida* colonization as a risk factor needs surveillance cultures from different bodily sites, which are not readily available in most centers, and adds to the cost of health care.[4]

In a multicenter study, risk factors that could predict IC infection included antibiotics use combined with central venous catheter placement within the last 3 days, in addition to 2 of the following risk factors: surgery, immunosuppression, immunosuppression, steroid use, and pancreatitis, within the last 7 days, in addition to total parenteral nutrition and/or dialysis within last 3 days. By implementing this rule, clinicians can safely rule out patients who are not at high risk of IC (negative predictive value of 97%).[7]

The authors believe that patients are at greatest risk of IC when they have been in the ICU on mechanical ventilation, with a recent history of major abdominal surgery, on broad-spectrum antibiotics, with a central venous line, total parenteral nutrition, pancreatitis, dialysis, severity of illness, immunosuppression, and steroid use. However, the ability of these risk factors to predict IC depends in part on each unit's IC incident rates.[6–11]

DIAGNOSIS

The management of IC is time sensitive, because delaying diagnosis and starting the right antifungal therapy carries a high mortality risk.[3,12–14] Among all diagnostic methods, microbiological culture still plays a major role and is considered the cornerstone for diagnosis. However, blood culture sensitivity varies depending on the type of IC. It can achieve up to 80% sensitivity in cases of candidemia, but it can be as low as 21% in deep-seated IC. The overall combined sensitivity of blood cultures in BSI and deep-seated IC is thought to be ~50%.[5,15,16] Furthermore, cultures have long turn-around times (2–5 days) and therefore carry the risk of delayed diagnosis and treatment.[5]

Several non–culture-based diagnostic methods have been proposed to tackle this problem (**Table 1**).

β-D-Glucan is an important component of the fungal cell wall that has been targeted for detection of invasive fungal infections (IFIs). It has a rapid turn-around time and has a high sensitivity (up to 75% when used in serial testing[17,18]). However, it can yield low specificity, especially in critically ill patients.[19] False-positives can occur in the presence of other fungal infections (eg, molds, *Pneumocystis jiroveci* and *Trichosporon* species), mucositis, bacterial infections, use of some antibacterial agents (piperacillin-tazobactam and amoxicillin-clavulanate), glucan-containing surgical objects (gauzes), blood products, or hemodialysis using cellulose membranes.[17]

If properly used, β-D-glucan can be used to rule out IC, and can be used as a tool to recognize high-risk patients who would benefit from empiric antifungal therapy.[20,21] In addition, β-D-glucan has been shown to be helpful in assessing the patient's response to therapy.[22]