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Preventing invasive candida infections. Where could we do better?

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SUMMARY

Invasive candidiasis is associated with high mortality rates, ranging from 35% to 60%, in the range reported for septic shock. The epidemiology and pathogenesis of invasive candidiasis differ according to the patient's immune status; the majority of cases in immunocompromised hosts are candidaemia, whereas non-candidaemic systemic candidiasis accounts for the majority of cases in critically ill patients. In contrast to candidaemia, non-candidaemic systemic candidiasis is difficult to prove, especially in critically ill patients. Up to 80% of these patients are colonized, but only 5–30% develop invasive infection. The differentiation of colonization and proven infection is challenging, and evolution from the former to the latter requires seven to 10 days. This continuum from colonization of mucosal surfaces to local invasion and then invasive infection makes it difficult to identify those critically ill patients likely to benefit most from antifungal prophylaxis or early empirical antifungal treatment. Early empirical treatment of non-candidaemic systemic candidiasis currently relies on the positive predictive value of risk assessment strategies, such as the colonization index, candida score, and predictive rules based on combinations of risk factors such as candida colonization, broad-spectrum antibiotics, and abdominal surgery. Although guidelines recently scored these strategies as being supported by limited evidence, they are widely used at bedside and have substantially decreased the incidence of invasive candidiasis.

Introduction

Candida spp. colonization develops in up to 80% of critically ill patients staying more than one week in intensive care, whereas invasive candidiasis is documented in only 5–10% of them.[1–5] Early diagnosis of invasive candidiasis is difficult; it is generally late in the course of the infection before microbiological evidence is found.[6–8] This may delay appropriate antifungal treatment and may be in part responsible for its high crude and attributable mortality rates, comparable to those reported for septic shock.[9–11]

Antifungal prophylaxis and early empirical treatment of severe candidiasis has improved survival, but may result in overuse of antifungal agents if indiscriminately prescribed to all patients colonized by *Candida* spp.[12–14] Indeed, extensive use of antifungals has promoted a shift to *Candida* spp. with reduced susceptibility.[15,16] Recent guidelines resulting from expert consensus provided no high-level recommendations about antifungal prophylaxis and empirical antifungal

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treatment.[8,17,18] Despite limited evidence, antifungal prophylaxis and empirical treatment currently rely on the identification of patients with a high documented risk and on the positive predictive value of risk assessment strategies, such as the colonization index, candida score, and predictive rules based on combinations of risk factors.[19–21]

Identification of patients who could benefit from antifungal prophylaxis and empirical treatment may, however, be improved by taking into account some pathophysiological specificities of invasive candidiasis.[22,23]

Epidemiology and pathophysiology of invasive candidiasis

Invasive candidiasis includes two closely related and often confused conditions: candidaemia and non-candidaemic systemic candidiasis. Candidaemia requires the growth of *Candida* spp. from the blood of a patient with temporally related signs of infection. In the intensive care unit (ICU), candidaemia ranges from five to 10 cases per 1000 admissions or three to 15 episodes per 10,000 patient days (five to 10 times the incidence on general hospital wards).[6,24,25] Non-candidaemic systemic candidiasis corresponds to candida invasion, established by culture or histology, of normally sterile sites. Accordingly, the epidemiology of non-candidaemic systemic candidiasis is hard to determine. In a worldwide prevalence study performed in 1265 ICUs in May 2007, candida infection was reported in 17% (841/4947) of patients with microbiologically documented infection, but candidaemia was documented in only 99 cases.[2,5] Invasive candidiasis is characterized by specific physiopathological characteristics (Table I).

Exogenous nosocomial transmission of candida has been reported, but studies using genotyping of candida strains showed that endogenous colonization is responsible for the large majority of severe candidiasis.[26–28] This explains why invasive candidiasis is characterized by seven- to 10-day delay between exposure to risk factors and development of infection.[29–31] The pathophysiology of invasive candidiasis differs markedly between immunocompromised and critically ill patients.[22,23] In immunocompromised patients, prolonged neutropenia or functional impairment (transplanted patients), with eventual mucosal injuries resulting from chemotherapy combined with the selective pressure of frequent and repetitive exposure to antibacterial agents, results in high prevalence of invasive candidiasis with a large proportion of bloodstream infections.

In critically ill patients, other factors explain the high prevalence of invasive candidiasis. Prolonged support of failing organs combined with the selective pressure of broad-spectrum antibiotics constitutes key risk factors for invasive candidiasis in non-surgical critically ill patients.[1,5] These factors may explain progressive colonization in a high proportion of patients after prolonged stay in the ICU. They may also explain a higher proportion of catheter-related infections in the absence of severe immune impairment.[6,32–34]

Additional factors play a specific role in patients after abdominal surgery.[35] Opening or perforation of the bowel results in contamination of the peritoneum by digestive flora. Surgical cleaning of the abdominal cavity combined with antibiotics is sufficient to allow full recovery in most cases, where the identification of *Candida* spp. has no clinical significance.[22,36] Alternatively, colonization may progress to invasive candidiasis in recurrent peritonitis following anastomotic leakage.[37–40] These factors may explain why candidaemia is not documented in most cases of invasive candidiasis in surgical patients until late in the disease, if at all.[40]

The interval between exposure to risk factors and development of invasive disease opens a window of about one week for a structured evaluation to identify patients who may truly benefit from antifungal prophylaxis or early empirical antifungal treatment according to the underlying condition and immune status.[7,19,41]

Antifungal prophylaxis

The bad prognosis of invasive candidiasis has stimulated the use of systematic antifungal prophylaxis in most immunocompromised patients over the past three decades.[42] This is considered to be responsible for the evolution of the epidemiology of candida infections, characterized by breakthrough

Table I
Pathophysiological characteristics of invasive candidiasis according to immune status

Pathophysiological characteristics	Immunocompromised patients	Critically ill patients
Immunity		
Neutrophils	Decreased	Increased
Macrophages	Decreased	Increased
T-cells	Decreased	Normal
Ulcerations of mucosal surfaces		
Oropharyngeal	++ to +++	0 to +
Upper digestive tract	++ to +++	0 to +
Lower digestive tract	++ to +++	0 to +
Typhlitis	++ to +++	0
Digestive surgery	0	+ + to +++
Antibiotic exposure	++ to +++	+ to ++
Organ failure	+ to ++	++ to +++
Candida colonization	++ to +++	++ to +++
Invasive candidiasis		
Candidaemia	++ to +++	0 to +
Non-candidaemic systemic candidiasis	0 to +	++ to +++