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Clinical Aspects of Invasive Candidiasis in the Surgical Patient

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Abstract

Improvements in post-surgical care have led to decreased mortality, but to an increased number of critically ill surgical patients at high risk of fungal colonization and invasive disease. Use of catheters, enteral nutrition, antibacterials and haemodialysis add to the risk. Although *Candida albicans* remains the most common species causing invasive candidiasis in the post-surgical setting, there has been an increase in the prevalence of non-*albicans* species associated with the increased use of fluconazole prophylaxis in surgical intensive care units. The prompt diagnosis of candidiasis is complicated by a lack of specific clinical symptoms and difficulties in laboratory diagnosis; therefore, it is vital to recognize at-risk patients and initiate therapy promptly in these individuals. While *Candida* scoring systems to identify at-risk patients have been developed, these need to be validated in prospective interventional trials. Newer azole and echinocandin antifungal agents have expanded the range of available treatments, and prophylactic antifungal therapy in at-risk, critically ill surgical patients has been shown to be effective.

The incidence of nosocomial candidaemia rose sharply over the 1980–91 period; in particular, the incidence of *Candida* infections in surgical patients more than doubled from 2.5 to 5.6 per 1000 hospital discharges.[1] This increase in nosocomial candidal infections has been associated with the increased use of immunosuppressive and antineoplastic drugs, broad-spectrum antibacterials and hyperalimentation in patients with severe underlying diseases.[2,3] Moreover, improvements in supportive medical and surgical care have contributed to the increased survival of many critically ill surgical patients at high risk of fungal colonization, and subsequent invasive fungal disease.[3,4]

Patients admitted to surgical intensive care units (ICUs) are at the greatest risk for developing a candidal bloodstream infection, due to extensive surgery, and the frequent use of central venous catheters, indwelling bladder catheters, enteral or intravenous nutrition, antibacterials, haemodialysis and/or mechanical ventilation.[3,5,6] Surgical procedures such as cardiothoracic surgery, upper gastrointestinal tract surgery and liver transplantation are associated with high rates of candidal colonization and invasive *Candida* infections, as are gastrointestinal perforation, anastomotic leakage and surgery for acute pancreatitis, with exceedingly high mortality rates, prolonged hospital stay and increased healthcare costs.[5,7-13] The purpose of this brief review is to summarize the challenges posed by *Candida* infections in the surgical patient. Invasive candidiasis in solid organ transplant patients has

been reviewed in more detail by Grossi[14] in this supplement.

1. Species Identification

In the NEMIS (National Epidemiology of Mycosis Survey) study, which included 4276 patients admitted to surgical ICUs, there were 9.8 nosocomial bloodstream infections due to *Candida* species per 1000 admissions, and the *Candida* species most frequently isolated from blood were *C. albicans* (48% of cases), *C. glabrata* (24%), *C. tropicalis* (19%), *C. parapsilosis* (7%) and *Candida* species not otherwise specified (2%).[15] Most cases of candidal bloodstream infection occurred within 3 weeks of admission to the SICU, and 41% of patients with candidal bloodstream infections died.[5] Risk factors that were independently associated with increased risk of candidaemia included prior surgery, acute renal failure and receipt of parenteral nutrition.

Recent epidemiological studies have reported a trend of decreasing isolation of *C. albicans* (which still remains the most common species causing invasive candidiasis) and increased isolation rates of non-*albicans* species, such as *C. tropicalis* and *C. parapsilosis*.[16] The increased use of fluconazole prophylaxis in SICUs has been associated with an increase in the prevalence of non-*albicans* species (namely, *C. glabrata* and *C. krusei* isolates), which are often less susceptible to conventional azole antifungal treatment.[17]

2. Clinical Aspects

Colonization of skin and mucosal membranes (i.e. gastrointestinal and genitourinary) by *Candida* and/or the alteration of natural host barriers (due to surgical procedures, wounds, insertion of indwelling intravascular and urinary catheters, etc.) may predispose to invasive *Candida* infection.[18] The gut represents an important portal for intra-abdominal candidal infections. Other frequent clinical manifestations of invasive candidiasis in surgical and ICU patients are candidal bloodstream infection, disseminated candidiasis and candidiasis of the urinary tract. Candidal endophthalmitis, pulmonary candidiasis and *Candida* endocarditis occur less frequently.[18] *Candida* peritonitis may occur as a complication of a perforation of the gastrointestinal tract, after gastrointestinal surgery, or as a consequence of anastomotic leakage or peritoneal dialysis. In patients with *Candida* peritonitis, an Acute Physiology and Chronic Health Evaluation (APACHE) II score of at least 17 and respiratory failure (which indicate severity on admission to the ICU), peritonitis of upper gastrointestinal tract origin and peritoneal fluid found to be positive for *Candida* upon direct examination were shown to be independently associated with mortality.[19]

Patients having surgery for acute pancreatitis have been reported to have an increased likelihood of *Candida* infection.[13]

As clinical symptoms frequently lack specificity and laboratory diagnosis is difficult, the diagnosis of severe candidiasis is frequently based on the overall clinical status of the patient and eventually positive fungal cultures. Recognition of patients at risk for colonization and subsequent invasion/dissemination is paramount to clinical diagnosis and prompt initiation of therapy, as delays in treatment are associated with increased mortality.[4,20,21] Several *Candida* scoring systems have been developed to help identify those at risk of candidaemia,[22] including colonization index and corrected colonization index in critically ill surgical patients.[23] Prospective studies are required in order to assess the value of these systems in the clinical management of patients.

The prophylactic administration of fluconazole to critically ill surgical patients at high risk of *Candida* infection (pre-emptive therapy) is of proven value.[24-26] The current Infectious Diseases Society of America (IDSA) guidelines for management of candidiasis[27] recommend prophylactic therapy for high-risk patients hospitalized in the ICU (and for liver, pancreas and small bowel transplant recipients). Empirical antifungal therapy should be considered for at-risk critically ill patients with no other known cause of fever.[27] Therefore the current IDSA guidelines recommend the use of an echinocandin (anidulafungin, caspofungin and micafungin) as initial therapy of proved or suspected Invasive Candidiasis in

high-risk non-neutropenic adult patients with moderately severe to severe illness and for patients with recent azole exposure. Transition to fluconazole after initial echinocandin is appropriate in many cases. Moreover the IDSA guidelines recommend fluconazole for patients who are less critically ill and who have no recent azole exposure.[27] The same therapeutic approach is advised for children, with attention to differences in dosing regimen.[27]

3. Discussion and Conclusions

Despite their high mortality, invasive fungal infections are frequently recognized and treated late, due to difficulties in formulating the diagnosis of invasive candidiasis. An early pre-emptive therapy based on the recognition of risk factors may be appropriate, particularly in cases of broad-spectrum antibacterial treatment, in the presence of central venous lines and other devices traversing the epithelial barrier, in patients receiving total parenteral nutrition or immunosuppression, and in severe illness (APACHE II score >10 and ventilator use >48 hours).[4] Prophylaxis of candidal infections has been shown to provide benefits among critically ill surgical ICU patients.[28,29] Further clinical data are needed, however, to better identify patients who might warrant antifungal prophylaxis, minimizing the risk of resistant fungal strains emergence, while drastically reducing morbidity and mortality.

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