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What Is the Most Recent Evidence on the Prevention and Early Treatment of Invasive Fungal Infections in Nonneutropenic Critically Ill Patients?

Andrea Cortegiani,[1,*] Vincenzo Russotto,[1] Pasquale Iozzo,[2] Santi Maurio Raineri,[1] and Antonino Giarratano[1]

[1]Department of Biopathology and Medical Biotechnologies (DIBIMED), Section of Anesthesia Analgesia Intensive Care and Emergency, Pocliclinico P. Giaccone University of Palermo, Italy
[2]General Intensive Care Unit, Policlinico P. Giaccone. University of Palermo, Italy

[*]*Corresponding author*: Andrea Cortegiani, Department of Biopathology and Medical Biotechnologies (DIBIMED), Section of Anesthesia Analgesia Intensive Care and Emergency, Pocliclinico P. Giaccone University of Palermo, Italy. Tel: +39-916552730, Fax: +39-916552716, E-mail: cortegiania@gmail.com

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Abstract

Invasive fungal infections (IFIs) are associated with high morbidity and mortality in intensive care units. *Candida* species are the most important fungal pathogens and among the most frequent causes of infection in critically ill patients. Studies have evaluated the correlation between the onset of antifungal treatment and survival. However, definitive diagnosis of IFI is time-consuming in clinical practice. Antifungal prophylaxis and preemptive or empirical treatments are among therapeutic strategies to prevent or treat early fungal infections in selected patients. Recently, new evidence from randomized controlled trials and systematic reviews has been published. Moreover, new clinical practice guidelines from international communities are available. The aim of this review was to present updated evidence on this topic.

Keywords: Invasive Fungal Infection, Candida spp., Antifungal Treatment, Fungal Sepsis

1. Background

Invasive fungal infections (IFI) are among the leading causes of morbidity and mortality in critically ill nonneutropenic patients (1). The common definition of IFI is the presence of fungi in a sterile body site with signs and symptoms of infection. IFIs are also one of the most common nosocomial infections. *Candida* species are the most common fungi responsible for IFI. They are ranked the fourth most common cause of nosocomial bloodstream infection and the third most common isolated pathogen in intensive care units (ICUs) (2). Moreover, *Candida* species represent the fourth and sixth leading causes of nosocomial sepsis in Europe and the United States, respectively.

The most common types of IFI caused by *Candida* species are bloodstream infection and intraabdominal candidiasis (3). Mortality due to *Candida* species is high in both general wards and ICUs, ranging from 42% to 71%, depending on the patient's characteristics and clinical setting (4-7). Moreover, IFI imposes a major economic burden, mainly due to prolonged ICU stay, high cost of antifungal drugs, and overall use of hospital resources.

Several risk factors for *Candida* infections have been identified, including broad-spectrum antibiotic therapy, total parenteral nutrition, major abdominal surgeries, central venous catheters, multiple-site *Candida* colonization, and impairment of immunological responses (1). Considering these factors, clinical scoring systems have been developed and implemented in clinical practice (e.g., *Candida* score and Ostrosky-Zeichner score) to recognize patients at risk of *Candida* infections (3).

The correlation between the onset of antifungal treatment and mortality has been largely investigated (8-10). Most studies have described a major correlation between an early and adequate antifungal treatment and improved survival. However, definitive microbiological diagnosis of fungal infections via standard culture-based methods is time-consuming, typically longer than 2 - 3 days (10). Despite being the gold standard, culture-based microbiological methods have suboptimal sensitivity for *Candida* identification, missing almost 50% of cases (11). Therefore, antifungal strategies have been described and frequently implemented in clinical practice to prevent and/or treat early fungal infections (12, 13).

The most common antifungal strategies with respec-

tive definitions include: 1, prophylaxis, defined as administration of antifungal agents in patients without confirmed or suspected fungal infection, but with risk factors for its development; 2, empirical treatment, defined as antifungal administration for infection signs and symptoms in patients at risk of IFI; 3, preemptive treatment, defined as treatment selected based on fungal evidence from biomarkers or nonculture-based methods, without definitive identification via standard culture-based tests (e.g., 1-3-beta-D-glucan, procalcitonin, mannan and antimannan antibodies, and polymerase chain reaction) (14, 15). These strategies, defined globally as untargeted antifungal treatments, are different from targeted therapy, which is characterized by the definition of therapy after identification of microorganisms.

Several randomized controlled trials (RCTs) have investigated the effectiveness of various antifungal drugs in the prevention of fungal infections before the definitive diagnosis of IFI. In 2006, a Cochrane systematic review summarized the available evidence from RCTs on the use of antifungal agents for the prevention of IFI in nonneutropenic critically ill patients (16). The review included 12 studies and 1606 patients. Most of the included studies investigated fluconazole or other azoles. The review concluded that antifungal agents are associated with the reduced incidence of IFI (about 50%) and reduced mortality (about 25%). This review presents important evidence on untargeted antifungal treatments.

2. Updated Evidence

In the past decade, major multicenter RCTs have investigated the use of antifungals for similar purposes in different settings among different populations, including emergency postsurgical patients, febrile critically ill patients, and high-risk ICU patients. Notably, most of these new studies have investigated echinocandins (e.g., micafungin and caspofungin) (17-19).

We recently reviewed the available data in a Cochrane systematic review, including 22 RCTs and 2761 patients (20, 21). The interventions included any form of untargeted antifungal treatment, encompassing prophylactic preemptive or empirical treatment in comparison to the placebo or non-antifungal treatment. Untargeted antifungal treatment was not associated with a significant reduction in mortality (RR, 0.93; 95% CI, 0.79 - 1.09; P = 0.36; evidence of moderate-quality). However, antifungal agents reduced the incidence of IFI by nearly 45% with low-quality evidence (RR, 0.57; 95% CI, 0.52 - 0.97; P = 0.03).

Subanalyses have not indicated any survival advantages by the use of either prophylactic or empirical treatment (22). Only one RCT evaluated the preemptive approach with beta-D-glucan, while it included few patients and had an inadequate design. These findings were recently confirmed in the most recent RCT on this subject by Timsit et al., which recruited 260 nonneutropenic critically ill patients with ICU-acquired sepsis, multiple-site *Candida* colonization, multiple organ failure, and broad-spectrum antibiotic therapy (23, 24).

In this trial, a high rate of critical diseases was reported (median sepsis organ failure assessment score of 8). The patients were randomized to receive empirical antifungal treatment with micafungin (100 mg daily for 14 days) or placebo. The primary outcome was survival without confirmed IFI at 28 days after randomization, which was not significantly different between the groups (68% in the micafungin group vs. 60.2% in the placebo group; hazard ratio, 1.62; 95% CI, 0.87 - 2.08). The use of empirical micafungin reduced the incidence of IFI, compared to the placebo (3% vs. 12%; P = 0.008).

3. Paradoxical Evidence

Evidently, contradictions arise from the available evidence. Use of antifungal agents before the definitive diagnosis of IFI is associated with the reduced incidence of IFI, but without any significant effects on the mortality of nonneutropenic patients (25). Considering the high mortality of IFI and the correlation between timing of antifungal administration and patient survival, the question arises as how to interpret these findings. It should be noted that many studies underlining the correlation between antifungal treatment timing and mortality were retrospective and did not consider the patients' status or disease severity.

Recent data reveal that IFI is a marker of impaired immunological function and immune exhaustion (26). An effective pharmacological intervention, which aims at eradicating fungi from deep body sites, may not be adequate for reverting the patients' outcomes (27, 28). Moreover, the positive results from early RCTs may be attributed to the 'small trial effect' and potentially biased by the low methodological quality and/or low sample size.

Other criteria for the selection of proper antifungal treatments in an early clinical phase may be arguably more effective, with an impact on survival. New strategies based on the combined role of risk factors and biomarkers (e.g., *Candida* score $\geq$ 3 plus beta-D-glucan $\geq$ 80 pg/mL) have been recently proposed with positive results for optimizing exposure to antifungals (29). However, the actual effects of these strategies in randomized studies and their applications in larger clinical settings should be investigated (30).

4. Guideline Recommendations

The most recent clinical guidelines from the European society of clinical microbiology and infectious diseases (ESCMID) for diagnosis and management of *Candida* infections support the use of fluconazole prophylaxis in non-neutropenic patients, who recently underwent abdominal surgery and had reoperations for perforation or anastomotic leakage (14). On the contrary, empirical and preemptive treatments based on beta-D-glucan are not supported due to lack of evidence. It should be noted that these guidelines were published in 2012 and do not include the latest randomized trials and Cochrane reviews on this topic.

In 2016, the infectious diseases society of America (IDSA) published the updated clinical practice guidelines for the management of candidiasis (31). Regarding antifungal prophylaxis, a loading dose of 800 mg of fluconazole, followed by 400 mg of fluconazole daily could be used in high-risk adult patients in ICUs with a high rate of invasive candidiasis (> 5%; poor recommendation; moderate-quality evidence). It was stated that empirical antifungal therapy should be considered in critically ill patients with risk factors for invasive candidiasis and no other known cause of fever; treatment should be based on the clinical assessment of risk factors, surrogate markers, and/or culture data from nonsterile sites (strong recommendation; moderate-quality evidence).

It was also suggested that empirical antifungal therapy should be initiated immediately in patients with risk factors and signs of septic shock (strong recommendation; moderate-quality evidence). The suggested drugs for this purpose include echinocandin (caspofungin with a loading dose of 70 mg, followed by 50 mg daily), micafungin (100 mg daily), and anidulafungin (loading dose of 200 mg, followed by 100 mg daily). The recommended duration of empirical therapy is 2 weeks in patients with improvement, while for those with no clinical response at 4-5 days or a negative nonculture-based diagnostic assay (a high negative predictive value), antifungal use should be terminated (strong recommendation; low-quality-evidence).

For the treatment of intraabdominal candidiasis, IDSA stated that empirical antifungal therapy should be considered in patients with clinical evidence of intraabdominal infection and significant risk factors for candidiasis, including recent abdominal surgery, anastomotic leakage, and necrotizing pancreatitis in association with source control (strong recommendation; moderate-quality evidence).

When interpreting these recommendations, it should be noted that IDSA guidelines have not considered the evidence from a recent RCT by Knitsch et al. on the effects of antifungal treatment with micafungin (100 mg daily) in 241 patients undergoing emergency abdominal surgery for generalized or localized intraabdominal infections; no difference was found in terms of the incidence of invasive candidiasis or mortality, compared to the placebo. Similarly, the latest Cochrane systematic review and the study by Timsit et al. on the empirical treatment of septic patients with *Candida* colonization have not been included.

The widespread use of antifungal drugs before definitive diagnosis of IFI should be considered in light of 2 factors: 1, the overall cost of antifungal treatment, and 2, the increasing rate of resistance to antifungals (32). Concerning the latter factor, it should be noted that increased resistance is not limited to only older antifungals, but even echinocandins have an increased rate of resistance, which is correlated with the use of molecules. Moreover, the increasing rate of resistance to echinocandins is particularly true for *Candidaglabrata* with specific genetic mutations and outbreaks, as described in the literature. Finally, infections due to resistant *Candida* species are associated with poor outcomes (33, 34).

5. Conclusion

According to available evidence from RCTs, administration of antifungal agents before definitive diagnosis of IFI may lead to a reduction in the incidence of IFI, without any survival advantages in nonneutropenic critically ill patients (35). Physicians should evaluate case-by-case risks and benefits of antifungal treatment after considering treatment timing, risk factors, local microbiological epidemiology, costs, available biomarkers, and diagnostic microbiological assays in their institutions (36, 37). Future research should evaluate the effectiveness and applicability of combined strategies using several methods to correctly select patients, who may benefit from timely and adequate untargeted antifungal treatment.

Footnotes

Authors' Contribution: All authors equally contributed to the concept and preparation of the manuscript.

Conflicts of Interest: The authors declare no conflicts of interest.

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