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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 +++

invasive candidiasis and infections caused by candida strains resistant to the antifungal agent used for prophylaxis.[15,43–45]

The success of antifungal prophylaxis in bone marrow and solid organ transplant recipients has stimulated investigators to promote it in critically ill patients. Clinical results, however, should be interpreted with caution. Studies involving unselected critically ill patients at low risk (<10%) of invasive candidiasis failed to demonstrate any benefit of antifungal prophylaxis [number needed to treat (NNT): 20–50].[46,47] To avoid overuse of antifungals, we and others have emphasized that prophylaxis should target only critically ill patients in whom it has been shown useful.[19,38,39,48,49] In these highly selected populations, representing only 1–3% of all ICU admissions, the NNT ranged from three to 10. This concept has been acknowledged and validated in guidelines for the management of invasive candidiasis in immunocompetent hosts.[17,18] Based on the available evidence, they state that institutions in which high rates of invasive candidiasis in adult ICU patients persist despite standard infection-control procedures should consider fluconazole prophylaxis only for highly selected ICU patients.[17–19] Two small prospective studies, including one placebo-controlled, suggested that antifungal prophylaxis in patients presenting with anastomotic leakage after abdominal surgery may prevent the development of invasive candidiasis.[18,38,39]

Antifungal prophylaxis, however, should not be given to all ICU patients. In the absence of routinely available biomarkers to guide early empirical antifungal treatment, several risk-based strategies have been proposed to identify patients likely to benefit most.

Risk-based strategies to guide empirical antifungal treatment

Non-candidaemic systemic candidiasis represents the majority of invasive candidiasis cases occurring in critically ill patients, and early empirical antifungal treatment avoids delayed treatment of documented infection, which significantly worsens the outcome.[12,13,50] Unfortunately, the definition of microbiologically demonstrated infection is restrictive and cannot be used to guide antifungal initiation in clinical practice.[19–21,23,34] Thus, early empirical treatment currently relies on the positive predictive value of risk assessment strategies, such as (1) colonization index, (2) candida score, and (3) predictive rules.[19,21,23,30,51–54] These risk-based strategies share common characteristics: first, they are based on combinations of several risk factors, such as candida colonization, previous use of broad-spectrum antibiotics, and previous abdominal surgery; second, their positive predictive values (PPVs) are used for the early prediction of invasive candidiasis; third, their negative predictive values (NPVs) are much higher than their PPVs, for which they were developed (Table II).

Colonization index

The documentation of increasing amounts of *Candida* spp. in semiquantitative cultures from multiple sites predicts the subsequent development of invasive candidiasis.[1] The evaluation of colonization dynamics by periodic colonization index calculation accurately predicted the development of invasive candidiasis.[33,35,36] In a prospective cohort study of critically ill surgical patients, Pittet *et al.* assessed the degree of colonization by daily colonization index defined as the ratio of the number of distinct non-blood body sites colonized by *Candida* spp. to the total number of body sites cultured.[30] Only strains of *Candida* spp. with the same genetic identity were considered.[29] Eleven of 29 heavily colonized patients developed invasive candidiasis, which was independently predicted by the degree of colonization. Average candida colonization indices in colonized and infected patients were 0.47 and 0.7, respectively ($P < 0.01$). Furthermore, a colonization index threshold of ≥0.5 enabled the identification of all infected patients on average six days before the diagnosis of infection.

A recent review on candida colonization index showed that it has been successfully used to characterize colonization dynamics, to assess the significance of candiduria, and to evaluate the impact of antifungal prophylaxis.[23] Despite limited bedside practicability, we concluded that the colonization index remains an important surrogate of the dynamics of colonization, which increases early in patients who develop invasive candidiasis.

Candida score

The candida score is a development of the colonization index.[51] In a prospective cohort study of 1699 patients staying more than seven days in the ICU, Leon *et al.* found that surgery [odds ratio (OR): 2.71; 95% confidence interval (CI): 1.45–5.06], multifocal colonization (OR: 3.04; 95% CI: 1.45–6.39), total parenteral nutrition (OR: 2.48; 95% CI: 1.16–5.31), and severe sepsis (OR: 7.68; 95% CI: 4.14–14.22) predicted invasive candidiasis. When one point was attributed to each risk factor (but two for severe sepsis) and a cut-off value of 2.5 was used, the candida score showed 81% sensitivity and 74% specificity. We and others showed that the accuracy of a candida score ≥3 was greater than that of a colonization index ≥0.5.[40,58,59] The usefulness of this score in ruling out the risk of invasive candidiasis has also been demonstrated.[58] In a multicentre cohort of 1007 patients staying more than seven days in ICU, only 13/565 (2.3%) patients with candida scores <3 developed candidiasis, corresponding to an NPV of 98%. However, the usefulness of the candida score to guide empirical antifungal treatment has not been tested in prospective clinical studies.

Predictive rules

Up to five risk factors associated with invasive candidiasis in retrospective analyses of cohorts of critically ill patients were combined to develop predictive rules for the early identification of critically ill patients at high risk of developing invasive candidiasis.[21] Despite progressive improvement in the accuracy of these rules, three industry-sponsored studies failed to demonstrate their clinical usefulness in guiding the early initiation of empirical antifungal treatment in critically ill patients. A predictive rule was used in a multicentre, randomized, double-blind, placebo-controlled trial comparing caspofungin with placebo as antifungal prophylaxis in 222 critically ill patients with ICU stays of three or more days who were ventilated, received antibiotics, had a central line catheter, and had one of the following additional risk factors: parenteral nutrition, dialysis, surgery, pancreatitis, systemic steroids, or other immunosuppressants.[60] The incidence of

Table II
Accuracy of risk prediction models for invasive candidiasis in critically ill patients[a]

Reference	Population, IC	Risk-based prediction model	Accuracy of prediction
Pittet *et al.*[30]	29 patients heavily colonized with *Candida* spp. (11 developed IC)	Colonization index: threshold = 0.5	PPV = 66% NPV = 100%
Paphitou *et al.*[52]	327 ICU patients staying ≥4 days [23 (11%) developed IC]	Predictive rule – one of the following: diabetes, total parenteral nutrition, prior ICU stay, new onset haemodialysis, on broad-spectrum antibiotics	Captured 52% of IC Sensitivity = 83% Specificity = 50% PPV = 11% NPV = 98%
Leon *et al.*[51]	1669 patients [97 (6%) with IC] staying ≥7 days in 73 mixed Spanish ICUs	Candida score – to predict IC, sum of: severe sepsis (2 points), surgery (1), total parenteral nutrition (1), multifocal candida colonization (1). Threshold = 2.5 points.	Captured 81% of IC Sensitivity = 81% Specificity = 74% PPV = 16% NPV = 98%
Ostrosky-Zeichner *et al.*[53]	2890 patients [88 (3%) with proven or probable IC] staying ≥4 days in nine US/Brazilian ICUs	Predictive rule – both systemic antibiotics and central venous catheter (day 1–3 of ICU stay); plus two of total parenteral nutrition (day 1–3 of ICU stay), dialysis (day 1–3 of ICU stay), major surgery (day −7 to 0 of ICU stay), pancreatitis (day −7 to 0 of ICU stay), steroids (day −7 to 3 of ICU stay), other immunosuppressive agents (day −7 to 0 of ICU stay)	Captured 34% of IC Sensitivity = 34% Specificity = 90% PPV = 10% NPV = 97%
Ostrosky-Zeichner *et al.*[54]	649 patients from mixed ICUs [12 (1.8%) developed IC]. Risk factors as above combined with the presence of *Candida* in specimens routinely collected	Predictive rule: all of: mechanical ventilation, broad-spectrum antibiotics and central venous catheter (day 1–3 of ICU stay); plus one of: total parenteral nutrition (day 1–3 of ICU stay), dialysis (day 1–3 of ICU stay), major surgery (day −7 to 0 of ICU stay), pancreatitis (day −7 to 0 of ICU stay), steroids (day −7 to 3 of ICU stay), other immunosuppressive agents (day −7 to 0 of ICU stay) plus presence of *Candida* spp. in any clinical specimen	Captured 66% of IC Sensitivity = 66% Specificity = 87% PPV = 9% NPV = 99%
Charles *et al.*[55]	136 ICU patients without bacterial infection staying ≥7 days in 36 mixed ICUs [20 (15%) developed IC]	Candida score ≥3 points at day 7 [sum of: severe sepsis (2 points), surgery (1), total parenteral nutrition (1), multifocal candida colonization (1)] plus procalcitonin ≥0.3 ng/mL	Captured 80% of IC Sensitivity = 80% Specificity = 74% PPV = 59% NPV = 89%
Ostrosky-Zeichner *et al.*[56]	597 ICU patients [22 (4%) with proven or probable IC] staying ≥4 days in six US ICUs	Predictive rule: all of: mechanical ventilation, broad-spectrum antibiotics and central venous catheter (day 1–3 of ICU stay); plus one of: total parenteral nutrition (day 1–3 of ICU stay), dialysis (day 1–3 of ICU stay), major surgery (day −7 to 0 of ICU stay), pancreatitis (day −7 to 0 of ICU stay), steroids (day −7 to 3), other immunosuppressive agents (day −7 to 0 of ICU stay)	Captured 90% of IC Sensitivity = 90% Specificity = 48% PPV = 6% NPV = 99%
Hermsen *et al.*[57]	Matched case of IC (88) vs control (352) study	Predictive rule (Nebraska Medical Center rule) all of: broad-spectrum antibiotics and central venous catheter and total parenteral nutrition and steroids and abdominal surgery (day 1–3 of ICU stay)	Captured 85% of IC Sensitivity = 84% Specificity = 60% PPV = 5% NPV = 99%

IC, invasive candidiasis; ICU, intensive care unit; PPV, positive predictive value; NPV, negative predictive value.
[a] Adapted from Eggimann and Ostrosky-Zeichner.[21]

invasive candidiasis was 16.7% (14/84) in patients receiving placebo and 9.8% (10/102) in patients receiving caspofungin ($P = 0.14$). Treatment safety, length of stay, antifungal use, and mortality did not differ between groups. The authors concluded that caspofungin prophylaxis was safe, with a non-significant tendency to reduce invasive candidiasis. Two currently unpublished studies demonstrated no clinical usefulness of predictive rules based on clinical factors in guiding empirical antifungal treatment. The first, entitled 'Pilot feasibility study with patients who are at high risk for developing invasive candidiasis in a critical care setting' (ClinicalTrials.gov identifier: NCT01045798), was terminated due to a low recruitment rate after the inclusion of only 15 patients. The second study, entitled 'An exploratory study to compare the efficacy and safety of micafungin as a pre-emptive treatment of invasive candidiasis versus placebo in high risk surgical subjects — a multicentre, randomized, double-blind study' (ClinicalTrials.gov identifier: NCT01122368), included only surgical critically ill patients. Preliminary results showed a high proportion of invasive candidiasis cases at study entry. The overall rate of infection did not differ between patients receiving pre-emptive antifungal treatment (11.1%) and those receiving placebo (8.9%), but the number of patients excluded from the analysis resulted in insufficient statistical power.[61]

These three studies strongly suggest that despite better positive predictive value than colonization index and candida score, predictive rules may not be feasible at the bedside.

The clinical paradox arising from the use of risk-based strategies

The laborious nature of the clinical use and the limited availability of solid clinical data explain the low level of evidence attributed by experts to these risk-based strategies in consensus guidelines. Nevertheless, they are widely used at bedside and have succeeded in decreasing the incidence of invasive candidiasis.[14,17,18,25,62] This picture reflects opposing strategies: clinicians concerned by the worse prognosis of delayed treatment start antifungals early, even in low-risk patients; whereas experts, more concerned by the negative ecological impact and cost of antifungals, recommend delayed prescription, which risks failing to identify patients requiring early treatment.

New insight into risk-based strategies

We have emphasized that these diagnostic risk-based strategies result in the following paradigm: the most sensitive method (colonization index) increases the number of patients receiving useless treatment, whereas the most specific method (predictive rules) increases the number of patients not receiving early antifungals and developing invasive candidiasis.[7,21,23] Objective analysis of the accuracy of the risk-based strategies shows that the NPVs of these strategies are much higher than their PPVs, for which they were developed (Table II).[30,51–54,56] Among them, only the NPV of the candida

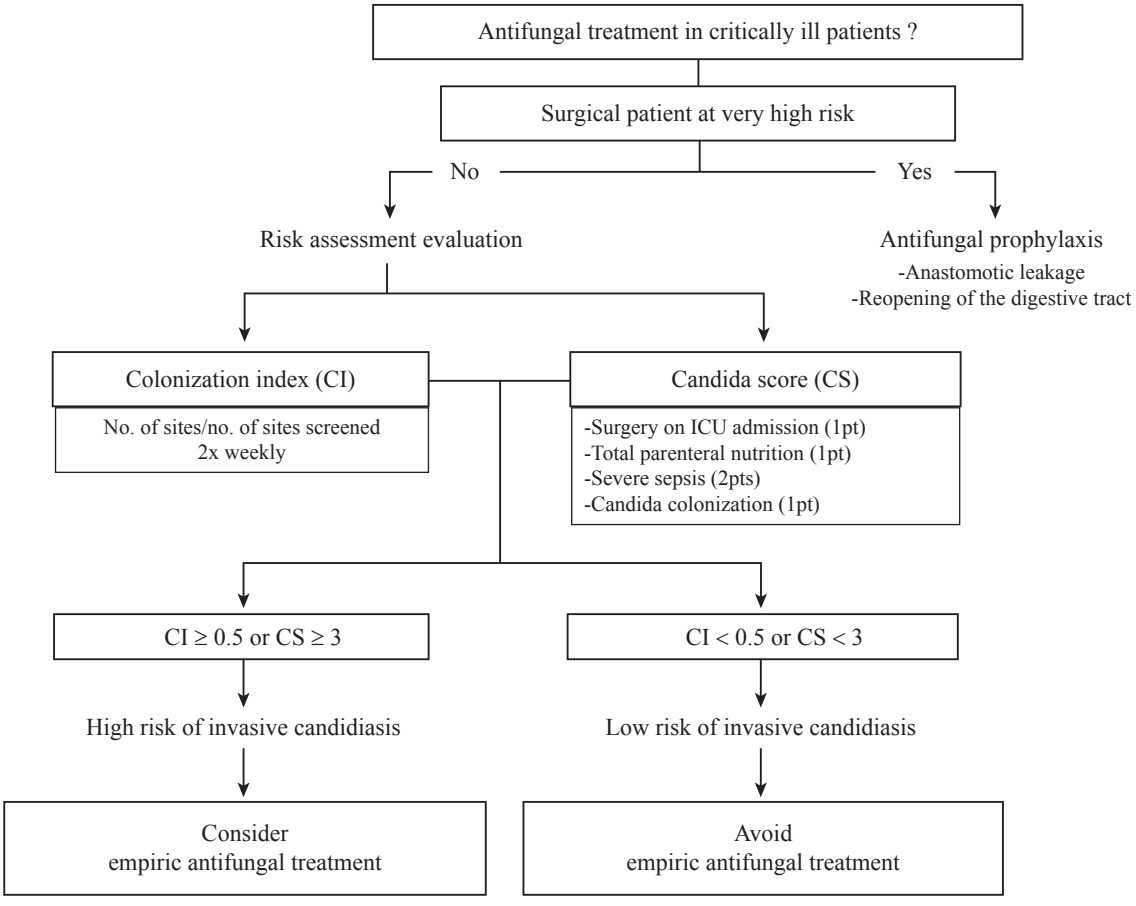

Figure 1. Risk assessment strategies for antifungal treatment.

score has been validated in a multicentre prospective clinical trial.[55]

A practical approach for antifungal treatment in critically ill patients

In patients perceived to be at risk of invasive candidiasis, we propose to evaluate the appropriateness of early empirical antifungal treatment by using both the PPVs and NPVs of the risk assessment strategies (Figure 1). We suggest restricting antifungal prophylaxis to surgical patients presenting with anastomotic leakage after abdominal surgery or reopening of the digestive tract during the same hospitalization to prevent the development of invasive candidiasis.[18,38,39] For patients in whom invasive candidiasis is suspected, early empirical antifungal treatment should be considered when the candida score is ≥ 3. In these cases, a colonization index calculated using the available microbiological data of ≥ 0.5 strengthens the evidence of a very high risk of invasive candidiasis. Early empirical antifungal treatment should not be started in patients identified to be at low risk by a candida score <3. In these situations, a colonization index calculated using the available microbiological data of <0.5 strengthens the case for avoiding empirical antifungal treatment; further exposure or additional risk factors are required for the development of invasive candidiasis, and these will be captured by an increase in candida score or colonization index.

Conflict of interest statement

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