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EDITORIAL

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Intra-abdominal candidiasis: the guidelines—forgotten non-candidemic invasive candidiasis

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Invited editorial to comment on: A research agenda on the management of intra-abdominal candidiasis: results from a consensus of experts of the Italian Society of Intensive Care (SITI) and the International Society of Chemotherapy (ISC).

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Several consensus and guidelines recently updated their recommendations for the management of *Candida* infection. Interestingly, neither the Infectious Diseases Society of America (IDSA) guidelines [1] nor the European consensus [2] gave any clarification on the issues raised by *Candida* peritonitis, while epidemiological data over the last decades have shown that non-candidemic invasive candidiasis, mostly peritonitis, is a frequent and life-threatening complication in surgical critically ill patients [3–5].

In their article published in the current issue of *Intensive Care Medicine*, Bassetti et al. [6] propose specific recommendations from a consensus of experts. This laudable attempt is a first and welcome step but, as expected, it also highlights the moderate or low quality of evidence in many fields. Patients who test positive for fungal infection during the course of intra-abdominal infections share many similarities with those infected with other forms of invasive candidiasis [3–5, 7, 8]. These features are a source of confusion to many physicians, leading to a reductive assimilation of the peritonitis cases with those of other forms of invasive candidiasis and candidemia, and this approach may unfortunately be responsible for a large overuse of antifungals [1, 2].

Candida peritonitis cases have a number of important specific characteristics that deserve a specific treatment approach and specific management (Fig. 1).

The first of these is the pathophysiology of peritoneal contamination. The common issues of risk factors, progressive colonization, and invasion do not matter when a perforation of the hollow viscus releases *Candida* cells contained in the bowel flora within the peritoneum. These are typical cases of community-acquired peritonitis where surgical management, including cleaning of the abdominal cavity and a short antibiotic course, will result in a rapid complete recovery. In these cases, microbiological cultures are not recommended [9], except for patients with septic shock and multiple organ failure, the isolation of *Candida* does not reflect *Candida* peritonitis, and additional antifungals should be avoided [3, 5, 10]. This situation contrasts with recurrent peritonitis, such as anastomotic leakage, in which the process described for invasive candidiasis might be more significant and for which there is some evidence for the benefits of early empirical antifungal treatment [11, 12]. The difficult cases, such as patients who underwent a first re-operation for postoperative peritonitis, fall in

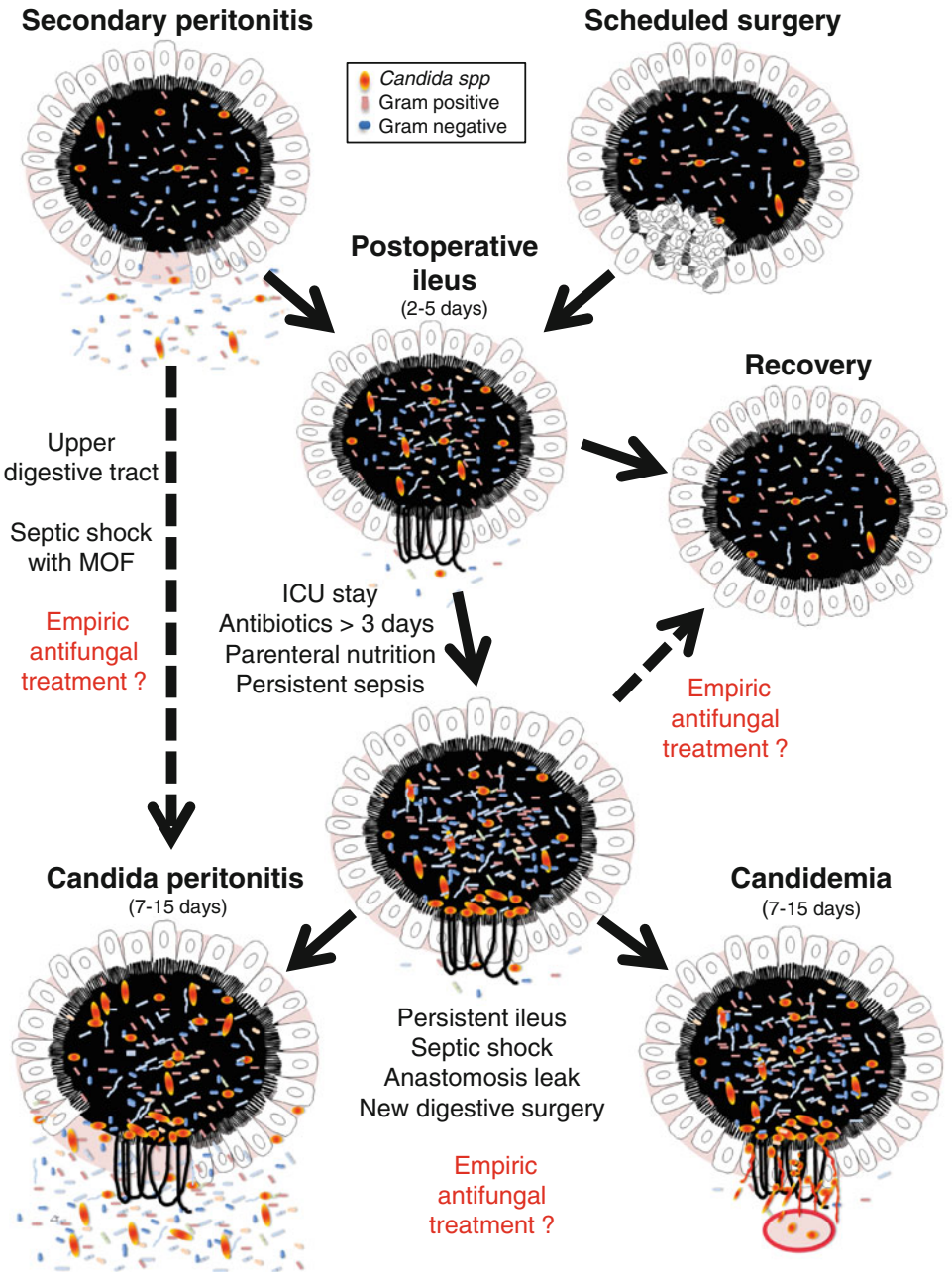

Fig. 1 Specific characteristics of *Candida* peritonitis. Secondary perforation of the hollow viscus releases *Candida* cells within the peritoneum. Except for patients with septic shock and multiple organ failure, antifungals are not recommended in this setting. In recurrent peritonitis, such as anastomotic leakage, invasive candidiasis might be more significant, and early empirical antifungal treatment might be beneficial. Intermediate between these situations, such as patients who underwent a first re-operation for postoperative peritonitis, the prediction of *Candida* peritonitis is challenging, and an emergency antifungal treatment is not a validated approach. *ICU* Intensive Care Unit

between these two sketched situations and represent situations where the prediction of *Candida* peritonitis is challenging.

The second specific characteristic of *Candida* peritonitis is that additional circumstances have been reported where *Candida* cells emerge progressively, influenced through combined exposure to well-known risk factors, such as broad-spectrum antibiotic pressure, previous abdominal surgery, parenteral nutrition, renal replacement therapy, central venous catheter, among others. In these "at high risk" cases, the issue is no longer "do we need" to treat these cases but rather "when" should we initiate the antifungal treatment. In these circumstances, infection will not develop within hours but over days [3, 5, 13], and except for candidemia reported in a minority of the peritonitis cases [4, 5], an emergency antifungal treatment is not a validated approach, as would be the case in the treatment of sepsis of bacterial origin. A large part of the common confusion lies in these different clinical situations, as they complicate the decision-making process of the experts in coming to a consensus regarding the diagnosis and treatment.

To improve readability and prioritization of the long list of recommendations provided by Bassetti et al. [6], we would like to emphasize several points which may help clinicians identify early those surgical patients who truly would benefit from treatment with.

First, we do not have any good tool to determine whether fungi cultured from mixed polymicrobial bacterial and fungal samples should be considered, and the time course of colonization and infection may be unknown compared to the known process of infection that has been well-described in candidemia. For this very reason, specific clinical scores [10], which are not suitable for candidemia, may help the clinician in choosing to initiate antifungal treatment, especially in the most severe patients, while awaiting mycological results. Alternatively, high negative predictive values of clinical scores might help to eliminate yeast infection in community-acquired or nosocomial non-postoperative infections and avoid useless antifungal treatments [14]. However, theses scores remain to be validated in large multicenter cohorts of patients.

Second, there is currently insufficient scientific evidence supporting the reduction of further yeast intra-abdominal infection with prophylaxis or preemptive treatment, even in subgroups of high-risk patients. We are eagerly awaiting the results of the largest randomized trial (INTENSE) that ended in 2012 (NCT01122368) in which micafungin was compared to placebo in 252 high-risk surgical patients (anastomotic leakage or a stay in the ICU for >4 days after abdominal surgery).

Third, commonly used biomarkers are largely inaccurate for the diagnosis of non-candidemic infections (Table 1). C-reactive protein is not specific, and procalcitonin levels rise modestly compared to bacteriological infections [15]. Among the specific fungal biomarkers, PCR can be used to detect candidemia early, but the assay is insensitive for other candidiasis. (1 → 3)-β-D-Glucan (BG), part of the fungal wall, is a useful biomarker for the diagnosis of invasive mycoses in high-risk hemato-oncological patients. In patients who have undergone abdominal surgery, several studies have recently shown that BG has higher positive predictive values than the colonization index and *Candida* scores, with increasing levels 3–5 days before the development of non-candidemic invasive candidiasis correlating well with disease development [16–18]. In addition, the levels of BG have been found to decrease in patients responding to antifungals but to remain high or even increase in cases of treatment failure [18]. However, the eventual clinical impact of its use remains to be determined in specific prospective studies.

Fourth, the importance of organ dysfunction or septic shock in the need to initiate early antifungal treatment remains to be assessed. While evidence supporting early antifungal treatment in the course of candidemia and other form of invasive candidiasis is available, we do not yet know if any delay in providing empirical treatment in these life-threatening cases of community-acquired or nosocomial cases will have negative effects.

Thanks to the contribution of Bassetti et al. [6], we have now to explore which questions need to addressed and identify the most interesting approaches with the aim of improving the diagnosis, initiating and developing an efficient therapy, and preserving the efficacy of the anti-

Table 1 Limitations of current clinical/biological tools in the diagnosis and treatment of intra-abdominal candidiasis

Current clinical/biological tools	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Usefulness to guide empirical antifungal treatment
Clinical risk factors					
Colonization index	Medium high	Medium	++	+++	++ if dynamics is followed
Candida scores	Medium	Medium high	++	+++	++
Predictive rules (+colonization)	Medium	Medium (high)	++	++ (+)	++ (+ if ongoing studies positives)
Biomarkers					
C-reactive protein	Low	Low	+	++	Not useful
Procalcitonin	Low	Medium	+	+++	++ if added to *Candida* score
Mannan/anti-mannan antibodies	Very high	High	++	+++	+++ if dynamics is followed
Beta-D-glucans	Very high	Very high	+++	+++	+++ in high risk patients
Secondary peritonitis					
+*Candida* and nosocomial infection	High	Very high	++	++	++ (but overtreatment)
+*Candida* + upper digestive tract perforation	High	Very high	++	++	++ (but overtreatment)
+Septic shock	High	Very high	++	++	++ (but overtreatment)
Tertiary peritonitis					
Anastomotic leakage	Very high	Very high	+++	+	+++ (>35 % risk of candidiasis)
Repetitive surgery	Very high	Very high	+++	+	+++ (>50 % risk of candidiasis)

Table 2 Unsolved questions in the field of intra-abdominal candidiasis

Field of investigation	Specific points to address	Type of investigation
Pathophysiological role of *Candida* spp isolated from the peritoneum	–Synergisms and antagonisms with bacteria (*Pseudomonas* spp, *Enterococci*, *Staphylococci*…)	In vitro experimental studies
	–Mechanisms of adhesion/invasion of the epithelial intestinal cell	In vivo animal models
	–Role of biofilms	In vivo epidemiological studies
	–Role of host defense mechanisms (innate immunity)	
Distinction between colonization and infection	–Enhanced predictivity of described tools in high risk groups:	Multicenter clinical studies
	–Exclusion of low risk patients by negative predictive value of colonization index, of clinical scores and of predictive rules	
	–Positive predictive value of biomarkers in these patients	
	–Role of fungi isolated from mixed cultures	
	–Time course of colonization and infection	
Prophylaxis and preemptive antifungal treatment	–When, how, to whom, what drug	Clinical studies
	–What dose, for how long time	
Therapeutic challenges	–Comparison of antifungal agents (fungicidal versus fungistatic)	In vivo animal models
	–Effects of combinations of antifungals	
	In different but homogenous clinical settings:	Clinical studies
	–Severe or mild to moderate fungal infection	
	–Community-acquired versus nosocomial/health-care associated infections	
	–Prolonged or persistent fungal peritonitis	
	–Clinical and biological makers of clinical and microbiological response	
	–Optimal duration of treatment	
	–Feasibility and advantages of de-escalation	

fungal agents. A list of some of the issues to be addressed is given in Table 2.

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