Candida peritonitis

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Purpose of review

The review highlights current insights in the epidemiology, diagnosis and therapy of *Candida* peritonitis, focusing on complicated secondary and tertiary peritonitis.

Recent findings

Candida peritonitis is still associated with poor prognosis. Antifungal prophylaxis is therefore recommended in patients with an overt risk profile for invasive candidiasis (immunodeficiency and prior antibiotic exposure). The clinical and microbiological diagnosis of *Candida* peritonitis remains problematic. It is still unclear which peritonitis patients may benefit from antifungal treatment. Antifungal therapy can be suggested in critically ill patients with nosocomial peritonitis where *Candida* is diagnosed based on perioperatively sampled peritoneal fluid. Patients with prior exposure to fluconazole are at risk for *Candida* nonalbicans spp. involvement with possible reduced susceptibility.

Summary

The main challenge in *Candida* peritonitis remains the interpretation of *Candida* cultured from the peritoneal cavity. Future research should focus on more conclusive diagnosis and on factors potentially confounding outcome, such as site of the perforation and failure of surgical source control. While awaiting progress to discriminate *Candida* colonization from invasive infection, antifungal therapy is recommended in high-risk critically ill surgical patients. Rapid detection of *Candida* might be beneficial in this regard. Besides antifungal therapy, adequate source control is of key importance.

Keywords

antifungal, *Candida*, diagnosis, intra-abdominal infection, peritonitis

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Abbreviations

GI gastrointestinal
ICU intensive care unit

1070-5295

Introduction

Candida spp. have become predominant pathogens in critically ill patients, causing a broad spectrum of invasive diseases such as catheter-related candidemia, disseminated candidiasis, endocarditis, thrombophlebitis, osteomyelitis, etc [1]. Most frequently encountered types of invasive candidiasis are candidemia and *Candida* peritonitis. In contrast to candidemia, *Candida* peritonitis is more challenging because of a problematic clinical and microbiological diagnosis. Peritonitis refers to an inflammation of the peritoneal membrane, most frequently following an intra-abdominal infection, resulting in purulent exudate in the peritoneal cavity [2••]. Peritonitis differs from other infections through the broad variety in causes and severity of infection, the often mixed aetiology, the microbiological results that are difficult to interpret and the essential role of surgical intervention. Peritonitis is usually classified based on the cause of the inflammatory process, and is further differentiated into primary, secondary and tertiary peritonitis. In primary peritonitis, no breach in the gastrointestinal (GI) tract is present. Secondary peritonitis is the most frequent form of peritonitis, and is the result of a local infectious process within the abdominal cavity, with or without a hollow viscous perforation, and can lead to diffuse peritonitis. Tertiary peritonitis is an ill-defined entity, and is generally referred to as a persistent or recurrent peritonitis after initial adequate treatment for secondary peritonitis [2••]. The focus of this review is on the latter two forms of *Candida* peritonitis, as these are most frequently diagnosed in critically ill patients, and are most challenging with regard to diagnosis, and may cause multiple organ failure resulting in death.

Epidemiology and risk factors

The incidence of *Candida* involvement in secondary peritonitis strongly varies depending on the type of peritonitis and its source. Some authors have found *Candida* spp. to be the leading or second most frequently isolated pathogen in secondary or tertiary peritonitis [3–5]. In a study of 120 patients with secondary peritonitis, *Candida* spp. were present in only 12% of the cases, ranking seventh [6]. Using a selective yeast medium for the microbiological diagnosis, Sandven *et al.* [7] demonstrated *Candida* involvement in 32 of 81 patients with secondary (nonappendicitis) peritonitis (39.5%). After exclusion of cases with community-acquired peritonitis, this percentage increased to 45%. *Candida* is more frequently isolated in nosocomial peritonitis as typical predisposing risk factors

for *Candida* involvement are immunodeficiency and prolonged exposure to antibiotics [6,8•]. *Candida* is also more frequently seen in upper GI tract perforations in which adequate surgical source control is often more difficult to achieve. One should therefore always take into account the possibility of *Candida* involvement in patients experiencing tertiary peritonitis. In addition, overgrowth of opportunistic pathogens such as *Candida* in these patients is triggered by the exposure to broad-spectrum antibiotics and critical illness-associated immune dysfunction due to prolonged illness and multiple surgical procedures.

Aetiology

In general *C. albicans* is responsible for about 65% of all *Candida* infections in intensive care units (ICUs) [9,10]. During the past decade, *Candida* nonalbicans spp. have emerged as important pathogens in immunosuppressed and ICU patients [11–13]. The most frequently isolated species have been *C. tropicalis*, *C. glabrata* and *C. parapsilosis*. The clinical relevance of this shift is that some *Candida* nonalbicans spp., particularly *C. glabrata* are less susceptible or dose-dependent susceptible to fluconazole. *C. krusei* is intrinsically resistant but an increase in infections with this species has not been reported yet.

In secondary and tertiary peritonitis, *C. albicans* remains the most frequent fungal pathogen. In patients with recent exposure to fluconazole, however, a high suspicion for *Candida* nonalbicans spp. is warranted because this seems to select for less susceptible strains [11,14•]. On the other hand, local high volume fluconazole consumption could not be linked with shifts in candidal ecology on a hospital scale [14•].

Clinical significance of *Candida* isolation from the peritoneum: the ongoing controversy

In critically ill patients with secondary or tertiary peritonitis, the significance of *Candida* isolation is controversial [15••]. Some studies have found *Candida* spp. to have only a limited significance [16,17], while others found it quite germane [18,19]. Only in cases with perioperatively documented *Candida* plaques on the peritoneum, or on histology, can a definite diagnosis of *Candida* peritonitis be made. Performing direct examination of peritoneal fluid may be of some value as results are rapidly available and the detection of *Candida* is associated with worse outcome within a group of patients with *Candida* peritonitis [20]. The value of a direct examination positive for *Candida* in a general population with peritonitis remains uncertain. In addition, microbiological cultures are not straightforward as these do not distinguish contaminants from true causative pathogens. In cases where perioperative cultures could be sampled from an intra-abdominal abscess, the relevance of *Candida* isolation is higher. Diagnosis should preferably be based on perioperative sampled fluid or tissue. *Candida* positive samples taken via drains days after surgery should be interpreted with caution. In addition, it is unclear to what extent the use of a selective yeast medium results in more – but probably less significant – *Candida* isolation.

New diagnostic methods aiming for a more rapid identification of *Candida* spp. from peritoneal samples have been developed. By using Raman spectroscopy, the diagnosis of *Candida* involvement is possible within a 12–24-h timeframe [21]. This approach, however, does not distinguish between *Candida* colonization and invasive infection. In an experimental model (1→3) β-D-glucan proved to be valuable for differentiating *Candida* colonization from infection in mice with GI infection [22], but to the best of our knowledge, no important human data are yet available.

Apart from the problems with interpretation of microbiological results, several issues regarding *Candida* in peritonitis have been inadequately addressed, thereby hampering a straightforward clinical appraisal. First, as far as we know, the impact of failure of source control in *Candida* peritonitis has not been explored. *Candida* isolated following upper GI tract perforation is often considered as clinically relevant because of the high associated mortality. The high mortality associated with upper GI tract perforations may however be due to the problematic source control in contrast with lower GI tract perforation, where exteriorization of the intestine is an option [23]. Upper GI tract perforations are often difficult to control, and most probably therefore associated with high fatality rates. A second unclear issue is the duration between perforation and the index source control procedure. For bacterial peritonitis, a 12-h and 24-h delay is considered necessary to have an established intra-abdominal infection in case of lower and upper GI tract perforation respectively. If patients are operated within these timeframes, antibiotic treatment longer than 24 h is not recommended. Such data, however, are not available from reports on patients with *Candida* peritonitis. A third unresolved issue is that most studies do not differentiate patients with secondary from tertiary peritonitis. In tertiary peritonitis, *Candida* is frequently isolated [24], but its relevance can be questioned. The creation of fistulas, which often contaminate the peritoneum to some extent, and the use of open abdomen techniques make it even more difficult to discern between colonization and infection.

Furthermore, the type of patients in whom *Candida* is isolated seems to affect the relevance. With the exception of immunocompromised patients, the significance of *Candida* isolation in community-acquired peritonitis can

be doubted. Mortality in patients with community-acquired peritonitis with *Candida* involvement was similar to mortality in matched controls without *Candida* involvement (19% vs. 24% respectively) [25••]. In addition, the clinical relevance of *Candida* isolates in ICU patients is not straightforward. Intuitively one ought to believe that *Candida* isolated from the peritoneum in ICU patients is clinically relevant because of the debilitated state of the patients and the high associated fatality rates (cf. infra). Studies exploring the effect of *Candida* involvement on survival in peritonitis, however, have failed to adjust for major (multiple) organ failure, the utmost confounding factor [26]. As long as the abovementioned aspects of peritonitis are not clarified, the relevance of isolation from the peritoneal cavity will remain a point of controversy.

Impact of *Candida* peritonitis

Candida peritonitis in critically ill surgical patients carries a very poor prognosis. Mortality rates between 52% and 75% are described [19,27,28]. In a series of 271 patients with peritonitis, Dupont *et al.* [20] investigated outcome and risk factors for mortality in patients with *Candida* peritonitis. Mortality in patients without *Candida* involvement was 41%, while in the 83 patients with *Candida* peritonitis, ICU mortality was 52%. In this subset of patients, the following independent predictors for death were identified: an APACHE II score of $\geq$17, respiratory failure on admission, an upper GI tract site of peritonitis, and results of direct examination of peritoneal fluid that were positive for *Candida*.

In a multicentre matched cohort study, Montravers *et al.* [25••] compared 91 patients with *Candida* isolated from the peritoneal cavity with 168 matched control subjects. Patients eligible for study inclusion were those operated for peritonitis with focus on complex problems such as perforation, bowel necrosis and anastomotic leakages. Cases were matched for nosocomial or community-acquired peritonitis, severity of disease (simplified acute physiology II score), age and year of hospitalization. Upper or lower GI tract source of peritonitis was not however considered as a matching criterion, notwithstanding the fact that source control is more difficult to achieve in upper GI tract perforations. In nosocomial peritonitis, mortality was significantly higher among patients with *Candida* peritonitis (48% vs. 28%; $P < 0.05$). Additionally, *Candida* peritonitis was identified as an independent predictor of mortality, after adjustment for major confounders such as source of peritonitis and inappropriate empiric antimicrobial therapy, but not for failure of source control, which is well known as a major factor contributing to unfavourable outcomes. Analogously with the study from Dupont *et al.* [20], an upper GI tract site of peritonitis was independently associated with increased mortality.

Therapy

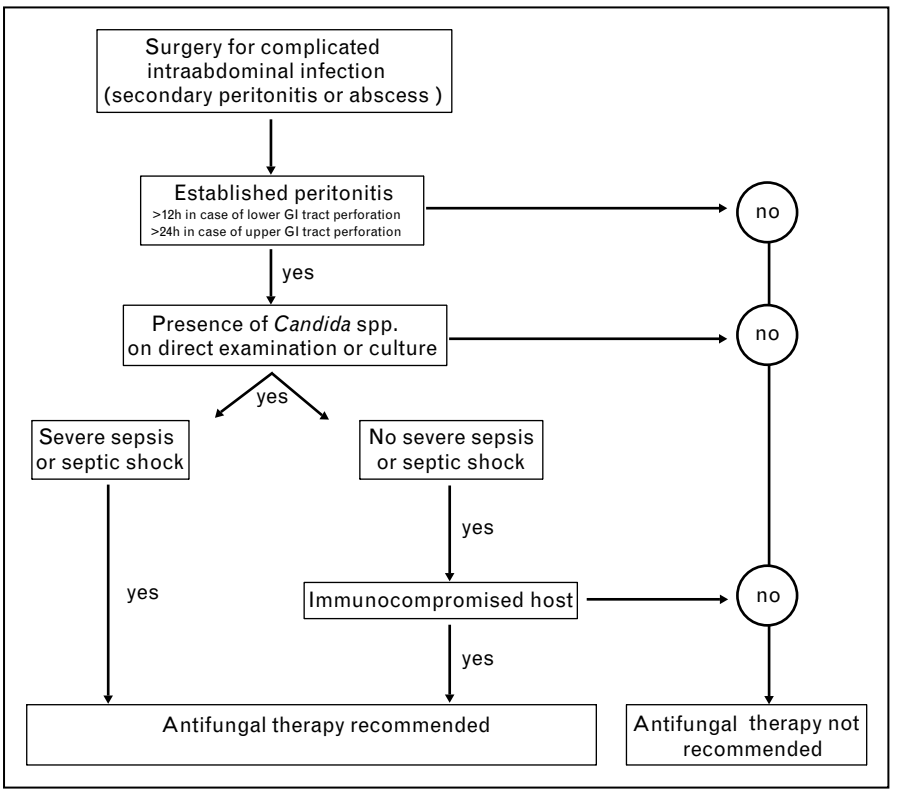
The data from Montravers *et al.* [25••] suggest that *Candida* isolation should not be disregarded. Unfortunately, on the issue of antifungal therapy, the study remains elusive. No beneficial effect of antifungal therapy could be demonstrated. Given the high general disease severity (mortality in the control group was 28%) it can be assumed that the study was underpowered to detect a difference in attributable mortality between cases with and without adequate antifungal coverage. In addition, in patients with abdominal sepsis, outcome might be strongly associated with the severity of the inflammation triggered by the peritoneal irritation. Nevertheless, the available data [18,19,25••] suggest that *Candida* should be treated when isolated in cases of severe or persistent peritoneal infection even though it can only affect a portion of the inflammatory process. Indeed, in patients with candidemia, delayed antifungal therapy has been demonstrated to have a deleterious effect on outcome [29•,30]. Figure 1 demonstrates an algorithm that can be used as a guideline to distinguish those patients who might benefit from antifungal therapy from those unlikely to benefit.

Early antifungal therapy

Antifungal prophylaxis is indicated in patients with an overt risk profile for *Candida* peritonitis because of the problematic diagnosis and the high fatality rates in case of *Candida* involvement [1]. Antifungal prophylaxis with fluconazole has been demonstrated to reduce *Candida* infections in patients with a pronounced high-risk profile for invasive intra-abdominal candidiasis [1,31,32]. In a placebo-controlled trial, it was shown that prophylaxis with fluconazole significantly reduced the risk for intra-abdominal candidiasis in high-risk surgical patients with recurrent GI perforations and anastomotic leakages [32]. Observational data from patients operated for acute necrotizing pancreatitis also suggest the beneficial effect of prophylaxis with fluconazole [31]. Although evidence is lacking for other indications, the findings of these studies are often generalized to other patients with complicated intra-abdominal conditions due to the favourable safety profile of fluconazole. Routine treatment of patients with *Candida* spp. isolated following rapid and uncomplicated repair of an intra-abdominal perforation is however not recommended if they are otherwise healthy and without clinical signs of sepsis [1,17,33].

Dupont *et al.* [34] identified four independent risk factors of yeast isolation in the peritoneal fluid in critically ill patients: female gender, an upper GI tract origin of the peritonitis, intraoperative cardiovascular failure, and previous antimicrobial therapy at least 48 h prior to the onset of peritonitis. The presence of at least three of these factors was associated with a high rate of yeast detection. This approach, although not validated, might be helpful to initiate early antifungal therapy in critically ill patients.

Figure 1 Algorithm to identify patients with secondary peritonitis that might benefit from antifungal therapy



Definite therapy

In secondary peritonitis, surgical source control is essential in the treatment of *Candida* peritonitis. Antifungal therapy should support surgical intervention and must be initiated immediately after the diagnosis of *Candida* peritonitis. Fluconazole is the drug of choice for most patients as it is effective and well tolerated. The typical dosage of fluconazole for invasive candidiasis is a loading dose of 12 mg/kg (~800 mg/day) followed by 6 mg/kg/day (~400 mg/day). Dosages as high as 1200–1600 mg/day can be tolerated because of the drug's favourable safety profile. In patients with a creatinine clearance of 11–50 ml/min, a 50% dosage reduction is recommended. While awaiting yeast identification, broad-spectrum antifungals, such as caspofungin or voriconazole, are recommended in patients with prior exposure to fluconazole. In case of dose-dependent susceptibility or intrinsic resistance to fluconazole, more broad-spectrum azoles (e.g. voriconazole), echinocandins (e.g. caspofungin, micafungin), or amphotericin B (either conventional or lipid-associated) can be used. We advocate the use of azoles and echinocandins because of their more favourable safety profile. The use of voriconazole requires a loading dose of 6 mg/kg twice daily and a maintenance dose of 4 mg/kg/day. Caspofungin requires a loading dose of 70 mg/day and a maintenance dose of 50 mg/day. Although hepatic failure is not considered as a contraindication, a dosage reduction in case of hepatic insufficiency is needed for voriconazole and caspofungin. Renal insufficiency also necessitates a dosage reduction for voriconazole. Micafungin is a new echinocandin that is as effective as caspofungin for invasive candidiasis [35]. For invasive candidiasis, a daily dose of 100 mg is recommended. No dosage adjustments are necessary in case of renal or hepatic insufficiency. In the light of these newer and well tolerated broad-spectrum antifungals, we can no longer recommend amphotericin B – either conventional or lipid-associated – because of the associated renal toxicity or transfusion-related reactions. Intraperitoneal amphotericin B is not recommended as it may cause chemical peritonitis. Antifungal therapy should last for about 2–3 weeks. Once the GI tract is functional, a switch to oral antifungals can be considered (fluconazole or voriconazole in case of *Candida* spp. with reduced susceptibility).

Conclusion

The clinical and microbiological diagnosis of *Candida* peritonitis is problematic and the effect of several potential confounders remains unexplored. Despite recent information, whether or not *Candida* isolated from the peritoneal cavity is of clinical significance remains

controversial. In case of intraoperative isolation of *Candida* in critically ill patients, antifungal therapy is warranted. Direct examination and prompt reporting of *Candida* isolation can therefore be recommended. Fluconazole is the drug of choice. In patients with prior exposure to fluconazole, empiric therapy should consist of an agent with a broader antifungal spectrum. Therapy should be continued for 2–3 weeks. Besides this, adequate surgical source control is of key importance.

References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 240–241).

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