The Role of *Candida* in Abdominal Sepsis

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19.1 Introduction

Candida is frequently isolated on microbiologic samples from patients with abdominal sepsis. A very large number of studies have been published on candidemia, but only limited data are available concerning abdominal sepsis. The management of patients with *Candida* peritonitis is largely extrapolated from that proposed for candidemia. In addition, many definitions have been proposed for *Candida* peritonitis, reflecting the variety of clinical circumstances in which *Candida* spp. are reported. The broad definition proposed by Bassetti et al. takes into account the specificities of *Candida* in abdominal sepsis (Table 19.1) [2].

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M. Sartelli et al. (eds.), *Abdominal Sepsis*, Hot Topics in Acute Care Surgery and Trauma, https://doi.org/10.1007/978-3-319-59704-1_19

Table 19.1 Circumstances in which detection of *Candida* is defined as an episode of invasive abdominal candidiasis

Candida detection by direct microscopy examination
Candida growth in culture from purulent or necrotic intra-abdominal specimens obtained during surgery or by percutaneous aspiration
Candida growth from bile, intra-biliary duct devices
Candida growth from biopsy of intra-abdominal organs
Candida growth from blood cultures in a clinical setting of secondary and tertiary peritonitis in the absence of any other pathogen
Candida growth from drainage tubes only if placed less than 24 h before cultures

Adapted from Bassetti et al. [1]

19.2 What Is the Impact of *Candida* in Intra-abdominal Infections

19.2.1 Circumstances of *Candida* Isolation in Intra-abdominal Infections

The pathogenicity of *Candida* spp. in intra-abdominal infections is a controversial issue due to the diverse effects observed when *Candida* spp. are involved. *Candida albicans* and *C. glabrata* are saprophytic hosts of the digestive tract in healthy subjects and are reported in 23 up to 76% of the population, in low concentrations (between 10^2 and 10^4 CFU/mL or g depending on the site) throughout the digestive tract [3]. In animal models of infection, the pathogenicity of *Candida* is only reported at high concentrations and in mixed bacterial and fungal infections [4]. In typical cases of community-acquired peritonitis, perforation of a hollow viscus releases these *Candida* cells present in the gut flora into the peritoneum, consequently raising the issue of whether these organisms need to be taken into account in management.

In other circumstances, such as recurrent or tertiary peritonitis, *Candida* colonization emerges progressively. Infection usually develops over several days in a limited number of colonized cases, but the mechanisms of transition from colonization to invasive intra-abdominal candidiasis remain unclear. Broad-spectrum antibiotic agents obviously play a key role in enhancing *Candida* colonization of mucosal surfaces, but many other risk factors have also been described [2] (Table 19.2). The most common source of confusion concerns difficult cases, such as patients undergoing a first reoperation for postoperative peritonitis, in which the process described for invasive candidiasis might be less significant than in recurrent peritonitis and for which the evidence in favor of the benefits of early empiric antifungal treatment remains debated.

Table 19.2 Risk factors for intra-abdominal candidiasis

Surgery-related risk factors
– Recurrent abdominal surgery (open and laparoscopic procedures)
– Recurrent gastrointestinal perforation
– Gastrointestinal anastomosis leakage
Multifocal colonization by *Candida* spp.
Nonspecific risk factors
– Acute renal failure
– Central venous catheter placement
– Total parenteral nutrition
– ICU stay
– Severity of sepsis
– Diabetes
– Immunosuppression
– Prolonged broad-spectrum antibacterial therapy

Adapted from Bassetti et al. [1]

19.2.2 Types of *Candida* Involved in Intra-Abdominal Infections

Due to their presence in the normal gut flora, *C. albicans* is the most common causative yeast, and *C. glabrata* is the leading *Candida* non-*albicans* pathogen in intra-abdominal infections [1, 5–9]. Other *Candida* species are reported in small numbers of cases. De Ruiter et al. reported up to 41% of positive cultures of abdominal fluid yielding *Candida* obtained from gastroduodenal injuries compared to 8.7% in biliary tract and 11.8% in colorectal perforations [10]. These authors observed the same trends when comparing community-acquired and postoperative infections. High proportions of *Candida* have been reported in some specific subpopulations, such as patients with postoperative peritonitis following bariatric surgery [11, 12], more commonly in late-onset peritonitis and often associated with multidrug-resistant bacteria [12]. The frequency of *Candida* spp. in persistent and tertiary peritonitis remains stable over time and reaches proportions ranging between 40% and 50% of isolates during repeated surgery [10, 13].

19.2.3 Role of *Candida* in the Prognosis of Intra-abdominal Infections

The pathogenic role of *Candida* has been debated for decades, but many reports suggest a potential pathogenic role of *Candida*. Candidemia during intra-abdominal infection is a factor of poor prognosis, although positive blood cultures are rare in most series, ranging between 6% and 15% of patients [14, 15]. In a cohort of patients with candidemia, an intra-abdominal source was associated with an increased risk

of death (OR = 8.15; 95% CI, 1.75–37.93; $p = 0.008$) compared to other sources of sepsis [16]. In addition, the detection of *Candida* on direct examination of peritoneal fluid, indicating a heavy fungal inoculum, is associated with an increased mortality rate (OR = 4.7; 95% CI, 1.2–19.7; $p = 0.002$) [6]. However, this analysis is not systematically performed in routine clinical practice.

Septic shock complicating intra-abdominal candidiasis is also associated with high mortality rates. In a large international observational study comprising 481 patients with intra-abdominal candidiasis, the risk factors for death identified on multivariate analysis were age, high APACHE II score, secondary peritonitis, septic shock, and absence of adequate abdominal source control [1]. In these patients with septic shock, absence of source control was correlated with mortality rates higher than 60% irrespective of administration of adequate antifungal therapy. Similarly, in a prospective observational study involving 180 patients with secondary generalized peritonitis (community acquired and postoperative), septic shock complicating intra-abdominal candidiasis was associated with high mortality rates [17]. In addition, yeasts cultured from peritoneal fluid of patients with postoperative peritonitis were an independent risk factor for death in patients with septic shock.

In healthcare-associated (mainly postoperative) peritonitis, intra-abdominal candidiasis is associated with increased mortality rates. In an observational case-control study, isolation of *Candida* spp. was an independent risk factor for death in nosocomial peritonitis patients [8]. On the contrary, the role of *Candida* spp. in the prognosis of community-acquired infections is difficult to demonstrate. Indirect evidence suggesting the low pathogenicity of *Candida* in this setting is provided by published data suggesting that antifungal treatment is not necessary in patients with community-acquired peritonitis [18–20]. In a multicenter case-control study in intensive care unit (ICU) patients, the mortality rate was not increased in cases of community-acquired peritonitis [8].

19.3 When and How to Treat Intra-abdominal Candidiasis?

19.3.1 Early Recognition of Intra-abdominal Candidiasis

Diagnosing invasive candidiasis is often difficult and often takes several days [21, 22]. Intra-abdominal candidiasis is associated with bacterial co-infection in the majority of cases, complicating analysis of the symptoms related to bacterial and/or fungal infection [1, 14, 15, 23]. In addition, blood cultures have insufficient diagnostic performances [24, 25] and are only reported in small proportions of patients with invasive candidiasis, ranging from 1–3% of cases in a recent study [15] to 28% of patients [23], but usually ranging between 10% and 15% of cases [1, 7, 15]. Clinical and laboratory criteria are not sufficiently relevant to discriminate *Candida* peritonitis from non-microbiologically confirmed suspicion [15]. Antifungal therapy is therefore often initiated empirically, despite the lack of consensus on decision-making criteria [16, 21]. A large proportion of these patients suspected of having *Candida* peritonitis unduly receives empiric antifungal therapy. Overuse

of antifungal therapy has been described in patients suspected of having invasive candidiasis [26] including intra-abdominal infections [15].

19.3.2 Value of Clinical Scores

Several risk factor-based predictive scores have been proposed to improve the early recognition of intra-abdominal candidiasis by clinicians [27–32] (Table 19.3), but the value of these scores remains debated. A major limitation to the use of several scores is the need for fungal mapping [28, 31], which cannot be obtained in emergency patients and/or patients transferred from another institution. These scores have a high

Table 19.3 Criteria used in the clinical scores for prediction of intra-abdominal candidiasis

Pittet [31]	Number of distinct body sites colonized with *Candida* spp. Two sites or more More than two sites Three sites or more *Candida* colonization index *Candida* corrected colonization index
Dupont [27]	Cardiovascular failure Upper gastrointestinal tract origin Female Ongoing antimicrobial therapy
Leon [33]	Multifocal *Candida* species colonization Surgery on ICU admission Severe sepsis Total parenteral nutrition
Ostrosky [29]	Any systemic antibiotic (days 1–3) Or presence of a central venous catheter (days 1–3) And at least two of the following: Total parenteral nutrition (days 1–3) Any dialysis (days 1–3) Any major surgery (days −7–0) Pancreatitis (days −7–0) Any use of steroids (days −7–3) Use of other immunosuppressive agents (days −7–0)
Ostrosky [30]	Mechanically ventilated for at least 48 h Antibacterial antibiotic use (days 1–3) Central venous catheter (days 1–3) At least one of the following: Any surgery (days −7–0) Immunosuppressive use (days −7–0) Pancreatitis (days −7–0) Total parenteral nutrition (days 1–3) Any dialysis (days 1–3) Steroid use (days −7–0)
Dupont [32]	Length of stay ≥48 h before surgery Intraoperative cardiovascular failure Generalized peritonitis Upper gastrointestinal tract perforation

negative predictive value, allowing intra-abdominal candidiasis to be ruled out, while their positive predictive value remains insufficient [34, 35]. In contrast, the efficacy of these scores for the detection of intra-abdominal candidiasis has rarely been assessed in non-selected surgical populations. In a prospective, multicenter, observational study comprising 204 patients receiving antifungal therapy for suspected intra-abdominal candidiasis, the *Candida* and peritonitis scores failed to discriminate patients with *Candida* peritonitis from those without *Candida* infection [15].

19.3.3 Place of Nonspecific Biomarkers

The operative value of biomarkers such as C-reactive protein and procalcitonin has been evaluated in intra-abdominal candidiasis. These tests are more reflective of the inflammatory response to surgical injury than fungal infection. In a prospective cohort of 176 non-neutropenic ICU patients, CRP and PCT assays were performed twice a week [36]. CRP and PCT concentrations could not be used to differentiate patients with invasive candidiasis from those who were neither colonized nor infected, or who presented *Candida* colonization, regardless of sample collection times.

19.3.4 Value of Non-culture-Based Tests

The use of non-culture-based tests has been proposed to help clinicians discriminate cases of colonization from cases of infection and to select patients requiring early antifungal therapy. However, the use of these tests is associated with considerable confusion. Most studies assessing the efficacy of these tests have included mixed cases of candidemia and invasive candidiasis, but few studies have specifically focused on intra-abdominal candidiasis. Evaluation of these tests is rarely performed in real time, and their results are not available during the decision-making process. Despite the potential improvement of clinical management that could be provided by these tests, they are only rarely used in routine clinical practice because of their limited distribution and their high cost when repeated assays are required.

BD-glucan assay has been reported to be useful in ICU patients with complicated abdominal surgery, abdominal leakage, and acute pancreatitis [36, 37]. Various cut-offs for the detection of intra-abdominal candidiasis have been discussed. The sensitivity of BD-glucan assay at a positive cutoff of 80 pg/mL was 76.7% (95% CI, 57.7–90.1), with a specificity of 57.2% (49.9–64.3) and a negative predictive value of 94.1% (89.1–96.8) [38]. In order to improve the accuracy of this parameter, several authors have proposed repeated samples, at least twice weekly [36, 37]. Positive BDG on two consecutive samples had a sensitivity of 76.7% (95% CI 57.7–90.1) and a specificity of 57.2% (95% CI 49.9–64.3) [38].

More recently, there has been a growing interest in *Candida albicans* germ tube antibodies (CAGTA). The sensitivity of CAGTA at a positive cutoff of 1/60 was 53.3% (95% CI, 34.3–71.7) with a specificity of 64.3% (57.2–71.0) and a negative

predictive value of 90.1% (86.0–93.2) [38]. These authors also proposed a combination of two or possibly more than two tests to increase the performance for the detection of intra-abdominal candidiasis. The combination of positive CAGTA and BDG in a single sample or at least one positive biomarker in two consecutive samples improved the performance of the test with a sensitivity of 90.3% (95% CI 74.2–98.0), a specificity of 42.1% (95% CI 35.2–98.8), and a negative predictive value of 96.6% (95% CI 90.5–98.8) [38]. These results have been confirmed in a study of a general population including ICU and non-ICU patients that reported a sensitivity and negative predictive value of the combination of CAGTA and BDG of 97% for the entire population [39]. The best performance was observed in ICU patients with a sensitivity and negative predictive value of 100% [39].

Mannan antigens and anti-mannan antibodies have been rarely evaluated in intra-abdominal candidiasis. The combination of these two tests increases their specificity and sensitivity. However, in a prospective study evaluating 233 non-neutropenic ICU patients, mannan antigens (≥60 pg/mL) and anti-mannan antibodies (≥10 AU/mL), assayed twice a week, demonstrated a low discriminating capacity [38].

The value of polymerase chain reaction (PCR) remains debated because of the major drawbacks of this technique. The absence of any commercially available test and the lack of methodologic standardization and multicenter validation are key issues limiting the interest for this test. Several studies have reported a good correlation between PCR and other tests, such as BD-glucan [24, 40], while other studies have reported a low discriminating capacity [38].

19.3.5 Adequacy of Source Control

Before addressing the issue of antifungal therapy, the fundamental importance of source control must be stressed. Recently, Bassetti et al., in a large cohort of 216 patients with septic shock attributable to *Candida*, demonstrated the critical role of source control in the outcome of these patients [41]. In multivariate analysis, a 2.99-fold increased mortality rate was reported in the case of inadequate source control. The issue of source control is of particular importance in patients with septic shock with mortality rates as high as 60% [1] and has been confirmed in another study with a 77.40-fold (95% CI 21.52–278.38) increased mortality rate [42].

19.3.6 Adequate Timing of Antifungal Therapy

The need for adequate antifungal therapy is the second key point in the anti-infective management of intra-abdominal candidiasis. However, the optimal timing of initiation of antifungal therapy in intra-abdominal candidiasis has been poorly addressed. Over the last decade, several reports have demonstrated that delayed empiric antifungal therapy in patients with candidemia and invasive candidiasis significantly worsened the prognosis and survival of these high-risk cases [42–44]. By extension based on these observations, early initiation of systemic antifungal therapy is

recommended for patients with suspected intra-abdominal candidiasis by experts and the most recent guidelines. However, the deleterious impact of delayed initiation of systemic antifungal therapy has never been formally demonstrated for *Candida* intra-abdominal infection. In a recent prospective observational study in 158 patients with intra-abdominal candidiasis, including patients receiving empiric therapy and patients with documented antifungal therapy, the time to initiation of antifungal therapy ranged between the day of surgery and six or more days after surgery [15]. The time to initiation of antifungal therapy did not appear to influence the outcome in these two groups of patients, except for the less severely ill patients (SOFA score < 7), who displayed an increased mortality in the case of delayed therapy ($p = 0.04$).

This concept of early antibiotic therapy has led to the definition of pre-emptive therapy and empiric therapy [21]. According to the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines, a pre-emptive approach is a diagnosis-driven prescription defined as therapy triggered by microbiological evidence of candidiasis without proof of invasive fungal infection. The empiric approach is a fever-driven prescription in the clinical situation of a patient at risk for invasive candidiasis who is persistently febrile with no microbiological evidence of infection. However, these definitions are a source of confusion in the field of intra-abdominal infections, conditions that differ considerably from the context surgical patients, except possibly for ICU patients with tertiary or recurrent peritonitis. Interestingly, the recently updated Infectious Diseases Society of America (IDSA) guidelines no longer mention pre-emptive therapy [25].

While early antifungal therapy for microbiology-proven infection makes sense, few pre-emptive therapies have been assessed in patients at risk of developing intra-abdominal candidiasis. In an exploratory, randomized, double-blind, placebo-controlled trial, Knitsch et al. evaluated a pre-emptive antifungal approach with micafungin or placebo in intensive care unit patients requiring surgery for intra-abdominal infection [45]. This study was unable to provide any evidence that pre-emptive administration of an echinocandin was effective in preventing intra-abdominal candidiasis in high-risk surgical intensive care unit patients with intra-abdominal infections. Interestingly, patients with positive plasma BD-glucan assay were 3.66 (95% CI, 1.01–13.29) times more likely to have confirmed invasive candidiasis than those with a negative result [45].

19.3.7 Adequate Spectrum of Antifungal Therapy

The adequacy of antifungal therapy is the second major prognostic factor.

Susceptibility to antifungal agents of *Candida* strains cultured from peritonitis is rarely assessed in the literature [1, 6, 8, 15, 18, 23]. Most studies report good susceptibility of *C. albicans* to antifungal agents and decreased susceptibility of

C. glabrata to azoles. Bassetti et al. reported 98% of *Candida* strains susceptible to echinocandins, 89% to fluconazole, and 96% to voriconazole [1]. Sartelli et al. in a large multicenter international study observed 98% of *C. albicans* strains susceptible to fluconazole and 97% of *C.* non-*albicans* strains [9]. These data were confirmed in a recent multicenter study reporting the susceptibility profile of 125 peritoneal isolates: 100% of *Candida* spp. were susceptible to echinocandin and 84% were susceptible to fluconazole, while only 40% of *C. glabrata* strains were susceptible to fluconazole [15].

The EUCAST guidelines consider *C. glabrata* to be resistant to azoles [46]. These organisms are the second most common isolates among surgical isolates, ranging between 12% and 22% of all *Candida* strains [1, 12, 15, 23, 27, 41].

According to the IDSA and ESCMID guidelines, appropriate management of IC includes administration of an appropriate antifungal agent [21, 25]. For suspected invasive candidiasis as well as proven candidemia, IDSA guidelines recommend the use of fluconazole or an echinocandin (caspofungin, micafungin, or anidulafungin) and preferably an echinocandin for critically ill patients or for fluconazole-resistant *Candida* species [25, 47]. Fluconazole is an appropriate choice for treatment when *Candida albicans* is isolated. Finally, amphotericin B is not recommended as initial therapy for toxicity reasons [47], but a lipid formulation should be considered in the presence of intolerance, limited availability, or resistance to other antifungal agents [25]. On the contrary, ESCMID guidelines do not modulate their recommendations according to patient severity, but also recommend the use of echinocandins as first-line therapy [21].

Several guidelines define the profile of patients who should receive empiric antifungal therapy (Table 19.4). Two IDSA guidelines have addressed this issue, the first focusing on the diagnosis and management of complicated intra-abdominal infections [47] and the second corresponding to the 2016 updated guidelines for the management of candidiasis [25]. Interestingly, the ESCMID guidelines do not provide a real picture of the patients requiring treatment for intra-abdominal candidiasis [21]. The recommendations of the consensus of multinational experts differ from the other guidelines by proposing broad criteria for initiation of empiric therapy [2]. The World Society of Emergency Surgery (WSES) more clearly defines immunosuppressed patients [48].

However, these recommendations for intra-abdominal infections are a source of concern, as they are based on a very limited level of proof. No study has ever specifically evaluated the efficacy of antifungal therapy in intra-abdominal candidiasis. In recent randomized trials focusing on antifungal therapy of invasive candidiasis, the proportion of patients with a diagnosis of intra-abdominal candidiasis was extremely low [50–53], and it is impossible to draw any solid conclusions concerning these surgical cases or to recommend any agent based on clinical results. In summary, the extensive use of echinocandins in surgical patients suspected of intra-abdominal candidiasis deserves additional proof.

Table 19.4 Type of patients in whom empiric antifungal therapy is recommended according to recent guidelines

IDSA 2010 [47]	Patients with severe community-acquired or healthcare-associated infection if *Candida* is grown from intra-abdominal cultures
	Not recommended for adult and pediatric patients with mild-to-moderate community-acquired intra-abdominal infection
IDSA 2016 [25]	Patients with clinical evidence of intra-abdominal infection and significant risk factors for candidiasis, including recent abdominal surgery, anastomotic leaks, or necrotizing pancreatitis
WSES [48]	Patients with nosocomial infection and critically ill patients with community-acquired infections Patients with community-acquired intra-abdominal infections recently exposed to broad-spectrum antimicrobials and immunocompromised patients (due to neutropenia, concurrent administration of immunosuppressive agents such as glucocorticosteroid chemotherapeutic agents and immunomodulators)
	Not recommended for patients with community-acquired intra-abdominal infections with no risk factors
Consensus of multinational experts [2]	Patients with a diagnosis of intra-abdominal infection and at least one specific risk factor for *Candida* infection Patients with intra-abdominal infection with or without a specific risk factor for *Candida* infection, empiric antifungal treatment should be administered if a positive mannan/anti-mannan or BDG or PCR test result is present
French consensus [49]	In severe peritonitis (community-acquired or postoperative), in the presence of at least three of the following criteria: hemodynamic failure, female gender, upper gastrointestinal surgery, antibiotic therapy for more than 48 h In healthcare-associated intra-abdominal infection when a yeast is detected on direct examination In all cases of healthcare-associated IAI in which peritoneal fluid culture (apart from closed suction drains and drainage systems, etc.) is positive for yeasts
	Not recommended for patients with community-acquired intra-abdominal infections in the absence of signs of severity

19.3.8 Adequate Dose of Antifungal Therapy

Recent data assessing plasma concentrations of fluconazole and echinocandins have suggested that trough concentrations are highly variable and could be quite low in ICU patients [54, 55]. The peritoneal concentrations of antifungal agents have rarely been determined. A peritoneal fluid/plasma ratio of 0.3 and a median (interquartile ratio IQR) maximal peritoneal concentration of 0.9 (0.6–1.5) mg/L were observed between 5 and 8 h after the start of micafungin infusion [55]. Surprisingly, no data are available regarding the peritoneal diffusion of fluconazole in patients with peritonitis. Overall, the daily dose of fluconazole should be considered cautiously, especially in patients with renal replacement therapy, in whom daily doses higher than 200 mg may be required [54].

19.3.9 De-escalation of Antifungal Therapy

De-escalation of empiric antifungal therapy is a safe procedure as recently illustrated in two studies. A multicenter prospective observational study analyzed 158 ICU patients receiving systemic antifungal therapy for documented or suspected

intra-abdominal candidiasis [15]. Antifungal therapy was fairly rapidly (after 3–5 days) modified in 42% of cases, including de-escalation in 49 (31%) patients, and escalation in 16 (10%) patients. The SOFA score at D7 after antifungal initiation was similar in patients who underwent de-escalation and those who did not (3 [2;5.75] versus 3.5 [1;6], respectively, $p = 0.529$). In a study based on 206 patients with healthcare-associated intra-abdominal infections, de-escalation was performed in 53% of cases, including de-escalation of antifungal agents in 49% of the cases receiving antifungal therapy [56]. De-escalation was not a risk factor for mortality on multivariate analysis. These results suggest that antifungal de-escalation may be safe in these patients.

19.3.10 Duration of Antifungal Therapy

The adequate duration of antifungal therapy for patients with CP has not been established. The IDSA guidelines provided recommendations for patients with fungal cIAI, but no clear recommendations for duration of therapy [25]. Similarly, ESCMID guidelines did not specifically address intra-abdominal candidiasis [21]. French experts recommended a duration of antibacterial therapy of 7–15 days for severe bacterial healthcare-associated intra-abdominal infections [49]. Due to the high rates of recurrence and relapse in intra-abdominal candidiasis, experts recommended longer durations of therapy, around 2–3 weeks [57]. In recent observational studies, patients received antifungal therapy for 17 days (median, IQR 13–21) in a multicenter prospective study [15] and 14 (range: 1–88) days in a single-center retrospective analysis [14].

Conclusions

Despite progress in the understanding of the mechanisms driving intra-abdominal candidiasis, the diagnosis and decision-making process for this disease remain highly complex. The physician in charge of a patient with suspected intra-abdominal candidiasis remains torn between over-response with ecological and financial issues and delayed therapy with life-threatening complications. The next goal to achieve will be to find rapid response tools for differentiating colonization from infection allowing early initiation of antifungal therapy.

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