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ORIGINAL

A research agenda on the management of intra-abdominal candidiasis: results from a consensus of multinational experts

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Take-home message: A group of clinical experts endorsed by the Italian Society of Intensive Care and the International Society of Chemotherapy elaborated specific statements and practice recommendations addressing the management of intra-abdominal invasive candidiasis based on the best direct and indirect evidence. International guidelines do not specifically address this particular clinical setting and scant direct evidence is available.

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Abstract *Introduction:* intra-abdominal candidiasis (IAC) may include *Candida* involvement of peritoneum or intra-abdominal abscess and is burdened by high morbidity and mortality rates in surgical patients. Unfortunately, international guidelines do not specifically address this particular clinical setting due to heterogeneity of definitions and scant direct evidence. In order to cover this unmet clinical need, the Italian Society of Intensive Care and the International Society of Chemotherapy endorsed a project aimed at producing practice recommendations for the management of immune-competent adult patients with IAC. *Methods:* A multidisciplinary expert panel of 22 members (surgeons, infectious disease and intensive care physicians) was convened and assisted by a methodologist between April 2012 and May 2013. Evidence supporting each statement was graded according to the European Society of Clinical Microbiology and Infection Diseases (ESCMID) grading system. *Results:* Only a few of the numerous recommendations can be summarized in the Abstract. Direct microscopy examination for yeast detection from purulent and necrotic intra-abdominal specimens during surgery or by percutaneous aspiration is recommended in all patients with nonappendicular abdominal infections including secondary and tertiary peritonitis. Samples obtained from drainage tubes are not valuable except for evaluation of colonization. Prophylactic usage of fluconazole should be adopted in patients with recent abdominal surgery and recurrent gastrointestinal perforation or anastomotic leakage. Empirical antifungal treatment with echinocandins or lipid formulations of amphotericin B should be strongly considered in critically ill patients or those with previous exposure to azoles and suspected intra-abdominal infection with at least one specific risk factor for *Candida* infection. In patients with nonspecific risk factors, a positive mannan/antimannan or (1→3)-β-D-glucan (BDG) or polymerase chain reaction (PCR) test result should be present to start empirical therapy. Fluconazole can be adopted for the empirical and targeted therapy of non-critically ill patients without previous exposure to azoles unless they are known to be colonized with a *Candida* strain with reduced susceptibility to azoles. Treatment can be simplified by stepping down to an azole (fluconazole or voriconazole) after at least 5–7 days of treatment with echinocandins or lipid formulations of amphotericin B, if the species is susceptible and the patient has clinically improved. *Conclusions:* Specific recommendations were elaborated on IAC management based on the best direct and indirect evidence and on the expertise of a multinational panel.

Keywords *Candida* · Abdominal infections · Consensus

Abbreviations

SITI	Italian Society of Intensive Care
ISC	International Society of Chemotherapy
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
EP	Expert panel
GI	Gastrointestinal
IAC	intra-abdominal candidiasis
ICU	Intensive care unit
CLSI	Clinical and Laboratory Standards Institute
EUCAST	European Committee on Antimicrobial Susceptibility Testing
CAGTA	*C. albicans* germ tube antibodies
BDG	(1→3)-β-D-Glucan
IDSA	Infectious Diseases Society of America
CNS	Central nervous system

Introduction

Thirty to forty percent of patients with secondary and tertiary peritonitis may develop intra-abdominal candidiasis (IAC), mainly represented by, but not limited to, *Candida* peritonitis or intra-abdominal abscesses in patients with abdominal surgery. *Candida* peritonitis is burdened by a mortality reported between 25 and 60 % [1–3].

European studies have demonstrated a predominance of *C. albicans* isolates (ranging from 65 to 82 %), followed by *C. glabrata* in intra-abdominal *Candida* infections in European ICUs [1, 2]. Increased rates of nonalbicans isolates from abdominal samples compared with other studies (42 versus 26 %, respectively) have been reported by Montravers et al. [4]. No specific predictors of mortality have been identified, while the overall prognosis of IAC is known to be influenced by selected site-dependent (i.e., infection extension, nonappendicular origin) and host-related factors (i.e., age, comorbidities). Clinical signs of IAC are not specific, and early microbiological documentation remains a major challenge. Cultures from nonsterile sites are frequently positive, but lack specificity for differentiating infection from colonization. IAC high mortality is partly related to diagnostic difficulties, including low sensitivity and specificity along with prolonged timing of culture results before and at the occurrence of suspected IAC. Moreover, it is still unclear which patients may benefit from empirical antifungal treatment and which may be at risk of infections due to fluconazole-resistant strains [4].

Recently updated international guidelines preferentially targeted candidemia and not complicated intra-abdominal infections [5–8]. Only a few statements in the above-mentioned guidelines specifically targeted IAC management aspects, probably because of the lack of standardized diagnostic criteria. IAC pathogenesis is quite different from "medical" candidemia, since in IAC an anatomic breach exists within the intestinal mucosa, whereas the yeast pathway from the gut lumen to the systemic compartment is far more complex in the latter case. Due to limitations of the current literature, the scientific community has been able neither to accurately predict IAC nor to identify populations that benefit from prophylaxis or empirical treatment. In the light of the medical need to analyze the scientific evidence in the field of IAC, the Italian Society of Intensive Care (SITI) and the International Society of Chemotherapy (ISC) developed comprehensive and practical guidance for clinicians to facilitate decision-making. According to the policy of other scientific societies [9–11], a formal consensus process was endorsed to develop specific recommendations.

Materials and methods

The executive board of the SITI decided to proceed first with a consensus for IAC. The members of the SITI group were first asked if they wanted to participate. Participants were chosen on the basis of their expertise in the field of medical mycology and in particular *Candida* disease, and further on their experience in generating guidelines. Contact was made through the SITI executive committee with the Fungal Infection Working Group of the ISC. The ISC approved the list of SITI experts and made additional suggestions for experts to include in the group as panel authors.

The multidisciplinary expert panel (EP) included 23 experts in IAC research and clinical practice: 3 surgeons (S.C., G.S., C.E.), 15 infectious disease (M.B., C.T., M.T., F.C., F.G.D.R., E.R., A.C., T.J.W., P.M., E.R., G.P., A.A., F.M., C.V., P.V.), and 4 intensive care (J.G.M., D.H.K., G.D.R., A.F.S., O.L.) physicians. A clinical statistician (M.M.) with expertise in critical care, clinical epidemiology, and guidelines development ensured proper and transparent application according to consensus development methods [12].

Framing the domain

The EP agreed on the goal of developing recommendations for the IAC clinical domain in nonneutropenic adults, excluding recipients of solid organ transplants and patients with peritoneal catheter. Secondary and tertiary *Candida* peritonitis as well as abdominal abscesses were included in this domain as mainly surgery-related diseases. Secondary peritonitis refers to localized or diffuse intra-abdominal infection (i.e., diffuse peritoneal inflammation or abscess formation) due to disruption of anatomical barriers by perforation, infection, ischemia, necrosis or surgery [13]. Tertiary peritonitis was defined in patients with previous abdominal surgery or trauma undergoing single or multiple surgical interventions without resolution of the infectious process or with ongoing intra-abdominal infection despite successful surgical source control [14].

The consensus process

The nominal group consensus methodology and the Delphi technique best suited the project [15]. According to the former methodology, during face-to-face meetings experts were asked to comment in a round-robin fashion on the proposed items in order to approve or discard each one: if at least 80 % of the EP agreed, the choice was set, otherwise further discussion was started. If a consensus could not be reached, the issue was declared uncertain. According to the latter methodology, participants were mailed questionnaires to score the relevance of questions or statements. The items receiving more than 80 % agreement were approved, while the newly proposed ones were discussed and possibly approved during meetings.

Three consensus face-to-face meetings were held according to the nominal group technique from April 2012 to March 2013 by the SITI experts. During the first meeting, the EP agreed on the domain and selected six areas of IAC deserving further appraisal: risk factors, conventional and new diagnostics, prophylaxis, empirical therapy, and targeted therapy.

Subsequently, the EP elaborated and selected the key issues within each area. According to a Delphi process, a questionnaire was mailed to the participants, who scored the relevance of 40 proposed questions. Twelve key questions were selected. Each panel member (PM) reviewed the available published evidence of one or more issues in order to produce the statements. The methodologist ensured that the revision of literature was made on a systematic base. Only PubMed indexed papers after 1990 were included, with the exception of studies on risk factors, which were allowed since 1980. The keywords used for the web search were: "(intra-abdominal infect* OR peritonitis) AND (Candida OR mycosis) NOT (transplant* OR dialysis)". The search for original articles was limited to patients above 18 years and to papers in the English language, while the meta-analysis search was not limited to the English language. Diagnostic test review was extended to meta-analyses of *Candida* infections in critically ill patients.

During the second and third meetings, proposed statements were approved and rephrased. Finally, the writing committee (M.B., M.M., F.G.D.R.) assigned grades to the suitable statements according to ESCMID [16] (Table 1). Subsequently, documents and views were shared by email and in two teleconferences between SITI and ISC experts. All the experts of the enlarged panel agreed with the level of evidence provided for each statement.

Results

Question 1: Which are the risk factors related to IAC?

The EP tried to highlight differences regarding the pathogenesis of IAC as compared with invasive candidiasis or candidemia with the aim of reporting the best available evidence on specific risk factors for IAC. Microbiological studies enrolling surgical patients reported *Candida* isolation from intra-abdominal samples in 20 % of peritonitis [17]. *Candida* was reported to be isolated in <5 % of appendicular, in 12 % of colorectal, 35 % of small bowel, and 41 % of upper gastrointestinal sites [2, 17, 18]. High rates of positive cultures for *Candida* were reported in cases of recurrent gastrointestinal perforations [18]. Other known risk factors, such as prolonged use of antibiotics or indwelling device placement as well as surgical interventions, further increased the risk of invasive candidiasis. Dupont et al. developed and validated a predictive score for likelihood of *Candida* involvement in peritonitis; factors included were female sex, upper gastrointestinal tract origin of peritonitis, perioperative cardiovascular failure, and previous antimicrobial therapy. However, both Dupont and Ostrosky's *Candida* scores, originally developed for candidemia and critically ill patients, were validated in a population with low IAC rates, probably because of the greater amount of time needed for the pathogenesis of IAC [19, 20]. Despite very low positive predictive value (PPV) of the above-mentioned scores, *Candida* colonization predicted candidemia in ICU and in patients with peritonitis due to *Candida* [2]. A 6-month prospective study by Pittet et al. in 29 critically ill surgical patients showed that 11 patients had invasive infections (eight candidemias) and the remaining 18 were heavily colonized by *Candida*, suggesting that systemic disease, including abdominal infections, may follow multifocal colonization [21]. In the above-mentioned study, the strains causing colonization and infection had the same genotype. The *Candida* score developed by Leon et al. [22, 23] and validated in his second study is unique in combining multiple-site colonization with pathogenesis and disease severity with previous abdominal surgery in a predictive clinical tool of invasive candidiasis, not specifically addressing IAC. However, regarding IAC, the EP recognizes that multifocal colonization may not be required to significantly affect the peritoneum from an abdominal source. *Candida* has been found in 15–70 % of infected necrotic tissues of patients requiring surgery, and these high proportions

Table 1 Strength of ESCMID recommendations by quality of evidence [16]

Strength of recommendation	
Grade A	ESCMID *strongly* supports a recommendation for use
Grade B	ESCMID *moderately* supports a recommendation for use
Grade C	ESCMID *marginally* supports a recommendation for use
Grade D	ESCMID *supports* a recommendation against use
Quality of evidence	
Level I	Evidence from at least one properly designed randomized, controlled trial
Level II	Evidence from at least one well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time series; or from dramatic results of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies

have been repeatedly related to prior antibiotic exposure, which promotes overgrowth of unaffected microorganisms. Table 2 reports the risk factors for secondary and tertiary *Candida* peritonitis that were judged by the EP to be relevant. *C. albicans* was isolated in about 60 % of IAC, while non-*C. albicans* species were more frequent in those patients with previous azole exposure [17, 24–27]. However, only ten studies in the last 10 years addressed the risk factors for non-*C. albicans* species in the setting of critically ill patients, including those with intra-abdominal infections. Gastrointestinal surgery was itself shown to be a risk factor for acquisition of non-*C. albicans* species-related infections. Prior azole exposure was consistently reported to increase the rate of azole-resistant species in several case–control studies [28–31], although the EP reports that no IAC was ever mentioned.

After reviewing the literature and discussing this topic, the EP concluded that, despite several studies reporting the importance of *Candida* colonization in the pathogenesis of IAC, further clinical studies are necessary in this field. The question may therefore be best answered by the possibility of developing animal models of IAC, with semiquantitative cultures and with various levels of therapeutic intervention such as prophylaxis, preemptive and perhaps empirical treatment.

Table 2 Risk factors for intra-abdominal *Candida* infection

Risk factor	Notes	References
1. Specific		
Recurrent abdominal surgery	Laparoscopies included	[33]
GI tract perforations	Recurrent perforations and/or perforations untreated within 24 h[a]	[17]
Gastrointestinal anastomosis leakage	More severe if the leakage is in the upper GI tract[b]	[2, 3, 17, 31]
Multifocal colonization by *Candida* spp.		
2. Additional nonspecific		
Acute renal failure, central venous catheter placement, total parenteral nutrition, ICU stay, severity of sepsis, diabetes and immunosuppression, prolonged broad-spectrum antibacterial therapy		[20, 31]

[a] Surgical control of upper gastrointestinal perforations is more problematic [65]

[b] Gastroduodenal surgery, in particular that involving the esophagus

Question 2: Which samples should undergo direct microscopy and microbiological cultures for *Candida*?

Microscopy of a sample obtained during surgery demonstrating the presence of neutrophils and yeasts is generally sufficient for diagnosis of *Candida* infection. However, Gram stain examination may fail to detect low fungal load [32]. Rather, microscopic examination revealing yeasts was frequently associated with an upper gastrointestinal tract perforation and repeated laparotomies [17, 33]. Despite direct microscopy having a relatively low sensitivity, its high specificity and timely results were judged relevant and recommended by the EP in all patients, except in those at low risk for developing IAC. The EP also advised that cultures from purulent and necrotic intra-abdominal samples are adequate for microbiological testing when obtained surgically, while superficial swabs are not considered suitable for culture. A minimal volume of samples has to be sent for cultural examinations, and it should be at least 1 ml of liquid material or more than 1 g of tissue.

Although high fungal concentration allows *Candida* to grow also in nonspecific media, indication for fungal cultures should be provided to the laboratory in order to improve the diagnostic yield. Timely seeding of the material may not be necessary, provided that samples are adequately stored by the laboratory.

According to Calandra et al. [34], quantitative cultures should be performed in order to characterize patients with more severe IAC. *Candida* spp. obtained from surgical drainage are not sufficient for diagnosis of IAC, considering the high capability of *Candida* to adhere to foreign bodies. These results may be useful if the drainage was inserted from <24 h; otherwise it should be considered as a colonization.

Samples should be obtained from different sites of the body (feces, urine, axilla, tracheal aspirates, and gastric aspirates) in order to measure the colonization index [27] and/or establish multifocal colonization [20, 21, 35]. These cultures are useful only for deciding when to start empirical antifungal therapy in high-risk patients, using prediction rules. Candidemia was reported in about only 10–20 % of patients with nosocomial or complicated secondary and tertiary peritonitis, while *Candida* isolation from blood is uncommon in other cases [3]. The role of blood cultures has limited application in these patients. Therefore, blood cultures should not replace cultures obtained at the time of surgery or through sterile invasive means; rather, blood cultures should serve as supplementary data, especially in patients at high risk for IAC. Because fungal-specific media might improve the diagnosis of fungemia, these specific media are recommended by the EP in high-risk patients [36]. Although *Candida* susceptibility to antifungal agents is generally predictable depending on the species isolated, single isolates do not necessarily follow the general pattern; thus, azole

resistance might dampen the clinical benefit of timely therapy [37]. Indeed, in the prospective study of Montravers et al., 28 % of *Candida* spp. isolated from IAC were resistant to fluconazole [4]. The mortality rate was not related to azole susceptibility, and fluconazole resistance rates did not appear higher in IAC patients previously exposed to azoles [3, 4, 38]. The EP judged that species identification and in vitro susceptibility testing should always be performed on all clinically significant isolates, notwithstanding the general limitations associated with *Candida* and previous azole administration. Minimum inhibitory concentration (MIC) testing can be performed for all antifungals by standardized techniques according to CLSI (M27 S3 and S4) and EUCAST [39, 40]. The correlation between MIC and response to therapy for invasive candidiasis has been reported for fluconazole, voriconazole, and echinocandins, while no data are currently available for amphotericin B suggesting predictive value of the MIC for treatment outcome [41]. Despite limited data and the lack of breakpoints, obtaining MIC values for antifungal drugs is suggested.

Recommendations

1. Direct microscopy examination for yeast detection from purulent and necrotic intra-abdominal specimens obtained during surgery or by percutaneous aspiration is recommended in all patients with nonappendicular abdominal infections including secondary and tertiary peritonitis (AII).
2. Samples obtained from drainage tubes are not valuable except for determination of colonization (DIII).
3. Intra-abdominal specimens should be specifically cultured for *Candida* spp. (AII), and species identification should always be requested when *Candida* is isolated (AII).
4. Superficial swabs of abdominal specimens should not be collected for culture (DIII).
5. Tissue or liquid samples (preferably in syringe) should be sent to the laboratory as soon as possible (AIII).
6. The minimal volume of samples sent for culture should be 1 ml (or 1 g of tissue) (BIII).
7. Blood cultures should be taken through peripheral vein punctures upon diagnosis or suspicion of intra-abdominal infections and tertiary peritonitis, and specific media for fungi are recommended, if available (AII).
8. Other surveillance cultures, including swabs for *Candida*, are not required once intra-abdominal infection is diagnosed (DIII), but before the diagnosis they may be useful to calculate the *Candida* colonization in patients with suspected IAC (CIII).
9. Antifungal susceptibility testing should be performed on yeast isolates from blood, sterile sites, and other appropriate specimens (BIII). MICs should be reported to the clinicians, specifying the reference method used (CLSI versus EUCAST) (BIII).

Question 3: How should culture positivity for *Candida* be interpreted?

When *Candida* is isolated from intra-abdominal samples, obtained surgically, it should be considered significant for IAC: in this case, positive cultures are associated with higher mortality [18, 42]. *Candida* isolation may be considered significant if high yeast concentrations are recovered from a drain inserted within 24 h from the cultures. All these results, if associated with nonculture methods positivity (see question 4) and signs and symptoms of IAC, may be useful for diagnosis of IAC.

Recommendations

1. Systemic antifungal treatment should be considered when adequate intra-abdominal specimens (obtained surgically or within 24 h from external drainage) are positive for *Candida*, irrespective of the fungal concentration and the associated bacterial growth (AII).
2. Positive cultures from drains should not be treated, especially if the drains have been in place for more than 24 h (DIII).

Question 4: Which patients should be tested by non-culture-based methods?

Although non-culture-based methods can be considered a useful tool for early diagnosis of invasive candidiasis in comparison with microbiological cultures, all data on nonculture methods are based on observations made in candidemia. Very few data are available on the real value of mannans, β-D-glucan, and PCR in *Candida* intra-abdominal infections, especially in noncandidemic cases. Mannan and antimannan display high specificity (93 and 83 %, respectively) but low sensitivity (58 and 59 %, respectively), the latter increasing to 83–96 % when the two tests are combined [43]. Furthermore, the results of mannan antigen tests depend on the species of *Candida* involved (i.e., *C. parapsilosis* and *C. krusei* produce less amount of mannan). Unfortunately, the studies performed in surgical patients have several limitations in the diagnostic yield of nonculture methods, and to date no study has been designed to validate these methods in patients with IAC (Table 3). However, the EP judged that indirect evidence obtained through mannan and antimannan tests is sufficient to recommend their application in IAC, since the time to start of antifungal therapy is critical for

mortality. Another blood test for *Candida* invasive infections is based on the measurement of (1→3)-β-D-glucan (BDG): in a recent bivariate meta-analysis, sensitivity of 76 % and specificity of 85 % were reported [44]. As the negative predictive value of BDG is consistently higher than its positive predictive value, the test appears more useful to exclude rather than to confirm fungal infection [11]. False-positive results may be related to other fungal infections (i.e., *Aspergillus*, *Fusarium*, *Pneumocystis*, etc.), albumin use, immunoglobulins, gauze (particularly used in the setting of abdominal surgery), hemodialysis, bacteremia or antibiotic use (especially colistin).

A reliable threshold value for positivity of this test in case of invasive candidiasis may depend on the method, but a value of 80 pg/ml (Fungitell©) is suggested as a reasonable level for candidemia [54, 55]. When BDG is used with antibodies against the surface of *C. albicans* germ tube (CAGTA), a high value of BDG is strongly predictive of IAC [54]. A recent prospective Swiss study on the diagnostic accuracy of BDG supports the use of this fungal biomarker for anticipating diagnosis of IAC in high-risk surgical ICU patients [45]. In patients with recurrent GI tract perforation, BDG ≥80 pg/ml discriminated IAC from colonization and preceded microbiological documentation of IAC by intra-abdominal cultures. The use of BDG results led to an earlier prescription of antifungal therapy by a median of five and six days, respectively, thus suggesting a BDG's potential role for guiding prompt and targeted initiation of antifungal therapy on a pre-emptive basis.

Table 3 summarizes the sensitivity and specificity of mannan/antimannan and BDG tests and the rate of patients with IAC in studies that included patients with invasive candidiasis [46–53].

Direct molecular detection of *Candida* DNA from human samples is not yet standardized, and so far it is not clear whether PCR or other molecular methods may be useful as early markers of invasive candidiasis [43, 54, 55].

Recently, Nguyen et al. compared a validated PCR method with BDG and blood cultures in the diagnosis of invasive candidiasis (IAC accounted for 89 % of deep-seated candidiasis). PCR was more sensitive than BDG and blood culture in diagnosis of invasive candidiasis, especially in the cases of deep-seated candidiasis (89 versus 53 %, respectively, $p = 0.004$) [44].

Since all these nonculture methods are not widely available, clinicians should know that a validated PCR may be better than a mannan test alone or combination of mannan/antimannan tests and BDG. From a clinical point of view, the EP considers these tests useful to anticipate the diagnosis of IAC.

Amongst other methods to identify *Candida*, together with a significant reduction of time delay, matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) analysis allows the identification of bacteria and yeasts from isolated colonies, obtained by culture, in a few minutes with accuracy of more than 90 % when compared with conventional methods [56]; this new technique is based on measurement of the molecular masses of proteins and other microbial components. Also, Raman spectroscopy has been used to identified yeast from peritonitis with accuracy of 90 % [57].

Recommendations

1. When available, mannan and antimannan tests and BDG should be performed in patients with secondary or tertiary peritonitis and at least one specific risk factor for IAC (BII).
2. Validated PCR tests might be more sensitive in diagnosing IAC than other nonculture methods, although there are concerns about costs, technical issues, and capacity to differentiate normal colonization, pathogenic colonization, and real infection (BIII).

Table 3 Diagnostic yield of non-culture-based tests in surgical patients

Test	Sample *N*	Design	Setting	*N* of patients	Sensitivity (%)	Specificity (%)	References
Mn/A-Mn	32/43	R	ICU	16	42/56	98/97	[47]
Mn/A-Mn	32/45	R	ICU	15	58/53	n/a	[79]
Mn/A-Mn	41/53	R	ICU	27	52/44	n/a	[48]
MN	21/26	R, CC	ICU	4	69	97	[49]
Mn/A-Mn	14/16	R	ICU	4	67/78	n/a	[51]
G	163	P, CC, MC	ICU	13	64; 78 (CE)	92	[80]
G	15C	CC	Various	15	88; 93 (CE)	46; 77 (CE)	[52]
G	27C + 39PC	R, CC	Various	27C + 39PC	52	100	[79]
G	26C	R, CC	Various	26	73	70	[81]
G	53C + 47EC	P	ICU and surgery	152	77	83	[53]
G	81C	P	ICU	89	83	40	[45]

R retrospective, *P* prospective, *CC* case–control, *MC* multicenter, *C* candidiasis, *PC* probable candidiasis, *MN* mannan antigen test, *A-MN* antimannan test, *G* β-D-glucan test, *CE* candidemia, *ICU* intensive care unit, *EC* esophageal candidiasis

Question 5: Which patients deserve antifungal prophylaxis?

To date, the ideal timing of antifungal prophylaxis remains unknown, since this question has not been sufficiently addressed in clinical trials. In a clinical trial, patients who had recently undergone abdominal surgery and had recurrent gastrointestinal perforation or anastomotic leakage were treated either with prophylactic fluconazole 400 mg per day or with placebo in order to prevent intra-abdominal *Candida* infections [58]. The rate of IAC was significantly lower in the fluconazole prophylaxis group. This study exhibited high technical quality, but was limited by enrolling only 43 evaluable patients [58]. While the authors of this study classified the fluconazole use as prophylaxis, the risk factor of gastrointestinal perforation or anastomotic leakage would lead others to deem the use as presumptive. In a small, noncomparative trial, standard-dose caspofungin treatment was evaluated with the same indication, but no evidence can be derived [59]. On the other hand, prophylaxis with fluconazole did not improve patient outcome in case of lower GI tract perforations, in a prospective, noncomparative study encompassing 19 patients with recurrent GI perforation, anastomotic leakage, or acute necrotizing pancreatitis receiving caspofungin, and only one breakthrough *Candida* infection occurred [60]. In two studies at university hospitals in Copenhagen, azole use in case of GI tract perforation or reoperation after colorectal surgery reduced the rate of *Candida* infections from 0.15 to 0.03 %.

Recommendation

1. In patients with recent abdominal surgery and recurrent gastrointestinal perforation or anastomotic leakage, prophylaxis with fluconazole should be considered (BI); an echinocandin should be considered if there is a high likelihood of azole resistance (CII).

Question 6: Which patients deserve empirical antifungal therapy?

Empirical therapy is based on administration of antifungal agents in patients with signs and symptoms of infection along with specific risk factors for IAC, irrespective of biomarkers. Some authors defined as "presumptive" the therapy that started in a more specific setting, i.e., including evidence of *Candida* colonization or early disease biomarkers [61].

There are five meta-analyses that have investigated early antifungal therapy in critically ill surgical patients: three studies have suggested that fluconazole reduces the rate of invasive fungal infections and mortality [25, 62], while two studies have not shown any benefit [63, 64]. In the specific setting of surgical patients with intra-abdominal infection, only some retrospective studies have reported a significant reduction of mortality [65]. After reviewing the literature and discussing this topic, the EP concluded that further clinical studies are necessary in this field.

In the practical setting, however, empirical treatment is often necessary to improve the major clinical endpoints [20, 66]. Mainly based on indirect evidence, the EP recommended to consider empirical or presumptive therapy in patients with specific risk factors and positive mannan/antimannan test or BDG.

Recommendations

1. Empirical antifungal treatment may be considered in patients with a diagnosis of intra-abdominal infection and at least one specific risk factor for *Candida* infection (Table 2) (CIII).
2. In patients with intra-abdominal infection with or without specific risk factor for *Candida* infection, empirical antifungal treatment should be administered if a positive mannan/antimannan or BDG or PCR test result is present (BII).

Question 7: What is the recommended empirical first-line antifungal therapy?

The choice of the appropriate empirical antifungal agent for IAC is mainly supported by indirect evidence from studies on invasive candidiasis. Fluconazole has been associated with a higher rate of treatment failure [67, 68] compared with fungicidal agents, although its use may be cost-effective in settings with a low rate of azole resistance (<25 % of *Candida* strains) [69]. A recent meta-analysis reported favorable data for micafungin [70]. The EP chose to adhere to general guidelines for invasive candidiasis (i.e., IDSA, ESCMID) [7, 16] and recommended fungicidal agents for critically ill patients or those with prior exposure to azoles. As far as the empirical first-line therapy of intra-abdominal candidiasis is concerned, the panel decided to give emphasis to the role of fungicidal agents, similarly to the IDSA guidelines where both echinocandins and liposomal amphotericin B had the highest evidence (with "A" meaning good evidence), rather than to simply refer to the recent ESCMID guidelines where only echinocandins had the best evidence (with "A" meaning excellent). First of all, abdominal candidiasis often results from failure of primary surgical and medical treatment in the context of ICU stay and prolonged care where other antifungal agents

have already been administered, thus limiting the treatment choices. Secondly, from a pharmacological point of view, micafungin, caspofungin, and anidulafungin have differences in volume of distribution and plasma concentrations which need to be explored in the context of abdominal candidiasis in the ICU. Variations in extracellular fluid are often the result of multiple changes, possibly including ascites, peritoneal exudates, surgical drainages as well as edema, fluid therapy, and hypoalbuminemia: such parameters are of paramount importance for critically ill patients and deserve specific future studies for the three echinocandins [71]. Finally, the use of lipid formulations of amphotericin B in the setting of abdominal disease with possible fluid leakage may be reasonable for the specific hydrophilic properties, although the three lipid formulations have significantly different structural, physical, chemical, pharmacokinetic, pharmacodynamic, and toxicological characteristics (of note, only liposomal and lipid complex are available in Europe) [72].

Besides antifungal therapy, in cases requiring debridement of devitalized tissue, drainage, and appropriate wound management or infections complicated by bowel perforation, early source control is mandatory [73]. However, venous catheter withdrawal is not justified in candidemia with abdominal origin [74].

Recommendations

1. Fungicidal antifungal agents (i.e., echinocandins or lipid formulation of amphotericin B) should be prescribed for the empirical therapy of all critically ill patients or for patients with previous exposure to azoles (AII).
2. In this setting, the presence of organ failure should guide the drug choice (BIII).
3. For the subgroup of patients with *C. parapsilosis* colonization, lipid formulations of amphotericin B or fluconazole may be preferred (BII).
4. Azoles (fluconazole and voriconazole) can be prescribed for the empirical therapy of non-critically ill patients without previous exposure to azoles unless they are known to be colonized with a *Candida* strain with reduced susceptibility to azoles (BII).
5. Amphotericin B deoxycholate should not be used due to its well-documented significant toxicity (DII).

Question 8: Which patients should receive targeted therapy with azoles, echinocandins, and lipid formulations of amphotericin B?

The appropriate and timely choice of empirical antifungal agents is a crucial factor for IAC prognosis [75]. Indeed, empirical treatment needs to be changed after culture results are received in one-fifth of the cases [4].

Recent guidelines no longer consider fluconazole as the drug of choice for invasive candidiasis, especially in moderately to severely ill patients [16]. The rationale is based on the increasing prevalence of *Candida* species with decreased susceptibility to fluconazole and the lower clinical efficacy of fluconazole compared with anidulafungin in patients with candidemia and invasive candidiasis [76]. With regards to *Candida* infections, all three echinocandins (caspofungin, micafungin, and anidulafungin) are fungicidal and exhibit broad-spectrum activity, and acquired resistance is rare. Presently, all echinocandins are considered drugs of choice for IAC.

The safety profile of antifungals should also be considered. While amphotericin B deoxycholate is fungicidal but very poorly tolerated, liposomal amphotericin B is effective and less toxic, justifying a recommendation against Amphotericin B deoxycholate use [77]. In patients with invasive candidiasis, the efficacy of liposomal amphotericin B was similar to micafungin but the renal toxicity was higher [78].

Recommendations

1. Fungicidal agents such as echinocandins or lipid formulations of amphotericin B should be used for targeted therapy of all critically ill patients or for patients with previous exposure to azoles (BII).
2. In this setting, the presence of organ failures should lead to the choice of the drug (BIII).
3. For the subgroup of patients infected with *C. parapsilosis*, lipid formulations of amphotericin B or fluconazole should be preferred (BII).
4. Azoles can be used for targeted therapy of non-critically ill patients with IAC due to susceptible strain(s) (BII).
5. Amphotericin B deoxycholate should not be used due to its well-documented significant toxicity (DII).

Question 9: How should treated patients be monitored?

Similar to the treatment of invasive candidiasis, antifungal treatment in patients with IAC should aim for a combined clinical and microbiological response. Usual standard management for candidemia imposes continuation of antifungal treatment as long as blood cultures remain positive and for a certain duration after cultures' confirmed negativity. Nonculture methods are usually not useful to monitor treated patients, even if the role of PCR is still being explored for this use.

Recommendations

1. There is no evidence that serological tests are useful to monitor patients treated for *Candida* abdominal infections (DII).
2. In patients with proven IAC, repeated cultures of specimens from drains are not indicated (DIII).
3. Blood cultures should be repeated in patients with proven candidemia, according to published international guidelines (AIII).

Question 10: How long should antifungal therapy be continued?

The duration of treatment depends on the extent of organ involvement, the patient's clinical condition, and the presence or absence of positive blood cultures. Importantly, our recommendations are in immunocompetent patients. In a population without a documented organ involvement (i.e., heart, bone, CNS), treatment aims are to clear the infection, resolve the signs and symptoms, and at the same time avoid deep-organ involvement. In candidemia this can generally be achieved by treating the infection for 14 days. In the absence of new data, a similar duration of therapy should be prescribed for patients with IAC. Few data are available about duration of therapy in patients with IAC. In candidemia, negativization of blood culture is a useful marker to define the duration of therapy. In contrast, no microbiological marker is available in IAC, making the recommendation of the optimum duration of therapy especially difficult. In the study of Mortravers et al., median duration of antifungal treatment in patients with *Candida* peritonitis was 20 days in survivors [3].

Recommendations

1. In patients with IAC and clinically ameliorating, antifungal treatment should be continued for at least 10–14 days after the beginning of treatment for IAC (CIII).
2. In patients without proven *Candida* infection but clinically improved, empirical antifungal therapy should be discontinued after 3–5 days (BIII).
3. In patients without proven *Candida* infection and not clinically improved, empirical antifungal therapy should be stopped (BIII).

Question 11: Which step-down therapy should be chosen?

Step-down strategies in IAC should adhere to general recommendations for invasive candidiasis [16]. However, in patients with IAC the use of the oral route is not feasible in the majority of cases. Therefore, the use of an intravenous agent is fully justified.

Recommendation

1. Treatment can be simplified by stepping down to an azole (fluconazole or voriconazole) after 5–7 days of echinocandins or lipid formulations of amphotericin B, if the species is susceptible and the patient is clinically stable (BIII).

Question 12: Which second-line therapy should be started?

After clinical and radiological reassessment to exclude the need for reoperation and adequate source control, IAC therapy may need to be changed empirically, i.e., because of persisting fever or based on persisting positive cultures, or to be switched because of adverse effects, such as liver or renal toxicity or drug interactions. No single switch strategy has been shown to be superior to others.

Recommendations

1. Second-line treatment for patients initially treated with fluconazole should include an echinocandin or lipid formulations of amphotericin B (BIII).
2. Second-line treatment for patients initially treated with an echinocandin should include lipid formulations of amphotericin B (BIII).

The most important statements and treatment recommendations are summarized in Tables 4 and 5.

Conclusions

Fungal infections adversely affect the outcome of patients with peritonitis. Isolation of *Candida* from peritoneal fluid is associated with high mortality [2, 3]. Unfortunately, notwithstanding the fact that several antifungal agents are nowadays available for empirical and targeted treatment of IAC, diagnosis based on both culture and nonculture tests for IAC has several limitations.

The feasibility of randomized clinical trials in IAC patients is scarce. Moreover, international guidelines preferentially target clinical settings such as candidemia or bacterial intra-abdominal infections, without providing enough clinical support for the management of IAC patients.

Based on the best direct and indirect evidence and on the clinical expertise of a multidisciplinary EP, specific

Table 4 Principal recommendations on the management of intra-abdominal candidiasis

Topic	Recommendation	Quality of evidence and strength of recommendation
Diagnosis	Direct microscopy examination for yeast detection from purulent and necrotic intra-abdominal specimens obtained during surgery or by percutaneous aspiration is recommended in all patients with nonappendicular abdominal infections including secondary and tertiary peritonitis	AII
	Samples obtained from drainage tubes are not valuable except for study of colonization	DIII
	Blood cultures should be taken through peripheral vein punctures upon diagnosis or suspicion of intra-abdominal infections and tertiary peritonitis, and specific media for fungi are recommended, if available	AII
	Antifungal susceptibility test should be performed on yeast isolates from blood, sterile sites, and other appropriate specimens. MICs should be reported to the clinicians, specifying the reference method used (CLSI versus EUCAST)	BIII
Culture interpretation	Systemic antifungal treatment should be considered when adequate intra-abdominal specimens (obtained surgically or within 24 h from external drainage) are positive for *Candida*, irrespective of the fungal concentration and the associated bacterial growth	AII
	Positive cultures from drains should not be treated, especially if the drains are in place for more than 24 h	DIII
Nonculture test	When available, mannan and antimannan tests and BDG should be performed in patients with secondary or tertiary peritonitis and at least one specific risk factor for IAC	BII
Prophylaxis	Patients with recent abdominal surgery and recurrent gastrointestinal perforation or anastomotic leakage should receive treatment with fluconazole	BII
	An echinocandin should be considered if there is a high likelihood of azole resistance	CII
Empirical therapy	Empirical antifungal treatment may be considered in patients with a diagnosis of intra-abdominal infection and at least one specific risk factor for *Candida* infection (Table 2)	CIII
	In patients with intra-abdominal infection with or without specific risk factor for *Candida* infection, empirical antifungal treatment should be administered if a positive mannan/antimannan or BDG or PCR test result is present	BII
	Fungicidal antifungal agents (i.e., echinocandins or lipid formulation of amphotericin B) should be prescribed for the empirical therapy of all critically ill patients or patients with previous exposure to azoles	AII
	Azoles can be adopted for the empirical therapy of non-critically ill patients without previous exposure to azoles unless they are known to be colonized with a *Candida* strain with reduced susceptibility to azoles	BII
Targeted therapy	Fungicidal agents such as echinocandins or lipid formulations of amphotericin B should be used for targeted therapy of all critically ill patients or patients with previous exposure to azoles	BII
	For the subgroup of patients infected with *C. parapsilosis*, lipid formulations of amphotericin B or fluconazole should be preferred	BII
	Azoles (fluconazole) can be used for targeted therapy of non-critically ill patients without previous exposure to azoles unless there is evidence of multisite colonization with a *Candida* strain characterized by reduced susceptibility to azoles	BII
Treatment duration	In patients with IAC and clinically ameliorating, antifungal treatment should be continued for at least 10–14 days after the beginning of treatment for IAC	CIII
	In patients without proven *Candida* infection but clinically improved, empirical antifungal therapy should be discontinued after 3–5 days	BIII
	In patients without proven *Candida* infection and not clinically improved, empirical antifungal therapy should be stopped	BIII
Step-down therapy	Treatment can be simplified to an azole (fluconazole or voriconazole) after 5–7 days of echinocandins or lipid formulations of amphotericin B, if the species is susceptible and the patient is clinically stable	BIII

Table 5 Treatment recommendations

Strategy	Drug	Quality of evidence and strength of recommendation
Prophylaxis	Fluconazole	BII
	Caspofungin	CII
Empirical therapy	Caspofungin	AII
	Micafungin	
	Anidulafungin	
	Liposomal amphotericin B	AII
	Amphotericin B lipid complex	
	Fluconazole	BII
	Voriconazole	
	Amphotericin B deoxycholate	DII
Targeted therapy	Caspofungin	AII
	Micafungin	
	Anidulafungin	
	Liposomal amphotericin B	AII
	Amphotericin B lipid complex	
	Fluconazole	BII
	Voriconazole	
	Amphotericin B deoxycholate	DII

statements addressing IAC management were elaborated. The EP, however, notes the urgent need for dedicated studies in this clinical setting for the validation of the proposed statements.

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