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Abstract	<p>Invasive candidiasis (IC) has primarily been studied in intensive care unit (ICU) patients, although, in reality, a vast majority of these infections occur outside of the ICU. The recent publication of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines also deal with the non-ICU population, but many uncertainties remain on the management of IC, particularly in non-critically ill patients. Therefore, the Italian Society of Antimicrobial Therapy, Società Italiana di Terapia Antimicrobica (SITA), produced practical, hospital-wide recommendations on the management of <i>Candida</i> infection in non-immunocompromised patients in the hospital ward. Our focus is on patient stratification in terms of risk factors for IC and of clinical severity, emphasising a high index of suspicion to ensure early diagnosis, early treatment and de-escalation when a patient is clinically stable, in order to optimise resource allocation.</p>	
Keywords (separated by '-')	<p>Invasive candidiasis - Diagnosis - Management - Risk stratification - Clinical severity - Review - Consensus - Recommendations</p>	
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2 **An Italian consensus for invasive candidiasis management**  
3 **(ITALIC)**

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**Introduction** 30

The rising incidence of candidaemia and deep-seated 31  
infections due to *Candida* (i.e. invasive candidiasis, IC) is 32  
paralleling the increasing complexity of surgical proce- 33  
dures and the larger patient populations at risk of infection, 34  
as well as changes in patient demographic characteristics. 35  
IC, in its various clinical pictures, is burdened by a variable 36  
mortality rate ranging from 40 to 75 % [1–5]. While 37  
*Candida albicans* has been, for a long time, the species 38  
more frequently involved in candidaemia, recently, a shift 39  
towards non-*albicans* species has been reported, especially 40  
in haematological, transplant and intensive care unit (ICU) 41  
patients [6–8]. There is growing evidence that IC is a 42  
hospital-wide issue, not confined to specific health care 43  
contexts (e.g. the ICU) and it seems, therefore, extremely 44  
important to broaden awareness, knowledge and skills for 45  
optimal management in the more diverse clinical settings. 46  
This is particularly relevant when we consider the evidence 47  
that inappropriate initial therapy and/or delay in prescrip- 48  
tion are associated to worse outcome and to the selection of 49  
resistant strains [9–11]. 50

Between 2009 and 2012, both the Infectious Diseases 51  
Society of America (IDSA) and the European Society of 52  
Clinical Microbiology and Infectious Diseases (ESCMID) 53  
produced a set of guidelines, which, though comprehen- 54  
sive, suggest different therapeutic choices, and, more 55

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56 relevantly, did not address many uncertainties regarding  
 57 the practical management of this severe infection, such as  
 58 actual criteria for empirical therapy and prophylaxis in the  
 59 daily clinical practice, the management of *Candida* peri-  
 60 tonitis and others [12, 13]. In addition, at least the Euro-  
 61 pean guidelines address the issue almost only in the ICU  
 62 patient, forgetting that, in reality, a vast majority of these  
 63 infections occur outside of the ICU [2]. An additional  
 64 difficulty is that the vast majority of the literature data is  
 65 based on candidaemia, while it is increasingly recognised  
 66 that deep-seated *Candida* disease, though probably under-  
 67 diagnosed owing to the intrinsic limits of current diagnostic  
 68 methods, represents a relevant proportion of IC [14].

69 For these reasons, the Italian Society of Antimicrobial  
 70 Therapy, Società Italiana di Terapia Antimicrobica (SITA),  
 71 decided to endorse a national consensus process involving  
 72 several medical disciplines to review the available evi-  
 73 dence and produce practical, hospital-wide recommenda-  
 74 tions about the management of severe *Candida* infections  
 75 in non-immunocompromised patients, excluding patients  
 76 with haematological diseases and those who had undergone  
 77 solid organ and hematopoietic stem cell transplants.

**Table 1** ITALIC definition of diagnostic categories of invasive candidiasis (IC)

“Invasive candidiasis (IC)”, indicating both deep-seated *Candida* infection and candidaemia

In terms of certainty of diagnosis and consequent therapeutic strategies, the following diagnostic categories (modified from [166]) were used:

Proven IC: cultural evidence of *Candida* or evidence of yeast cells or hyphae or pseudohyphae at histology or at direct examination, in a normally sterile tissue or organ, i.e. excluding urine, sputum, fluids from bronchoalveolar lavage, mucous membrane swabs and specimens from skin sites.

Probable IC: concomitant presence of an underlying disease predisposing to IC, adequate risk factors (see risk stratification), with signs of active infection [26], with at least one positive antigen test (e.g. BDG, mannan/antimannan).

Possible IC: concomitant presence of an underlying disease predisposing to IC, adequate risk factors (see risk stratification), with signs of active infection [26], but without any microbiological confirmation.

**Table 2** ITALIC definitions of treatment strategies of IC

Treatment strategy	Certainty of diagnosis	RF (including multi-site colonisation)	Clinical signs	Biomarkers	Microbiological diagnosis
Prophylaxis	Not applicable	+	None	Not applicable	Not applicable
Pre-emptive	Probable	+	–	+ <sup>a</sup>	–
Empirical	Possible	+	+	–/not available	–/not available
Presumptive	Probable	+/-	+	+	–/not available
Targeted	Proven	+/-	+/- <sup>a</sup>	+/-/not available	+

<sup>a</sup> Unlikely combination

Differently from the above-mentioned international  
 guidelines, the present document takes into consideration a  
 practical approach to antifungal therapy, aiming to give a  
 guideline that is useful for daily clinical practice.

## Consensus methods

The consensus panel involved 30 infectious disease consultants, surgeons and intensive care physicians, and a clinical epidemiologist, with two external discussants (a microbiologist and a clinical pharmacologist). Five working areas were identified:

- Risk stratification
- Diagnosis and clinical management
- Prophylaxis
- Therapy of possible/probable IC
- Therapy of proven IC

Preliminary consensus on definitions was achieved (Tables 1 and 2).

The consensus strategy was based on a combination of the nominal group technique and the Delphi method (when the EP was involved) [15].

For assessing the quality of evidence and strength of recommendations, we adopted the GRADE profile, since it allows in-depth assessment and description of the available evidence [16–20]. Recommendations were classed following the National Institute for Health and Clinical Excellence (NICE) guidelines, which encompass five categories (“must”, “must not”, “should”, “should not” and “could”) [21].

## Results

Before delving into the discussion of the five clinical areas of interest, all the “actors” recommend a careful periodical evaluation of the epidemiological situation in each hospital, in terms of new patients at risk, emergence of specific species and resistance patterns. Indeed, local epidemiological surveillance is mandatory, since the antifungal

113 policy may have an impact on the antifungal resistance of  
 114 local *Candida* strains [22–24].

115 Area 1: risk stratification

116 The major risk factor for IC is the severity of the patient’s  
 117 underlying condition, mainly represented by the APACHE  
 118 II score. The severity of the underlying disease dictates the  
 119 occurrence of additional risk factors, such as the use of  
 120 broad-spectrum antibacterial agents, total parenteral nutri-  
 121 tion, indwelling vascular device (central venous catheters,  
 122 haemodialysis catheters, peripherally inserted central  
 123 catheters and implanted ports) and major surgery [25].

124 Important studies were performed with the aim of  
 125 identifying both a single predicting risk factor or a com-  
 126 bination of them for building models able to identify  
 127 patients more at risk of being affected by IC, and eventu-  
 128 ally apply the most effective management strategy.

129 In the *Candida* literature, the term “at risk” is used  
 130 somewhat inconsistently: in a strictly epidemiological  
 131 interpretation, a patient “at risk” of IC is a patient without  
 132 IC who might develop it at a later time, with risk depending  
 133 on a number of patient characteristics (and possibly  
 134 deserving a prophylactic approach); however, in many  
 135 studies on IC, “patient at risk” is a patient likely to actually  
 136 have IC, based on a number of clinical features and risk  
 137 factors (thus deserving an empirical treatment approach).  
 138 Another meaning of “risk” is stratification according to the  
 139 risk of death, which implies a judgement on the severity of  
 140 the clinical conditions of the patient (for instance, as we  
 141 suggest, by adopting the sepsis score) [26].

142 Some clinical prediction rules have been developed  
 143 combining different parameters to predict which patient is  
 144 affected (symptoms of infection are already there) or is  
 145 likely to later develop an IC (no symptoms, but a situation  
 146 which might deserve specific prophylaxis). The oldest,  
 147 purely microbiological, stratification tool was the *Candida*  
 148 colonisation index (CCI), based on the ratio between the  
 149 number of distinct body sites colonised with *Candida* and  
 150 the total number of sites tested. The so-called “corrected  
 151 CCI (cCCI)”, which came later, is the product of the CCI  
 152 times the ratio of the number of sites showing heavy  
 153 growth to the total of sites growing *Candida* spp. [27].  
 154 Subsequently, based on previous studies [28] in ICU pop-  
 155 ulations, Ostrosky-Zeichner et al. [29] found that the  
 156 combined presence of previous or concomitant systemic  
 157 antibiotic therapy and a central venous catheter, plus two or  
 158 more of the following variables (parenteral nutrition,  
 159 dialysis, major surgery, pancreatitis and treatment with  
 160 steroids or other immunosuppressive agents) was able to  
 161 predict the development of IC with positive and negative  
 162 predictive values of 10 and 97 %, respectively. The score

163 did not depend on the presence of a clinical situation  
 164 compatible with infection.

165 More recently, León et al. derived, from a large popu-  
 166 lation of ICU patients with signs and symptoms of infection,  
 167 the so-called “*Candida* score” (CS). The final predicting  
 168 model included parenteral nutrition, surgery, multi-focal  
 169 colonisation and severe sepsis. Each independent variable  
 170 was weighted for the strength of its association with the  
 171 outcome variable, with a score of 1 for the first three vari-  
 172 ables and a score of 2 for the fourth variable. Subjects with a  
 173 score >2.5 were almost eight times more likely to later have  
 174 candidiasis than those with a score <2.5 [30]. The CS has  
 175 been later validated in a different cohort [31]. The above-  
 176 mentioned risk factors and clinical prediction rules are  
 177 certainly useful for stratifying ICU patients according to  
 178 their risk of IC, but their discriminating ability is still  
 179 unsatisfactory, so many patients without IC might receive  
 180 an unnecessary antifungal therapy.

181 *Recommendations*

- 182 1. Patient stratification:
- 183 • For a correct management of IC and candidaemia,  
 184 physicians should take into account the individual

**Table 3** Risk factors for IC

Hospitalisation in ICU
Acute/chronic organ dysfunction requiring intensive care/invasive procedures (e.g. mechanical ventilation, vasoactive drugs, renal substitution and extracorporeal circulation systems, high-volume fluid or haemocomponents infusions, tracheostomy and others)
Solid organ transplantation (and type) <sup>a</sup>
Onco-haematological diseases (and type) and stem cell transplantation, especially with graft-versus-host disease (GVHD) <sup>a</sup>
Surgery (especially abdominal surgery and surgical revision), trauma and burn patients
Paediatric and neonatal intensive care units <sup>a</sup>
Multiple underlying medical conditions (e.g. elderly patients in medical wards)
Immunosuppressive therapy
Renal failure requiring haemodialysis or haemofiltration
Neutropaenia <sup>a</sup>
APACHE score
Multiple site colonisation
Duration of hospital stay
Previous history of <i>Candida</i> infection
Total parenteral nutrition and use of indwelling catheters
Diabetes mellitus
Previous prolonged antibiotic therapy

<sup>a</sup> Will not be discussed because they are not within the scope of the present consensus

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185 risk profile of each patient. Factors to use to stratify  
186 the risk for a patient of being affected by IC are  
187 listed in Table 3.

188 2. Corrected *Candida* colonisation index [27, 31–33]:

- 189 • A corrected *Candida* colonisation index  $\geq 0.4$  is an  
190 important risk factor for IC, but in many clinical  
191 settings, other stratification tools should be pre-  
192 ferred owing to their greater simplicity of use.

193 3. Ostrosky-Zeichner prediction rule [28–31, 34–38]:

- 194 • The Ostrosky-Zeichner prediction rule (based on  
195 risk factors in asymptomatic ICU patients) is  
196 probably best applied to exclude patients not at  
197 risk (rather than to identify those at risk) of  
198 developing IC, due to its low positive predictive  
199 value and high negative predictive value.

200 4. *Candida* score [30, 31, 37, 38]:

- 201 • The *Candida* score (based on clinical symptoms  
202 and signs of severe sepsis/septic shock) can be used  
203 as a tool for predicting the likelihood of actually  
204 having IC in symptomatic ICU patients, but it is  
205 probably best applied to identify patients without  
206 (rather than those with) IC, due to its low positive  
207 predictive value and high negative predictive  
208 value.

#### 209 *Unresolved issues*

210 A more discriminant stratification tool would be welcome.  
211 In addition, existing prediction rules should be validated  
212 prospectively in randomised and interventional clinical  
213 trials. This would be desirable not only for ICU patients,  
214 but also for other settings, such as surgery, internal medi-  
215 cine and geriatrics. It is currently difficult to quantify the  
216 impact of previous exposure to antibiotics on the risk of IC.  
217 Other settings should be considered in the future, like, for  
218 example, the use of biological response modifiers.

#### 219 Area 2: microbiological diagnosis and clinical 220 management

221 Blood cultures are currently considered the gold standard  
222 for the diagnosis of IC, despite it being shown that blood  
223 cultures are negative in roughly 50 % of patients with  
224 biopsy-proven disseminated IC and in 30 % of those with  
225 single-organ IC [39]. This might be due to the fact that, in  
226 deep-seated *Candida* disease following haematogenous  
227 spread, viable *Candida* cells are rapidly eliminated from  
228 the bloodstream, thus limiting the time window when  
229 *Candida* can be successfully detected in blood [14].

230 Another drawback of blood cultures is that it normally  
231 takes 24–72 h to identify a *Candida* strain growing in the  
232 blood culture. Hence, waiting for culture results before  
233 making a clinical decision determines a delay in the  
234 diagnosis and initiation of appropriate antifungal therapy.  
235 In conclusion, earlier markers of fungal infection are need-  
236 ed in order to improve diagnosis of IC [14]. Among  
237 earlier markers, the detection of galactomannan in blood or  
238 other body fluids is generally considered reliable for the  
239 diagnosis of invasive aspergillosis. For the diagnosis of IC,  
240 two methods have been proposed. The search for mannan  
241 antigen and antimannan antibodies separately have low  
242 sensitivity and specificity, which improve substantially  
243 when the two methods are combined [40–43]. The sensi-  
244 tivity and specificity of these tests have been questioned  
245 when used separately, but a number of reports indicate that,  
246 when they are used in combination, the performance  
247 improves substantially [41, 44]. The beta-D-glucan (BDG)  
248 test is a panfungal test which looks for an antigen that is  
249 present on many fungal cells [45–47], but not on mam-  
250 malian and bacterial cells [46]. Thus, its detection in blood  
251 or other bodily specimens may represent a marker of a  
252 fungal disease. The test has been shown to possess good  
253 sensitivity and a very good negative predictive value [48–  
254 50] when a proper cut-off value is used. Owing to its high  
255 negative predictive value, the BDG test can probably be  
256 used better to exclude an invasive fungal infection (IFI)  
257 [14]. All these diagnostic tests may diagnose an IC earlier  
258 than clinical or culture-based measures [40, 41].

259 Nucleic acid-based diagnostic techniques are, perhaps,  
260 the fastest-growing segment of fungal diagnostics [51].  
261 Generally speaking, molecular-based diagnostic tests can  
262 potentially be very sensitive in detecting an IFI and may  
263 provide results more rapidly than standard diagnostic pro-  
264 cedures, thereby enabling the possibility for earlier diag-  
265 nosis and more timely initiation of antifungal therapy [46,  
266 47, 51, 52]. Many molecular platforms are currently under  
267 investigation [45, 47, 53].

#### 268 *Recommendations*

- 269 1. Significance of *Candida* isolation from non-sterile  
270 body sites [54]:
  - 271 • In the asymptomatic patient, the isolation of a  
272 *Candida* strain from a non-sterile body site (bron-  
273 chial aspirate, tracheal aspirate, bronchoalveolar  
274 lavage fluid or sputum) should not prompt any  
275 antifungal treatment and should be merely consid-  
276 ered as colonisation.
  - 277 • However, in a patient with signs and symptoms of  
278 infection, multiple *Candida* colonisation, including  
279 isolation from urine in a patient fitted with a

280	bladder catheter, might be suggestive of a <i>Candida</i>	96 h of adequate antifungal treatment and despite	328
281	infection and might prompt antifungal treatment.	removal of the central venous catheter, if originally	329
282	• The repeated isolation of <i>Candida</i> from fluids	present), to rule out <i>Candida</i> endocarditis.	330
283	obtained from a surgical drainage should not be	• These patients should be monitored for at least 6	331
284	underestimated and should prompt additional	months, since late <i>Candida</i> endocarditis is not	332
285	investigations, even in the absence of clinical signs	uncommon.	333
286	and symptoms.		
287	• The same applies to <i>Candida</i> isolation from	7. Fundus oculi examination [87–90]:	334
288	peritoneal fluids in a patient undergoing peritoneal	• A fundus oculi examination should be performed	335
289	dialysis.	and possibly repeated in every patient with IC,	336
290	2. Blood cultures [55–62]:	even in the absence of visual disturbances, to rule	337
291	• As a general rule, at least two blood cultures (each	out chorioretinitis and endophthalmitis.	338
292	with both aerobes and anaerobes bottles) should be		
293	obtained in the presence of signs and symptoms	<i>Unresolved issues</i>	339
294	suggestive of infection. One of the two blood	An agreement should be reached among experts about the	340
295	cultures should be obtained both from a peripheral	optimal methodology for polymerase chain reaction (PCR)	341
296	vein and from the central catheter, if present.	and other methods of biomolecular diagnosis [53].	342
297	Patients receiving steroid therapy might have low-	Regarding the BDG antigen detection, open issues are what	343
298	grade fever only. In these patients, a high level of	is the most appropriate cut-off able to maximise the posi-	344
299	suspicion should be maintained.	tive and negative predictive values and to discriminate	345
300	3. Role of BDG [31, 33, 50, 63–76]:	between infection and colonisation. The use of the test in	346
301	• The BDG test as a diagnostic test in a patient with	different patient populations should also be explored, as	347
302	signs and symptoms of infection might be effective	well as its prognostic value and its possible ability to	348
303	in the early diagnosis or exclusion of IC. However,	correlate with clinical severity [90]. Other research options	349
304	the results should be interpreted in the setting of	include the value of the antigen test as a screening test in	350
305	the presence of other risk factors and the patient's	asymptomatic high-risk patients [71, 91], the best initial	351
306	clinical conditions.	timing and the timing of repeat testing [65, 91, 92] and,	352
307	• There is insufficient evidence to recommend the	finally, the possible benefit of combining BDG antigen and	353
308	use of the BDG test as a screening tool in patients	antibody detection [93]. In <i>Candida</i> endophthalmitis, the	354
309	without symptoms.	timing of fundus oculi examination should be better	355
310	• Turnaround time of the results is essential for	defined, as well as the need for and timing of repeated	356
311	timely clinical decisions.	examinations, since small lesions might go initially	357
312	4. Role of the mannan antigen/antimannan antibody test	undetected.	358
313	[40, 41, 77–79]:		
314	• The mannan/antimannan detection test may be	Area 3: prophylaxis	359
315	useful for the diagnosis of IC. The separate	Prophylaxis is the administration of a drug to a patient with	360
316	detection of either mannan or antimannan cannot	risk factors for IC (Table 2) and without clinical signs and	361
317	be recommended.	symptoms of infection. The administration of an antifungal	362
318	5. Nucleic acid-based diagnostic techniques [52, 53, 75,	prophylaxis in a non-immunocompromised patient in the	363
319	80–82]:	ICU without symptoms is not supported by published	364
320	• Diagnostic techniques using biomolecular methods	evidence. The administration of an antifungal in compli-	365
321	are not yet recommended, because of the hetero-	cated surgical patients, such as those with anastomotic	366
322	geneity of the available results, the lack of reliable	leakage or recurrent intestinal perforation, reported as an	367
323	reference standards and differences in techniques.	indication for antifungal prophylaxis in other guidelines,	368
324	6. Echocardiography [83–86]:	should not be defined as prophylaxis but rather as an	369
325	• An echocardiography should be performed in all	empirical, presumptive or pre-emptive therapy. We agree	370
326	patients with persistent candidaemia (defined as	that these patients should receive an antifungal but disagree	371
327	blood cultures persistently positive after at least	to define this practice as prophylaxis. Indeed, these patients	372
		have an infection, often of unknown but probably	373
		polymicrobial aetiology, and usually receive antibacterial	374



375 and antifungal treatments. The issue is dealt with in the  
376 appropriate section of this article.

### 377 Recommendation

- 378 1. Antifungal prophylaxis [28, 31, 94–104]:
- 379 • Antifungal prophylaxis should not be administered  
380 in non-immunocompromised patients.

### 381 Unresolved issues

382 There might be subgroups of patients, such as, for example,  
383 those with obstructive chronic bronchopulmonary disease  
384 or those staying for a long time in the ICU, that might  
385 deserve antifungal prophylaxis. Future studies should aim  
386 to identify these populations and test antifungal prophylaxis  
387 in these specific settings. Studies of antifungal prophylaxis  
388 in asymptomatic patients at high risk for candidaemia  
389 are being performed [105].

### 390 Area 4: therapy for possible/probable IC

391 The administration of antifungal drugs in patients with risk  
392 factors for IC and signs and symptoms of infection but no  
393 definitive documentation of fungal infection (negative or  
394 pending cultures) has been defined in several ways. Some  
395 authors call it “empirical therapy”, while others call it  
396 “pre-emptive” or “presumptive” therapy. As shown in  
397 Table 3, in general, empirical therapy means administering  
398 an antifungal in the absence of any indication other than  
399 fever and compatible symptoms, while the presumptive or  
400 pre-emptive approach implies the existence of additional  
401 factors increasing the likelihood that a fungal infection is  
402 present. However, in a very practical approach (as opposed  
403 to research settings), we believe that these are more  
404 semantic than practical issues, since the bottom line is that,  
405 in such instances, physicians start an antifungal therapy  
406 because they think that there are reasons to believe that the  
407 patient might have a fungal infection. What differs is the  
408 likelihood of the presence of a fungal infection and the risk  
409 of treating too early, too late or unnecessarily: what physicians  
410 need to know is whom and when to treat.

411 In 2005, Morrell and coworkers first demonstrated the  
412 clinical significance of delaying treatment in patients with  
413 IC. In a cohort of 134 patients, the initiation of antifungal  
414 therapy more than 12 h after the first positive blood culture  
415 was associated with an increased risk of death: the longer  
416 the time interval, the higher the mortality [9]. This was  
417 later confirmed by Garey and coworkers in a retrospective  
418 multi-centre cohort study of 230 patients who were pre-  
419 scribed fluconazole: the time to the initiation of fluconazole  
420 therapy was strongly related with outcome [10]. More

recently, another retrospective cohort study of adult  
patients with IC reached the same conclusion, even when  
echinocandins were used [11]. The logical consequence of  
these observations prompted some investigators to assess  
the performance of an empirical antifungal approach in  
ICU patients with persistent fever not responding to anti-  
bacterial therapy, without trying to select patients at higher  
risk for candidaemia. In a multi-centre, prospective and  
randomised clinical trial in 270 critically ill ICU patients,  
Schuster et al. [106] failed to demonstrate any advantage  
for fluconazole compared to placebo using a composite  
endpoint for success.

Subsequently, in 2009, the IDSA guidelines for the  
management of candidiasis introduced the concept of  
empirical treatment for critically ill patients with risk factors  
for IC and no other known cause of fever, recommending  
that the decision should be based on the clinical assessment  
of risk factors, serologic markers for IC and/or culture data  
from non-sterile sites [12]. This approach is considered valid  
by many experts and the general opinion is that the administration  
of antifungal therapy should be guided by the evaluation of risk  
factors, use of clinical prediction rules and biological markers.

### Recommendations

1. Timing of treatment [1, 9, 10, 31, 33, 41, 65, 67, 69–72, 77, 107–111]:
  - The decision of starting an antifungal therapy in the absence of a positive culture from a normally sterile site should be based on a careful estimation of the individual risk of being affected by a (so far) occult fungal infection. This estimation should preferably be based on criteria or scores stemming from multi-variable analyses and validated prospectively (including multi-site colonisation) (see León’s rule).
  - The detection of biological markers for *Candida* (BDG, mannan/antimannan) makes the presence of a fungal infection even more likely and may be an important adjunctive tool, whose results should be evaluated within the overall clinical setting.
  - Patients who underwent multiple laparotomies with intra-abdominal leakage are likely affected by a fungal infection and certainly deserve an antifungal therapeutic intervention.
2. Treatment [111–119]:
  - An echinocandin should be preferred as the first-line therapy because of:
    - Fungicidal activity
    - Activity against strains embedded in biofilms

- 470 • Activity against fluconazole-resistant and non-  
471 *albicans* strains that are resistant to fluconazole  
472 • Favourable safety profile  
473 • Low propensity for interactions
- 474 • This is particularly true for medical or surgical  
475 critically ill patients with prolonged hospital stay  
476 (over 1 month), prior prolonged antibiotic therapy  
477 and recent fluconazole exposure, all of which are  
478 factors potentially able to affect the selection of  
479 fluconazole non-susceptible *Candida* strains.
- 480 • Significant alternatives, in critically ill patients, are  
481 lipid formulations of amphotericin B (especially  
482 the liposomal preparation) and, to a lesser extent,  
483 voriconazole, but not amphotericin B deoxycho-  
484 late, in particular when a site other than the blood  
485 infection site is suspected (e.g. peritonitis). This is  
486 supported by the lack of pharmacokinetic/pharma-  
487 codynamic (PK/PD) consideration of echinocan-  
488 dins in peritoneal fluid, although strong evidence is  
489 also lacking for amphotericin B.
- 490 • Therapy should be reassessed after 72–96 h, based  
491 on the patient's clinical conditions and microbiol-  
492 ological results.
- 493 • Intravenous or oral fluconazole still remains a valid  
494 option but should be reserved for second-line or  
495 step-down therapy.

#### 496 *Unresolved issues*

497 Large prospective studies are needed in order to validate  
498 the classification of therapeutic strategies and its usefulness  
499 and applicability both in the clinical practice and in the  
500 context of clinical trials. Additionally, optimal duration of  
501 empirical therapy is still undefined. The true epidemio-  
502 logical impact of *Candida* spp. in peritonitis is far from  
503 being defined and comparative studies are lacking. In this  
504 respect, studies about the PK/PD behaviour of echinocan-  
505 dins in the abdominal compartment should be performed.

#### 506 Area 5: targeted therapy

507 Several randomised clinical trials have demonstrated the  
508 efficacy of echinocandins in the treatment of candidaemia  
509 [86, 120–123]. Caspofungin was shown to be as effective as  
510 and less toxic than deoxycholate amphotericin B, mica-  
511 fungin was both as effective and less toxic than liposomal  
512 amphotericin B in one study, and as effective as caspo-  
513 fungin in another study, while anidulafungin was more  
514 effective than fluconazole in a study in which candidaemias  
515 due to *C. krusei* were excluded, although the statistical  
516 conclusion of superiority was criticised. As a consequence,  
517 international guidelines have included echinocandins as the

first choice for antifungal therapy in proven *Candida* 518  
infections [12, 13, 124]. Recently, a systematic review of all 519  
randomised antifungal clinical trials in documented candi- 520  
daemia and deep-seated *Candida* disease which led to the 521  
approval of the three available echinocandins showed that 522  
the administration of an echinocandin, as compared with 523  
any other antifungal therapy, was significantly associated 524  
with survival and success of therapy [120, 121, 123, 125]. 525  
Survival is associated with indwelling catheter removal 526  
[126]. In a previous analysis, Gafter-Gvili et al. [127] 527  
showed a decreased mortality rate in patients with candi- 528  
daemia and other invasive *Candida* infections treated with 529  
an echinocandin in comparison with other antifungal drugs. 530  
Which echinocandin should be preferred is an unresolved 531  
issue. Firstly, there is no evidence for the superiority of one 532  
echinocandin over another. There are differences in fungal 533  
minimum inhibitory concentration (MIC) values, liver 534  
toxicity, volume of liquids infused and PK/PD parameters, 535  
but no clinical study has been performed to analyse whether 536  
or not these differences have clinical implications in terms 537  
of efficacy or toxicity. The indications are different, with 538  
caspofungin having the higher number of indications. All 539  
three agents are approved for the treatment of IC in non- 540  
neutropaenic adults, although according to the European 541  
Medicines Agency (EMA) summary of product character- 542  
istics, the efficacy of anidulafungin in patients with deep- 543  
seated *Candida* infections or intra-abdominal abscess and 544  
peritonitis has not been established. A subsequent phase III 545  
exploratory study shows that these indications would also 546  
be covered [128]. In addition, caspofungin and micafungin 547  
are approved not only for non-neutropaenic but also for 548  
neutropaenic patients with candidaemia and for paediatric 549  
patients (micafungin for newborns, as well). Other 550  
approved indications are, only for caspofungin, salvage 551  
therapy in invasive aspergillosis and empirical therapy of 552  
febrile neutropaenia and, only for micafungin, prophylaxis 553  
of fungal infections in the first month after hematopoietic 554  
stem cell transplantation (HSCT). Probably the main 555  
downside for all echinocandins is their lack of ocular pen- 556  
etration, which can be an issue, since *Candida* endoph- 557  
thalmitis can seldom be observed as a complication in 558  
candidaemia. To reduce direct health care costs and impact 559  
on local resistance patterns, de-escalation from echinocan- 560  
dins to fluconazole is advisable, if the isolated *Candida* 561  
strain is fluconazole-susceptible and the patient is clinically 562  
stable [12, 120, 122, 123]. However, there is no evidence 563  
about the timing of such de-escalation. The reduced in vitro 564  
susceptibility to echinocandins of certain *Candida* strains, 565  
such as *C. parapsilosis* and *C. guilliermondii*, has been 566  
shown in several studies, although this finding does not 567  
appear to be consistently relevant in clinical practice [86, 568  
129–133]. A large study in French hospitals has shown that, 569  
among patients pre-exposed to caspofungin (the 570

571 echinocandin most often used in Europe), the spectrum of  
572 subsequent *Candida* infections shows an increasing number  
573 of species with higher MICs to echinocandins. The use of  
574 micafungin is complicated in Europe because the EMA  
575 decided to put a warning related to the possible risk of  
576 hepatic toxicity as observed experimentally in animal  
577 models, despite the lack of clinical demonstration that this  
578 is really an issue in practical terms. For this reason,  
579 according to the EMA, the drug should be used only in the  
580 absence of any other alternative.

581 Alternatives to echinocandins and fluconazole are lipo-  
582 somal amphotericin B, which is also fungicidal and active  
583 against biofilm, but maintains a certain degree of renal  
584 toxicity and is quite expensive, and voriconazole, which is  
585 potentially very useful in ocular, central nervous system  
586 (CNS) and bone infections, but shows several problems  
587 related to possible azole acquired cross-resistance, hepatic  
588 and neurological toxicity, and drug interactions [86, 113,  
589 120–123, 134–143]. The PK/PD behaviour of several drugs  
590 in bones is suboptimal, particularly unpredictable and even  
591 disappointing; it is, therefore, more relevant than in other  
592 settings to consider the MIC of the isolated pathogen(s).  
593 Itraconazole and posaconazole are not currently indicated,  
594 due to the lack of controlled, randomised, large-scale  
595 clinical trials [144].

## 596 Recommendations

### 597 1. First-line therapy [86, 113, 120–123, 134–142]:

- 598 • All patients with isolation of a *Candida* strain from  
599 a sterile site deserve antifungal therapy.
- 600 • An echinocandin should be used as the first-line  
601 treatment in critically ill patients with IC.
- 602 • There are no data on which echinocandin should be  
603 used and the choice should be based on the  
604 respective indications of use, possibly PK/PD  
605 factors and personal experience regarding use.
- 606 • Acceptable alternatives in critically ill patients are  
607 lipid formulations of amphotericin B (especially the  
608 liposomal preparation) and, to a lesser extent,  
609 voriconazole, but not amphotericin B deoxycholate.
- 610 • In stable patients, fluconazole is an acceptable  
611 alternative, although it should be used with great  
612 caution, since the drug is not active on strains  
613 embedded in biofilms, has only fungistatic activity,  
614 is not active against *C. krusei* and is poorly active  
615 against *C. glabrata*. In addition, azole resistance in  
616 previously sensitive strains is increasing.
- 617 • Itraconazole and posaconazole are not currently  
618 indicated.

### 619 2. Treatment in case of risk of resistance [22, 120, 125, 620 145, 146]:

- In patients with prior relevant exposure to an  
antifungal agent, a change in class, especially for  
azoles, should be encouraged. 621  
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- 3. Treatment duration [120, 122, 123]: 624
  - Patients should be treated for at least 14 days after  
the last positive blood culture (this requires blood  
cultures to be performed daily until negativisation). 625  
626  
627
  - De-escalation from an echinocandin to intravenous  
or oral fluconazole should be encouraged when the  
patient is clinically stable and the isolated strain is  
susceptible to fluconazole. However, the exact  
timing for shifting to fluconazole is basically  
unknown and may vary from patient to patient,  
depending on the patient- and pathogen-related  
factors. 628  
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  - Treatment duration might be much longer in deep-  
seated infections. 636  
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- 4. *Candida* endocarditis [83, 147]: 638
  - *Candida* endocarditis should be treated with an  
echinocandin (mostly caspofungin, because of the  
largest amount of evidence) or liposomal amphi-  
tericin B plus flucytosine. 639  
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  - Surgical intervention and removal of intracardiac  
devices is certainly recommended, whenever poss-  
ible. When cardiosurgery is impossible, long-term  
suppressive fluconazole might be an option, once  
clinical remission has been obtained with first-line  
therapy and the isolated strain is susceptible to  
fluconazole. 643  
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- 5. Ocular candidiasis [89, 148–152]: 650
  - In *Candida* endophthalmitis, the preferred treat-  
ment should be voriconazole, because of its ability  
to concentrate in the eyes, although resistance  
problems might be considered. Liposomal amphi-  
tericin B and fluconazole (for fluconazole-sensitive  
strains) are valid alternatives. The echinocandins  
are contraindicated because of their poor ocular  
penetration. 651  
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  - The optimal duration of treatment is unknown, but  
should certainly be longer (at least until the  
resolution of ophthalmologic signs) than in uncom-  
plicated IC. 659  
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  - In case of vitritis, vitrectomy and intravitreal  
infection, deoxycholate amphotericin B should be  
considered. 663  
664  
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- 6. Management of intravascular catheters in IC [86, 153]: 666
  - Intravascular catheters should definitely be  
removed in patients with documented IC. If an  
intravenous line is indispensable, it should be 667  
668  
669

- 670 inserted in a different vein. The timing of removal  
671 is questionable, although it seems reasonable to  
672 proceed to removal as soon as possible.
- 673 • In the rare instances in which the catheter cannot  
674 be removed (e.g. long-term, tunnelled catheters or  
675 in the absence of viable alternatives), an agent  
676 active against strains embedded in biofilm (echi-  
677 nocandin or polyene) should be preferred. Lock  
678 therapy with the same drug (in addition to intra-  
679 venous therapy) might be an option, though good  
680 evidence is lacking on this issue.
- 681 7. Central nervous system [154–158]:
- 682 • In CNS *Candida* infections, voriconazole or  
683 liposomal amphotericin B plus flucytosine should  
684 be first-line agents. Consider a long-term sup-  
685 pressive regimen (i.e. until normalisation of  
686 clinical and laboratory signs), usually with  
687 fluconazole.
- 688 8. Urinary candidiasis [159, 160]:
- 689 • A positive culture for *Candida* in urine from a  
690 patient without a urinary catheter deserves  
691 treatment.
  - 692 • If the infection is due to a fluconazole-susceptible  
693 strain, then fluconazole should be the first choice.  
694 With fluconazole-non-susceptible strains, a liposo-  
695 mal preparation of amphotericin B should be used.
  - 696 • Treatment should be continued for at least 7 days  
697 in uncomplicated cystitis, but longer in  
698 pyelonephritis.
  - 699 • Patients fitted with a urinary catheter and with a  
700 positive urine culture for *Candida* should be  
701 carefully observed for possible systemic infec-  
702 tion, especially in the presence of other coloni-  
703 sation sites. Catheter replacement should be  
704 considered, upon clinical judgement, and culture  
705 repeated.
- 706 9. Bone and joint infections [161–164]:
- 707 • Treatment of *Candida* bone and joint infections  
708 should be based on susceptibility data (if available)  
709 and PK/PD considerations.
  - 710 • Septic arthritis should be treated for at least  
711 6 weeks, while osteomyelitis and prosthetic joint  
712 infections should probably require longer treat-  
713 ments (6–12 months).
  - 714 • In septic arthritis, debridement must be performed,  
715 considering the risk of long-term sequelae of  
716 untreated arthritis.
  - 717 • Infected prosthetic devices should be removed,  
718 whenever feasible. If removal is not feasible,  
719 chronic suppressive therapy is an option.

## Unresolved issues

720  
721 Several areas for research are currently open. For example,  
722 there is not enough information available about combina-  
723 tion therapy in severe, deep-seated infections (e.g. perito-  
724 nitis) or in IC with septic shock or endocarditis. Indications  
725 about the time to de-escalation to fluconazole is another  
726 open issue. No information is available about posaconazole  
727 and, to a lesser extent, itraconazole. The role of higher  
728 dosages of echinocandins should be investigated, again in  
729 the most severe infections, as well as the role of lock  
730 therapy with echinocandins, particularly when the central  
731 venous catheter cannot be removed; on this issue, some  
732 trials have been designed [165]. CNS infections are rare,  
733 but little information is available about treatment [89, 148,  
734 149].

## Discussion

735  
736 The diagnosis and management of IC is an extremely  
737 complex exercise, especially in settings where the index of  
738 suspicion is low. The recently published ESCMID guide-  
739 lines provide an excellent state-of-the-art of the existing  
740 evidence in this field [13]. With this set of guidelines, we  
741 offer a different perspective on several issues.

742 An innovative trait of our work is that we attempted to  
743 reconcile discrepancies in the literature by developing a  
744 comprehensive set of definitions of diagnostic categories  
745 and treatment strategies. In particular, the pre-emptive  
746 definition was adopted to account for those (rare) patients  
747 with positive biomarkers and no symptoms, in analogy to  
748 the cytomegalovirus (CMV) setting, where the definition of  
749 pre-emptive is based on the molecular detection of viral  
750 DNA in the absence of symptoms and signs of diseases.  
751 The presumptive strategy was adopted to stress the growing  
752 relevance of biomarkers as opposed to microbiological  
753 isolates in the diagnosis of IC. We believe that the adoption  
754 of these definitions may help to define inclusion criteria in  
755 future studies and improve the comparability of results  
756 from current and future studies.

757 On the other hand, we decided to have a very practical  
758 approach and to avoid semantic considerations trying to  
759 differentiate in practice between empirical, presumptive  
760 and pre-emptive therapy: there is only one therapy for a  
761 patient in which the attending physician is convinced  
762 (based on clinical and microbiological considerations) that  
763 a *Candida* infection is possible/likely or proven.

764 We aimed to stress candidaemia and IC as a hospital-  
765 wide issue, as opposed to an infection limited to ICU  
766 and surgical patients, from where most of the literature  
767 has been derived. In our view, one of the greatest  
768 challenges in the management of IC is to raise awareness



769 in internal medicine wards and other situations in which  
 770 IC was rare in the past. Another important issue it to  
 771 optimise the use of the new microbiological diagnostic  
 772 techniques. Once the diagnosis is suspected, further  
 773 management should be guided by experts in clinical  
 774 microbiology, infectious diseases and pharmacology,  
 775 abreast of the latest developments in the field. Risk  
 776 stratification (in terms of estimating the risk of actually  
 777 having IC) is extremely important when deciding whether  
 778 or not to start therapy, allowing better resource  
 779 allocation (high-cost diagnostics, high-cost drugs); in this  
 780 setting, a better stratification tool would be welcome.  
 781 However, stratification in terms of clinical risk also  
 782 applies to the setting of targeted treatment; for instance,  
 783 allowing de-escalation to lower-cost drugs (e.g. fluco-  
 784 nazole) as soon as the patient becomes clinically stable.  
 785 We are convinced that the BDG test should be used for  
 786 the identification of patients deserving early treatment  
 787 (with the proviso that the local logistics ensures timely  
 788 results) to improve the likelihood of diagnosis. However,  
 789 in these times of resource constraints, we realise that not  
 790 all hospitals can afford the relevant expense for this test.  
 791 For this reason, we believe that the clinical prediction  
 792 rules are also useful and can represent a reliable method  
 793 for making clinical decisions. We feel confident in recom-  
 794 mending the administration of echinocandins, but we  
 795 also believe that a de-escalation approach, when feasible,  
 796 is safe and cost-saving. The time to de-escalate is con-  
 797 troversial and every recommendation is arbitrary, in the  
 798 absence of specific studies. However, we believe that the  
 799 10 days indication in the ESCMID guidelines is exces-  
 800 sive and that a 72–96-h limit should be more suitable  
 801 [120, 122, 123].

802 PK/PD considerations are important for making ther-  
 803 apeutic decisions, especially when published experience  
 804 is missing or based on small numbers. For this reason,

we strongly support the use of voriconazole for patients  
 with CNS or ocular infections, despite the risk of dealing  
 with an azole-resistant strain [143].

We hesitate in recommending an echocardiography  
 (especially transesophageal) in all patients with docu-  
 mented IC and would prefer to limit the indication to  
 patients with persistently positive blood cultures.

Other limitations and difficulties that we encountered in  
 the consensus process mainly stem from the lack of high-  
 quality evidence on many issues related to IC, owing to a  
 number of factors: the relative rarity of the condition, not  
 allowing large generalisable studies; wide variability in  
 diagnostic methods, definitions and inclusion criteria  
 across studies, with, for instance, likely selection bias  
 (patients in wards other than the ICU are less likely to be  
 correctly investigated and diagnosed), limiting between-  
 study comparisons and generalisability; suboptimal per-  
 formance of the available diagnostic tools for early iden-  
 tification, possibly generating a misclassification bias in  
 many studies, reducing our ability to assess the efficacy of  
 interventions, as in the case of empirical treatment strategy.

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## Appendix

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