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Original Article

MEDical wards Invasive Candidiasis ALgorithms (MEDICAL): Consensus proposal for management

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ABSTRACT

Introduction: A majority of invasive *Candida* infections occur in medical wards; however, evidence for management in this setting is scarce and based primarily on the intensive care or surgical setting. On behalf of the Italian Society for Anti-Infective Therapy (SITA) and the Italian Federation of Associations of Hospital Doctors on Internal Medicine (FADOI), the MEDICAL group produced practical management algorithms for patients in internal medicine wards.

Methods: The MEDICAL group panel, composed of 30 members from internal medicine, infectious disease, clinical pharmacology, clinical microbiology and clinical epidemiology, provided expert opinion through the RAND/UCLA method.

Results: Seven clinical scenarios were constructed based on clinical severity and probability of invasive candidiasis. For each scenario, the *appropriateness* of 63 different diagnostic, imaging, management, or therapeutic procedures was determined in two Delphi rounds. The *necessity* for performing each *appropriate* procedure, was then determined in a third Delphi round. Results were summarized in algorithms.

Discussion: The proposed algorithms provide internal medicine physicians and managers with an easy to interpret tool that is exhaustive, clear and suitable for adaption to individual local settings. Attention was paid to individual patient management and resource allocation.

1. Introduction

Invasive candidiasis (IC) is increasingly recognized as a frequent problem among patients hospitalized in internal medicine wards, owing to the high prevalence of frail patients in this setting. Such patients often have risk factors, including mucosal or cutaneous barrier disruptions, invasive procedures, endovascular devices, parenteral nutrition, cancer, chronic renal failure, renal transplantation, liver disease, immunosuppressive treatments for systemic connective tissue diseases, extensive exposure to broad spectrum antibiotics and multisite Candida colonization [1–7].

Moreover, mortality from IC in medical wards is high, often comparable to that in intensive care units (ICUs). In contrast, the level of

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diagnostic suspicion and timely therapy are variable and frequently inadequate [8,9]. These epidemiological features have contributed to defining IC as a public health problem with excess mortality, prolonged hospital stays, and significant costs [10].

Despite attention to IC in medical wards, the evidence-base for management and treatment is primarily derived from other settings, such as ICU, transplant units, surgery or hematology wards, and most guidelines are directed towards these settings [11,12]. However, patients in medical wards are often more complex and have more and different comorbidities than those "traditionally" studied in earlier experiences on IC. In our opinion it is not appropriate to directly apply guidelines created for other settings to the internal medicine setting [13,14].

To address the need for practical guidance on medical patients, based on imperfect evidence, the Italian Society for Anti-Infective Therapy (SITA) and the Italian Federation of Associations of Hospital Doctors in Internal Medicine (FADOI) have supported this consensus process to develop indications on the diagnosis, management and treatment of IC, and to support antifungal stewardship programs [15,16]. This document applies to a patient admitted to a medical hospital ward who:

- Has not received a solid organ transplant in the last 24 months
- Does not present a surgical reason for admission (excluding post-operative medical management)
- Does not present severe absolute neutropenia (neutrophil count < 0.5×10^9/L) [17]
- Does not present with septic shock on admission to the medical ward (such patient should be managed as an ICU patient)

Table 1
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2. Methods

2.1. Project design, expert panel and literature search

The project was managed by the MEDICAL group, a three-layer (supervisory, steering committee, expert panel), multidisciplinary team, including experts in infectious diseases and internal medicine, clinical microbiology, clinical pharmacology, and methodology (Table 1). The final project structure, composition of the expert panel, methods, Authorship criteria, and management of potential conflicts of interest were decided in two preparatory rounds. Expert opinion from the 30-member panel was elicited through a modified Delphi process (RAND/UCLA Method) [18].

The entire process, including preparatory meetings, literature search, three Delphi rounds, an *interim* meeting of the steering committee and the final consensus conference took place between January and October 2015.

Evidence was collected by searching the PubMed literature database with the query terms (candid*[all fields] OR invasive fungal disease*[all fields] OR invasive fungal infection*[all fields]). In addition, the bibliographies of retrieved papers were manually scanned to identify additional evidence. Search results were updated weekly throughout the project.

2.2. Consensus process

The panel scored the *appropriateness* of 63 different diagnostic, imaging, management, or therapeutic procedures in seven clinical scenarios. Two scoring rounds were conducted by email. *Appropriateness* was scored on a scale of 1 (usually not appropriate) to 9 (always appropriate). Terminology for classifying the procedures is presented in Box 1 [19].

The median score and the 30–70 interpercentile range corrected for asymmetry (IPRAS) were calculated. Procedures were classified as inappropriate, uncertain, appropriate with disagreement or appropriate without disagreement. After viewing the results of the first round, in which their own responses were highlighted, panel members were asked to review their choices in the second round. Then, in a third scoring round, experts rated the *necessity* (Box 1) of each procedure that had been classified "appropriate" without disagreement.

Steering committee members drafted separate clinical management algorithms for sepsis and severe sepsis. The reader is referred to published guidelines for treatment of specific clinical localizations of IC (e.g., osteomyelitis, endophthalmitis) [20]. At a consensus conference on October 1–2, 2015, the panel finalized the algorithms, taking healthcare costs into consideration, as well as benefits. Consensus was defined as ≥90% agreement.

2.3. Operational definitions

Invasive Candida infections are more common in certain populations, due to the higher incidence of risk factors. We identified candidate risk factors from published studies and risk scores developed and validated for ICU patients [8,21–27]. 5 days of antibiotic exposure, 10 days prior hospitalization, and prior candida infections were chosen as risk factor for IC following consensus procedure, based upon literature review and clinical expertise of participants. Risk factors considered relevant by ≥90% of the panel were included in the analysis (Box 2). Stable clinical conditions were defined as normal vital signs and no organ failure.

Operational definitions were adopted also for IC (Box 3), and the concepts of sepsis, severe sepsis and septic shock [20,28,29]. Persistent candidemia was defined as isolation of the same Candida species > 72 h after initiation of antifungal therapy [30,31]. Surveillance cultures were defined as sampling from distinct non-blood body sites in absence of any clinical indication, performed only to determine colonization status. Fundus oculi and echocardiographic evaluations imply serial assessments, because pathological changes may not be evident in early phases of IC.

2.4. Clinical scenarios

Likelihood of IC was operationally defined as certainty (patients with microbiological diagnosis (blood culture positivity) of IC, high (patients with two or more risk factors), or low (patients with one risk factor only). Hypothetical patients were stratified into one of seven clinical

Box 1
Terminology used to describe procedures

- "*Could be considered*" refers to a procedure that is indicated only in specific clinical conditions.
- "*Appropriate*" is used when the overall benefits of the procedure outweigh harms, and the procedure is recommended if it is available in the specific clinical setting
- "*Necessary*" is used when there is a reasonable chance that the procedure will benefit the patient, and it would be improper care not to offer it to a patient.

Box 2
Selected risk factors for invasive candidiasis

Broad spectrum antibiotic treatment ongoing for at least 5 days
Central venous catheter (CVC) or peripherally inserted central catheter (PICC)
Parenteral nutrition
Chemotherapy for solid and hematological tumors (including steroids)
Hospitalization > 10 days in previous 3 months (including nursing homes/long-term care facilities)
Prior candidemia
Candida colonization in >1 site
Transferred from ICU
Dialysis

Box 3
Definition of invasive candidiasis

Invasive candidiasis (IC) indicates either a deep-seated Candida infection or candidemia. The following categories of diagnostic certainty were used:

- Proven IC: microbiological evidence of Candida, or yeast cells, hyphae or pseudohyphae at histology or on direct examination in a normally sterile tissue or organ (i.e., *excluding* urine, sputum, bronchoalveolar lavage, mucous membrane swabs and specimens from skin).
- Probable IC: concomitant presence of an underlying disease predisposing to IC, two or more risk factors (Box 2), with signs of active infection [32], and at least one positive antigen test (e.g., beta-D-glucan, mannan/antimannan).
- Possible IC: concomitant presence of an underlying disease predisposing to IC, one risk factor (Box 2), with signs of active infection [32], but without microbiological confirmation.

Table 2
Clinical scenarios based on severity of sepsis and risk factors for invasive candidiasis.

	Lower IC probability 1 risk factor	Higher IC probability 2 or more risk factors	Proven IC Microbiological diagnosis
Asymptomatic	Not considered	Scenario 1	Not applicable
Sepsis	Scenario 2	Scenario 3	Scenario 4 (excluding diagnostic procedures)
Severe sepsis	Scenario 5	Scenario 6	Scenario 7 (excluding diagnostic procedures)

Note: septic shock/critically ill patients (with a life-threatening condition, with changes in one or more vital functions – circulation, breathing, mental status – and in need of organ support) is not within the scope of this consensus.

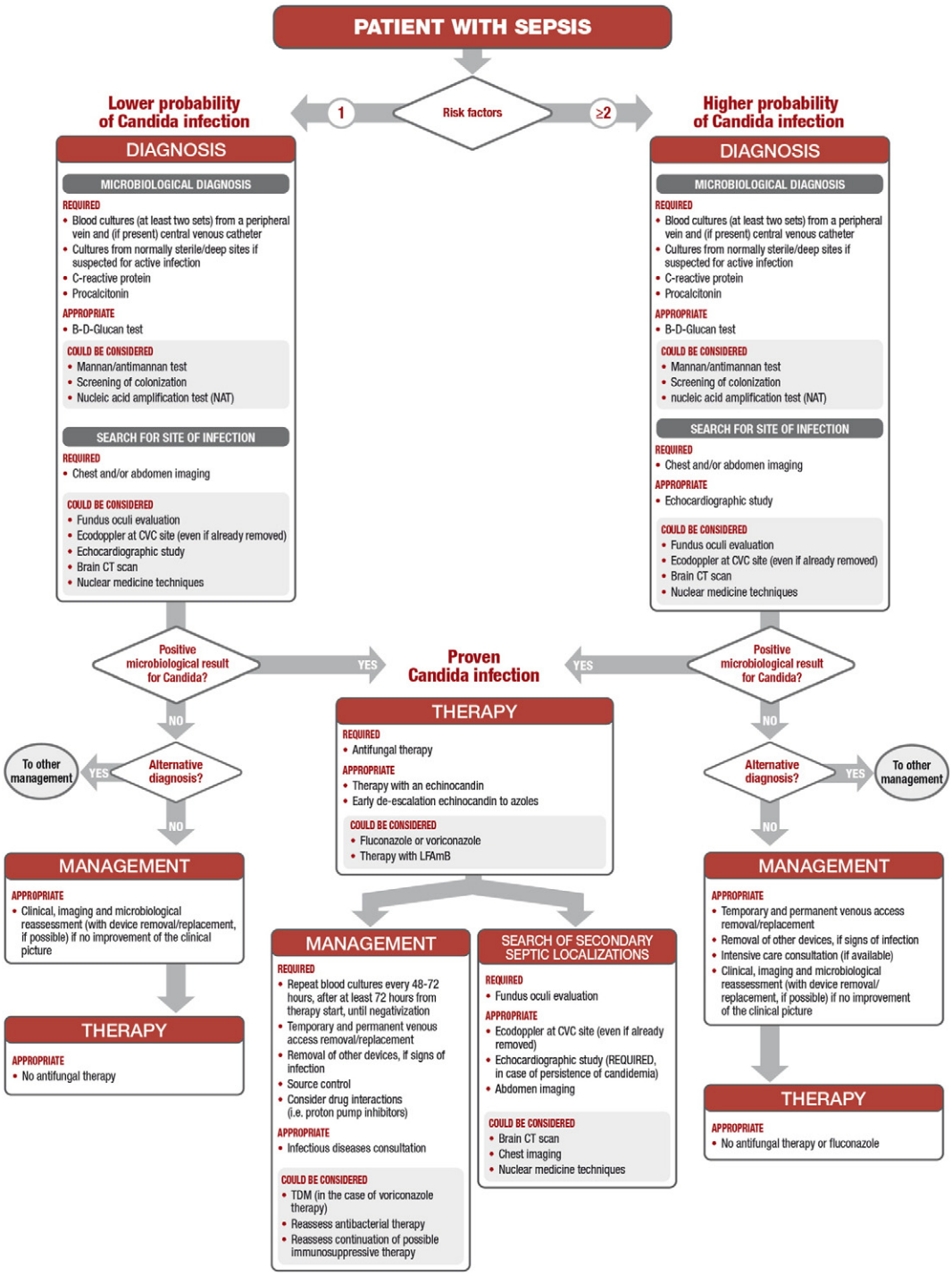

Fig. 1. Proposed algorithm for the management of a patient with sepsis in internal medicine wards. Procedures deemed *necessary* in the RAND/UCLA process are required.

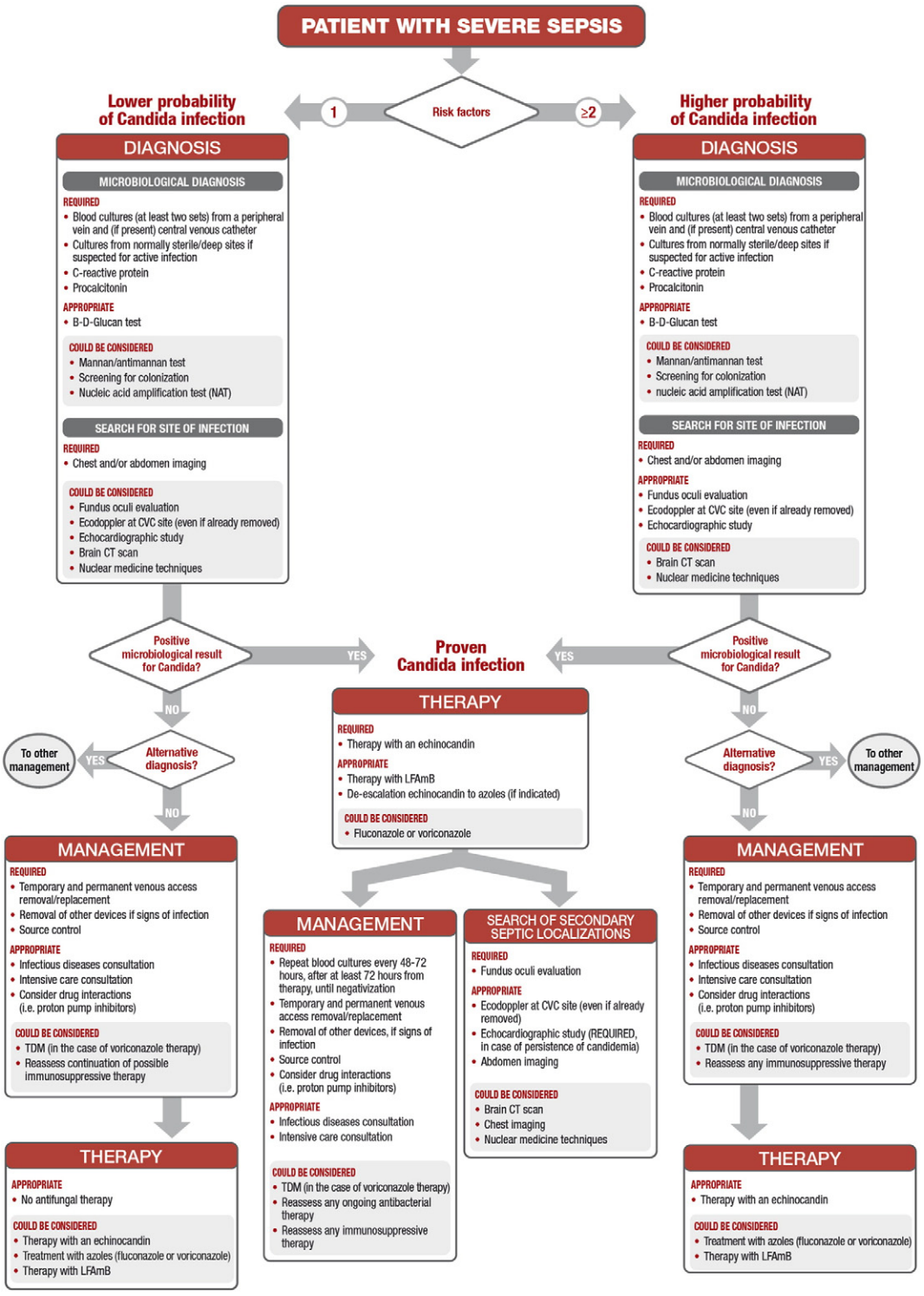

Fig. 2. Proposed algorithm for the management of a patient with severe sepsis in internal medicine wards. Procedures deemed *necessary* in the RAND/UCLA process are required.

scenarios (Table 2), based on both clinical severity (asymptomatic, sepsis or severe sepsis) (1) and the likelihood of having IC, as defined in Box 3.

3. Results

The algorithms are presented according to clinical severity: patients with sepsis (Fig. 1) or severe sepsis (Fig. 2), each with three corresponding scenarios: lower risk of IC, higher risk for IC and proven diagnosis (defined in Box 3). Asymptomatic patients have not been included in the algorithms; their management is described in Section 3.1.

3.1. Asymptomatic patient with risk factors for IC

Neither therapy nor prophylaxis is recommended for this group of patients. The primary goal should be to reduce the risks of developing IC. Multiple colonization is not a risk factor per se, but, because endogenous colonization is the source for the majority of severe episodes of IC,

it should be taken into account if the patient develops signs and symptoms of IC [33]. The cost/benefit ratio for colonization screening in the medical setting is not well established and should be discourage.

The indication for peripherally or centrally infused parenteral nutrition in the medical setting should be reassessed frequently in patients with risk factors for invasive candidiasis [34]. Patients with diabetes or concomitant *C. difficile* colitis might have invasive candidiasis without fever and rarely also without SIRS, patients with these comorbidities and risk factors for invasive candidiasis should undergo a diagnostic work-up for invasive candida infections, including non-cultural serologic methods, where available. The group agrees that there is no indication for empirical or pre-emptive antifungal treatment in this setting.

3.2. Symptomatic patients

A patient with signs and symptoms of infection must have at least two blood cultures sets performed, one from a central venous catheter (CVC), if present. Additional samples from any clinical site suspect for localization of infection should be tested. In addition, plasma levels of the C-reactive protein and procalcitonic concentrations should be evaluated, despite their low specificity and sensitivity. Beta-D-glucan (BDG) has a high negative predictive value, which may help to exclude IC. However, this test was graded as *appropriate* but not *necessary* because it is not available in all settings. The mannan-antimannan assay can also be considered, although there is less evidence on the clinical use of this test. Surveillance cultures may be performed, with the sole aim of assessing colonization, which is not per se an indication for antifungal therapy. To date, PCR and other nucleic acid-based tests are not recommended for widespread use at the clinical level.

3.2.1. Non-critically ill patients with sepsis: Algorithm 1 (Fig. 1)

This patient shows signs and symptoms of infection, but is in relatively stable clinical condition. Whereas the causative agent could be *Candida* spp., the likelihood of a *Candida* infection is lower if ≤1 risk factor is present (scenario 2), and higher if ≥2 risk factors are present (scenario 3). In medical wards, most patients present multiple known risk factors for IC, thus the "high-risk" scenario is probably more frequent there. The management goal is correct diagnosis of IC (and its complications) or its exclusion, and selecting the correct empirical treatment.

3.2.2. Patients without confirmed IC infection

A watchful waiting approach, is *appropriate*, with re-assessment as clinically indicated. If antifungal treatment is started, fluconazole is an acceptable choice, unless there are risk factors for infection with fluconazole-resistant strains (e.g., previous therapeutic courses of fluconazole).

If microbiological tests do not lead to a diagnosis of *Candida* infection and clinical conditions do not improve, then clinical, imaging and microbiological reassessment (with device removal/replacement, if possible) are appropriate.

3.2.3. Patients with confirmed IC infection

In patients with a confirmed microbiological diagnosis, but relatively stable clinical condition (scenario 4), the aim of management to select the correct targeted therapy, reduce the risk of complications or relapse, and carefully screen for secondary localizations.

Even if the patient is not critically ill, clinicians should administer antifungal therapy as early as possible, preferably an echinocandin. Early de-escalation to fluconazole is appropriate, if supported by species identification and susceptibility tests. Possible therapeutic alternatives, depending on the isolated strain and/or local epidemiology, are fluconazole, voriconazole or a lipid formulation of amphotericin B (LF-AmB), especially if already started empirically or for other reasons (e.g., treatment with an echinocandin during the previous 30 days).

Clinical follow-up would necessarily include repeat blood culture every 48–72 h, device removal and possibly source control if imaging results reveal a suspected deep infection; an infectious disease clinician should be consulted. Screening of secondary septic localizations, including fundus oculi evaluation, echocardiograph, and ultrasound scan of neck or arm vessels at the CVC site, are *necessary,* especially in patients with persistently positive blood cultures.

3.3. Critically ill patients with severe sepsis: Algorithm 2 (Fig. 2)

This patient shows severe signs and symptoms of infection and is clinically unstable. The causative agent could be *Candida* spp.; the probability is lower if there are ≤1 risk factor (scenario 5), and higher if there are ≥2 risk factors (scenario 6). As noted above, scenario 5 is much more frequent in the medical ward, because of patient complexity and comorbidities. In patients with severe sepsis, but a low likelihood of IC, the aims of management are the diagnosis of IC (and its complications) and selecting the appropriate empiric treatment.

3.3.1. Patients without confirmed IC infection

Imaging studies upon clinical suspicion are indicated for investigating the source of sepsis. Removal of unnecessary devices is considered good practice. Infectious disease and intensive care consultations are *necessary*, and additional consultations (e.g., surgery, cardiac surgery, interventional cardiology, vascular surgery) should be sought according to the clinical picture.

For patients with ≤1 risk factor, it is acceptable to not administer an antifungal treatment as first line therapy, given the low risk of IC in this scenario. If an antifungal therapy is started, the first choice is usually an echinocandin, with de-escalation to azoles as soon as the patient is clinically stable. Drug interactions should be considered, in particular when the selected therapy is an azole.

Unstable patients with ≥2 risk factors require prompt initiation of an appropriate treatment. In these patients, early antifungal treatment with an echinocandin is recommended, with de-escalation to an azole when the patient is clinically stable. An LF-AmB can be a useful option in some patients.

3.3.2. Patients with confirmed IC infection

In patients with confirmed IC and severe sepsis (scenario 7), the aim of management is the prompt initiation of adequate therapy, reduction of risk of complications or relapse, and diagnosis of any secondary localizations.

In this setting, besides the management recommendations outlined above for previous scenarios, first-line therapy with an echinocandin is *necessary*, with an LF-AmB being an alternative. Again, de-escalation to an azole is appropriate as soon as the patient is clinically stable.

4. Discussion

We propose management algorithms for IC in medical wards, envisioned as practical assessment and treatment tools. Our proposals are based on a two-way risk stratification strategy that considers both clinical severity (sepsis vs. severe sepsis) and the likelihood that *Candida* spp. is a causative agent. We chose a modified Delphi method (RAND/UCLA) to identify *appropriate* and *necessary* practices in this setting, because formal evidence from controlled clinical trials is lacking. Using it, we sought to combine the best available scientific evidence, also from the ICU setting, and the collective judgment of experts with extensive experience in managing IC in medical wards.

4.1. IC is common in internal medicine wards

IC in the medical ward setting is understudied and possibly underestimated, but there is increasing evidence of a rising incidence [2,3,35]. Also, IC mortality among medical patients appears higher than in other settings, possibly due to delayed diagnosis, compromised

underlying clinical conditions and difficulties in adhering to guidelines that have been elaborated for less complex patients [9,14,32].

The typical patient admitted to a general medical ward is an elderly subject with multiple comorbidities, including many of the recognized risk factors for IC [1]. Some IC risk factors are modifiable (e.g., prolonged antibiotic treatment, indwelling devices) and efforts should be made to avoid exposing frail patients to unnecessary risk, when still asymptomatic for infection [25,34]. In any scenario, careful reassessment of parenteral nutrition or ongoing antibiotic therapy should aim at withdrawing unnecessary treatment to avoid these modifiable risks for IC (e.g., when the patient's condition stabilizes). Microbiological diagnosis should be sought if there is no response after 72–96 h of empirical therapy. Surveillance cultures might be useful to identify colonized patients, as often suggested in ICU patients [36]. Whereas, colonization with *Candida* spp., per se, is not an indication for treatment, it should be taken into consideration when assessing patients who become symptomatic.

4.2. Early diagnosis or exclusion of IC requires proper microbiological diagnosis

Early diagnosis and treatment of invasive candidiasis are associated with improved survival [37,38]. Elderly and patients with comorbidities may have blunted inflammatory and febrile response due to impaired immune function as a direct consequence of advanced age (immune aging) [39,40] and/or to steroid or other immune suppressive therapy, including cancer therapy. Other components of the systemic inflammatory response syndrome may be lacking, including tachycardia due to beta-blocker use, tachypnea due to muscle atrophy and hypocapnia due to chronic respiratory failure. Diabetes mellitus may impair response to infections and favor fungal growth. Afebrile patients with candidemia have been described [41], and in one study, up to 20% of patients with candidemia did not show SIRS criteria [42]. In the absence of fever, IC mortality may be higher than in patients with fever or pyrexia [33,43].

In this clinical setting, signs and symptoms of infections may be mild or absent, and detecting IC presents a difficult albeit necessary task. Considering that up to 50% of IC diagnoses are estimated to be missed, attending physicians need a high index of suspicion to hasten microbiological diagnosis and manage these potentially severe infections [44]. The search for the source of infection does not differ from good practice in any clinical setting [45]; however, issues specific to early diagnosis or exclusion of IC (pivotal from a clinical as well as from an antimicrobial stewardship perspective) involve proper microbiological diagnosis, with proper blood culturing in all cases. More advanced diagnostic techniques (e.g., fungal antigen testing) might be reserved to high-risk patients, and centralized in referral microbiology facilities [46–49].

In order to hasten microbiological diagnosis, blood cultures from an arterial line might reduce the time to confirmation of candidiasis especially in patients with few symptoms [50]. Source identification and control are *necessary* in patients with severe sepsis. This may require CVC removal, as well as consultations in surgery (general, heart or vascular as clinically appropriate), radiology, intensive care and infectious diseases. In particular, removal of all potentially infected devices is pivotal, as there is strong evidence supporting improved outcomes with CVC removal in patients with IC [32,38,51,52].

The stable patient with low risk of IC has no need of aggressive management or treatment; on the other hand, an empirical antifungal treatment can be considered in patients with ≥2 risk factors, pending blood culture results, and according to clinical judgment; in this case fluconazole is an appropriate choice [9]. In severely ill patients at high risk for IC, it is widely accepted that first-line therapy should be an echinocandin [11,53]. The actual choice of molecule within the echinocandin class should be based on approved indications, personal experience, known side effects, PK/PD parameters and evidence. However, to reduce costs and limit impact on local resistance patterns, de-escalation from echinocandins to fluconazole is advisable when the patient is stable, especially if the isolated *Candida* strain is fluconazole-susceptible [54,55]. The correct timing of de-escalation is still matter of debate; the panel recommends reassessment at 72/96 h [24,56]. Echinocandins are the drug of choice when the diagnosis of IC is confirmed, independent of clinical severity. Once again, de-escalation is an appropriate management strategy [53,54]. The overall duration of therapy is not established, but there is consensus that treatment should be continued until blood cultures are repeatedly negative; pursuing both clinical and microbiological cure is critical to reducing the risk of relapse.

4.3. Limitations

We acknowledge a number of limitations in this project. First, although risk factor selection was based on an extensive literature review, the list of risk factors is arbitrary; currently, it is not possible to assign relative weights to individual risk factors. Also, implicit in the RAND/UCLA method, most recommendations are derived from evidence obtained in other settings or from expert opinion.

4.4. Conclusions

Applying the correct diagnostic and therapeutic approaches to IC in the medical setting would greatly improve clinical outcomes and advance hospital cost-containment strategies [15,16]. One aim of this Consensus is to raise awareness in internal medicine wards, where the risk of IC risk is increasing. Another important issue is to optimize the use of new microbiological diagnostic techniques, because early diagnosis with prompt initiation of antifungal treatment can improve survival [5,57]. We propose two algorithms for this purpose, developed to provide hospital managers and the physicians caring for medical patients with a simple but comprehensive tool to support decision-making around the issue of IC. We believe our proposed algorithms can be adapted to different hospitals and settings.

Learning points

- *Candida* and IC are underestimated in general medical wards, but there is increasing evidence of rising incidence
- Early diagnosis of IC with prompt and adequate treatment is associated with improved survival
- Patients with IC may have blunted inflammatory and febrile responses, therefore it is important to recognize these patients through their risk factors, to facilitate the diagnosis of IC
- In all symptomatic patients, at least two blood cultures (one from a CVC, if present) are mandatory to confirm *Candida* infection
- High risk patients with severe sepsis are similar in severity to patients admitted to ICUs, and therefore early antifungal treatment with an echinocandin is recommended

Disclosures

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Conflict of interests

The authors state that they have no conflicts of interest

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