Review

Francisco Javier Candel[1]
Carmen Pazos Pacheco[2]
Isabel Ruiz-Camps[3]
Emilio Maseda[4]
Maria del Rosario Sánchez-Benito[2]
Ana Montero[4]
Mireia Puig[3]
Fernando Gilsanz[4]
Juan Aguilar[3]
Mayra Matesanz[5]

Update on management of invasive candidiasis

[1]Department of Clinical Microbiology, Hospital Clínico San Carlos, IdISSC, Universidad Complutense de Madrid, Spain.
[2]Department of Clinical Microbiology, University Hospital San Pedro de Alcantara, Caceres, Spain.
[3]Department of Infectious Diseases. University Hospital Vall d'Hebron, Barcelona, Spain.
[4]Department of Anaesthesiology, Surgical ICU, University Hospital La Paz de Madrid, Spain.
[5]Department of Internal Medicine, Hospital Clínico San Carlos, Universidad Complutense de Madrid, Madrid.

ABSTRACT

Given the growing incidence of invasive candidiasis in critically ill and haemato-oncological patients and its poor outcomes, an early diagnosis and treatment are need for get a better prognosis. This document reviews the current approaches that help in diagnosis of invasive candidiasis based on culture-independent microbiological tests. The combination of clinical prediction scores with fungal serological markers could facilitate the approach in antifungal therapy, optimizing it. This article also reviews the epidemiology and primary risk factors for invasive candidiasis in these patients, updating the therapeutic approach algorithms in both clinical contexts based on the main evidence and international guidelines.

Keywords: Invasive candidiasis, Diagnosis, Drug therapy.

Actualización del tratamiento de la candidiasis invasiva

RESUMEN

Dada la creciente incidencia de candidiasis invasiva en pacientes críticos y hematooncológicos y sus malos resultados, es necesario un diagnóstico y tratamiento precoz para obtener un mejor pronóstico. Este documento revisa los enfoques actuales que ayudan en el diagnóstico de candidiasis invasiva basado en pruebas microbiológicas independientes del cultivo. La combinación de puntuaciones de predicción clínica con marcadores serológicos fúngicos podría facilitar el enfoque en la terapia antifúngica, optimizándola. Este artículo también revisa la epidemiología y los principales factores de riesgo de candidiasis invasiva en estos pacientes, actualizando los algoritmos de abordaje terapéutico en ambos contextos clínicos basados en la evidencia publicada y en las guías internacionales.

Palabras clave: Candidiasis invasiva, Diagnóstico, Terapia farmacológica.

INTRODUCTION

The incidence of invasive candidiasis (IC), as with other opportunistic infections, has increased in recent decades in hospitalised patients as the result of increased use of therapeutic, medical and surgical procedures. The main population groups that develop these infections are critically ill patients (mainly postsurgical patients and those with large burns), haemato-oncological patients and solid organ recipients, as shown by the main national and international published registries[1,2], which report that *Candida* spp. is responsible for 11-18.5% of infectious processes experienced by these patients.

Intraabdominal candidiasis is the second leading form of invasive candidiasis. This condition is defined by the isolation of *Candida* in a sample of peritoneal fluid obtained via laparotomy or percutaneous puncture from patients with associated symptoms and risk factors. This increased rate of IC is partly due to the patients' greater age, the use of broad spectrum antimicrobials, the patients' comorbidity and the complexity of the diagnostic and therapeutic procedures. The clinical consequences of invasive candidiasis are severe. Its onset increases hospital stays and doubles the risk of mortality compared with nosocomial bacterial infections. However, the incidence of IC has decreased significantly in patients with haematologic disease due to the routine use of azoles.

This document reviews the current approaches that help diagnose IC and reviews the epidemiology and primary risk factors for IC in these patients, updating the therapeutic approach algorithms in both clinical contexts based on the main evidence and international guidelines.

Correspondence:
Dr Francisco Javier Candel González
Department of Clinical Microbiology and Infectious Diseases. Hospital Clínico San Carlos. IDISSC. Universidad Complutense. Avda Profesor Martín Lagos s/n, 28040. Madrid, Spain.
E-mail: fj.candel@gmail.com
Phone: +34 91 330 3486
Fax: +34 91 330 3478

MICROBIOLOGICAL DIAGNOSIS OF INVASIVE CANDIDIASIS

Invasive candidiasis is still a significant clinical challenge due to its increased incidence, high morbidity and mortality and the need for rapid diagnostic methods that ensure an early start to preemptive and/or targeted treatment. The proper management of these infections ranges from promoting the creation of joint work strategies to establishing diagnostic-therapeutic algorithms based on a combination of scores and traditional culture-independent microbiological diagnostic tools.

The growth of IC is associated with the presence of risk factors (clinical severity, advanced age or new born, intensification of therapies with corticosteroids and other immunosuppressive drugs, prolonged use of invasive devices, intense and sustained neutropenia, solid organ transplantation or neoplasia, broad-spectrum antibiotics, previous use of antifungals, renal failure, pancreatitis, etc.)[3], the primary of which is multifocal colonisation by *Candida* spp.[4] There are various clinical predictor indices for determining the risk of developing invasive candidiasis[5]. The most widely used of which is the *Candida* score[4]. This score assesses hospitalised patients who have spent at least 7 days in an intensive care unit and uses 4 parameters (multifocal colonisation, 1 point; surgery, 1 point; parenteral nutrition, 1 point; and severe sepsis, 2 points). If the score is greater than 3, the patient has a high probability of developing IC, with a sensitivity of 77.6% and a specificity of 66.2%. This tool serves as screening for fungal infection. To improve their prognosis, patients with a *Candida* score >3 are the selected targets for early preemptive antifungal therapy and have raw and attributable mortality rates of 40-78% and 20-40%, respectively[6].

What role does microbiology play in this complex scenario? The objective of microbiology is to achieve a correct diagnosis of these infections as early as possible by implementing microbiological techniques that lead to the start of preemptive antifungal treatment and safe de-escalation therapy.

The current reference technique for the diagnosis of invasive candidiasis is still blood culture, despite its moderate sensitivity (between 50% and 75%), due in part to the transient presence of the fungus in peripheral blood (both intracellularly within the phagocytes and trapped in the capillaries) and to the slow growth rate and multiplication of the fungus. The new automated systems have reduced the growth time of the yeast (2-3 days); however, it is advisable to increase the number of extracted blood cultures to increase the diagnostic rate (e.g., 2 serial blood cultures every 2-3 days while the suspicion of invasive candidiasis persists)[6]. After positivisation, Gram staining can provide a presumption of fungaemia in minutes after observing yeast-like fungal structures under optical microscope; however, definitive identification and susceptibility studies require at least 48-72 h.

To balance this lack of sensitivity and accelerate the diagnostic response of traditional blood cultures, 2 new microbiological techniques for early diagnosis have been developed: matrix-assisted laser desorption/ionisation-time-of-flight mass spectrometry (MALDI-TOF-MS) and PNA-FISH Yeast Traffic Light.

The first of these techniques (MALDI-TOF-MS) uses mass spectrometry through smooth ionisation and performs a proteomic analysis of colonies grown on solid culture plates (on which blood culture steps have been performed). The technique also performs an analysis of liquid medium of the blood culture bottle, which results positive (because it does not require prior magnification of the target). This process identifies yeasts in approximately 30 min to 2 h, respectively, with a high correlation with conventional methods (95.9% for *Candida albicans* and 86.5% for *Candida* spp.) and with a sensitivity of 94%, a specificity of 100% and a positive predictive value of 94%[7]. The technique also helps detect (within approximately 15 h) the presence of yeast strains with *fks* mutations that cause reduced susceptibility to caspofungin and can optimise the prescribed antifungal treatment[8].

The second of these techniques (PNA-FISH Yeast Traffic Light) uses peptide nucleic acid (PNA) species-specific probes that hybridise *in situ* with the target DNA of several species of *Candida*. The technique identifies yeasts simply and quickly (in approximately 90 min), depending on the colour emitted in a fluorescence microscope (green for *C. albicans* and *Candida parapsilosis*, yellow for *Candida tropicalis* and red for *Candida krusei*), and has a sensitivity of 99%, a specificity of 98% and a positive predictive value of 99%[9]. The technique also has the advantage of identifying yeast species with a high probability of fluconazole susceptibility if local epidemiological map is known, and can be used effectively for antifungal therapy optimisation programmes. Therefore, it appears that the identification of yeast directly from blood cultures can provide fast, high-quality information and act as an early diagnostic tool for fungaemia. A recently conducted study compared Gram staining, MALDI-TOF-MS and PNA-FISH Yeast Traffic Light[10]. The study found better results with PNA-FISH (96%) than with MALDI-TOF-MS (78%) or Gram staining (72%). The main disadvantage of PNA-FISH is its cost, given that each PNA-FISH assay costs $57 versus the $2.17 for MALDI-TOF-MS and $0.17 for Gram staining.

In addition to blood cultures when faced with suspected invasive candidiasis, the microbiology laboratory should also be sent all sterile fluids and/or tissues involved in this infection to perform cultures in the appropriate media. Although these cultures are slow (up to 21 days) and have low sensitivity (30%) and specificity (they do not always allow differentiation between colonisation, contamination and infection), they are indispensable for isolating the pathogen and studying susceptibility to the various antifungal agents. Direct viewing under the microscope using various stainings (Gram staining, KOH and/or lactophenol) should also be performed whenever possible to offer a rapid presumptive diagnosis.

A specific commentary requires peritoneal fluid, because one of the most common forms related to a poor prognosis

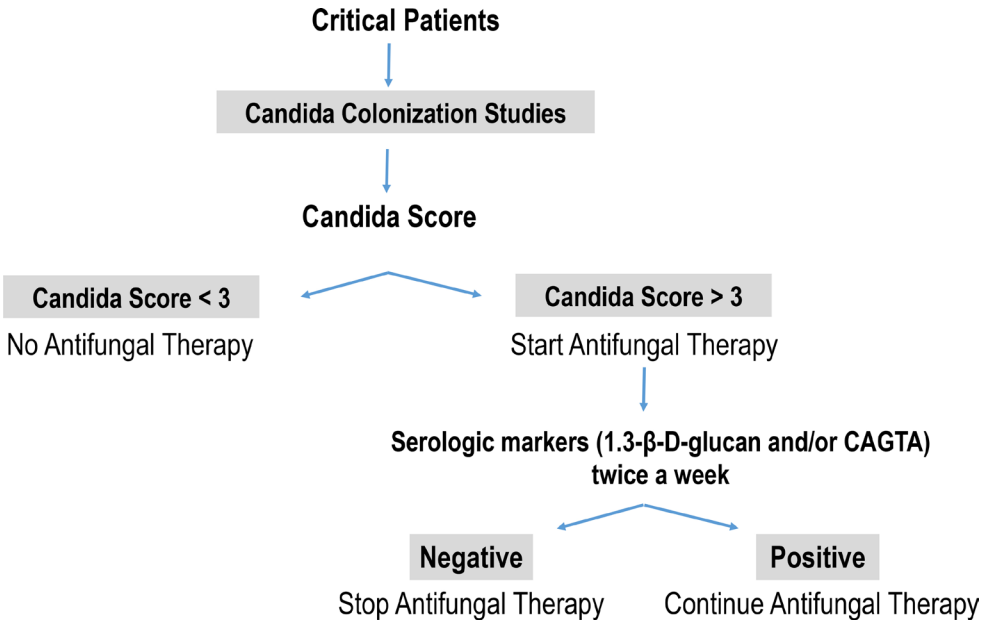

Figure 1 Early diagnostic algorithm for invasive candidiasis in patients in critical care units to optimize antifungal treatment.

among critically ill postsurgical patients with invasive candidiasis is intraabdominal candidiasis, defined by the isolation of *Candida* spp. in a perioperative peritoneal fluid sample obtained by laparotomy or percutaneous puncture in patients with associated symptoms and risk factors. The proper obtaining of this sample and its transport within the first 2 h are key points for performing a correct diagnosis. It might be useful to collect the fluid in blood culture bottles or sterile tubes, because it increases the volume to be processed and the possible microbial load and provides precocity and quality by including a continuous automated reading. The yeast isolates from intraabdominal drainage should also be carefully assessed, given that, in many cases, they only represent colonisations.

Another important tool in the microbiology laboratory for performing an alternative nonconventional diagnosis consists of culture-independent microbiological methods where fungal serological markers play a main role: detection and quantification of germ tube antibodies (*Candida* IFA IgG Vircell), detection of mannan antigen and mannan antibody (Platelia® *Candida*), detection and quantification of 1.3-β-D-glucan (Glucatell©) and detection of fungal nucleic acid. A sample of the patient's serum helps show infection without yet having clinical evidence of disease, enabling their use as tools for early diagnosis and preemptive therapy.

Detection and quantification of germ tube antibodies in serum (*Candida* IFA IgG, Vircell) detects (through immunofluorescence) antibodies against antigens of the mycelial phase of the germ tube (CAGTA), discriminating between superficial colonisation and invasive candidiasis, with good sensitivity (84.4%) and specificity (96%) results[11] and for all species of *Candida*. The diagnosis is performed with positive antibody titres greater than 1:160, enabling antifungal monitoring of the treatment response[12]. An indirect chemiluminescent assay (VirCLIA, Vircell) has recently been marketed with the same technical foundation and monotest format with ready-to-use reagents. The assay has a simple and automated protocol with no need for microscopy and obtains rapid results in less than 1 h and could be useful for emergency samples.

Combined detection of mannan antigen and mannan antibodies (Platelia® *Candida*) using an enzyme-linked immunosorbent assay (ELISA) detects mannose residues attached by α bonds of the mannan (main and immunodominant antigen of the *Candida* cell wall, which, being present in virtually all individuals, presents a high capacity for inducing mannan antibodies and forming complexes that pass into the blood). The release of the mannan of the immune complexes is the most critical step of the technique and, along with the transience of the mannanaemia, is the cause of the test's low sensitivity (40-70%)[13].

Detection and quantification of 1.3-β-D-glucan (Glucatell©) uses a kinetic ELISA. Glucan is a component of the fungal cell wall, which is released during the infection and can be detected in the biologic fluids (mainly serum) of patients with various genera of mycoses such as candidiasis, aspergillus and pneumocystosis (glucan is not detected in cryptococcosis or zygomycosis). Glucan is employed as a panfungal marker of invasive fungal infection but is unable to identify among species[13]. The sensitivity and specificity readings range from 83.3% to 86.2%[12]. The most critical point of the technique is undoubtedly where to set the cut-off for considering a posi-

tive result, given that it varies from 80 pg/mL (as recommended by the manufacturer of the Glucatell© assay kit, Associates of Cape Cod Inc., US) to 120 pg/mL[12] and even up to 158 pg/mL[14]. The technique's predictive value of greater than 90% is its major strength. This is useful for ruling out invasive infection and safely withdrawing antifungal treatment, especially if is combined with germ tube antibody detection (CAGTA)[11].

Detection of nucleic acids using polymerase chain reaction (PCR) has high theoretical sensitivity, which has not been confirmed in clinical practice, perhaps due to the lack of standardisation and study methodologies employed. There are marketed techniques such as SeptiFast (Roche Diagnostics, US) and FilmArray (BioFire DX, US) that, using real-time multiplex PCR or low-density DNA microarrays, can detect *Candida* species in whole blood or in sterile fluids[11].

Lastly and representing the start of a new stage in the molecular diagnosis of invasive candidiasis, there is the commercialisation of an automated platform (T2Dx) that detects the DNA of yeast bound to metal nanoparticles using T2 magnetic resonance on a whole blood sample (T2Candida assay, T2 Biosystems, Inc., US), with a sensitivity of 96.4%, a short assay time (4 h) and no prior culture or preparation of the sample[15].

There have been many technical developments in recent years in terms of sensitivity, specificity and cost. The current difficulty consists of integrating them into the clinical context to reach an early diagnosis at an efficient cost and thereby optimise the antifungal treatment, facilitating early de-escalation and discontinuation of the therapy. Figure 1 shows a proposed algorithm for the early diagnosis and monitoring of invasive candidiasis to optimise antifungal therapy.

EPIDEMIOLOGY AND TREATMENT OF *CANDIDA* PERITONITIS

Epidemiology. The incidence of *Candida* peritonitis varies between 13% and 33% in postoperative peritonitis compared with 7-23%[16-18] in community-acquired peritonitis. This rate increases to 70%[19] in seriously ill patients hospitalised in intensive care units who undergo surgery and is an independent predictor of death. There are significant differences in the prevalence of candidiasis depending on the origin of the peritonitis, with a greater prevalence in upper gastrointestinal tract perforations (41%) than in those originating in the lower gastrointestinal tract (35% small intestine, 12% colorectal and <5% appendicular).

Approximately 95% of invasive candidiasis cases are caused by 5 species of *Candida*: *C. albicans*, *C. parapsilosis*, *C. glabrata*, *C. tropicalis* and *C. krusei*. The following *Candida* species are most often identified in peritoneal cavity samples: *C. albicans* (58%), *C. glabrata* (20%), *C. krusei* (8%), *C. kefyr* (5), *C. parapsilosis* (3%), *C. tropicalis* (3%), *C. ciferii* (2%) and *C. lusitaniae* (1%)[20]. A significant epidemiological change has been observed in recent decades. There has been an increase in non-albicans *Candida* species, as well as an emergence of species with reduced susceptibility to standard antifungals.

A study conducted by Montravers et al.[17] observed that the prognosis for *Candida* peritonitis depended on the community or nosocomial origin of the infection, showing significantly greater morbidity and mortality in the patient group with candidal peritonitis of nosocomial origin compared with community-acquired peritonitis. In this study, the origin of the peritonitis in the upper gastrointestinal tract (odds ratio [OR], 4.9; 95% CI 1.6-14.8) and the isolation of *Candida* in the peritoneal fluid (OR, 3.0; 95% CI 1.3-6.7; p<.001) were independent risk factors of mortality in those patients with peritonitis of nosocomial origin. The study by Dupont et al.[18] analysed a sample of patients with peritonitis hospitalised in intensive care units, 30.6% of whom showed *Candida* peritonitis. The most frequently isolated species was *C. albicans* (74%), followed by *C. glabrata* (17%). The multivariate analysis designated the following independent risk factors associated with mortality: APACHE II score >17 (OR, 28.4), respiratory failure (OR, 10.6), peritonitis origin in the upper gastrointestinal tract (OR, 7.8) and isolation of *Candida* in the direct examination of peritoneal fluid (OR, 4.7).

Risk factors. *Candida* is part of the microbiota of the skin, mucous membranes, gastrointestinal tract and genital and urinary apparatus of humans. There are numerous risk factors associated with *Candida* peritonitis. The main risk factors are those that promote *Candida* colonisation and impairment of the host's immunity. The most relevant factors include the origin of the peritonitis (perforation of the upper gastrointestinal tract), type of peritonitis (tertiary peritonitis in patients with multiple surgeries), severe acute pancreatitis, high degree of severity (APACHE score >25 points, septic shock), prolonged paralytic ileus, total parenteral nutrition, prolonged antibiotic therapy, prolonged stay in the intensive care unit, presence of catheters and/or drainage and antisecretory therapy (proton pump inhibitors, anti-H2)[21-23].

The fact that mortality from invasive fungal infections remains high despite the use of active antifungals against these infections implies the presence of inadequate host immunity. An observational prospective study conducted between 2013 and 2015 with patients with candidaemia hospitalised in intensive care units showed the presence of a special immunophenotype in this type of patient, characterised by T-cell exhaustion, impaired T-cell response against the pathogens and a concomitant reduction in co-stimulatory molecules, which are essential for T-cell activation[24]. Likewise, a prospective study conducted in a unit for critically ill postoperative patients showed an association between the presence of certain promoter polymorphisms (rs1800629) of tumour necrosis factor-α and an increase in susceptibility to intraabdominal candidiasis[25]. These findings might help explain the fact that patients with invasive fungal infection have high mortality despite appropriate antifungal treatment. The implementation of measures aimed at increasing host immunity could be useful for improving patient survival.

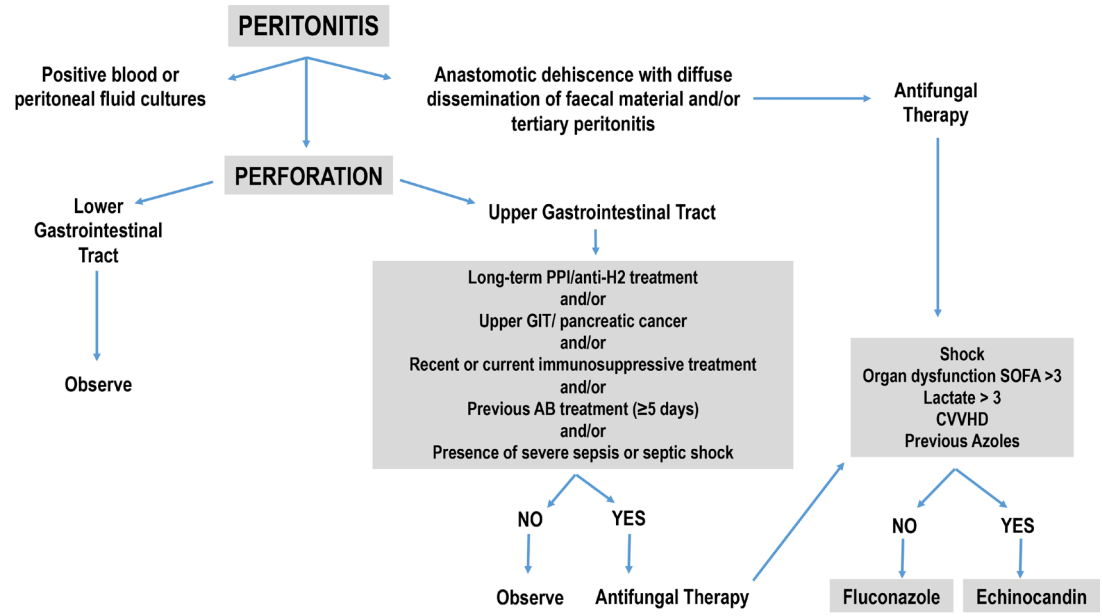

Figure 2 Therapeutic algorithm for abdominal candidiasis. Taken from Maseda E et al[28]

AB, antibacterial; CVVHD, continuous venovenous haemodiafiltration; GIT, gastrointestinal tract; PPI, proton pump inhibitors; SOFA, sepsis-related organ failure assessment score.

Treatment. Mortality for candidal peritonitis is high, approximately 20-70%[26] depending on the series. Controlling the focus of infection and establishing early and appropriate antifungal treatment are determinants of the infection[27]. Understanding the local epidemiology of the species causing the candidaemia is essential when establishing an empiric antifungal treatment due to the marked differences in antifungal susceptibility among the various species. The distribution of species has significant geographical differences.

The literature lacks sufficient evidence to endorse the routine use of empiric antifungal treatment for patients with community-acquired secondary peritonitis of the lower gastrointestinal tract. There is no clear evidence in terms of the use of empiric antifungal treatment in perforations of the upper gastrointestinal tract (above the angle of Treitz), although experts have recommended it for certain conditions: pancreatic neoplasia, immunosuppressive therapy, upper gastrointestinal neoplasia, previous antibiotic treatment (5 or more days), septic shock and long-term therapy with proton pump inhibitors or histamine-2-receptor antagonists. By contrast, there is sufficient evidence supporting the use of empiric antifungal treatment for patients with secondary peritonitis of nosocomial origin and tertiary peritonitis, given that these patients' prognosis worsens with the isolation of *Candida* in peritoneal fluid (figure 2)[28].

The antifungal treatment of choice for critically ill patients with candidal peritonitis should be established by the administration of an echinocandin in the following cases: unstable patient, previous treatment with azoles, isolation of fluconazole-resistant *Candida* (peritoneal fluid) or the need for renal replacement techniques. The literature shows evidence that echinocandins can decrease mortality when compared with other antifungal treatments. A retrospective multicentre study conducted by the Perioperative Infections Workgroup of the Spanish Society of Anaesthesiology, Resuscitation and Pain Relief (SEDAR) included 139 patients with intraabdominal candidiasis hospitalised in postsurgical intensive care units for at least 24 h and treated with anidulafungin. The study showed that peritonitis was the most common presentation (77.7%), with a high percentage of patients developing septic shock (67.6%). The main species responsible were *C. albicans* (52.8%) followed by *C. glabrata* (27.8%). Treatment with anidulafungin (200-mg loading dose followed by 100 mg daily) for these patients was mainly empiric (59.7%), followed by targeted treatment (20.9%). A favourable response was achieved in 79.1% of the patients (76.6% in the patients with septic shock), as well as an intra-ICU mortality of 25.9% (28.7% in the patients with septic shock). This study represents the largest cases series with intraabdominal candidiasis treated with anidulafungin, with excellent results and favourable safety profile, even in the patient subgroup with septic shock, without requiring dose adjustment in the patients with renal or hepatic failure[29].

The initial empiric treatment in adult patients with neutropenia and invasive candidiasis should be performed with echinocandins[30]. De-escalation therapy of echinocandins to azoles should be assessed in those patients for whom early antifungal treatment was started, azole-susceptible strains were isolated and clinical improvement was observed after the surgery.

EPIDEMIOLOGY AND TREATMENT OF INVASIVE CANDIDIASIS IN PATIENTS WITH NEUTROPENIA

For more than 2 decades, however, the incidence of IC has been declining significantly in patients with haematologic disease due to the routine use of azoles in prophylaxis[31]. In recent studies, only 1.9% of patients who received posaconazole in prophylaxis presented invasive forms of candidiasis[32]. However, this situation is not found in patients with solid tumours, for whom the incidence rate is higher. Despite having new antifungal agents, invasive infections by *Candida* are accompanied by high mortality (between 20% and 50% in various series and depending on the patient type[33-35]. We update the epidemiology, risk factors and treatment of IC for patients with oncological-haematologic disease and especially in patients with neutropenia.

Epidemiology. The latest prospective population surveillance study conducted in Spain on candidaemia in 2010-2011 (CANDIPOP)[36] recorded 752 episodes of candidaemia in 729 patients, which represents an incidence of 8.1 cases/10^5 inhabitants/year. Of the 752 cases, 238 (32.6%) corresponded to patients with oncohaematologic diseases: 195 (82%) cases were recorded in patients with solid tumours, and 43 (18%) cases were recorded in patients with malignant haemopathies[37]. A total of 35 (15.9%) episodes were breakthrough fungaemia. The most frequently isolated species was *C. albicans* (41.6%), followed by *C. parapsilosis* (19.3%), *C. glabrata* (17.7%), *C. tropicalis* (10.3%), *C. krusei* (2.9%), *C. guilliermondii* (2.5%) and other species (5.8%). The various species of *C. albicans* (*C. tropicalis* and *C. guilliermondii*) were more common in the patients with haematological disease than those with cancer (71.6% vs. 55.6%).[37] This low rate of *C. albicans* in favour of non-albicans species was also confirmed in other studies[38-40], which was attributed to the use of prophylaxis, predominantly with azoles.

A total of 67 of the 243 (27.6%) isolated species presented reduced fluconazole resistance or susceptibility, with no differences between the patients with haematological disease and those with cancer (28.9% vs. 27.3%). This finding points to the fact that other variables, in addition to prior exposure to antifungals, can contribute to the selection of resistant strains (suboptimal dosage, treatment duration, etc.).

The risk factors for IC in patients with oncohaematologic disease are divided into 3 groups: host-related (mucositis, previous colonisation by *Candida*), disease-related and treatment-related (neutropenia, central venous catheter [CVC], parenteral nutrition, abdominal surgery, steroids) and complications-related (graft-versus-host disease, cytomegalovirus infection, etc.)[41].

When the risk factors in the haemato-oncological population of the CANDIPOP study were analysed[37], it was observed that the patients with haematologic disease had more frequently undergone chemotherapy or corticosteroid therapy during the previous month. These patients also had neutropenia and mucositis at the onset of the candidaemia and were carriers of long-term CVC. In contrast, the patients with cancer were older, had more frequently received parenteral nutrition or had undergone prior abdominal surgery (3 months). There were no differences in the rate of catheter-related candidaemia (37.2% vs. 36.4%), which increased to 42.9% if breakthrough fungaemias were analysed[37]. Breakthrough candidaemias are more common in patients with leukaemia, neutropenia and mucosal barrier disruption (mucositis). It is therefore conceivable that translocation from the gastrointestinal tract could be the origin of the candidaemias. Fluconazole-resistant species are isolated in most cases, especially *C. krusei*, in relation to the change in colonisation experienced by patients who use azoles.

Treatment. Treatment selection will depend of local microbiological epidemiology, patient's clinical severity, underlying disease (patient with haematologic disease, transplant or CVC) and use of prior prophylaxis with azoles. However, given the increase in isolates of non-albicans *Candida* species with lower susceptibility to fluconazole, it is reasonable to start treatment with an echinocandin until an antifungal susceptibility test is available. Table 1 shows the various antifungals with the level of evidence they present in the 3 most recent guidelines (the ESCMID guidelines, the European Conference on Infection in Leukaemia and Haemopoietic Stem-cell Transplantation guidelines and the Infectious Diseases Society of America [IDSA] guidelines)[30,42,43].

In the latest IDSA guidelines[30], the 3 echinocandins have the same level of evidence in the treatment of patients with neutropenia and candidaemia. In a report presented in the Congress of the European Haematology Association in 2014[44], 46 patients with neutropenia were treated with anidulafungin, with clinical and microbiological results comparable to those obtained by the other echinocandins in pivotal studies. The overall response was 56.5%, with clear differences between those who recovered neutropenia (80% vs. 53.8%)[1].

There are 3 considerations to consider with these patients. The first is the withdrawal or not of the catheter. As with patients without neutropenia, it has been clearly shown that early catheter withdrawal has a protective effect on mortality. For patients with neutropenia, this finding is not so clear because the source of candidaemia could be translocation at the intestinal level[30,42,43,45,46]. According to the IDSA guidelines, catheter withdrawal should therefore be individualised (strong recommendation, low level of evidence). If the catheter is not withdrawn, the patient should be treated with an echinocandin or liposomal amphotericin B due to the effect they have on the biofilm[30,42,43]. In the CANDIPOP study[36,37], early catheter withdrawal (<48 h) combined with early effective antifungal treatment was associated with greater survival.

The second issue to consider, both for patients with neutropenia and those without (also resolved by another study of CANDIPOP[47]), is that treatment with echinocandins during the first 72 h of patients who showed candidaemia by *C. parapsi-*

Table 1 **Treatment of candidemia and invasive candidiasis in oncological-haematological neutropenic patients according to the European Conference on Infections in Leukaemia (ECIL), European Society of Clinical Microbiology and Infection (ESCMID), Infectious Diseases Society of America (IDSA) guidelines.**

	ECIL-5	ESCMID	IDSA
Caspofungin	AII	AII	Strong recommendation
			Moderate-quality evidence
Micafungin	AII	AII	Strong recommendation
			Moderate-quality evidence
Anidulafungin	AIII	BII	Strong recommendation
			Moderate-quality evidence
Posaconazole		DIII	
Voriconazole	BII[1]	CII	Weak recommendation
			Low-quality evidence
Itraconazole		DIII	
Fluconazole	CIII[1,2]	CII	Weak recommendation
			Low-quality evidence
Liposomal amphotericin B	AII	BII	Strong recommendation
			Moderate-quality evidence
Amphotericin B colloidal dispersion	BII	CIII	
Amphotericin B lipid complex	BII	CII	
Amphotericin B deoxycholate	CII	DIII	

[1]Nonsevere patients
[2]Patients with no previous azoles. The evidence levels are assessed differently among different therapeutic guidelines

Iosis (second most common) and with reduced susceptibility to echinocandins had no impact on the clinical response of the candidaemia.

The third point to consider would be that, once the species and its susceptibility to antifungals is known, the treatment should be "de-escalated", if the patient's condition allows for it. A recent study[48] that included 250 patients with various forms of IC (although only 9 of them showed neutropenia) compared the response between those who continued with anidulafungin throughout the treatment and those who, due to their clinical condition and at the physician's discretion, transferred to azole treatment starting on the fifth day. The overall response of this group was 83.7%, regardless of the isolated *Candida* species and with no differences compared with the patients who continued with intravenous treatment or compared with the pivotal study by Reboli et al.[49] on anidulafungin. Additionally, microbiological eradication in this study was achieved in a mean of 2 days, an important result especially in the patients with neutropenia. Thus, when possible, de-escalating constitutes a valid and more economical option that decrease the onset of resistant species.

Outcome and mortality. In the Spanish study on patients with haemato-oncological disease,[37] the cumulative mortality was 12.2% at day 7 and 31.5% at day 30, with no differences between the patients with cancer and those with hematologic disease, with data similar to the overall data of the CANDIPOP study[36]. In this population, mortality was occasionally correlated with the underlying disease[38]. In the multivariate analysis and after adjusting by propensity score, the combined treatment (appropriate antifungal plus catheter withdrawal) during the first 48 h was related to mortality at 7 days (OR, 0.05; 95% CI 0.01-0.42). These data agree with the European guidelines[42] but cannot be generalised to the entire population with neutropenia because, in the Spanish study, neutropenia was only detected in 6.3% of the patients. When studying the factors related to mortality at 30 days, early catheter withdrawal combined with the effective use of antifungals was once again associated with lower mortality, while the primary candidaemia (OR, 3.47; 95% CI 2.05-5.89) and isolation of *C. krusei* (OR,

12.59; 95% CI 2.46-64.48) could be considered as prognostic factors of mortality.

CONCLUSIONS

The main factors associated with IC are the increase in fungal translocation (CVC, mucositis) and a reduction in its clearance (neutropenia). The species of *Candida* most often identified in *Candida* peritonitis are *C. albicans* and *C. glabrata*; however, in patients with neutropaenia, the second most often isolated species is *C. parapsilosis*. The new microbiological techniques for early culture-independent diagnosis (germ tube antibodies, mannan antigens and antibodies, detection of 1.3-β-D-glucan, MALDI-TOF and PNA-FISH) have shortened the diagnosis time for IC, facilitating both the early inclusion of antifungal therapy and the shortening of this therapy. When included in clinical protocols, these techniques have high sensitivity and negative predictive value for optimising antifungal therapy and can facilitate stewardship programs. The initial empiric therapy for adult patients with IC with or without neutropaenia should be an echinocandin, de-escalating to an azole once the species and its susceptibility to antifungals are known, if the patient's clinical conditions allow for it. Despite the diagnostic and therapeutic advances, candidiasis-associated mortality has not decreased significantly in patients with or without neutropaenia.

CONFLICT OF INTEREST

None to declare

REFERENCES

1. Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martín CD et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA 2009; 302 (21): 2323-29.
2. SEMICYUC. Annual reports ENVIN-UCI. Available at hws.vhebron.net/envin-helics/
3. Zaragoza R, Ramírez P, Borges M, Pemán J. Puesta al día en la candidiasis invasora en el paciente crítico no neutropénico. Rev Iberoam Micol 2016; 33 (3): 145-151.
4. León C, Alvarez-Lerma F, Ruiz-Santana S, León MA, Nolla J, Jordá R et al. Usefulness of the "*Candida* score" for discriminating between Candida colonization and invasive candidiasis in non-neutropenic critically ill patients: A prospective multicenter study. Crit Care Med 2009; 37(5): 1624-33.
5. Garnacho-Montero J, Díaz-Martín A, Ruiz Pérez de Piappón M y García-Cabrera E. Enferm Infecc Microbiol Clin 2012; 30 (6): 338-43.
6. Zaragoza R, Llinares P, Maseda E, Ferrer R, Rodríguez A y Grupo Proyecto EPICO. Proyecto EPICO: formulación de unas recomendaciones educativas con metodología DELPHI para pacientes adultos críticos no neutropénicos y con candidiasis invasiva. Rev Iberoam Micol 2013; 30 (3S1): 135-49
7. Spanu T, Posteraro B, Fiori B, D´Inzeo T, Capolli S, Ruggeri A et al. Direct maldi-tof mass spectrometry assay of blood culture broths for rapid identification of Candida species causing bloodstream infections: an observational study in two large microbiology laboratories. J Clin Microbiol 2012; 50: 176-9.
8. Vella A, de Carolis E, Vaccaro L, Posterato P, Perlin DS, Kostrzewa M et al. Rapid antifungal susceptibility testing by matrix-assisted laser desorption ionization-time of flight mass spectrometry analysis. J Clin Microbiol 2013; 51: 2964-9.
9. Farina C, Perin S, Andreoni S, Conte M, Fazii P, Lombardi G et al. Evaluation of the peptide nucleic acid fluorescence in situ hybridization technology for yeast identification directly from positive blood cultures: an Italian experience. Mycoses 2012; 55 (5): 388-92
10. Gorton RI, Ramnarain P, Barker K, Stone N, Rattenbury S, McHugh TD et al. Comparative analysis of Gram´s stain, PNA-FISH and Sepsityper with MALDI-TOF MS for identification of yeast direct from positive blood cultures. Mycoses 2014; 57: 592-601.
11. Pemán J y Quindós G. Aspectos actuales de las enfermedades invasoras causadas por *Candida* y otros hongos levaduriformes. Rev Iberoam Micol 2016; 33: 133-9.
12. Pazos C, Moragues MD, Quindós G. Pontón J and del Palacio A. Diagnostic potential of 1,3-β-D-glucan and anti-*Candida albicans* germ tube antibodies for the diagnosis and therapeutic monitoring of invasive candidiasis in neutropenic adult patients. Rev Iberoam Micol 2006; 23: 209-15.
13. Pontón J. Utilidad de los marcadores bilógicos en el diagnóstico de la candidiasis invasora. Rev Iberoam Micol 2009; 26: 8-14.
14. Cornely OA. Can we start or stop antifungal therapy based on biomarkers detection? 25th ECCMID, Copenhagen, Denmark, 25-28 September 2015.
15. Phaller MA, Wolk DM and Lowery TJ. T2MR and T2Candida: novel technology for the rapid diagnosis of candidemia and invasive candidiasis. Future Microbiol 2015: 11: 103-17.
16. Pfaller MA, Diekema DJ. Epidemiology of invasive candidiasis: A persistent public health problem. Clin Microbiol Rev. 2007; 20: 133–63.
17. Montravers P, Dupont H, Gauzit R, Veber B, Auboyer C, Blin P. Candida as a risk factor for mortality in peritonitis. Crit Care Med. 2006; 34: 646-52.
18. Dupont H, Paugam-Burtz C, Muller-Serieys C, Fierobe L, Chosidow D, Marmuse JP, et al. Predictive factors of mortality due to polymicrobial peritonitis with Candida isolation in peritoneal fluid in critically ill patients. Arch Surg. 2002; 137:1341-6.
19. Blot S, De Waele JJ. Critical issues in the clinical management of complicated intraabdominal infections. Drugs. 2005; 65: 1611-20.
20. Montravers P, Mira JP, Gangneux J P, Leroy O, Lortholary O. A multicentre study of antifungal strategies and outcome of *Candida* spp. peritonitis in intensive-care units. Clin Microbiol Infect 2011; 17: 1061-7.
21. Blot SI, Vandewoude K, De Wele JJ. Candida peritonitis. Curr Opin Crit Care 2007; 13:195-9.
22. Carneiro HA, Mavrakis A, Mylonakis E. Candida peritonitis: an up-

date on the latest research and treatments. World J Surg 2011; 35: 2650-9

23. Pittet D, Monod M, Suter PM, Frenk E, Auckenthaler R. Candida colonization and subsequent infections in critically ill surgical patients. Ann Surg 1994; 220: 751-8.
24. Spec A, Shindo Y, Burnham CA, Wilson S, Ablordeppey EA, Beiter ER, et al. T cells from patients with Candida sepsis display a suppressive immunophenotype. Cuidado Crit. 2016; 20: 15.
25. Wójtowicz A, Tissot F, Lamoth F, Orasch C, Eggimann P, Siegemund M, et al. Polymorphisms in tumor necrosis factor-α increase susceptibility to intra-abdominal *Candida* infection in high-risk surgical ICU patients. Crit Care Med 2014; 42: e304-e308.
26. Schneider CP, Seyboth C, Vilsmaier M, Küchenhoff H, Hofner B, Jauch KW, et al. Prognostic factors in critically ill patients suffering from secondary peritonitis: a retrospective, observational, survival time analysis. World J Surg 2009; 33: 34-43.
27. Kollef M, Micek S, Hampton N, Doherty JA, Kumar A. Septic shock attributed to Candida infection: importance of empiric therapy and source control. Clin Infect Dis 2012 ; 54: 1739-46
28. Maseda E, Rodríguez AH, Aguilar G, Pemán J, Zaragoza R, Ferrer R et al. Recommendations on invasive candidiasis in patients with complicated intra-abdominal infection and surgical patients with ICU extended stay. Rev Iberoam Micol. 2016; 33: 196-205.
29. González-Serrano M, Mouriz L, Álvarez-Escudero J, Ojeda N, Granizo J J, Giménez MJ et al. Intraabdominal candidiasis in surgical ICU patients treated with anidulafungin: A multicenter retrospective study. Rev Esp Quimioter 2016; 29(1), 32-9.
30. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Disease Society of America. Clin Infect Dis. 2016; 62:e1-e50.
31. Tomblyn M, Chiller T, Einsele H, Gress R, Sepkowitz K, Storek J, et al.; Center for International Blood and Marrow Research; National Marrow Donor program; European Blood and Marrow Transplant Group; American Society of Blood and Marrow Transplantation; Canadian Blood and Marrow Transplant Group; Infectious Diseases Society of America; Society for Healthcare Epidemiology of America; Association of Medical Microbiology and Infectious Disease Canada; Centers for Disease Control and Prevention. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant. 2009; 15: 1143-238.
32. Duarte RF, Sánchez-Ortega I, Cuesta I, Arnan M, Patiño B, Fernández de Sevilla A, et al. Serum galactomannan-based early detection of invasive aspergillosis in hematology patients receiving effective antimold prophylaxis. Clin Infect Dis. 2014; 59: 1696-702.
33. Kontoyiannis DP, Marr KA, Park BJ, Alexander BD, Anaissie EJ, Walsh TJ, *et al.* Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001-2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. Clin Infect Dis. 2010; 50: 1091-100.
34. Pagano L, Caira M, Nosari A, Van Lint MT, Candoni A, Offidani M, et al. Fungal infections in recipients of hematopoietic stem cell transplants: results of the SEIFEM B-2004 study--Sorveglianza Epidemiologica Infezioni Fungine Nelle Emopatie Maligne. Clin Infect Dis. 2007; 45: 1161-70.
35. Slavin MA, Sorrell TC, Marriott D, Thursky KA, Nguyen Q, Ellis DH, *et al.*; Australian Candidemia Study, Australian Society for Infectious Diseases. Candidemia in adult cancer patients: risks for fluconazole-resistant isolates and death. J Antimicrob Chemother. 2010; 65:1042-51
36. Puig-Asensio M, Padilla B, Garnacho-Montero J, Zaragoza O, Aguado JM, Zaragoza R, et al; CANDIPOP Project; GEIH-GEMICOMED (SEIMC); REIPI. Epidemiology and predictive factors for early and late mortality in *Candida* bloodstream infections: a population-based surveillance in Spain. Clin Microbiol Infect. 2014; 20: O245-54.
37. Puig-Asensio M, Ruiz-Camps I, Fernández-Ruiz M, Aguado JM, Muñoz P, Valerio M, et al; CANDIPOP Project, GEIH-GEMICOMED (SEIMC), and REIPI. Epidemiology and outcome of candidaemia in patients with oncological and haematological malignancies: results from a population-based surveillance in Spain. Clin Microbiol Infect. 2015; 21:491.e1-491.e10.
38. Bergamasco MD, Garnica M, Colombo AL, Nucci M. Epidemiology of candidemia in patients with hematologic malignancies and solid tumours in Brazil. Mycoses. 2013; 56: 256-63.
39. Lortholary O, Desnos-Ollivier M, Sitbon K, Fontanet A, Bretagne S, Dromer F. Recent exposure to caspofungin or fluconazole influences the epidemiology of candidemia: a prospective multicenter study involving 2,441 patients. Antimicrob Agents Chemother. 2011; 55: 532-8.
40. Mann PA, McNicholas PM, Chau AS, et al. Impact of antifungal prophylaxis on colonization and azole susceptibility of *Candida* species. Antimicrob Agents Chemother. 2009; 53: 5026-34.
41. Vallejo Llamas JC, Ruiz-Camps I. Invasive fungal infection in haematology patients. Enferm Infecc Microbiol Clin. 2012; 30: 572-9.
42. Ullmann AJ, Akova M, Herbrecht R, Viscoli C, Arendrup MC, Arikan-Akdagli S, et al.; ESCMID Fungal Infection Study Group. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: adults with haematological malignancies and after haematopoietic stem cell transplantation (HCT). Clin Microbiol Infect. 2012;18 Suppl 7:53-67.
43. Herbretch R, Tissot F, Agrawal S, Pagano L, Pettrikos G, Viscoli C et al. 2013-Updated of the ECIL guidelines for antifungal therapy in leukemia and HSCT patients (ECIL-5). http://www.kobe.fr/ecil/telechargements2013/ECIL5%20Antifungal%20Therapy.
44. Herbrecht R, Conte U, Biswas P, Capparella MR, Aram J. Efficacy and safety of anidulafungin in the treatment of invasive candidiasis in neutropenic patients: analysis of pooled data from five prospective studies. 19th Congress of European Haematology Association 2014 (P- 1187).
45. Pemán J, Ruiz I. Enfermedad fúngica invasora. En: Almirante B. Infección fúngica invasora producida por Candida spp. y otras levaduras. En: La infección fúngica invasora. Albert Pahissa. Ed: Entheos. Madrid 2010. Pp 125-60
46. Pemán J, Salavert M. Epidemiology and prevention of nosocomial

invasive infections by filamentous fungi and yeasts. Enferm Infecc Microbiol Clin. 2013; 31: 328-41.

47. Fernández-Ruiz M, Aguado JM, Almirante B, Lora-Pablos D, Padilla B, Puig-Asensio M, et al; CANDIPOP Project; GEIH-GEMICOMED (SEIMC); REIPI. Initial use of echinocandins does not negatively influence outcome in Candida parapsilosis bloodstream infection: a propensity score analysis. Clin Infect Dis. 2014; 58: 1413-21.
48. Vazquez J, Reboli AC, Pappas PG, Patterson TF, Reinhardt J, Chin-Hong P, et al. Evaluation of an early step-down strategy from intravenous anidulafungin to oral azole therapy for the treatment of candidemia and other forms of invasive candidiasis: results from an open-label trial. BMC Infect Dis. 2014; 14: 97.
49. Reboli AC, Rotstein C, Pappas PG, Chapman SW, Kett DH, Kumar D et al.; Anidulafungin Study Group. Anidulafungin versus fluconazole for invasive candidiasis. N Engl J Med. 2007; 356: 2472-82.