IFUCISTRATEGY: A Spanish Survey on the Management of Invasive Fungal Infection (IFI) in Critically Ill Patients

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Article

IFUCISTRATEGY: A Spanish Survey on the Management of Invasive Fungal Infection (IFI) in Critically Ill Patients

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Abstract

Background: The objective was to identify management strategies of IFI in critically ill patients through a Spanish national survey. **Methods:** A cross-sectional multicentre survey among ICU specialist, experienced in IFI was performed (22-April-25-July 2024). The survey consisted of 13 questions with four closed answers. **Results:** Sixty-three experts from 51 hospitals of 16 regions completed the survey. 95% stated that, in high-risk patients with clinical suspicion of Pulmonary Aspergillosis (PA), request galactomannan in BAL to initiate treatment. In the treatment of patients with PA and influenza, 86% declared that isavuconazole and liposomal amphotericin B are recommended treatments and in high suspicion of aspergillus coinfection, 76% recommended empirical treatment waiting for microbiological confirmation. 90% declared that the use of Extracorporeal Membrane Oxygenation (ECMO) and Renal Replacement Therapies (RRT) could be associated with lower azole levels. Regarding intraabdominal candidiasis, 78% that physiopathological changes in critically ill patients, reduce their entry into the peritoneal fluid. **Conclusion:** The majority of the experts agreed (>80%) on: In suspicion of PA, Galactomannan in BAL to guide treatment is mandatory; In case of aspergillosis and influenza, isavuconazole and liposomal amphotericin B are the recommended treatments; The use of ECMO and RRT could be associated with lower azole levels.

Keywords: invasive fungal infection; critically ill patients; antifungal resistance; aspergillosis; candidiasis

1. Introduction

Nowadays, available estimates of fungal disease incidence and mortality remain uncertain. Since 2013, the Leading International Fungal Education (LIFE) portal has facilitated the estimation of the burden of serious Fungal Infections (FIs) on a country-by-country basis. According to these estimates, more than 300 million people suffer from systemic FIs more than 300 million people suffer from systemic FIs every year worldwide every year. Of these cases, 6.5 million people are affected by an immediately life-threatening fungal disease, and around 2.5 million people die from a FI [1,2]. In addition, some pathogenic fungi benefit from climate change, gradually adapting to higher temperatures and becoming more frequent and possibly more virulent. Thus, an increase in Invasive Fungal Infections (IFIs) is expected in the coming years [3].

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Additionally, the global burden of IFIs has shown an upsurge in recent years due to the higher load of immunocompromised patients suffering from various diseases. The role of early and accurate diagnosis in the aggressive containment of the IFI at the initial stages becomes crucial thus, preventing the development of a life-threatening situation. Over the past decade, a change has been observed in the clinical profile of patients with invasive aspergillosis in the ICU, even surpassing the neutropenic immunocompromised patient. Non-neutropenic patients with virus-induced acute respiratory distress syndrome, treated with corticosteroids, as well as patients receiving immunomodulatory therapies, are identified as being at risk for invasive fungal infection[4] Timely diagnosis of IFI is necessary to prevent the high morbidity and mortality associated with systemic FI, as late diagnosis always equates with a poor prognosis [5].

Recent advancements have improved our understanding of invasive fungal diseases, leading to revised definitions and diagnostic criteria [6]. However, the diagnostic difficulties in Intensive Care Unit (ICU) patients remain unresolved, highlighting the need for further research and evidence generation [7]. Both Invasive Candidiasis (IC) and Invasive Aspergillosis (IA) remain important problems in critical patients, due to the appearance of new risk factors and new species, the growing use of new extracorporeal technologies and new devices, the increase in resistances, and the real need for new diagnostic techniques capable of serving as the new gold standards [8]. IC is the most prevalent form of invasive fungal disease in non-neutropenic ICU patients, presenting as candidemia and deep-seated candidiasis. On the other hand, IA predominantly manifests as Invasive Pulmonary Aspergillosis (IPA) in ICU patients, often associated with comorbidities and respiratory deterioration in viral pneumonia. Antifungal management involves tailored therapy based on guidelines and individual patient factors. The complexity of diagnosing and managing invasive fungal diseases in ICU patients underscore the importance of ongoing research and the need for updated diagnostic criteria and treatment approaches [7].

In addition to the introduction of new drugs, we hope that the coming years will see the creation of multidisciplinary packages of measures designed to reduce incidence of FIs, improve diagnostics tools and reduce both morbidity and mortality of these patients [8].

Nevertheless, significant gaps persist in the epidemiological characterization of IFI and clinical management in Spain. Previous initiatives, such as the IFISTRATEGY project, a Spanish national survey focused on hemato-oncologic patients, have provided valuable insights into diagnostic and therapeutic practices in high-risk patients [9]. However, data regarding critically ill patients in ICU settings is scarce.

To address this gap, we have performed this survey with the aim of understanding the current situation and strategies for diagnosing and managing IFI in critically ill patients, according to Spanish intensive care specialists.

2. Materials and Methods

A national, multicentre, cross-sectional survey was conducted across different centres within the Spanish National Health System (NHS) with Intensive care specialist with expertise in infectious diseases in critically ill patients as respondents.

Data collection was accomplished between 22 April and 25 July 2024 through an online survey developed on the Microsoft Forms platform. The survey questionnaire, designed for intensive care specialist, comprised 13 items, each of them with four predefined answers. In most cases, it was possible to choose more than one answer.

Subsequently, a descriptive analysis of the responses was conducted. Therefore, frequency distributions and their corresponding percentages were calculated based on the total number of participants.

Multiple-choice questions that allowed more than one answer are presented using bar charts. The total number of participants who selected each option was calculated and divided by the total number of participants who responded to the survey. Therefore, the sum of the percentages does not equal 100%.

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3. Results

A total of sixty-three ICU experts from fifty-one different hospitals across Spain participated in the survey. These experts represented sixteen Autonomous Communities (94%) with Andalusia, Catalonia, and the Valencian Community showing the highest response rates. La Rioja was the only region without representation. All the experts presented experience in treating IFIs with a mean number of years of practice of 22,86± 8,28 years. The survey achieved a 100% participation rate among invited participants. The complete questionnaire and the answers provided by the participants are shown in Table 1.

Table 1. Questions included in the survey and answers provided by the participants.

Questions	Answers N (%)
1. Pulmonary aspergillosis (PA) in critically ill patients*:	
In patients with influenza/COVID19 the diagnosis is usually initiated when there is clinical deterioration that is not explained by any other cause upon admission to the ICU.	42 (67%)
In high-risk patients with clinical suspicion, bronchoscopic Bronchoalveolar Lavage (BAL) is usually performed to obtain samples from the lower respiratory tract, requesting galactomannan to guide treatment.	60 (95%)
I start antifungal treatment without waiting for microbiological results when there is clinical deterioration in patients at risk that is not explained by any other cause upon admission to the ICU.	43 (68%)
I am guided by the result of galactomannan in tracheal aspirate to initiate treatment.	17 (27%)
2. The latest epidemiological studies on resistance to *Aspergillus* carried out in Spain (ASPEIN I and ASPEIN II) confirm the existence of azole-resistant *Aspergillus fumigatus**.	
I ask the laboratory or other institution to study azole sensitivity when *Aspergillus spp* is identified in the culture	44 (70%)
I request the laboratory or other institution to determine resistance mutations when *Aspergillus spp* is identified in the culture	7 (11%)
It is necessary to start considering the presence of azole resistance in patients where no clinical improvement is observed	55 (87%)
Most of the observed azole resistances are of environmental origin	17 (27%)
3. In case of suspected azole resistance in a patient who is being treated for aspergillosis, what strategy would you pursue?	
Association of another antifungal from a different family than the one you are receiving	25 (40%)
Change of antifungal family to a broad-spectrum family	28 (44%)
Increasing the dose of the antifungal	0 (0%)
Combined treatment with two new antifungals from different families other than azoles	10 (16%)
4. In the treatment of aspergillosis in patients with influenza*:	
Isavuconazole and liposomal amphotericin B are recommended treatments	54 (86%)
I would start it with a galactomannan + Bronchoalveolar Lavage (BAL)	51 (81%)
Empirical treatment in the absence of laboratory tests remains valid when there is high clinical suspicion	48 (76%)
I believe that prophylaxis must be done in ventilated critical patients	4 (6%)
5. Some antifungals do not reach levels during the first few days of administration. In this situation, in case of suspicion of Invasive Aspergillosis (IA), which strategy do you consider most appropriate?	
Associate a broad-spectrum antifungal from another family and wait for clinical improvement of the patient	3 (5%)
Check that the patient is not at risk of low levels of antifungals due to interactions and maintain monotherapy	20 (32%)

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Associate an antifungal from another family and perform levels before returning to monotherapy	27 (43%)
If Therapeutic Drug Monitoring (TDM) for azoles is not available, I avoid using them.	13 (21%)
6. In your opinion, azole-resistant *Candida parapsilosis**:	
Liposomal amphotericin B is one of the main treatment options	50 (79%)
It is not associated with the use of previous azoles	15 (24%)
It is associated with higher mortality compared to non-resistant strains	27 (43%)
I consider it an emerging concern in my clinical setting	37 (59%)
7. In your opinion, *Candida auris**:	
I recommend combination therapy	46 (73%)
Echinocandins and liposomal amphotericin B are the main treatment options	43 (68%)
It is associated with higher mortality compared to other forms of Invasive Candidiasis (IC)	48 (76%)
I consider *Candida auris* an emerging threat in my clinical setting.	24 (38%)
8. In what situations would you start antifungal treatment for Invasive Candidiasis (IC)?*	
I do not start treatment until culture results are available and positive	1 (2%)
I rely on the determination of B-D-glucan to guide my decision	22 (35%)
I initiate treatment when the Candida score is greater than 3	46 (73%)
I start treatment in patients with persistent fever, poor clinical evolution, and no response to antibiotics, even before microbiological results are available	49 (78%)
9. What do you think about the monitoring of antifungals in critically ill patients?*	
In practice, it is difficult to implement it well or receive results in time	50 (79%)
High-dose corticosteroids can reduce azole concentrations	23 (37%)
Monitoring isavuconazole may be advisable in specific situations, such as in obese patients BMI >25m^2 or when techniques like Extracorporeal Membrane Oxygenation (ECMO) and renal replacement therapies (RRT) are used	53 (84%)
The use of ECMO and RRT may be associated with low azole levels	57 (90%)
10. In your opinion, regarding Intra-Abdominal Candidiasis (IAC)*:	
Echinocandins are associated with the development of resistance of *Candida glabrata*, especially in this location	36 (57%)
Pathophysiological changes in critically ill patient especially affect water-soluble drugs, reducing their penetration into the peritoneal fluid	49 (78%)
Candida glabrata is increasing its incidence in this condition	46 (73%)
This infection is frequently underdiagnosed	50 (79%)
11. I initiate antifungal treatment in Intra-Abdominal Candidiasis (IAC)*:	
I would like to have the determination of B-D-glucan on peritoneal fluid	38 (60%)
I rely on the isolation of yeasts in the peritoneal fluid to guide treatment	36 (57%)
I initiate therapy only when the Candida score is positive	4 (6%)
In the immediate postoperative period of suture dehiscence in a situation of septic shock	58 (92%)
12. Regarding Mucor infection in critically ill patients with severe viral lung infection*:	
I would like to have the determination of C-reactive protein (CRP) in bronchoscopic Bronchioalveolar Lavage (BAL)	48 (76%)
The treatment of choice is liposomal amphotericin B	55 (87%)
Diagnosis is primarily based on culture from bronchoscopic BAL samples	29 (46%)
I consider this infection rare in our setting, but it should remain on our radar	59 (94%)
13. In my hospital I have access to*:	
Galactomannan testing and Bronchoalveolar Lavage (BAL)	57 (90%)
Real-time antifungal Therapeutic Drug Monitoring (TDM)	10 (16%)
Lateral Flow assays	28 (44%)
24/7 fiberoptic bronchoscopy	55 (87%)

*Multiple answers were permitted.

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3.1. Pulmonary Aspergillosis (PA) in Critically Ill Patients:

Answers provided by the coordinators: (a) In patients with influenza/COVID19 the diagnosis is usually initiated when there is clinical deterioration that is not explained by any other cause upon admission to the ICU (67%). (b) In high-risk patients with clinical suspicion, bronchoscopic Bronchoalveolar Lavage (BAL) is usually performed to obtain samples from the lower respiratory tract, requesting galactomannan to guide treatment (95%). (c) I start antifungal treatment without waiting for microbiological results when there is clinical deterioration in patients at risk that is not explained by any other cause upon admission to the ICU (68%). (d) I am guided by the result of galactomannan in tracheal aspirate to initiate treatment (27%).

Comments and discussion: Invasive Pulmonary Aspergillosis (IPA) is the most severe form of aspergillosis that usually occurs in in patients with risk factors for developing aspergillosis, such as virus-induced ARDS, corticosteroid treatment, immunomodulatory therapies, and immunosuppressed states [10]. Furthermore, viral infections such as COVID-19 and influenza are widely recognized as predisposing factors for IPA [10]. Based on Spanish practical recommendations for the diagnosis and management of PA associated with COVID-19 (CAPA) or influenza (IAPA), these diseases should be suspected as part of a differential diagnosis of respiratory superinfection in ICU patients with viral pneumonia who suffer clinical deterioration not attributable to other factors [11]. Following these recommendations, diagnosis should be based on the determination in respiratory samples of galactomannan levels, direct microscopic examination, culture on selective media, and molecular detection of Aspergillus DNA by Polymerase Chain Reaction (PCR), whenever available [11]. If possible, it is recommended to obtain samples from the lower respiratory tract using a flexible bronchoscope to collect a BAL sample. Respiratory samples not obtained by fiberoptic bronchoscopy such as sputum, tracheal aspirate and Non-Bronchoscopic Lavage (NBAL) are found to be insufficient for diagnosis this type of patients and thus, are not recommended. In addition, these recommendations suggests that antifungal treatment should be initiated when clinical suspicion is high and results are either not available for some time or inconclusive. Afterwards, depending on the results, antifungal treatment can be modified or discontinued [11,12].

The results obtained from the survey support the recommendations obtained from the consensus, suggesting that clinicians might know and guide the diagnosis and treatment of CAPA and IAPA according to them.

3.2. The Latest Epidemiological Studies on Resistance to Aspergillus Carried out in Spain (ASPEIN I and ASPEIN II) Confirm the Existence of Azole-Resistant Aspergillus Fumigatus.

Answers provided by the coordinators: (a) I request the laboratory or other relevant institution to assess azole sensitivity whenever *Aspergillus spp* is identified in the culture (70%). (b) I request the laboratory or other relevant institution to determine resistance mutations when *Aspergillus spp* is detected in the culture (11%). (c) It is necessary to start considering the presence of azole resistance in patients where no clinical improvement is observed (87%). (d) Most of the observed azole resistances are of environmental origin (27%).

Comments and discussion: *Aspergillus fumigatus* is one of the main aetiological agents causing aspergillosis in Spain [13,14]. It encompasses a broader species complex that includes *Aspergillus fumigatus sensu stricto* and several cryptic species that usually differ in antifungal susceptibility [15]. Recently, the results of the ASPEIN surveillance study carried out in 29 Spanish hospitals has been published [15]. This study aimed to assess the burden of azole resistance in 847 clinical *Aspergillus fumigatus* isolates extracted from a total of 725 patients from 15 February to 14 May 2019. Isolates were mostly from the lower respiratory tract (94.0%) and 97.8% corresponded to *Aspergillus fumigatus sensu stricto* and 2.2% to cryptic species. Among the 847 isolates, 63 (7.4%) showed resistance to at least one azole, being markedly higher in cryptic species compared to *Aspergillus fumigatus sensu stricto* (94.7% vs. 5.5%). Moreover, only cryptic species were amphotericin B resistant. The authors concluded that antifungal resistance is present in Spain and that tackling resistances is of utmost importance as they are associated with increased mortality rates.

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To diagnose and treat life-threatening diseases caused by *Aspergillus* spp, several guidelines have been developed [16–18]. The ESCMID 2018 guidelines and the GEMICOMED 2018 recommends antifungal susceptibility testing in patients with Invasive Aspergillosis (IA) in regions where antifungal resistance has been detected. In addition, the guidelines highlighted that antifungal resistance should be suspected when therapeutic failure occurs and when cryptic species are identified as causative agents of IA. These recommendations are highly consistent with the results obtained from the survey, suggesting that experts are familiar with and adhere to published guidelines.

3.3. In case of Suspected Azole Resistance in a Patient who is Being Treated for Aspergillosis, What Strategy Would You Pursue?

Answers provided by the coordinators: (a) Association of another antifungal from a different family than the one you are receiving (40%). (b) Change of antifungal family to a broad-spectrum family (44%). (c) Increasing the dose of the antifungal (0%). (d) Combined treatment with two new antifungals from different families other than azoles (16%).

Comments and discussion: There is limited evidence available in the literature that can help decide on the best treatment options in the case of suspected azole resistance in patients with aspergillosis. However, the evidence has demonstrated that azole resistance is associated with increased mortality rates, especially in patients admitted to the ICU [19–21]. A five-year retrospective cohort study carried out at 3 tertiary care medical centres in the Netherlands analysed clinical characteristics and mortality rates of 196 patients with Invasive Aspergillosis (IA) [20]. The authors found that voriconazole resistance was observed in 19% of the patients, increasing to 24% in patients admitted to the ICU. Voriconazole resistance was linked to higher overall mortality compared to susceptible cases: 49% vs 28% at day 42 (P = .017) and 62% vs 37% at day 90 (P = .0038). Similar finding has been encountered in another retrospective cohort study conducted in a single ICU of a tertiary university hospital in the Netherlands [21]. A total of 136 patients were treated for suspected FI of which 28% had a positive culture for *Aspergillus fumigatus.* Azole resistance was identified in 26% of these patients admitted in ICU while comparable rates (24%) correspond to all other departments in the hospital. Among patients with IA caused by azole-resistant *Aspergillus fumigatus*, 90-day mortality was 100% compared to 82% in azole-susceptible patients. The author highlighted the importance of implementing appropriate diagnosis and reconsidering empirical antifungal therapy [21].

According to the clinical guidelines published by the Study Group of FIs (GEMICOMED) from the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), treatment with amphotericin B (AIII) or with a combination of voriconazole with an echinocandin (CIII) in case of IA caused by cryptic species or resistant to voriconazole species (MIC > 2 mg/L) are recommended [16]. In addition, this guideline suggests that in areas with a rate of azole resistance >10%, azole monotherapy should be avoided, proposing a change in the treatment strategy. Thus, the results of the survey indicate that clinicians adhere to clinical guidelines, with no apparent preference between the two recommended approaches.

3.4. In the Treatment of Aspergillosis in Patients with Influenza:

Answers provided by the coordinators: (a) Isavuconazole and liposomal amphotericin B are recommended treatments (86%). (b) I would start it with a galactomannan + Bronchoalveolar Lavage (BAL) (81%). (c) Empirical treatment in the absence of laboratory tests remains valid when there is high clinical suspicion (76%). (d) I believe that prophylaxis must be done in ventilated critical patients (6%).

Comments and discussion: In cases of a positive Aspergillus culture in patients with severe viral pneumonia due to influenza, an individualized approach should be taking into account. Firstly, it is essential to determine whether the patient's situation is critical and involves severe respiratory compromise, followed by prompt and appropriate antifungal treatment [11]. If subsequent respiratory deterioration occurs, collecting new high-quality respiratory specimens, such as

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bronchoalveolar lavage.and initiating early treatment is recommended, since the influenza virus is risk factor for the development of Invasive Pulmonary Aspergillosis (IPA) [11]. The mould-active azoles, voriconazole or isavuconazole, are the first-choice antifungal drugs to treat Influenza Associated Pulmonary Aspergillosis (IAPA), with liposomal amphotericin B as an alternative in settings where azole resistance is prevalent [22].

Additionally, data from the study by Peral *et al.* show indicate that in cases of severe pneumonia due to influenza virus, bronchoscopy should be performed as soon as possible [11]. Similarly, another study published by Feys *et al* demonstrated that, in the case of IAPA in critically ill patients, BAL sampling for culture, galactomannan testing, and Polymerase Chain Reaction (PCR) should be considered the cornerstone of the diagnosis, whereas visual examination of the tracheobronchial tract during bronchoscopy is required to detect Invasive Aspergillus (IA) tracheobronchitis. Besides that, galactomannan testing on BAL fluid is the most valuable mycological tool to establish diagnosis of IAPA. [22]. Therefore, it can be said that the results found in both studies coincide with the data obtained from this survey.

On the other hand, according to the study by Peral *et al*, there is no scientific evidence to support specific recommendations when a positive Aspergillus culture is obtained in a patient with severe viral pneumonia due to Influenza [11]. However, data obtained in our study indicate that more than three-quarters of experts were in favour of empirical treatment in the absence of laboratory tests when there is high clinical suspicion. This supports the hypothesis that the high morbidity and mortality associated with invasive pulmonary aspergillosis is related to delayed treatment initiation, emphasizing the importance of minimizing these poor prognoses through early therapy.

Regarding antifungal prophylaxis, it is not recommended in patients with severe influenza [11]. This result coincides with data obtained in our survey, as a very low percentage of experts supported prophylaxis in critically ill ventilated patients.

3.5. Some Antifungals do not Reach Levels During the First Few Days of Administration. In this Situation, in Case of Suspicion of Invasive Aspergillosis (IA), Which Strategy do you Consider most Appropriate?

Answers provided by the coordinators: (a) Associate a broad-spectrum antifungal from another family and wait for clinical improvement of the patient (5%). (b) Check that the patient is not at risk of low levels of antifungals due to interactions and maintain monotherapy (32%). (c) Associate an antifungal from another family and perform levels before returning to monotherapy (43%). (d) If Therapeutic Drug Monitoring (TDM) for azoles is not available, I avoid using them (21%).

Comments and discussion: Aspergillus resistance to antifungal drugs should be suspected in every therapeutic failure scenario (regardless of the isolated species) and when cryptic species are identified as causative agents of IA [23]. Every isolate coming from an invasive infection should be tested for antifungal resistance. Currently, AntiFungal Susceptibility Testing (AFST) is still the most reliable procedure in determining the best clinically active antifungal agent and detecting resistance in Aspergillus spp. However, the true rates of global antifungal resistance in these pathogens are unknown but purportedly low in Spain. Antifungal combination therapy should not be generally recommended for primary treatment of IA, but for salvage treatment of refractory IA, the addition to another agent to initial therapy may be consider in some patients [23].

According to IDSA guidelines, an individualised approach that considers the speed, severity and extent of the infection, the patient's comorbidities and excludes the emergence of a new pathogen is recommended [24]. The duration of antifungal therapy for Invasive Aspergillosis (IA) is not well defined. These guidelines generally recommend that treatment for Invasive Pulmonary Aspergillosis (IPA) should continue for a minimum of 6–12 weeks, depending on the severity [24]. Echinocandins are effective in salvage therapy (either alone or in combination) against IA, but routine use as monotherapy for the primary treatment of IA is not recommended. In the context of salvage therapy, an additional antifungal agent may be added to the current therapy, or combined antifungal medications from classes other than those in the initial regimen may also be used [24]. In contrast,

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the clinical practice guidelines developed by García *et al*, highlighted that the use of two or more antifungal drugs may also result in increased toxicity or drug interactions [23].

For therapies in which drug interactions with azoles are anticipated, TDM is recommended to prevent therapeutic failures attributable to suboptimal drug exposures, and to minimize toxicities potentially associated with voriconazole [24].

TDM of antifungal agents is generally recommended, particularly in situations non-compliance, non-linear pharmacokinetics, inadequate absorption, a narrow therapeutic window, suspected drug interaction or unexpected toxicity [23]. However, in Spain, a national survey distributed among colleagues of GEMICOMED, found out that TDM was not available in almost half of the hospitals and samples were sent to reference hospitals [25].

IDSA guidelines highlight the heterogeneity of the results found in published studies. Additional questions regarding optimal drug combinations, adequate drug dosages, pharmacokinetic interactions and potential toxicities associated with primary combined antifungal therapy require further investigation [24].

The results of these studies and clinical guidelines agree with the results of this survey, since several hospitals in Spain do not have TDM, there is no consensus among experts on the most appropriate strategy when antifungals do not reach adequate levels during the first days of administration.

3.6. In your Opinion, Azole-Resistant Candida Parapsilosis:

Answers provided by the coordinators: (a) Liposomal amphotericin B is one of the main treatment options (79%). (b) It is not associated with the use of previous azoles (24%). (c) It is associated with higher mortality compared to non-resistant strains (43%). (d) I consider it an emerging concern in my clinical setting (59%).

Comments and discussion: *Candida parapsilosis* is one of the most common causative species of Invasive Candidiasis (IC) and candidemia, especially in immunocompromised and critically ill patients [26]. In the last years, there has been an increase in fluconazole-resistant strains, becoming a worldwide concern due to its high morbidity and mortality rates [26]. Consequently, *Candida parapsilosis* is considered in the WHO priority pathogen list [26,27].

In Spain, several fluconazole-resistant *Candida parapsilosis* outbreaks have been reported in regions such as Madrid and Castilla y Léon [28,29]. The authors highlighted that hospital control measures should be implemented to prevent further spreading of the infection [28,29].

Mortality in IC infections caused by *Candida parapsilosis* ranged from 14,5% to 47,0%. However, different observational studies suggest that fluconazole-resistant *Candida parapsilosis* is not associated with higher mortality rates than fluconazole-susceptible *Candida parapsilosis* [30,31]. These findings are consistent with the responses that were obtained in the survey.

Regarding the treatment of *Candida parapsilosis*, no specific guidelines or recommendations have been found in the literature. Conversely, the global guideline published in 2025 by the European Confederation for Medical Mycology (ECMM) in cooperation with International Society of Human and Animal Mycology (ISHAM) and American Society for Microbiology (ASM) provides several recommendations for the treatment of candidiasis. Echinocandins are recommended as a first-line therapeutic option [32]. In addition, L-AMB is strongly recommended in patients who cannot be treated with echinocandins due to proven or suspected drug resistance, treatment failure or intolerance. Moreover, this guideline also underscored the importance of considering local epidemiology when deciding treatment [32].

3.7. In Your Opinion, Candida Auris:

Answers provided by the coordinators: (a) I recommend combination therapy (73%). (b) Echinocandins and liposomal amphotericin B are the main treatment options (68%). (c) It is associated with higher mortality compared to other forms of Invasive Candidiasis (IC) (76%). (d) I consider *Candida auris* an emerging threat in my clinical setting (38%).

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Comments and discussion: *Candida auris* is an emerging multidrug-resistant pathogen that causes different nosocomial outbreaks in several countries around the world [33,34]. In Spain, several clinicians have informed of different *Candida auris* outbreaks in a few hospitals in Valencia [33,35–38]. However, in other geographic regions such as Madrid, *Candida auris* has not been detected [29]. This is aligned with the fact that just 38% of the participants stated that *Candida auris* is an emerging treat in their clinical setting.

Moreover, *Candida auris* exhibits high levels of antifungal resistance to fluconazole and voriconazole and variable susceptibility to amphotericin B and echinocandins [34,37]. In addition, multidrug resistance and even pan-resistance have been documented in some *Candida auris* isolates [34]. Thus, *Candida auris* is a life-threatening infection that is associated with high mortality rates (29%-72%) due to its difficult antifungal management [27,34,37,39].

Treatment of *Candida auris* remains challenging. However, echinocandins are currently recommended as a first-line therapeutic option [32]. If the patient is colonized or has had a history of infection with echinocandin-resistant strains, liposomal amphotericin B is moderately recommended [32]. Nevertheless, some Spanish outbreaks, L-AmB has been added to echinocandin treatment in a high percentage of patients (35,4%) when persistent candidemia was observed [37]. In our survey, 73% of the respondents recommended combination therapy, suggesting that it may be more widely used in the Spanish setting.

3.8. In What Situations Would you Start Antifungal Treatment for Invasive Candidiasis (IC)?

Answers provided by the coordinators: (a) I do not start treatment until culture results are available and positive (2%). (b) I rely on the determination of B-D-glucan to guide my decision (35%). (c) I initiate treatment when the Candida score is greater than 3 (73%). (d) I start treatment in patients with persistent fever, poor clinical evolution, and no response to antibiotics, even before microbiological results are available (78%).

Comments and discussion: IC is one of the most challenging and potentially fatal infections in critical care [40,41]. Recently, there has been a worldwide epidemiological trend towards decreasing proportions of *Candida albicans*. However, the proportion of non-*albicans Candida* spp. as the main causative agent has increased [40,41]. The distribution of non-*albicans Candida* spp. vary widely between geographic regions [40]. In Spain, the CANDIMAD multicentre surveillance study carried out between 2020 and 2022 analysed the epidemiology and antifungal resistances of 766 Candida sp. Isolates from 686 patients [29]. During the described period of time, *C. albicans* remained the most frequent species followed by C.*parapsilosis* complex fluconazole susceptible and C.*glabrata.* Nevertheless, there was a significant increase of fluconazole-resistant *C. parapsilosis* [29].

Timely and accurate diagnosis could enhance treatment success for critically ill patients with IC [41]. Thereby, the European Confederation for Medical Mycology (ECMM) has published in 2025 some clinical recommendations for the management of IC [32]. This guideline moderately recommends initiating empirical antifungal therapy in patients presenting with septic shock or patients with clinical deterioration who exhibit additional risk factors for candidemia, including prolonged ICU stay, presence of indwelling vascular catheter or documented colonization by *Candida* species [32]. Furthermore, serum β-D-glucan (BDG) testing for diagnosing IC and candidemia is moderately recommended. However, they highlighted that the diagnosis should not be exclusively based on BDG testing [32].

In addition, the Spanish guideline developed in 2011 by the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) also provides recommendations for the treatment of IC in critically ill patients [42]. Prophylactic treatment of IC in critically ill patients is recommended in high-risk patients identified based on the degree of colonization or on the presence of specific risk factor such as the Candida score [42]. Additionally, this guideline underscored the importance of timely initiation of antifungal therapy as delayed treatment is associated with increased mortality rates [42].In addition, the Spanish guideline developed in 2011 by the SEIMC also provides recommendations for the treatment of IC in critically ill patients [42]. Prophylactic treatment of IC in

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critically ill patients is recommended in high-risk patients identified based on the degree of colonization or on the presence of specific risk factor such as the Candida score [42–44]. Additionally, this guideline underscored the importance of timely initiation of antifungal therapy as delayed treatment is associated with increased mortality rates [42].

Our survey findings suggests that clinicians generally comply with established clinical guidelines.

3.9. What do you Think about the Monitoring of Antifungals in Critically ill Patients?

Answers provided by the coordinators: (a) In practice, it is difficult to implement it well or receive results in time (79%). (b) High-dose corticosteroids can reduce azole concentrations (37%). (c) Monitoring isavuconazole may be advisable in specific situations, such as in obese patients BMI >25m^2 or when techniques like Extracorporeal Membrane Oxygenation (ECMO) and renal replacement therapies (RRT) are used (84%). (d) The use of ECMO and RRT may be associated with low azole levels (90%).

Comments and discussion: Therapeutic drug monitoring (TDM) of antifungals has been postulated as a useful tool to determine antifungal dosage, monitor efficacy and minimize drug toxicity [25]. According to clinical guidelines, TDM is generally recommended, especially in critically ill patients or patients at risk of low or high drug exposures, non-linear pharmacokinetics, narrow therapeutic index, suspected drug–drug interactions, or unexpected toxicity [16,32]. Commonly, TDM should be considered when using itraconazole, posaconazole or voriconazole [45]. However, TDM is also recommended in patients with variable pharmacokinetics, including critically ill patients, treated with echinocandins or isavuconazole [45,46]. Moreover, recent real-world studies indicate that conditions such as obesity, renal replacement therapy and extracorporeal membrane oxygenation are linked to suboptimal isavuconazole levels [46–48].

In Spain, a national survey distributed among colleagues of GEMICOMED, found out that TDM was not available in almost half of the hospitals and samples were sent to reference hospitals [25]. However, participants stated that it was routinely carried out for antifungals such as voriconazole [25]. This limited on-site laboratory availability, in addition to delayed turnaround times, highlight some of the barriers to the implementation of TDM, reducing its clinical utility in real-time drug monitoring.

Our survey results align closely with published guidelines and recommendations, reinforcing their applicability in the real-world setting in Spain.

3.10. In your Opinion, Regarding Intra-Abdominal Candidiasis (IAC):

Answers provided by the coordinators: (a) Echinocandins are associated with the development of resistance of *Candida glabrata*, especially in this location (57%). (b) Pathophysiological changes in critically ill patient especially affect water-soluble drugs, reducing their penetration into the peritoneal fluid (78%). (c) *Candida glabrata* is increasing incidence in this condition (73%). (d) This infection is frequently underdiagnosed (79%).

Comments and discussion: Intra-abdominal candidiasis (IAC) is caused by an overgrowth of *Candida* spp. within the abdominal cavity [49]. It accounts for 10-30% of all intra-abdominal infections diagnosed in ICU and it is associated with significantly higher morbidity and mortality rates [50]. Moreover, IAC can be associated or not with candidemia, defined as the presence of *Candida* spp. in blood [49]. Recently, there has been an epidemiological shift from *Candida albicans* to non-albicans species, such as *Candida glabrata* or *Candida auris* which often presents antifungal drug resistance, representing a health threat to human health [49,51]. Consequently, some of this species has been included in the WHO fungal priority pathogen list [27]. Moreover, it has been revealed by Polymerase Chain Reaction (PCR) testing that C. *glabrata* infections are often underdiagnosed [49].

A prospectively study carried out between 2019 and 2021 in patients admitted to 16 hospitals in the area of Madrid, monitored the epidemiology and antifungal susceptibility of *Candida* spp. from blood cultures and intra-abdominal samples following the EUCAST E.Def 7.3.2 procedure [52]. From

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2,107 Candida isolates collected from blood and intra-abdominal samples, five species (C. *albicans*, C. *glabrata*, C. *parapsilosis*, C. *tropicalis*, and C. *krusei*) accounted for 96.9% of cases and C. *auris* was not detected. Overall, resistance rates were 8.6% for fluconazole and 0.7% for echinocandins. Nevertheless, intra-abdominal samples of *Candida glabrata* showed higher resistance rates. Cross-resistance to echinocandins and azoles in *Candida glabrata* is becoming a concern [52].

Moreover, it is important to consider that this infection appears in the peritoneal cavity. Penetration of antifungals in this cavity is particularly essential, especially in critically ill patients where pathophysiological facts compromised drug distribution [53]. Several studies have demonstrated that echinocandin exposure is suboptimal in critically ill patients and thus, dose adjustments would be necessary to adequately treat IAC [45,54,55]. Consequently, the use of Therapeutic Drug Monitoring (TDM) is recommended to optimize drug concentrations and effectiveness in critically ill patients and patients at risk of suboptimal antifungal exposure [45,54].

Our survey results corroborate these findings, revealing comparable challenges and priorities among clinicians.

3.11. I initiate Antifungal Treatment in Intra-Abdominal Candidiasis (IAC):

Answers provided by the coordinators: (a) I would like to have the determination of B-D-glucan on peritoneal fluid (60%). (b) I rely on the isolation of yeasts in the peritoneal fluid to guide treatment (57%). (c) I initiate therapy only when the Candida score is positive (6%). (d) In the immediate postoperative period of suture dehiscence in a situation of septic shock (92%).

Comments and discussion: The diagnosis and management of Invasive Candidiasis (IC) have widely improved in the last years. However, its diagnosis and treatment remains a challenge for critical care specialists due to the fact that it is usually accompanied by bacterial cross-infections [56]. To optimize the diagnosis and treatment of the Working Group on Perioperative Infections of IAC, the Spanish Society of Anaesthesiology, Resuscitation and Pain Management (GTIPO-SEDAR) has published several recommendations based on multidisciplinary experts opinions [56]. Upon suspicion of IAC, the experts recommended the determination of B-D-glucan in plasma and peritoneal fluid. Moreover, the experts also recommend analysing abdominal fluid using molecular tests such as Polymerase Chain Reaction (PCR) to identify species as *C. glabrata* which are associated with higher antifungal resistance [56]. In the survey, 60% of the participants stated that they would like to have the determination of B-D-glucan on peritoneal fluid which is aligned with the aforementioned recommendations. In addition, just 6% of the participants commented that they initiate therapy only when the Candida score is positive which is accurate considering that B-D-glucan determination has demonstrated to be superior to *Candida* score [57]. Furthermore, a narrative review emphasizes that early antifungal treatment is crucial in critically ill patients with abdominal surgery, septic shock or patients with postoperative complications which is consistent with current findings [49].

3.12. Regarding Mucor Infection in Critically Ill Patients with Severe Viral Lung Infection:

Answers provided by the coordinators: (a) I would like to have the determination of C-reactive protein (CRP) in bronchoscopic Bronchioalveolar Lavage (BAL) (76%). (b) The treatment of choice is liposomal amphotericin B (87%). (c) Diagnosis is primarily based on culture from bronchoscopic BAL samples (46%). (d) I consider this infection rare in our setting, but it should remain on our radar (94%).

Comments and discussion: Mucormycosis is a rare life-threatening FI that tends to progress rapidly and presents high morbidity and mortality. Early diagnosis and urgent multidisciplinary intervention are extremely important to maximize survival rates. To facilitate clinical decision-making the European Confederation of Medical Mycology (ECMM), together with the Mycoses Study Group Education & Research Consortium (MSG ERC) has developed a guidance document [58].

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Diagnosis of mucormycosis should be rapid, combining imaging, histopathology and culture of deep tissue samples from the affected site, such as BAL fluid in cases of pulmonary involvement.

Once it is already diagnosed, early complete surgical treatment in addition to systemic antifungal treatment is strongly recommended. First-line drug treatment with high-dose liposomal amphotericin B is strongly recommended across all patterns of organ involvement. Moreover, Isavuconazole is also recommended for first-line treatment with moderate strength. Strongly recommended treatment of mucormycosis in critically ill patients admitted in the ICU includes correction of the underlying conditions where feasible, source control, appropriate antifungal therapy, and relevant supportive care [58].

Survey responses demonstrated that clinicians usually follow this guideline regarding drug treatment and that in Spain remains as a rare infection.

3.13. In my Hospital I have Access to:

Answers provided by the coordinators: (a) Galactomannan testing and Bronchoalveolar Lavage (BAL) (90%). (b) Real-time antifungal Therapeutic Drug Monitoring (TDM) (16%). (c) Lateral Flow assays (44%). (d) 24/7 fibreoptic bronchoscopy (87%).

Comments and discussion: Early diagnosis and more precise species identification of IFI are of crucial importance to initiate prompt antifungal therapy, as delayed diagnosis is associated with significantly higher mortality specially in immunocompromised patients, as well as in critically ill individuals admitted in the ICUs [3,59]. Nevertheless, accurate IFI diagnosis remains a challenge.

Nowadays, conventional techniques such as fungal culture, direct microscopy, and histopathology, remain the standard of care for diagnosing IFI [3]. Despite allowing pathogen identification and AntiFungal Susceptibility Testing (AFST), these techniques provide suboptimal sensitivity and delayed reporting. However, novel techniques such as serological assays (β-D-glucan and galactomannan detection), Polymerase Chain Reaction (PCR), MALDI-TOF, lateral-flow have been developed to overcome these limitations [3].

In Spain, according to the obtained responses, access to rapid diagnostics and TDM remains heterogeneous. However, the presence of galactomannan testing and BAL, in addition to 24/7 fibreoptic bronchoscopy in most of the hospitals surveyed supports guidelines recommended diagnosis.

In contrast, although TDM of antifungal agents is generally recommended (***AII***) by the clinical guidelines published by GEMICOMED, its implementation in the Spanish setting is heterogenic. This finding contrast with the results obtained from a survey completed by 22 clinicians in Spain, where 45,5% of the respondents stated that TDM was not available in their center and thus, samples were sent to reference hospitals and 9,0% commented that was neither available onsite nor sent to a central laboratory [25].

Overall, these findings underscore the importance of ensuring access to advanced diagnostic and monitoring technologies in Spanish hospitals to enable timely detection and treatment of IFI.

4. Discussion

This study describes the current situation and strategies for diagnosing and managing IFI in critically ill patients in Spain and has the strength of gathering, through a survey, the expert opinions of intensivists, thereby reflecting real-world clinical practice. The observed variability in survey responses is considered justifiable due to the lack of consistent randomized clinical trials providing robust evidence. Most of the existing evidence in the field of fungal infections comes from studies conducted in immunocompromised patients, largely from hematology, and these results have often been extrapolated to critically ill patients, who, although sharing some similarities, present a distinct clinical profile, as evidenced in our detailed analysis of each survey question. Another notable strength is the high representativeness of most regions of Spain, enhancing the generalizability of the findings. Although inviting participants to the survey may introduce a potential selection bias, it

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should be emphasized that the respondents were intensivists specialized in infectious diseases and recognized as key opinion leaders within their respective units.

Based on these results, it can be concluded that most experts agree on: (1) In case of PA in high-risk patients, when clinically suspected, BAL is usually performed to obtain samples from the lower respiratory tract, requesting galactomannan to guide treatment. (2) It is necessary to begin considering the presence of azole resistance in patients who show no clinical improvement, and its management should be based on another broad-spectrum antifungal family. (3) The use of isavuconazole and liposomal amphotericin B are recommended for the treatment of aspergillosis in patients with influenza. (4) It would be advisable to monitor isavuconazole in specific situations. Furthermore, the use of Extracorporeal Membrane Oxygenation (ECMO) and Renal Replacement Therapies (RRT) may be associated with low levels of azoles. (5) Antifungal treatment for IAC must be initiated immediately after surgery in cases of suture dehiscence in septic shock. (6) Mucor infection in critically ill patients with severe viral lung infection is rare, but the treatment of choice would be liposomal amphotericin B.

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