Original

THE EPICO PROJECT GROUP*

EPICO PROJECT. Development of educational recommendations using the DELPHI technique on invasive candidiasis in non- neutropenic critically ill adult patients

ABSTRACT

Introduction. Although there has been an improved management of Invasive Candidiasis in the last decade, controversial issues still remain, especially in the diagnostic and therapeutic approaches.

Objectives. We sought to identify the core clinical knowledge and to achieve high level agreement recommendations required to care for critically ill adult patients with Invasive Candidiasis.

Methods. Prospective Spanish survey reaching consensus by the Delphi technique, anonymously conducted by electronic e-mail in a first term to 25 national multidisciplinary experts in invasive fungal infections from five national scientific societies, including Intensivists, Anesthesiologists, Microbiologists, Pharmacologists and Infectious Disease Specialists, responding to 47 questions prepared by a coordination group after a strict review of the literature in the last five years. The educational objectives spanned five categories, including epidemiology, diagnostic tools, prediction rules, and treatment and de-escalation approaches. The level of agreement achieved among the panel experts in each item should exceed 75% to be selected. In a second term, after extracting recommendations from the selected items, a face to face meeting was performed where more than 80 specialists in a second round were invited to validate the preselected recommendations.

Measurements and Main Results. In the first term, 20 recommendations were preselected (Epidemiology 4, Scores 3, Diagnostic tools 4, Treatment 6 and De-escalation approaches 3). After the second round, the following 12 were validated: **Epidemiology:** Think about Candidiasis in your ICU and do not forget that *non-albicans* species also exist. **Diagnostic tools**: Blood cultures should be performed under suspicion every 2-3 days and, if positive, every 3 days until obtaining the first negative result. Obtain sterile fluid and tissue, if possible (direct examination of the sample is important). Use nonculture based methods of microbiological tools, whenever possible. Determination of antifungal susceptibility is mandatory. **Scores:** As screening tool, use the *Candida* Score and determine multicolonization in high risk patients. **Treatment:** Start early. Choose Echinocandins. Withdraw the catheter. Fundoscopy is needed. **De-escalation:** Only applied when knowing susceptibility determinations and after 3 days of clinical stability. The higher rate of agreement was achieved in the optimization of microbiological tools and the withdrawal of the catheter, whereas the lower rate corresponded to de-escalation therapy and the use of scores.

Conclusions. The management of invasive candidiasis in ICU patients requires the application of a broad range of knowledge and skills that our summarized in our recommendations. These recommendations may help to identify the potential patients, standardize their global management and improve their outcomes, based on the DELPHI methodology.

KEY WORDS: Invasive candidiasis, Delphi technique, Non-neutropenic critically ill patients, educational project, recommendations.

PROYECTO ÉPICO. Desarrollo de unas recomendaciones educacionales mediante metodología DELPHI en pacientes críticos adultos no neutropénicos con candidiasis invasiva.

ABSTRACT

Introducción. Aunque en la última década se ha mostrado una mejoría en el manejo de la Candidiasis Invasiva, todavía existe controversia, especialmente en cuanto al diagnóstico y enfoques terapéuticos.

Objetivos. Identificar los principales conocimientos clínicos y elaborar recomendaciones con un alto nivel de consenso, necesarios en el cuidados de los pacientes adultos críticos no neutropénicos con Candidiasis Invasiva.

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Métodos. Cuestionario prospectivo español, que mide el consenso mediante la técnica Delphi, se realizó de forma anónima y por correo electrónico con 25 expertos multidisciplinarios nacionales, especialistas en infecciones fúngicas invasivas de cinco sociedades científicas nacionales, incluyendo Intensivistas, Anestesistas, Microbiólogos, Farmacólogos y Especialistas en Enfermedades Infecciosas que respondieron a 47 preguntas preparadas por el grupo de coordinación, tras una revisión exhaustiva de la literatura de los últimos cinco años. Los objetivos educativos contemplaron cinco categorías, incluyendo epidemiología, técnicas diagnósticas, scores, tratamiento y desescalada. El nivel de acuerdo alcanzado entre los expertos en cada uno de las categorías debería superar el 75% para ser seleccionada. En un segundo término, después de extraer las recomendaciones de los temas seleccionados, se celebró una reunión presencial con más de 80 especialistas y se les solicitó la validación de las recomendaciones pre-seleccionadas.

Mediciones y Resultados Principales. En un primer término, se realizó una pre-selección de 20 recomendaciones (Epidemiología 4, Scores 3, Diagnóstico de laboratorio 4, Tratamiento 6 y Desescalado 3). Después de la segunda ronda, las siguientes 12 recomendaciones fueron validadas: **Epidemiología:** Piensa en la Candidiasis en su UCI y no olvide que las especies *no albican*s también existen. **Técnicas diagnósticas**: Se deben realizar hemocultivos ante sospecha cada 2-3 días y, si es positivo, cada 3 días hasta obtener el primer resultado negativo. Cuando es posible, obtener fluidos y tejidos estériles, (es importante realizar una evaluación directa de las muestras). Siempre que sea posible, realizar pruebas microbiológicas no basadas en cultivos. La determinación de la susceptibilidad antifúngica es obligatoria. **Scores:** Utilice la *Candida* Score como herramienta de evaluación y determinar la multicolonización en pacientes con alto riesgo. **Tratamiento:** Inicie el tratamiento de forma precoz. Elija equinocandinas. Retire el catéter. Se requiere realización de fondo de ojo. **Desescalada:** Solo cuando se confirme la sensibilidad a fluconazol, después de 3 días de estabilidad clínica.

El mayor nivel de acuerdo fue alcanzado en la optimización de técnicas microbiológicas y en la retirada del catéter, mientras que el menor nivel correspondió al desescalado y scores.

Conclusiones. El manejo de la candidiasis invasiva en pacientes de UCI requiere la aplicación de los conocimientos y destrezas que se detallan en nuestras recomendaciones. Estas recomendaciones pueden ayudar a identificar a los pacientes potenciales, estandarizar su manejo global y mejorar su pronóstico, basados en la metodología DELPHI.

PALABRAS CLAVE: Candidiasis invasiva, Metodología Delphi, pacientes críticos no neutropénicos, proyecto educacional, recomendaciones.

INTRODUCTION

The incidence of candidemia in non-neutropenic critically ill patients has significantly increased in the past years[1-6]. In our country, the incidence of candidemia is estimated at 4.3 episodes/10^5 habitants[7], of which 33 to 55% of the cases are located in the Intensive Care Units (ICU)[8], although this percentage may have decreased in the last few years.

In addition to the increased incidence, a change in the distribution of the different *Candida* species has been observed[9]. *Candida albicans* continues to be the predominant species in the ICU[10] representing approximately half of the isolates. According to a recent epidemiological study published[9], in our country *C. parapsilosis* and *C. glabrata* are the second and third most common isolated species.

In addition to the important financial burden on the health systems, in general, *Candida* spp. infections and candidemia, in particular, are associated to an elevated mortality rate in critically ill patients. Candidemia is, therefore, associated in the United States with a 14.5% increase of the mortality rate in adults, and a 10% increase in pediatric patients[11]. On the other hand, the crude mortality rates and mortality rates associated to invasive candidiasis have been established at 40-78% and 20-40%, respectively[12-13].

During the last few years, new anti-fungal agents have offered different alternatives in the treatment of invasive candidiasis. However, and due to the heterogeneity of the recommendations from the different scientific societies[1,14,15], the most effective therapeutic strategy has not yet been established, resulting in a remarkable lack of consensus when establishing the diagnosis and most appropriate treatment for this patient population.

The main objective of this research study is to analyze the present situation in the management of non-neutropenic critically ill patients in our country's hospitals. For this purpose, between January and September 2012, a panel of specialists from 5 scientific societies was formed – The Spanish Association of Mycology (AEM) as promoter, the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC); the Spanish Society of Anesthesiology, Reanimation and Pain Therapeutics (SEDAR); The Spanish Society of Critical, Intensive and Coronary Medicine Units (SEMICYUC); and the Spanish Society of Chemotherapy (SEQ) – with extensive experience in the treatment of non-neutropenic critically ill patients, who were requested to complete a questionnaire elaborated by the 5 coordinators responsible for the research, after having made a thorough review of the literature of the last five years. In the cases in which no consensus was reached, the experts detailed the reasons for the divergent opinions.

In second place, and after the group coordinator elaborated the resulting recommendations, a second face to face meeting was held with 80 specialists from the entire national geography, who commonly care for critically ill adult patients with invasive candidiasis, who voted and validated the preselected recommendations.

METHODOLOGY

The panel of specialists was composed of 25 specialists with a wide geographical distribution in our country, pertaining to the five scientific societies collaborating in the research. The criteria of inclusion were based on their experience in the research of candidemia and on the prognostic and clinical management of non-neutropenic critically ill patients with a suspected or confirmed onset of invasive candidiasis.

The Delphi technique was used to carry out the study with the objective of optimizing the consultation process of the 25 panel members. Specifically, the Delphi methodology enables group opinions, and not merely individual opinions, from the experts in the different areas of information provided by the coordinators. A consensus greater than 75% (19 to 25) is required from the total number of experts consulted in each of the questions formulated. In the cases in which the majority of the responses to a given question were shared by 15-18 participants, the degree of consensus was established as medium, meanwhile in those cases in which consensus was only shared by 14 or less experts, the degree of consensus was defined as low.

The 47 total questions elaborated by the coordinators (table 1) are distributed in five different sections or specialties: Epidemiological section, 7 questions (developed by E.M. and P.L.); Scores section, 5 questions (developed by A.R. and R.Z.); Laboratory diagnosis section, 14 questions (developed by R.Z. and A.R.); Treatment section, 12 questions (developed by P.L. and E.M.); and Therapeutic de-escalation section, 9 questions (developed by R.F. and R.Z.).

Table 1 EPICO Study list of coordinators

Name	Scientific society
Dr. Pedro Llinares Mondéjar	SEQ*
Dr. Rafael Zaragoza Crespo	AEM*
Dr. Emilio Maseda Garrido	SEDAR*
Dr. Ricard Ferrer Roca	SEMICYUC/EDUSEPSIS*
Dr. Alejandro H. Rodríguez Oviedo	SEMICYUC*

*The Spanish Association of Mycology (AEM) as promoter, the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC); the Spanish Society of Anesthesiology, Reanimation and Pain Therapeutics (SEDAR); The Spanish Society of Critical, Intensive and Coronary Medicine Units (SEMICYUC); and the Spanish Society of Chemotherapy (SEQ).

The methodology used contemplated two phases. In the first, and with the objective to detect the degree of consensus, between May 18 and 29, 2012, the 25 specialists (table 2) anonymously completed on internet the categorical and metric scale questionnaire (majority). The coordinators responsible for the systematic search of the literature to elaborate the questions did not respond the questionnaire.

The questions that did not achieve the necessary consensus – the answers of the majority of the participants should coincide with at least 19 to 25 experts to reach a consensus of 75%, usually required in the Delphi studies, were included in the second phase, carried out between June 8 and 14, 2012 on internet with the anonymous participation of 22 of the 25 specialists included in the initial sample.

Table 2 List of experts who participated in the EPICO Study

Name	Scientific Society*
Dr. Benito Almirante Guajeda	SEIMC
Dr. Rafael González de Castro	SEDAR
Dr. Miguel Salavert Lletí	SEQ
Dr. José María Aguado García	SEIMC
Dra. María Izascun Azcárate Egaña	SEMICYUC
Dra. Mercedes Bouzada Rodriguez	SEDAR
Dr. Jesús Rico Feijoo	SEDAR
Dr. Cristóbal León Gil	SEMICYUC
Dr. Gerardo Aguilar Aguilar	SEDAR
Dr. José Ignacio Gómez Herreras	SEDAR
Dr. Juan Carlos del Pozo Laderas	SEMICYUC
Dr. José Garnacho Montero	SEMICYUC
Dra. Beatriz Galván Guijo	SEMICYUC
Dr. Javier Pemán García	AEM
Dr. Guillermo Quindós Andrés	AEM
Dr. Manuel Cuenca Estrella	AEM
Dra. Marisa Pérez del Molino Bernal	SEIMC
Dra. Patricia Muñoz García	SEIMC
Dr. Francisco Álvarez Lerma	SEMICYUC
Dra. Carmen Fariñas Álvarez	SEIMC
Dr. Jesús Fortun Abete	SEMICYUC
Dr. Rafael León López	SEMICYUC
Dr. César Aragón González	SEMICYUC
Dr. Juan Carlos Valía Vera	SEDAR
Dr. Marcio Borges Sa	SEMICYUC

The Spanish Association of Mycology (AEM) as promoter, the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC); the Spanish Society of Anesthesiology, Reanimation and Pain Therapeutics (SEDAR); The Spanish Society of Critical, Intensive and Coronary Medicine Units (SEMICYUC); and the Spanish Society of Chemotherapy (SEQ).

The second phase aimed to identify the reasons that explained for the spread of opinions among the experts. Likewise, the coordinators, responsible for the analysis and identification of the questions with greatest deviation of opinion, were not included in the second phase.

After this, as explained above, the list of recommendations was validated in the face to face meeting held on September 15, 2012.

RESULTS

FIRST PHASE – DEPHI EXPERTS

Epidemiological Section

1.- Among the risk factors that may affect critically ill patients, in your opinion, to what extent do you believe the development of invasive candidiasis (IC) is important?

Introduction: The *Candida* species are a significant cause of infection in critically ill patients[13,16-18]. The results of the EPIC II study, carried out with 13,796 adult patients admitted to 1.265 ICUs in 76 countries, evidenced that 51% of the patients presented an infectious process, whereas *Candida* spp. were the third microorganism implicated in the infection (17% of the patients infected) after *Staphylococcus aureus* (20.5%) and *Pseudomonas* spp. (19.9%)[19]. In the United States, the *Candida* spp. infection was the main cause of fungal infection in hospitalized patients11. In addition, the incidence of *Candida* spp. infections in the UCIs has increased in different countries throughout the last few years[6].

A large majority of the experts consulted (88%) confirmed the importance of the possibility of developing candidiasis among the risk factors that could affect critically ill patients. Specifically, and based on a 0 to 10 point scale, where 10 represents the maximum level of importance, 22 experts granted 7 or more points to candidiasis. The average score was established at 7.7 points, with a standard deviation of 1.9 points. The consensus level achieved was high (>75%).

2.- *To what extent do you consider candidemia an important factor of mortality associated with critically ill patients?*

Introduction: Invasive candidiasis is a major cause of direct and indirect mortality in neutropenic and non-neutropenic critically ill patients. The crude mortality rates and those associated with IC are, 40-78% and 20-40%, respectively[12,13]. In the United States, candidemia is associated with a 14.5% increase of mortality in adults, as well as 10% in pediatric patients[11]. Nevertheless, invasive candidiasis in immunocompromised patients with cancer can be a severe marker, whereas it is difficult to differentiate mortality directly attributable to invasive candidiasis from that of a concurrent infection or an underlying tumor disease.

76% of the expert panel members considered candidemia a very important mortality factor associated with critically ill patients. Specifically, and based on a scale of 0 to10 points, 19 experts granted 7 or more points to candidemia as a mortality factor. The average score was 7.4 points, with a standard deviation of 2.2 points. The degree of consensus reached by the experts was high (>75%).

3.- *To what extent do you consider important the distribution of Candida species in the last few decades and their impact on the antifungal susceptibility patterns*?

Introduction: In the last few years, a change in the distribution of *Candida* species in ICUs has been experimented[9,20]. *C. albicans* is still the predominant specie in the intensive care units[10], followed by *C. parapsilosis* and *C. glabrata*[21], whereas approximately 15% have reduced sensitivity to fluconazole. Also, the distribution of species varies with age: the incidence of candidemia due to *C. glabrata* increases with age, opposite to what occurs with *C. parapsilosis* and *C. tropicalis*[22].

Approximately 85% of the experts consulted consider the change in the distribution of *Candida* species in the last few years very relevant, as well as its impact on the antifungal susceptibility patterns. Specifically, and using a 0 to 10 point scale, 21 experts granted 7 or more points to the change in the distribution of *Candida* spp. The average score was 7.6 points, with a standard deviation of 1.8 points. The degree of consensus achieved was high (>75%).

4. -*To what extent do you consider important the identification of risk factors predisposing to Candida infections, species other than C. albicans?*

Introduction: Studies have identified several factors predisposing to infections caused by species, other than *C. albicans* (predominantly *C. glabrata* and *C. krusei*). Among these, prior triazole therapy, gastrointestinal tract surgery in the 30 days prior to the onset of candidemia, as well as patients over 65 years of age, can be highlighted[20]. This factor should be taken into account since *C. glabrata* and *C. krusei* are both potentially resistant to fluconazol[23]. For its part, the emergence of *C. parapsilosis* has been associated with younger ages, the administration of echinocandins and deficient infection control practices, while *C. tropicalis* is particularly common in neutropenic patients with an underlying hematological disease[21,22].

The vast majority of the specialists consulted (92%) consider the identification of risk factors that may favor the emergence of *Candida* species, other than *C.albicans,* of utmost importance. Specifically, 10 points the highest score and 0 the lowest, 23 experts granted 7 or more points to the importance of identifying these risk factors. The average score was 8.5 points, with a standard deviation of 1.4 points. The degree of consensus achieved was again very high (>75%).

5. - *To what extent do you consider importantthe evaluation of the clinical features of critically ill patients, taking into account that they can condition the presentation of invasive candidiasis?*

Introduction: Invasive candidiasis can manifest as isolated candidemia, undocumented invasive candidiasis or a combination of the both. Prior surgery and patients with solid tumors are significantly more frequent in patients with invasive candidiasis, while prior antibiotic therapy,

neutropenia and hematological tumors are significantly more common in patients with candidemia[17]. Additionally, the crude mortality rate due to candidemia in critically ill patients remains high and is related to the host (diagnosis upon admission to the ICU), and not to the variables of the treatment[13]. Metastatic processes occur in a considerable proportion of the patients in the ICU with candidemia and care must be given to possible secondary foci.

A large majority of the experts consulted (88%) highlighted the importance of evaluating the clinical features of critically ill patients, since they can condition the presentation of candidiasis. Specifically, and based on a scale of 0 to 10, where 10 represents the maximum level of importance, 22 experts granted 7 or more points to the evaluation of clinical features. The average score was established at 8.2 points, with a standard deviation of 1.4 points. The degree of consensus reached was high (>75%).

6.- *Indicate your level of agreement with the following statements: 1) Candida species are adetermining factor in mortality associated with invasive candidiasis. And 2) the underlying disease is a determining factor in mortality associated with invasive candidiasis.*

Introduction: In addition to an adequate control of the infectious focus, the infectious process is conditioned by three factors: the sensitivity of the infecting organism[24,25]; the virulence of the organism[26,27]; and the severity of the underlying disease[24,28]. *C. krusei*, *C. tropicalis* and *C. glabrata* have been associated with an elevated rate of mortality, while *C. parapsilosis* has been associated with a low pathogenicity. The severity of the underlying disease is an important mortality factor and, in fact, the total mortality is greater in candidemic critically ill patients, than in the general population. In the Marriott et al. study[29], the age, the diagnoses upon admission to the ICUs (other than politraumatisms) and the mechanical ventilation upon onset of the candidemia, were independent mortality factors in the multivariate analysis. Recent studies[26] evidenced that the use of echinocandins and the early administration of antifungal therapy resulted in lower mortality rates of invasive candidiasis. Perhaps the benefits of optimized antifungal treatment are hidden in ICU patients by a severe underlying disease affecting mortality.

1) Close to 85% of the panel members consider *Candida* species a determining factor of mortality associated with candidiasis. Specifically, on a scale of 1 to 5 points, in which 5 represents the maximum level of agreement, 21 experts granted 4 or 5 points in favor. The average score was established at 4.1 points. A high degree of consensus was reported (>75%).

2) When considering an underlying disease as a determining factor of mortality associated with candidiasis, total consensus was achieved. Based on 1 to 5 point scale, the 25 experts consulted granted 4 or 5 points in favor, establishing an average of 4.8 points.

Score Section

1.-*On what factors do you base the initiation of antifungal therapy in patients with severe sepsis, fever, broad-spectrum antibiotic treatment and negative culture results?* The coordinators responses: Risk Factors, *Candida* Score, Multicolonization, Markers, Poor evolution.

The majority of the experts consulted based the initiation of antifungal treatment in patients with severe sepsis, fever, broad-spectrum antifungal therapy and negative blood culture results on risk factors (8 experts) or the *Candida* Score (8 experts). Only 1 specialist claimed to base treatment on markers, while multicolonization or poor evolutions were options selected in each case by 4 of the experts. A medium degree of consensus was achieved (>50% y <75%).

2. – *Multicolonization is one of the factors contemplated in the Candida Score. Do you consider the evaluation of multicolonization indispensable to use the Candida Score?*

Introduction: Studies published in the literature have demonstrated that multicolonization is a prognostic factor in proven candidiasis[30], and the colonization index is directly correlated to invasive fungal infection[31].

An ample majority of the experts consulted (83%) considered indispensable the evaluation of multicolonization to use the *Candida Score*. Specifically, based on a 0 to 10 point scale, where 10 is of utmost importance, 21 experts granted 7 or more points to the evaluation of clinical features. The average score was 8.0 points, with a standard deviation of 1.9 points. A high degree of consensus was achieved (> 75%).

3.-*To what extent do you use the corrected colonization index (CCI) to guide the treatment of IC?*

Introduction: The Pittet Index or CCI (ratio of highly positive samples/total number of samples analyzed) was described in surgical patients and demonstrated that a corrected colonization with a threshold of >0.4 has a positive predictive value[32] and a 100%[33] negative predictive value on the development of invasive candidiasis.

76% of the experts consulted confirmed they did not use the corrected colonization index (CCI) to guide the treatment of invasive candidiasis, or only used it sporadically. Specifically, 10 experts confirmed the use of CCI 'in some cases' and 9 did not use it 'in any case', while 6 admitted its use 'in the majority of the cases'. A high degree of consensus was reached (>75%).

4. – *In how many cases out of ten, of patients at risk of acquiring invasive fungal infection, do you use the Candida Score to guide the treatment of IC?*

Introduction: The *Candida Score* is useful to evaluate the risk of developing invasive fungal infections, with a low positive predictive value and a very high negative predictive value. Therefore, it is highly improbable that non-neutropenic critically ill patients with *Candida* spp. colonization, with a *Candida Score* below 3, are at risk of developing IC[34],

only benefiting from the administration of early antifungal therapy, patients with a *Candida Score* exceeding 2.5[30].

72% of the experts consulted confirmed the use of the *Candida Score* to evaluate the risk of developing invasive fungal infections. Specifically, 18 of the experts confirmed that they used this score in at least 7 out of 10 non-neutropenic critically ill patients with *Candida* spp. colonization, while 3 used it in 6 patients, 2 in 5 patients, 1 in 4 patients and 1 expert in no case. The experts reached a medium degree of consensus (>50% y <75%).

Taking into account that the question did not achieve a minimum degree of consensus in accordance with the Delphi technique, it was included in the second phase, in which the experts were asked to explain why they did not use the *Candida Score* on a regular basis in these situations. Among the explanations offered, we highlight: 1) *'its poor positive predictive value; only useful to not administer antifungal therapy, since the negative predictive value is very good'*. And 2) '*the difficulties encountered in obtaining surveillance cultures; even when they have been performed, since results are only obtained after 72 hours, impeding early treatment that reduces the rate of mortality'*.

5. – *To what extent do you agree on only using a rectal sample and urine to detect colonization?*

Introduction: An important contribution resulting from the CAVA Study[34] is the independent identification of predictive values of IC, from each of the colonization sample locations, limiting the number of samples for colonization evaluation to those that were significant: rectal sample and urine.

80% of the experts consulted considered the use of a rectal sample and urine sufficient for colonization detection. Specifically, based on a 0 to 10 point scale, where 10 is the maximum level of importance, 20 experts granted 7 or more points to the exclusive use of both samples. The average score was 7.4 points, with a standard deviation of 2.5 points. A high degree of consensus was achieved.

Laboratory Diagnostic Section

1. – In your opinion, and in suspected cases of IC, with what frequency would you recommend to perform blood cultures?

Introduction: At present, hemocultures are the *Gold standard* in diagnosing invasive candidiasis[35–37]. However, this technique only offers a sensitivity of 50% in the diagnosis of IC[37] therefore; an increased number of tests could increase this diagnostic rate.

92% of the experts consulted recommended performing hemocultures on a daily basis or, at least, every two or three days. Specifically, 6 experts advocated performing them on a daily basis and 16 every two or three days, while 1 specialist recommended performing hemocultures once a week, and 2 to perform only one hemoculture and wait for results. A high degree of consensus was achieved (> 75%).

2 – *Indicate to what extent you request each of the following two diagnostic tests to diagnose non-candidemic invasive candidiasis.*

2.1- *To what extent do you request the test 'to obtain sterile fluids and/or tissue samples' to diagnose IC?*

2.2- *To what extent to you request the 'direct vision technique of sterile fluids and/or tissues' to diagnose IC?*

Introduction questions 2.1 and 2.2: Nowadays, it is very difficult to diagnose non-candidemic invasive candidiasis with certainty[38], since it requires the histological identification of *Candida* spp. tissue invasion and/or evidence of yeast in sterile fluids[36,39].

Regarding question 2.1, the large majority (96%) of the experts consulted considered very important to request the test to obtain sterile fluids and/o tissue to accurately diagnose IC. Specifically, based on a scale of 0 to 10 points, where 10 represents the highest level of importance, 24 experts granted 7 or more points to this diagnostic test. The average score was 9.1 points, with at standard deviation of 1.3 points.

With respect to question 2.2, 84% of the experts consulted considered the direct microscopy technique of sterile fluids and/or tissue samples to diagnose IC very relevant. Specifically, basedon a 0 to 10 point scale, 21 experts granted 7 or more points to this diagnostic test. The average score was 8.2 points, with a standard deviation of 1.4 points. Both questions achieved a high degree of consensus (> 75%).

2.3 -*In the case of a patient with suspected peritonitis caused by Candida spp., to what extent do you consider sending perioperative samples to the microbiology laboratory necessary?*

Introduction: In cases of suspected peritonitis caused by *Candida* spp., the diagnosis should be preferably based on the analysis of perioperative samples of fluid and/or peritoneal tissue[40-42], a diagnostic test that has demonstrated an elevated prognostic value[43].

The complete panel consideredsending perioperative samples of fluids and/or peritoneal tissue in cases of suspected peritonitis caused by *Candida* spp. necessary. In fact, the entire panel granted 7 or more points to this statement, for which a high degree of consensus was achieved.

3. – *Do you consider isolation of Candida spp. from respiratory samples a diagnosis of candidiasic pneumonia?*

Introduction: 60% of the non-neutropenic critically ill population of patients after admission to intensive care units for more than 7 days presents *Candida* colonization[38]. However, and despite the remarkable frequency of isolation of *Candida* spp. in the respiratory tract, Meersseman et al.[44], in a study that lasted 2 years, observed the complete absence of cases of candidiasic pneumonia in the autopsies performed on patients with evidence of pneumonia, thus confirming that pneumonia caused by *Candida* spp. is extremely unusual in patients in ICUs[36].

All of the experts consulted did not consider the isolation of *Candida* in respiratory tract samples in critically ill patients sufficient to diagnose candidiasic pneumonia. Specifically, 18 experts did not consider isolation in any case, while 7 confirmed that they could consider this option only in certain specific cases. A high degree of consensus was reached, 100%.

4. – *In accordance with the epidemiological changes in invasive candidiasis, do you consider that in cases of IC, it is important to know the sensitivity pattern of the different antifungal agents?*

Introduction: During the last decades, the main epidemiological trend in invasive candidiasis in ICUs and Oncology Units has been the reduction of *C. albicans,* facing the increase of *C. no albicans* species, very especially *C. glabrata*, *C. tropicalis, C. krusei* and *C. parapsilosis* [9,10,11,20]. In this context, the IDSA guidelines published in 2009 established the recommendation of carrying out sensitivity studies only in cases of treatment failure, as well as testing fluconazole in those with *C. glabrata* isolates[15].

The vast majority (96%) of the experts consulted highlighted the relevance of knowing the sensitivity to the different antifungal agents in cases of confirmed IC. Specifically, based on a 0 to 10 point scale to value its importance, 24 experts granted 7 or more points to the need of establishing the sensitivity to the drug treatment. The average score was 8.8 points, with a standard deviation of 1.2 points. The level of consensus achieved was high, exceeding 75%.

5. -*In your opinion, to what extent do you consider useful the measurement of serum procalcitonin in the diagnosis of suspected candidemia?*

Introduction: Serum procalcitonin measurements have been very precise discerning between bacteremia and non-infectious inflammatory conditions in critically ill patients with clinical signs of sepsis[45]. Two studies performed in non-neutropenic and/or surgical patients determined that serum procalcitonin is lower in candidemia than in bacteremia, both presenting elevated negative predictive values below 2 and 5 ng/ml[46,47].

76% of the experts consulted highlighted the usefulness of serum procalcitonin measurements in the diagnosis of suspected candidemia. Specifically, 4 specialists consider it 'very useful', while 15 define the procalcitonin measurements as 'quite useful'. A high degree of consensus was achieved, exceeding 75%.

6. - *At present, to what extent do you consider the use of non-culture based methods of microbiological diagnostic techniques necessary for the diagnosis of IC?*

Introduction: The combination of traditional diagnostic methods with non-culture based microbiological tools could be the clue to improving the diagnosis and prognosis of fungemias in critically ill patients[37,38,41,48] To date, results published on the detection of (1,3)-β-D-glucan, galactomannan, manannan and anti-manannan, *C. albicans* germ tube antibodies or nucleic acid are promising and could be very useful to guide early antifungal treatment. In general, it is recommended as screening once or twice a week in critically ill patients with risk factors, especially in surgical patients, after 5–7 days of hospitalization[48]. However, and still today, non-culture based methods of microbiological diagnostic tools are not available in the majority of the hospital centers in our country.

80% of the experts consulted considered the use of non-culture based methods of microbiological tools for the diagnosis of IC very necessary. Specifically, based on a scoring scale of importance from 0 to 10 points, 19 experts granted 7 or more points to the need for microbiological diagnostic tools. The average score was 8.0 points, with a standard deviation of 1.7 points. A high degree of consensus was reached.

7. - *To what extent would you use the combined detection of mannan antigen and antimannan antibodies for the diagnosis of IC, if this technique was available in your hospital?*

Introduction: The detection of mannan antigen and antimannan antibodies against *Candida* antigen in an ELISA format has demonstrated useful in the diagnosis of invasive candidiasis[36,37] and has been commercialized for many years. Also, with the objective of avoiding the poor performance of these techniques when used separately, the joint implementation of these tests in all patients with suspected invasive candidiasis is recommended[49].

The majority of the experts consulted did not share a general opinion regarding the convenience of using combined detection of mannan antigen and anti-mannan antibodies in the diagnosis of IC. Specifically, 5 and 8 specialists, respectively, considered their use in 'almost all cases' and 'in the majority of the cases'. On the contrary, 12 experts considered that their use is only convenient 'in some cases'. A medium degree of consensus was achieved, 52% (>50% and <75%). Therefore, this question was included in the second phase of the Delphi study.

8. *To what extent do you use the (1,3)-ß-d-glucan detection as a diagnostic tool for IC?*

Introduction: The detection of betaglucan, by means of a technique presently available in the market, offers high specificity[36-38,50] and positive predictive value (PPV)[3,34,51] in patients with probable or confirmed IFI.

The responses revealed a divergent behavior among the experts consulted with respect tohow often (1,3)-ß-d-glucan testing should be used in the diagnosis of IC. Specifically, 16 experts, 64% of the sample, considered its use in 'only some cases' or 'in no case'; while 7 and 2 specialists responded that it should be used 'in the majority of the cases' or' in almost all cases'. A medium degree of consensus of 64% was reached, whereas the question was selected for the second phase of the Delphi study.

9.-*To what extent do you use the indirect immunofluorescence method (C. albicans IFA IgG, VircelI) for the detection*

of anti-mycelial antibodies in the diagnosis of IC, if this technique is available in your hospital?

Introduction: Indirect immunofluorescence (*C. albicans* IFA IgG, Vircell) for the detection of *C. albicans* germ tube antibodies (CAGTA) shows high sensitivity and specificity in cases of candidemia[37,52,53], which could prove crucial in the diagnosis of IC in surgical ICU patients[22].

The majority of the experts consulted did not share a general pattern of behavior in relation to how often they used CAGTA detection in the diagnosis of IC. Only 13 experts, 52% of the sample, considered its use in 'only some cases' or 'in no case', while 9 and 3 specialists, respectively, responded that they use it 'in the majority of the cases' or 'almost always'. A medium degree of consensus was reached. The question was selected for the second phase of the Delphi Study.

10.-*To what extent do you use nucleic acids detection in the diagnosis of IC, if molecular methods of polymerase chain reaction (PCR) techniques are available in your hospital?*

Introduction: New molecular detection methods of real-time polymerase chain reaction (PCR), as evidenced in numerous articles in the literature[36,37,54-56], are an interesting alternative for the quick diagnosis of IFI.

The answers reveal the absence of a general pattern of behavior among the majority of the experts consulted. Only 13 experts, 52% of the sample, consider the detection of nucleic acids in the diagnosis of IC necessary in 'only some cases' or 'in no case', while 7 and 5 specialists, respectively, answered that it should be performed 'in the majority of the cases' or 'in almost all cases'. A medium degree of consensus was achieved, 52%, for which the question was selected to be included in the second phase of the study.

Since the questions regarding the non-culture based method of microbiological techniques, questions 7–10, did not achieve the minimum consensus contemplated in the Delphi technique, the 22 experts participating in the second phase of the study were consulted on the manannan antigen and anti-manannan antibody techniques; (1,3)-ß-d-glucan detection; anti-mycelial antibody detection; and nucleic acids detection, they would recommend for the diagnosis of IC. The responses identified (1,3)- ß-d-glucan detection, chosen by 10 experts, and the detection of nucleic acids, chosen by 8 experts, as the techniques most widely recommended by the specialists consulted.

11. - *Indicate your level of agreement with the following statements: 1) The combination of several non-culture based methods of microbiological techniques can increase diagnostic performance in IC and, 2) The combination of scores of clinical prediction, together with the use of nonculture based methods of microbiological techniques, can be adequate strategies to initiate early IC treatment.*

Introduction: The use of the different nonculture based methods, such as the mannan antigen/antimannan antibodies, beta-glucan detection and, very especially, the detection of nucleic acids by PCR, may significantly assist in the diagnosis of IC[2]. Also, the combination of the tests with traditional diagnostic methods could be the clue to improve both the diagnosis, as well as the prognosis of IC in critically ill patients[37].

1) 96% of the experts consulted indicated that combining various techniques can increase the diagnostic performance in IC. Specifically, based on a scale of 1 to 5 points, where 5 represents the highest score, 24 experts granted 4 or 5 points to the statement. The average score was 4.8 points. A high degree of consensus was achieved, exceeding 75%.

2) The combination of scores and nonculture based methods of microbiological techniques was considered an adequate strategy, achieving full consensus. Based again on a scale of 1 to 5 points, the 25 experts consulted granted 4 or 5 points to the statement, establishing an average of 4.8 points.

Treatment Section

1.-*In your opinion, do you consider the use of echinocandins as a first-line choice of treatment for invasive candidiasis?*

Introduction: The recommendations established in the Clinical Practice Guidelines of the different national and supranational societies[1,14,15] have generated some controversy on the treatment of invasive candidiasis. In this context, a work carried out by Andes et al.[26] demonstrated that the treatment with echinocandins is associated to a significant decrease of the mortality rate due to IC.

76% of the experts consulted, 19 out of the 25 specialists, consider that echinocandins should be the first-choice antifungal therapy for invasive candidiasis in all cases, regardless of whether the patient hada history of recent azole exposure. A high degree of consensus was reached, (>75%).

The specialists who coincided that echinocandins should only be the first-line antifungal therapy in patients, who have received prior azole therapy, were consulted in the second phase of the study and explained the reasons that justify their response. We display below two of the reasons offered by the specialists: 1) '*It depends on the epidemiology of the center and the characteristics of the patient. If the patient is stable and has not received previous azole therapy in a hospital with prevalence of Candida albicans strains, I find no reason to administer echinocandins*'. And 2) '*It is evident that the affirmative response to the statement, 'do you consider necessary prior azole therapy' is not correct. I believe that there are certain specific situations in which fluconazole could be indicated in patients with documented candidemia with sensitivity to this antifungal agent (in 70–80% of the occasions) and with clinical stability (...)'.*

2.-*To what extent do you agree with the administration of echinocandins at higher doses than the standard recommended doses for the treatment of endocarditis caused by Candida or other types of invasive candidiasis?*

Introduction: Clinical trials have demonstrated the efficacy and confirmed the safety associated to echinocandin therapy at higher doses than the standard-dose therapy in the management of invasive candidiasis[57,58]. Thus, IDSA guidelines published in 2009 established the possibility of administering higher doses of echinocandins for the treatment of endocarditis caused by *Candida*[15].

The responses reveal the divergent opinions encountered among the experts consulted with respect to administering higher doses of echinocandinsin the treatment of endocarditis caused by *Candida*. Specifically, based on a scale from 1 to 5 points, where 5 represents the highest level of agreement, only 13 specialists (52%) claimed to be 'somewhat in agreement' or 'totally in agreement', granting 4 or 5 points to the administration of higher doses. The average was 3.4 points and a medium degree of consensus was reached (>50% and <75%).

The question did not achieve the minimum consensus contemplated in the Delphi technique, for which it was selected to be included in the second phase of the study, where the experts who favored the administration of higher doses of echinocandins in the treatment of endocarditis caused by *Candida* or other types of IC, were asked to indicate their motives. We display two of the reasons the specialists mentioned: 1) '*It is contemplated in clinical trials and expert's opinions. Also, it is mentioned in the IDSA guidelines published in 2009 regarding the treatment of endocarditis*.' And 2) '*Due to the seriousness of IC or endocarditis, optimization of the treatment, according to the Pk/Pd target based on the AUC/MIC ratio, is a priority in reaching levels of the focus. Also, these drugs have linear pharmacokinetics and few adverse effects'.*

3. - *Taking into account a critically ill patient on echinocandintherapy, with C. parapsilosis isolates detected in blood cultures, please indicate your level of agreement with each of the following two statements: 1) Echinocandin therapy should be substituted by fluconazole, regardless of the patient's clinical evolution, and 2) Fluconazole should be administered together with an echinocandin, until clinical improvement is observed.*

Introduction: The recommendations established in the Clinical Practice Guidelines of different national societies[1,15] have raised some controversy regarding the treatment of choice for invasive candidiasis due to *C. parapsilosis*. In this context, while Pfaller et al.[59] concluded that fluconazole was superior to candins in the treatment of *C. parapsilosis* due to the mutations of the fks genes of *Candida*, the Kale-Pradhan et al. study demonstrated the noninferiority of the efficacy of echinocandins against nonechinocandins or other antifungal agents in the treatment of IC caused by *C. parapsilosis*[60].

1) 60% of the experts consulted disagreed with the convenience of changing the treatment. Specifically, based on a scale of 1 to 5 points, where 5 is the highest score, 15 experts granted 1 or 2 points to this statement. The average score was 2.6 points. A mediumdegree of consensus was achieved. The question was selected to be included in the second phase of the Delphi study, in which the degree of divergence was similar.

2) 64% of the experts consulted disagreed with the convenience of combining fluconazole and an echinocandin. Specifically, based on a scale of 1 to 5 points to evaluate the level of disagreement, 16 experts granted 1 or 2 points to the statement. The average score was established at 2.3 points. A medium degree of consensus was reached.

4. - *In case you consider that patients with candidemia should receive an ophthalmological evaluation, when would you carry it out?*

Introduction: Few studies in the literature address eye disorders during candidemia. In this context, while chorioretinitis is the most common disorder described (9-16%); a much lower percentage of cases of endophthalmitis have been reported (1.6%)[61,62]. However, and contrary to that established in the recommendations of the Clinical Practice Guidelines[14,15], the need for an ophthalmological evaluation in all patients with candidemia is contemplated in few situations.

The large majority of the experts consulted (96%) considered an ophthalmological evaluation necessary in patients with candidemia, either during the first week or between the first and second weeks. Only 1 specialist indicated that the ophthalmological evaluation should not be carried out on a conscious patient without clinical signs. Therefore, a high degree of consensus was achieved.

5. - *In the case of a patient with candidemia on echinocandin therapy with ocular involvement, should the treatment be switched to another antifungal agent?*

Introduction: The eye is a protected compartment, for which the degree of penetration of systemic antifungal agents varies significantly[15]. According to evidence reported by Ridell et al.[63], neither echinocandins nor posaconazole achieve adequate therapeutic concentrations in the vitreous. In contrast, voriconazole has been defined as the most effective antifungal agent in the treatment of ocular manifestations.

72% of the experts consulted considered that, in patients with candidemia and ocular involvement treated with echinocandins, should switch treatment to another antifungal agent 'in all cases' or 'in the majority of the cases'. On the contrary, 3 specialists considered that the change of treatment should only be made 'in some cases', 3 that the change 'does not necessarily need to be made', and 1 that the change 'depends on the clinical evolution'. A high degree of consensus was reached.

6. - *In your opinion, should the central venous catheter be removed in all critically ill patients with candidemia?*

Introduction: The convenience of withdrawing or maintaining the central venous catheter (CVC) in patients with candidemia has raised controversy in different publications. Specifically, and while studies have not demonstrated the

benefit associated with the withdrawal of the CVC[65], several articles confirm that its removal has reported a statistically significant improvement in survival of the patient[20,26,65].

Absolute consensus among the experts consulted on the need to withdraw the central venous catheter in all cases of candidemia was achieved (100%).

7.-*In your opinion, to what extent does the risk of hepatotoxicity affect the election of a specific echinocandin?*

Introduction: The degree of hepatic dysfunction (Child) can condition the election and dosage of each of the echinocandins, due to their distinct metabolism and pathway of elimination. The Wang et al.[66] study demonstrated that 9.3% of the patients treated with echinocandins presented elevated liver enzyme levels, although there was no need to interrupt treatment.

56% of the experts consulted considered that the risk of hepatotoxicity has 'considerable influence' or 'much influence' on the election of the type of echinocandin administered. Specifically, based on a scale of 1 to 5 points, where 5 is the maximum level of influence, 15 experts granted 4 or 5 points. The average score was established at 2.6 points. A medium degree of consensus was achieved.

8.-*Please indicate your level of agreement with the following statement: 'Empirical therapy of fluconazole in critically ill patients with IC should not be used and only administered in cases where the species and sensitivity of Candida has been identified in hemodynamically stable patients'.*

Introduction: The indication for fluconazole treatment in critically ill patients has changed in the last few years[1,14]. Both *C. glabrata* and *C. krusei* are potentially fluconazole-resistant[23].

60% of the specialists consulted agree with the statement. Specifically, based on a scale of 1 to 5 points to evaluate the level of agreement, 15 experts granted 4 or 5 points to this statement. The average was 3.6 points and a medium degree of consensus was achieved.

9.-*Do you consider that all patients with candidemia should be screened for endocarditis by a transesophageal echocardiography?*

Introduction: The possibility of candidemia causing an infective endocarditis is a critical component in its clinical management, requiring a longer treatment and, serious consideration should be given to valve surgery in the majority of the patients[28].

72% of the experts consulted considered that the transesophageal echocardiography for screening endocarditis in patients with candidemia should only be performed in exceptional cases. In contrast, 3 and 4 specialists hold that it should be carried out 'in all cases' and 'in the majority of the cases', respectively. A medium level of consensus was reached.

10. -*Can the type of antifungal agent administered in the treatment of IC reduce the mortality rate associated with invasive candidiasis?*

Introduction: Numerous publications have demonstrated that the election of the antifungal agent plays an essential role in the survival of critically ill patients with IC. Echinocandin therapy is associated with significantly reduced mortality[26]. For its part, prior therapy with azoles is considered a mortality risk factor[20,27].

An ample majority of the experts consulted (92%) considered that the type of antifungal agent used in the treatment of IC can reduce the mortality associated with invasive candidiasis. Therefore, based a scale of 1 to 5 points, where 5 represents the maximum level of agreement, 23 experts granted 4 or 5 points to this statement.

11.-*Can early IC treatments reduce mortality rates associated with invasive candidiasis?*

Delayed IC treatment in critically ill patients is associated with increased mortality[24,25]. In this context, however, the Marriott et al. study[29] did not observe any relationship between the rate of mortality and the time of treatment initiation.

All of the experts consulted (100%) considered that early IC treatment can reduce mortality associated with invasive candidiasis. A high degree of consensus was reached.

Therapeutic De-escalation Section

Introduction: Susceptibility patterns to antifungal agents vary, depending on the *Candida* species. *C. albicans, C. tropicalis* and *C. parapsilosis* are generally fluconazole-sensitive, while *C. glabrata* is generally susceptible dose-dependent or resistant, and *C. krusei* is intrinsically resistant[68]. Fluconazole achieved better results than candins in the treatment of *C. parapsilosis* due to mutations in the fks genes of *Candida*[59].

In the treatment of candidemia in non-neutropenic patients, fluconazole is recommended in stable patients with no history of azole exposure. In hemodynamically unstable patients (APACHE II ≥15) or patients with criteria of severe sepsis or having received previous azole therapy or suspected azole-resistant candidemia, empirical echinocandin therapy is recommended[14,15].

The determination of the sensitivity to antifungal agents could be useful for optimizing antifungal treatment, including de-escalation to fluconazole[68,69]. However, the determination of susceptibility is not carried out in all centers, for several reasons, such as the delay in receiving results and their cost. The identification of the species, as well as the determination of the susceptibility to antifungal agents, requires a 5 day average. On the other hand, the determination of the susceptibility to antifungal agents has proven cost-effective in the context of candidemia and could help identify patients with drug-resistant *Candida* species receiving inappropriate treatment and patients who would be candidates for de-escalation to fluconazole[69].

Based on expert's opinions, IDSA Guidelines suggest that susceptibility testing of fluconazole should routinely

be performed against *C. glabrata* and other *Candida* species that do not respond to empirical antifungal therapy or if resistance to azole antifungals is highly suspected[15].

The de-escalation of antifungal therapy is not usually well protocolized; it is not done on a regular basis and there is a lack of supportive scientific evidence, especially in critically ill patients. To optimize the appropriate use of antimicrobials to achieve the maximum effectiveness, reduce the adverse effects and administer a cost-effective treatment, we must ensure the correct initial antifungal therapy, but also de-escalate when possible in terms of antimycotic efficacy and reduced costs[68,69].

Antifungal de-escalation should be guided by microbiological results, antifungal susceptibility, concomitant medications the patient is taking and clinical evolution. This information is usually not available until after 5 days, so the decision to de-escalate is often taken late.

1. - *In confirmed invasive candidiasis caused by C. albicans in patients on empirical echinocandin therapy, should treatment always de-escalate to fluconazole, regardless of the clinical condition?*

Introduction: Antifungal therapy should be based on the *Candida* species and clinical condition of the patient[69]. Therefore, empirical echinocandin therapy is recommended in hemodynamically unstable patients (APACHE II ≥15) or patients with criteria of severe sepsis[14,15]. Also, the Andes et al.[26] study demonstrated that echinocandin therapy was associated to significantly decreased mortality due to IC.

76% of the experts consulted did not agree that it is always convenient to de-escalate to fluconazole, regardless of the patient's clinical condition, in confirmed invasive candidiasis due to *C. albicans* in patients on empirical echinocandin therapy. Specifically, based on a scale of 1 to 5 points, where 5 represents the maximum level of agreement, 19 experts granted 1 or 2 points to the statement. The average score was established at 2.0 points. A high degree of consensus was achieved (>75%).

2. - *Can treatment be de-escalated, regardless of the determination of fluconazole sensitivity in confirmed invasive candidiasis due to C. albicans in patients on empirical echinocandin therapy?*

Introduction: The sensitivity of fluconazole to *C. albicans* is very elevated. In the Zulaga et al.[67] Study, 95.2% of the isolates of *C. albicans* were sensitive to fluconazole, and no resistant isolates were identified.

80% of the experts consulted considered that in confirmed invasive candidiasis due to *C. albicans* in patients receiving empirical echinocandin therapy should not de-escalate without determining the sensitivity to fluconazole. Specifically, based on a 1 to 5 point scale to evaluate the level of agreement, 20 experts granted 1 or 2 points to the statement. The average score was 2.0 points, and a high degree of consensus was achieved.

3.-*In confirmed invasive candidiasis caused by C. glabrata in patients receiving empirical echinocandin therapy, always de-escalate to fluconazole, regardless of the patient's clinical condition.*

Introduction: The use of fluconazole is recommended in the treatment of candidemia in non-neutropenic stable patients, without prior azole therapy. The use of empirical echinocandin therapy is recommended in hemodynamically unstable patients (APACHE II ≥15) or those with criteria of severe sepsis or prior azole therapy or suspected candidemia due to azole-resistant *Candida*[14,15].

The vast majority of the experts consulted (96%) considered that the clinical condition of the patient must be considered before de-escalating to fluconazole in confirmed invasive candidiasis caused by *C. glabrata* in patients receiving empirical echinocandin therapy. Thus, based on a 1 to 5 point scale, where 5 represents the maximum level of agreement, 24 experts granted 1 or 2 points to this statement. A high degree of consensus was achieved.

4.-*In confirmed invasive candidiasis caused by C. glabrata in patients receiving empirical echinocandin therapy, de-escalation can be performed regardless of determining the sensitivity to fluconazole.*

Introduction: The 2009 IDSA guidelines recommend performing sensitivity testing only in cases of therapeutic failure, although they also recommend testing fluconazole in patients with *C. glabrata* isolates[15]. As reported in the Garnacho-Montero et al.[23] Study, *C. glabrata* is potentially fluconazole-resistant. On the other hand, the Collins et al.[68] Study concluded that performing fluconazole sensitivity testing in patients with confirmed invasive candidiasis caused by *C. glabrata* provided improved outcomes, not only in economic, but clinical terms.

96% of the experts consulted considered that in confirmed invasive candidiasis due to *C. glabrata* in patients receiving empirical echinocandin therapy, de-escalation should not be performed without previously determining the fluconazole-sensitivity. Specifically, based on a 1 to 5 point scale to evaluate the level of agreement, 24 experts granted 1 or 2 points to the statement. The average score was 1.2 points. Once again, a high degree of consensus was achieved.

5. - *Patients with infection caused by C. krusei with favorable evolution and receiving empirical echinocandin therapy should be de-escalated to voriconazole*.

Introduction: C krusei is intrinsically fluconazole-resistant to *Candida* species[40]. On its part, voriconazole presents a superior activity than fluconazole against *C. krusei*[70].

76% of the specialists consulted considered that in patients with infection caused by *C. krusei,* with favorable evolution and on empirical echinocandin therapy, de-escalation to voriconazole is not adequate. Specifically, based on a 1 to 5 point scale, where 5 represents the maximum level of agreement, 19 experts granted 1 or 2 points to the

statement. The average score was 1.8 points and a high degree of consensus was reached.

The question was selected for the second phase of the Delphi Study to learn about the reasons why the experts considered de-escalation to voriconazol adequate under these circumstances. We display below two of the reasons offered by the specialists: 1) '*If the clinical evolution is good, C. krusei also displays high sensitivity to voriconazol and very low MICs, for which it would be a very good option*'. And 2) '*This is a fully valid alternative, accepted in different guidelines. If there areno contraindications for the use of voriconazole (and as long as we have plasma level determinations) it is always an alternative and a possibility to de-escalate and/or switch to oral therapy.*

6. - *In patients receiving antifungal therapy for suspectedbut unproven invasive candidiasis, after 5 days of good clinical evolution, what action would you take?*

The responses showed enormous disparity between the opinions of the experts consulted in relation to the measures to be taken in this situation. Thus, 7 specialists (28%) would opt for suspending the antifungal therapy; 6 experts (24%) would continue with the same treatment during 14 days; 6 specialists would de-escalate to an azole; and 2 experts (8%) did not know what measure to take. In conclusion, a low degree of consensus was achieved (<50%).

7. - *In patients receiving antifungal therapy for suspected but unproven invasive candidiasis, after 10 days without good clinical improvement, what action would you take?*

76% of the experts consulted confirmed that in patients with antifungal therapy due to suspected but unproven invasive candidiasis, in which clinical improvement is not observed after 10 days, they would interrupt the antifungal therapy and reevaluate the patient. Also, 3 specialists assured they would only modify the treatment, while 2 would continue treatment for 14 days and 1 would add another antifungal agent. The degree of consensus achieved was high.

8 .- *In patients with candidemia caused by a fluconazole-sensitive Candida species, initially treated with an echinocandin and stable, when do you believe the treatment should be changed to fluconazole oral therapy?*

The large majority of the experts consulted (84%) believe that in patients with candidemia caused by a fluconazole-sensitive species of *Candida,* who have initially received echinocandin therapy and that are stable, should be transitioned to fluconazole oral therapy within a maximum period of two or three days after stabilization. A high degree of consensus was established.

While the question achieved sufficient consensus in accordance with the Delphi methodology, the 4 experts that considered necessary a period of 2-3 days after stabilization, were asked to indicate the motives that justify their response in the second phase of the Study. We display below two of the reasons provided by the specialists: 1) '*First of all, in the context of a critically ill patient, oral therapy can only be administered on few occasions, despite its excellent absorption by the digestive tract.In second place, and although there are no supportive studies, I believe that 2 or 3 days is a very short period. The guidelines recommend 7 to 10 days. Personally, I do it after 5-7 days, as long as the evolution is favorable, the CVC has been removed in case of being the origin of the infection and it is fluconazole-sensitive*'. And 2) '*The basic issue of this question is the underlying belief that the patient can have an infection due to fluconazole-resistant species. The microbiological sensitivity testing in vitro is not exactly equivalent to that in vivo. Therefore, I do not believe that linking the stability of the patient and the microbiological sensitivity to the same result is reasonable*'.

9.-*In general, under what circumstances should patients with invasive candidiasis not be de-escalated?*

In general, 72% of the experts consulted considered adequate to de-escalate in invasive candidiasis in critically ill patients. Specifically, based on a 1 to 5 point scale, where 5 represents the maximum level of agreement, 18 experts granted 1 or 2 points to the statement. A medium degree of consensus was reached, below 76%.

FIRST PHASE RECOMMENDATIONS

After learning the results of the Delphi methodology applied to non-neutropenic critically ill patients with suspected or confirmed invasive candidiasis, the following 20 recommendations have been developed (table 3) based on the questions that achieved a high level of agreement, subsequently validated in the meeting in person with the hospital panel experts.

SECOND PHASE: IN PERSON MEETING OF HOSPITAL EXPERTS

FINAL RECOMMENDATIONS

Using the same methodology, 80 experts met in person to vote the recommendations described in table 3. Only those that achieved a consensus over 75% were chosen. Please find the final recommendations in table 4.

CONCLUSION

The management of patients with suspected or confirmed Invasive Candidiasis requires a great deal of knowledge. The recommendations developed, based on the Delphi methodology, summarize this knowledge for educational purposes and can assist in the early identification of potential patients, standardize its management and improve prognostic performance.

Table 3 Recommendations First Phase

Epidemiological Section

1. Since the incidence of invasive candidiasis admitted to intensive care units has increased in the last decades, consider early treatment in critically ill patients with an infectious process.

2. The most common fungal infections in critically ill patients are caused by *Candida* species and, although *C. albicans* is still the species that produces the majority of the candidiasis, consider that no albicans *Candida* species is detected with increased frequency, exceeding *Candida albicans* in some series.

3. While it is essential to know the local epidemiology in critically ill patients with invasive candidiasis, consider the possibility of fluconazole-resistant *Candida* species in neutropenic patients with chronic renal failure, who have received previous triazole therapy.

4. Since certain *Candida* species, such as *C. tropicalis, C. krusei* y *C. glabrata* have been associated with elevated mortality in critically ill patients; consider the early use of efficient antifungal agents against these species.

Scores Section

1. Determination of the *Candida* score should be performed as a screening tool in all critically ill patients with invasive candidiasis.

2. Investigate the presence of multicolonization in all patients at risk

3. Associate the determination of biomarkers to the *Candida* Score.

Diagnostic Laboratory Section

1. Perform blood cultures at the time of suspected invasive candidiasis and every 2-3 days, provided it persists. In case of a positive result, perform controls until a negative result is obtained.

2. Submit sterile fluids and tissues for fungal culture and use direct vision (microscopy), whenever possible.

3. In patients with suspected invasive candidiasis, use the routine non-culture based microbiological technique, if available in your center.

4. In patients with confirmed invasive candidiasis, request an antifungal sensitivity study.

Treatment Section

1. Initiate early treatment, at the time of considering the diagnosis of invasive candidiasis, since early treatment is associated to lower mortality rates.

2. An echinocandin should be the first-choice empirical treatment in critically ill patients, regardless of prior administration of azole therapy.

3. Only in special situations in hemodynamically stable patients without prior azole therapy and with knowledge of a local epidemiology, treatment with azoles can be considered.

4. At least one ophthalmological evaluation is recommended in all patients with candidemia at risk of developing chorioretinitis and endophthalmitis, since an ocular affectation is a marker of prolonged treatment.

5. The antifungal treatment should be changed in patients with ocular affectation and on echinocandin therapy, due to its poor penetration.

6. Whenever possible, remove the central catheter in patients with candidemia.

Therapeutic Deescalation Section

1. In critically ill patients with confirmed invasive candidiasis due to *C. albicans* or *C. glabrata* receiving empirical echinocandin therapy, consider deescalating to fluconazol treatment, in light of clinical stability and the specie is fluconazole-susceptible.

2. In critically ill patients with confirmed invasive candidiasis due to fluconazole-susceptible species *Candida* receiving empirical echinocandin therapy, consider de-escalating to fluconazole 2 or 3 days after achieving clinical stability.

3. In patients receiving antifungal therapy due to suspected invasive candidiasis that has not been confirmed by the tenth day and without clinical improvement, suspend the antifungal treatment and reevaluate the patient.

Table 4 The EPICO Final Recommendations

Epidemiological Section
1. Since the incidence of invasive candidiasis admitted to intensive care units has increased in the last decades, consider early treatment in critically ill patients with an infectious process.
2. While it is essential to know the local epidemiology in critically ill patients with invasive candidiasis, consider the possibility of fluconazole-resistant *Candida* species in neutropenic patients with chronic renal failure, who have received previous triazole therapy.
Scores Section
1. As a screening tool, investigate the presence of candidiasic multicolonization and determine the *Candida* Score in all critically ill patients with suspected invasive candidiasis.
Laboratory Diagnostic Section
1. Perform blood cultures at the time of suspected invasive candidiasis and every 2-3 days, provided it persists. In case of a positive result, perform hemoculture controls until a negative result is obtained.
2. Submit sterile fluids and tissues for fungal culture and use direct vision (microscopy), whenever possible.
3. In patients with suspected invasive candidiasis, use the routine non-culture based microbiological technique, if available in your center.
4. In patients with confirmed invasive candidiasis, request an antifungal sensitivity study.
Treatment Section
1. Initiate early treatment, at the time of considering the diagnosis of invasive candidiasis.
2. An echinocandin should be the first-line choice of empirical therapy in critically ill patients.
3. At least one ophthalmological evaluation is recommended in all patients with candidemia. In case of ocular affectation, consider the poor penetration of echinocandins.
4. Whenever possible, remove the central catheter in patients with candidemia.
Therapeutic Desescalation Section
1. In critically ill patients with confirmed invasive candidiasis due to fluconazole-susceptible *Candida* species receiving empirical echinocandin therapy, consider de-escalating to fluconazole after 2 or 3 days of clinical stability.

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CONFLICT OF INTERESTS

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