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# EPICO 2.0 PROJECT. Development of educational therapeutic recommendations using the DELPHI technique on invasive candidiasis in critically ill adult patients in special situations

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## ABSTRACT

**Introduction.** Although there has been an improved management of Invasive Candidiasis in the last decade, still controversial issues remain, especially in different therapeutic critical care scenarios.

**Objectives.** We sought to identify the core clinical knowledge and to achieve high agreement recommendations required to care for critically ill adult patients with Invasive Candidiasis for antifungal treatment in special situations and different scenarios.

**Methods.** Second Prospective Spanish survey reaching consensus by the Delphi technique, conducted anonymously by electronic e-mail in the first phase to 23 national multidisciplinary experts in invasive fungal infections from five national scientific societies including Intensivists, Anesthesiologists, Microbiologists, Pharmacologists and Infectious disease specialists, answering 30 questions prepared by a coordination group after a strict review of literature in the last five years. The educational objectives spanned four categories, including peritoneal candidiasis, immunocompromised patients, special situations and organ failures. The agreement among panellists in each item should be higher than 75% to be selected. In a second phase, after extracting recommendations from the selected items, a meeting was held with more than 60 specialists in a second round invited to validate the preselected recommendations.

**Measurements and Main Results.** In the first phase, 15 recommendations were preselected (peritoneal candidiasis (3), immunocompromised patients (6), special situations (3) and organ failures (3)). After the second round the following 13 were validated: **Peritoneal candidiasis (3):** Source control and early adequate antifungal treatment is mandatory; empirical antifungal treatment is recommended in secondary no-

socomial peritonitis with *Candidasp* colonization risk factors and in tertiary peritonitis. **Immunocompromised patients (5):** Consider hepatotoxicity and interactions before starting antifungal treatment with azoles in transplanted patients; treat candidemia in neutropenic adult patients with antifungal drugs at least 14 days after the first negative blood culture and until normalization of neutrophil count is achieved. Caspofungin, if needed, is the echinocandin with most scientific evidence to treat candidemia in neutropenic adult patients; Caspofungin is also the first choice drug to treat febrile candidemia; in neutropenic patients with candidemia remove catheter. **Special situations (2):** In moderate hepatocellular failure, patients with invasive candidiasis use echinocandins (preferably low doses of anidulafungin and caspofungin) and try to avoid azoles; in case of possible interactions review all of the drugs involved and preferably use Anidulafungin. **Organ failures (3):** Echinocandins are the safest antifungal drugs; reconsider the use of azoles in patients under renal replacement therapy; all of the echinocandins are accepted for the treatment of patients under continuous renal replacement therapy and do not require dosage adjustment.

**Conclusions.** Treatment of Invasive Candidiasis in ICU patients requires a broad range of knowledge and skills as summarized in our recommendations. These recommendations may help to optimize the therapeutic management of these patients in special situations and different scenarios and improve their outcome based on the DELPHI methodology.

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

## PROYECTO ÉPICO 2.0. Desarrollo de unas recomendaciones terapéuticas educacionales mediante metodología DELPHI en pacientes críticos adultos no neutropénicos con candidiasis invasiva en situaciones especiales

### RESUMEN

**Introducción.** Aunque en la última década se ha mostra-

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do una mejoría en el manejo de la candidiasis invasiva, todavía existe controversia, especialmente en el tratamiento antifúngico en situaciones clínicas especiales.

**Objetivos.** Identificar los principales conocimientos clínicos y elaborar recomendaciones con un alto nivel de consenso, necesarios para la elección del tratamiento antifúngico en situaciones especiales en sus diversos escenarios en pacientes adultos críticos no neutropénicos con candidiasis invasiva.

**Métodos.** Cuestionario prospectivo español, que mide el consenso mediante la técnica Delphi, se realizó de forma anónima y por correo electrónico con 23 expertos multidisciplinarios nacionales, especialistas en infecciones fúngicas invasivas de cinco sociedades científicas nacionales, incluyendo Intensivistas, Anestesiólogos, Microbiólogos, Farmacólogos y Especialistas en Enfermedades Infecciosas que respondieron a 30 preguntas preparadas por el grupo de coordinación, tras una revisión exhaustiva de la literatura de los últimos cinco años. Los objetivos educativos contemplaron cuatro categorías, incluyendo candidiasis peritoneal, pacientes inmunodeprimidos, situaciones especiales y fracasos orgánicos. 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 60 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 15 recomendaciones (Candidiasis peritoneal (3), Pacientes inmunosuprimidos (6), Situaciones especiales (3), Fracasos orgánicos (3)). Después de la segunda ronda, las siguientes 13 recomendaciones fueron validadas: **Candidiasis peritoneal:** Debido al mal pronóstico de la peritonitis candidiásica, se recomienda un adecuado control del foco infeccioso junto a un tratamiento antifúngico precoz y apropiado. Se recomienda iniciar un tratamiento antifúngico empírico en pacientes con peritonitis secundaria nosocomial y con factores de riesgo de colonización por *Candida* spp. o en aquellos pacientes con peritonitis terciaria. En la peritonitis candidiásica, se recomienda utilizar una equinocandina en los pacientes inestables o en aquellos que han recibido previamente azoles o en los que se aísla *Candida* spp. resistente a fluconazol. **Pacientes inmunodeprimidos.** En el tratamiento de la candidiasis invasora con azoles en un paciente con trasplante de órgano sólido, deben considerarse sus interacciones y hepatotoxicidad. En el paciente neutropénico, la duración del tratamiento de la candidemia debe ser de 14 días desde el primer cultivo negativo y hasta la normalización de la cifra de neutrófilos. En un paciente neutropénico con candidemia, caspofungina es la equinocandina con más respaldo científico. Caspofungina es la equinocandina de elección en la neutropenia febril con sospecha de candidemia. En un paciente neutropénico inestable con candidemia y catéter venoso central de fácil recambio, es aconsejable la retirada del mismo. **Situaciones especiales:** En el tratamiento de la candidiasis invasiva en pacientes con disfunción hepática moderada (Child B) se recomienda utilizar equinocandinas (preferentemente

anidulafungina o caspofungina con ajuste de dosis) y se debe evitar el uso de azoles. Aunque las interacciones farmacológicas de las equinocandinas son pocas, se recomienda revisar la medicación concomitante y en caso de posible interacción, utilizar preferentemente anidulafungina. **Fracasos orgánicos:** 1.-En lo que a seguridad se refiere las equinocandinas son la familia de antifúngicos de primera elección. Todas las equinocandinas son iguales para el tratamiento de los pacientes que necesitan técnicas continuas de depuración extrarrenal y no precisan ajuste de dosis. El uso de azoles precisa importantes ajustes de dosis en el paciente en tratamiento con técnica continua o intermitente de depuración extrarrenal.

**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 ayudan a optimizar el tratamiento de los pacientes críticos con candidiasis invasiva en distintos escenarios y situaciones clínicas y mejorar su pronóstico, basados en la metodología DELPHI.

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

## INTRODUCTION

The main objective of this research study is to analyze the present situation of the management of critically ill patients in our country's hospitals and, in this second edition, to develop a set of therapeutic recommendations in special situations in critically ill adult patients and the different scenarios using the DELPHI technique. For this purpose, since 2012 a panel of specialists from five scientific societies has been 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 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, as carried out in the first edition of this project<sup>1</sup>.

In a second phase and after the coordinating group had elaborated the recommendations, a second round in a meeting with 60 national specialists who treat critically ill adult patients with Invasive Candidiasis voted and validated the pre-selected recommendations.

## METHODS

The panel was made up of 23 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

critically ill adult patients with confirmed invasive candidiasis.

The DELPHI technique was used to perform the study with the objective of optimizing the consultation process of the 23 panel members. In particular, the DELPHI technique 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% (18-23) of the experts consulted in each of the questions formulated, either the "Top 4" (7 or more points) or the "Bottom 4" (4 or less points) of the questions in metric scale, or the "Top 2" ("Fully agreed" or "Broadly agreed", or "Always" or "Almost always") or the "Bottom 2" ("Slightly agreed" or "Fully disagreed", or "Almost never" or "Never") in the categorical questions.

In the cases in which the majority of the answers to a given question were shared by 13-17 participants (> 50% and ≤ 75% of the panel members), a medium level of consensus was established, meanwhile a low consensus was established when only 12 or less panel members shared the same answer.

The total 30 questions elaborated by the coordinators (Annex 1) were distributed in 4 different sections or specialties: peritoneal candidiasis section, 9 questions (written by E.M. and A.R.); Treatment in immunocompromised and transplanted patients section, 7 questions (written by P.L. and R.Z.); antifungal treatment in special situations section, 7 questions (written by R.F. and P.L.); and antifungal treatment in presence of organ failure, 7 questions (written by R.Z. and R.F.).

The methodology of the study contemplated the development of two phases. In the first and with the aim of learning the levels of consensus of the questions formulated, between June 7 and 14, 2013, the 23 participating specialists (Annex 1) anonymously responded the questionnaire made up of metric scale (majority) and categorical questions. The coordinators, responsible for the systematic research in literature to elaborate the questions, did not answer the questionnaire.

The questions that did not achieve a sufficient level of consensus - at least 19 of the 24 participating experts must coincide to achieve a level of consensus greater than 75%, normally required in the Delphi studies- were proposed for inclusion in the second phase of the study, developed between June 17 and 21, 2013 on internet with the anonymous participation of 19 of the 24 specialists included in the initial sample.

In accordance with the above mentioned, recommendations were elaborated for validation in the meeting held on September 25, 2013.

## RESULTS

### FIRST PHASE. DELPHI EXPERTS

#### 'Peritoneal candidiasis' Section

1.-Indicate your level of agreement with the following statement: *In critically ill surgical patients, Candida peritonitis is a poor prognostic factor.*

**Rationale:** The mortality rate associated with *Candida* peritonitis is very high, ranging from 20-70%<sup>2-4</sup>.

The vast majority of the experts consulted (95.6%) considered *Candida* peritonitis a poor prognostic factor in surgical patients. Specifically, and based on a scale of 1 to 5 points, where 5 represents the highest level of consensus, 22 of the 23 specialists granted 4 or 5 points to this statement. The level of consensus achieved was high (Top 2 > 75%).

2.- Indicate your level of agreement with the following statements: a) *The control of the infectious focus is a determining factor in the progression of Candida peritonitis, despite the antifungal therapy used;* b) *Early and appropriate antifungal therapy is the most important factor in the mortality rates associated with Candida peritonitis;* c) *The control of the infectious focus and early and appropriate antifungal therapy are determining factors in the mortality rates associated with Candida peritonitis.*

**Rationale:** There is some debate regarding the meaning of positive peritoneal fluid cultures for *Candida*<sup>5,6</sup> and whether antifungal therapy reduces mortality rates. Nevertheless, different studies on patients with invasive candidiasis have revealed that early and appropriate antifungal therapy in patients with adequate control of the focus reduces mortality<sup>2,3,7,8</sup>.

a) 65.2% of the panel experts coincide that the control of the infectious focus is a determining factor in the progression of *Candida* peritonitis, despite the treatment used. Specifically, 8 of the 23 specialists stated that they "fully agreed" with the statement, while 7 experts indicated that they "broadly agreed". However, a medium level of consensus was achieved (Top 4 > 50% y ≤ 75%).

b) Again, only 65.2% of the specialists consulted stated that early and appropriate antifungal therapy is the most important factor in the mortality rates associated with *Candida* peritonitis. Specifically, and using a scale of 1 to 5 points, where 5 represents the highest level of agreement, 15 of the 23 specialists granted 4 or 5 points to the statement. A medium level of consensus was achieved (Top 4 > 50% y ≤ 75%).

c) Full consensus is reached when the control of the infectious focus and early and appropriate antifungal therapy are considered determining factors in the mortality associated with *Candida* peritonitis. Using a scale of 1 to 5 points, the 23 panel members granted 4 or 5 points to this statement.

3.-Indicate how important you consider the initiation of an empirical antifungal therapy in patients with secondary peritonitis of the lower gastrointestinal tract acquired in the community.

**Rationale:** There is insufficient evidence in the literature that endorses the routine use of an empirical antifungal therapy, even in high risk patients and those with secondary peritonitis acquired in the community<sup>2,6,8-11</sup>.

Only 6 of the total 23 panel specialists consulted (26%) considered important the initiation of an empirical antifungal therapy in patients that present secondary peritonitis of the

lower gastrointestinal tract acquired in the community. Specifically, and using a scale of 0 to 10 points, where 10 represents the greatest level of importance, 9 experts granted 4 or less points to the statement, while 6 specialists granted 4-6 points. An average of 4.2 points (DT: 2.56) was established, achieving a low consensus (Top 4  $\leq$  50%).

4.-Indicate how important you consider the initiation of an empirical antifungal therapy in patients with secondary nosocomial peritonitis with risk factors of isolation of *Candida* spp. (colonization).

**Rationale:** Evidence suggests that patients with nosocomial *Candida* peritonitis have greater mortality than patients with community-acquired *Candida* peritonitis<sup>2,6,8,11</sup>.

The vast majority (91.2%) of the panel members considered important the initiation of an empirical therapy in patients with secondary nosocomial peritonitis and risk factors of *Candida* spp. colonization. Specifically, and using a scale of 0 to 10 points, where 10 represents the greatest level of importance, 21 specialists granted 7 or more points to this statement, achieving an average of 8.91 points (DT: 1.50). A high level of consensus was reached (Top 4 > 75%).

5.-Indicate how important you consider the initiation of an empirical antifungal therapy in patients with tertiary peritonitis.

**Rationale:** The initiation of an empirical therapy in patients with secondary nosocomial peritonitis and tertiary peritonitis should be considered, since *Candida* spp. isolation worsens the prognosis<sup>2,8-10,12-14</sup>.

All of the panel members considered that the initiation of an empirical antifungal therapy in patients with tertiary peritonitis is important. Specifically, and using a scale of 0 to 10 points, where 10 represents the greatest level of importance, 12 specialists granted 10 points to the statement, 5 experts granted 9 points and 6 gave 8 points, establishing an average of 9.26 points (DT: 0.86). Again the level of consensus was high (Top 4 > 75%).

6.-Indicate how important you consider the initiation of an empirical antifungal therapy in patients with secondary peritonitis of the upper gastrointestinal tract acquired in the community.

**Rationale:** No evidence exists in the literature that clearly supports the use of an empirical antifungal therapy in this situation<sup>15</sup>.

The majority of the panel members (60.9%) coincided in highlighting the importance of initiating an empirical antifungal therapy in patients with secondary peritonitis of the upper gastrointestinal tract acquired in the community. Specifically, and using a scale of 0 to 10 points, where 10 represents the greatest level of importance, 14 specialists granted 7 or more points to the statement, establishing an average of 6.13 points

(DT: 272). A high level of consensus was achieved (Top 4 > 50% and  $\leq$  75%).

7.-To what extent do you consider echinocandins the first-line antifungal therapy for critically ill patients with *Candida* peritonitis?

Coordinators' answers: when *Candida* resistant to fluconazole is isolated in the peritoneal fluid, when the patient is unstable, when the patient has previously received azole therapy, in all of the cases.

**Rationale:** There is evidence in the literature that demonstrates that echinocandins can reduce mortality when compared with other antifungal agents (27% vs. 36%)<sup>16,17</sup>. The European clinical practice guidelines on the antifungal treatment of adult non-neutropenic patients with invasive candidiasis highly recommend (IA) candins as the initial empirical treatment<sup>15</sup>.

The total number of experts considered that the first-line antifungal therapy in critically ill patients with *Candida* peritonitis should be echinocandins, when identifying *Candida* spp. isolates, fluconazole-resistant in the peritoneal fluid, the patient is unstable, or the patient has previously received azole therapy. In these cases, high consensus was achieved. (Top 2 > 75%). In other cases, only 56.5% of the specialists confirmed they "always" or "almost always" use an echinocandin as first-line treatment, for which a medium level of consensus was reached (Top 4 > 50% and  $\leq$  75%).

8.-Indicate which echinocandins you use in critically ill patients with *Candida* peritonitis.

Coordinators' answers: anidulafungin, caspofungin, micafungin.

**Rationale:** No studies exist in the literature that evidence a superior response to the different candins in the treatment of patients with *Candida* peritonitis<sup>8,18,19</sup>.

An elevated level of consensus was achieved (Top 4 > 75%) when using anidulafungin, caspofungin or micafungin in the management of critically ill patients with *Candida* peritonitis. Specifically, and based on a scale from 0 to 10 points, where 10 represents the greatest level of importance, 86.9% of the panel members granted 7 or more points to caspofungin (median: 8.52 points) and micafungin (median: 8.09 points) and anidulafungin (median: 8.13 points) was shared by 78.2% of the specialists.

9.- Frequency of each of the actions, when empirical antifungal therapy has been initiated due to suspected nosocomial *Candida* peritonitis and without subsequent microbiological confirmation of the cultures taken in the operating room.

Coordinators' answers: I do not trust the cultures and if the patient has improved their clinical condition, continue with the initial antifungal treatment during 2 weeks, despite the negative cultures, continue with the initial antifungal

treatment during 7–10 days, suspend the antifungal treatment after the third day of clinical stability, and suspend the antifungal treatment in any case.

**Rationale:** No evidence exists in the literature that clearly supports the use of empirical antifungal treatment under these circumstances<sup>15</sup>.

The majority of the experts consulted (65.2%) admitted that they "never" or "almost never" continued with initial antifungal treatment during 2 weeks in patients with suspected nosocomial *Candida* peritonitis that show clinical improvement, despite the lack of microbiological confirmation. Likewise, only 47.8% of the specialists confirmed they continue with the initial empirical treatment in all or in the majority of the patients under these circumstances, meanwhile only 34.8% considered to "always" or "almost always" suspend the treatment after the third day of clinical stability. Finally, 5 panel members (21.7%) considered "almost always" to suspending the treatment in any of the cases; an option that 8 of the 23 specialists admitted they "never" or "almost never" adopted. Consequently, a low level of consensus was reached for all answers (Top 2 y Bottom 2  $\leq$  50%). Due to the aforementioned and taking into account that no significant difference was detected in the Coordinator's answer, this question was selected for the second phase of the study.

### Section on the 'Treatment in immunocompromised and transplanted patients'

1.-Indicate your level of agreement with the following statement: *The use of azole agents is a problem in the treatment of invasive candidiasis in critically ill non-neutropenic patients with a solid organ transplant due to the risk of hepatotoxicity and interaction with anticalcineurin agents.*

**Rationale:** All guides indicate the limitations of the use of amphotericin B desoxicolate in transplant recipients with candidiasis due to the nephrotoxicity, and with azole therapy due to the possible drug interaction with the anticalcineurins, since the metabolism of both depend on cytochrome P450, for which monitorization of the plasma levels in both the immunosuppressive and azole agents is important<sup>20–22</sup>.

The majority of the specialists consulted (78.3%) agreed that due to the risk of hepatotoxicity and drug interaction with anticalcineurins, the use of azole agents can be problematic in the treatment of invasive candidiasis in non-neutropenic critically ill patients with a solid organ transplant. Specifically, and based on a scale of 0 to 10 points, where 10 represents the greatest level of importance, 18 experts granted 7 or more points to this statement. An average of 7.70 points (DT: 1.84) was established. A high level of consensus was reached (Top 4 > 75%).

2.-Indicate your level of agreement with the following statement: *The treatment of invasive candidiasis should be different from that of other types of patients.*

**Rationale:** The characteristics of the transplant recipients could have an impact on the selection of the antifungal treatment, especially due to the use of concomitant immunosuppressive therapy<sup>23,24</sup>.

Only 14 of the 23 panel members (65.2%) considered that a transplant is a very special situation when administering treatment for invasive candidiasis. Specifically, and based on a scale of 0 to 10, where 10 represents the greatest level of importance, 15 specialists granted 7 or more points to the statement, whereas a median of 6.91 points was established (DT: 2.52). This question was selected for the second phase of the study, in which the experts who had evaluated the statement with 7 or more points, dropped to 52.6%. Consequently, the level of consensus for both phases was medium (Top 4 > 50% and  $\leq$  75%).

3.-*In transplanted patients with invasive candidiasis and on echinocandin treatment, please indicate to what extent you prefer/use each of them.*

Coordinators' answers: anidulafungin, caspofungin, micafungin.

**Rationale:** Unlike caspofungin and micafungin, anidulafungin is not metabolized by cytochrome P450, for which there are no interactions with calcineurins and other drugs used in transplanted patients<sup>23,24</sup>.

Regarding the selection of anidulafungin or caspofungin in the treatment of transplanted patients with invasive candidiasis, a high level of consensus was achieved by the panel members (Top 4 > 75%) Specifically, and based on a scale of 0 to 10 points, where 10 represents the greatest level of importance, 78.3% of the panel members granted 7 or more points both to the use of caspofungin (median: 7.39 points) and anidulafungin (median: 7.35 points). On the contrary, only 43.4% granted 7 or more points to the treatment with micafungin (median: 5.70), reaching a low consensus (Top 4  $\leq$  50%).

4.-Indicate your level of agreement with the following statement: *The treatment of candidemia in a neutropenic patient should be administered during 14 days after the last negative culture and until the neutrophil count is normalized.*

**Rationale:** All of the consensus guidelines agree that the treatment of candidemia in neutropenic patients is the same as that for non-neutropenic patients, and until the neutrophil counts are normalized<sup>18,20,25</sup>.

All other panel experts considered that the duration of the treatment of candidemia in neutropenic patients should be 14 days after the last negative culture and until the confirmation of normalized neutrophil count. Specifically and based on a score of 1 to 5 points, where 5 represents the greatest level of importance, 13 experts granted 5 points to the statement and 10 specialists awarded 4 points. An elevated level of consensus was achieved (Top 2 > 75%).

5.-In the case of neutropenic patients with candidemia, please indicate to what extent you consider adequate the administration of the following treatments with respect to their safety and experience

Coordinators' answers: anidulafungin, caspofungin, micafungin.

**Rationale:** Among the different echinocandins, caspofungin and micafungin have been included in most studies of neutropenic patients (approximately 10%), meanwhile studies with anidulafungin include less patients (<3%). The IDSA Clinical Guidelines<sup>18</sup> and those of the SEIMC<sup>20</sup> recommend the use of caspofungin as first-line echinocandin.

When evaluating the experience and safety of the administration of caspofungin in the treatment of neutropenic patients with candidemia achieved total consensus among the specialists (100%). In this case, and based on a scale of 0 to 10 points, where 10 represents the greatest level of importance, the 23 panel members awarded 7 or more points to the use of caspofungin (median: 9.39 points). However, a medium level of consensus was obtained (Top 4 > 50% and ≤ 75%) for micafungin (median: 6.87 points) and anidulafungin (median: 6.22 points), the specialists consulted granted 7 or more points to this option, 65.2% and 52.1%, respectively.

6.-Please, indicate under what circumstances you consider positive the administration of each of the following treatments:

Coordinators' answers: anidulafungin, caspofungin, micafungin.

**Rationale:** Liposomal amphotericin B or caspofungin constitute the same level of evidence (A-1), the first choice empirical treatment in neutropenic patients with suspected invasive candidiasis<sup>18,20,25</sup>. Caspofungin demonstrated a similar efficacy to that of liposomal amphotericin, although with better tolerance<sup>26</sup>. No studies exist with anidulafungin or micafungin as empirical treatment of neutropenic patients.

Once again, the panel experts reached full consensus in selecting caspofungin as the empirical treatment for patients with febrile neutropenia and suspected candidemia. Based on a scale of 0 to 10 points, where 10 represents the greatest level of importance, 56.6% of the specialists awarded 7 or more points to the administration of micafungin (median: 6.09 points), for which a medium level of consensus was achieved (Top 4 > 50% and ≤ 75%). Finally, only 47.4% of the experts granted 7 or more points to the treatment with anidulafungin (median: 4.83 points), achieving a low level of consensus (Top 4 ≤ 50%).

7.-Should the central venous catheter be removed in neutropenic patients with candidemia?

**Rationale:** The management of intravascular catheters in neutropenic patients with candidemia is more difficult than in non-neutropenic patients, as its removal seems clearer. In

these patients, it can be difficult to distinguish between candidemia associated with the digestive tract and that associated with the vascular catheter. Data regarding catheter removal are less convincing and, on occasions, the venous access can cause problems. In any case, the majority of the authors recommend its removal, especially if the candidemia is persistent and the new venous access is not especially difficult<sup>20,25,27</sup>.

The majority of the experts consulted (82.6%) confirmed that the removal of the central venous catheter (CVC) should be contemplated in all or almost all occasions in neutropenic patients with candidemia. Specifically, and based on a scale of 1 to 5 points, where 5 represents the greatest level of importance, 19 specialists awarded 4 or 5 points to the removal of the CVC under these circumstances. Once again, an elevated level of consensus was reached (Top 2 > 75%).

### "Antifungal treatment in special situations" Section

1.-Indicate your level of agreement with the following statement: It is important to adjust the doses of echinocandins in accordance with the patient's body weight.

**Rationale:** Echinocandins are concentration-dependent antifungal agents. The dose depends on the patient's weight; a very relevant issue in the obese population with morbid obesity<sup>28,29</sup>.

The majority of the specialists (78.2%) coincided in pointing out the importance of adjusting the dose of the echinocandin in accordance with the patient's weight in the treatment of patients with invasive candidiasis. Specifically, and based on a scale of 1 to 5 points, where 5 represents the greatest level of importance, 18 specialists granted 4 or 5 points to this statement. A high level of consensus was achieved (Top 2 > 75%).

2.-When considering the administration of doses in morbidly obese patients, to what extent do you consider efficient and safe the use of the following echinocandins?

Coordinators' answers: anidulafungin, caspofungin, micafungin.

**Rationale:** Echinocandins are concentration-dependent antifungal agents. The dose can depend on the patient's weight, a very relevant issue in the morbidly obese population<sup>28,29</sup>.

The vast majority of the panel members (91.2%) considered that the administration of higher doses of caspofungin is effective and safe in the management of patients with morbid obesity and candidiasis. In the cases of micafungin and anidulafungin, 69.5% and 65.1%, respectively, of the panel members supported the statement. Specifically, and using a scale of 0 to 10 points, where 10 represents the greatest level of importance, the following median points were obtained: 8.09 points for caspofungin (DT: 1.56), 7.04 points for micafungin (DT: 1.66) and 6.57 points for anidulafungin (DT: 2.81). An elevated level

of consensus was thereafter achieved for caspofungin (Top 4 > 75%), and a medium level of consensus was achieved for micafungin and anidulafungin (Top 4 > 50 y ≤ 75%).

*3.-When considering the administration of higher doses of antifungal agents, please indicate how important you consider each of the following factors:*

Coordinators' answers: type of antifungal agent, need for increasing efficacy, toxicity risks, increased costs, patient's weight.

**Rationale:** Echinocandins are concentration-dependent antifungal agents. The dose can depend on the patient's weight, a very relevant issue in the morbidly obese population<sup>28,29</sup>. Although dose escalation has demonstrated beneficial under certain circumstances, also consider the safety and increased costs associated to this strategy<sup>30,31</sup>.

The total number of panel experts (100%) coincide in pointing out that the weight is an important factor when considering the administration of higher doses of antifungal agents. 96.6% of the specialists regarding the type of antifungal therapy to be administered; 95.5% when increased efficacy is needed; and 86.9% in the case of risk of toxicity also shared this evaluation. Specifically, and based on a scale of 0 to 10 points, where 10 represents the greatest level of importance, the average score corresponding to the patient's weight was established at 8.57 points (DT: 0.95); 8.91 points corresponding to the type of antifungal therapy (DT: 1.12); 8.3 points for the need to increase the efficacy (DT: 1.56); and 8.61 points associated with the risk of toxicity (DT: 1.37). Consequently, the level of consensus obtained for each of the different options was elevated (Top 4 > 75%).

On the contrary, only 52.1% of the specialists granted 7 or more points to the importance of increased costs in this situation, establishing a median score of 6.61 points (DT: 2.02) and achieving a medium level of consensus (Top 4 > 50 y ≤ 75%).

*4.-Indicate your level of agreement with the following statements regarding the treatment of invasive candidiasis in patients with hepatic affectation (Child B).*

Coordinators' answers: we can use micafungin, we can use anidulafungin, we can use caspofungin, we should avoid the use of amphotericin B, and we should avoid the use of azoles.

**Rationale:** The liver metabolizes echinocandins, and therefore altering the plasma concentrations, although in a different manner in the case of hepatic dysfunction<sup>32</sup>. In moderate hepatic dysfunction (Child B), generally, the levels of caspofungin are increased, while those of micafungin are reduced and those of anidulafungin are not altered<sup>33</sup>. There is a risk of hepatotoxicity with azole therapy that could also require dosage adjustment in the case of moderate liver failure.

The specialists reached full consensus on the administration of anidulafungin in the treatment of invasive candidiasis in patients with liver affectation (Child B). In this situation,

82.6% of the specialists also agreed on the use of caspofungin and 78.2% agreed to avoid the use of azole therapy. Therefore, a high level of consensus of the three options abovementioned was achieved (Top 2 > 75%). In the case of micafungin in this patient population, 60.9% of the panel members reached a medium level of consensus, (Top 2 > 50 and ≤ 75%); and only 30.4% of the panel members "agreed" or "strongly agreed" with avoiding the use of amphotericin B (low level of consensus; Top 2 ≤ 50%).

*5.-Interactions between echinocandins. Please indicate the level of interactions between echinocandins.*

Coordinators' answers: Low level of interactions for anidulafungin, caspofungin and micafungin.

**Rationale:** Critically ill patients are typically polymedicated. Echinocandins generally present few pharmacological interactions, since they are not appreciable substrates of CYP and P-glycoprotein systems, for which the interactions are not relevant in clinical practice<sup>32,34</sup>.

The majority of the experts consulted (82.6%) stated that anidulafungin has a low level of drug-drug interactions. Specifically, and based on a scale of 0 to 10 points, where 10 represents the highest score, 19 of the 23 specialists gave 4 or less points to anidulafungin's interaction profile, resulting in an average score of 2.61 points. A high level of consensus was achieved (Bottom 4 > 75%).

When evaluating the interactions profiles of caspofungin and micafungin, no consensus was reached. Specifically, 56.5% of the specialists indicated that caspofungin and micafungin present a high level of drug-drug interactions. The average score was 6.22 points with a medium level of consensus (Top 4 > 50 and ≤ 75%). On the other hand, only 47.7% of the panel members indicated that micafungin has a low level of drug-drug interactions, reaching an average score of 4.78 points and a low level of consensus (Bottom 4 ≤ 50%).

*6.-Echinocandin interactions. Please indicate how important these interactions are in clinical practice.*

Coordinators' answers: Low importance of interactions/ High importance of interactions for anidulafungin, caspofungin, micafungin.

**Rationale:** Critically ill patients are typically polymedicated. Echinocandins generally present few pharmacological interactions since they are not appreciable substrates of the CYP and P-glycoprotein systems, therefore the interactions are not relevant in clinical practice<sup>32,34</sup>.

The majority of the specialists (82.6%) granted low importance to the interactions associated with anidulafungin. Specifically, and using a scale of 0 to 10 points, where 10 represents the greatest level of importance, 19 of the 23 specialists awarded 4 or less points to the importance of anidulafungin's interactions, establishing an average of 2.96 points (DT: 2.48). High level of consensus (Bottom 4 > 75%).

Once again, there was no consensus on the importance of the role of the interactions when administering caspofungin or micafungin. Therefore, while 43.4% of the experts indicated that the interactions with the administration of caspofungin are important (low level of consensus; Top 4  $\leq$  50%), 60.9% considered the interactions with micafungin not very significant (medium level of consensus; Bottom 4  $>$  50 and  $\leq$  75%).

*7.-In the cases of patients with invasive candidiasis on echinocandin treatment receiving other medications, evaluate the level of importance of the following factors:*

- a) Review the concomitant medication to evaluate echinocandin dosage adjustment.
- b) Review the concomitant medication to evaluate dosage adjustment.
- c) Use drugs with few interactions.
- d) Measure plasma drug concentrations.

**Rationale:** Critically ill patients are typically polymedicated. Echinocandins generally present few pharmacological interactions, since they are not appreciable substrates of the CYP and P-glycoprotein systems, for which the interactions are not relevant in clinical practice<sup>32,34</sup>. In the case of possible interactions, the alternatives are to use echinocandins with fewer interactions<sup>34</sup>, adjust the dose of the drugs implicated, and closely monitor the concentrations.

a) 82.7% of the experts indicated that the review of the concomitant medication is a factor to take into account when modifying the doses of the echinocandin in a patient with invasive candidiasis. Specifically, and based on a scale of 0 to 10, where 10 represents the greatest level of importance, 19 specialists gave 7 or more points to the statement, establishing an average of 7.61 points (DR: 2.50). A high level of consensus was achieved (Top 4  $>$  75%).

b) 78.3% of the specialists indicated that the review of the concomitant medication is important in those cases that require a modification. An average of 7.22 points was established (DT: 2.26). A high level of consensus was reached (Top 4  $>$  75%).

c) The use of drug with few interactions is an important factor for 78.1% of the panel members in the management of patients with invasive candidiasis on echinocandin treatment receiving other medications. An average of 7.22 points was obtained (DT: 2.46). A high level of consensus was achieved (Top 4  $>$  75%).

d) 65.2% of the specialists considered the measurement of the drug plasma concentrations in patients with invasive candidiasis on echinocandin treatment and receiving other medications important. The average score, based on a scale of 0 to 10 points, was 7.09 points (DT: 2.84), and a medium level of consensus was achieved (Top  $>$  50 and  $\leq$  75%).

## "Antifungal treatment in presence of organic failure" Section

*1.-Please evaluate the safety profile of the following antifungal agents.*

Coordinators' answer: azoles, liposomal amphotericin B, anidulafungin, caspofungin, micafungin.

**Rationale:** In clinical studies published on invasive candidiasis, all of the echinocandins proved to be safer than those compared to<sup>35</sup>, especially in terms of nephrotoxicity with the amphotericins<sup>36,37</sup>, whereas no difference was reported when compared against each other<sup>38,39</sup>.

The total number of specialists considered the treatment with anidulafungin and caspofungin safe. Specifically, and based on a scale of 0 to 10, where 10 represents the greatest level, the average score obtained for anidulafungin and caspofungin was 8.70 points (DT: 0.88) and 8.17 points (DT: 0.94), respectively. In addition, the vast majority (91.3%) of the panel members considered the administration of micafungin safe, establishing an average of 7.87 points (DT: 1.18). Ultimately, a high level of consensus was achieved with the three echinocandins (Top 4  $>$  75%).

On the contrary, a low level of consensus was reached when evaluating the safety profile of treatments with azoles or liposomal amphotericin B. Specifically, only 39.1% of the experts granted 7 or more points to the safety profile of azoles (average score: 6.26; DT: 1.21). In the case of liposomal amphotericin B, 47.8% of the panel members granted 7 or more points (average score: 6.09; DT: 1.88).

*2.-Importance of dosage adjustment in patients on ECMO therapy and invasive candidiasis and on treatment with the following antifungal agents.*

Coordinators' answers: Low importance dosage adjustment/High importance dosage adjustment of azoles, liposomal amphotericin B, anidulafungin, caspofungin, micafungin.

**Rationale:** No evidence exists in the literature that clarifies this situation.

The majority of the panel experts (82.5%) considered important to carry out dosage adjustment of the azole therapy in the management of patients with invasive candidiasis on ECMO therapy. Specifically, and based on a scale of 0 to 10 points, where 10 represents the greatest level of importance, 19 of the 23 specialists granted 7 or more points to dosage adjustment in this situation, achieving an average of 8.61 points (DT: 1.14) and obtaining a high level of consensus (Top 4  $>$  75%).

On the other hand, and due to the absence of consensus for the rest of the treatment options provided by the coordinators, the question was selected for the second phase of the Delphi study, in which only a significant increase of the percentages was observed, whereas the specialists awarded low importance to the need for dosage adjustment in this situation



in treatments with anidulafungin (47.8% to 74%), caspofungin (39.1% to 68%) and, very specially, micafungin (39.1 to 79%).

3.- *Indicate how often you consider that dosage adjustment of echinocandins should be considered in patients with renal failure and without the need for renal replacement therapy?*

**Rationale:** There is no need for dosage adjustment in patients with renal dysfunction, due to the low renal excretion of anidulafungin, caspofungin and micafungin<sup>40-43</sup>.

The vast majority of the specialists (91.3%) stated they did not adjust the doses of echinocandins in patients with renal failure that do not require renal replacement therapy. Specifically, 7 of the 23 experts consulted confirmed they "never" adjusted the doses, while 14 only contemplated adjusting the doses on rare occasions. A high level of consensus was achieved (Bottom 2 > 75%).

4.- *Importance of dosage adjustment in patients on conventional dialysis and on treatment with the following drugs:*

Coordinators' answers: Low importance of dosage adjustment/High importance of dosage adjustment for azoles, liposomal amphotericin B, anidulafungin, caspofungin, micafungin.

**Rationale:** There is no need for dosage adjustment in patients with renal dysfunction, due to the low renal excretion of anidulafungin, caspofungin and micafungin<sup>40-43</sup>. The high degree of plasma protein binding of the echinocandins, as well as their high molecular weight, make the elimination by dialysis and other continuous techniques hardly perceivable, as evidenced in different clinical studies<sup>33,44</sup>. Fluconazole is cleared by renal excretion, and the dosage should be adjusted when creatinine clearance falls below 60 ml/min to half of the dosage<sup>45</sup>. Fluconazole is dialyzable, for which the post-dialysis dosage must be adjusted<sup>45</sup>. In the case of CVWH, important increases of the dose is necessary<sup>46</sup> due to the SC values greater than 0.7<sup>46,47</sup>. However, voriconazole does not require dosage adjustment<sup>48</sup> although it should be not used when creatinine clearance is below 30 ml/min, the intravenous formulation due to the accumulation and possible toxicity of the cyclodextrins<sup>48</sup>. Nevertheless, its use has been described in patients with renal failure<sup>49</sup>.

The vast majority of the experts consulted (91.2%) considered important the dosage adjustment of azoles in the treatment of patients on conventional dialysis. Specifically, and based on a scale of 0 to 10 points, where 10 represents the greatest level of importance, 21 of the 23 specialists granted 7 or more points to the dosage adjustment in this situation, establishing an average of 8.61 points (DT: 1.14). A high level of consensus was achieved (Top 4 > 75%).

Likewise, the level of consensus was high (Bottom 4 > 75%) for the dosage adjustment of echinocandins in the management of patients on conventional dialysis. Specifically, in the case of caspofungin, the need for dosage adjustment was considered low by 82,6% of the experts (average score: 2.83;

DT: 1.87); by 78.2% for anidulafungin (average score: 2.91; DT: 2.13); and for micafungin, 78.2% (average score: 2.87; DT: 2.01).

On the other hand, only 52.1% considered important the need to adjust the dosage of liposomal amphotericin B in this situation, for which a medium level of consensus was obtained (Top 4 > 50 and ≤ 75%).

5.- *Indicate how important you consider dosage adjustment in patients who require continuous renal replacement therapy and who are receiving treatment with the following drugs:*

Coordinators' answers: Low importance of dosage adjustment/High importance of dosage adjustment for azoles, liposomal amphotericin B, anidulafungin, caspofungin, micafungin.

**Rationale:** Due to the low renal excretion of anidulafungin, caspofungin and micafungin, patients with renal dysfunction have no need for dosage adjustment<sup>40-43</sup>. Due to the high level of binding of the echinocandins to plasma proteins, as well as their high molecular weight, elimination by dialysis and continuous techniques is hardly perceived, as demonstrated in different clinical studies<sup>33,44</sup>. Fluconazole is cleared by renal excretion, for which the dose must be adjusted when creatinine clearance drops below 60 ml/min to half of the dose<sup>45</sup>. Fluconazole is dialyzable, for which post-dialysis doses must be administered<sup>45</sup>. In the case of CVWH, important dose increases are necessary<sup>46</sup> due to the SC values greater than 0.7<sup>46,47</sup>. However, voriconazole does not require dosage adjustment<sup>48</sup> although it should not be used when creatinine clearance falls below 30 ml/min, and its intravenous formulation due to the accumulation and possible toxicity of cyclodextrin excipients<sup>48</sup>. Nevertheless, its use on patients with renal failure has been described in the literature<sup>49</sup>.

Once again, the vast majority of the experts consulted (91.3%) considered dosage adjustment important with azoles in the management of patients that require continuous renal replacement therapy. Specifically, and on a scale of 0 to 10 points, where 10 represents the greatest level of importance, 21 of the 23 specialists granted 7 or more points to dosage adjustment in this situation, establishing an average of 8.83 points (DT: 1.30). High level of consensus (Top 4 > 75%).

The level of consensus was again high (Bottom 4 > 75%) when evaluating the need to adjust the dose of the echinocandins in the management of patients in this situation. Specifically, in the case of micafungin, the need for dosage adjustment was considered low by 91.3% of the panel members (average score: 2.48; DT: 1.62); by 86.9% for caspofungin (average score: 2.61; DT: 1.50); and by 86.2% in the case of anidulafungin (average score: 2.70; DT:1.74).

Finally, the percentage of specialists that evaluated the importance of dosage adjustment of liposomal amphotericin B in this situation was only 52.1%, for which the level of consensus achieved was again medium (Top 4 > 50 y ≤ 75%).

**Table 1** Recommendations from the first phase.*"Peritoneal candidiasis" Section*

- 1.- *Candida* peritonitis is a poor prognostic factor and the early and appropriate use of antifungal treatment, together with the efficient control of the infectious focus, is recommended.
- 2.- The initiation of an empirical antifungal treatment is recommended in patients with secondary nosocomial peritonitis and with risk factors of *Candida* spp isolation (colonization) or in patients with tertiary peritonitis.
- 3.- The use of an echinocandin is recommended in patients with unstable *Candida* peritonitis or in those who have previously received azole therapy or in those who have reported *Candida* spp isolates in the abdominal fluid, resistant to fluconazole.

*"Immunocompromised and transplanted patients" Section*

- 1.- Consider the interactions and hepatotoxicity in the treatment of invasive candidiasis with azole therapy in solid organ transplant recipients.
- 2.- In neutropenic patients, the treatment for candidemia should be 14 days since the last negative culture and until normalization of the neutrophil counts.
- 3.- In neutropenic patients with candidemia, caspofungin is the first choice echinocandin.
- 4.- Caspofungin is the first-line therapy for febrile neutropenia with suspected candidemia.
- 5.- In transplanted patients with invasive candidiasis, anidulafungin and caspofungin are the echinocandins recommended.
- 6.- Remove the catheter in unstable neutropenic patients with candidemia and an easily removable central venous catheter.

*"Antifungal treatment in special situations" Section*

- 1.- With the aim of maximizing the efficacy in patients with invasive candidiasis, the doses of echinocandins should be increased (preferably caspofungin) in accordance with the patients' body weight.
- 2.- Although echinocandins present few pharmacological interactions, concomitant medication should be reviewed and in view of possible interactions, preferably use anidulafungin.
- 3.- In morbidly obese patients with invasive candidiasis, increase the dose of the echinocandin.

*"Antifungal treatment in presence of organic failures" Section*

- 1.- As far as the safety is concerned; echinocandins are the family of first-line antifungal therapy.
- 2.- All of the echinocandins is the same for the treatment of patients that require continuous renal replacement therapy and do not require dosage adjustment.
- 3.-Azole therapy requires important dosage adjustments in patients that require continuous or intermittent renal replacement therapy.

6.-Indicate your level of agreement with this statement: All echinocandins are the same for the treatment of patients that require continuous renal replacement therapy.

**Rationale:** Neither micafungin<sup>50</sup> nor anidulafungin<sup>51</sup> nor caspofungin<sup>52</sup> seem to require dosage adjustment with the use of continuous renal replacement therapy. Adsorption of echinocandins to hemofilter membranes has been demonstrated (up to 20% in the case of anidulafungin) although they do not affect the minimum plasma levels required.

The majority of the experts consulted (73.9%) considered that no differences existed to determine the selection of a spe-

cific echinocandin in the treatment of a patient that requires continuous renal replacement therapy. Specifically 4 of the 23 specialists "Strongly agreed" with the statement, whereas 13 indicated they broadly agreed". However, and since the level of agreement was lower than 75%, a medium level of consensus was achieved (Top 2 > 50% and ≤ 75%).

7.-Based on your experience, please indicate which echinocandins you use in patients who require continuous renal replacement therapy.

Coordinators' answers: anidulafungin, caspofungin, mi-

**Table 2** EPICO 2.0 Final Recommendations.*"Peritoneal candidiasis" Section*

1. - Due to the poor prognosis of *Candida* peritonitis, adequate control of the infectious focus, together with early and appropriate antifungal treatment are recommended.
- 2.- The initiation of an empirical antifungal treatment in patients with secondary nosocomial peritonitis and with risk factors of *Candida* spp. colonization or in patients with tertiary peritonitis is recommended.
- 3.- Use echinocandins in unstable patients with *Candida* peritonitis and who have previously received azole therapy or in those identified with *Candida* spp. isolates resistant to fluconazole.

*"Immunocompromised and transplanted Patients" Section*

1. - Consider the interactions and hepatotoxicity in the treatment of invasive candidiasis with azole therapy in solid organ transplanted patients.
- 2.- The duration of the treatment in neutropenic patients with candidemia should be 14 days after the first negative culture and until normalization of the neutrophil count.
- 3.- Caspofungin is the echinocandin with most scientific support for patients with candidemia.
- 4.- Caspofungin is the first-line echinocandin therapy in febrile neutropenia and suspected candidemia.
5. - Remove the catheter in unstable neutropenic patients with candidemia and an easily removable central venous catheter.

*"Antifungal treatment in special situations" Section*

- 1.- In the treatment of invasive candidiasis in patients suffering from moderate liver dysfunction (Child B), the use of echinocandins (preferably anidulafungin or caspofungin with dosage adjustment) are recommended, and avoid the use of azole therapy.
- 2.- Although echinocandins present few pharmacological interactions, it is recommendable to review the concomitant medication and, in view of possible interactions, preferably use anidulafungin.

*"Antifungal treatment in presence of organic failures" Section*

- 1.- As far as safety is concerned; echinocandins are the family of first-line antifungal therapy.
- 2.- Fluconazole requires dosage adjustment, its use should therefore be reconsidered in patients requiring continuous or intermittent renal replacement therapy.
- 3.- All echinocandins are accepted and similar for the treatment of patients that require renal replacement therapy, either continuous or intermittent, and do not require dosage adjustment.

cafungin.

**Rationale:** The three echinocandins have been studied on patients receiving renal replacement therapy<sup>50-52</sup>.

The election of micafungin for the treatment of patients who require continuous renal replacement therapy was contemplated by 73.8% of the experts consulted. In the cases of caspofungin and anidulafungin, 69.5% and 60.7%, respectively, were contemplated by the experts consulted. Specifically, and based on a scale of 0 to 10 points, where 10 represents the highest score, the following are the average scores for each echinocandin: 7.22 points for micafungin (DT: 2.81); 6.57

points for anidulafungin (DT: 2.76); and 6.43 points for caspofungin (DT: 3.12).

Due to the absence of a high level of consensus (Top 4 ≤ 75%), this question was selected for the second phase of the Delphi study. No significant variation was observed. Finally, after two phases of the study, a medium level of consensus was achieved (Top 4 >50% and ≤ 75%).

**Recommendations after the first phase**

Once the results of the Delphi technique applied to the

management of critically ill patients with confirmed invasive candidiasis are known, the following 15 recommendations were elaborated (see table 1), based on all of the questions that achieved a high/medium level of consensus and, thereafter, validated in the meeting held with the hospital experts.

## SECOND PHASE. MEETING HELD WITH HOSPITAL EXPERTS

Using the same methodology, 60 hospital experts held a meeting in which they voted the recommendations described in table 1. Only the statements that received a level of consensus greater than 75% were selected. The final recommendations are shown in table 2.

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## CONFLICT OF INTERESTS

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