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Jávea consensus guidelines for the treatment of *Candida* peritonitis and other intra-abdominal fungal infections in non-neutropenic critically ill adult patients

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ABSTRACT

Background: Although the management of the invasive candidiasis has improved in the last decade, controversial issues yet remain, especially in the diagnostic and therapeutic approaches to *Candida* peritonitis and other forms of intra-abdominal fungal infections.

Aims: We sought to identify core clinical knowledge about intra-abdominal fungal infections and to achieve high-agreement recommendations required to care for critically ill adult patients with *Candida* peritonitis and other forms of intra-abdominal fungal infection.

Methods: A biregional Spanish survey, to elucidate the consensus about the already mentioned fungal infections by means of the Delphi technique, was conducted anonymously by e-mail with 29 multidisciplinary experts in invasive fungal infections from 14 hospitals in the Valencia and Murcia communities during 2014. Respondents included intensivists, anesthesiologists, microbiologists, pharmacologists, and infectious disease specialists, who answered 31 questions prepared by a coordination group after a strict review of the literature from the 5 previous years. The educational objectives spanned 6 categories: epidemiology, microbiological diagnosis, clinical diagnosis, antifungal treatment, de-escalation therapy, and special situations. The agreement required among the panelists for each item to be selected had to be higher than 70%. After extracting the recommendations from the selected items, a meeting at which the experts were asked to validate the previously selected recommendations in a second round of scoring took place.

Results: After the second round, 36 recommendations were validated according to the following distribution: epidemiology (5), microbiological diagnosis (4), clinical diagnosis (4), antifungal treatment (3), de-escalation therapy (4), and special situations (16).

Conclusions: Treatment of *Candida* peritonitis and other forms of intra-abdominal fungal infections in ICU patients requires a broad range of knowledge application and skills that our recommendations address. Based on the DELPHI methodology, these recommendations might help to optimize the therapeutic management of these patients in special situations and in various scenarios to improve their outcome.

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Documento de consenso de Jávea para el tratamiento de la candidiasis peritoneal y otras formas de infecciones fúngicas intraabdominales en pacientes adultos críticos no neutropénicos

RESUMEN

Antecedentes: Aunque en la última década se ha observado una mejoría en el manejo de la candidiasis invasora todavía existe controversia, especialmente en la aproximación diagnóstico-terapéutica de la candidiasis peritoneal y otras formas de infección fúngica invasora intraabdominal en el paciente crítico no neutropénico.

Palabras clave:

Peritonitis candidiásica

Metodología Delphi

Pacientes críticos no neutropénicos

Recomendaciones

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[◇] All members are listed in Annexes 1 and 2.

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Objetivos: Identificar los principales conocimientos clínicos sobre las infecciones fúngicas intraabdominales y elaborar recomendaciones con un alto nivel de consenso, necesarias para el diagnóstico y el tratamiento de la candidiasis peritoneal y otras infecciones fúngicas intraabdominales en pacientes adultos críticos no neutropénicos.

Métodos: Se realizó un cuestionario prospectivo en dos comunidades autónomas para estimar mediante la técnica Delphi el consenso en el diagnóstico y tratamiento de las infecciones mencionadas. El cuestionario se realizó en el año 2014, de forma anónima y por correo electrónico, con 29 expertos de varias disciplinas, especialistas en infecciones fúngicas invasivas de 14 hospitales de la Comunidad Valenciana y Murciana, entre los que se incluían intensivistas, anestesiólogos, microbiólogos, farmacéuticos y especialistas en enfermedades infecciosas, que respondieron a 31 preguntas preparadas por el grupo de coordinación, tras una revisión exhaustiva de la literatura de los 5 años previos. Los objetivos educativos contemplaron 6 categorías que incluían epidemiología, diagnóstico microbiológico, diagnóstico clínico, tratamiento antifúngico, desescalado del tratamiento farmacológico y situaciones especiales. El nivel de acuerdo alcanzado entre los expertos en cada una de las categorías debía 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 29 especialistas y se les solicitó la validación de las recomendaciones preseleccionadas.

Resultados: Después de la segunda ronda, 36 recomendaciones fueron validadas siguiendo la siguiente distribución: epidemiología (5), diagnóstico microbiológico (4), diagnóstico clínico (4), tratamiento antifúngico, (3), desescalado (4) y situaciones especiales (16).

Conclusiones: El manejo de la peritonitis candidiásica en pacientes de UCI requiere la aplicación de los conocimientos y destrezas que se detallan en nuestras recomendaciones. Estas recomendaciones, basadas en la metodología DELPHI, ayudan a optimizar el tratamiento de los pacientes críticos con candidiasis invasiva en distintos escenarios y situaciones clínicas y a mejorar su pronóstico.

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Invasive fungal infections have been increasing worldwide in recent decades. Intra-abdominal candidiasis (IAC), which includes peritonitis and intra-abdominal abscesses, occur in approximately 40% of patients following repeat gastrointestinal (GI) surgery, GI perforation, or necrotizing pancreatitis. It is the predominant invasive candidiasis (IC) after candidemia in intensive care units (ICUs), with approximately 25–60% mortality rates.^{9,41,55} In immunologically competent patients, IAC normally stems from gastrointestinal barrier breaches, causing a confined or diffuse spread of fungi in the abdominal cavity. However, the pathological importance of intra-abdominal *Candida* isolation is not clear in many clinical situations. In patients with perforation of hollow viscera or with intra-abdominal surgical drains, the recovery of bacteria along with *Candida* in peritoneal fluid samples is common, and the role of *Candida* as a pathogen, co-pathogen, or innocent spectator is undefined.⁵²

Fungal etiology accounts for at least 12% of all cases of intra-abdominal infection. *Candida* is the most common cause of fungal peritonitis, whereas other fungi, such as *Aspergillus*, *Paecilomyces*, *Penicillium*, and Zygomycetes, are infrequent protagonists of intra-abdominal fungal infections (IAFI). Although *Candida albicans* remains the most frequent yeast causing intra-abdominal infection, a shift toward other *Candida* species, such as *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis*, *Candida krusei*, and *Candida lusitanae*, has been observed (some of them with reduced susceptibility to antifungal drugs).⁴²

Despite its high incidence in surgical ICUs (59.1% of all IC),³ the etiological diagnosis of non-candidemic IC remains elusive. Neither the guidelines from the Infectious Diseases Society of America (IDSA) nor the European consensus (ESCMID) provide any clarification on IAC diagnosis.^{13,46}

The high mortality associated with IAC could be related to diagnostic problems, such as the low sensitivity and specificity of both culture- and non-culture-based techniques. It is also still unclear which patients could benefit from empiric antifungal treatment and which might be infected by fluconazole-resistant strains; IAC has recently been described as a hidden reservoir of echinocandin-resistant *Candida*.⁵⁷ In recent years, new antifungal

agents have offered various alternatives in the treatment of IC. However, the most effective therapeutic strategy for IAC has not yet been established, resulting in a remarkable lack of consensus when establishing the diagnosis and the most appropriate treatment for this patient population.

We aimed to achieve a consensus on the clinical and therapeutic management of peritoneal candidiasis (PC) based on the Epico strategy.^{37,64–66}

Methods

A panel of 29 specialists from 14 hospitals in the Valencia and Murcia communities ([Annex 1](#)) with wide experience in the treatment of critically ill patients were asked to vote on and validate the recommendations previously established by the 6 coordinators ([Annex 2](#)) responsible for the research.

The criteria for inclusion were based on the participants' experience with the clinical management of critically ill patients with a suspected or confirmed IAFI. The DELPHI technique was used to perform the study with the objective of optimizing the consultation process of the panel members. Specifically, the DELPHI methodology enables to consider group opinions, not merely individual opinions, from experts in the different medical items provided by the coordinators. A consensus of the experts greater than 70% (21–29) in Top 3 (score of 7 or more points) was required to finally consider each item as a recommendation. In those cases in which the majority of the responses to a given question were shared by 15–20 participants, the degree of consensus was established as medium, whereas in those cases in which consensus was only shared by 15 or fewer experts, the degree of consensus was defined as low.

The study was performed in three phases. Initially the coordinators responsible for the systematic search of the literature established 31 questions distributed in 6 categories: (1) epidemiology, 5 questions (developed by J.P. and D.N.); (2) microbiological diagnosis, 4 questions (developed by J.P. and D.N.); (3) clinical diagnosis, 6 questions (developed by R.Z. and J.C.V.); (4) antifungal treatment, 5 questions (developed by R.Z. and G.A.); (5)

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