



## Special article

## EPICO 4.0. 'Total quality' in the management of invasive candidiasis in critically ill patients by analysing the integrated process



Rafael Zaragoza<sup>a,\*</sup>, Ricard Ferrer<sup>b</sup>, Pedro Llinares<sup>c</sup>, Emilio Masada<sup>d</sup>, Alejandro Rodríguez<sup>e</sup>, Santiago Grau<sup>f</sup>, Guillermo Quindós<sup>g</sup>, on behalf of EPICO Project Group<sup>◇</sup>

<sup>a</sup> Unidad de Sepsis, Medicina Intensiva, Hospital Universitario Dr. Peset, Valencia, Spain

<sup>b</sup> Servicio de Medicina Intensiva, Hospital Universitario Valle de Hebrón, Barcelona, Spain

<sup>c</sup> Unidad de Enfermedades Infecciosas, Complejo Hospitalario Universitario de A Coruña (CHUAC), A Coruña, Spain

<sup>d</sup> Servicio de Anestesiología y Reanimación, Hospital Universitario La Paz, Madrid, Spain

<sup>e</sup> Unidad de Cuidados Intensivos, Hospital Universitario Juan XXIII, Tarragona, Spain

<sup>f</sup> Servicio de Farmacia, Hospital del Mar, Barcelona, Spain

<sup>g</sup> Departamento de Inmunología, Microbiología y Parasitología, Facultad de Medicina y Odontología, Universidad del País Vasco (UPV/EHU), Bilbao, Vizcaya, Spain

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## ABSTRACT

**Background:** A high quality integrated process in the clinical setting of non-neutropenic critically ill patients at risk for invasive candidiasis is a necessary tool to improve the management of these patients.

**Aims:** To identify the key points on invasive candidiasis in order to develop a set of recommendations with a high level of consensus required for the creation of a total quality integrated process for the management of non-neutropenic critically ill patients at risk of invasive candidiasis.

**Methods:** After a thorough review of the literature of the previous five years, a Spanish prospective questionnaire, which measured consensus by the Delphi technique, was anonymously conducted by e-mail, including 31 national multidisciplinary experts with extensive experience in invasive fungal infections, from six national scientific societies. The experts included a specialist in intensive care medicine, anesthesiologists, microbiologists, pharmacologists, and specialists in infectious diseases that responded 27 questions prepared by the coordination group. The educational objectives considered six processes that included knowledge of the local epidemiology, the creation and development of multidisciplinary teams, the definitions of the process, protocols, and indicators (KPI), an educational phase, hospital implementation, and the measurement of outcomes. The level of agreement among experts in each category to be selected should exceed 70%. In a second phase, after drawing up the recommendations of the selected processes, a face to face meeting with more than 60 specialists was held. The specialists were asked to validate the pre-selected recommendations.

**Measures and main outcomes:** Firstly, 20 recommendations from all the sections were pre-selected: Knowledge of local epidemiology (3 recommendations), creation and development of multidisciplinary teams (3), definition of the process, protocols and indicators (1), educational phase (3), hospital implementation (3), and measurement of outcomes (7). After the second phase, 18 recommendations were validated, and it was concluded that the minimum team or core necessary for the development of an efficient program in the use of antifungal drugs in non-neutropenic critically ill patients must consist of a specialist in infectious diseases, a clinical pharmacist, a microbiologist, a specialist in intensive care medicine, a specialist in anesthesia and recovery, and an administrator or member of the medical management team, and, in order to be cost-effective, it should be implemented in hospitals with over 200 beds. In addition, it is recommended to apply a consensual check list for the evaluation of the diagnostic process and treatment of invasive candidiasis in patients that have started an antifungal treatment. The management of external knowledge and individual learning stand out as active educational strategies. The main strategies for measuring patient safety outcomes are the analysis of the results achieved, and learning activities; assess, review and refine the deployment of the processes; quality control; epidemiological surveillance and applied research; benchmarking; and basic research. The results of the integrated process should be annually disseminated outside the hospital.

\* Corresponding author.

E-mail address: [zaragoza\\_raf@gva.es](mailto:zaragoza_raf@gva.es) (R. Zaragoza).

◇ All members are listed in Annex 1, 2 and 3.

**Conclusions:** Optimizing the management of invasive candidiasis requires the application of the knowledge and skills detailed in our recommendations. These recommendations, based on the Delphi methodology, facilitate the creation of a total quality integrated process in critically-ill patients at risk for invasive candidiasis.

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## ÉPICO 4.0. «Calidad total» en el manejo de la candidiasis invasiva en el paciente crítico mediante el análisis del proceso integrado

### R E S U M E N

#### Palabras clave:

Candidiasis invasiva  
Método Delphi  
Paciente crítico  
Proceso integrado  
Calidad  
Recomendaciones

**Antecedentes:** El adecuado manejo de los pacientes críticos no neutropénicos en situación de riesgo de contraer una candidiasis invasiva requiere la implementación de protocolos de alta calidad en la actuación clínica.

**Objetivos:** Identificar los principales conocimientos y elaborar recomendaciones con un alto nivel de consenso, necesarios para la creación de un proceso integrado de calidad total para el manejo del paciente crítico no neutropénico con riesgo de candidiasis invasiva.

**Métodos:** Se realizó un cuestionario prospectivo que mide el grado de consenso mediante la técnica Delphi, de forma anónima y por correo electrónico, entre 31 expertos multidisciplinares, especialistas en infecciones fúngicas invasivas de seis sociedades científicas, que incluyen intensivistas, anestesiólogos, microbiólogos, farmacólogos y especialistas en enfermedades infecciosas que respondieron a 27 preguntas preparadas por el grupo de coordinación, tras una revisión exhaustiva de la literatura de los últimos cinco años. Los objetivos educativos contemplaron seis procesos, que incluían el conocimiento de la epidemiología local, la creación y el desarrollo de equipos multidisciplinares, la definición de proceso, protocolos e indicadores (KPI), una fase educacional, la implementación hospitalaria y la medición de resultados. El grado de acuerdo alcanzado entre los expertos en cada una de las categorías debía superar el 70% para ser seleccionada. Después de extraer las recomendaciones de los procesos escogidos, se celebró una reunión presencial con más de 60 especialistas y se les solicitó la validación de las recomendaciones preseleccionadas.

**Medidas y resultados principales:** En un primer término se realizó una preselección de 20 recomendaciones de los siguientes apartados: Conocimiento de la epidemiología local (3), Creación y desarrollo de equipos multidisciplinares (3), Definición de proceso, protocolos e indicadores (1), Fase educacional (3), Implementación hospitalaria (3), Medición de resultados (7). Después de la segunda ronda se validaron 18 recomendaciones que se resumen en que el equipo mínimo (núcleo) necesario para un programa eficiente en el uso de fármacos antifúngicos para el paciente crítico no neutropénico debe estar integrado por un especialista en enfermedades infecciosas, un farmacéutico, un microbiólogo, un especialista en medicina intensiva, un especialista en anestesia y reanimación y un gestor o miembro de la dirección médica. Debería implementarse en hospitales de más de 200 camas para ser coste-efectivo. Además, se recomienda aplicar una lista de comprobación consensuada para la evaluación del proceso de diagnóstico y tratamiento de la candidiasis invasiva en los pacientes en los que se inicie un tratamiento antifúngico. Se destacan como estrategias de educación activa la gestión del conocimiento externo y del aprendizaje individual. Las principales estrategias para medir los resultados de seguridad del paciente son el análisis de los resultados obtenidos que comprenden la comprobación y revisión del proceso, control de calidad, vigilancia epidemiológica, benchmarking e investigación básica. Los resultados del proceso integrado deberían difundirse anualmente fuera del hospital.

**Conclusiones:** La optimización del manejo de la candidiasis invasiva requiere de la aplicación de los conocimientos y destrezas que se detallan en nuestras recomendaciones. Estas recomendaciones basadas en la metodología Delphi, facilitan la creación de un proceso integrado de manejo con calidad total del paciente crítico con riesgo de candidiasis invasiva.

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Total quality management consists of organization-wide efforts to install and make permanent a climate in which an organization continuously improves its ability to deliver high-quality products and services to customers. The current study mainly aims to design a total quality integrated process in the clinical setting of non-neutropenic critically ill patients at risk for invasive candidiasis.

For this purpose, a Coordinating Group of 7 members from six scientific societies, Spanish Society of Mycology (AEM), as the promoter; the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC); the Spanish Society of Anesthesiology, Critical Care and Pain Therapeutics (SEDAR); the Spanish Society of Intensive Care, Critical Care and Coronary Units (SEMICYUC); the Spanish Society of Chemotherapy (SEQ); the Spanish Society

of Hospital Pharmacy (SEFH), prepared a questionnaire after conducting a thorough review of the literature.

The Consensus with the final recommendations was reached after two phases: Delphi consensus by experts and discussions in a face-to-face meeting with a broader group of hospital specialists.

### Methodology

The Coordinating Group ([Annex 1](#)) prepared a questionnaire with 27 questions in 6 different areas of the process: 'Knowledge of local epidemiology', 5 questions (drafted by A.R. and G.Q.); 'Creation and development of multidisciplinary teams', 4 questions

(drafted by R.Z. and S.G.); 'Definition of process, protocols and indicators (KPI)', 3 questions (drafted by R.F., S.G. and R.Z.); 'Educational phase', 3 questions (drafted by E.M., R.F., P.L. and A.R.); 'Hospital implementation', 5 questions (drafted by P.L., E.M. and A.R.); and 'Measurement of results', 7 questions (drafted by S.G., R.Z. and R.F.).

The validation of the recommendations from the questionnaire contemplated two phases.

### Phase 1

In order to identify the levels of consensus of the different questions, between 9 and 25 June 2015 the expert panel of 31 members (Annex 2) anonymously responded an online questionnaire fully structured with questions in metric (majority) and categorical scales. The coordinators did not complete the questionnaire.

The panel consisted of 31 specialists with a wide geographical distribution in our country pertaining to the six scientific societies collaborating in the study. The criteria for inclusion of the panelists were based on both their experience in the prognosis and clinical management of critically-ill patients with invasive candidiasis and the development of stewardship programs in the management of antimicrobial therapy.

The Delphi methodology was used to conduct the study with the objective of optimizing the consultation process among the 31 panel members. Specifically, the Delphi methodology enables the identification of group opinions and not merely individual opinions of the experts in the different areas of information submitted by the coordinators. This requires a level of consensus greater than 70% (24 of 31) of the total number of experts consulted in each of the questions formulated in metric scale, either in the 'Top 4' (rating of 7 or more points) or 'Bottom 4' (score of 3 or less points), or equal to or greater than 50% (16 of 31) in the nominal questions with direct answer 'agree' or 'disagree'.

The questions that did not achieve sufficient level of consensus – a majority response had to be shared by at least 24 of the 31 participating experts to reach consensus greater than 70% of the metric scale questions, and 16 of the 31 specialists to establish consensus greater than 50% of the categorical scale questions – were proposed for inclusion in the second round carried out between July 6 and 15, 2015 via internet with the anonymous participation of 28 of the 31 specialists included in the initial sample. The coordinators, responsible for the analysis and identification of issues in greater divergence of opinion, did not answer the questions included in the second round.

### Phase 2

In a second phase, after drawing up the recommendations of the selected processes in the first phase, a physical meeting was held on November 5, 2015 with more than 60 specialists from different hospitals in which they were asked to discuss and validate the pre-selected recommendations (Annex 3).

## Results

### 'Knowledge of local epidemiology' process

1. Please indicate your level of agreement with the following statement: An increase of invasive infection due to non-*Candida albicans* species has been observed.

**Rationale.** Although the distribution of *Candida* species varies between institutions and geographic areas, *Candida albicans* remains the most frequently isolated species in invasive candidiasis in non-neutropenic critically-ill patients.<sup>21,38</sup> However, an

increase in invasive candidiasis due to non-*C. albicans* *Candida* species, such as *Candida parapsilosis* and *Candida glabrata*, has been observed,<sup>40,43</sup> which is due, although partially, to the widespread use of fluconazole prophylaxis in critically ill patients.<sup>46</sup>

The majority (89.3%) of the experts consulted agreed that the incidence of invasive infection due to non-*C. albicans* *Candida* species has increased in Critical Care Units in our country. In particular, and on a scale of 0 to 10 points in which 10 represents the maximum degree of agreement, 26 of the 31 specialists granted 7 or more points to this statement. A high level of consensus was achieved (Top 4 > 70%).

2. Please indicate your degree of agreement with the following statement: Patients' risk factors or co-morbidities should be considered, since these may be related to infections due to non-*C. albicans* *Candida* species.

**Rationale.** The recognition of co-morbidities and risk factors in population at risk for invasive candidiasis due to non-*C. albicans* *Candida* species is vital to define the more effective antifungal drug patients should receive with the less toxicity.<sup>9,10,45,49</sup>

The vast majority of the panel members (93.5%) considered that patients' risk factors or co-morbidities should be taken into account since they may be related to invasive fungal infections due to non-*C. albicans* *Candida* species. Specifically, and on a scale of 0 to 10 points in which 10 represents the highest degree of agreement, 29 specialists granted 7 or more points to this statement, for which a high level of consensus was reached (Top 4 > 70%).

3. Please indicate your level of agreement with the following statement: Knowledge of the local epidemiology of infections due to *Candida* species may optimize initial empirical treatment.

**Rationale.** Considering the relative frequency of fluconazole resistance to *C. albicans* and the increasing frequency of invasive candidiasis due to *C. parapsilosis* and *C. glabrata*,<sup>43,49</sup> knowledge of the local etiology of invasive candidiasis is necessary to optimize the antifungal treatment<sup>44</sup> that can improve patient survival when administered early and adequately.<sup>17</sup>

Due to its benefits in optimizing initial empirical treatment, the vast majority of the experts (93.5%) granted great importance to the knowledge of the local epidemiology of *Candida* infections. Specifically, and on a scale of 0 to 10 points in which 10 represents the maximum level of significance, 29 of the 31 experts gave 7 or more points to the statement, establishing a consensus agreement (Top 4 > 70%).

4. Please indicate your level of agreement with the following statement: Active research of *Candida* colonization is advisable to determine local epidemiology.

**Rationale.** The isolation of *Candida* from clinical specimens other than blood is an important challenge for clinicians, as it can represent anywhere from a single colonization, multiple sites colonization or local infection to severe invasive candidiasis. Early detection of invasive candidiasis through active research is important since it enables the determination of local epidemiology, the implementation of antifungal treatment and the improvement of patients' prognosis.<sup>21,27,38,54</sup>

Experts' level of consensus was high (Top 4 > 70%) when recommending active research of *Candida* colonization to determine local epidemiology. Specifically, and on a scale of 0 to 10 points in which 10 represents the highest level of agreement, 83.9% of the experts granted 7 or more points to this statement.

5. Please indicate your level of agreement with the following statement: *It is very important to know the local profile to antifungal agents of Candida species causing invasive candidiasis.*

**Rationale.** In the last few years, in vitro susceptibility of *Candida* to fluconazole has decreased.<sup>19</sup> This decrease could be partly due to the rise of infections due to *C. glabrata*.<sup>43</sup> Furthermore, there has been a significant increase of *Candida tropicalis* and other rare species resistant to fluconazole.<sup>2</sup> In order to optimize the empirical antifungal treatment, this situation requires identifying the local profile of the etiology of invasive candidiasis and the susceptibility patterns to fluconazole and other current antifungal drugs of the predominant species.<sup>55</sup>

The great majority of the specialists (90.3%) confirmed they find it necessary to know the local antifungal susceptibility patterns of the different *Candida* species causing invasive candidiasis. In particular, and on a scale of 0 to 10 in which 10 represents the highest level of agreement, 28 of the panel members granted 7 or more points to this statement, establishing a high level of consensus (Top 4 > 70%).

#### 'Creation and development of multidisciplinary teams' process

6. Please indicate your level of agreement with the following statement: *The minimum team (core) necessary to elaborate an efficient program on the use of antifungal agents in non-neutropenic critically-ill patients should consist of a pharmacist, a specialist in anesthesia and reanimation, a specialist in intensive care medicine, a microbiologist and a specialist in infectious diseases.*

**Rationale.** There is a considerable amount of literature that evidence the need for implementing stewardship programs for antimicrobial use in hospitals.<sup>3,25,48,51,53,56,57</sup> In 2007, the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) published guidelines underlining that the creation of a responsible multidisciplinary team to carry out the tasks of an institutional program to enhance the Program for Optimizing the Use of Antimicrobial Agents (PROA, Acronym in Spanish) on antifungal treatment in invasive candidiasis, is a key strategy for the program's success.<sup>12</sup> The 2012 consensus document drafted by the Study Group of Nosocomial Infections (GEIH) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), the Spanish Society of Hospital Pharmacy (SEFH) and the Spanish Society of Preventive Medicine, Healthcare and Hygiene (SEMPSPH) establishes that for the development of an institutional program to enhance antimicrobial stewardship programs, the core of the multidisciplinary team should at least consist of a specialist in infectious diseases or a clinician expert in infectious diseases, a clinical pharmacist specialist in antimicrobial agents and a microbiologist specialist in antimicrobial drug resistance.<sup>50</sup> To date, it has been established that the minimum team for a PROA on antifungal treatment in invasive candidiasis should be made up by a specialist in infectious diseases, a clinical pharmacist specialist in infectious diseases, a microbiologist, a specialist in intensive care medicine and a member of the reanimation unit.<sup>50</sup>

The level of consensus of the panel members was high (Top 4 > 70%) when considering that the statement regarding the minimum team required for the development of an efficient program on the use of antifungal drugs for non-neutropenic critically-ill patients requires the inclusion of a pharmacist, a specialist in anesthesiology and reanimation, a specialist in intensive care medicine, a microbiologist, and a specialist in infectious diseases. Specifically, and on a scale of 0 to 10 in which 10 represents

the greatest level of agreement, 87.1% of the experts gave 7 or more points to this statement.

7. Please indicate which of the following specialties you consider should be added to the minimum team (core) for an efficient program on the use of antifungal agents in non-neutropenic critically-ill patients. (Following your criteria, select one, two or three specialties)

The following responses were provided by the coordinators: Preventivist, Hematologist, and Administrator/Medical Management.

**Rationale.** The consensus document drafted in 2012 by the Study Group of Nosocomial Infections (GEIH) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), the Spanish Society of Hospital Pharmacy (SEFH) and the Spanish Society of Preventive Medicine, Healthcare and Hygiene (SEMPSPH) establishes that for the development of an institutional program to enhance antimicrobial stewardship programs, the core of the multidisciplinary team should at least consist of a specialist in infectious diseases or a clinician specialist in infectious diseases, a clinical pharmacist specialist in antimicrobials and a microbiologist specialist in antimicrobial drug resistance.<sup>50</sup> No matter how ambitious it may be, no PROA on antifungal treatment in invasive candidiasis can achieve the objectives unless the program is shared by a member of the management team of the hospital.<sup>26</sup>

None of the coordinators' proposed response options achieved 50% required to establish a consensus agreement – preventivist (35.5%), hematologist (32.2%), administrator/medical management (48.4%). This question was selected for the second phase of the study, in which the majority of the panelists (92.1%) considered the inclusion of an Administrator/Medical Management to the minimum team in order to elaborate an efficient program on microbial use in non-neutropenic critically-ill patients. In contrast, no consensus was achieved regarding the preventivist (28.6%) and the hematologist (21.4%).

8. How often do you believe the core team should meet?

The following response options were provided by the coordinators: daily, weekly, biweekly, monthly, and quarterly basis.

**Rationale.** Different types of minimum teams required for an efficient antifungal stewardship program are published in the literature.<sup>3,25,48,51,57</sup>

Again, the answers showed the lack of expert consensus with each and every one of the response options – daily (19.4%), weekly (25.8%), biweekly (9.7%), monthly (29.0%), and quarterly basis (16.1%). The question was reformulated – *How often do you consider the core team should meet to take decisions or make recommendations?* – and was selected for the second phase of the study, in which the specialists agreed with the appropriateness of establishing a monthly meeting of the core team, therefore reaching a consensus agreement (≥50%). In contrast, no agreement was reached with the other response options: daily (7.1%), weekly (39.3%), biweekly (0%), and quarterly basis (3.6%).

9a. Please indicate your level of agreement with the two following blocks of statements regarding the roles and functions, as an advisory body, of a stewardship program on antifungal drugs use in non-neutropenic critically-ill patients.

The coordinators provided the following answers (Block A): Raising awareness of the problem of inadequate use of antimicrobials; Convey the need to form teams to lead the PROAs to improve the quality of care; Improve suitability of empirical antifungal treatment; Optimize dosing regimens based on the



pharmacokinetic-pharmacodynamics (PK-PD) indices of antifungal drugs; and Discontinue antifungal treatment in the absence of proven fungal infection.

**Rationale.** The literature contains many studies in which the roles and responsibilities of the multidisciplinary team for antimicrobial stewardship programs in hospitals are defined.<sup>3,25,48,53,56,57</sup> Thus, and as a guide for action, some papers describe stewardship programs for antibiotic treatment similar to PROA on antifungal treatment in invasive candidiasis.<sup>51</sup> Multidisciplinary teams for monitoring antifungal treatment can reduce pharmacological costs without reducing quality of care.<sup>29</sup>

Experts reached a consensus agreement (Top 4 > 70%) for each and every one of the response options proposed by the Coordinators. Specifically, the order of the options rated with 7 or more points was the following: raising awareness of the problem of inadequate use of antimicrobials, 100%; improve suitability of empirical antifungal treatment, 100%; optimize dosing regimens based on PK-PD indices of antifungal drugs, 96.8%; discontinue antifungal treatment in the absence of proven fungal infection, 96.8%; and convey the need to form teams to lead the PROAs to improve the quality of care, 87.1%.

*9b. Please indicate your level of agreement with the following roles and functions that a stewardship program for the use of antifungal drugs in non-neutropenic critically-ill patients should include.*

The following answers were provided by the coordinators (Block B): Establish a treatment with the most cost-effective antifungal drug when the fungal etiology and outcome of microbiological study are known; Set the duration of the antifungal treatment based on available scientific evidence; Development of institutional guidelines for management of invasive candidiasis and candidemia; Avoid drug combinations that may represent unnecessary overlap in antimicrobial spectra; Avoid antifungal treatment in febrile processes in which no fungus has been isolated or in the event the microorganisms have been isolated from non-sterile specimens and were considered as contamination or colonization; Avoid inadequate empirical antifungal treatments; and Avoid prescribing inadequate antifungal therapy in the treatment of confirmed fungal infections.

**Rationale.** The literature contains many studies in which the roles and responsibilities of the multidisciplinary team for antimicrobial stewardship programs in hospitals are defined.<sup>3,25,48,53,56,57</sup> Thus, and as a guide for action, some reports describe stewardship programs for antibiotic treatment similar to the PROA on antifungal treatment in invasive candidiasis.<sup>51</sup> Multidisciplinary teams for follow-up of antifungal treatment can reduce pharmacological costs without impairing quality of care.<sup>29</sup>

Again, the answers of the panel members showed a consensus agreement (Top 4 > 70%) for each and every one of the response options. In this case, the order of responses that rated 7 or more points (Top 4) was as follows: avoid drug combinations that may represent unnecessary overlap in antimicrobial spectra, 100%; avoid inadequate empirical antifungal treatments, 100%; avoid prescribing inadequate antifungal therapy in the treatment of confirmed fungal infections, 100%; development of institutional guidelines for the management of invasive candidiasis and candidemia, 96.8%; set the duration of antifungal treatment based on available scientific evidence, 93.5%; establish a treatment with the most cost-effective antifungal molecule when the fungal etiology and outcome of microbiological study are known, 90.3%; and avoid antifungal treatment in febrile processes in which no fungus has been isolated or in the event the microorganisms have been isolated

from non-sterile specimens and were considered as contamination or colonization, 83.9%.

*'Definition of process, protocols and indicators (KPI)' process*

*10. To what extent do you deem appropriate the following algorithm (MAGICS Algorithm) to at least be performed in the initial process of diagnosis, assessment and treatment of non-neutropenic critically-ill patients with suspected invasive candidiasis?*

**Rationale.** The EPICO 1.0<sup>61</sup> and EPICO 2.0 projects<sup>62</sup> established a set of consensus recommendations for the diagnosis and treatment of invasive candidiasis. The 'MAGICS Algorithm' was produced from quantifiable measures contained in these recommendations (Fig. 1).

The vast majority of the specialists (80.6%) considered performing the 'MAGICS Algorithm' (Fig. 1) necessary in the initial approach of non-neutropenic critically-ill patients with suspected invasive candidiasis. Specifically, on a scale of 0 to 10 in which 10 represents the maximum level of significance, 25 of the 31 experts granted 7 or more points to this consideration, reaching a consensus.

*11. Please indicate which of the following actions you consider should be included in the previous protocol*

The following answers were provided by the coordinators: Therapeutic de-escalation; Dose and drug adjustment according to organic failures; Sequential therapy; Monitoring plasma levels; and Suspension of treatments due to evidence of no fungal infection.

**Rationale.** The EPICO 1.0<sup>61</sup> and EPICO 2.0 projects<sup>62</sup> established a set of consensus recommendations for the diagnosis and treatment of invasive candidiasis. The 'MAGICS Algorithm' was produced from quantifiable measures contained in these recommendations (Fig. 1).

Panel members reached a consensus agreement when considering the inclusion of four of the response options proposed by the coordinators in the 'MAGIS Algorithm'. Specifically, the following items reached consensus ( $\geq 50\%$ ): suspension of treatments due to evidence of no fungal infection, 93.5%; therapeutic de-escalation, 87.1%; dose and drug adjustment according to organic failures, 67.7%; and sequential therapy, 58.1%. In contrast, no consensus was reached in the case of monitoring plasma levels, whereas inclusion in the algorithm was only considered by 35.5% of the specialists.

*12a. Please indicate the appropriateness of the following two blocks of KPI to be included in the evaluation of a stewardship program on the use of antifungal drugs for non-neutropenic critically-ill patients*

The following answers were provided by the coordinators (Block A; process indicators: operating performance of the deployment process/protocols): Days without antifungal treatment in the ICU; Days without antifungal therapy in patients who have received such treatment; Days without antifungal prophylaxis treatment; Time delay of antifungal treatment from positive blood culture; Patients suffering from invasive candidiasis detected by time frame; Patients on antifungal treatment by time frame; Patients on empirical treatment who actually suffered from invasive candidiasis; Patients with sepsis/septic shock treated with antifungal drugs during the first three hours; Inadequate empirical antifungal treatments; Modification of inadequate empirical antifungal treatments; Modification of antifungal treatments due to 'therapeutic escalation'; Suspension of treatments due to evidence of no fungal infection; Use of antifungal drugs as directed therapy; Changes of

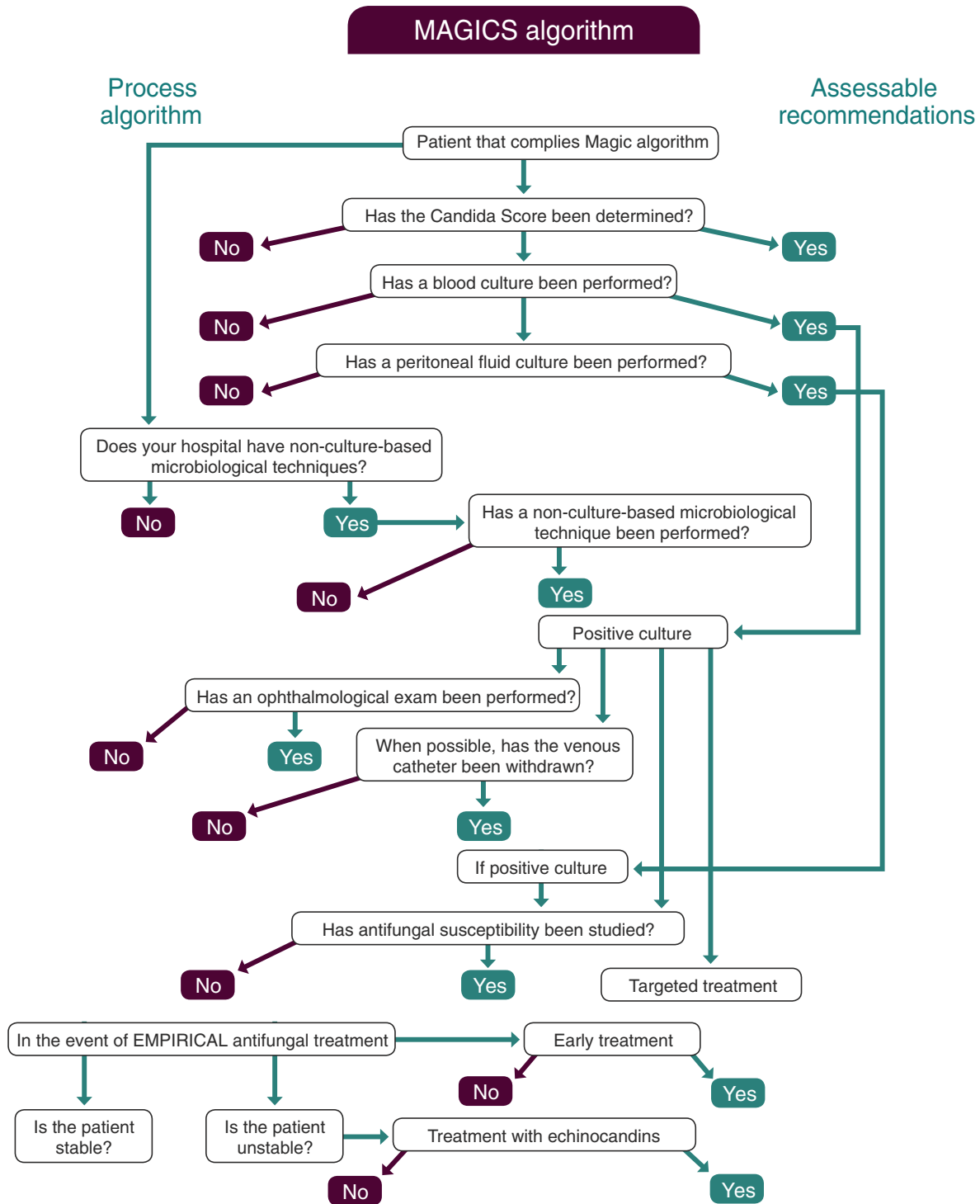


Fig. 1. MAGIC algorithm for the diagnosis and treatment of invasive candidiasis.

antifungal drugs used as treatment; and Monitoring and control of the implementation of clinical protocols.

**Rationale.** The quality indicator is the quantitative measure used as a guide to monitor and assess the quality of important aspects of clinical practice. Its design should include a description of different sections to ensure their validity and reliability, process indicators (carried out with the available resources, protocols and scientific evidence) being those evaluating how clinical practice develops.<sup>52</sup> The indicators proposed in the literature for monitoring the use of

antibiotics,<sup>58</sup> including those specific for critically ill patients,<sup>59</sup> can be adapted to the use of antifungal drugs.<sup>3</sup>

Experts reached a consensus agreement for 13 of the 15 response options proposed by the coordinators. Specifically, the order of the items that reached consensus based on the percentage of responses rated with 7 or more points was: monitoring and control of the implementation of clinical protocols, 90.3%; patients on antifungal treatment by time frame, 87.1%; inadequate empirical antifungal treatments, 87.1%; patients on empirical therapy who actually suffered from invasive candidiasis, 87.1%; time delay of antifungal treatment from positive blood culture, 87.1%; use of

antifungal drugs as directed therapy, 87.1%; modification of inadequate empirical antifungal treatments, 83.9%; modification of antifungal treatments due to 'therapeutic escalation', 83.9%; changes of antifungal drugs used as treatment, 83.9%; suspension of treatment due to evidence of no fungal infection, 80.6%; days without antifungal prophylaxis therapy, 74.2%; and patients with sepsis/septic shock treated with antifungal drugs during the first three hours, 74.2%.

In contrast, no consensus was reached in the cases of days without antifungal treatment in patients who have received such treatment and, the days without antifungal treatment in ICU. The percentages of responses in the Top 4 were established at 45.2% and 38.7%, respectively.

*12b. Please indicate the degree of appropriateness of the following two blocks of KPI to be included in the assessment of a stewardship program on the use of antifungal drugs in non-neutropenic critically-ill patients*

The following answers were provided by the Coordinators (Block B; indicators of economic and non-economic results that show that the targets set in the deployment process/protocols have been achieved): Mortality; Cost per process; Cost per patient; Budget compliance; Average stay related to invasive candidiasis; Antifungal consumption by Defined Daily Dose 100 rooms day (DDD/100 stay-day); Antifungal consumption by Days of Therapy per 100 stays-day; and Antifungal resistance.

*Rationale.* The quality indicator is the quantitative measure used as a guide to monitor and assess the quality of important aspects of clinical practice. Its design should include a description of different sections to ensure its validity and reliability, outcome indicators being those that quantify the consequences of the clinical practice, in terms of complications, mortality, missed opportunities, circuit failures, quality of life, etc.<sup>52</sup> The indicators proposed in the literature for monitoring the use of antibiotics,<sup>58</sup> including those specific for critically ill patients,<sup>59</sup> can be adapted to the use of antifungal drugs.<sup>3</sup>

The responses showed a consensus agreement (Top 4 > 70%) reached by the panelists in 7 of the 8 response options proposed by the coordinators. In this case, the order of the items that reached consensus based on the percentage of responses rated with 7 or more points was as follows: antifungal resistance, 90.3%; consumption of antifungal drugs by Defined Daily Dose per 100 days-stay, 83.9%; mortality, 80.6%; average stay related to invasive candidiasis, 80.6%; cost per process, 77.4%; consumption of antifungal drugs by Days of Therapy per 100 days-stay, 77.4%; and cost per patient, 71.0%. Finally, in the case of budget compliance, the percentage of responses was 38.7%, so no consensus was established.

'Educational Phase' process

*13. Please indicate your level of agreement with the following two statements: Education is considered an essential element in an EXCELLENCE IN MANAGEMENT program (an integrated clinical process of management and resources) on antifungal treatment designed to influence prescribing behavior; the educational phase of an antifungal EXCELLENCE IN MANAGEMENT program should be led by a multidisciplinary team.*

*Rationale.* Education is considered a 'persuasive intervention'.<sup>6</sup> Education in safe and judicious antimicrobial prescribing is an important element of any antimicrobial stewardship program.<sup>12,13,26,29,39,51</sup>

All (100%) of the panel members agreed with both of the above statements, establishing in both cases a consensus agreement (Top 4 > 70%).

*14. To what extent do you consider each of the following statements important strategies for knowledge management?*

Coordinators provided the following answers: External knowledge management strategies (research, analysis, distribution and protection of relevant information found in external sources); Internal communication strategies (socializing within the organization the knowledge generated using the lessons learned and the 'know-how': LinkedIn, blogs, WhatsApp, Skype, Blackboard, . . .); Retention of expert's knowledge strategies (access, dissemination and use of expert's knowledge: MediaWikis, knowledge map, LMS, wikis, Creately, moodle, joinme, . . .); Document management strategies (fast and structured access to documentation generated: Alfresco, Nuxeo, Documentum, Sharepoint, . . .); Individual learning strategy (acquire, consolidate and optimize the ability of the organization to ensure the transfer of explicit knowledge among people: PLE, virtual classroom, social networks, Wikipedia, . . .); Organizational learning strategies (collaborative work environments by creating working groups and communities and social networks to share and 'co-create' knowledge: Zyncro, PiuPoint, Yammer, Socialcast, . . .); and Improvement and innovation strategy (continuous reflection for the application of knowledge in order to improve the effectiveness and efficiency: Nosco, Kindling, SpiritEngage, BrainBank, . . .).

*Rationale.* Active learning techniques have proven more effective in achieving a change in behavior of prescribers than mere passive diffusion of information.<sup>4,11,26,47</sup>

Experts achieved a consensus agreement (Top 4 > 70%) for each and every one of the response options proposed by the coordinators. Specifically, the order of the items that reached consensus based on the percentage of responses rated with 7 or more points was: external knowledge management strategies, 83.9%; individual learning strategy, 83.9%; internal communication strategies, 80.6%; improvement and innovation strategy, 80.6%; retention of expert's knowledge strategies, 77.4%; document management strategies, 77.4%; and organizational learning strategies, 74.2%.

*15. Please indicate your level of agreement with the following four statements: Guidelines based on scientific evidence are key elements to any EXCELLENCE IN MANAGEMENT program (an integrated clinical process of management and resources); Undergraduate training should be a primary goal of EXCELLENCE IN MANAGEMENT programs on antifungal treatment; A web or updated presence of social networking in the hospital intranet is an essential tool to disseminate the professionals' EXCELLENCE IN MANAGEMENT programs on antifungal treatment; and Establish a strategy for managing learning and collaboration networks in order to identify opportunities for improvement, creativity and innovation.*

*Rationale.* Clinical guidelines based on scientific evidence are considered a key element of any stewardship program on the management of the antifungal treatment.<sup>14,18</sup> A key objective of any stewardship program on the management of antifungal treatment is to increase the adherence of prescribers to the use of clinical guidelines.<sup>34,35</sup> Adequate undergraduate training on the knowledge and treatment of infectious diseases is the basis for safe and appropriate prescribing of antimicrobial drugs.<sup>35</sup> The establishment of an updated intranet web of the different institutions is as an excellent way to provide easy and convenient access to information of the stewardship programs on antifungal treatment.<sup>26</sup>

The answers show a consensus agreement among the specialists consulted (Top 4 > 70%) of 3 of the 4 statements proposed by the coordinators. Specifically the percentage of responses rated with 7 or more points were the following: clinical guidelines based on scientific evidence are considered a key element of any EXCELLENCE IN MANAGEMENT program, 96.8%; establish a strategy to manage learning and collaboration networks in order to identify opportunities of improvement, creativity and innovation, 90.3%; and a web or updated presence in social networks on the hospitals intranet is an essential tool to disseminate the professionals' EXCELLENCE IN MANAGEMENT programs on antifungal treatment, 83.9%.

Meanwhile, as the percentage of panel members that agreed with the statement 'Undergraduate training should be a primary goal of the EXCELLENCE IN MANAGEMENT programs on antifungal treatment' was established at 67.7%, the statement was selected for inclusion in the second phase of the Delphi study, in which 74.1% of the specialists awarded 7 or more points to this consideration, establishing an agreement (Top 4 > 70%).

#### 'Hospital implementation' process

##### 16. To what extent do you deem the creation of multidisciplinary teams for monitoring invasive candidiasis in Spanish hospitals?

**Rationale.** The positive experience with multidisciplinary teams for monitoring invasive candidiasis created in our country<sup>25,56</sup> and other non-Spanish hospitals<sup>29,32</sup> support the feasibility of creating these units.

Most panel members (74.2%) agreed in stating that the creation of multidisciplinary teams for monitoring invasive candidiasis in Spanish hospitals is completely feasible. Specifically, on a scale from 0 to 10 points in which 10 represents the highest level of importance level, 23 of the 31 specialists granted 7 or more points to this consideration, establishing a consensus agreement.

##### 17. In your opinion, to what extent do you consider the investment of resources is justified for the implementation of an EXCELLENCE IN MANAGEMENT program to monitor invasive candidiasis?

**Rationale.** The creation of multidisciplinary teams for monitoring invasive candidiasis leads to a marked decrease in healthcare expenditure by facilitating the de-escalation and suspension of a considerable number of antifungal treatments.<sup>3,29,31,33,51,57</sup>

Most of the experts (80.6%) agreed that the investment of resources is always justified for the implementation of a program of EXCELLENCE IN MANAGEMENT to monitor invasive candidiasis. Specifically, and on a scale of 0 to 10 points in which 10 represents the highest degree of agreement, 25 specialists awarded 7 or more points to this consideration, establishing a consensus agreement.

##### 18. Please rate the usefulness of each of the following techniques for an EXCELLENCE IN MANAGEMENT program (integrated clinical process of management and resources): Utility of a technique for detecting beta glucan; and Usefulness of other non-culture-based microbiological techniques.

**Rationale.** Blood culture is the method of choice in diagnosing candidemia, although its usefulness is restricted by up to 50% of the cases.<sup>1</sup> Thus, the availability of other non-culture-based microbiological diagnostic techniques may be useful for both diagnosis and de-escalation, even though currently none of them are fully standardized.<sup>5,30,31,51</sup>

The answers show the level of agreement of the panel members when assessing the usefulness of the availability of the technique for detecting beta-glucan as part of an integrated clinical process of

management and resources for monitoring of invasive candidiasis. Specifically, 77.4% of the panelists granted 7 or more points to this assessment, so an agreement was achieved. By contrast, the non-culture-based microbiological techniques was valued by only 21 of the 31 experts consulted (67.7%), so no consensus was reached (Top 4 < 70%).

This question was selected for inclusion in the second phase of the Delphi study, in which the specialists were requested to assess the *Usefulness of non-culture-based microbiological techniques*, reaching a high level of consensus – 92.6% of the responses were rated with 7 or more points.

##### 19. To what extent do you deem cost-effective the implementation of an EXCELLENCE IN MANAGEMENT program (integrated clinical process of management and resources) for monitoring invasive candidiasis?

The following answers were provided by the coordinators: In hospitals with less than 200 beds; In hospitals with 200–500 beds; and In hospitals with more than 500 beds.

**Rationale.** The creation of multidisciplinary teams for monitoring invasive candidiasis has greater utility in hospitals with a greater population at risk of acquiring this fungal infection, which is significantly more common in larger hospitals.<sup>25,51,56</sup>

The vast majority of the panel members (96.8%) stated that the implementation of EXCELLENCE IN MANAGEMENT programs for monitoring invasive candidiasis are cost-effective in hospitals with more than 500 beds. No consensus was however reached regarding cases of hospitals with less than 200 beds – response rate in the Top 4 of only 16.1%. No agreement was reached either in the case of hospitals with 200 – 500 beds – response rate in the Top 4: 67.7%, so this question was selected for inclusion in the second phase of the Delphi study in which a consensus agreement was reached – 77.8% of the responses were rated with 7 or more points.

##### 20. Which of the following characteristics do you consider top priority in measuring, reviewing and improving the deployment of processes and protocols?

The following answers were provided by the coordinators: Measurement (focused on measuring the efficacy and efficiency); Learning and creativity (focused on creating opportunities for improvement and innovation); and Improvement and innovation (focused on assessing and establishing priorities of improvement and innovation).

**Rationale.** Standardization of clinical practice decreases the disparity in the treatment of patients using a similar approach. The implementation of the protocols also improves the distribution of responsibilities among the physicians involved in clinical procedures. Procedures subject to protocols are mainly those involving a larger number of patients, high cost and affecting medical areas where risk patients are located.<sup>36</sup>

The experts reached a consensus agreement for each and every one of the statements proposed by the coordinators. Specifically, based on the responses rated with 7 points or more, the following order of the items was established: improvement and innovation, 93.9%; measurement, 83.9%; and learning and creativity, 87.1%.

#### 'Measurement of results' process

##### 21. Please indicate the level of importance you grant to the measurement of results regarding the following aspects

The following answers were provided by the coordinators: Comparison of indicators strategy (benchmarking) among different hospitals; Epidemiological surveillance, Applied research, Basic research; Quality assurance; Patient safety; Analysis of the results



achieved and learning activities; and Evaluate, revise and refine the deployment process.

**Rationale.** Quality as such is meaningless, therefore different authors have proposed that improving quality of care requires a process involving the definition of this concept.<sup>20</sup> However, at least sometimes, it is difficult to differentiate between processes that provide high levels of quality and those considered low quality.<sup>7</sup> Thus, the quality of healthcare should be defined within a framework that provides ongoing improvement in this area.<sup>42</sup>

The panel members reached a consensus agreement (Top 4 > 70%) for each and every one of the response options provided by the coordinators. Specifically, the order of importance awarded to each of the responses based on the answers rated with 7 or more points were: patient safety, 100%; analysis of the results achieved and learning activities, 96.8%; assess, revise and refine the deployment process, 96.8%; quality assurance, 93.5%; epidemiological surveillance, 90.3%; applied research, 90.3%; comparison of indicators strategy (benchmarking) among different hospitals, 87.1%; and basic research, 77.4%.

## 22. What kind of measures do you consider most important to carry out in order to establish process and outcome indicators?

The following answers were provided by the coordinators: Economic and financial management; Processing costs; Process performance; Performance of *partners* and suppliers; Technology, information and knowledge; Perception of stakeholders (affected groups of interest); Activity; and Population health outcomes.

**Rationale.** Quality as such is meaningless, therefore different authors have proposed that improving quality of care requires a process involving the definition of this concept.<sup>20</sup> However, at least sometimes, it is difficult to differentiate between processes that provide high levels of quality and those considered low quality.<sup>7</sup> Thus, the quality of healthcare should be defined within a framework that provides ongoing improvement in this area.<sup>42</sup>

Experts reached a consensus agreement in 7 of the 8 measures proposed by the coordinators. In this case, the order based on the percentage of respondents that rated the measures with 7 or more points was: population health outcomes, 93.5%; process performance, 87.1%; process costs, 83.9%; technology, information and knowledge, 83.9%; perception of stakeholders (affected groups of interest), 80.6%; activity, 80.6%; and economic and financial management, 77.4%.

Meanwhile, the percentage of respondents that granted 7 or more points to 'Performance of *partners* and suppliers' was 61.3%, thus it was selected for inclusion in the second phase of the Delphi study where a consensus agreement was reached – 21 responses of the 28 (77.8%).

## 23. Which of the following characteristics do you consider most relevant for the measurement of process and outcome indicators?

The following answers were provided by the coordinators: Scope and relevance (indicators are aligned with the strategy, goals and needs of the agents involved – interest groups); Integrity (indicators are timely, reliable and accurate); Segmentation (the indicators are properly segmented); and Performance (indicators have sustained trends, defined objectives, external comparisons available and confidence in the understanding of the causes and effects on results based on the deployed actions).

**Rationale.** To date, a number of terms that identify the quality of process and outcome indicators have been accepted. This is the case of integrity, which establishes whether the indicators are timely, reliable and accurate,<sup>37</sup> and performance that is established by the ability of the indicators to achieve sustained trends, define

objectives, external comparisons available and confidence in the understanding of the causes and effects of the results based on the deployed actions.<sup>22</sup> Additionally, segmentation of results implies the need for these to not only be globally analysed, but also from the perspective that the overall outcomes come from the aggregation of the individual outcomes of each of the indicators that have been analysed separately.<sup>28</sup>

The responses showed a high level of agreement (Top 4 > 70%) among the specialists regarding the relevance of all of the response options proposed by the coordinators.

The order of the characteristics granted 7 or more points is: integrity, 100%; performance, 100%; scope and relevance; 93.5%; and segmentation, 90.3%.

## 24. To whom would you disseminate the outcomes IN THE HOSPITAL?

The following responses were provided by the coordinators: To their team; To the critical care units; To the infection committee; To the pharmacy committee; To medical management; To all the services involved; To the attendees of the general hospital information sessions; To the hospital board; and To all who have access to the hospital web.

**Rationale.** The dissemination to the different services and to the hospital of the results obtained following the implementation of optimization programs in the management of antimicrobial therapy has proven to be a useful strategy in monitoring trends in the use of antimicrobial drugs and to identify the critical areas that require special attention to succeed in achieving proper prescription.<sup>24</sup> In fact, doctors and staff related to antibiotic therapy are considered key elements that should be informed about the objectives and results of the antibiotic stewardship programs.<sup>8</sup> Moreover, the dissemination of information on bacterial and fungal resistance is an essential element of training.<sup>8</sup> However, disseminating the results of monitoring programs of certain infections and antibiotic use has not always translated into improved outcomes.<sup>16</sup> In this context, in our country we have a study called 'Study on the Prevalence of Nosocomial Infections in Spain' (EPINE, Acronym in Spanish), whose results are disseminated to the participating hospitals,<sup>15</sup> and the 'Surveillance Study of Nosocomial Infections in Catalonia (VINCat, Acronym in Spanish), which is a standardized surveillance program that provides individualized information to each participating center and conducts benchmarking of specific results.<sup>60</sup> Meanwhile, expert clinical decision support systems based primarily on software tools, have been proposed as elements to be considered to enhance the dissemination of the results of antibiotic stewardship programs.<sup>41</sup>

Panel members reached a consensus agreement ( $\geq 50\%$ ) for 6 of the 9 response options proposed by the coordinators. Specifically, the percentage of positively valued responses in items that reached consensus were: inform to the infection committee, 96.8%; to their team, 93.5%; to the critical care units, 87.1%; to the medical management, 83.9%; to all of the services implicated, 83.9%; and to the pharmacy committee, 71%.

On the other hand, the percentage of responses with positive assessment for the options 'to the attendees of general hospital information sessions', 'to all who have access to the hospital web' and 'to the hospital board' were respectively 48.4%, 35.5% and 32.3%, so no consensus was established in any of these cases.

## 25. How often would you report the results IN THE HOSPITAL?

The following responses were provided by the Coordinators: Once a month; Every 3 months; Every 6 months; and Annually.

**Rationale.** As part of the 'National Healthcare Safety Network' (NHSN), the Centers for Disease Control and Prevention of the

**Table 1**  
Recommendations of the first phase.

**'Knowledge of local epidemiology' process**

- Identify comorbidities and/or risk factors of invasive candidiasis due to non-*Candida albicans* species to define the best treatment.
- Identify local epidemiology of infections due to *Candida* to optimize antifungal treatment.
- It is very important to determine the local antifungal susceptibility profiles of isolates of *Candida* causing invasive candidiasis.

**'Creation and development of multidisciplinary teams' process**

- The minimum team (core) necessary to elaborate an efficient program on the use of antifungal agents in non-neutropenic critically-ill patients should consist of a specialist in infectious diseases, a clinical pharmacist specialist in infectious diseases, a microbiologist, a specialist in intensive care medicine, a specialist in anesthesiology and reanimation, and an administrator/member of medical management.
- It is advisable for the core team required for an efficient program on the use of antifungal agents for non-neutropenic critically ill patients to establish a monthly meeting to take decisions and draw up recommendations.
- The functions that a minimum team (core) of a Program for Optimizing the use of antifungal agents in non-neutropenic critically-ill patients must consider are included in the following decalogue:
  - Raise awareness of the problem of inadequate use of antimicrobials.
  - Convey the need to form teams to lead the Programs for Optimizing the Use of Antimicrobial Agents in Spanish hospitals (PROA, Acronym in Spanish) to improve the quality of care.
    - Improve suitability of empirical antifungal treatment.
    - Optimize dosing regimens based on the pharmacokinetic-pharmacodynamic indices of antifungal drugs.
    - Discontinue antifungal treatment in the absence of proven fungal infection.
    - Establish a treatment directed to the most cost-effective antifungal molecule when the fungal etiology and outcome of microbiological study are known.
    - Set the duration of antifungal treatment based on available scientific evidence.
    - Develop institutional guidelines for the management of invasive candidiasis and candidemia.
    - Avoid drug combinations that may represent unnecessary overlap in antimicrobial spectra.
    - Avoid antifungal treatment in febrile processes in which no fungus has been isolated or in the event the microorganisms have derived from samples considered as contamination or colonization.
    - Avoid inadequate empirical antifungal treatments.
    - Avoid prescribing inadequate antifungal therapy in the treatment of confirmed fungal infections.

**'Definition of process, protocols and indicators (KPI)' process**

It is advisable to use the following algorithm (Fig. 1) to assess the process of diagnosis and treatment of invasive candidiasis in patients who have started an antifungal treatment

**'Educational phase' process**

- Education is considered an essential element in an excellence in management program on antifungal treatment designed to influence prescribing behavior, which should be led by a multidisciplinary team.
- In any excellence in management program on antifungal treatment the following are considered essential to disseminate knowledge: the use of clinical guidelines based on scientific evidence; programs that target undergraduate training; websites, social networks and updating on hospital intranet; and the establishment of learning and collaboration networks among working groups in order to identify opportunities for improvement, creativity and innovation.

**'Hospital implementation' process**

- Due to their cost-effectiveness, the creation of multidisciplinary teams are necessary for monitoring antifungal treatment.
- The availability of other non-culture-based microbiological diagnostic techniques improve monitoring antifungal treatment.
- The creation of monitoring units of invasive candidiasis are cost-effective in hospitals with more than 200 beds and, especially, in those with more than 500.

**'Measurement of results' process**

- All of the strategies proposed were considered important for the measurement of the results of the integrated process of antifungal treatment optimization in the following order based on the percentage of the consensus reached: patient safety; analysis of the results achieved and learning activities; evaluate, revise and refine the deployment process; quality assurance; epidemiological surveillance and applied research; benchmarking; and basic research.

Table 1 (Continued)

- All of the measures proposed to establish process and outcome indicators in the programs for the optimization of antifungal treatment were considered important in the following order based on the percentage of consensus achieved: population health outcomes; process performance; process costs and technology, information and knowledge; activity and perception of the stakeholders involved; and partners and suppliers performance.
- All of the attributes proposed for the measurement of the process and outcome indicators were considered relevant, highlighting integrity and performance, followed by scope and relevance and, finally, appropriate segmentation.
- The main recipients of the dissemination of the integrated process outcomes in the hospital by level of consensus would be: infections committee, the team, critical care units and rest of services involved, medical management, and pharmacy committee.
- Outcomes of the integrated process should be disseminated on a quarterly basis in the hospital.
- The main recipients of the dissemination of the integrated process outcomes outside the hospital would be the scientific journals, Autonomous Community Administration, scientific societies and other hospitals.
- Outcomes of the integrated process should be annually disseminated outside the hospital.

United States (CDC) have developed an application to introduce information regarding the days of therapy with antimicrobial drugs (DOT) for subsequent monthly exploitation. This information primarily has software maintenance. CDC will add a 'risk adjustment' function to the application to enable benchmarking.<sup>8</sup>

The response option, 'every three months' for the dissemination of results in the hospital, was considered suitable by 51.6% of the specialists, whereas a consensus agreement was established ( $\geq 50\%$ ). This was not the case for the other response options, since they were not considered adequate by at least half of the panel members – every 6 months, 25.8%; once a month, 22.6%; and annually, 0.0%.

**26. To whom would you disseminate the results OUTSIDE THE HOSPITAL?**

The coordinators provided the following response options: I would not disseminate the results outside the hospital; I would disseminate them; To Autonomous Community Administrations; To the National Administration; To specialized press; To non-specialized general press; To scientific journals; and To other hospitals (to promote the comparison of performance with other organizations).

**Rationale.** The dissemination of information on bacterial and fungal resistance is an essential element of training, as well as refresher courses for improving the prescription of antimicrobial drugs.<sup>8</sup> In this context, we have in our country a study called EPINE, which results are disseminated to the participating hospitals,<sup>15</sup> and the VINCat study, which is a standardized surveillance program that provides individualized information to each participating center and conducts benchmarking of specific results.<sup>60</sup>

The vast majority of the experts (96.8%) agreed on disseminating the results outside the hospital, reaching a consensus agreement. Specifically, 71.3% agreed on disseminating the results to scientific journals, and 67.7% to Autonomous Community Administrations, 6.3% to scientific societies, and 51.6% to other hospitals to compare performance, so a consensus agreement was established for the dissemination to scientific journals.

In contrast, no consensus was reached in the case of communicating the results to the National Administration and to specialized press, where a positive response was only obtained by 25.8% and 12.9% of the experts, respectively. Moreover, in the case of non-specialized general press, this response option was completely ruled out by all panel members.

**Table 2**  
Final recommendations.**'Knowledge of local epidemiology' process**

- Identify comorbidities and/or risk factors of invasive candidiasis due to non-*Candida albicans* species to help choosing the best treatment.
- Identify local epidemiology of infections due to *Candida* to optimize antifungal treatment.
- It is very important to determine the local sensitivity profile to antifungal agents of *Candida* species causing invasive candidiasis.

**'Creation and development of multidisciplinary teams' process**

- The minimum team (core) necessary to elaborate an efficient program on the use of antifungal agents in non-neutropenic critically-ill patients should consist of a specialist in infectious diseases, a clinical pharmacist specialist in infectious diseases, a microbiologist, a specialist in intensive care medicine, a specialist in anesthesiology and reanimation, and an administrator/member of medical management.
- It is advisable for the core team required for an efficient program on the use of antifungal agents for non-neutropenic critically ill patients to establish a monthly meeting to take decisions and draw up recommendations.
- The functions that a minimum team (core) of a program for optimizing the use of antifungal agents in non-neutropenic critically-ill patients must consider are included in the following Decalogue:
  - Raise awareness of the problem of inadequate use of antimicrobials.
  - Convey the need to form teams to lead the Programs for Optimizing the Use of Antimicrobial Agents in Spanish hospitals (PROA, Acronym in Spanish) to improve the quality of care.
  - Improve suitability of empirical antifungal treatment.
  - Optimize dosing regimens based on the pharmacokinetic-pharmacodynamic indices of antifungal drugs.
  - Discontinue antifungal treatment in the absence of proven fungal infection.
  - Establish a treatment directed to the most cost-effective antifungal molecule when the fungal etiology and outcome of microbiological study are known.
  - Set the duration of antifungal treatment based on available scientific evidence.
  - Develop institutional guidelines for the management of invasive candidiasis and candidemia.
  - Avoid drug combinations that may represent unnecessary overlap in antimicrobial spectra.
  - Avoid antifungal treatment in febrile processes in which no fungus has been isolated or in the event the microorganisms have derived from samples considered as contamination or colonization.
  - Avoid inadequate empirical antifungal treatments.
  - Avoid prescribing inadequate antifungal therapy in the treatment of confirmed fungal infections.

**'Definition of process, protocols and indicators (KPI)' process**

- It is advisable to use the following checklist to assess the process of diagnosis and treatment of invasive candidiasis in patients who have started an antifungal treatment:
  1. *Process indicators*:
    - Delayed antifungal prescription since a positive blood culture is obtained.
    - Inadequate empirical antifungal treatments.
    - Patients on empirical treatment who actually had invasive candidiasis.
    - Use of antifungal drugs as targeted therapy.
  2. *Outcome and Economic indicators*:
    - Mortality rate of patients with candidemia.
    - Antifungal consumption by Defined Daily Dose 100 rooms day (DDD/100 stays-day).
    - Resistance to fluconazole in *Candida* isolated from blood cultures.
    - Resistance to candins in *Candida* isolated from blood cultures.

**'Educational phase' process**

- Education is considered an essential element in an excellence in management program on antifungal treatment designed to influence prescribing behavior and should be led by a multidisciplinary team.
- The use of different active learning strategies adapted to each center environment is recommended.
- In any excellence in management program on antifungal treatment the following are considered essential for the dissemination of knowledge:
  - Use of clinical guidelines based on scientific evidence.
  - Programs that target undergraduate training.
  - Websites, social networks and updating on hospital intranet.
  - Establishment of learning and collaboration networks among working groups in order to identify opportunities for improvement, creativity and innovation.

Table 2 (Continued)

**'Hospital implementation' process**

- The creation of multidisciplinary teams for monitoring antifungal treatment is cost-effective.
- The availability of other non-culture-based microbiological diagnostic techniques improves monitoring antifungal treatment.
- The creation of monitoring units of invasive candidiasis in hospitals with more than 500 beds is recommended. The complexity of the patients should be assessed in hospitals with less beds.

**'Measurement of results' process**

- The main recipients of the dissemination of the integrated process outcomes in the hospital by level of consensus would be: infections committee, the team, critical care units and rest of services involved, medical management, and pharmacy committee.
- The main recipients of the dissemination of the integrated process outcomes outside the hospital would be the scientific journals, Autonomous Community Administration, scientific societies and other hospitals.
- Outcomes of the integrated process should be annually disseminated outside the hospital.

**27. How often would you disseminate the results OUTSIDE THE HOSPITAL?**

The coordinators provided the following response options: Once a month; Every 3 months; Every 6 months; and Annually.

*Rationale.* Although Law 14/1986 of April 25, includes several sections on actions of health services, no information is available about the need to report on issues related to this document.<sup>23</sup>

The vast majority of experts (96.7%) considered that the dissemination of results outside the hospital should be conducted annually, establishing a consensus agreement. Other response options proposed by the coordinators were not considered adequate for at least half of the members of the panel – every 6 months, 3.3%; every 3 months, 0%; and once a month 0%.

**Recommendations**

Once the results achieved with the Delphi methodology were known and applied to the creation of a total quality integrated process for the management of non-neutropenic critically ill patients at risk for invasive candidiasis, the 20 recommendations exhibited in Table 1 were extracted as conclusions, based on the answers that achieved a high level of consensus,

**Phase 2: face-to-face meeting with hospital specialists**

A physical meeting was held on November 5, 2015 with 60 specialists (Annex 3) from different hospitals in which they were asked to discuss and validate the pre-selected recommendations (Table 1). The 22 final recommendations are presented in Table 2. In this second phase, two new recommendations on process and outcome indicators that were voted unanimously by all 60 participants were added (Table 2). An algorithm describing the process of management of invasive candidiasis was finally designed (Fig. 1).

**Conflict of interests**

This consensus has been sponsored by MSD Laboratories, Spain. MSD Spain only provided support to this research. MSD did not contribute to the scientific content nor to the final recommendations.

This research has been endorsed by the following Spanish Societies: the Spanish Society of Mycology (AEM), the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), the Spanish Society of Anesthesiology, Reanimation and Pain Therapeutics (SEDAR), the Society of Intensive and Critical Care Medicine and Coronary Units (SEMICYUC), the Spanish Society of Chemotherapy (SEQ); the Spanish Society of Hospital Pharmacies (SEFH).

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### Annex 1. COORDINATORS

#### Rafael Zaragoza Crespo

Servicio de Medicina Intensiva, Hospital Universitario Dr. Peset. Valencia

#### Ricard Ferrer Roca

Servicio de Medicina Intensiva, Hospital Universitario Mútua de Terrasa. Terrasa, Barcelona

#### Pedro Llinares Mondéjar

Unidad de Enfermedades Infecciosas, Complejo Hospitalario Universitario de A Coruña (CHUAC). A Coruña

#### Emilio Maseda Garrido

Servicio de Anestesiología y Reanimación, Hospital Universitario La Paz. Madrid

#### Alejandro H. Rodríguez Oviedo

Unidad de Cuidados Intensivos, Hospital Universitario Juan XXIII. Tarragona

#### Santiago Grau Cerrato

Servicio de Farmacia, Hospital del Mar. Barcelona

#### Guillermo Quindós Andrés

Departamento de Inmunología, Microbiología y Parasitología, Facultad de Medicina y Enfermería, Universidad del País Vasco (UPV/EHU). Bilbao, Vizcaya

### Annex 2. REPRESENTATIVE EXPERTS

#### Marcio Borges Sa

Unidad de Sepsis, Hospital Son Llàtzer, Palma de Mallorca

#### José Garnacho Montero

UCI, Hospital Universitario Virgen del Rocío, Sevilla

#### José Ignacio Gómez Herreras

Anestesiología, Hospital Clínico Universitario de Valladolid, Valladolid

#### Cristóbal León Gil

Servicio de Cuidados Críticos y Urgencias, Hospital Nuestra Señora de Valme, Sevilla

#### Rafael León López

Servicio de Medicina Intensiva, Hospital Universitario Reina Sofía, Córdoba

#### Leonor Periañez Parraga

Servicio de Farmacia Hospitalaria, Hospital Universitario Son Espases, Palma de Mallorca

#### Jordi Nicolás Picó

Servicio de Farmacia Hospitalaria. Hospital Universitari Mútua Terrassa, Barcelona

#### Miguel Salavert Lleti

Unidad de Enfermedades Infecciosas, Hospital Universitari i Politècnic La Fe, Valencia

#### M<sup>a</sup> Carmen Fariñas Álvarez

Servicio de Enfermedades Infecciosas, Hospital Universitario Marqués de Valdecilla, Santander

#### Eva Romá Rosa

Farmacia, Hospital Universitari i Politècnic La Fe, Valencia

#### César Aragón González

Servicio de Medicina Intensiva, Hospital Regional Universitario de Málaga

#### Mercedes Bouzada Rodríguez

Servicio de Anestesiología, Complejo Hospitalario Universitario de Santiago de Compostela, A Coruña

#### Izaskun Azcárate Egaña

Servicio de Microbiología, Hospital Universitario Donostia, Guipúzcoa

#### Jesús Rico Feijoo

Servicio de Anestesiología y Reanimación, Hospital Universitario Río Hortega, Valladolid

#### M<sup>a</sup> Dolores Rodríguez Mayo

Servicio de Microbiología, Complejo Hospitalario Universitario de A Coruña

#### Patricia Muñoz

Servicio de Microbiología-Enfermedades Infecciosas, Hospital General Universitario Gregorio Marañón, Madrid

#### Dr. Javier Pemán García

Servicio de Microbiología, Hospital Universitari i Politècnic La Fe, Valencia

#### Jesús Fortún Abete

Servicio de Enfermedades Infecciosas, Hospital Universitario Ramón y Cajal, Madrid

#### Pedro M. Olaechea Astigarraga

Hospital de Galdakao, Usansolo, Vizcaya

#### Gerardo Aguilar Aguilar

Servicio de Anestesiología y Reanimación, Hospital Clínico Universitario de Valencia

#### Isabel Ruiz Camps

Servicio de Enfermedades Infecciosas, Hospital Universitari Vall d'Hebron, Barcelona

#### Rafael González de Castro

Servicio de Anestesiología, Complejo Asistencial de León

#### José María Aguado García

Unidad de Enfermedades Infecciosas, Hospital Universitario 12 de Octubre, Madrid

#### Rafael Huarte Lacunza

Servicio de Farmacia Hospitalaria, Hospital Universitario Miguel Servet, Zaragoza

#### M<sup>a</sup> Luisa Pérez del Molino

Servicio de Microbiología, Complejo Hospitalario Universitario de Santiago de Compostela, A Coruña

#### Benito Almirante Gragera

Servicio de Enfermedades Infecciosas, Hospital Universitari Vall d'Hebron, Barcelona

#### Juan Carlos del Pozo Laderas

Servicio de Medicina Intensiva, Hospital Universitario Reina Sofía de Córdoba

#### Francisco Álvarez Lerma

Servicio de Medicina Intensiva-UCI, Hospital del Mar, Barcelona

#### José Ramón Iruetagoiena Amiano

Servicio de Medicina Intensiva, Hospital Universitario Cruces, Barakaldo, Vizcaya

#### Beatriz Galván Guijo

Servicio de Medicina Intensiva, Hospital Universitario La Paz, Madrid

### Annex 3. HOSPITAL EXPERTS

- Dra. Esther María López Ramos (Hospital Universitario Príncipe de Asturias, Alcalá de Henares, Madrid).
- Dra. Margarita Sánchez Castilla (Hospital Universitario Puerta de Hierro-Majadahonda, Madrid).
- Dr. Luis Tamayo Lomas (Hospital Universitario Río Hortega, Valladolid).
- Dr. Luis Gajate Martín (Hospital Universitario Ramón y Cajal, Madrid).
- Dra. Teresa Tabuyo Bello (Complejo Hospitalario Universitario de A Coruña).
- Dr. David Pestaña Lagunas (Hospital Universitario Ramón y Cajal, Madrid).



- Dra. Ana Pérez Carbonell (Hospital General Universitario de Elche, Alicante).
- Dr. José Blanquer Olivas (Hospital Clínic Universitari de Valencia).
- Dr. Fernando Maroto Monserrat (Hospital San Juan de Dios del Aljarafe, Bormujos, Sevilla).
- Dr. Luis Alberto Olaondo (Clínica Universidad de Navarra, Pamplona, Navarra).
- Dr. Pedro Castro Rebollo (Hospital Clínic de Barcelona).
- Dr. Francisco Javier González de Molina Ortiz (Hospital Universitario Mutua de Terrassa, Terrassa, Barcelona).
- Dra. Eva Benveniste Pérez (Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona).
- Dr. Mauro Lonaiz Bardanabe (Complejo Hospitalario de Navarra, Pamplona, Navarra).
- Dr. Miguel Ángel Arribas Santamaría (Hospital Arnau de Vilanova, Valencia).
- Dr. José Manuel Soto Blanco (Hospital Universitario San Cecilio, Granada).
- Dr. José Castaño Pérez (Hospital Universitario Virgen de las Nieves, Granada).
- Dra. Lorena Mouriz Fernández (Hospital Universitario Lucus Augusti, Lugo).
- Dr. José Miguel Marcos Vidal (Hospital Universitario de León).
- Dr. Vicente Torres Pedrol (Hospital Universitario Son Espases, Palma de Mallorca, Islas Baleares).
- Dr. Jorge Pereira Tamayo (Hospital do Meixoeiro, Vigo, Pontevedra).
- Dr. Enrique Samsó Sabé (Hospital del Mar, Barcelona).
- Dr. César Aldecoa Álvarez-Santullano (Hospital Universitario Río Hortega, Valladolid).
- Dr. Juan Ramón Fernández Villanueva (Complejo Hospitalario Universitario de Santiago Compostela, A Coruña).
- Dr. Luis Suárez Gonzalo (Hospital Universitario La Paz, Madrid).
- Dr. Sergio Osssa Echeverri (Hospital Universitario de Burgos).
- Dr. José Ignacio Ayestarán Rota (Hospital Universitario Son Espases, Palma de Mallorca, Islas Baleares).
- Dra. Marina Varela Durán (Complejo Hospitalario Universitario de Pontevedra).
- Dra. Carolina Giménez-Esparza Vich (Hospital Vega Baja, Orihuela, Alicante).
- Dr. Demetrio Pérez Civantos (Hospital Universitario Infanta Cristina, Parla, Madrid).
- Dra. Rocío Armero Ibáñez (Hospital Universitario Doctor Peset, Valencia).
- Dr. Eduardo Tamayo Gómez (Hospital Clínico Universitario de Valladolid).
- Dr. Ángel Caballero Sáez (Hospital San Pedro, Logroño, La Rioja).
- Dra. Pilar Luque Gómez (Hospital Clínico Universitario Lozano Blesa, Zaragoza).
- Dr. Luis Quecedo Gutiérrez (Hospital Universitario de La Princesa, Madrid).
- Dr. María José Bartolomé Pacheco (Hospital Universitario Marqués de Valdecilla, Santander).
- Dra. María del Carmen Martínez Ramagge (Hospital La Línea (AGS Campo de Gibraltar), La Línea de la Concepción, Cádiz).
- Dra. María José Gutiérrez Fernández (Hospital San Agustín, Avilés, Asturias).
- Dr. Ignacio Moreno Puigdollers (Hospital Universitari i Politècnic La Fe, Valencia).
- Dr. Ricardo Gimeno Costa (Hospital Universitari i Politècnic La Fe, Valencia).
- Dr. Unai Begoetxea Uriarte (Hospital de Basurto, Bilbao, Vizcaya).
- Dr. Andrés Carrillo Alcaraz (Hospital General Universitario Morales Meseguer, Murcia).
- Dr. Manuel Rodríguez Carvajal (Hospital Juan Ramón Jiménez, Huelva).
- Dr. Miguel Ángel Pereira Loureiro (Hospital do Meixoeiro, Vigo, Pontevedra).
- Dra. Paula Vera Artazloz (Hospital de la Santa Creu i Sant Pau, Barcelona).
- Dr. Joaquín Lobo Palanco (Complejo Hospitalario de Navarra, Pamplona, Navarra).
- Dr. María José Pérez Pedrero Sánchez Belmonte (Hospital Virgen de la Salud, Toledo).
- Dra. Susana Sancho Chinesta (Hospital Universitario Doctor Peset, Valencia).
- Dr. David Domínguez García (Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Tenerife).
- Dr. Fernando Armestar Rodríguez (Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona).
- Dr. Juan Carlos Sotillo Díaz (Hospital General Universitario Gregorio Marañón, Madrid).
- Dr. Juan Francisco Machado Casas (Complejo Hospitalario de Jaén).
- Dra. María Victoria de la Torre Prados (Hospital Universitario Virgen de la Victoria, Málaga).
- Dr. César Aragón González (Hospital Regional Universitario Carlos Haya, Málaga).
- Dra. María Ángeles Ballesteros Sanz (Hospital Universitario Marqués de Valdecilla, Santander).
- Dra. Catalina Sánchez Ramírez (Hospital Universitario de Gran Canaria Doctor Negrín, Las Palmas de Gran Canaria, Gran Canaria).
- Dra. Marta Gurpegui Puente (Hospital Universitario Miguel Servet, Zaragoza).
- Dr. Juan Carlos Pardo Talavera (Hospital General Universitario Reina Sofía, Murcia).
- Dra. Milagros Cid Manzano (Complejo Hospitalario Universitario de Ourense).
- Dr. Pau Garro Martínez (Hospital General de Granollers, Barcelona).
- Dr. Felipe Bombillo del Amo (Hospital Clínico Universitario San Carlos, Madrid).
- Dra. Montserrat Vallverdi Vidal (Hospital Universitari Arnau de Vilanova, Lleida).
- Dr. Marcos Pérez Carrasco (Hospital Universitari Vall d'Hebron, Barcelona).
- Dr. Rafael Franco Llorente (Hospital Universitario Virgen de las Nieves, Granada).
- Dr. Juan Carlos Martínez Cejudo (Hospital Universitario Infanta Elena, Valdemoro, Madrid).
- Dr. Juan Carlos Valía Vera (Consortio Hospital General Universitario de Valencia).
- Dra. Rosa Pyo-Guerrero Lahoz (Hospital Son Llàtzer, Palma de Mallorca, Islas Baleares).
- Dr. José Garnacho Montero (Hospital Universitario Virgen del Rocío, Sevilla).
- Dra. María Elena Vilas Otero (Complejo Hospitalario Universitario de Vigo, Pontevedra).
- Dra. Belén Civantos Martín (Hospital Universitario La Paz, Madrid).
- Dra. Rosa Ana Álvarez Fernández (Hospital Universitario Central de Asturias, Oviedo, Asturias).
- Dr. Emilio García Prieto (Hospital Universitario Central de Asturias, Oviedo, Asturias).
- Dr. Pedro Picatto Hernández (Hospital Universitario Central de Asturias, Oviedo, Asturias).

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